Table 2. Recommended Dose Modifications for CAMPTOSAR/5-Fluorouracil (5-FU)/Leucovorin (LV) Combination Schedules

Patients should return to pre-treatment bowel function without requiring antidiarrhea medications for at least 24 hours before the next chemotherapy administration. A new cycle of therapy should not begin until the granulocyte count has recovered to ≥1500/mm^3, and the platelet count has recovered to ≥100,000/mm^3, and treatment-related diarrhea is fully resolved. Treatment should be delayed 1 to 2 weeks to allow for recovery from treatment-related toxicities. If the patient has not recovered after a 2-week delay, consideration should be given to discontinuing therapy.

Toxicity NCI CTC Grade[a] (Value)	During a Cycle of Therapy	At the Start of Subsequent Cycles of Therapy[b]
No toxicity	Maintain dose level	Maintain dose level
Neutropenia		
1 (1500 to 1999/mm^3)	Maintain dose level	Maintain dose level
2 (1000 to 1499/mm^3)	↓ 1 dose level	Maintain dose level
3 (500 to 999/mm^3)	Omit dose until resolved to ≤ grade 2, then ↓ 1 dose level	↓ 1 dose level
4 (<500/mm^3)	Omit dose until resolved to ≤ grade 2, then ↓ 2 dose levels	↓ 2 dose levels
Neutropenic fever	Omit dose until resolved, then ↓ 2 dose levels	
Other hematologic toxicities	Dose modifications for leukopenia or thrombocytopenia during a cycle of therapy and at the start of subsequent cycles of therapy are also based on NCI toxicity criteria and are the same as recommended for neutropenia above.	
Diarrhea		
1 (2-3 stools/day > pretx[c])	Delay dose until resolved to baseline, then give same dose	Maintain dose level
2 (4-6 stools/day > pretx)	Omit dose until resolved to baseline, then ↓ 1 dose level	Maintain dose level
3 (7-9 stools/day > pretx)	Omit dose until resolved to baseline, then ↓ 2 dose levels	↓ 1 dose level
4 (≥10 stools/day > pretx)		↓ 2 dose levels
Other nonhematologic toxicities[d]		
1	Maintain dose level	Maintain dose level
2	Omit dose until resolved to ≤ grade 1, then ↓ 1 dose level	Maintain dose level
3	Omit dose until resolved to ≤ grade 2, then ↓ 1 dose level	↓ 1 dose level
4	Omit dose until resolved to ≤ grade 2, then ↓ 2 dose levels	↓ 2 dose levels
	For mucositis/stomatitis decrease only 5-FU, not CAMPTOSAR	*For mucositis/stomatitis decrease only 5-FU, not CAMPTOSAR.*

[a] National Cancer Institute Common Toxicity Criteria (version 1.0)
[b] Relative to the starting dose used in the previous cycle
[c] Pretreatment
[d] Excludes alopecia, anorexia, asthenia

2.2 Colorectal Single Agent Regimens 1 and 2

Administer CAMPTOSAR as a 90-minute intravenous infusion. The currently recommended regimens are shown in Table 3.

A reduction in the starting dose by one dose level of CAMPTOSAR may be considered for patients with any of the following conditions: prior pelvic/abdominal radiotherapy, performance status of 2, or increased bilirubin levels. Dosing for patients with bilirubin >2 mg/dL cannot be recommended because there is insufficient information to recommend a dose in these patients.

Table 3. Single-Agent Regimens of CAMPTOSAR and Dose Modifications

Regimen 1 (weekly)[a]	125 mg/m^2 intravenous infusion over 90 minutes, days 1,8,15,22 then 2-week rest		
	Starting Dose and Modified Dose Levels[c] (mg/m^2)		
	Starting Dose	Dose Level -1	Dose Level -2
	125	100	75
Regimen 2 (every 3 weeks)[b]	350 mg/m^2 intravenous infusion over 90 minutes, once every 3 weeks[c]		
	Starting Dose and Modified Dose Levels (mg/m^2)		
	Starting Dose	Dose Level -1	Dose Level -2
	350	300	250

[a]Subsequent doses may be adjusted as high as 150 mg/m^2 or to as low as 50 mg/m^2 in 25 to 50 mg/m^2 decrements depending upon individual patient tolerance.
[b]Subsequent doses may be adjusted as low as 200 mg/m^2 in 50 mg/m^2 decrements depending upon individual patient tolerance.
[c]Provided intolerable toxicity does not develop, treatment with additional cycles may be continued indefinitely as long as patients continue to experience clinical benefit.

Dose Modifications

Based on recommended dose-levels described in Table 3, Single-Agent Regimens of CAMPTOSAR and Dose Modifications, subsequent doses should be adjusted as suggested in Table 4, Recommended Dose Modifications for Single-Agent Schedules. All dose modifications should be based on the worst preceding toxicity.

Table 4: Recommended Dose Modifications For Single-Agent Schedules[a]

A new cycle of therapy should not begin until the granulocyte count has recovered to ≥1500/mm^3, and the platelet count has recovered to ≥100,000/mm^3, and treatment-related diarrhea is fully resolved. Treatment should be delayed 1 to 2 weeks to allow for recovery from treatment-related toxicities. If the patient has not recovered after a 2-week delay, consideration should be given to discontinuing CAMPTOSAR.

Worst Toxicity NCI Grade[b] (Value)	**During a Cycle of Therapy**	**At the Start of the Next Cycles of Therapy (After Adequate Recovery), Compared with the Starting Dose in the Previous Cycle[a]**	
	Weekly	Weekly	Once Every 3 Weeks
No toxicity	Maintain dose level	↑ 25 mg/m^2 up to a maximum dose of 150 mg/m^2	Maintain dose level
Neutropenia 1 (1500 to 1999/mm^3) 2 (1000 to 1499/mm^3) 3 (500 to 999/mm^3) 4 (<500/mm^3)	Maintain dose level ↓ 25 mg/m^2 Omit dose until resolved to ≤ grade 2, then ↓ 25 mg/m^2 Omit dose until resolved to ≤ grade 2, then ↓ 50 mg/m^2	Maintain dose level Maintain dose level ↓ 25 mg/m^2 ↓ 50 mg/m^2	Maintain dose level Maintain dose level ↓ 50 mg/m^2 ↓ 50 mg/m^2
Neutropenic fever	Omit dose until resolved, then ↓ 50 mg/m^2 when resolved	↓ 50 mg/m^2	↓ 50 mg/m^2
Other hematologic toxicities	Dose modifications for leukopenia, thrombocytopenia, and anemia during a cycle of therapy and at the start of subsequent cycles of therapy are also based on NCI toxicity criteria and are the same as recommended for neutropenia above.		
Diarrhea 1 (2-3 stools/day > pretx[c]) 2 (4-6 stools/day > pretx) 3 (7-9 stools/day > pretx) 4 (≥10 stools/day > pretx)	Maintain dose level ↓ 25 mg/m^2 Omit dose until resolved to ≤ grade 2, then ↓ 25 mg/m^2 Omit dose until resolved to ≤ grade 2 then ↓ 50 mg/m^2	Maintain dose level Maintain dose level ↓ 25 mg/m^2 ↓ 50 mg/m^2	Maintain dose level Maintain dose level ↓ 50 mg/m^2 ↓ 50 mg/m^2
Other nonhematologic[d] toxicities 1 2 3 4	Maintain dose level ↓ 25 mg/m^2 Omit dose until resolved to ≤ grade 2, then ↓ 25 mg/m^2 Omit dose until resolved to ≤ grade 2, then ↓ 50 mg/m^2	Maintain dose level ↓ 25 mg/m^2 ↓ 25 mg/m^2 ↓ 50 mg/m^2	Maintain dose level ↓ 50 mg/m^2 ↓ 50 mg/m^2 ↓ 50 mg/m^2

[a] All dose modifications should be based on the worst preceding toxicity
[b] National Cancer Institute Common Toxicity Criteria (version 1.0)
[c] Pretreatment
[d] Excludes alopecia, anorexia, asthenia

2.3 Dosage in Patients with Reduced UGT1A1 Activity

When administered in combination with other agents, or as a single-agent, a reduction in the starting dose by at least one level of CAMPTOSAR should be considered for patients known to be homozygous for the UGT1A1*28 allele *[see Dosage and Administration (2.1 and 2.2) and Warnings and Precautions (5.3)]*. However, the precise dose reduction in this patient

population is not known, and subsequent dose modifications should be considered based on individual patient tolerance to treatment (see Tables 1-4).

2.4 Premedication

It is recommended that patients receive premedication with antiemetic agents. In clinical studies of the weekly dosage schedule, the majority of patients received 10 mg of dexamethasone given in conjunction with another type of antiemetic agent, such as a 5-HT^3 blocker (e.g., ondansetron or granisetron). Antiemetic agents should be given on the day of treatment, starting at least 30 minutes before administration of CAMPTOSAR. Physicians should also consider providing patients with an antiemetic regimen (e.g., prochlorperazine) for subsequent use as needed. A similar antiemetic regimen should be used with Camptosar in combination therapy.

Prophylactic or therapeutic administration of atropine should be considered in patients experiencing cholinergic symptoms.

2.5 Preparation of Infusion Solution

Inspect vial contents for particulate matter and discoloration and repeat inspection when drug product is withdrawn from vial into syringe.

CAMPTOSAR Injection 20 mg/mL is intended for single use only and any unused portion should be discarded.

CAMPTOSAR Injection must be diluted prior to infusion. CAMPTOSAR should be diluted in 5% Dextrose Injection, USP, (preferred) or 0.9% Sodium Chloride Injection, USP, to a final concentration range of 0.12 mg/mL to 2.8 mg/mL. Other drugs should not be added to the infusion solution.

The solution is physically and chemically stable for up to 24 hours at room temperature and in ambient fluorescent lighting. Solutions diluted in 5% Dextrose Injection, USP, and stored at refrigerated temperatures (approximately 2° to 8°C, 36° to 46°F), and protected from light are physically and chemically stable for 48 hours. Refrigeration of admixtures using 0.9% Sodium Chloride Injection, USP, is not recommended due to a low and sporadic incidence of visible particulates. Freezing CAMPTOSAR and admixtures of CAMPTOSAR may result in precipitation of the drug and should be avoided.

The CAMPTOSAR Injection solution should be used immediately after reconstitution as it contains no antibacterial preservative. Because of possible microbial contamination during dilution, it is advisable to use the admixture prepared with 5% Dextrose Injection, USP, within 24 hours if refrigerated (2° to 8°C, 36° to 46°F). In the case of admixtures prepared with 5% Dextrose Injection, USP, or Sodium Chloride Injection, USP, the solutions should be used within 4 hours if kept at room temperature. If reconstitution and dilution are performed under strict aseptic conditions (e.g. on Laminar Air Flow bench), CAMPTOSAR

Injection solution should be used (infusion completed) within 12 hours at room temperature or 24 hours if refrigerated (2° to 8°C, 36° to 46°F).

2.6 Safe Handling

Care should be exercised in the handling and preparation of infusion solutions prepared from CAMPTOSAR Injection. The use of gloves is recommended. If a solution of CAMPTOSAR contacts the skin, wash the skin immediately and thoroughly with soap and water. If CAMPTOSAR contacts the mucous membranes, flush thoroughly with water. Several published guidelines for handling and disposal of anticancer agents are available.

2.7 Extravasation

Care should be taken to avoid extravasation, and the infusion site should be monitored for signs of inflammation. Should extravasation occur, flushing the site with sterile water and applications of ice are recommended.

3 DOSAGE FORMS AND STRENGTHS

CAMPTOSAR Injection is available in three single-dose sizes:

- 2 mL-fill vial containing 40 mg irinotecan hydrochloride
- 5 mL-fill vial containing 100 mg irinotecan hydrochloride
- 15 mL-fill vial containing 300 mg irinotecan hydrochloride

4 CONTRAINDICATIONS

- CAMPTOSAR Injection is contraindicated in patients with a known hypersensitivity to the drug or its excipients.

5 WARNINGS AND PRECAUTIONS

5.1 Diarrhea and Cholinergic Reactions

Early diarrhea (occurring during or shortly after infusion of CAMPTOSAR) is usually transient and infrequently severe. It may be accompanied by cholinergic symptoms of rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, and intestinal hyperperistalsis that can cause abdominal cramping. Bradycardia may also occur. Early diarrhea and other cholinergic symptoms may be prevented or treated. Consider prophylactic or therapeutic administration of 0.25 mg to 1 mg of intravenous or subcutaneous atropine (unless clinically contraindicated). These symptoms are expected to occur more frequently with higher irinotecan doses.

Late diarrhea (generally occurring more than 24 hours after administration of CAMPTOSAR) can be life threatening since it may be prolonged and may lead to dehydration, electrolyte imbalance, or sepsis. Grade 3-4 late diarrhea occurred in 23-31% of

patients receiving weekly dosing. In the clinical studies, the median time to the onset of late diarrhea was 5 days with 3-week dosing and 11 days with weekly dosing. Late diarrhea can be complicated by colitis, ulceration, bleeding, ileus, obstruction, and infection. Cases of megacolon and intestinal perforation have been reported. Patients should have loperamide readily available to begin treatment for late diarrhea. Begin loperamide at the first episode of poorly formed or loose stools or the earliest onset of bowel movements more frequent than normal. One dosage regimen for loperamide is 4 mg at the first onset of late diarrhea and then 2 mg every 2 hours until the patient is diarrhea-free for at least 12 hours. Loperamide is not recommended to be used for more than 48 consecutive hours at these doses, because of the risk of paralytic ileus. During the night, the patient may take 4 mg of loperamide every 4 hours. Monitor and replace fluid and electrolytes. Use antibiotic support for ileus, fever, or severe neutropenia. Subsequent weekly chemotherapy treatments should be delayed in patients until return of pretreatment bowel function for at least 24 hours without anti-diarrhea medication. Patients must not be treated with irinotecan until resolution of the bowel obstruction. If grade 2, 3, or 4 late diarrhea recurs, subsequent doses of CAMPTOSAR should be decreased *[see Dosage and Administration (2)]*.

Avoid diuretics or laxatives in patients with diarrhea.

5.2 Myelosuppression

Deaths due to sepsis following severe neutropenia have been reported in patients treated with CAMPTOSAR. In the clinical studies evaluating the weekly dosage schedule, neutropenic fever (concurrent NCI grade 4 neutropenia and fever of grade 2 or greater) occurred in 3% of the patients; 6% of patients received G-CSF for the treatment of neutropenia. Manage febrile neutropenia promptly with antibiotic support *[see Warnings and Precautions (5.2)]*. Hold CAMPTOSAR if neutropenic fever occurs or if the absolute neutrophil count drops $<1000/mm^3$. After recovery to an absolute neutrophil count $\geq 1000/mm^3$, subsequent doses of CAMPTOSAR should be reduced *[see Dosage and Administration (2)]*.

When evaluated in the trials of weekly administration, the frequency of grade 3 and 4 neutropenia was higher in patients who received previous pelvic/abdominal irradiation than in those who had not received such irradiation (48% [13/27] versus 24% [67/277]; p=0.04). Patients who have previously received pelvic/abdominal irradiation are at increased risk of severe myelosuppression following the administration of CAMPTOSAR. Based on sparse available data, the concurrent administration of CAMPTOSAR with irradiation is not recommended.

Patients with baseline serum total bilirubin levels of 1.0 mg/dL or more also had a greater likelihood of experiencing first-cycle grade 3 or 4 neutropenia than those with bilirubin levels that were less than 1.0 mg/dL (50% [19/38] versus 18% [47/266]; p<0.001). Patients with deficient glucuronidation of bilirubin, such as those with Gilbert's syndrome, may be at greater risk of myelosuppression when receiving therapy with CAMPTOSAR.

5.3 Patients With Reduced UGT1A1 Activity

Individuals who are homozygous for the UGT1A1*28 allele (UGT1A1 7/7 genotype) are at increased risk for neutropenia following initiation of CAMPTOSAR treatment.

In a study of 66 patients who received single-agent CAMPTOSAR (350 mg/m^2 once-every-3-weeks), the incidence of grade 4 neutropenia in patients homozygous for the UGT1A1*28 allele was 50%, and in patients heterozygous for this allele (UGT1A1 6/7 genotype) the incidence was 12.5%. No grade 4 neutropenia was observed in patients homozygous for the wild-type allele (UGT1A1 6/6 genotype).

In a prospective study (n=250) to investigate the role of UGT1A1*28 polymorphism in the development of toxicity in patients treated with CAMPTOSAR (180 mg/m^2) in combination with infusional 5-FU/LV, the incidence of grade 4 neutropenia in patients homozygous for the UGT1A1*28 allele was 4.5%, and in patients heterozygous for this allele the incidence was 5.3%. Grade 4 neutropenia was observed in 1.8% of patients homozygous for the wild-type allele.

In another study in which 109 patients were treated with CAMPTOSAR (100-125 mg/m^2) in combination with bolus 5-FU/LV, the incidence of grade 4 neutropenia in patients homozygous for the UGT1A1*28 allele was 18.2%, and in patients heterozygous for this allele the incidence was 11.1%. Grade 4 neutropenia was observed in 6.8% of patients homozygous for the wild-type allele.

When administered in combination with other agents or as a single-agent, a reduction in the starting dose by at least one level of CAMPTOSAR should be considered for patients known to be homozygous for the UGT1A1*28 allele. However, the precise dose reduction in this patient population is not known and subsequent dose modifications should be considered based on individual patient tolerance to treatment *[see Dosage and Administration (2)]*.

UGT1A1 Testing

A laboratory test is available to determine the UGT1A1 status of patients. Testing can detect the UGT1A1 6/6, 6/7 and 7/7 genotypes.

5. 4 Hypersensitivity

Hypersensitivity reactions including severe anaphylactic or anaphylactoid reactions have been observed. Discontinue CAMPTOSAR if anaphylactic reaction occurs.

5. 5 Renal Impairment/Renal Failure

Renal impairment and acute renal failure have been identified, usually in patients who became volume depleted from severe vomiting and/or diarrhea.

5. 6 Pulmonary Toxicity

Interstitial Pulmonary Disease (IPD)-like events, including fatalities, have occurred in patients receiving irinotecan (in combination and as monotherapy). Risk factors include pre-existing lung disease, use of pneumotoxic drugs, radiation therapy, and colony stimulating factors. Patients with risk factors should be closely monitored for respiratory symptoms before and during irinotecan therapy. In Japanese studies, a reticulonodular pattern on chest x-ray was observed in a small percentage of patients. New or progressive, dyspnea, cough, and fever should prompt interruption of chemotherapy, pending diagnostic evaluation. If IPD is diagnosed, irinotecan and other chemotherapy should be discontinued and appropriate treatment instituted as needed *[see Adverse Reactions (6.1)]*.

5.7 Toxicity of the 5 Day Regimen

Outside of a well-designed clinical study, CAMPTOSAR Injection should not be used in combination with a regimen of 5-FU/LV administered for 4-5 consecutive days every 4 weeks because of reports of increased toxicity, including toxic deaths. CAMPTOSAR should be used as recommended in Table 2 *[see Dosage and Administration (2)]*.

5.8 Increased Toxicity in Patients with Performance Status 2

In patients receiving either irinotecan/5-FU/LV or 5-FU/LV in the clinical trials, higher rates of hospitalization, neutropenic fever, thromboembolism, first-cycle treatment discontinuation, and early deaths were observed in patients with a baseline performance status of 2 than in patients with a baseline performance status of 0 or 1.

5.9 Pregnancy

CAMPTOSAR can cause fetal harm when administered to a pregnant woman. Irinotecan was embryotoxic in rats and rabbits at doses significantly lower than those administered to humans on a mg/m^2 basis. In rats, at exposures approximately 0.2 times those achieved in humans at the 125 mg/m^2 dose, irinotecan was embryotoxic and resulted in decreased learning ability and female fetal body weight in surviving pups; the drug was teratogenic at lower exposures (approximately 0.025 times the AUC in humans at the 125 mg/m^2 dose).There are no adequate and well-controlled studies of irinotecan in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with CAMPTOSAR.

5.10 Patients with Hepatic Impairment

The use of CAMPTOSAR in patients with significant hepatic impairment has not been established. In clinical trials of either dosing schedule, irinotecan was not administered to patients with serum bilirubin >2.0 mg/dL, or transaminase >3 times the upper limit of normal if no liver metastasis, or transaminase >5 times the upper limit of normal with liver metastasis. In clinical trials of the weekly dosage schedule, patients with modestly elevated baseline serum total bilirubin levels (1.0 to 2.0 mg/dL) had a significantly greater likelihood

of experiencing first-cycle, grade 3 or 4 neutropenia than those with bilirubin levels that were less than 1.0 mg/dL (50% [19/38] versus 18% [47/226]; p<0.001) *[see Dosage and Administration (2.1), Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)]*.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.
Common adverse reactions (≥30%) observed in combination therapy clinical studies are: nausea, vomiting, abdominal pain, diarrhea, constipation, anorexia, mucositis, neutropenia, leukopenia (including lymphocytopenia), anemia, thrombocytopenia, asthenia, pain, fever, infection, abnormal bilirubin, and alopecia.

Common adverse reactions (≥30%) observed in single agent therapy clinical studies are: nausea, vomiting, abdominal pain, diarrhea, constipation, anorexia, neutropenia, leukopenia (including lymphocytopenia), anemia, asthenia, fever, body weight decreasing, and alopecia.

Serious opportunistic infections have not been observed, and no complications have specifically been attributed to lymphocytopenia.

First-Line Combination Therapy

A total of 955 patients with metastatic colorectal cancer received the recommended regimens of irinotecan in combination with 5-FU/LV, 5-FU/LV alone, or irinotecan alone. In the two phase 3 studies, 370 patients received irinotecan in combination with 5-FU/LV, 362 patients received 5-FU/LV alone, and 223 patients received irinotecan alone *[see Dosage and Administration (2)]*.

In Study 1, 49 (7.3%) patients died within 30 days of last study treatment: 21 (9.3%) received irinotecan in combination with 5-FU/LV, 15 (6.8%) received 5-FU/LV alone, and 13 (5.8%) received irinotecan alone. Deaths potentially related to treatment occurred in 2 (0.9%) patients who received irinotecan in combination with 5-FU/LV (2 neutropenic fever/sepsis), 3 (1.4%) patients who received 5-FU/LV alone (1 neutropenic fever/sepsis, 1 CNS bleeding during thrombocytopenia, 1 unknown) and 2 (0.9%) patients who received irinotecan alone (2 neutropenic fever). Deaths from any cause within 60 days of first study treatment were reported for 15 (6.7%) patients who received irinotecan in combination with 5-FU/LV, 16 (7.3%) patients who received 5-FU/LV alone, and 15 (6.7%) patients who received irinotecan alone. Discontinuations due to adverse events were reported for 17 (7.6%) patients who received irinotecan in combination with 5FU/LV, 14 (6.4%) patients who received 5-FU/LV alone, and 26 (11.7%) patients who received irinotecan alone.

In Study 2, 10 (3.5%) patients died within 30 days of last study treatment: 6 (4.1%) received irinotecan in combination with 5-FU/LV and 4 (2.8%) received 5-FU/LV alone. There was one potentially treatment-related death, which occurred in a patient who received irinotecan

in combination with 5-FU/LV (0.7%, neutropenic sepsis). Deaths from any cause within 60 days of first study treatment were reported for 3 (2.1%) patients who received irinotecan in combination with 5-FU/LV and 2 (1.4%) patients who received 5-FU/LV alone. Discontinuations due to adverse events were reported for 9 (6.2%) patients who received irinotecan in combination with 5FU/LV and 1 (0.7%) patient who received 5-FU/LV alone.

The most clinically significant adverse events for patients receiving irinotecan-based therapy were diarrhea, nausea, vomiting, neutropenia, and alopecia. The most clinically significant adverse events for patients receiving 5-FU/LV therapy were diarrhea, neutropenia, neutropenic fever, and mucositis. In Study 1, grade 4 neutropenia, neutropenic fever (defined as grade 2 fever and grade 4 neutropenia), and mucositis were observed less often with weekly irinotecan/5-FU/LV than with monthly administration of 5-FU/LV.

Tables 5 and 6 list the clinically relevant adverse events reported in Studies 1 and 2, respectively.

Table 5. Study 1: Percent (%) of Patients Experiencing Clinically Relevant Adverse Events in Combination Therapies[a]

Adverse Event	Study 1					
	Irinotecan + Bolus 5-FU/LV weekly x 4 every 6 weeks N=225		Bolus 5-FU/LV daily x 5 every 4 weeks N=219		Irinotecan weekly x 4 every 6 weeks N=223	
	Grade 1-4	Grade 3&4	Grade 1-4	Grade 3&4	Grade 1-4	Grade 3&4
TOTAL Adverse Events	100	53.3	100	45.7	99.6	45.7
GASTROINTESTINAL						
Diarrhea	84.9	22.7	69.4	13.2	83.0	31.0
late	--	15.1	--	5.9	--	18.4
grade 3	--	7.6	--	7.3	--	12.6
grade 4	45.8	4.9	31.5	1.4	43.0	6.7
early						
Nausea	79.1	15.6	67.6	8.2	81.6	16.1
Abdominal pain	63.1	14.6	50.2	11.5	67.7	13.0
Vomiting	60.4	9.7	46.1	4.1	62.8	12.1
Anorexia	34.2	5.8	42.0	3.7	43.9	7.2
Constipation	41.3	3.1	31.5	1.8	32.3	0.4
Mucositis	32.4	2.2	76.3	16.9	29.6	2.2
HEMATOLOGIC						
Neutropenia	96.9	53.8	98.6	66.7	96.4	31.4
grade 3	--	29.8	--	23.7	--	19.3
grade 4	--	24.0	--	42.5	--	12.1
Leukopenia	96.9	37.8	98.6	23.3	96.4	21.5
Anemia	96.9	8.4	98.6	5.5	96.9	4.5
Neutropenic fever	--	7.1	--	14.6	--	5.8
Thrombocytopenia	96.0	2.6	98.6	2.7	96.0	1.7
Neutropenic infection	--	1.8	--	0	--	2.2
BODY AS A WHOLE						
Asthenia	70.2	19.5	64.4	11.9	69.1	13.9

Pain	30.7	3.1	26.9	3.6	22.9	2.2
Fever	42.2	1.7	32.4	3.6	43.5	0.4
Infection	22.2	0	16.0	1.4	13.9	0.4
METABOLIC & NUTRITIONAL						
Bilirubin	87.6	7.1	92.2	8.2	83.9	7.2
DERMATOLOGIC	0.9	0	3.2	0.5	0	0
Exfoliative dermatitis	19.1	0	26.5	0.9	14.3	0.4
Rash	43.1	--	26.5	--	46.1	--
Alopecia[b]						
RESPIRATORY						
Dyspnea	27.6	6.3	16.0	0.5	22.0	2.2
Cough	26.7	1.3	18.3	0	20.2	0.4
Pneumonia	6.2	2.7	1.4	1.0	3.6	1.3
NEUROLOGIC						
Dizziness	23.1	1.3	16.4	0	21.1	1.8
Somnolence	12.4	1.8	4.6	1.8	9.4	1.3
Confusion	7.1	1.8	4.1	0	2.7	0
CARDIOVASCULAR	9.3	0.9	5.0	0	9.0	0
Vasodilatation	5.8	1.3	2.3	0.5	5.8	1.7
Hypotension	9.3	--	11.4	--	5.4	--
Thromboembolic events[c]						

[a]Severity of adverse events based on NCI CTC (version 1.0)
[b]Complete hair loss = Grade 2
[c]Includes angina pectoris, arterial thrombosis, cerebral infarct, cerebrovascular accident, deep thrombophlebitis, embolus lower extremity, heart arrest, myocardial infarct, myocardial ischemia, peripheral vascular disorder, pulmonary embolus, sudden death, thrombophlebitis, thrombosis, vascular disorder.

Table 6. Study 2: Percent (%) of Patients Experiencing Clinically Relevant Adverse Events in Combination Therapies[a]

Adverse Event	Study 2			
	Irinotecan + 5-FU/LV infusional days 1&2 every 2 weeks N= 145		5-FU/LV infusional days 1&2 every 2 weeks N=143	
	Grades 1-4	Grades 3&4	Grades 1-4	Grades 3&4
TOTAL Adverse Events	100	72.4	100	39.2
GASTROINTESTINAL				
Diarrhea	72.4	14.4	44.8	6.3
late	--	10.3	--	4.2
grade 3	--	4.1	--	2.1
grade 4	28.3	1.4	0.7	0
Cholinergic syndrome[b]				
Nausea	66.9	2.1	55.2	3.5
Abdominal pain	17.2	2.1	16.8	0.7
Vomiting	44.8	3.5	32.2	2.8
Anorexia	35.2	2.1	18.9	0.7
Constipation	30.3	0.7	25.2	1.4
Mucositis	40.0	4.1	28.7	2.8
HEMATOLOGIC				
Neutropenia	82.5	46.2	47.9	13.4
grade 3	--	36.4	--	12.7
grade 4	--	9.8	--	0.7
Leukopenia	81.3	17.4	42.0	3.5
Anemia	97.2	2.1	90.9	2.1
Neutropenic fever	--	3.4	--	0.7
Thrombocytopenia	32.6	0	32.2	0
Neutropenic infection	--	2.1	--	0
BODY AS A WHOLE				
Asthenia	57.9	9.0	48.3	4.2
Pain	64.1	9.7	61.5	8.4
Fever	22.1	0.7	25.9	0.7
Infection	35.9	7.6	33.6	3.5
METABOLIC AND NUTRITIONAL				
Bilirubin	19.1	3.5	35.9	10.6
DERMATOLOGIC	10.3	0.7	12.6	0.7
Hand and foot syndrome	17.2	0.7	20.3	0
Cutaneous signs	56.6	--	16.8	--
Alopecia[c]				
RESPIRATORY				
Dyspnea	9.7	1.4	4.9	0

CARDIOVASCULAR	3.4	1.4	0.7	0
Hypotension	11.7	--	5.6	--
Thromboembolic events[d]				

[a] Severity of adverse events based on NCI CTC (version 1.0)
[b] Includes rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, abdominal cramping or diarrhea (occurring during or shortly after infusion of irinotecan)
[c] Complete hair loss = Grade 2
[d] Includes angina pectoris, arterial thrombosis, cerebral infarct, cerebrovascular accident, deep thrombophlebitis, embolus lower extremity, heart arrest, myocardial infarct, myocardial ischemia, peripheral vascular disorder, pulmonary embolus, sudden death, thrombophlebitis, thrombosis, vascular disorder.

Second-Line Single-Agent Therapy

Weekly Dosage Schedule

In three clinical studies evaluating the weekly dosage schedule, 304 patients with metastatic carcinoma of the colon or rectum that had recurred or progressed following 5-FU-based therapy were treated with CAMPTOSAR. Seventeen of the patients died within 30 days of the administration of CAMPTOSAR; in five cases (1.6%, 5/304), the deaths were potentially drug-related. One of the patients died of neutropenic sepsis without fever. Neutropenic fever occurred in nine (3.0%) other patients; these patients recovered with supportive care.

One hundred nineteen (39.1%) of the 304 patients were hospitalized because of adverse events; 81 (26.6%) patients were hospitalized for events judged to be related to administration of CAMPTOSAR. The primary reasons for drug-related hospitalization were diarrhea, with or without nausea and/or vomiting (18.4%); neutropenia/leukopenia, with or without diarrhea and/or fever (8.2%); and nausea and/or vomiting (4.9%).

The first dose of at least one cycle of CAMPTOSAR was reduced for 67% of patients who began the studies at the 125-mg/m^2 starting dose. Within-cycle dose reductions were required for 32% of the cycles initiated at the 125-mg/m^2 dose level. The most common reasons for dose reduction were late diarrhea, neutropenia, and leukopenia. Thirteen (4.3%) patients discontinued treatment with CAMPTOSAR because of adverse events. The adverse events in Table 7 are based on the experience of the 304 patients enrolled in the three studies described in *CLINICAL STUDIES (14.1)*.

Table 7. Adverse Events Occurring in >10% of 304 Previously Treated Patients with Metastatic Carcinoma of the Colon or Rectum[a]

Body System & Event	% of Patients Reporting	
	NCI Grades 1-4	NCI Grades 3 & 4
GASTROINTESTINAL		
Diarrhea (late)[b]	88	31
7-9 stools/day (grade 3)	—	(16)
≥10 stools/day (grade 4)	—	(14)
Nausea	86	17
Vomiting	67	12
Anorexia	55	6
Diarrhea (early)[c]	51	8
Constipation	30	2
Flatulence	12	0
Stomatitis	12	1
Dyspepsia	10	0
HEMATOLOGIC		
Leukopenia	63	28
Anemia	60	7
Neutropenia	54	26
500 to <1000/mm^3 (grade 3)	—	(15)
<500/mm^3 (grade 4)	—	(12)
BODY AS A WHOLE		
Asthenia	76	12
Abdominal cramping/pain	57	16
Fever	45	1
Pain	24	2
Headache	17	1
Back pain	14	2
Chills	14	0
Minor infection[d]	14	0
Edema	10	1
Abdominal enlargement	10	0
METABOLIC AND NUTRITIONAL		
↓ Body weight	30	1
Dehydration	15	4
↑ Alkaline phosphatase	13	4
↑ SGOT	10	1
DERMATOLOGIC		
Alopecia	60	NA[e]
Sweating	16	0
Rash	13	1
RESPIRATORY		
Dyspnea	22	4
↑ Coughing	17	0
Rhinitis	16	0
NEUROLOGIC		
Insomnia	19	0
Dizziness	15	0
CARDIOVASCULAR		
Vasodilation (flushing)	11	0

Table 7. Adverse Events Occurring in >10% of 304 Previously Treated Patients with Metastatic Carcinoma of the Colon or Rectum[a]

[a] Severity of adverse events based on NCI CTC (version 1.0)
[b] Occurring > 24 hours after administration of CAMPTOSAR
[c] Occurring ≤24 hours after administration of CAMPTOSAR
[d] Primarily upper respiratory infections
[e] Not applicable; complete hair loss = NCI grade 2

Once-Every-3-Week Dosage Schedule

A total of 535 patients with metastatic colorectal cancer whose disease had recurred or progressed following prior 5-FU therapy participated in the two phase 3 studies: 316 received irinotecan, 129 received 5-FU, and 90 received best supportive care. Eleven (3.5%) patients treated with irinotecan died within 30 days of treatment. In three cases (1%, 3/316), the deaths were potentially related to irinotecan treatment and were attributed to neutropenic infection, grade 4 diarrhea, and asthenia, respectively. One (0.8%, 1/129) patient treated with 5-FU died within 30 days of treatment; this death was attributed to grade 4 diarrhea.

Hospitalizations due to serious adverse events occurred at least once in 60% (188/316) of patients who received irinotecan, 63% (57/90) who received best supportive care, and 39% (50/129) who received 5-FU-based therapy. Eight percent of patients treated with irinotecan and 7% treated with 5-FU-based therapy discontinued treatment due to adverse events.

Of the 316 patients treated with irinotecan, the most clinically significant adverse events (all grades, 1-4) were diarrhea (84%), alopecia (72%), nausea (70%), vomiting (62%), cholinergic symptoms (47%), and neutropenia (30%). Table 8 lists the grade 3 and 4 adverse events reported in the patients enrolled to all treatment arms of the two studies described in *CLINICAL STUDIES (14.1)*.

Table 8: Percent Of Patients Experiencing Grade 3 & 4 Adverse Events In Comparative Studies Of Once-Every-3-Week Irinotecan Therapy[a]

	Study 1		Study 2	
Adverse Event	**Irinotecan N=189**	**BSC [b] N=90**	**Irinotecan N=127**	5-FU **N=129**
TOTAL Grade 3/4 Adverse Events	79	67	69	54
GASTROINTESTINAL				
Diarrhea	22	6	22	11
Vomiting	14	8	14	5
Nausea	14	3	11	4
Abdominal pain	14	16	9	8
Constipation	10	8	8	6
Anorexia	5	7	6	4
Mucositis	2	1	2	5
HEMATOLOGIC				
Leukopenia/Neutropenia	22	0	14	2
Anemia	7	6	6	3
Hemorrhage	5	3	1	3
Thrombocytopenia	1	0	4	2

Infection				
without grade 3/4 neutropenia	8	3	1	4
with grade 3/4 neutropenia	1	0	2	0
Fever				
without grade 3/4 neutropenia	2	1	2	0
with grade 3/4 neutropenia	2	0	4	2
BODY AS A WHOLE				
Pain	19	22	17	13
Asthenia	15	19	13	12
METABOLIC AND NUTRITIONAL				
Hepatic [c]	9	7	9	6
DERMATOLOGIC				
Hand and foot syndrome	0	0	0	5
Cutaneous signs [d]	2	0	1	3
RESPIRATORY [e]	10	8	5	7
NEUROLOGIC [f]	12	13	9	4
CARDIOVASCULAR [g]	9	3	4	2
OTHER [h]	32	28	12	14

[a] Severity of adverse events based on NCI CTC (version 1.0)
[b] BSC = best supportive care
[c] Hepatic includes events such as ascites and jaundice
[d] Cutaneous signs include events such as rash
[e] Respiratory includes events such as dyspnea and cough
[f] Neurologic includes events such as somnolence
[g] Cardiovascular includes events such as dysrhythmias, ischemia, and mechanical cardiac dysfunction
[h] Other includes events such as accidental injury, hepatomegaly, syncope, vertigo, and weight loss

The incidence of akathisia in clinical trials of the weekly dosage schedule was greater (8.5%, 4/47 patients) when prochlorperazine was administered on the same day as CAMPTOSAR than when these drugs were given on separate days (1.3%, 1/80 patients). The 8.5% incidence of akathisia, however, is within the range reported for use of prochlorperazine when given as a premedication for other chemotherapies.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of CAMPTOSAR. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Myocardial ischemic events have been observed following irinotecan therapy. Thromboembolic events have been observed in patients receiving CAMPTOSAR.

Symptomatic pancreatitis, asymptomatic pancreatic enzyme elevation have been reported. Increases in serum levels of transaminases (i.e., AST and ALT) in the absence of progressive liver metastasis have been observed.

Hyponatremia, mostly with diarrhea and vomiting, has been reported.

Transient dysarthria has been reported in patients treated with CAMPTOSAR; in some cases, the event was attributed to the cholinergic syndrome observed during or shortly after infusion of irinotecan.

Interaction between irinotecan and neuromuscular blocking agents cannot be ruled out. Irinotecan has anticholinesterase activity, which may prolong the neuromuscular blocking effects of suxamethonium and the neuromuscular blockade of non-depolarizing drugs may be antagonized.

7 DRUG INTERACTIONS

7.1 5-Fluorouracil (5-FU) and Leucovorin (LV)

In a phase 1 clinical study involving irinotecan, 5-fluorouracil (5-FU), and leucovorin (LV) in 26 patients with solid tumors, the disposition of irinotecan was not substantially altered when the drugs were co-administered. Although the C_{max} and AUC_{0-24} of SN-38, the active metabolite, were reduced (by 14% and 8%, respectively) when irinotecan was followed by 5-FU and LV administration compared with when irinotecan was given alone, this sequence of administration was used in the combination trials and is recommended *[see Dosage and Administration (2)]*. Formal *in vivo* or *in vitro* drug interaction studies to evaluate the influence of irinotecan on the disposition of 5-FU and LV have not been conducted.

7.2 Strong CYP 3A4 Inducers

Anticonvulsants and other strong inducers: Exposure to irinotecan and its active metabolite SN-38 is substantially reduced in adult and pediatric patients concomitantly receiving the CYP3A4 enzyme-inducing anticonvulsants phenytoin, phenobarbital or carbamazepine. The appropriate starting dose for patients taking these anticonvulsants or other strong inducers such as rifampin and rifabutin has not been defined. Consideration should be given to substituting non-enzyme inducing therapies at least 2 weeks prior to initiation of irinotecan therapy.

St. John's wort: Exposure to the active metabolite SN-38 is reduced in patients receiving concomitant St. John's wort. St. John's wort should be discontinued at least 2 weeks prior to the first cycle of irinotecan, and St. John's wort is contraindicated during irinotecan therapy.

Dexamethasone, a moderate CYP3A4 inducer, does not appear to alter the pharmacokinetics of irinotecan.

7.3 Strong CYP 3A4 Inhibitors

Ketoconazole is a strong inhibitor of CYP3A4 enzymes. Patients receiving concomitant ketoconazole have increased exposure to irinotecan and its active metabolite SN-38. Patients should discontinue ketoconazole at least 1 week prior to starting irinotecan therapy and ketoconazole is contraindicated during irinotecan therapy.

7.4 Atazanavir Sulfate

Coadministration of atazanavir sulfate, a CYP3A4 and UGT1A1 inhibitor has the potential to increase systemic exposure to SN-38, the active metabolite of irinotecan. Physicians should take this into consideration when co-administering these drugs.

7.5 Drug-Laboratory Test Interactions

There are no known interactions between CAMPTOSAR and laboratory tests.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D *[see Warnings and Precautions (5.9)]*

CAMPTOSAR can cause fetal harm when administered to a pregnant woman. Radioactivity related to ^{14}C-irinotecan crosses the placenta of rats following intravenous administration of 10 mg/kg (which in separate studies produced an irinotecan C_{max} and AUC about 3 and 0.5 times, respectively, the corresponding values in patients administered 125 mg/m^2). Intravenous administration of irinotecan 6 mg/kg/day to rats and rabbits during the period of organogenesis resulted in increased post-implantation loss and decreased numbers of live fetuses. In separate studies in rats, this dose produced an irinotecan C_{max} and AUC of about 2 and 0.2 times, respectively, the corresponding values in patients administered 125 mg/m^2. In rabbits, the embryotoxic dose was about one-half the recommended human weekly starting dose on a mg/m^2 basis. Irinotecan was teratogenic in rats at doses greater than 1.2 mg/kg/day and in rabbits at 6.0 mg/kg/day. In separate studies in rats, this dose produced an irinotecan C_{max} and AUC about 2/3 and 1/40th, respectively, of the corresponding values in patients administered 125 mg/m^2. In rabbits, the teratogenic dose was about one-half the recommended human weekly starting dose on a mg/m^2 basis. Teratogenic effects included a variety of external, visceral, and skeletal abnormalities. Irinotecan administered to rat dams for the period following organogenesis through weaning at doses of 6 mg/kg/day caused decreased learning ability and decreased female body weights in the offspring. There are no adequate and well-controlled studies of irinotecan in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with CAMPTOSAR.

8.3 Nursing Mothers

Radioactivity appeared in rat milk within 5 minutes of intravenous administration of radiolabeled irinotecan and was concentrated up to 65-fold at 4 hours after administration relative to plasma concentrations. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from CAMPTOSAR, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of

the drug to the mother.

8.4 Pediatric Use

The effectiveness of irinotecan in pediatric patients has not been established. Results from two open-label, single arm studies were evaluated. One hundred and seventy children with refractory solid tumors were enrolled in one phase 2 trial in which 50 mg/ m^2 of irinotecan was infused for 5 consecutive days every 3 weeks. Grade 3-4 neutropenia was experienced by 54 (31.8%) patients. Neutropenia was complicated by fever in 15 (8.8%) patients. Grade 3-4 diarrhea was observed in 35 (20.6%) patients. This adverse event profile was comparable to that observed in adults. In the second phase 2 trial of 21 children with previously untreated rhabdomyosarcoma, 20 mg/m^2 of irinotecan was infused for 5 consecutive days on weeks 0, 1, 3 and 4. This single agent therapy was followed by multimodal therapy. Accrual to the single agent irinotecan phase was halted due to the high rate (28.6%) of progressive disease and the early deaths (14%). The adverse event profile was different in this study from that observed in adults; the most significant grade 3 or 4 adverse events were dehydration experienced by 6 patients (28.6%) associated with severe hypokalemia in 5 patients (23.8%) and hyponatremia in 3 patients (14.3%); in addition Grade 3-4 infection was reported in 5 patients (23.8%) (across all courses of therapy and irrespective of causal relationship).

Pharmacokinetic parameters for irinotecan and SN-38 were determined in 2 pediatric solid-tumor trials at dose levels of 50 mg/m^2 (60-min infusion, n=48) and 125 mg/m^2 (90-min infusion, n=6). Irinotecan clearance (mean ± S.D.) was 17.3 ± 6.7 L/h/m^2 for the 50mg/m^2 dose and 16.2 ± 4.6 L/h/m^2 for the 125 mg/m^2 dose, which is comparable to that in adults. Dose-normalized SN-38 AUC values were comparable between adults and children. Minimal accumulation of irinotecan and SN-38 was observed in children on daily dosing regimens [daily x 5 every 3 weeks or (daily x 5) x 2 weeks every 3 weeks].

8.5 Geriatric Use

Patients greater than 65 years of age should be closely monitored because of a greater risk of early and late diarrhea in this population *[see Clinical Pharmacology (12.3)* and *Adverse Reactions (6.1)]*. The starting dose of CAMPTOSAR in patients 70 years and older for the once-every-3-week-dosage schedule should be 300 mg/m^2 *[see Clinical Pharmacology (12.3) and Dosage and Administration (2)]*.

The frequency of grade 3 and 4 late diarrhea by age was significantly greater in patients ≥65 years than in patients <65 years (40% [53/133] versus 23% [40/171]; p=0.002). In another study of 183 patients treated on the weekly schedule, the frequency of grade 3 or 4 late diarrhea in patients ≥65 years of age was 28.6% [26/91] and in patients <65 years of age was 23.9% [22/92].

8.6 Renal Impairment

The influence of renal impairment on the pharmacokinetics of irinotecan has not been

evaluated. Therefore, use caution in patients with impaired renal function. Irinotecan is not recommended for use in patients on dialysis.

8.7 Hepatic Impairment

Irinotecan clearance is diminished in patients with hepatic impairment while exposure to the active metabolite SN-38 is increased relative to that in patients with normal hepatic function. The magnitude of these effects is proportional to the degree of liver impairment as measured by elevations in total bilirubin and transaminase concentrations. Therefore, use caution in patients with hepatic impairment. The tolerability of irinotecan in patients with hepatic dysfunction (bilirubin greater than 2 mg/dl) has not been assessed sufficiently, and no recommendations for dosing can be made *[see Dosage and Administration (2.1), Warnings and Precautions (5.10) and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

In U.S. phase 1 trials, single doses of up to 345 mg/m^2 of irinotecan were administered to patients with various cancers. Single doses of up to 750 mg/m^2 of irinotecan have been given in non-U.S. trials. The adverse events in these patients were similar to those reported with the recommended dosage and regimen. There have been reports of overdosage at doses up to approximately twice the recommended therapeutic dose, which may be fatal. The most significant adverse reactions reported were severe neutropenia and severe diarrhea. There is no known antidote for overdosage of CAMPTOSAR. Maximum supportive care should be instituted to prevent dehydration due to diarrhea and to treat any infectious complications.

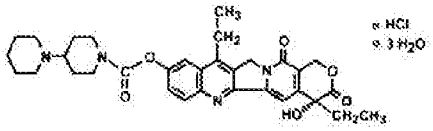
11 DESCRIPTION

CAMPTOSAR Injection (irinotecan hydrochloride injection) is an antineoplastic agent of the topoisomerase I inhibitor class.

CAMPTOSAR is supplied as a sterile, pale yellow, clear, aqueous solution. Each milliliter of solution contains 20 mg of irinotecan hydrochloride (on the basis of the trihydrate salt), 45 mg of sorbitol, NF, and 0.9 mg of lactic acid, USP. The pH of the solution has been adjusted to 3.5 (range, 3.0 to 3.8) with sodium hydroxide or hydrochloric acid. CAMPTOSAR is intended for dilution with 5% Dextrose Injection, USP (D5W), or 0.9% Sodium Chloride Injection, USP, prior to intravenous infusion. The preferred diluent is 5% Dextrose Injection, USP.

Irinotecan hydrochloride is a semisynthetic derivative of camptothecin, an alkaloid extract from plants such as *Camptotheca acuminata* or is chemically synthesized.

The chemical name is *(**S**)*-4,11-diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo1*H*-pyrano[3',4':6,7]-indolizino[1,2-b]quinolin-9-yl-[1,4'bipiperidine]-1'-carboxylate, monohydrochloride, trihydrate. Its empirical formula is $C_{33}H_{38}N_4O_6 \cdot HCl \cdot 3H_2O$ and molecular weight is 677.19. It is slightly soluble in water and organic solvents. Its structural formula is as follows:



Irinotecan Hydrochloride

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Irinotecan is a derivative of camptothecin. Camptothecins interact specifically with the enzyme topoisomerase I, which relieves torsional strain in DNA by inducing reversible single-strand breaks. Irinotecan and its active metabolite SN-38 bind to the topoisomerase I-DNA complex and prevent religation of these single-strand breaks. Current research suggests that the cytotoxicity of irinotecan is due to double-strand DNA damage produced during DNA synthesis when replication enzymes interact with the ternary complex formed by topoisomerase I, DNA, and either irinotecan or SN-38. Mammalian cells cannot efficiently repair these double-strand breaks.

12.2 Pharmacodynamics

Irinotecan serves as a water-soluble precursor of the lipophilic metabolite SN-38. SN-38 is formed from irinotecan by carboxylesterase-mediated cleavage of the carbamate bond between the camptothecin moiety and the dipiperidino side chain. SN-38 is approximately 1000 times as potent as irinotecan as an inhibitor of topoisomerase I purified from human and rodent tumor cell lines. *In vitro* cytotoxicity assays show that the potency of SN-38 relative to irinotecan varies from 2- to 2000-fold; however, the plasma area under the concentration versus time curve (AUC) values for SN-38 are 2% to 8% of irinotecan and SN-38 is 95% bound to plasma proteins compared to approximately 50% bound to plasma proteins for irinotecan *[see Clinical Pharmacology (12.3)]*. The precise contribution of SN-38 to the activity of CAMPTOSAR is thus unknown. Both irinotecan and SN-38 exist in an active lactone form and an inactive hydroxy acid anion form. A pH-dependent equilibrium exists between the two forms such that an acid pH promotes the formation of the lactone, while a more basic pH favors the hydroxy acid anion form.

Administration of irinotecan has resulted in antitumor activity in mice bearing cancers of rodent origin and in human carcinoma xenografts of various histological types.

12.3 Pharmacokinetics

After intravenous infusion of irinotecan in humans, irinotecan plasma concentrations decline in a multiexponential manner, with a mean terminal elimination half-life of about 6 to 12 hours. The mean terminal elimination half-life of the active metabolite SN-38 is about 10 to

20 hours. The half-lives of the lactone (active) forms of irinotecan and SN-38 are similar to those of total irinotecan and SN-38, as the lactone and hydroxy acid forms are in equilibrium.

Over the recommended dose range of 50 to 350 mg/m^2, the AUC of irinotecan increases linearly with dose; the AUC of SN-38 increases less than proportionally with dose. Maximum concentrations of the active metabolite SN-38 are generally seen within 1 hour following the end of a 90-minute infusion of irinotecan. Pharmacokinetic parameters for irinotecan and SN-38 following a 90-minute infusion of irinotecan at dose levels of 125 and 340 mg/m^2 determined in two clinical studies in patients with solid tumors are summarized in Table 9:

Table 9. Summary of Mean (±Standard Deviation) Irinotecan and SN-38 Pharmacokinetic Parameters in Patients with Solid Tumors

Dose (mg/m^2)	Irinotecan					SN-38		
	C_{max} (ng/mL)	AUC_{0-24} (ng·h/mL)	$t_{1/2}$ (h)	V_z (L/m^2)	CL (L/h/m^2)	C_{max} (ng/mL)	AUC_{0-24} (ng·h/mL)	$t_{1/2}$ (h)
125 (N=64)	1,660 ±797	10,200 ±3,270	5.8[a] ±0.7	110 ±48.5	13.3 ±6.01	26.3 ±11.9	229 ±108	10.4[a] ±3.1
340 (N=6)	3,392 ±874	20,604 ±6,027	11.7[b] ±1.0	234 ±69.6	13.9 ±4.0	56.0 ±28.2	474 ±245	21.0[b] ±4.3

C_{max} - Maximum plasma concentration
AUC_{0-24} - Area under the plasma concentration-time curve from time 0 to 24 hours after the end of the 90-minute infusion
$t_{1/2}$ - Terminal elimination half-life
V_z - Volume of distribution of terminal elimination phase
CL - Total systemic clearance
[a] Plasma specimens collected for 24 hours following the end of the 90-minute infusion.
[b] Plasma specimens collected for 48 hours following the end of the 90-minute infusion. Because of the longer collection period, these values provide a more accurate reflection of the terminal elimination half-lives of irinotecan and SN-38.

Distribution

Irinotecan exhibits moderate plasma protein binding (30% to 68% bound). SN-38 is highly bound to human plasma proteins (approximately 95% bound). The plasma protein to which irinotecan and SN-38 predominantly binds is albumin.

Metabolism

The metabolic conversion of irinotecan to the active metabolite SN-38 is mediated by carboxylesterase enzymes and primarily occurs in the liver. *In vitro* studies indicate that irinotecan, SN-38 and another metabolite aminopentane carboxylic acid (APC), do not inhibit cytochrome P-450 isozymes. SN-38 is subsequently conjugated predominantly by the enzyme UDP-glucuronosyl transferase 1A1 (UGT1A1) to form a glucuronide metabolite. UGT1A1 activity is reduced in individuals with genetic polymorphisms that lead to reduced enzyme activity such as the UGT1A1*28 polymorphism. Approximately 10% of the North American population is homozygous for the UGT1A1*28 allele (also referred to as UGT1A1 7/7 genotype). In a prospective study, in which irinotecan was administered as a single-agent (350 mg/m^2) on a once-every-3-week schedule, patients with the UGT1A1 7/7 genotype had a higher exposure to SN-38 than patients with the wild-type UGT1A1 allele (UGT1A1 6/6 genotype) *[see Warnings and Precautions (5.3) and Dosage and Administration (2)]*. SN-38

glucuronide had 1/50 to 1/100 the activity of SN-38 in cytotoxicity assays using two cell lines *in vitro*.

Excretion

The disposition of irinotecan has not been fully elucidated in humans. The urinary excretion of irinotecan is 11% to 20%; SN-38, <1%; and SN-38 glucuronide, 3%. The cumulative biliary and urinary excretion of irinotecan and its metabolites (SN-38 and SN-38 glucuronide) over a period of 48 hours following administration of irinotecan in two patients ranged from approximately 25% (100 mg/m^2) to 50% (300 mg/m^2).

Effect of Age

The pharmacokinetics of irinotecan administered using the weekly schedule was evaluated in a study of 183 patients that was prospectively designed to investigate the effect of age on irinotecan toxicity. Results from this trial indicate that there are no differences in the pharmacokinetics of irinotecan, SN-38, and SN-38 glucuronide in patients <65 years of age compared with patients ≥65 years of age. In a study of 162 patients that was not prospectively designed to investigate the effect of age, small (less than 18%) but statistically significant differences in dose-normalized irinotecan pharmacokinetic parameters in patients <65 years of age compared to patients ≥65 years of age were observed. Although dose-normalized $AUC_{0\text{-}24}$ for SN-38 in patients ≥65 years of age was 11% higher than in patients <65 years of age, this difference was not statistically significant. No change in the starting dose is recommended for geriatric patients receiving the weekly dosage schedule of irinotecan *[see Dosage and Administration (2)]*.

Effect of Gender

The pharmacokinetics of irinotecan do not appear to be influenced by gender.

Effect of Race

The influence of race on the pharmacokinetics of irinotecan has not been evaluated.

Effect of Hepatic Impairment

Irinotecan clearance is diminished in patients with hepatic impairment while exposure to the active metabolite SN-38 is increased relative to that in patients with normal hepatic function. The magnitude of these effects is proportional to the degree of liver impairment as measured by elevations in total bilirubin and transaminase concentrations. However, the tolerability of irinotecan in patients with hepatic dysfunction (bilirubin greater than 2 mg/dl) has not been assessed sufficiently, and no recommendations for dosing can be made *[see Dosage and Administration (2.1), Warnings and Precautions (5.10) and Use in Specific Populations (8.7)]*.

Effect of Renal Impairment

The influence of renal impairment on the pharmacokinetics of irinotecan has not been evaluated. Therefore, caution should be undertaken in patients with impaired renal function. Irinotecan is not recommended for use in patients on dialysis *[see Use in Specific Populations (8.6)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenicity studies with irinotecan were not conducted. Rats were, however, administered intravenous doses of 2 mg/kg or 25 mg/kg irinotecan once per week for 13 weeks (in separate studies, the 25 mg/kg dose produced an irinotecan C_{max} and AUC that were about 7.0 times and 1.3 times the respective values in patients administered 125 mg/m^2 weekly) and were then allowed to recover for 91 weeks. Under these conditions, there was a significant linear trend with dose for the incidence of combined uterine horn endometrial stromal polyps and endometrial stromal sarcomas. Irinotecan was clastogenic both *in vitro* (chromosome aberrations in Chinese hamster ovary cells) and *in vivo* (micronucleus test in mice). Neither irinotecan nor its active metabolite SN-38 was mutagenic in the *in vitro* Ames assay.

No significant adverse effects on fertility and general reproductive performance were observed after intravenous administration of irinotecan in doses of up to 6 mg/kg/day to rats and rabbits; however, atrophy of male reproductive organs was observed after multiple daily irinotecan doses both in rodents at 20 mg/kg and in dogs at 0.4 mg/kg. In separate studies in rodents, this dose produced an irinotecan C_{max} and AUC about 5 and 1 times, respectively, of the corresponding values in patients administered 125 mg/m^2 weekly. In dogs this dose produced an irinotecan C_{max} and AUC about one-half and 1/15th, respectively, of the corresponding values in patients administered 125 mg/m^2 weekly.

14 CLINICAL STUDIES

Irinotecan has been studied in clinical trials in combination with 5-fluorouracil (5-FU) and leucovorin (LV) and as a single agent *[see Dosage and Administration (2)]*. When given as a component of combination-agent treatment, irinotecan was either given with a weekly schedule of bolus 5-FU/LV or with an every-2-week schedule of infusional 5-FU/LV. Weekly and once-every-3-week dosage schedules were used for the single-agent irinotecan studies. Clinical studies of combination and single-agent use are described below.

14.1 Metastatic Colorectal Cancer

First Line Therapy in Combination with 5-FU/LV: Studies 1 and 2

Two phase 3, randomized, controlled, multinational clinical trials support the use of CAMPTOSAR Injection as first-line treatment of patients with metastatic carcinoma of the colon or rectum. In each study, combinations of irinotecan with 5-FU and LV were compared with 5-FU and LV alone. Study 1 compared combination irinotecan/bolus 5-FU/LV therapy given weekly with a standard bolus regimen of 5-FU/LV alone given daily for 5 days every 4 weeks; an irinotecan-alone treatment arm given on a weekly schedule was also included. Study 2 evaluated two different methods of administering infusional 5-FU/LV, with or without irinotecan. In both studies, concomitant medications such as antiemetics, atropine, and loperamide were given to patients for prophylaxis and/or management of symptoms from

treatment. In Study 2, a 7-day course of fluoroquinolone antibiotic prophylaxis was given in patients whose diarrhea persisted for greater than 24 hours despite loperamide or if they developed a fever in addition to diarrhea. Treatment with oral fluoroquinolone was also initiated in patients who developed an absolute neutrophil count (ANC) $<500/mm^3$, even in the absence of fever or diarrhea. Patients in both studies also received treatment with intravenous antibiotics if they had persistent diarrhea or fever or if ileus developed.

In both studies, the combination of irinotecan/5-FU/LV therapy resulted in significant improvements in objective tumor response rates, time to tumor progression, and survival when compared with 5-FU/LV alone. These differences in survival were observed in spite of second-line therapy in a majority of patients on both arms, including crossover to irinotecan-containing regimens in the control arm. Patient characteristics and major efficacy results are shown in Table 10.

Table 10. Combination Dosage Schedule: Study Results

	Study 1			Study 2	
	Irinotecan + Bolus 5-FU/LV weekly x 4 every 6 weeks	Bolus 5-FU/LV daily x 5 every 4 weeks	Irinotecan weekly x 4 every 6 weeks	*inotecan* + Infusional 5-FU/LV	Infusional 5-FU/LV
Number of patients	231	226	226	198	187
Demographics and treatment administration					
Female/Male (%)	34/65	45/54	35/64	33/67	47/53
Median age in years (range)	62 (25-85)	61 (19-85)	61 (30-87)	62 (27-75)	59 (24-75)
Performance status (%)					
0	39	41	46	51	51
1	46	45	46	42	41
2	15	13	8	7	8
Primary tumor (%)					
Colon	81	85	84	55	65
Rectum	17	14	15	45	35
Median time from diagnosis to randomization (months, range)	1.9 (0-161)	1.7 (0-203)	1.8 (0.1-185)	4.5 (0-88)	2.7 (0-104)
Prior adjuvant 5-FU therapy (%)					
No	89	92	90	74	76
Yes	11	8	10	26	24
Median duration of study treatment[a] (months)	5.5	4.1	3.9	5.6	4.5
Median Relative Dose Intensity (%)[a]					
Irinotecan	72	—	75	87	—
5-FU	71	86	—	86	93
Efficacy Results					
Confirmed objective tumor response rate[b] (%)	39	21 (p<0.0001)[c]	18	35	22 (p<0.005)[c]
Median time to tumor progression[d] (months)	7.0	4.3 (p=0.004)[d]	4.2	6.7	4.4 (p<0.001)[d]
Median survival (months)	14.8	12.6 (p<0.05)[d]	12.0	17.4	14.1 (p<0.05)[d]

[a] Study 1: N=225 (irinotecan/5-FU/LV),N=219 (5-FU/LV),N=223 (irinotecan)
Study 2: N=199 (irinotecan/5-FU/LV),N=186 (5-FU/LV)
[b] Confirmed ≥ 4 to 6 weeks after first evidence of objective response
[c] Chi-square test
[d] Log-rank test

Improvement was noted with irinotecan-based combination therapy relative to 5-FU/LV when response rates and time to tumor progression were examined across the following demographic and disease-related subgroups (age, gender, ethnic origin, performance status, extent of organ involvement with cancer, time from diagnosis of cancer, prior adjuvant therapy, and baseline

laboratory abnormalities). Figures 1 and 2 illustrate the Kaplan-Meier survival curves for the comparison of irinotecan/5-FU/LV versus 5-FU/LV in Studies 1 and 2, respectively.

Figure 1. Survival
First-Line Irinotecan/5-FU/LV vs 5-FU/LV
Study 1

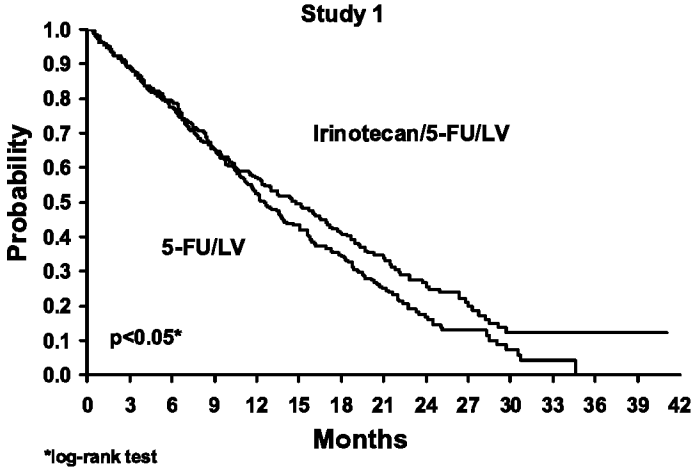
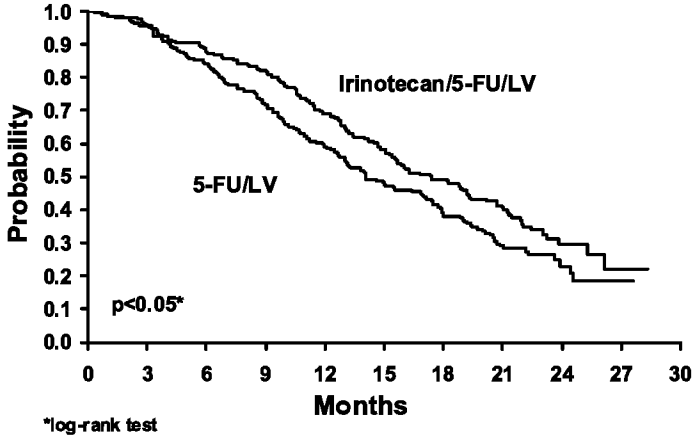


Figure 2. Survival
First-Line Irinotecan/5-FU/LV vs 5-FU/LV
Study 2



Second-Line Therapy After 5-FU-Based Treatment

4 Weekly Doses on a 6-Week Cycle: Studies 3, 4, and 5

Data from three open-label, single-agent, clinical studies, involving a total of 304 patients in 59 centers, support the use of CAMPTOSAR in the treatment of patients with metastatic cancer of the colon or rectum that has recurred or progressed following treatment with 5-FU-based therapy. These studies were designed to evaluate tumor response rate and do not provide information on effects on survival and disease-related symptoms. In each study, CAMPTOSAR was administered in repeated 6-week cycles consisting of a 90-minute intravenous infusion once weekly for 4 weeks, followed by a 2-week rest period. Starting doses of CAMPTOSAR in these trials were 100, 125, or 150 mg/m^2, but the 150-mg/m^2 dose was poorly tolerated (due to high rates of grade 4 late diarrhea and febrile neutropenia). Study 3 enrolled 48 patients and was conducted by a single investigator at several regional hospitals. Study 4 was a multicenter

study conducted by the North Central Cancer Treatment Group. All 90 patients enrolled in Study 4 received a starting dose of 125 mg/m^2. Study 5 was a multicenter study that enrolled 166 patients from 30 institutions. The initial dose in Study 5 was 125 mg/m^2 but was reduced to 100 mg/m^2 because the toxicity seen at the 125-mg/m^2 dose was perceived to be greater than that seen in previous studies. All patients in these studies had metastatic colorectal cancer, and the majority had disease that recurred or progressed following a 5-FU-based regimen administered for metastatic disease. The results of the individual studies are shown in Table 11.

Table 11. Weekly Dosage Schedule: Study Results

	Study			
	3	4	5	
Number of Patients	48	90	64	102
Starting Dose (mg/m^2/week x 4)	125[a]	125	125	100
Demographics and Treatment Administration				
Female/Male (%)	46/54	36/64	50/50	51/49
Median Age in years (range)	63 (29-78)	63 (32-81)	61 (42-84)	64 (25-84)
Ethnic Origin (%)				
White	79	96	81	91
African American	12	4	11	5
Hispanic	8	0	8	2
Oriental/Asian	0	0	0	2
Performance Status (%)				
0	60	38	59	44
1	38	48	33	51
2	2	14	8	5
Primary Tumor (%)				
Colon	100	71	89	87
Rectum	0	29	11	8
Unknown	0	0	0	5
Prior 5-FU Therapy (%)				
For Metastatic Disease	81	66	73	68
≤ 6 months after Adjuvant	15	7	27	28
> 6 months after Adjuvant	2	16	0	2
Classification Unknown	2	12	0	3
Prior Pelvic/Abdominal Irradiation (%)				
Yes	3	29	0	0
Other	0	9	2	4
None	97	62	98	96
Duration of Treatment with CAMPTOSAR (median, months)	5	4	4	3
Relative Dose Intensity[b] (median %)	74	67	73	81
Efficacy				
Confirmed Objective Response Rate (%)[c] (95% CI)	21 (9.3 - 32.3)	13 (6.3 - 20.4)	14 (5.5 - 22.6)	9 (3.3 - 14.3)
Time to Response (median, months)	2.6	1.5	2.8	2.8
Response Duration (median, months)	6.4	5.9	5.6	6.4
Survival (median, months)	10.4	8.1	10.7	9.3
1-Year Survival (%)	46	31	45	43

Table 11. Weekly Dosage Schedule: Study Results

[a] Nine patients received 150 mg/m^2 as a starting dose; two (22.2%) responded to CAMPTOSAR.

[b] Relative dose intensity for CAMPTOSAR based on planned dose intensity of 100, 83.3, and 66.7 mg/m^2/wk corresponding with 150, 125, and 100 mg/m^2 starting doses, respectively.

[c] Confirmed ≥ 4 to 6 weeks after first evidence of objective response.

In the intent-to-treat analysis of the pooled data across all three studies, 193 of the 304 patients began therapy at the recommended starting dose of 125 mg/m^2. Among these 193 patients, 2 complete and 27 partial responses were observed, for an overall response rate of 15.0% (95% Confidence Interval [CI], 10.0% to 20.1%) at this starting dose. A considerably lower response rate was seen with a starting dose of 100 mg/m^2. The majority of responses were observed within the first two cycles of therapy, but responses did occur in later cycles of treatment (one response was observed after the eighth cycle). The median response duration for patients beginning therapy at 125 mg/m^2 was 5.8 months (range, 2.6 to 15.1 months). Of the 304 patients treated in the three studies, response rates to CAMPTOSAR were similar in males and females and among patients older and younger than 65 years. Rates were also similar in patients with cancer of the colon or cancer of the rectum and in patients with single and multiple metastatic sites. The response rate was 18.5% in patients with a performance status of 0 and 8.2% in patients with a performance status of 1 or 2. Patients with a performance status of 3 or 4 have not been studied. Over half of the patients responding to CAMPTOSAR had not responded to prior 5-FU. Patients who had received previous irradiation to the pelvis responded to CAMPTOSAR at approximately the same rate as those who had not previously received irradiation.

Once-Every-3-Week Dosage Schedule

Single Arm Study: Study 6

Data from an open-label, single-agent, single-arm, multicenter, clinical study involving a total of 132 patients support a once every-3-week dosage schedule of irinotecan in the treatment of patients with metastatic cancer of the colon or rectum that recurred or progressed following treatment with 5-FU. Patients received a starting dose of 350 mg/m^2 given by 30-minute intravenous infusion once every 3 weeks. Among the 132 previously treated patients in this trial, the intent-to-treat response rate was 12.1% (95% CI, 7.0% to 18.1%).

Randomized Studies: Studies 7 and 8

Two multicenter, randomized, clinical studies further support the use of irinotecan given by the once-every-3-week dosage schedule in patients with metastatic colorectal cancer whose disease has recurred or progressed following prior 5-FU therapy. In Study 7, second-line irinotecan therapy plus best supportive care was compared with best supportive care alone. In Study 8, second-line irinotecan therapy was compared with infusional 5-FU-based therapy. In both studies, irinotecan was administered intravenously at a starting dose of 350 mg/m^2 over 90 minutes once every 3 weeks. The starting dose was 300 mg/m^2 for patients who were 70 years and older or who had a performance status of 2. The highest total dose permitted was 700 mg. Dose reductions and/or administration delays were permitted in the event of severe hematologic and/or nonhematologic toxicities while on treatment. Best supportive care was provided to patients in both arms of Study 7 and included antibiotics, analgesics, corticosteroids, transfusions, psychotherapy, or any other symptomatic therapy as clinically indicated. In both studies, concomitant medications such as antiemetics, atropine, and loperamide were given to patients for prophylaxis and/or management of symptoms from treatment. If late diarrhea

persisted for greater than 24 hours despite loperamide, a 7-day course of fluoroquinolone antibiotic prophylaxis was given. Patients in the control arm of the Study 8 received one of the following 5-FU regimens: (1) LV, 200 mg/m^2 IV over 2 hours; followed by 5-FU, 400 mg/m^2 IV bolus; followed by 5-FU, 600 mg/m^2 continuous IV infusion over 22 hours on days 1 and 2 every 2 weeks; (2) 5-FU, 250 to 300 mg/m^2/day protracted continuous IV infusion until toxicity; (3) 5-FU, 2.6 to 3 g/m^2 IV over 24 hours every week for 6 weeks with or without LV, 20 to 500 mg/m^2/day every week IV for 6 weeks with 2-week rest between cycles. Patients were to be followed every 3 to 6 weeks for 1 year.

A total of 535 patients were randomized in the two studies at 94 centers. The primary endpoint in both studies was survival. The studies demonstrated a significant overall survival advantage for irinotecan compared with best supportive care (p=0.0001) and infusional 5-FU-based therapy (p=0.035) as shown in Figures 3 and 4. In Study 7, median survival for patients treated with irinotecan was 9.2 months compared with 6.5 months for patients receiving best supportive care. In Study 8, median survival for patients treated with irinotecan was 10.8 months compared with 8.5 months for patients receiving infusional 5-FU-based therapy. Multiple regression analyses determined that patients' baseline characteristics also had a significant effect on survival. When adjusted for performance status and other baseline prognostic factors, survival among patients treated with irinotecan remained significantly longer than in the control populations (p=0.001 for Study 7 and p=0.017 for Study 8). Measurements of pain, performance status, and weight loss were collected prospectively in the two studies; however, the plan for the analysis of these data was defined retrospectively. When comparing irinotecan with best supportive care in Study 7, this analysis showed a statistically significant advantage for irinotecan, with longer time to development of pain (6.9 months versus 2.0 months), time to performance status deterioration (5.7 months versus 3.3 months), and time to > 5% weight loss (6.4 months versus 4.2 months). Additionally, 33.3% (33/99) of patients with a baseline performance status of 1 or 2 showed an improvement in performance status when treated with irinotecan versus 11.3% (7/62) of patients receiving best supportive care (p=0.002). Because of the inclusion of patients with non-measurable disease, intent-to-treat response rates could not be assessed.

Figure 3. Survival
Second-Line Irinotecan vs Best Supportive Care (BSC)
Study 7

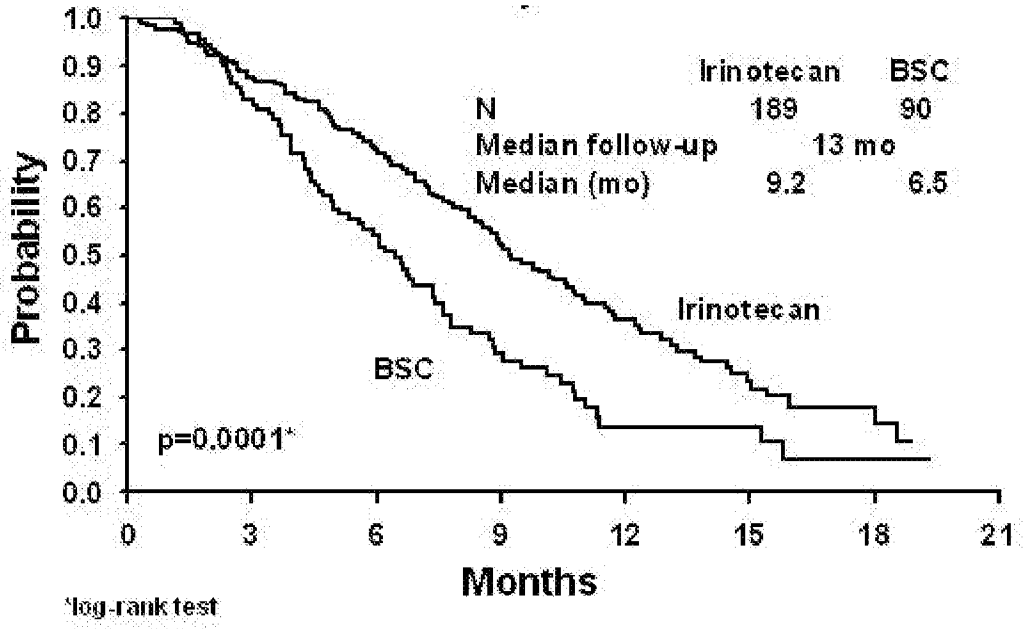


Figure 4. Survival
Second-Line Irinotecan vs Infusional 5-FU
Study 8

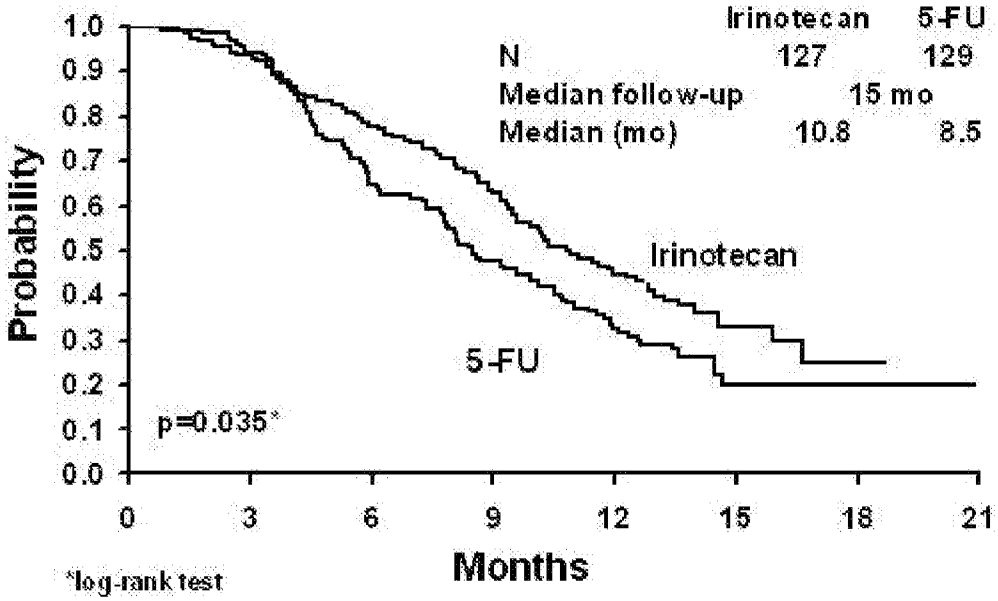


Table 12. Once-Every-3-Week Dosage Schedule: Study Results

	Study 7		Study 8	
	Irinotecan	BSC[a]	Irinotecan	5-FU
Number of patients	189	90	127	129
Demographics and treatment administration				
Female/Male (%)	32/68	42/58	43/57	35/65
Median age in years (range)	59 (22-75)	62 (34-75)	58 (30-75)	58 (25-75)
Performance status (%)				
0	47	31	58	54
1	39	46	35	43
2	14	23	8	3
Primary tumor (%)				
Colon	55	52	57	62
Rectum	45	48	43	38
Prior 5-FU therapy (%)				
For metastatic disease	70	63	58	68
As adjuvant treatment	30	37	42	32
Prior irradiation (%)	26	27	18	20
Duration of study treatment (median, months) (Log-rank test)	4.1	--	4.2 (p=0.02)	2.8
Relative dose intensity (median %)[b]	94	--	95	81-99
rvival				
Survival (median, months) (Log-rank test)	9.2 (p=0.0001)	6.5	10.8 (p=0.035)	8.5

[a] BSC = best supportive care

[b] Relative dose intensity for irinotecan based on planned dose intensity of 116.7 and 100 mg/m^2/wk corresponding with 350 and 300 mg/m^2 starting doses, respectively.

In the two randomized studies, the EORTC QLQ-C30 instrument was utilized. At the start of each cycle of therapy, patients completed a questionnaire consisting of 30 questions, such as "Did pain interfere with daily activities?" (1 = Not at All, to 4 = Very Much) and "Do you have any trouble taking a long walk?" (Yes or No). The answers from the 30 questions were converted into 15 subscales, that were scored from 0 to 100, and the global health status subscale that was derived from two questions about the patient's sense of general well being in the past week. The results as summarized in Table 13 are based on patients' worst post-baseline scores. In Study 7, a multivariate analysis and univariate analyses of the individual subscales were performed and corrected for multivariate testing. Patients receiving irinotecan reported significantly better results for the global health status, on two of five functional subscales, and on four of nine symptom subscales. As expected, patients receiving irinotecan noted significantly more diarrhea than those receiving best supportive care. In Study 8, the multivariate analysis on all 15 subscales did not indicate a statistically significant difference between irinotecan and infusional 5-FU.

Table 13. EORTC QLQ-C30: Mean Worst Post-Baseline Score[a]

QLQ-C30 Subscale	Study 7			Study 8		
	Irinotecan	BSC	p-value	Irinotecan	5-FU	p-value
Global health status	47	37	0.03	53	52	0.9
Functional scales						
Cognitive	77	68	0.07	79	83	0.9
Emotional	68	64	0.4	64	68	0.9
Social	58	47	0.06	65	67	0.9
Physical	60	40	0.0003	66	66	0.9
Role	53	35	0.02	54	57	0.9
Symptom Scales						
Fatigue	51	63	0.03	47	46	0.9
Appetite loss	37	57	0.0007	35	38	0.9
Pain assessment	41	56	0.009	38	34	0.9
Insomnia	39	47	0.3	39	33	0.9
Constipation	28	41	0.03	25	19	0.9
Dyspnea	31	40	0.2	25	24	0.9
Nausea/Vomiting	27	29	0.5	25	16	0.09
Financial impact	22	26	0.5	24	15	0.3
Diarrhea	32	19	0.01	32	22	0.2

[a] For the five functional subscales and global health status subscale, higher scores imply better functioning, whereas, on the nine symptom subscales, higher scores imply more severe symptoms. The subscale scores of each patient were collected at each visit until the patient dropped out of the study.

15 REFERENCES

- NIOSH Alert: Preventing occupational exposures to antineoplastic and other hazardous drugs in healthcare settings. 2004. U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No. 2004-165.
- OSHA Technical Manual, TED 1-0.15A, Section VI: Chapter 2. Controlling Occupational Exposure to Hazardous Drugs. OSHA, 1999. http://www.osha.gov/dts/osta/otm/otm_vi/otm_vi_2.html
- American Society of Health-System Pharmacists. ASHP guidelines on handling hazardous drugs. *Am J Health-Syst Pharm.* 2006; 63:1172-1193.
- Polovich, M., White, J. M., & Kelleher, L.O. (eds.) 2005. Chemotherapy and biotherapy guidelines and recommendations for practice (2nd. ed.) Pittsburgh, PA: Oncology Nursing Society.

16 HOW SUPPLIED/STORAGE AND HANDLING

CAMPTOSAR Injection is available in single-dose brown glass vials in the following package sizes:

2 mL NDC 0009-7529-02
5 mL NDC 0009-7529-01

CAMPTOSAR Injection is available in single-dose amber colored polypropylene CYTOSAFE® vials in the following package sizes:

2 mL NDC 0009-7529-04
5 mL NDC 0009-7529-03
15 mL NDC 0009-7529-05

Store at controlled room temperature 15° to 30°C (59° to 86°F). Protect from light. Keep the vial in the carton until the time of use.

Inspect the vial for damage and visible signs of leaks before removing from the carton. If damaged, incinerate the unopened package.

17 PATIENT COUNSELING INFORMATION

- Patients and caregivers should be informed of gastrointestinal complications, such as nausea, vomiting, abdominal cramping, and diarrhea. Patients should have loperamide readily available to begin treatment for late diarrhea (generally occurring more than 24 hours after administration of CAMPTOSAR). Begin loperamide at the first episode of poorly formed or loose stools or the earliest onset of bowel movements more frequent than normal. One dosage regimen for loperamide is 4 mg at the first onset of late diarrhea and then 2 mg every 2 hours until the patient is diarrhea-free for at least 12 hours. Loperamide is not recommended to be used for more than 48 consecutive hours at these doses, because of the risk of paralytic ileus. During the night, the patient may take 4 mg of loperamide every 4 hours. Patients should contact their physician if any of the following occur: diarrhea for the first time during treatment; black or bloody stools; symptoms of dehydration such as lightheadedness, dizziness, or faintness; inability to take fluids by mouth due to nausea or vomiting; or inability to get diarrhea under control within 24 hours.

- Patients should be warned about the potential for dizziness or visual disturbances which may occur within 24 hours following the administration of CAMPTOSAR.

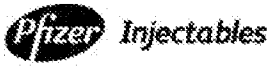
- Explain the significance of routine blood cell counts. Instruct patients to monitor their temperature frequently and immediately report any occurrence of fever or infection.

- CAMPTOSAR may cause fetal harm. Advise patients to avoid becoming pregnant while receiving this drug.

- Patients should be alerted to the possibility of alopecia.

- Contains sorbitol.

This product's label may have been updated. For current full prescribing information, please visit www.pfizer.com.



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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all of the information needed to use ONIVYDE™ safely and effectively. See full prescribing information for ONIVYDE™

ONIVYDE™ (irinotecan liposome injection), for intravenous use
Initial U.S. Approval: 1996

WARNING: SEVERE NEUTROPENIA and SEVERE DIARRHEA
See full prescribing information for complete boxed warning

- **Fatal neutropenic sepsis occurred in 0.8% of patients receiving ONIVYDE. Severe or life-threatening neutropenic fever or sepsis occurred in 3% and severe or life-threatening neutropenia occurred in 20% of patients receiving ONIVYDE in combination with fluorouracil and leucovorin. Withhold ONIVYDE for absolute neutrophil count below 1500/mm^3 or neutropenic fever. Monitor blood cell counts periodically during treatment (2.3), (5.1).**
- **Severe diarrhea occurred in 13% of patients receiving ONIVYDE in combination with fluorouracil and leucovorin. Do not administer ONIVYDE to patients with bowel obstruction. Withhold ONIVYDE for diarrhea of Grade 2-4 severity. Administer loperamide for late diarrhea of any severity. Administer atropine, if not contraindicated, for early diarrhea of any severity (2.3), (5.2).**

INDICATIONS AND USAGE

ONIVYDE is a topoisomerase inhibitor indicated, in combination with fluorouracil and leucovorin, for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy. (1)

Limitation of Use: ONIVYDE is not indicated as a single agent for the treatment of patients with metastatic adenocarcinoma of the pancreas. (1)

DOSAGE AND ADMINISTRATION

- **Do not substitute ONIVYDE for other drugs containing irinotecan HCl.** (2.1)
- Recommended dose of ONIVYDE is 70 mg/m^2 intravenous infusion over 90 minutes every two weeks. (2.2)
- Recommended starting dose of ONIVYDE in patients homozygous for UGT1A1*28 is 50 mg/m^2 every two weeks. (2.2)
- There is no recommended dose of ONIVYDE for patients with serum bilirubin above the upper limit of normal. (2.2)
- Premedicate with a corticosteroid and an anti-emetic. 30 minutes prior to ONIVYDE. (2.2)

DOSAGE FORMS AND STRENGTHS

Injection: 43 mg/10 mL single dose vial (3)

CONTRAINDICATIONS

Severe hypersensitivity reaction to ONIVYDE or irinotecan HCl. (4, 5.4)

WARNINGS AND PRECAUTIONS

- Interstitial lung disease (ILD): Fatal ILD has occurred in patients receiving irinotecan HCl. Discontinue ONIVYDE if ILD is diagnosed. (5.3)
- Severe hypersensitivity reaction: Permanently discontinue ONIVYDE for severe hypersensitivity reactions. (5.4, 4)
- Embryo-fetal toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception. (5.5, 8.1, 8.3)

ADVERSE REACTIONS

The most common adverse reactions (≥ 20%) of ONIVYDE: diarrhea, fatigue/asthenia, vomiting, nausea, decreased appetite, stomatitis, and pyrexia. The most common laboratory abnormalities (≥ 10% Grade 3 or 4) were lymphopenia and neutropenia. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Merrimack Pharmaceuticals, Inc. at 1-844-441-6225 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Strong CYP3A4 Inducers: Avoid the use of strong CYP3A4 inducers if possible. Substitute non-enzyme inducing therapies at least 2 weeks prior to initiation of ONIVYDE. (7.1)
- Strong CYP3A4 Inhibitors: Avoid the use of strong CYP3A4 or UGT1A1 inhibitors, if possible; discontinue strong CYP3A4 inhibitors at least 1 week prior to starting therapy. (7.2)

USE IN SPECIFIC POPULATIONS

- Lactation: Do not breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 10/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

WARNING: SEVERE NEUTROPENIA and SEVERE DIARRHEA

Fatal neutropenic sepsis occurred in 0.8% of patients receiving ONIVYDE. Severe or life-threatening neutropenic fever or sepsis occurred in 3% and severe or life-threatening neutropenia occurred in 20% of patients receiving ONIVYDE in combination with fluorouracil and leucovorin. Withhold ONIVYDE for absolute neutrophil count below 1500/mm^3 or neutropenic fever. Monitor blood cell counts periodically during treatment *[see Dosage and Administration (2.2) and Warnings and Precautions (5.1)]*.

Severe diarrhea occurred in 13% of patients receiving ONIVYDE in combination with fluorouracil and leucovorin. Do not administer ONIVYDE to patients with bowel obstruction. Withhold ONIVYDE for diarrhea of Grade 2-4 severity. Administer loperamide for late diarrhea of any severity. Administer atropine, if not contraindicated, for early diarrhea of any severity *[see Dosage and Administration (2.2) and Warnings and Precautions (5.2)]*.

1 INDICATIONS AND USAGE

ONIVYDE™ is indicated, in combination with fluorouracil and leucovorin, for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy.

Limitation of Use: ONIVYDE is not indicated as a single agent for the treatment of patients with metastatic adenocarcinoma of the pancreas *[see Clinical Studies (14)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Important Use Information

DO NOT SUBSTITUTE ONIVYDE for other drugs containing irinotecan HCl.

2.2 Recommended Dose

Administer ONIVYDE prior to leucovorin and fluorouracil *[see Clinical Studies (14)]*.

- The recommended dose of ONIVYDE is 70 mg/m^2 administered by intravenous infusion over 90 minutes every 2 weeks.
- The recommended starting dose of ONIVYDE in patients known to be homozygous for the UGT1A1*28 allele is 50 mg/m^2 administered by intravenous infusion over 90 minutes. Increase the dose of ONIVYDE to 70 mg/m^2 as tolerated in subsequent cycles.
- There is no recommended dose of ONIVYDE for patients with serum bilirubin above the upper limit of normal *[see Adverse Reactions (6.1) and Clinical Studies (14)]*.

Premedication

Administer a corticosteroid and an anti-emetic 30 minutes prior to ONIVYDE infusion.

2.3 Dose Modifications for Adverse Reactions

Table 1: Recommended Dose Modifications for ONIVYDE

Toxicity NCI CTCAE v4.0†	Occurrence	ONIVYDE adjustment in patients receiving 70 mg/m^2	Patients homozygous for UGT1A1*28 without previous increase to 70 mg/m^2
Grade 3 or 4 adverse reactions	Withhold ONIVYDE. Initiate loperamide for late onset diarrhea of any severity. Administer intravenous or subcutaneous atropine 0.25 to 1 mg (unless clinically contraindicated) for early onset diarrhea of any severity. Upon recovery to ≤ Grade 1, resume ONIVYDE at:		
	First	50 mg/m^2	43 mg/m^2
	Second	43 mg/m^2	35 mg/m^2
	Third	Discontinue ONIVYDE	Discontinue ONIVYDE
Interstitial Lung Disease	First	Discontinue ONIVYDE	Discontinue ONIVYDE
Anaphylactic Reaction	First	Discontinue ONIVYDE	Discontinue ONIVYDE

† NCI CTCAE v 4.0=National Cancer Institute Common Toxicity Criteria for Adverse Events version 4.0

For recommended dose modifications of fluorouracil (5-FU) or leucovorin (LV), refer to the Full Prescribing Information; refer to Clinical Studies (14).

2.4 Preparation and Administration

ONIVYDE is a cytotoxic drug. Follow applicable special handling and disposal procedures.[1]

Preparation

- Withdraw the calculated volume of ONIVYDE from the vial. Dilute ONIVYDE in 500 mL 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP and mix diluted solution by gentle inversion.
- Protect diluted solution from light.
- Administer diluted solution within 4 hours of preparation when stored at room temperature or within 24 hours of preparation when stored under refrigerated conditions [2°C to 8°C (36°F to 46°F)]. Allow diluted solution to come to room temperature prior to administration.
- Do NOT freeze.

Administration

- Infuse diluted solution intravenously over 90 minutes. Do not use in-line filters. Discard unused portion.

3 DOSAGE FORMS AND STRENGTHS

Injection: 43 mg/10 mL irinotecan free base as a white to slightly yellow, opaque, liposomal dispersion in a single-dose vial.

4 CONTRAINDICATIONS

ONIVYDE is contraindicated in patients who have experienced a severe hypersensitivity reaction to ONIVYDE or irinotecan HCl.

5 WARNINGS AND PRECAUTIONS

5.1 Severe Neutropenia

ONIVYDE can cause severe or life-threatening neutropenia and fatal neutropenic sepsis. In Study 1, the incidence of fatal neutropenic sepsis was 0.8% among patients receiving ONIVYDE, occurring in one of 117 patients in the ONIVYDE plus fluorouracil/leucovorin (ONIVYDE/5-FU/LV) arm and one of 147 patients receiving ONIVYDE as a single agent. Severe or life-threatening neutropenia occurred in 20% of patients receiving ONIVYDE/5-FU/LV compared to 2% of patients receiving fluorouracil/leucovorin alone (5-FU/LV). Grade 3 or 4 neutropenic fever/neutropenic sepsis occurred in 3% of patients receiving ONIVYDE/5-FU/LV, and did not occur in patients receiving 5-FU/LV.

In patients receiving ONIVYDE/5-FU/LV, the incidence of Grade 3 or 4 neutropenia was higher among Asian patients [18 of 33 (55%)] compared to White patients [13 of 73 (18%)]. Neutropenic fever/neutropenic sepsis was reported in 6% of Asian patients compared to 1% of White patients *[see Clinical Pharmacology (12.3)]*.

Monitor complete blood cell counts on Days 1 and 8 of every cycle and more frequently if clinically indicated. Withhold ONIVYDE if the absolute neutrophil count (ANC) is below 1500/mm^3 or if neutropenic fever occurs. Resume ONIVYDE when the ANC is 1500/mm^3 or above. Reduce ONIVYDE dose for Grade 3-4 neutropenia or neutropenic fever following recovery in subsequent cycles *[see Dosage and Administration (2.2)]*.

5.2 Severe Diarrhea

ONIVYDE can cause severe and life-threatening diarrhea. Do not administer ONIVYDE to patients with bowel obstruction.

Severe or life-threatening diarrhea followed one of two patterns: late onset diarrhea (onset more than 24 hours following chemotherapy) and early onset diarrhea (onset within 24 hours of

chemotherapy, sometimes occurring with other symptoms of cholinergic reaction) *[see Cholinergic Reactions (6.1)]*. An individual patient may experience both early and late-onset diarrhea.

In Study 1, Grade 3 or 4 diarrhea occurred in 13% receiving ONIVYDE/5-FU/LV compared to 4% receiving 5-FU/LV. The incidence of Grade 3 or 4 late onset diarrhea was 9% in patients receiving ONIVYDE/5-FU/LV, compared to 4% in patients receiving 5-FU/LV. The incidence of Grade 3 or 4 early onset diarrhea was 3% in patients receiving ONIVYDE/5-FU/LV, compared to no Grade 3 or 4 early onset diarrhea in patients receiving 5-FU/LV. Of patients receiving ONIVYDE/5-FU/LV in Study 1, 34% received loperamide for late-onset diarrhea and 26% received atropine for early-onset diarrhea. Withhold ONIVYDE for Grade 2-4 diarrhea. Initiate loperamide for late onset diarrhea of any severity. Administer intravenous or subcutaneous atropine 0.25 to 1 mg (unless clinically contraindicated) for early onset diarrhea of any severity. Following recovery to Grade 1 diarrhea, resume ONIVYDE at a reduced dose *[see Dosage and Administration (2.2)]*.

5.3 Interstitial Lung Disease

Irinotecan HCl can cause severe and fatal interstitial lung disease (ILD). Withhold ONIVYDE in patients with new or progressive dyspnea, cough, and fever, pending diagnostic evaluation. Discontinue ONIVYDE in patients with a confirmed diagnosis of ILD.

5.4 Severe Hypersensitivity Reaction

Irinotecan HCl can cause severe hypersensitivity reactions, including anaphylactic reactions. Permanently discontinue ONIVYDE in patients who experience a severe hypersensitivity reaction.

5.5 Embryo-Fetal Toxicity

Based on animal data with irinotecan HCl and the mechanism of action of ONIVYDE, ONIVYDE can cause fetal harm when administered to a pregnant woman. Embryotoxicity and teratogenicity were observed following treatment with irinotecan HCl, at doses resulting in irinotecan exposures lower than those achieved with ONIVYDE 70 mg/m^2 in humans, administered to pregnant rats and rabbits during organogenesis. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with ONIVYDE and for one month following the final dose *[see Use in Specific Populations (8.1, 8.3), Clinical Pharmacology (12.1)]*.

6 ADVERSE REACTIONS

The following adverse drug reactions are discussed in greater detail in other sections of the label:

- Severe Neutropenia [see *Warnings and Precautions (5.1) and Boxed Warning]*
- Severe Diarrhea *[see Warnings and Precautions (5.2) and Boxed Warning]*
- Interstitial Lung Disease *[see Warnings and Precautions (5.3)]*

- Severe Hypersensitivity Reactions *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of ONIVYDE cannot be directly compared to rates in clinical trials of other drugs and may not reflect the rates observed in practice.

The safety data described below are derived from patients with metastatic adenocarcinoma of the pancreas previously treated with gemcitabine-based therapy who received any part of protocol-specified therapy in Study 1, an international, randomized, active-controlled, open-label trial. Protocol-specified therapy consisted of ONIVYDE 70 mg/m^2 with leucovorin 400 mg/m^2 and fluorouracil 2400 mg/m^2 over 46 hours every 2 weeks (ONIVYDE/5-FU/LV; N=117), ONIVYDE 100 mg/m^2 every 3 weeks (N=147), or leucovorin 200 mg/m^2 and fluorouracil 2000 mg/m^2 over 24 hours weekly for 4 weeks followed by 2 week rest (5-FU/LV; N=134) *[see Clinical Studies (14)]*. Serum bilirubin within the institutional normal range, albumin ≥ 3 g/dL, and Karnofsky Performance Status (KPS) ≥ 70 were required for study entry. The median duration of exposure was 9 weeks in the ONIVYDE/5-FU/LV arm, 9 weeks in the ONIVYDE monotherapy arm, and 6 weeks in the 5-FU/LV arm.

The most common adverse reactions (≥ 20%) of ONIVYDE were diarrhea, fatigue/asthenia, vomiting, nausea, decreased appetite, stomatitis, and pyrexia. The most common, severe laboratory abnormalities (≥ 10% Grade 3 or 4) were lymphopenia and neutropenia. The most common serious adverse reactions (≥ 2%) of ONIVYDE were diarrhea, vomiting, neutropenic fever or neutropenic sepsis, nausea, pyrexia, sepsis, dehydration, septic shock, pneumonia, acute renal failure, and thrombocytopenia.

Adverse reactions led to permanent discontinuation of ONIVYDE in 11% of patients receiving ONIVYDE/5-FU/LV; the most frequent adverse reactions resulting in discontinuation of ONIVYDE were diarrhea, vomiting, and sepsis. Dose reductions of ONIVYDE for adverse reactions occurred in 33% of patients receiving ONIVYDE/5-FU/LV; the most frequent adverse reactions requiring dose reductions were neutropenia, diarrhea, nausea, and anemia. ONIVYDE was withheld or delayed for adverse reactions in 62% of patients receiving ONIVYDE/5-FU/LV; the most frequent adverse reactions requiring interruption or delays were neutropenia, diarrhea, fatigue, vomiting, and thrombocytopenia.

Table 2 provides the frequency and severity of adverse reactions in Study 1 that occurred with higher incidence (≥5% difference for Grades 1-4 or ≥2% difference for Grades 3-4) in patients who received ONIVYDE/5-FU/LV compared to patients who received 5-FU/LV.

Table 2: Adverse Reactions with Higher Incidence (≥5% Difference for Grades 1-4* or ≥2% Difference for Grades 3 and 4) in the ONIVYDE/5-FU/LV Arm

Adverse Reaction	ONIVYDE/5-FU/LV N=117		5-FU/LV N=134	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Gastrointestinal disorders				
Diarrhea	59	13	26	4
Early diarrhea†	30	3	15	0
Late diarrhea‡	43	9	17	4
Vomiting	52	11	26	3
Nausea	51	8	34	4
Stomatitis§	32	4	12	1
Infections and infestations	38	17	15	10
Sepsis	4	3	2	1
Neutropenic fever/neutropenic sepsis♠	3	3	1	0
Gastroenteritis	3	3	0	0
Intravenous catheter-related infection	3	3	0	0
General disorders and administration site conditions				
Fatigue/asthenia	56	21	43	10
Pyrexia	23	2	11	1
Metabolism and nutrition disorders				
Decreased appetite	44	4	32	2
Weight loss	17	2	7	0
Dehydration	8	4	7	2
Skin and subcutaneous tissue disorders				
Alopecia	14	1	5	0

* NCI CTCAE v4.0
† Early diarrhea: onset within 24 hours of ONIVYDE administration
‡ Late diarrhea: onset >1 day after ONIVYDE administration
§ Includes stomatitis, aphthous stomatitis, mouth ulceration, mucosal inflammation.
♠ Includes febrile neutropenia

Cholinergic Reactions: ONIVYDE can cause cholinergic reactions manifesting as rhinitis, increased salivation, flushing, bradycardia, miosis, lacrimation, diaphoresis, and intestinal hyperperistalsis with abdominal cramping and early onset diarrhea. In Study 1, Grade 1 or 2 cholinergic symptoms other than early diarrhea occurred in 12 (4.5%) ONIVYDE-treated patients. Six of these 12 patients received atropine and in 1 of the 6 patients, atropine was administered for cholinergic symptoms other than diarrhea.

Infusion Reactions: Infusion reactions, consisting of rash, urticaria, periorbital edema, or pruritus, occurring on the day of ONIVYDE administration were reported in 3% of patients receiving ONIVYDE or ONIVYDE/5-FU/LV.

Laboratory abnormalities that occurred with higher incidence in the ONIVYDE/5-FU/LV arm compared to the 5-FU/LV arm (≥5% difference) are summarized in the following table.

Table 3: Laboratory Abnormalities with Higher Incidence (≥5% Difference) in the ONIVYDE/5-FU/LV Arm[*#]

Laboratory abnormality	ONIVYDE/5-FU/LV N=117		5-FU/LV N=134	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Hematology				
Anemia	97	6	86	5
Lymphopenia	81	27	75	17
Neutropenia	52	20	6	2
Thrombocytopenia	41	2	33	0
Hepatic				
Increased alanine aminotransferase (ALT)	51	6	37	1
Hypoalbuminemia	43	2	30	0
Metabolic				
Hypomagnesemia	35	0	21	0
Hypokalemia	32	2	19	2
Hypocalcemia	32	1	20	0
Hypophosphatemia	29	4	18	1
Hyponatremia	27	5	12	3
Renal				
Increased creatinine	18	0	13	0

[*] NCI CTCAE v4.0, worst grade shown.
[#] Percent based on number of patients with a baseline and at least one post-baseline measurement.

7 DRUG INTERACTIONS

7.1 Strong CYP3A4 Inducers

Following administration of non-liposomal irinotecan (i.e., irinotecan HCl), exposure to irinotecan or its active metabolite, SN-38, is substantially reduced in adult and pediatric patients concomitantly receiving the CYP3A4 enzyme-inducing anticonvulsants phenytoin and strong CYP3A4 inducers. Avoid the use of strong CYP3A4 inducers (e.g., rifampin, phenytoin, carbamazepine, rifabutin, rifapentine, phenobarbital, St. John's wort) if possible. Substitute non-enzyme inducing therapies at least 2 weeks prior to initiation of ONIVYDE therapy *[see Clinical Pharmacology (12.3)]*.

7.2 Strong CYP3A4 or UGT1A1 Inhibitors

Following administration of non-liposomal irinotecan (i.e., irinotecan HCl), patients receiving concomitant ketoconazole, a CYP3A4 and UGT1A1 inhibitor, have increased exposure to irinotecan and its active metabolite SN-38. Co-administration of ONIVYDE with other inhibitors of CYP3A4 (e.g., clarithromycin, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telaprevir, voriconazole) or UGT1A1 (e.g., atazanavir, gemfibrozil, indinavir) may increase systemic exposure to irinotecan or SN-38. Avoid the use of strong CYP3A4 or UGT1A1 inhibitors if possible. Discontinue strong CYP3A4 inhibitors at least 1 week prior to starting ONIVYDE therapy *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on animal data with irinotecan HCl and the mechanism of action of ONIVYDE, ONIVYDE can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. There are no available data in pregnant women. Embryotoxicity and teratogenicity were observed following treatment with irinotecan HCl, at doses resulting in irinotecan exposures lower than those achieved with ONIVYDE 70 mg/m^2 in humans, administered to pregnant rats and rabbits during organogenesis *[see Data]*. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

No animal studies have been conducted to evaluate the effect of irinotecan liposome on reproduction and fetal development; however, studies have been conducted with irinotecan HCl. Irinotecan crosses the placenta of rats following intravenous administration. Intravenous administration of irinotecan at a dose of 6 mg/kg/day to rats and rabbits during the period of organogenesis resulted in increased post-implantation loss and decreased numbers of live fetuses. In separate studies in rats, this dose resulted in an irinotecan exposure of approximately 0.002 times the exposure of irinotecan based on area under the curve (AUC) in patients administered ONIVYDE at the 70 mg/m^2 dose. Administration of irinotecan HCl resulted in structural abnormalities and growth delays in rats at doses greater than 1.2 mg/kg/day (approximately 0.0002 times the clinical exposure to irinotecan in ONIVYDE based on AUC). Teratogenic effects included a variety of external, visceral, and skeletal abnormalities. Irinotecan HCl administered to rat dams for the period following organogenesis through weaning at doses of 6 mg/kg/day caused decreased learning ability and decreased female body weights in the offspring.

8.2 Lactation

Risk Summary

There is no information regarding the presence of irinotecan liposome, irinotecan, or SN-38 (an active metabolite of irinotecan) in human milk, or the effects on the breastfed infant or on milk production. Irinotecan is present in rat milk *[see Data]*.

Because of the potential for serious adverse reactions in breastfed infants from ONIVYDE, advise a nursing woman not to breastfeed during treatment with ONIVYDE and for one month after the final dose.

Data

Radioactivity appeared in rat milk within 5 minutes of intravenous administration of radiolabeled irinotecan HCl and was concentrated up to 65-fold at 4 hours after administration relative to plasma concentrations.

8.3 Females and Males of Reproductive Potential

Contraception

Females

ONIVYDE can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment with ONIVYDE and for one month after the final dose.

Males

Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use condoms during treatment with ONIVYDE and for four months after the final dose *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

Safety and effectiveness of ONIVYDE have not been established in pediatric patients.

8.5 Geriatric Use

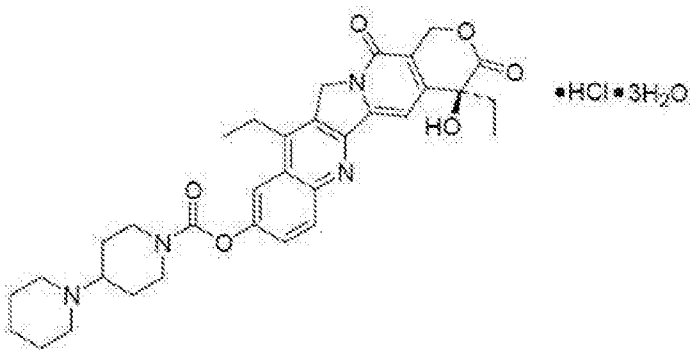
Of the 264 patients who received ONIVYDE as a single agent or in combination with 5-FU and leucovorin in Study 1, 49% were ≥ 65 years old and 13% were ≥ 75 years old. No overall differences in safety and effectiveness were observed between these patients and younger patients.

10 OVERDOSAGE

There are no treatment interventions known to be effective for management of overdosage of ONIVYDE.

11 DESCRIPTION

ONIVYDE is formulated with irinotecan hydrochloride trihydrate, a topoisomerase inhibitor, into a liposomal dispersion for intravenous use. The chemical name of irinotecan hydrochloride trihydrate is (S)-4,11-diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo1H-pyrano[3',4':6,7]-indolizino[1,2-b]quinolin-9-yl-[1,4'bipiperidine]-1'-carboxylate, monohydrochloride, trihydrate. The empirical formula is $C_{33}H_{38}N_4O_6 \cdot HCl \cdot 3H_2O$ and the molecular weight is 677.19 g/mole. The molecular structure is:



ONIVYDE is a sterile, white to slightly yellow opaque isotonic liposomal dispersion. Each 10 mL single-dose vial contains 43 mg irinotecan free base at a concentration of 4.3 mg/mL. The liposome is a unilamellar lipid bilayer vesicle, approximately 110 nm in diameter, which encapsulates an aqueous space containing irinotecan in a gelated or precipitated state as the sucrose octasulfate salt. The vesicle is composed of 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC) 6.81 mg/mL, cholesterol 2.22 mg/mL, and methoxy-terminated polyethylene glycol (MW 2000)-distearoylphosphatidyl ethanolamine (MPEG-2000-DSPE) 0.12 mg/mL. Each mL also contains 2-[4-(2-hydroxyethyl) piperazin-1-yl]ethanesulfonic acid (HEPES) as a buffer 4.05 mg/mL and sodium chloride as an isotonicity reagent 8.42 mg/mL.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Irinotecan liposome injection is a topoisomerase 1 inhibitor encapsulated in a lipid bilayer vesicle or liposome. Topoisomerase 1 relieves torsional strain in DNA by inducing single-strand breaks. Irinotecan and its active metabolite SN-38 bind reversibly to the topoisomerase 1-DNA complex and prevent re-ligation of the single-strand breaks, leading to exposure time-dependent double-strand DNA damage and cell death. In mice bearing human tumor xenografts, irinotecan liposome administered at irinotecan HCl-equivalent doses 5-fold lower than irinotecan HCl achieved similar intratumoral exposure of SN-38.

12.3 Pharmacokinetics

The plasma pharmacokinetics of total irinotecan and total SN-38 were evaluated in patients with cancer who received ONIVYDE, as a single agent or as part of combination chemotherapy, at doses between 50 and 155 mg/m^2 and 353 patients with cancer using population pharmacokinetic analysis.

The pharmacokinetic parameters of total irinotecan and total SN-38 following the administration of ONIVYDE 70 mg/m^2 as a single agent or part of combination chemotherapy are presented in Table 4.

Table 4: Summary of Mean (±Standard Deviation) Total Irinotecan and Total SN-38

Dose (mg/m^2)	Total Irinotecan					Total SN-38		
	C_{max} [µg/mL] (n=25)	$AUC_{0-\infty}$ [h·µg/mL] (n=23)	$t_{1/2}$ [h] (n=23)	CL [L/h] (n=23)	V_d [L] (n=23)	C_{max} [ng/mL] (n=25)	$AUC_{0-\infty}$ [h·ng/mL] (n=13)	$t_{1/2}$ [h] (n=13)
70	37.2 (8.8)	1364 (1048)	25.8 (15.7)	0.20 (0.17)	4.1 (1.5)	5.4 (3.4)	620 (329)	67.8 (44.5)

C_{max}: Maximum plasma concentration
$AUC_{0-\infty}$: Area under the plasma concentration curve extrapolated to time infinity
$t_{½}$: Terminal elimination half-life
CL: Clearance
V_d: Volume of distribution

Over the dose range of 50 to 155 mg/m^2, the C_{max} and AUC of total irinotecan increases with dose. Additionally, the C_{max} of total SN-38 increases proportionally with dose; however, the AUC of total SN-38 increases less than proportionally with dose.

Distribution

Direct measurement of irinotecan liposome showed that 95% of irinotecan remains liposome-encapsulated, and the ratios between total and encapsulated forms did not change with time from 0 to 169.5 hours post-dose. The mean volume of distribution is summarized in Table 4.

Plasma protein binding is <0.44% of the total irinotecan in ONIVYDE.

Elimination

Metabolism

The metabolism of irinotecan liposome has not been evaluated. Irinotecan is subject to extensive metabolic conversion by various enzyme systems, including esterases to form the active metabolite SN-38, and UGT1A1 mediating glucuronidation of SN-38 to form the inactive glucuronide metabolite SN-38G. Irinotecan can also undergo CYP3A4-mediated oxidative metabolism to several inactive oxidation products, one of which can be hydrolyzed by carboxylesterase to release SN-38. In the population pharmacokinetic analysis using the results of a subset with UGT1A1*28 genotypic testing, in which the analysis adjusted for the lower dose administered to patients homozygous for the UGT1A1*28 allele, patients homozygous (N=14) and non-homozygous (N=244) for this allele had total SN-38 average steady-state concentrations of 1.06 and 0.95 ng/mL, respectively.

Excretion

The disposition of ONIVYDE has not been elucidated in humans. Following administration of irinotecan HCl , the urinary excretion of irinotecan is 11 to 20%; SN-38, <1%; and SN-38 glucuronide, 3%. The cumulative biliary and urinary excretion of irinotecan and its metabolites (SN-38 and SN-38 glucuronide), over a period of 48 hours following administration of irinotecan HCl in two patients, ranged from approximately 25% (100 mg/m^2) to 50% (300 mg/m^2).

Specific Populations

Age, Gender, and Renal Impairment:

The population pharmacokinetic analysis suggests that age (28 to 87 years) had no clinically meaningful effect on the exposure of irinotecan and SN-38.

The population pharmacokinetic analysis suggests that gender (196 males and 157 females) had no clinically meaningful effect on the exposure of irinotecan and SN-38 after adjusting for body surface area (BSA).

In a population pharmacokinetic analysis, mild-to-moderate renal impairment had no effect on the exposure of total SN-38 after adjusting for BSA. The analysis included 68 patients with moderate (CLcr 30 - 59 mL/min) renal impairment, 147 patients with mild (CLcr 60 - 89 mL/min) renal impairment, and 135 patients with normal renal function (CLcr > 90 mL/min). There was insufficient data in patients with severe renal impairment (CLcr < 30 mL/min) to assess its effect on pharmacokinetics.

Ethnicity: The population pharmacokinetic analysis suggests that Asians (East Asians, N=150) have 56% lower total irinotecan average steady state concentration and 8% higher total SN-38 average steady state concentration than Whites (N=182).

Hepatic Impairment: The pharmacokinetics of irinotecan liposome have not been studied in patients with hepatic impairment. In a population pharmacokinetic analysis, patients with baseline bilirubin concentrations of 1-2 mg/dL (N=19) had average steady state concentrations for total SN-38 that were increased by 37% compared to patients with baseline bilirubin concentrations of <1 mg/dL (N=329); however, there was no effect of elevated ALT/AST concentrations on total SN-38 concentrations. No data are available in patients with bilirubin >2 mg/dL.

Drug Interactions

In a population pharmacokinetic analysis, the pharmacokinetics of total irinotecan and total SN-38 were not altered by the co-administration of fluorouracil/leucovorin.

Following administration of irinotecan HCl, dexamethasone, a moderate CYP3A4 inducer, does not alter the pharmacokinetics of irinotecan.

In vitro studies indicate that irinotecan, SN-38 and another metabolite, aminopentane carboxylic acid (APC), do not inhibit cytochrome P-450 isozymes.

12.5 Pharmacogenomics

Individuals who are homozygous for the UGT1A1*28 allele are at increased risk for neutropenia from irinotecan HCl. In Study 1, patients homozygous for the UGT1A1*28 allele (N=7) initiated ONIVYDE at a reduced dose of 50 mg/m^2 in combination with 5-FU/LV. The frequency of Grade 3 or 4 neutropenia in these patients [2 of 7 (28.6%)] was similar to the frequency in patients not homozygous for the UGT1A1*28 allele who received a starting dose of ONIVYDE of 70 mg/m^2 [30 of 110 (27.3%)].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been performed to assess the potential of irinotecan liposome for carcinogenicity, genotoxicity or impairment of fertility. Intravenous administration of irinotecan hydrochloride to rats once weekly for 13 weeks followed by a 91-week recovery period resulted in a significant linear trend between irinotecan HCl dosage and the incidence of combined uterine horn endometrial stromal polyps and endometrial stromal sarcomas. Irinotecan HCl was clastogenic both in vitro (chromosome aberrations in Chinese hamster ovary cells) and in vivo (micronucleus test in mice). Neither irinotecan nor its active metabolite, SN-38, was mutagenic in the in vitro Ames assay.

Dedicated fertility studies have not been performed with irinotecan liposome injection. Atrophy of male and female reproductive organs was observed in dogs receiving irinotecan liposome injection every 3 weeks at doses equal to or greater than 15 mg/kg, (approximately 3 times the clinical exposure of irinotecan following administration to ONIVYDE dosed at 70 mg/m^2) for a total of 6 doses. No significant adverse effects on fertility and general reproductive performance were observed after intravenous administration of irinotecan HCl in doses of up to 6 mg/kg/day to rats; however, atrophy of male reproductive organs was observed after multiple daily irinotecan HCl doses both in rodents at 20 mg/kg (approximately 0.007 times the clinical irinotecan exposure following ONIVYDE administration at 70 mg/m^2) and in dogs at 0.4 mg/kg (0.0007 times the clinical exposure to irinotecan following administration of ONIVYDE).

14 CLINICAL STUDIES

The efficacy of ONIVYDE was evaluated in Study 1, a three-arm, randomized, open-label trial in patients with metastatic pancreatic adenocarcinoma with documented disease progression, after gemcitabine or gemcitabine-based therapy. Key eligibility criteria included Karnofsky Performance Status (KPS) ≥70, serum bilirubin within institution limits of normal, and albumin ≥3.0 g/dL. Patients were randomized to receive ONIVYDE plus fluorouracil/leucovorin (ONIVYDE/5-FU/LV), ONIVYDE, or fluorouracil/leucovorin (5-FU/LV). Randomization was stratified by ethnicity (White vs. East Asian vs. other), KPS (70-80 vs. 90-100), and baseline albumin level (≥ 4 g/dL vs. 3.0-3.9 g/dL). Patients randomized to ONIVYDE/5-FU/LV received ONIVYDE 70 mg/m^2 as an intravenous infusion over 90 minutes, followed by leucovorin 400 mg/m^2 intravenously over 30 minutes, followed by fluorouracil 2400 mg/m^2 intravenously over 46 hours, every 2 weeks. The ONIVYDE dose of 70 mg/m^2 is based on irinotecan free base (equivalent to 80 mg/m^2 of irinotecan as the hydrochloride trihydrate). Patients randomized to ONIVYDE as a single agent received ONIVYDE 100 mg/m^2 as an intravenous infusion over 90 minutes every 3 weeks. Patients randomized to 5-FU/LV received leucovorin 200 mg/m^2 intravenously over 30 minutes, followed by fluorouracil 2000 mg/m^2 intravenously over 24 hours, administered on Days 1, 8, 15 and 22 of a 6-week cycle. Patients homozygous for the UGT1A1*28 allele initiated ONIVYDE at a reduced dose (50 mg/m^2 ONIVYDE, if given with 5-FU/LV or 70 mg/m^2 ONIVYDE as a single agent). When ONIVYDE was withheld or discontinued for adverse reactions, 5-FU was also withheld or discontinued. When the dose of

ONIVYDE was reduced for adverse reactions, the dose of 5-FU was reduced by 25%. Treatment continued until disease progression or unacceptable toxicity.

The major efficacy outcome measure was overall survival (OS) with two pair-wise comparisons: ONIVYDE versus 5-FU/LV and ONIVYDE/5-FU/LV versus 5-FU/LV. Additional efficacy outcome measures were progression-free survival (PFS) and objective response rate (ORR). Tumor status assessments were conducted at baseline and every 6 weeks thereafter. The trial was initiated as a two-arm study and amended after initiation to include a third arm (ONIVYDE/5-FU/LV). The comparisons between the ONIVYDE/5-FU/LV and the 5-FU/LV arms are limited to patients enrolled in the 5-FU/LV arm after this protocol amendment.

Four hundred seventeen patients were randomized to: ONIVYDE/5-FU/LV (N=117), ONIVYDE (N=151), or 5-FU/LV (N=149). Baseline demographics and tumor characteristics for the 236 patients randomized to ONIVYDE/5-FU/LV or 5-FU/LV (N=119) after the addition of the third arm to the study were a median age of 63 years (range 34-81 years) and with 41% $\geq$ 65 years of age; 58% were men; 63% were White, 30% were Asian, 3% were Black or African American, and 5% were other. Mean baseline albumin level was 3.97 g/dL, and baseline KPS was 90-100 in 53% of patients. Disease characteristics included liver metastasis (67%) and lung metastasis (31%). A total of 13% of patients received gemcitabine in the neoadjuvant/adjuvant setting only, 55% of patients had 1 prior line of therapy for metastatic disease, and 33% of patients had 2 or more prior lines of therapy for metastatic disease. All patients received prior gemcitabine (alone or in combination with another agent), 54% received prior gemcitabine in combination with another agent, and 13% received prior gemcitabine in combination with nab-paclitaxel.

Study 1 demonstrated a statistically significant improvement in overall survival for the ONIVYDE/5-FU/LV arm over the 5-FU/LV arm as summarized in Table 5 and Figure 1.

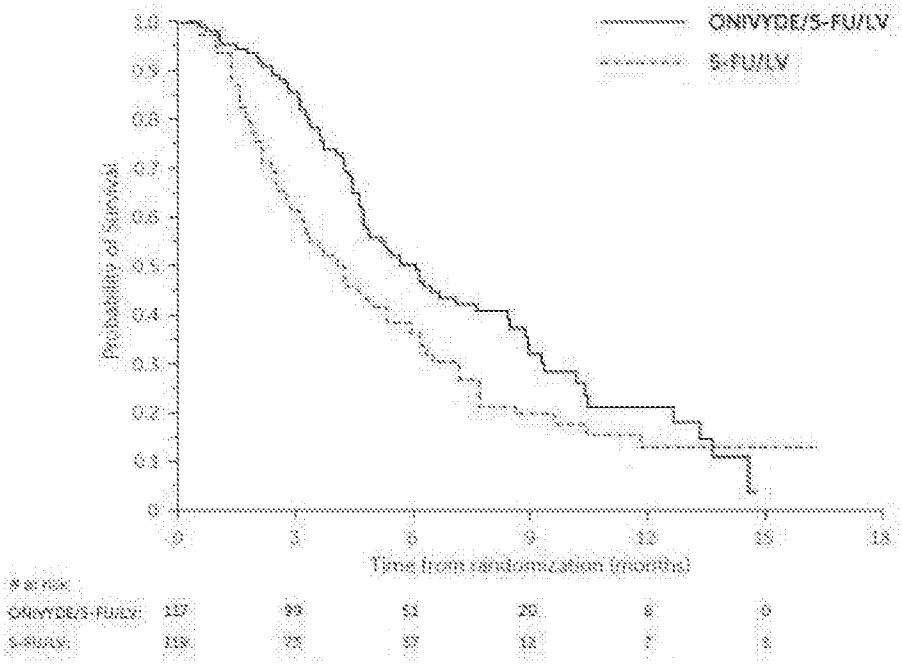
There was no improvement in overall survival for the ONIVYDE arm over the 5-FU/LV arm (hazard ratio=1.00, p-value=0.97 (two-sided log-rank test)).

Table 5: Efficacy Results from Study 1†

	ONIVYDE/5-FU/LV (N=117)	5-FU/LV (N=119)
Overall Survival		
Number of Deaths, n (%)	77 (66)	86 (72)
Median Overall Survival (months)	6.1	4.2
(95% CI)	(4.8, 8.5)	(3.3, 5.3)
Hazard Ratio (95% CI)	0.68 (0.50, 0.93)	
p-value (log-rank test)	0.014	
Progression-Free Survival		
Death or Progression, n (%)	83 (71)	94 (79)
Median Progression-Free Survival (months)	3.1	1.5
(95% CI)	(2.7, 4.2)	(1.4, 1.8)
Hazard Ratio (95% CI)	0.55 (0.41, 0.75)	
Objective Response Rate		
Confirmed Complete or Partial Response n (%)	9 (7.7%)	1 (0.8%)

† 5-FU/LV=5-fluorouracil/leucovorin; CI=confidence interval

Figure 1: Overall Survival



15 REFERENCES

1. OSHA Hazardous Drugs. *OSHA*. http://www.osha.gov/SLTC/hazardousdrugs/index.html

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

ONIVYDE is available in a single-dose vial containing 43 mg irinotecan free base at a concentration of 4.3 mg/mL

NDC: 69171-398-01

Storage and Handling

Store ONIVYDE at 2°C to 8°C (36°F to 46°F). Do NOT freeze. Protect from light.

ONIVYDE is a cytotoxic drug. Follow applicable special handling and disposal procedures.[1]

17 PATIENT COUNSELING INFORMATION

Advise patients of the following:

Severe Neutropenia
Advise patients of the risk of neutropenia leading to severe and life-threatening infections and the need for monitoring of blood counts. Instruct patients to contact their healthcare provider immediately if experiencing signs of infection, such as fever, chills, dizziness, or shortness of breath *[see Warnings and Precautions (5.1)]*.

Severe Diarrhea
Inform patients of the risk of severe diarrhea. Advise patients to contact their healthcare provider if they experience persistent vomiting or diarrhea; black or bloody stools; or symptoms of dehydration such as lightheadedness, dizziness, or faintness *[see Warnings and Precautions (5.2)]*.

Interstitial Lung Disease
Inform patients of the potential risk of ILD. Advise patients to contact their healthcare provider as soon as possible for new onset cough or dyspnea *[see Interstitial Lung Disease (5.3)]*.

Hypersensitivity to irinotecan HCl or ONIVYDE
Advise patients of the potential risk of severe hypersensitivity and that ONIVYDE is contraindicated in patients with a history of severe allergic reactions with irinotecan HCl or ONIVYDE. Instruct patients to seek immediate medical attention for signs of severe hypersensitivity reaction such as chest tightness; shortness of breath; wheezing; dizziness or faintness; or swelling of the face, eyelids, or lips *[see Contraindications (4) and Warnings and Precautions (5.4)]*.

Females and males of reproductive potential

Embryo-fetal toxicity: Inform females of reproductive potential of the potential risk to a fetus, to use effective contraception during treatment and for one month after the final dose, and to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.5), Use in Specific Populations (8.1, 8.3)]*.

Contraception: Advise male patients with female partners of reproductive potential to use condoms during treatment with ONIVYDE and for four months after the final dose *[see Females and Males of Reproductive Potential (8.3)]*.

Lactation

Advise women not to breastfeed during treatment with ONIVYDE and for one month after the final dose *[see Use in Special Populations (8.2)]*.

Manufactured for:
Merrimack Pharmaceuticals, Inc.
Cambridge, MA 02139

ONIVYDE is a trademark of Merrimack Pharmaceuticals, Inc.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/632,422	02/26/2015	Keelung Hong	239669-372963	6120

133156 7590 01/10/2017

Honigman Miller Schwartz and Cohn LLP
350 East Michigan Avenue
Suite 300
Kalamazoo, MI 49007

EXAMINER
SHOMER, ISAAC

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
01/10/2017	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@honigman.com
lbroecker@honigman.com
lzerby@honigman.com

Office Action Summary	Application No. 14/632,422	Applicant(s) HONG ET AL.	
	Examiner ISAAC SHOMER	Art Unit 1612	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 November 2016*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *1-5,13,14 and 24-36* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-5,13,14 and 24-36* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

4) ☐ Other: _____.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

The present application is being examined under the pre-AIA first to invent provisions.

In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

Substantial Duplicate Claims

Applicant is advised that should claim 13 be found allowable, claim 14 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Cited Prior Art

The instant claims are not rejected as anticipated or obvious under 35 U.S.C. 102 or 103.

As close and relevant prior art, the examiner cites Chou et al. (Journal of Bioscience and Bionegineering, Vol. 95 No. 4, 2003, pages 405-408). Chou et al. (hereafter referred to as Chou) is drawn to liposomes comprising irinotecan, as of Chou, page 405, title and abstract. These liposomes are prepared by pH gradient loading, as of Chou, page 405, title. Chou suggests an ammonium sulfate gradient loading method, as of Chou, page 408, end of first full paragraphs. Chou suggests the use of sulfated oligosaccharides to form an insoluble complex of irinotecan, as of Chou, page 408, left column, middle of first full paragraph.

Chou differs from the claimed invention because, although Chou teaches sulfated oligosaccharides, Chou does not teach sucrose octasulfate. Chou also does not teach a gradient with a substituted ammonium compound; in contrast, Chou suggests a gradient with ammonium sulfate, which is not a substituted ammonium compound.

Data in the instant specification show that liposomes comprising triethylamine (e.g. triethylammonium) (abbreviated as TEA) and sucrose octasulfate in addition to irinotecan, as of instant figure 6, reproduced below. These results are superior to the results in which sucrose octasulfate is substituted with triethylamine (TEA) in

combination with inositol hexaphosphate, and far superior to free irinotecan, as of instant figure 6, reproduced below.

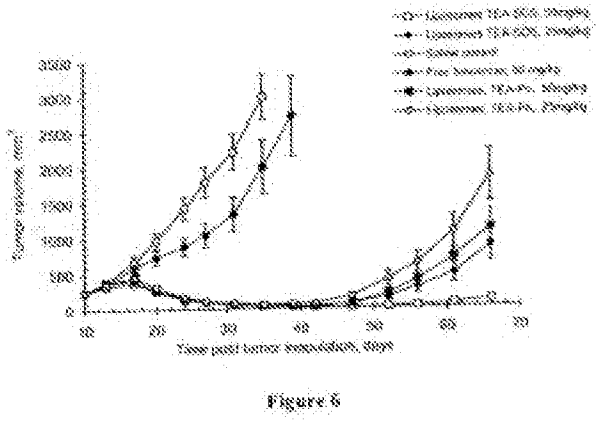

Figure 6

In addition, the examiner cites page 63, Example 14, and instant figure 5. In this example, it is noted that a liposome comprising CPT-11 (irinotecan) and the triethylammonium salt of sucrose octasulfate has a half-life of 56.8 hours. This appears to be significantly greater than the half life of drug in the liposomes of Chou, which appears to be between at most about 120 minutes (2 hours), as of Chou, Figures 1, 3, and 4. This increase in drug retention upon using sucrose octasulfate would not have been expected by the skilled artisan.

The examiner notes that the advantages of using sucrose octasulfate together with irinotecan have been discussed in related cases in the same case family as the instant case, e.g. as of applicant's response on 28 March 2016 in application 14/879,358 and on 1 June 2016 in application 14/965,140. The reasons set forth there are also understood to apply to the instant claims.

As such, no anticipation or obviousness rejection has been written over the Chou reference.

As additional relevant prior art, the examiner cites Rahman et al. (WO 2003/030864 A1). Rahman et al. (hereafter referred to as Rahman) is drawn to a liposomal formulation of irinotecan, as of Rahman, title and abstract. However, Rahman does not teach the steps of adding of sucrose octasulfate or a substituted ammonium compound. Nothing in Rahman would indicate to the skilled artisan that there would have been unexpected benefits in adding sucrose octasulfate or a substituted ammonium compound.

Non-Statutory Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(1) - 706.02(l)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

Claims 1-5, 13, 14, and 24-36 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-35 of U.S. Patent No.

8,147,867. Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons:

The instant claims are drawn to a method of preparing a liposomal irinotecan composition comprising providing a liposome containing sucrose octasulfate and a substituted ammonium compound and combining with cationic irinotecan.

Conflicting claim 1 is drawn to a liposomal irinotecan composition comprising irinotecan, sucrose octasulfate, and a substituted ammonium compound. Specific substituted ammonium compounds are recited in conflicting claim 10.

The instant and conflicting claims differ because the instant claims are drawn to a method of making a composition, whereas the conflicting claims are drawn to the composition itself. Nevertheless, the method of making of the instant claims appears to recite only the order in which the components of the composition are added, e.g. the substituted ammonium compound and sucrose octasulfate are added to the liposome first, and the irinotecan is added later. The selection of any order of adding ingredients is prima facie obvious in the absence of unexpected results. See MPEP 2144.04(IV)(C).

Claims 1-5, 13, 14, and 24-36 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-1 of U.S. Patent No. 8,992,970. Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons:

The instant claims are drawn to a method of preparing a liposomal irinotecan composition comprising providing a liposome containing sucrose octasulfate and a substituted ammonium compound and combining with cationic irinotecan.

Conflicting claim 1 is drawn to a liposomal composition comprising irinotecan, sucrose octasulfate, and a substituted ammonium compound.

The instant and conflicting claims differ because the instant claims are drawn to a method of making a composition, whereas the conflicting claims are drawn to the composition itself. Nevertheless, the method of making of the instant claims appears to recite only the order in which the components of the composition are added, e.g. the substituted ammonium compound and sucrose octasulfate are added to the liposome first, and the irinotecan is added later. The selection of any order of adding ingredients is prima facie obvious in the absence of unexpected results. See MPEP 2144.04(IV)(C).

Claims 1-5, 13, 14, and 24-36 rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-22 of U.S. Patent No. 8,658,203.

Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons:

The instant claims are drawn to a method of preparing a liposomal irinotecan composition comprising providing a liposome containing sucrose octasulfate and a substituted ammonium compound and combining with cationic irinotecan.

The conflicting claims are drawn to a method for treating a brain tumor. The conflicting claims utilize a liposome comprising irinotecan, sucrose octasulfate, and a substituted ammonium compound, as of conflicting claim 1. Specific substituted ammonium compounds are recited as of conflicting claims 8-10.

The instant and conflicting claims differ because the instant claims are drawn to a method of making a composition, whereas the conflicting claims are drawn to a method of using the composition. Nevertheless, the method of making of the instant claims appears to recite only the order in which the components of the composition are added, e.g. the substituted ammonium compound and sucrose octasulfate are added to the liposome first, and the irinotecan is added later. The selection of any order of adding ingredients is prima facie obvious in the absence of unexpected results. See MPEP 2144.04(IV)(C). With regard to a method of use, conflicting claim 1 is drawn to treating cancer, and the instant claims also recite that irinotecan is a cationic antineoplastic agent, as of instant claim 1, which would have been understood to have been useful for treating cancer.

Claims 1-5, 13, 14, and 24-36 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-16 of copending Application No. 14/966,458 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons:

Instant claim 1 is drawn to a method of preparing a liposomal irinotecan composition comprising providing a liposome containing sucrose octasulfate and a substituted ammonium compound and combining with cationic irinotecan.

Copending claim 1 is drawn to an irinotecan liposome composition. Although copending claim 1 is a product claim, the method by which the liposome is prepared is recited by the claims. This method includes forming a lipid vesicle (i.e. liposome) encapsulating a sulfated sugar and a substituted ammonium compound, and contacting this liposome with irinotecan at a specific temperature. The sulfated sugar may be sucrose octasulfate, as of copending claim 5.

The instant and copending claims differ because the instant claims are method claims, whereas the copending claims are product claims. Nevertheless, the copending product claims recite a method of making the copending product that is within the scope of the instant claims. As such, there is a prima facie case of anticipatory-type non-statutory double patenting.

Copending claim 1 differs from instant claim 1 because copending claim 1 recites contacting the lipid vesicle with irinotecan above the phase transition temperature, which is not recited by instant claim 1. Nevertheless, the process used in the product-by-process of the copending claims appears to be within the scope of the process recited by instant claim 1, resulting in a prima facie case of anticipatory-type non-statutory double patenting with respect to claim 1.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Claims 1-5, 13, 14, and 24-36 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-20 of copending Application No. 15/227,631 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons:

Instant claim 1 is drawn to a method of preparing a liposomal irinotecan composition comprising providing a liposome containing sucrose octasulfate and a substituted ammonium compound and combining with cationic irinotecan.

Copending claim 1 is drawn to a liposome comprising irinotecan and sucrose octasulfate. This liposome also includes a triethylammonium ion, as of copending claim 19.

The instant and copending claims differ because the instant claims are drawn to a method of making a composition, whereas the copending claims are drawn to the composition itself. Nevertheless, the method of making of the instant claims appears to recite only the order in which the components of the composition are added, e.g. the substituted ammonium compound and sucrose octasulfate are added to the liposome first, and the irinotecan is added later. The selection of any order of adding ingredients is prima facie obvious in the absence of unexpected results. See MPEP 2144.04(IV)(C).

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Table of Conflicting Patents and Copending Applications (1)

Instant Case	**Conflicting Patent/Application**	**Double Patenting?**
14/632,422	8,147,867	Yes
14/632,422	8,329,213	No (conflicting claims lack substituted ammonium ion)
14/632,422	8,703,181	No (conflicting claims lack substituted ammonium ion)
14/632,422	8,992,970	Yes
14/632,422	8,658,203	Yes
14/632,422	14/879,358	No (abandoned)
14/632,422	14/965,140 (allowed)	No (copending claims lack substituted ammonium ion)

Table of Copending Applications (2)

Instant Case	Copending Case	Double Patenting?
14/632,422	14/632,422	No (same case)
14/632,422	14/151,632	No (abandoned)
14/632,422	15/213,127	No (copending claims lack substituted ammonium ion)
14/632,422	14/879,302	No (conflicting claims lack substituted ammonium ion)
14/632,422	14/964,239	No (copending claims do not teach sucrose octasulfate and teach a polyphosphorylated polyol instead)
14/632,422	14/966,458	Yes
14/632,422	14/979,666	No, because copending claims do not teach irinotecan and teach docetaxel instead
14/632,422	14/181,583	No (copending claims lack substituted ammonium ion)

Table of Copending Applications (3)

Instant Case	Copending Case	Double Patenting?
14/632,422	15/227,631	Yes
14/632,422	15/227,561	No (conflicting claims lack substituted ammonium ion)
14/632,422	15/296,536	No (conflicting claims lack substituted ammonium ion)
14/632,422	15/364,021	No (copending claims lack both sucrose octasulfate and substituted ammonium)
14/632,422	15/363,761	No (copending claims lack both sucrose octasulfate and substituted ammonium)
14/632,422	15/363,923	No (copending claims lack both sucrose octasulfate and substituted ammonium)
14/632,422	15/363,978	No (copending claims lack both sucrose octasulfate and substituted ammonium)

The examiner notes that various conflicting and copending applications exist whose claims recite a liposome comprising irinotecan and sucrose octasulfate, but lack the required substituted ammonium cation. As there is no motivation in those conflicting/copending applications for the skilled artisan to have added a substituted ammonium cation, no double patenting rejection has been written in those cases.

Additional Note Regarding Provisional Non-Statutory Double Patenting

The examiner further notes that MPEP 804(I)(B)(1) states the following:

> If a "provisional" nonstatutory double patenting rejection is the only rejection remaining in an application having the earliest effective U.S. filing date (including any benefit claimed under 35 U.S.C. 120, 121, 365(c), or 386(c)) [but not provisional applications under 35 U.S.C. 119(e)] compared to the reference application(s), the examiner should withdraw the rejection in the application having the earliest effective U.S. filing date and permit that application to issue as a patent, thereby converting the "provisional" nonstatutory double patenting rejection in the other application(s) into a nonstatutory double patenting rejection when the application with the earliest U.S. effective filing date issues as a patent.

However, this section of the MPEP also states the following:

> If a "provisional" nonstatutory double patenting rejection is the only rejection remaining in an application, and that application has an effective U.S. filing date (including any benefit claimed under 35 U.S.C. 120, 121, 365(c), or 386(c)) that is later than, or the same as, the effective U.S. filing date of at least one of the reference application(s), the rejection should be maintained until applicant overcomes the rejection. In accordance with 37 CFR 1.111(b), applicant's reply must present arguments pointing out the specific distinctions believed to render the claims, including any newly presented claims, patentable over any applied references. Alternatively, a reply that includes the filing of a compliant terminal disclaimer in the later-filed application under 37 CFR 1.321 will overcome a nonstatutory double patenting rejection and is a sufficient reply pursuant to 37 CFR 1.111(b). Upon the filing of a compliant terminal disclaimer in a pending application, the nonstatutory double patenting rejection will be withdrawn in that application.

In this case, both instant and all copending applications over which the instant claims are rejected claim benefit back to prior application 11/121,294. As such, both the

instant and copending claims are understood to have the same effective filing date. As such, these double patenting rejections are applied herein.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ISAAC SHOMER whose telephone number is (571)270-7671. The examiner can normally be reached on 8:00 AM - 5:00 PM Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick F. Krass can be reached on (571)272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/ISAAC SHOMER/
Primary Examiner, Art Unit 1612

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/812,950	07/29/2015	ELIEL BAYEVER	239669-373912	7968

133156 7590 10/02/2015

Honigman Miller Schwartz and Cohn LLP
350 East Michigan Avenue
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EXAMINER	
STRONG, TORI	

ART UNIT	PAPER NUMBER
1629	

MAIL DATE	DELIVERY MODE
10/02/2015	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

First Action Interview Pilot Program Pre-Interview Communication	Application No. 14/812,950	Applicant(s) BAYEVER ET AL.	
	Examiner TORI M. STRONG	Art Unit 1629	AIA (First Inventor to File) Status No

-The MAILING OR NOTIFICATION DATE of this communication appears on the cover sheet with the correspondence address -

THE SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE **ONE MONTH OR THIRTY (30) DAYS,** WHICHEVER IS LONGER, FROM THE MAILING OR NOTIFICATION DATE OF THIS COMMUNICATION.

This time period for reply is extendable under 37 CFR 1.136(a) for only ONE additional MONTH.

This communication constitutes notice under 37 CFR 1.136(a)(1)(i).

Applicant must, within the time period for reply, file: (1) A letter requesting not to have a first action interview; (2) A reply under 37 CFR 1.111 waiving the first action interview and First Action Interview Office Action; or (3) An Applicant Initiated Interview Request Form (PTOL-413A) electronically via EFS-Web, accompanied by a proposed amendment or arguments, and schedule the interview within 2 months from the filing of the request. A failure to respond to this communication will be treated as a request not to have an interview. If applicant waives the First Action Interview Office Action, the instant Pre-Interview Communication is deemed the first Office Action on the Merits. The next subsequent Office action may be made final if appropriate. See MPEP 706.07(a).

Status

1)☒ Responsive to communication(s) filed on *29 July 2015*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

Disposition of Claims

2)☒ Claim(s) *1-19* is/are pending in the application.

2a) Of the above claim(s) _____ is/are withdrawn from consideration.

3)☐ Claim(s) _____ is/are allowed.

4)☒ Claim(s) ***1-19*** is/are rejected.

5)☐ Claim(s) _____ is/are objected to.

6)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

7)☐ The specification is objected to by the Examiner.

8)☒ The drawing(s) filed on *29 July 2015* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

9)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

Contact Information

Examiner's Telephone Number: (571)272-6333

Examiner's Typical Work Schedule: Monday-Friday 8am-5pm EST

Supervisor's Name: Jeffrey Lundgren

Supervisor's Telephone Number: (571)272-5541

Attachment(s)

1) ☒Notice of References Cited (PTO-892)

2) ☒Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.

3) ☐Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

First Action Interview Pilot Program Pre-Interview Communication	Application No. 14/812,950	Applicant(s) BAYEVER ET AL.	
	Examiner TORI M. STRONG	Art Unit 1629	AIA (First Inventor to File) Status No

Notification of Rejection(s) and/or Objection(s)

#	Claim(s)	Reference(s) (if applicable)	Rejection Statutory Basis	Brief Explanation of Rejection
1	1-19	Kozuch et al.	103(a)	Kozuch teaches a method of treating metastatic pancreatic cancer refractory to gemcitabine therapy through administration of a combination called G-FLIP which comprises irinotecan (80 mg/m2), leucovorin (600 mg/m2) and 5-fluorouracil (2000 mg/m2).
2	1-19	Tsai et al.	103(a)	Tsai teaches liposomal therapies for advanced pancreatic cancer to enhance drug delivery. Tsai teaches the liposomal irinotecan has superior efficacy over the free form and further teaches it to have a partial response in pancreatic cancer patients.
3	6 and 16-19	Grant et al.	103(a)	Grant teaches administration of dazopride, an antiemetic, prior to administering chemotherapy.

Expanded Discussion/Commentary

1		Kozuch teaches adminsitration of a 48 hour period repeated every 2 weeks. Kuzoch provides a similar composition that comprises the therapeutic agents and amounts instantly claimed.
2		Tsai provides teaching that one of ordinary skill in the art would substitute the liposomal form of irinotecan and further combine with the instantly claimed therapeutic agents. Based on the combined teaching of Kozuch and Tsai, a skilled artisan would arrive at the instantly claimed invention having a reasonable expectation of success.
3		Grant provides teaching that chemotherapy that causes emesis is often co-administered with an antiemetic. More particularly, Grant teaches the antiemetic is administered prior to the chemotherapy adminsitration, as well as throughout. Grant's teaching provides one of ordinary skill a reasonable expectation of success in incorporating the instant limitation for the dependent claims.

DATE: 30 September, 2015	/Tori Strong/ Examiner, AU 1629	/Kortney L. Klinkel/ Primary Examiner, AU 1611

Docket No.: 239669-373912
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Eliel Bayever *et al.*

Application No.: 14/812,950 | Confirmation No.: 7968

Filed: July 29, 2015 | Art Unit: 1629

For: METHODS FOR TREATING PANCREATIC CANCER USING COMBINATION THERAPIES COMPRISING LIPOSOMAL IRINOTECAN | Examiner: Tori Strong

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PRELIMINARY AMENDMENT UNDER 37 C.F.R. 1.115

Prior to examination on the merits, please amend the above-identified U.S. patent application as follows:

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 6 of this paper.

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of Claims

What is claimed is:

1. (Currently Amended) A method of treating metastatic adenocarcinoma of the pancreas in a human patient who has previously been treated with the antineoplastic agent gemcitabine, the method comprising intravenously administering to the patient once every two weeks 80 mg/m^2 of the antineoplastic agent MM-398 liposomal irinotecan in combination with 200 mg/m^2 of (*l*)-form of leucovorin or 400 mg/m^2 of the (*l+d*) racemic form of leucovorin and 2,400 mg/m^2 of the antineoplastic agent 5-fluorouracil to treat the metastatic adenocarcinoma of the pancreas in the human patient, where no other antineoplastic agent is administered to the human patient for treatment of the metastatic adenocarcinoma of the pancreas.

2. (Original) The method of claim 1, wherein the leucovorin is administered as 400 mg/m^2 of the (*l+d*) racemic form of leucovorin.

3. (Currently Amended) The method of claim 1, wherein the MM-398 liposomal irinotecan, leucovorin and 5-fluorouracil are administered to the patient over 48 hours ~~beginning on day 1 of a 2-week cycle wherein the method comprises multiple cycles~~.

4. (Original) The method of claim 3, wherein 400 mg/m^2 of the (*l+d*) racemic form of leucovorin is administered to the patient prior to the 5-fluorouracil.

5. (Original) The method of claim 4, wherein the MM-398 liposomal irinotecan is administered to the patient prior to the leucovorin.

6. (Original) The method of claim 5, further comprising pre-medicating the patient with dexamethasone and a 5-HT3 antagonist or other anti-emetic prior to administering the MM-398 liposomal irinotecan.

7. (Original) The method of claim 1, wherein the patient has metastatic pancreatic cancer that has progressed on gemcitabine-based therapy prior to the administration of the MM-398 liposomal irinotecan.

8. (Original) The method of claim 1, wherein the MM-398 liposomal irinotecan is administered to the patient over 90 minutes.

9. (Original) The method of claim 8, wherein the leucovorin is administered over 30 minutes and the 5-FU is administered over 46 hours.

10. (Original) The method of claim 9, wherein the MM-398 liposomal irinotecan is administered over 90 minutes, followed by administration of the leucovorin over 30 minutes, followed by the administration of the 5-fluorouracil over 46 hours.

11. (Original) The method of claim 10, wherein the MM-398 liposomal irinotecan, leucovorin and 5-fluorouracil are administered to the patient beginning on day 1 of a 2-week cycle wherein the method comprises multiple cycles, and the leucovorin is administered as 400 mg/m^2 of the *(l+d)* racemic form of leucovorin.

12. (Currently Amended) A method of treating metastatic adenocarcinoma of the pancreas in a human patient who has previously been treated with the antineoplastic agent gemcitabine, the method comprising, intravenously administering to the patient once in a 2-week cycle, beginning on day 1 of **[[a]]**the 2-week cycle, 80 mg/m^2 of the antineoplastic agent MM-398 liposomal irinotecan over 90 minutes, followed by 400 mg/m^2 of the *(l+d)* racemic form of leucovorin or 200 mg/m^2 of *(l)*-form of leucovorin, followed by 2,400 mg/m^2 of the antineoplastic agent 5-fluorouracil, where the method comprises multiple cycles and no other antineoplastic agent is administered during each 2-week cycle to treat the metastatic adenocarcinoma of the pancreas in the human patient.

13. (Cancelled).

14. (Original) The method of 12, wherein the leucovorin is administered over 30 minutes and the 5-fluorouracil is administered over 46 hours.

15. (Original) The method of claim 12, wherein the patient has metastatic pancreatic cancer that has progressed on gemcitabine-based therapy prior to the administration of the MM-398.

16. (Cancelled)

17. (Cancelled)

18. (Cancelled)

19. (Cancelled)

20. (New) A method of treating metastatic pancreatic cancer that has progressed on gemcitabine-based therapy, the method comprising administering an antineoplastic therapy over 48 hours once every two weeks to a patient in need thereof, to treat the metastatic pancreatic cancer in the patient, the antineoplastic therapy comprising a single intravenous administration of 80 mg/mm^2 of MM-398 liposomal irinotecan, a single intravenous administration 200 mg/m^2 of (*l*)-form of leucovorin or 400 mg/m^2 of the (*l*+*d*) racemic form of leucovorin, and a single intravenous administration of 2,400 mg/m^2 of 5-fluorouracil, where the antineoplastic therapy does not include administration of another antineoplastic agent to the patient.

21. (New) The method of claim 20, wherein the leucovorin is administered as 400 mg/m2 of the (l+d) racemic form of leucovorin.

22. (New) The method of claim 20, wherein the MM-398 liposomal irinotecan is administered prior to the 5-fluorouracil.

23. (New) The method of claim 22, wherein the administration of the MM-398 liposomal irinotecan is followed by the administration of the leucovorin.

24. (New) The method of claim 23, wherein the administration of the leucovorin is followed by the administration of the 5-fluorouracil.

25. (New) The method of claim 24, wherein the leucovorin is administered as 400 mg/m2 of the (l+d) racemic form of leucovorin.

26. (New) The method of claim 20, wherein the antineoplastic therapy consists of the administration of the MM-398 liposomal irinotecan, the leucovorin and the 5-fluorouracil.

27. (New) The method of claim 26, wherein the leucovorin is administered as 400 mg/m^2 of the (l+d) racemic form of leucovorin.

28. (New) The method of claim 20, wherein the antineoplastic therapy consists of the administration of the MM-398 liposomal irinotecan, followed by administration of the leucovorin, followed by administration of the 5-fluorouracil.

29. (New) The method of claim 28, wherein the leucovorin is administered as 400 mg/m^2 of the (l+d) racemic form of leucovorin.

30. (New) The method of claim 20, further comprising pre-medicating the patient with dexamethasone and a 5-HT3 antagonist or other anti-emetic prior to administering the MM-398 liposomal irinotecan.

31. (New) A method of treating metastatic pancreatic cancer that has progressed on gemcitabine-based therapy prior to the administration of a MM-398 liposomal irinotecan, the method comprising administering an antineoplastic therapy once every two weeks to a patient in need thereof to treat the metastatic pancreatic cancer in the patient, the antineoplastic therapy consisting of a single intravenous administration of 80 mg/mm^2 of MM-398 liposomal irinotecan over 90 minutes, followed by a single intravenous administration of 200 mg/m^2 of (*l*)-form of leucovorin or 400 mg/m^2 of the (*l*+*d*) racemic form of leucovorin over 30 minutes, followed by a single intravenous administration of 2,400 mg/m^2 of 5-fluorouracil over 46 hours.

32. (New) The method of claim 31, further comprising pre-medicating the patient with an anti-emetic medication prior to administering the antineoplastic therapy.

REMARKS

Amendments to the claims

Claims 1-27 were pending. In the claims, claims 1, 3, and 12 are currently amended. Claims 13 and 16-19 are cancelled. Claims 20-32 are new. Claims 2, 4-11, and 14-15 are original. Claims 1-12, 14-15, and 20-32 are curently pending. Support for the claim amendments can be found throughout the specification and claims as originally filed. *No new matter has been added.*

Information Disclosure Statement

Applicant requests consideration of the references listed on the attached PTO/SB/08a form. Applicant notes that the filing of the enclosed information disclosure statement shall not be construed to be an admission that the information cited in the statement qualifies as prior art under 35 U.S.C. §§ 102 or 103, or is considered to be material to patentability as defined in 37 C.F.R. § 1.56(b). It is believed that no additional fees are required for filing this statement.

Excess Claim Fees

Applicant submits herewith fees in the amount of $1,060, reflecting payment of $640 for 8 claims in excess of 20, and $420 for 1 independent claim in excess of three, with large entity status. Please charge Deposit Account No. 503145 for the $1,060 claim fees, and reference Attorney Docket Number 239669-373912.

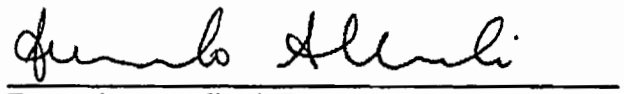
CONCLUSION

If a telephone conversation with Applicants' Attorney would expedite the prosecution of the above-identified application, the Examiner is urged to call the undersigned at (734) 418-4280.

The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 503145, under Attorney Docket No. 239669-373912.

Dated: October 22, 2015

Respectfully submitted,



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/844,500	09/03/2015	ELIEL BAYEVER	239669-375514	1041

133156 7590 12/16/2015

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EXAMINER
STRONG, TORI

ART UNIT	PAPER NUMBER
1629	

MAIL DATE	DELIVERY MODE
12/16/2015	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 14/844,500	Applicant(s) BAYEVER ET AL.	
	Examiner TORI M. STRONG	Art Unit 1629	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 September 2015*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *1-30* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-30* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☒ The drawing(s) filed on *03 September 2015* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

4) ☐ Other: _____.

DETAILED ACTION

Status of Claims

Claims 1-30 are pending in the instant application and are the subject of the Office Action below.

Information Disclosure Statement

The information disclosure statements (IDSs) submitted on 09/03/2015, 09/23/2015 and 10/15/2015 were filed on and after the mailing date of the application on September 03, 2015. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. Enclosed with this Office Action are return copies of Form PTO/SB/08B with the Examiner's initials and signature indicating those references that have been considered.

Claim Rejections - 35 USC § 112

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-27 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly

claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.

Regarding **claims 1, 3 and 18**, the phrase "…after previous intravenous administration of the MM-398 liposome…" renders the claims indefinite because the claims include elements not actually disclosed (those encompassed by "…after previous intravenous administration of the MM-398 liposome…"), thereby rendering the scope of the claims unascertainable. See MPEP § 2173.05(d). One cannot determine whether the one is measuring ANC after previous administration of MM-398 prior to the instantly claimed treatment that includes the entire therapeutic combination or measuring ANC after an initial administration of MM-398 within therapeutic regimen. **Claims 2, 4-16 and 19-27** depend on claims 1 and 18 and therefore encompass the limitations of the independent claims. Therefore claims 1-27 are indefinite.

Claim Rejections - 35 USC § 103

The following is a quotation of pre-AIA 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under pre-AIA 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under pre-AIA 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of pre-AIA 35 U.S.C. 103(c) and potential pre-AIA 35 U.S.C. 102(e), (f) or (g) prior art under pre-AIA 35 U.S.C. 103(a).

Claims 1-3 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Yoo *et al.* (British Journal of Cancer, 2009, 101, pp. 1658-1663; cited in IDS) and Tsai *et al.* (*Journal of Gastrointestinal Oncology*, 2011, Vol. 2, No. 3, pp. 185-194; cited

in IDS) in view of Hoskins *et al.* (*J. Natl. Cancer Inst.*, 2007, Vol. 99, Iss. 17, pp. 1290-1295; cited in IDS).

Applicant's invention, according to **claim 1**, is directed to a method of treating metastatic adenocarcinoma of the pancreas in a human patient comprising intravenous administration of 60 mg/m^2 of irinotecan as a MM-398 liposome (referred to as MM-398) in combination with 200 mg/m^2 of the (l)-form of leucovorin (or 400 mg/m^2 of the racemic form), and 5-fluorouracil (5-FU); wherein the patient has been previously treated with gemcitabine, the patient has had an absolute neutrophil count (ANC) of less than 1000 cells/mm^3 after previous administration of MM-398, and/or the patient is homozygous for the UGT1A1*28 allele.

Yoo teaches a method of treating metastatic pancreatic cancer refractory to gemcitabine therapy (abs) through administration of a drug combination regimen called FOIFIRI.3 which comprises irinotecan (70 mg/m^2), leucovorin (400 mg/m^2) and 5-fluorouracil (2000 mg/m^2) (p. 1659, col. 2, para. 3). Yoo teaches administration of 5-FU over a 46 hour period with the entire regimen repeated every 2 weeks. Yoo provides teaching of a similar composition that comprises the same therapeutic agents in similar amounts as instantly claimed. Yoo fails to explicitly teach irinotecan as a liposome and fails to note whether or not the subject receiving the drug combination has had an absolute neutrophil count of less than 100 cells/mm^3 after a previous intravenous administration of the MM-398 liposome (note the 112(b) rejection regarding this patient population) and/or whether the subject is homozygous for the UGT1A1*28 allele.

Tsai teaches liposomal therapies for advanced pancreatic cancer to enhance drug delivery (p. 187, para. 3). Tsai teaches the liposomal irinotecan has superior efficacy over the free form (p. 189, para. 3) and further teaches it to have a partial response in pancreatic cancer patients refractory to gemcitabine therapy (p. 189, para. 5). Tsai provides teaching that one of ordinary skill in the art would substitute the liposomal form of irinotecan and further combine with the instantly claimed therapeutic agents.

Hoskins teaches the effect of irinotecan on patients with UGT1A1*28 genotype. Hoskins teaches that there is an association with irinotecan-induced toxicities with patients who were homozygous for UGT1A1*28 allele (p. 1290, para. 2). Hoskins teaches that hematologic toxicity, neutropenia, or diarrhea was associated with irinotecan administration but not clarified as to the relationship. Hoskins further teaches that when the toxicities were further assessed, the relationship reveals that dosing of irinotecan caused different effects (p. 1291, para. 2). Hoskins teaches three categories of dosing; high doses (200-350 mg/m^2), intermediate dose (180 mg/m^2) and low doses (80-125 mg/m^2) where the hematologic toxicity, neutropenia, is associated with high doses of irinotecan in patients that are homozygous for UGT1A1*28 allele; and teaches that low doses the risk is the same with other genotypes (p. 1293, para. 3). Therefore one of ordinary skill in the art would readily utilize a low dose of irinotecan for patients that are homozygous for UGT1A1*28 allele knowing that any dosing lower than 125 mg/m^2 would generally not cause neutropenia.

Based on the combined teaching of Yoo, Tsai and Hoskins, a skilled artisan would arrive at the instantly claimed invention having a reasonable expectation of success; where Yoo teaches the a combination comprising the instantly claimed agents in a similar dose with Tsai teaching the benefit of using MM-398 instead of the free form of irinotecan and where Hoskins provides the rationale for the combination to patients that are homozygous for UGT1A1*28 allele due to containing a low dose of irinotecan and further having indicators for potential neutropenia, or low ANC. The prior art provides sufficient guidance for combining the chemotherapeutic agents for treating pancreatic cancer refractory to gemcitabine therapy and for combining in a way that limits the risk for hematologic toxicity; where Hoskins provides clear rationale that the instant combination would be safe for administering the subset population for pancreatic cancer. Furthermore it is routine and conventional for one of ordinary skill to optimize dosing particularly in this case where the dosing is in similar range for irinotecan (both 60 and 70 mg/m^2 are considered low doses) and identical dosing for leucovorin. Therefore at the time of invention, it was *prima facie* obvious to arrive at the instant claim based on the art of Yoo, Tsai and Hoskins.

Applicant's invention, according to **claim 2**, limits claim 1 and requires the patient to be homozygous for UGT1A1*28 allele and the 5-FU to be administered at a dose of 2400 mg/m^2.

A *prima facie* case of obviousness is established for applying the method of treatment to patients homozygous for UGT1A1*28 allele, see *supra*, where the low dose

(any dose less than 125 mg/m^2) of irinotecan would reduce the risk of toxicity. While Yoo teaches a dose of 2000 mg/m^2 of 5-FU; Kozuch, Tsai nor Hoskins provide an explicit dose of 5-FU at 2400 mg/m^2.

One of ordinary skill in the art would gleam from the prior art the overall combination of therapeutic agents and routinely optimize dosing for treatment. Yoo provides the same therapeutic agents within the claimed range of dosing for treating pancreatic cancer refractory to gemcitabine treatment. Yoo teaches second-line therapy comparisons for patients with gemcitabine-refractory advanced pancreatic cancer. Yoo explicitly teaches a combination (mFOLFIRI.3) that comprises, with total dosing, irinotecan (70 mg/m^2), leucovorin (400 mg/m^2), and 5-FU (2000 mg/m^2) (p. 1659, col. 2, para. 3). Yoo further teaches that another dose of 5-FU can be administered on a second day. Yoo provides teaching of 5-FU administered in a similar dose as instantly claimed. It would be routine and conventional for a skilled artisan to optimize dosing within a similar range for treating patients. One of ordinary skill in the art would have a reasonable expectation of success at applying the instant limitation of dosing towards treating pancreatic cancer refractory to gemcitabine therapy. Therefore the instant claim is *prima facie* obvious over Yoo, Tsai and Hoskins.

Applicant's invention, according to **claim 3**, limits claim 1 and requires the patient to have an ANC of less than 1000 cells/mm^3 after previous administration of MM-398, and the 5-FU to be administered at 1800 mg/m^2.

It is first noted that patients with an ANC less than 1000 cells/mm^3 carry a moderate risk of infection and chemotherapy is still often administered to such patients but further bolsters the rationale of low dose irinotecan to not induce neutropenia to further increase the risk of infection. A *prima facie* case of obviousness is established for administering the combination to patients who have moderate risk for infection with the instant range of neutrophil count considering the low dose of irinotecan is well within a safe dose range that should not induce neutropenia (or lowering of neutrophils), see *supra*. Furthermore, Yoo teaches administration of 5-FU of 2000 mg/m^2 which is well in the range of dosing of the instantly claimed amount for treatment.

One of ordinary skill in the art would readily modify the dosing, as expressed *supra*, routinely and conventionally to optimize treatment for patients. As previously mentioned, the combination of agents has been used for treating pancreatic cancer refractory to gemcitabine therapy at different dosing, covering a wide scope in range. There is a reasonable expectation of success in selecting the instantly claimed dose for 5-FU based on the teaching of the prior art of Yoo, Tsai and Hoskins. The art clearly recognizes the benefit of the combination and furthermore the challenge of infection risk and toxicity of irinotecan with patients homozygous for UGT1A1*28 allele. Therefore it remains *prima facie* obvious to incorporate the instant limitation based on the teaching of Yoo, Tsai and Hoskins.

Claims 4-26 and 28-30 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Yoo *et al.* (*British Journal of Cancer*, 2009, 101, pp. 1658-1663; cited in IDS) and Tsai *et al.* (*Journal of Gastrointestinal Oncology*, 2011, Vol. 2, No. 3, pp. 185-194; cited in IDS) in view of Hoskins *et al.* (*J. Natl. Cancer Inst.*, 2007, Vol. 99, Iss. 17, pp. 1290-1295; cited in IDS) as applied to claims 2 and 3, in further view of Kozuch *et al.* (*The Oncologist*, 2001, 6, pp. 488-495; cited in IDS).

Applicant's invention, according to **claims 4-7, 10-14 and 17**, limits claims 2 and 3; and requires MM-398, leucovorin and 5-FU are administered sequentially beginning on day 1 of a 2-week cycle (administered in the respective order listed); requires racemic leucovorin at a dose of 400 mg/m^2; and requires the metastatic adenocarcinoma of the pancreas to have progressed on gemcitabine-based therapy prior to administration of MM-398.

The combination of teachings of Yoo, Tsai and Hoskins provides a case of *prima facie* obviousness for the instantly claimed combination for treating pancreatic cancer. However, the teachings do not explicitly teach sequential administration of the chemotherapeutic regimen.

Kozuch teaches treatment of pancreatic cancer through sequential administration of the therapeutic agents where irinotecan, leucovorin and 5-FU is administered in the respective order (p. 490, para. 1) and teaches administration is repeated every 2 weeks (p. 488, abs), implicitly a 2-week cycle. Kozuch further teaches administration of racemic leucovorin at a total of 600 mg/m^2. Kozuch also teaches the combination to be

a second-line therapy to patients with metastatic pancreatic cancer that has progressed with prior administration of gemcitabine-based therapy (p. 480, abs).

A skilled artisan would readily gleam from the prior art of Kozuch to arrive at the instant limitations of sequential administration in a 2-week cycle, administering racemic leucovorin in the similar dosing range and administering the combination as second-line therapy. As previously discussed, dosing range adjustment is routine and conventional where both Yoo and Kozuch teach a similar range for the therapeutic agents . Yoo teaches the use of 400 mg/m^2 of racemic leucovorin (p. 1658, abs), the same dose as instantly claimed. Therefore there is a reasonable expectation of success at arriving at the instantly claimed limitations of sequential administration on day 1 of a 2-week cycle based on the teachings of Kozuch and the racemic leucovorin at a dose of 400 mg/m2 where the treatment is refractory to gemcitabine based on Yoo and Tsai. It remains *prima facie* obvious to incorporate the instant limitations based on the combined teachings of Yoo, Tsai,Hoskins and Kozuch.

Applicant's invention, according to **claims 8, 9, 15 and 16**, limits claims 2 and 3; and requires administration of MM-398 over a 90 minute period, leucovorin over a 30 minute period and 5-FU over a 46 hour period.

Kozuch teaches teaches administering irinotecan over 90 minutes and leucovorin over 30 minutes (p. 490, Fig. 1). Kozuch further teaches 5-FU to be administered with

the dosages divided in parts and administered over 8 hours on day one and over 8 hours on day two; broadly and reasonably interpreted to cover a 48 hour period overall.

A skilled artisan would reasonably arrive at the instantly claimed limitations of administering the therapeutic agents of the time periods having a reasonable expectation of success in treating pancreatic cancer based on the teaching of Kozuch. Kozuch explicitly teaches the therapeutic agents instantly claimed and the time periods of administration; which encompasses 5-FU over a two day period that can occur in a 46 hour period. Furthermore, Yoo explicitly teaches administration of 5-FU over a 46 hour period. Kozuch and Yoo provide sufficient guidance to arrive at the instant limitations therefore the invention as a whole remains *prima facie* obvious based on the combined teaching of Yoo, Tsai, Hoskins and Kozuch.

Applicant's invention, according to **claims 18, 22 and 26**, is directed to a method of treating metastatic adenocarcinoma of the pancreas in a human patient comprising intravenous administration of 60 mg/m^2 of MM-398 over 90 minutes, followed by 400 mg/m^2 of leucovorin over 30 minutes, followed by 5-FU over a 46 hours beginning day one of a 2-week cycle; wherein the patient has been previously treated with gemcitabine and the patient has had an ANC of less than 1000 cells/mm^3 after previous administration of MM-398.

Yoo provides teaching and sufficient guidance for arriving at treating patients with metastatic adenocarcinoma of the pancreas refractory to gemcitabine-based therapy

with the intravenous combination of irinotecan, leucovorin and 5-FU at the instantly claimed dosages and time period of administration for 5-FU.

Tsai provides teaching as to the use of MM-398 over the free form of irinotecan being more efficacious for treatment, having proven to be beneficial in pancreatic cancer.

Hoskins teaches how the effects of irinotecan-induced toxicity causing neutropenia is dose related and demonstrates that low dose, less than 125 mg/m^2, does not cause the toxic effects. This teaching is important to patients with reduced neutrophils who are at mild risk for infection, because it serves as guidance to the possible of effects of administering given amounts of MM-398.

Likewise, Kozuch provides sufficient guidance for arriving at treating patients with metastatic adenocarcinoma of the pancreas refractory to gemcitabine-based therapy with the intravenous combination of irinotecan, leucovorin and 5-FU at the instantly claimed dosages and time periods of administration.

When the teachings of Yoo, Tsai, Hoskins and Kozuch are combined, one of ordinary skill is given sufficient guidance is approaching a treatment regimen for patients with pancreatic cancer refractory to gemcitabine therapy. Yoo provides the basis for combining the therapeutic agents, where Tsai leads one to alternatively use MM-398 over the free form. Hoskins gives guidance to managing neutropenia in given patient populations based on the dosing control of irinotecan and Kozuch provides guidance to the method and time period of administration. There is a reasonable expectation of success at arriving at the instant claim based on these combined

teachings. Therefore, at the time of invention, it was *prima facie* obvious to arrive at the instant claim based on the combined teaching of Yoo, Tsai, Hoskins and Kozuch.

Applicant's invention, according to **claims 19 and 23**, limits claim 18 and requires 5-FU to be administered at 1800 mg/m^2.

As noted above, patients with an ANC less than 1000 cells/mm^3 carry a moderate risk of infection and thus a low dose of irinotecan is preferable to not induce neutropenia to further increase the risk of infection. A *prima facie* case of obviousness is established for administering the combination to patients who have moderate risk for infection with the instant range of neutrophil count, see *supra*. Furthermore, Yoo teaches administration of 5-FU of 2000 mg/m^2 which is well within the range of the instantly claimed amount for treatment to routinely optimize.

One of ordinary skill in the art would readily modify the dosing, as expressed *supra*, routinely and conventionally to optimize treatment for patients. As previously mentioned, the combination of agents has been used for treating pancreatic cancer refractory to gemcitabine therapy at different dosing, covering a wide scope in range. There is a reasonable expectation of success in selecting the instantly claimed dose for 5-FU based on the teaching of the prior art of Yoo, Kozuch, Tsai and Hoskins. The art clearly recognizes the benefit of the combination and furthermore the challenge of infection risk and toxicity of irinotecan. Therefore it remains *prima facie* obvious to incorporate the instant limitation based on the teaching of Yoo, Tsai, Hoskins and Kozuch .

Applicant's invention, according to **claim 20**, limits claim 19 and requires further administration comprising 50 mg/m^2 of MM-398 in a second or subsequent cycle in combination with leucovorin and 5-FU.

Kozuch teaches multiple cycles of treatment of the G-FLIP combination ranging from 1 to 25 cycles per patient; the median number of cycles per patient was 5 (p. 490, col. 2, para. 2). Kozuch further teaches that irinotecan throughout the cycles of treatment were administered at 60 mg/m^2; where the initial regimen was at 80 mg/m^2.

One of ordinary skill would arrive at the instant claim based on the combined teaching of Kozuch, Yoo, Tsai and Hoskins having a reasonable expectation of success. Kozuch demonstrates subsequent cycles of administration where a decrease in irinotecan is administered. Kozuch teaches a dose within the claimed range, where modifying dosing is routine and conventional in the art, as explained *supra*. Optimizing dose to avoid or in response to toxic effects is routine in the art. Therefore the instant limitation is well within reason as a routine modification of dosing. It remains prima facie obvious to modify the dose in subsequent cycles of treatment based on the teachings of Yoo, Tsai, Hoskins and Kozuch.

Applicant's invention, according to **claim 21**, limits claim 18 and requires further administration comprising 80 mg/m^2 of MM-398 in a second or subsequent cycle wherein the patient has an ANC of 1500 cells/mm^3 prior to administration.

A *prima facie* case of obviousness has been established for the instant combination where MM-398 is administered at 80 mg/m^2. While the instant claim increases the dose in subsequent cycles, it is noted that a patient with an ANC of 1500 cells/mm^3 has high neutrophil count with a low risk for infection. Hoskins teaches that the effects of irinotecan-induced hematological toxicity are affected by dose. One of ordinary skill would recognize that a patient with a higher neutrophil count would have the leeway to increase irinotecan dosing to 80 mg/m^2, which is still a relatively low dose according to the teaching of Hoskins. There is a reasonable expectation of success in increasing the dose, well within the low dose range, to the instantly claimed dose for subsequent cycles in treating pancreatic cancer. The invention as a whole remains *prima facie* obvious in light of the instant limitations based on the teaching of Yoo, Tsai, Hoskins and Kozuch.

Applicant's invention, according to **claim 24**, limits claim 23 and requires administration of MM-398, leucovorin and 5-FU in multiple cycles to treat the metastatic adenocarcinoma of the pancreas.

As previously expressed, Kozuch teaches multiple cycles of treatment for pancreatic cancer with irinotecan, leucovorin and 5-FU (p. 490, col. 2, para. 2).

Tsai teaches the use of MM-398 over the free form of irinotecan.

One of ordinary skill would arrive at the instant limitations based on the teachings of Kozuch teaching multiple cycles and Tsai utilizing MM-398. The instant claim remains *prima facie* obvious.

Applicant's invention, according to **claim 25**, limits claim 24 and requires further administration comprising 80 mg/m^2 of MM-398 in a second or subsequent cycle.

Kozuch teaches a regimen comprising 80 mg/m^2 of irinotecan in multiple cycles for treating pancreatic cancer.

Tsai teaches MM-398 as a more efficacious alternative to the free form of irinotecan, including in treatment of pancreatic cancer.

The art of Kozuch and Tsai, when combined, explicitly teach the instantly claimed limitations. One of ordinary skill would have a reasonable expectation of success at treating pancreatic cancer with multiple cycles utilizing the dosing as taught by Kozuch and the MM-398 as taught by Tsai. The invention as a whole remains *prima facie* obvious over Yoo, Tsai, Hoskins and Kozuch.

Applicant's invention, according to **claim 28**, is directed to a method of treating metastatic adenocarcinoma of the pancreas in a human patient who is homozygous for the UGT1A1*28 allele, comprising intravenous administration of 60 mg/m^2 of MM-398 in combination with 200 mg/m^2 of the (l)-form of leucovorin (or 400 mg/m^2 of racemic leucovorin) and 5-FU.

Yoo provides teaching and sufficient guidance for arriving at treating patients with metastatic adenocarcinoma of the pancreas with the intravenous combination of irinotecan, leucovorin and 5-FU at the instantly claimed dosages of administration.

Tsai provides teaching as to the use of MM-398 over the free form of irinotecan being more efficacious for treatment, having proven to be beneficial in pancreatic cancer.

Hoskins teaches how the effects of irinotecan-induced toxicity causing neutropenia is dose related particularly for patients who are homozygous for the UGT1A1*28 allele, demonstrating that low dose, less than 125 mg/m^2, does not cause the toxic effects of a high dose. This teaching serves as guidance to the possible of effects of administering given amounts of MM-398.

Kozuch provides teaching and sufficient guidance for arriving at treating patients with metastatic adenocarcinoma of the pancreas with the intravenous combination of irinotecan, leucovorin and 5-FU at the instantly claimed dosages of administration.

When the teachings of Yoo, Tsai, Hoskins and Kozuch are combined, one of ordinary skill is given sufficient guidance for a treatment regimen for patients with metastatic pancreatic cancer. Yoo and Kozuch provide the basis for combining the therapeutic agents, where Tsai leads one to alternatively use MM-398 over the free form. Hoskins gives guidance to managing neutropenia in the patient population who are homozygous for the UGT1A1*28 allele based on the dosing control of irinotecan. There is a reasonable expectation of success at arriving at the instant claim based on these combined teachings. Therefore, at the time of invention, it was *prima facie* obvious to arrive at the instant claim based on the combined teaching of Yoo, Tsai, Hoskins and Kozuch.

Applicant's invention, according to **claim 29**, limits claim 28 and requires 5-FU to be administered at a dose of 2400 mg/m^2.

A *prima facie* case of obviousness is established for applying the method of treatment to patients homozygous for UGT1A1*28 allele, where a low dose of irinotecan would reduce the risk of toxicity. While Yoo and Kozuch teaches a dose of 2000 mg/m^2 of 5-FU; Yoo, Kozuch, Tsai nor Hoskins provide an explicit dose of 5-FU at 2400 mg/m^2.

One of ordinary skill in the art would gleam from the prior art the overall combination of therapeutic agents and routinely optimize dosing for treatment. Yoo provides the same therapeutic agents within the claimed range of dosing for treating pancreatic cancer. Yoo explicitly teaches a combination (mFOLFIRI.3) that comprises, with total dosing, irinotecan (70 mg/m2), leucovorin (400 mg/m2), and 5-FU (2000 mg/m2) (p. 1659, col. 2, para. 3). Yoo further teaches that another dose of 5-FU can be administered on a second day. Yoo provides teaching that the range of 5-FU administered in a similar dose as instantly claimed. It would be routine and conventional for a skilled artisan to optimize dosing within a similar range for treating patients. One of ordinary skill in the art would have a reasonable expectation of success at applying the instant limitation of dosing towards treating pancreatic cancer refractory to gemcitabine therapy. Therefore the instant claim is prima facie obvious over Yoo, Tsai, Hoskins and Kozuch.

Applicant's invention, according to **claim 30**, limits claim 29 and requires MM-398 is increased to 80 mg/m^2 in a second or subsequent cycle.

Kozuch teaches a regimen comprising 80 mg/m^2 of irinotecan in multiple cycles for treating pancreatic cancer.

Tsai teaches MM-398 as a more efficacious alternative to the free form of irinotecan, including in treatment of pancreatic cancer.

The art of Kozuch and Tsai, when combined, explicitly teach the instantly claimed limitations. One of ordinary skill would have a reasonable expectation of success at treating pancreatic cancer with multiple cycles utilizing the dosing as taught by Kozuch and the MM-398 as taught by Tsai. The invention as a whole remains *prima facie* obvious over Yoo, Tsai, Hoskins and Kozuch.

Claim 27 is rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Yoo *et al.* (*British Journal of Cancer*, 2009, 101, pp. 1658-1663; cited in IDS)and Tsai *et al.* (*Journal of Gastrointestinal Oncology*, 2011, Vol. 2, No. 3, pp. 185-194; cited in IDS) in view of Hoskins *et al.* (*J. Natl. Cancer Inst.*, 2007, Vol. 99, Iss. 17, pp. 1290-1295) and Kozuch *et al.* (*The Oncologist*, 2001, 6, pp. 488-495; cited in IDS) as applied to claim 18, in further view of Munstedt *et al.* (*British Journal of Cancer*, 1999, 79(3/4) pp. 637-639).

Applicant's invention, according to **claim 27**, limits claim 18 and requires pre-medicating the patient with dexamethasone and a 5-HT3 antagonist prior to MM-398 infusion.

A *prima facie* case of obviousness is established for the method of treatment for pancreatic cancer with the claimed therapeutic combination. However, Yoo, Tsai, Hoskins and Kozuch fail to explicitly teach pre-medicating a patient with dexamethasone and 5-HT3 antagonists.

Munstedt teaches the combination of dexamethasone and 5-HT3 antagonists as prophylaxis of acute chemotherapy-induced nausea and vomiting. Munstedt teaches that the combination of dexamethasone at 20 mg and 5-HT3 antagonists is the "gold-standard dose for antiemetic prophylaxis" (abs).

One of ordinary skill in the art would arrive at the instant limitation based on the art of Munstedt. Munstedt explicitly teaches the benefit of prophylactically administering dexamethasone in combination with 5-HT3 antagonists for preventing acute nausea and vomiting. There is a reasonable expectation of success in administering the instantly claimed combination in treating pancreatic cancer patients to prevent nausea and vomiting with the administration of the claimed chemotherapeutic combination. Therefore at the time of invention it was *prima facie* obvious to pre-medicate the patient with the combination of dexamethasone and 5-HT3 antagonists prior to administering the claimed chemotherapeutic combination, based on the combined teaching of Yoo, Tsai, Hoskins, Kozuch and Munstedt.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the

unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the claims at issue are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the reference application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(1) - 706.02(l)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/forms/. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or

PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to http://www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

Claims 1-30 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-12, 14, 15 and 20-32 of copending Application No. 14/812,950. Although the claims at issue are not identical, they are not patentably distinct from each other because both applications set out to claim a method of treating pancreatic cancer refractory to gemcitabine therapy through intravenous administration of irinotecan as the MM-398 liposome, leucovorin as the (l)-form or racemic form and 5-fluorouracil. Both applications claim the combination in either a similar or identical dose for the therapeutic agents where the combination is administered in a two week cycle. The claims of the copending applications are obvious variants of each other.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TORI M. STRONG whose telephone number is

(571)272-6333. The examiner can normally be reached on Monday-Friday 8am-5pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Lundgren can be reached on 571-272-5541. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/TORI M STRONG/
Examiner, Art Unit 1629

/Kortney L. Klinkel/
Primary Examiner, Art Unit 1611

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Eliel Bayever, et al.

Application No.: 14/844,500 | Confirmation No.: 1041

Filed: September 3, 2015 | Art Unit: 1629

For: METHODS FOR TREATING PANCREATIC CANCER USING COMBINATION THERAPIES COMPRISING LIPOSOMAL IRINOTECAN | Examiner: Tori Strong

Mail Stop Amendments
Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT IN RESPONSE TO NON-FINAL OFFICE ACTION DATED DECEMBER 16, 2015

Dear Sir:

In response to the Non-Final Office action, dated December 16, 2015 ("Office Action"), please amend the application as follows and consider the remarks set forth below.

Amendments to the Claims are reflected in the listing of claims which begin on page 2 of this paper.

Remarks/Arguments begin on page 10 of this paper.

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions and listings of claims in the application. Please amend the claims as follows, and add new claims 31-41, as provided below.

Listing of Claims

1. (Currently Amended) A method of treating metastatic adenocarcinoma of the pancreas in a human patient in need thereof, the patient being homozygous for the UGT1A1*28 allele, the method comprising intravenously administering to the patient once in a two week treatment cycle 60 mg/m^2 of the antineoplastic agent ~~irinotecan as a~~ MM-398 ~~liposome~~ liposomal irinotecan in combination with 200 mg/m^2 of the (l)-form of leucovorin or 400 mg/m^2 of the (l+d) racemic form of leucovorin, and 2400 mg/m^2 of the antineoplastic agent 5-fluorouracil to treat the metastatic adenocarcinoma of the pancreas in the patient, wherein the patient has previously been treated with gemcitabine and no other antineoplastic agent is administered to the human patient in the two week treatment cycle for the treatment of the metastatic adenocarcinoma of the pancreas ~~the patient is known to meet at least one criterion selected from the group consisting of:~~

~~a. the patient has had an absolute neutrophil count (ANC) of less than 1000 cells/mm^3 after a previous intravenous administration of the MM-398 liposome to the patient for treatment of the metastatic adenocarcinoma of the pancreas, and~~

~~b. the patient is homozygous for the UGT1A1*28 allele~~.

2. (Cancelled)

3. (Cancelled)

4. (Currently Amended) The method of claim 1**[[2]]**, wherein beginning on day 1 of the two week treatment cycle, the MM-398 ~~liposome~~ liposomal irinotecan, leucovorin and 5-fluorouracil are administered sequentially to the patient ~~beginning on day 1 of a 2-week cycle~~.

5. (Original) The method of claim 4, wherein 400 mg/m^2 of the (l+d) racemic form of leucovorin is administered.

6. (Currently Amended) The method of claim 5, wherein ~~the~~ leucovorin is administered to the patient prior to the 5-fluorouracil.

7. (Currently Amended) The method of claim 6, wherein ~~the~~ MM-398 ~~liposome~~ liposomal irinotecan is administered to the patient prior to ~~the~~ leucovorin.

8. (Currently Amended) The method of claim [[2]]1, wherein ~~the~~ MM-398 ~~liposome~~ liposomal irinotecan is administered to the patient over 90 minutes.

9. (Currently Amended) The method of 8, wherein ~~the~~ leucovorin is administered over 30 minutes and ~~the~~ 5-fluorouracil is administered over 46 hours.

10. (Currently Amended) The method of claim [[2]]1, wherein the patient has metastatic adenocarcinoma of the pancreas that has progressed on gemcitabine-based therapy prior to the administration of the MM-398 ~~liposome~~ liposomal irinotecan.

11. (Currently Amended) The method of claim 1**[[**3**]]**, wherein beginning on day 1 of the two week treatment cycle, the MM-398 **[[**,]] liposomal irinotecan, 200 mg/m^2 of the (l) form of the leucovorin and the 5-fluorouracil are administered sequentially to the patient ~~beginning on day 1 of a 2-week cycle~~.

12. (Cancelled)

13. (Currently Amended) The method of claim [[12]]11, wherein ~~the~~ leucovorin is administered to the patient prior to the 5-flurouracil.

14. (Currently Amended) The method of claim 13, wherein ~~the~~ MM-398 liposomal

irinotecan is administered to the patient prior to ~~the~~ leucovorin.

15. (Cancelled)

16. (Currently Amended) The method of claim [[15]] 14, wherein ~~the~~ leucovorin is administered over 30 minutes and ~~the~~ 5-fluorouracil is administered over 46 hours.

17. (Currently Amended) The method of claim 5[[3]], wherein the patient has metastatic adenocarcinoma of the pancreas that has progressed on gemcitabine-based therapy prior to the administration of the MM-398 ~~liposome~~ liposomal irinotecan.

18. (Currently Amended) A method of treating metastatic adenocarcinoma of the pancreas in a human patient in need thereof who has previously been treated with gemcitabine, the patient being homozygous for the UGT1A1*28 allele, the method comprising: intravenously administering to the patient an antineoplastic therapy once every two weeks, the antineoplastic therapy consisting of intravenously administering either 50 mg/m^2 or 60 mg/m^2 of ~~irinotecan as a~~ MM-398 ~~liposome~~ liposomal irinotecan over 90 minutes, followed by 200 mg/m^2 of the (l) form of leucovorin ~~400 mg/m^2 of the (l+d) racemic form of leucovorin~~ over 30 minutes, followed by 2400 mg/m^2 of 5-fluorouracil over 46 hours beginning on day 1 of a two ~~2~~-week treatment cycle ~~to treat the metastatic adenocarcinoma of the pancreas in a patient having had an absolute neutrophil count (ANC) of less than 1000 cells/mm^3 and has received a previous intravenous administration of the MM-398 liposome to the patient for the metastatic adenocarcinoma of the pancreas~~.

19. (Cancelled)

20. (Cancelled)

21. (Cancelled)

22. (Currently Amended) The method of claim 18, wherein the patient has metastatic adenocarcinoma of the pancreas that has progressed on gemcitabine-based therapy prior to administration of ~~the~~ MM-398 ~~liposome~~ liposomal irinotecan.

23. (Cancelled)

24. (Cancelled)

25. (Cancelled)

26. (Cancelled)

27. (Currently Amended) The method of claim 18, further comprising premedicating the patient with ~~dexamethasone and a 5-HT3 antagonist~~ an anti-emetic prior to ~~a MM-398 liposome infusion~~ initiating each antineoplastic therapy.

28. (Currently Amended) A method of treating metastatic adenocarcinoma of the pancreas with disease progression after prior gemcitabine or gemcitabine containing therapy in a human patient in need thereof who is homozygous for the UGT1A1*28 allele, the method consisting of once every two weeks: ~~comprising~~ premedicating with an anti-emetic followed by intravenously administering to the patient a single infusion of 60 mg/m^2 of ~~irinotecan as a~~ MM-398 ~~liposome~~ liposomal irinotecan in combination with a single infusion of 200 mg/m^2 of the (l)-form of leucovorin ~~or 400 mg/m^2 of the (l+d) racemic form of leucovorin~~, and a single infusion of 2400 mg/m^2 of 5-fluorouracil to treat the metastatic adenocarcinoma of the pancreas in the human patient.

29. (Currently Amended) The method of claim 28, wherein the irinotecan is administered over 90 minutes, followed by administering the leucovorin over 30 minutes, followed by administration of the 5-fluorouracil ~~is administered~~ over 46 hours over a total of about

48 hours.~~at a dose of 2400 mg/m^2~~.

30. (Cancelled)

31. (New) The method of claim 1, further comprising one or more subsequent treatment cycles that include decreasing the dose of the MM-398 liposomal irinotecan, wherein the dose of the MM-398 liposomal irinotecan is reduced from 60 mg/m^2 to 50 mg/m^2 in a subsequent two week treatment cycle to a patient who experienced a Grade 3 or Grade 4 adverse event after administration of the MM-398 liposomal irinotecan in a previous two week treatment cycle.

32. (New) The method of claim 1, further comprising administering an anti-emetic to the patient prior to initiating the two week treatment cycle.

33. (New) The method of claim 1, further comprising administering to the patient at least three consecutive two week treatment cycles.

34. (New) The method of claim 33, further comprising increasing the dose of the MM-398 liposomal irinotecan from 60 mg/m^2 up to 80 mg/m^2 in at least one of the second or third consecutive two week treatment cycles.

35. (New) The method of claim 18, wherein the 200 mg/m^2 of the (l) form of leucovorin is administered as 400 mg/m^2 of the (l+d) racemic form of leucovorin.

36. (New) The method of claim 18, further comprising administering one or more subsequent antineoplastic therapies once every two weeks, wherein at least one of the one or more subsequent antineoplastic therapies comprises decreasing the dose of MM-398 liposomal irinotecan from 60 mg/m^2 to 50 mg/m^2 in a subsequent antineoplastic therapy to a patient who experienced a Grade 3 or Grade 4 adverse event after administration of MM-398 liposomal irinotecan in a previous two-week antineoplastic therapy.

37. (New) The method of claim 36, further comprising administering to the patient at least

three consecutive antineoplastic therapies once every two weeks to the patient.

38. (New) The method of claim 22, further comprising

a. administering an anti-emetic to the patient prior to initiating each antineoplastic therapy;
b. administering a first antineoplastic therapy to the patient, wherein the antineoplastic therapy consists of intravenously administering 50 mg/m^2 of MM-398 liposomal irinotecan;
c. administering the 200 mg/m^2 of the (l) form of leucovorin as 400 mg/m^2 of the (l+d) racemic form of leucovorin during each antineoplastic therapy; and
d. administering at least two subsequent antineoplastic therapies to the patient once every two weeks, wherein each subsequent antineoplastic therapy optionally includes decreasing the dose of MM-398 liposomal irinotecan from 60 mg/m^2 to 50 mg/m^2 in a subsequent antineoplastic therapy.

39. (New) The method of claim 28, wherein the 200 mg/m^2 of the (l) form of leucovorin is administered as 400 mg/m^2 of the (l+d) racemic form of leucovorin.

40. (New) A method of treating metastatic adenocarcinoma of the pancreas in a human patient in need thereof who has previously been treated with gemcitabine, the patient being homozygous for the UGT1A1*28 allele, the method comprising intravenously administering to the patient a treatment cycle of an antineoplastic therapy once every two weeks, the antineoplastic therapy comprising:

a. a first two-week treatment cycle consisting of intravenously administering to the patient: 60 mg/m^2 of MM-398 liposomal irinotecan over a 90 minute infusion, followed by 200 mg/m^2 of the (l)-form of leucovorin over 30 minutes, followed by 2400 mg/m^2 of 5-fluorouracil over 46 hours, the antineoplastic therapy being administered over a total of about 48 hours beginning on day one of the first two-week treatment cycle;
b. a second two-week treatment cycle consisting of intravenously administering to

the patient starting after the first two-week treatment cycle:

i. either 60 mg/m^2 or 80 mg/m^2 of MM-398 liposomal irinotecan over a 90 minute infusion if the patient has not experienced a Grade 3 or Grade 4 adverse event after administration of the MM-398 liposomal irinotecan in the first two-week treatment cycle, or 50 mg/m^2 of MM-398 liposomal irinotecan over a 90 minute infusion if the patient has experienced a Grade 3 or Grade 4 adverse event after administration of the MM-398 liposomal irinotecan in the first two-week treatment cycle; followed by

ii. 200 mg/m^2 of the (l)-form of leucovorin over 30 minutes, followed by 2400 mg/m^2 of 5-fluorouracil over 46 hours, the antineoplastic therapy being administered over a total of about 48 hours beginning on day one of the second two-week treatment cycle; and

c. a third two-week treatment cycle consisting of intravenously administering to the patient starting after the second two-week treatment cycle: 50 mg/m^2, 60 mg/m^2 or 80 mg/m^2 of MM-398 liposomal irinotecan over a 90 minute infusion, followed by 200 mg/m^2 of the (l)-form of leucovorin over 30 minutes, followed by 2400 mg/m^2 of 5-fluorouracil over 46 hours, the antineoplastic therapy being administered over a total of about 48 hours beginning on day one of the third two-week treatment cycle,

to treat the metastatic adenocarcinoma of the pancreas in the patient.

41. (New) The method of claim 40, wherein the 200 mg/m^2 of the (l) form of leucovorin is administered as 400 mg/m^2 of the (l+d) racemic form of leucovorin, and the method further comprises administering an anti-emetic to the patient prior to each two-week treatment cycle; and the third two-week treatment cycle consists of intravenously administering to the patient starting after the second two-week treatment cycle, either 60 mg/m^2 or 80 mg/m^2 of MM-398 liposomal irinotecan over a 90 minute infusion if the patient has not experienced a Grade 3 or Grade 4 adverse event after administration of the MM-398 liposomal irinotecan in the first two-week treatment cycle, or 50 mg/m^2 of MM-398 liposomal irinotecan over a 90 minute

infusion if the patient has experienced a Grade 3 or Grade 4 adverse event after administration of the MM-398 liposomal irinotecan in the first two-week treatment cycle.

REMARKS

Claim Status

Currently, claims 1, 4-11, 13, 14, 16-18, 22, 27-29 and 31-41 are pending in this application. Claims 2, 3, 12, 15, 19-21, 23-26 and 30 have been cancelled without prejudice or disclaimer. Claims 1, 4, 6-11, 13, 14, 16-18, 22 and 27-29 have been amended. New claims 31-41 are added. The claim amendments and new claims are supported in the specification as filed; no new matter is added. With the claim amendments, a total of 29 claims with 4 independent claims remain pending.

The amendments to and/or cancellation of the claims are being made for the purpose of expediting prosecution and to place the application in better condition for appeal, should an appeal be necessary, and are made without prejudice or waiver.

This listing of claims will replace all prior versions and listings of claims in the application. Applicant reserves the right to present the original claims in this or a continuing application.

Claim Rejections – 35 USC § 112

The Examiner has rejected claims 1-27 as being indefinite. The Examiner asserts that the phrase "…after previous intravenous administration of the MM-398 liposome" in claims 1, 3 and 18 is indefinite because the claims include elements not actually disclosed, thereby rendering the scope of the claims unascertainable. Furthermore, the Examiner asserts that since claims 2, 4-16 and 19-27 depend on claims 1 and 18, they are therefore indefinite. Claims 1 and 18 have been amended and claim 3 has been canceled. Applicants request reconsideration and withdrawal of this rejection.

Claim Rejections – 35 USC § 103

The Examiner has rejected claims 1-3 as being unpatentable over Yoo *et al.*, *British Journal of Cancer*, 2009, 101, pp. 1658-1663 ("Yoo") and Tsai *et al., Journal of Gastrointestinal Oncology*, 2011, vol. 2, no. 3, pp. 185-194 ("Tsai"), in view of Hoskins *et al., J. Nat'l Cancer Inst.,* 2007, vol. 99, Iss. 17, pp. 1290-1295 ("Hoskins"). The Examiner acknowledges "Yoo fails to explicitly teach irinotecan as a liposome and fails to note whether or not the subject receiving

the drug combination has had an absolute neutrophil count of less than 100 cells/mm^3" (Office Action at page 5), but asserts that "Tsai provides teaching that one of ordinary skill in the art would substitute the liposomal form of irinotecan and further combine the instantly claimed therapeutic agents" (Office Action at page 6) and that "Hoskins teaches the effect of irinotecan on patients with UTG1A1*28 genotype" (Office Action on page 6). The Examiner asserts that "[b]ased on the combined teaching of Yoo, Tsai and Hoskins, a skilled artisan would arrive at the instantly claimed invention having a reasonable expectation of success…" (Office Action at page 7).

Applicants respectfully request reconsideration and withdrawal of this rejection. Claims 2 and 3 have been cancelled, rendering the rejection moot. Claim 1 has been amended. As amended, claim 1 is now directed to:

> A method of treating metastatic adenocarcinoma of the pancreas in a human patient in need thereof, the patient being homozygous for the UGT1A1*28 allele, the method comprising intravenously administering to the patient once in a two week treatment cycle 60 mg/m^2 of the antineoplastic agent MM-398 liposomal irinotecan in combination with 200 mg/m^2 of the (l)-form of leucovorin or 400 mg/m^2 of the (l+d) racemic form of leucovorin, and 2400 mg/m^2 of the antineoplastic agent 5-fluorouracil to treat the metastatic adenocarcinoma of the pancreas in the patient, wherein the patient has previously been treated with gemcitabine and no other antineoplastic agent is administered to the human patient in the two week treatment cycle for the treatment of the metastatic adenocarcinoma of the pancreas.

The Examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness with respect to independent claim 1. If the Examiner does not produce a *prima facie* case, the applicant is under no obligation to submit secondary evidence to show nonobviousness. To reach a proper determination under 35 U.S.C. 103, the Examiner must step backward in time and into the shoes worn by the hypothetical "person of ordinary skill in the art" when the invention was unknown and just before it was made. In view of all factual information, the Examiner must then make a determination whether the claimed invention "as a whole" would have been obvious at that time to that person. Knowledge of applicant's disclosure must be put

aside in reaching this determination, yet kept in mind in order to determine the "differences," conduct the search and evaluate the "subject matter as a whole" of the invention. The tendency to resort to "hindsight" based upon applicant's disclosure is often difficult to avoid due to the very nature of the examination process. However, impermissible hindsight must be avoided and the legal conclusion must be reached on the basis of the facts gleaned from the prior art. MPEP 2142.

The Examiner has rejected claims 4-26 and 28-30 as being unpatentable over Yoo and Tsai in view of Hoskins in further view of Kozuch *et al.*, *The Oncologist,* 2001, 6, pp. 488-495 ("Kozuch"). The Examiner recognizes that the teachings of Yoo, Tsai and Hoskins "do not explicitly teach sequential administration of the chemotherapeutic regimen" (Office Action at page 10), but asserts that a skilled artisan would learn from Kozuch "to arrive at the instant limitations of sequential administration in a 2-week cycle, administering racemic leucovorin in the similar dosing range and administering the combination as second-line therapy" (Office Action at page 11). In particular, the Examiner has rejected claims 4-7, 10-14 and 17 over Yoo, Tsai, Hoskins and Kozuch (Office Action at pages 10-11), claims 8, 9, 15 and 16 over Kozuch in combination with Yoo (Office Action at pages 11-12), claims 18, 22 and 26 over Yoo, Tsai, Hoskins and Kozuch (Office Action at pages 12-14), claims 19 and 23 over Yoo, Kozuch, Tsai and Hoskins (Office Action at pages 14-15), and claim 21 over Hoskins (Office Action at pages 15-16), claim 24 over Kozuch, and Tsai (Office Action at pages 16), claim 25 over Kozuch and Tsai (Office Action at page 17), claim 28 over Yoo, Tsai, Hoskins and Kozuch (Office Action at pages 17-18), claim 29 over Yoo and Kozuch, and claim 30 over Kozuch and Tsai (Office Action at pages 19-20). Applicants respectfully request reconsideration and withdrawal of this rejection.

Claims 12, 15, 19-21, 23-26, and 30 have been cancelled, rendering these rejections moot. Applicants request reconsideration and withdrawal of these rejections.

Claims 4-11, 13-14, and 16-17 all depend from independent claim 1. For at least the reasons stated above, the Office Action does not provide a prima facie basis for the obviousness rejection against claim 1. Applicants request reconsideration and withdrawal of these rejections.

As amended, independent claim 18 recites:

A method of treating metastatic adenocarcinoma of the pancreas in a human

patient in need thereof who has previously been treated with gemcitabine, the patient being homozygous for the UGT1A1*28 allele, the method comprising: intravenously administering to the patient an antineoplastic therapy once every two weeks, the antineoplastic therapy consisting of intravenously administering either 50 mg/m^2 or 60 mg/m^2 of MM-398 liposomal irinotecan over 90 minutes, followed by 200 mg/m^2 of the (l) form of leucovorin over 30 minutes, followed by 2400 mg/m^2 of 5-fluorouracil over 46 hours beginning on day 1 of a two week treatment cycle.

Claim 22 depends from amended independent claim 18. The Examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness with respect to independent claim 18. If the Examiner does not produce a *prima facie* case, the applicant is under no obligation to submit secondary evidence to show nonobviousness. Applicants request reconsideration and withdrawal of these rejections.

As amended, independent claim 28 recites:

A method of treating metastatic adenocarcinoma of the pancreas with disease progression after prior gemcitabine or gemcitabine containing therapy in a human patient in need thereof who is homozygous for the UGT1A1*28 allele, the method consisting of once every two weeks premedicating with an anti-emetic followed by intravenously administering to the patient a single infusion of 60 mg/m^2 of MM-398 liposomal irinotecan in combination with a single infusion of 200 mg/m^2 of the (l)-form of leucovorin, and a single infusion of 2400 mg/m^2 of 5-fluorouracil to treat the metastatic adenocarcinoma of the pancreas in the human patient.

Claim 29 depends from amended independent claim 28. The Examiner bears the initial burden of factually supporting any prima facie conclusion of obviousness with respect to independent claim 28. If the Examiner does not produce a prima facie case, the applicant is under no obligation to submit secondary evidence to show non-obviousness. Applicants request reconsideration and withdrawal of these rejections.

The Examiner has rejected claim 27 as being unpatentable over Yoo and Tsai in view of Hoskins and Kozuch in further view of Munstedt *et al.*, *British Journal of Cancer,* 199, 79(3/4),

pp. 637-639 ("Munstedt"). The Examiner asserts that Munstedt explicitly teaches the benefit of prophylactically administering dexamethasone in combination with 5-HT3 antagonists for preventing acute nausea and vomiting (Office Action at page 21). Claim 27 depends from amended independent claim 28. For at least the reasons stated above, Applicants request reconsideration and withdrawal of this rejection.

Double Patenting

The Examiner has provisionally rejected claims 1-30 on the ground of the judicially created doctrine of non-statutory double patenting as allegedly being unpatentable over claims 1-12, 14, 15 and 20-32 of co-pending Application No. 14/812,950 (Office Action at pages 21-23).

A terminal disclaimer in compliance with 37 C.F.R. 1.321(c) is being electronically filed herewith, along with the required fee of $160.00, rendering moot the basis for this rejection. Applicant respectfully requests reconsideration and withdrawal of this rejection.

CONCLUSION

Applicant has provided a full and complete response to the Office Action. The application is in condition for allowance. Applicant respectfully requests entry of this paper, favorable reconsideration and withdrawal of the rejections of the application, and prompt issuance of a Notice of Allowance.

Applicant believes that no fees are required for the filing of this Response. However, if there are any additional charges or credits in direct relation to this filing please charge them to Deposit Account No.: 503145, referencing Attorney Docket No.: 239669-375514.

Respectfully submitted,

HONIGMAN MILLER SCHWARTZ AND COHN LLP

Dated: February 25, 2016

/Noel E. Day/

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EXAMINER
STRONG, TORI

ART UNIT	PAPER NUMBER
1629	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 14/851,111	Applicant(s) BAYEVER ET AL.	
	Examiner TORI M. STRONG	Art Unit 1629	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 November 2015*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *1-20* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-20* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☒ The drawing(s) filed on *25 November 2015* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

4) ☐ Other: _____.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

The present application is being examined under the pre-AIA first to invent provisions.

Status of Claims

Claims 1-20 are pending in the instant application and are the subject of the Office Action below.

Information Disclosure Statement

The information disclosure statements (IDSs) submitted on 09/11/2015, 09/23/2015, 10/15/2015 and 01/11/2016 were filed on and after the mailing date of the application on September 11, 2015. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. Enclosed with this Office Action are return copies of Form PTO/SB/08B with the Examiner's initials and signature indicating those references that have been considered.

Claim Rejections - 35 USC § 103

The following is a quotation of pre-AIA 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under pre-AIA 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under pre-AIA 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of pre-AIA 35 U.S.C. 103(c) and potential pre-AIA 35 U.S.C. 102(e), (f) or (g) prior art under pre-AIA 35 U.S.C. 103(a).

Claims 1-5 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Kozuch *et al.* (*The Oncologist*, 2001, 6, pp. 488-495; cited in IDS) and Tsai *et al.* (*Journal of Gastrointestinal Oncology*, 2011, Vol. 2, No. 3, pp. 185-194; cited in IDS) in view of American Cancer Society (ACS) (http://www.cancer.org/cancer/pancreaticcancer/detailedguide/pancreatic-cancer-what-is-pancreatic-cancer).

Applicant's invention, according to **claim 1**, is directed to a method of treating an exocrine pancreatic cancer comprising administering 60-80 mg/m^2 of irinotecan in a liposome injection formulation having a total volume of 500 mL over about 90 minutes, in combination with a therapeutically effective amount of leucovorin and 5-fluorouracil (5-FU); where the irinotecan liposome injection formulation comprises irinotecan encapsulated within a liposome comprising phosphatidylcholine, cholesterol, and a polyethyleneglycol-derivatized phosphatidyl-ethanolamine, and the irinotecan liposome having a diameter of approximately 80-140 nm. It is important to note that the liposomal irinotecan formulation is also referred to as MM-398 (see specification, p.3, Summary, para.1).

Kozuch teaches a method of treating metastatic pancreatic cancer refractory to gemcitabine therapy through administration of a combination called G-FLIP which comprises irinotecan (80 mg/m^2), leucovorin and 5-FU (abs). Kozuch teaches adminsitration of irinotecan, referred to as CPT-11, over 90 minutes (p.490, Fig.1). Kozuch provides a similar composition that comprises irinotecan at 80 mg/m^2 and the

other therapeutic agents as instantly claimed for treating pancreatic cancer. Kozuch does not teach irinotecan in liposomal form.

Tsai teaches liposomal therapies for advanced pancreatic cancer to enhance drug delivery. Tsai teaches the liposomal irinotecan has superior efficacy over the free form (p.189, col.1, para.3) and further teaches liposomal irinotecan designated as MM-398 to have a partial response in pancreatic cancer patients (p.189, col.2, para.2). Tsai further teaches the liposomal irinotecan in combination with 5-FU/LV. Tsai provides teaching that one of ordinary skill in the art would substitute the liposomal form of irinotecan and further combine with the instantly claimed therapeutic agents.

The American Cancer Society (ACS) teaches and defines pancreatic cancer for the general public. The ACS teaches that exocrine tumors are the most common type of pancreatic cancer; where 95% are exocrine cell adenocarcinomas. Therefore treatment that is directed towards pancreatic cancer in general refers to the most common form of exocrine pancreatic cancer.

One of ordinary skill in the art would arrive at the instantly claimed invention having a reasonable expectation of success based on the combined teaching of Kozuch, Tsai and the ACS. Kozuch provides clear teaching of treating pancreatic cancer, of which the ACS discloses exocrine pancreatic cancer is the most common, with the drug combination of irinotecan at 80 mg/m^2 with leucovorin and 5-FU. A skilled artisan would readily gleam from Tsai to interchange irinotecan with the more efficacious MM-398 to combine with leucovorin and 5-FU. The combined art provides rationale for the dosing of irinotecan and the expressed combination with other

therapeutic agents for treating pancreatic cancer. Therefore at the time of invention, it was *prima facie* obvious to arrive at the instant claim based on the combined teaching of Kozuch, Tai and the ACS.

Applicant's invention, according to **claims 2-5**, limits claim 1 and requires the described liposomal formulation that is also known as MM-398 to have a dose of 60-80 mg/m2 of irinotecan and that treatment is refractory to gemcitabine therapy.

As expressed *supra*, a *prima facie* case of obviousness is established with the combined teaching of Kozuch, Tsai and the ACS. Kozuch provides teaching of arriving at the dose of irinotecan at 80 mg/m^2, which is within the instantly claimed scope for dosing. Kozuch also teaches treatment refractory to gemcitabine therapy. Tsai provides teaching of the liposomal formulation of irinotecan as MM-398; further teaching its superior benefits over the free form. The instantly claimed limitations fall within the scope of the prior art teaching and therefore as whole remains *prima facie* obvious.

Claims 6-20 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Kozuch *et al.* (*The Oncologist*, 2001, 6, pp. 488-495) and Tsai *et al.* (*Journal of Gastrointestinal Oncology*, 2011, Vol. 2, No. 3, pp. 185-194) in view of American Cancer Society (ACS) (http://www.cancer.org/cancer/pancreaticcancer/detailedguide/pancreatic-cancer-what-is-pancreatic-cancer), in further view of Yoo *et al.* (*British Journal of Cancer*, 2009, 101, pp. 1658-1663; cited in IDS).

Applicant's invention, according to **claims 6-9**, limits claims 1 and requires leucovorin (l) at 200 mg/m2 (or racemic at 400 mg/m2); 5-FU at 2400 mg/m2; sequential administration beginning on day 1 of a 2 week cycle.

A *prima facie* case of obviousness is established with the combined teaching of Kozuch, Tsai and the ACS for combining liposomal irinotecan with leucovorin and 5-FU. Kozuch teaches treatment of pancreatic cancer through sequential administration of the therapeutic agents where irinotecan, leucovorin and 5-FU is administered in the respective order (p.490, para.1) on day 1 and teaches administration is repeated every 2 weeks (p.488, abs), implicitly a 2-week cycle. However the combined art does not explicitly teach the instantly claimed dosing for leucovorin and 5-FU.

Yoo teaches a method of treating metastatic pancreatic cancer refractory to gemcitabine therapy (abs) through administration of a drug combination regimen called FOIFIRI.3 which comprises irinotecan (70 mg/m2), leucovorin (400 mg/m2) and 5-fluorouracil (2000 mg/m2) (p.1659, col.2, para.3). Yoo teaches administration of 5-FU over a 46 hour period with the entire regimen repeated every 2 weeks. Yoo provides teaching of a similar composition that comprises the same therapeutic agents in similar amounts as instantly claimed.

One of ordinary skill would arrive at the instant limitations having a reasonable expectation of success based on the combine teaching of Kozuch, Tsai, the ACS and Yoo. Kozuch teaches instantly claimed limitations of sequential administration in a 2 week cycle, where Yoo provides for similar dosing in the chemotherapeutic regimen. As

skilled artisan would gleam from Yoo, through routine and conventional means, to optimize the range of dosing for treatment; see MPEP 2144.05 (II) for guidance for optimization of ranges. Therefore, the invention as a whole is *prima facie* obvious with the incorporation of the instant limitations.

Applicant's invention, according to **claims 10-19**, is directed to a method of treating an exocrine pancreatic cancer comprising administering 60-80 mg/m2 of irinotecan in a liposome injection formulation having a total volume of 500 mL over about 90 minutes, in combination with leucovorin (l) at 200 mg/m2 (or racemic at 400 mg/m2) and 5-FU at 1800-2400 mg/m2; where claims 11-15, 18 and 19 disclose limitations that describe MM-398; where claims 16 and 17 require treatment refractory to gemcitabine treatment.

As expressed *supra*, a case of *prima facie* obviousness is established over the instantly claimed limitations. Kozuch and Yoo teaches the drug regimen in similar dosing and Tsai teaches substituting MM-398 for the free form of irinotecan. Kozuch teaches administration over 90 minutes and the ACS teaches that the most common pancreatic cancer is exocrine pancreatic cancer. As explained *supra*, one of ordinary skill would arrive at the instant claims having a reasonable expectation of success and therefore the invention as whole remains *prima facie* obvious.

Applicant's invention, according to **claim 20**, is directed to a method of treating an exocrine pancreatic cancer comprising administering 60-80 mg/m2 of irinotecan in a

liposome injection formulation having a total volume of 500 mL, in combination with leucovorin (l) at 200 mg/m2 (or racemic at 400 mg/m2) and 5-FU at 2400 mg/m2; where the claim discloses limitations that describe MM-398; where administration is sequential administration beginning on day 1 of a 2 week cycle.

As expressed *supra*, a case of *prima facie* obviousness is established over the instantly claimed limitations. Kozuch and Yoo teaches the drug regimen in similar dosing and Tsai teaches substituting MM-398 for the free form of irinotecan. Kozuch teaches sequential administration on day 1 in a 2 week cycle and the ACS teaches that the most common pancreatic cancer is exocrine pancreatic cancer. As explained *supra*, one of ordinary skill would arrive at the instant claims having a reasonable expectation of success and therefore the invention as whole remains *prima facie* obvious.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the claims at issue are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir.

1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the reference application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(1) - 706.02(l)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/forms/. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to http://www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

Claims 1-20 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claim 1-30 of copending Application No. 14/844,500, over claims 28-45 of copending Application No. 14/406,776 and over claims 1-12, 14, 15 and 20-32 of allowed (but not issued) Application No. 14/812,950. Although the claims at issue are not identical, they are not patentably distinct from each other because each of the applications set out to claim a method of treating pancreatic cancer refractory to gemcitabine therapy through intravenous administration of irinotecan as the MM-398 liposome, leucovorin as the (l)-form or racemic form and 5-fluorouracil. All the applications claim the combination in either a similar or identical dose for the therapeutic agents where the combination is administered in a two week cycle. The claims of the copending applications are obvious variants of each other.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TORI M. STRONG whose telephone number is (571)272-6333. The examiner can normally be reached on Monday-Friday 8am-5pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Lundgren can be reached on 571-272-5541. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/TORI M STRONG/
Examiner, Art Unit 1629

/Kortney L. Klinkel/
Primary Examiner, Art Unit 1611

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Eliel Bayever, et al.

Application No.: 14/851,111 | Confirmation No.: 3126

Filed: September 11, 2015 | Art Unit: 1629

For: METHODS FOR TREATING PANCREATIC CANCER USING COMBINATION THERAPIES COMPRISING LIPOSOMAL IRINOTECAN | Examiner: Tori Strong

Mail Stop Amendments
Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT IN RESPONSE TO NON-FINAL OFFICE ACTION DATED FEBRUARY 25, 2016

Dear Madam:

In response to the Non-Final Office action, dated February 25, 2016 ("Office Action"), please amend the application as follows and consider the remarks set forth below.

Amendments to the Claims are reflected in the listing of claims which begin on page 2 of this paper.

Remarks/Arguments begin on page 9 of this paper.

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions and listings of claims in the application. Please amend the claims as follows.

Listing of Claims

1. (Currently Amended) A method of treating an exocrine pancreatic cancer, the method comprising intravenously administering an antineoplastic therapy once every two weeks to a human patient having the [[an]] exocrine pancreatic cancer, the antineoplastic therapy consisting of :~~60-80 mg/m^2 of irinotecan in an irinotecan liposome injection formulation having a total volume of 500 mL over about 90 minutes, in combination with a therapeutically effective amount of leucovorin and 5-fluorouracil,~~

   a. administering a 60-80 mg/m^2 dose of a liposomal irinotecan composition in a diluted irinotecan injection formulation to the human patient in a single infusion over about 90 minutes, the diluted irinotecan injection formulation comprising irinotecan liposomes in 500 mL of an injectable liquid and a volume of a 5 mg/mL liposomal irinotecan composition effective to deliver the dose of liposomal irinotecan, in combination with

   b. administering a therapeutically effective amount of leucovorin and 5-fluorouracil,

to treat the exocrine pancreatic cancer in the patient, wherein the irinotecan liposome composition comprises ~~injection formulation comprising an irinotecan liposome having irinotecan encapsulated within a liposome comprising~~ phosphatidylcholine, cholesterol, and a polyethyleneglycol-derivatized phosphatidyl-ethanolamine, and the irinotecan liposomes in the liposomal irinotecan composition have ~~liposome having~~ a diameter of approximately 80-140 nm.

2. (Currently Amended) The method of claim 1, wherein the polyethyleneglycol-derivatized phosphatidyl-ethanolamine is in the amount of approximately one polyethyleneglycol molecule for every 200 phospholipid molecules in the irinotecan ~~liposome~~ liposomes.

3. (Currently Amended) The method of claim 1, wherein the liposomal irinotecan ~~liposome~~ composition comprises ~~is a~~ liposomes that are unilamellar lipid bilayer ~~vesicle~~ vesicles comprising the phosphatidylcholine and cholesterol, encapsulating irinotecan sucrose octasulfate.

4. (Original) The method of claim 1, wherein the exocrine pancreatic cancer has progressed on gemcitabine based therapy prior to the administration of the irinotecan liposome.

5. (Cancelled)

6. (Currently Amended) The method of claim 1, wherein the therapeutically effective amount of leucovorin is 200 mg/m^2 of the (l) form of leucovorin optionally administered as 400 mg/m^2 of the (l+d) racemic form of leucovorin, and the therapeutically effective amount of 5-fluorouracil is a 2,400 mg/m^2 dose.

7. (Currently Amended) The method of claim 6, wherein the diluted irinotecan ~~liposome,~~ injection formulation, leucovorin and 5-fluorouracil are administered sequentially to the patient beginning on day 1 of a 2-week cycle, resulting in the irinotecan liposomes ~~liposome~~, leucovorin and 5-fluorouracil being simultaneously present in the blood of the patient.

8. (Currently Amended) The method of claim 7, wherein the diluted irinotecan ~~liposome~~ injection formulation is administered to the patient prior to ~~followed by the leucovorin, followed by~~ the 5-fluorouracil.

9. (Currently Amended) The method of claim 8, wherein:

a. the patient has previously been treated with gemcitabine;

b. the leucovorin is administered as 400 mg/m^2 of the (l+d) racemic form of leucovorin;

c. the exocrine pancreatic cancer has progressed on gemcitabine based therapy prior to the administration of the diluted irinotecan ~~liposome~~ injection formulation;

d. the irinotecan liposome composition comprises liposomes that are ~~is a~~ unilamellar lipid bilayer ~~vesicle~~ vesicles comprising phosphatidylcholine and cholesterol, encapsulating irinotecan sucrose octasulfate; and

e. the irinotecan liposome composition comprises a polyethyleneglycol-derivatized phosphatidyl-ethanolamine in the amount of approximately one polyethyleneglycol molecule for every 200 phospholipid molecules in the irinotecan liposome composition.

10. (Cancelled)

11. (Cancelled)

12. (Cancelled)

13. (Cancelled)

14. (Cancelled)

15. (Cancelled)

16. (Cancelled)

17. (Cancelled)

18. (Cancelled)

19. (Currently Amended) The method of claim 1 [[18]], further comprising storing the diluted irinotecan ~~liposome~~ injection formulation at a temperature of about 2-8°C for no more than 24 hours prior to administration.

20. (Currently Amended) A method of treating an exocrine pancreatic cancer in a human patient who has previously been treated with gemcitabine, the method comprising intravenously administering to the patient an antineoplastic therapy consisting of: ~~60-80 mg/m^2 of irinotecan in~~

~~an irinotecan liposome injection formulation in a total volume of 500 mL, in combination with 400 mg/m^2 of the (l+d) racemic form of leucovorin and 2,400 mg/m^2 5-fluorouracil~~

a. a 60-80 mg/m^2 dose of liposomal irinotecan composition comprising irinotecan liposomes in a diluted irinotecan injection formulation, the diluted irinotecan injection formulation obtained by diluting a volume of the liposomal irinotecan composition containing 5 mg/mL of liposomal irinotecan into 500 mL of an injectable liquid, in combination with

b. a 200 mg/m^2 dose of the (l) form of leucovorin and a 2,400 mg/m^2 dose of 5-fluorouracil,

to treat the exocrine pancreatic cancer in the patient, the irinotecan liposome composition ~~injection formulation~~ comprising irinotecan sucrose octasulfate encapsulated within [[a]] the irinotecan composition liposomes ~~liposome~~ comprising phosphatidylcholine, cholesterol, and a polyethyleneglycol-derivatized phosphatidyl-ethanolamine, and having a diameter of approximately 80-140 nm, wherein the diluted irinotecan injection formulation ~~liposome~~, leucovorin and 5-fluorouracil are administered sequentially to the patient beginning on day 1 of a 2-week cycle.

21. (New) The method of claim 20, further comprising storing the diluted irinotecan injection formulation at a temperature of about 2-8°C for no more than 24 hours prior to administration.

22. (New) The method of claim 21, wherein the irinotecan liposome composition comprises approximately one polyethyleneglycol (PEG) molecule for every 200 phospholipid molecules.

23. (New) The method of claim 22, wherein the patient has failed prior treatment with gemcitabine or become resistant to gemcitabine prior to administration of the diluted irinotecan injection formulation.

24. (New) The method of claim 23, wherein the 200 mg/m^2 dose of the (l) form of leucovorin is provided by administering a 400 mg/m^2 dose of the (l+d) form of leucovorin.

25. (New) The method of claim 24, wherein the dose of liposomal irinotecan dose is 60 mg/m^2, 70 mg/m^2 or 80 mg/m^2.

26. (New) The method of claim 25, wherein the dose of liposomal irinotecan dose is 80 mg/m^2 and the human patient is not homozygous for the UGT1A1*28 allele.

27. (New) The method of claim 26, wherein the liposomal irinotecan is administered as the diluted irinotecan injection as a 90-minute infusion, the leucovorin is administered after the irinotecan over 30 minutes and the 5-fluorouracil is administered after the leucovorin over 46 hours.

28. (New) The method of claim 27, wherein the irinotecan liposomes are a unilamellar lipid bilayer vesicle that encapsulates an aqueous space which contains irinotecan in a gelated or precipitated state with sucrose octasulfate salt of irinotecan.

29. (New) A method of treating pancreatic cancer in a human patient, whose cancer has progressed following gemcitabine based therapy, the method comprising administering an antineoplastic therapy to the human patient once every two weeks, the antineoplastic therapy consisting of intravenously administering to the human patient: a diluted irinotecan injection formulation providing a 60, 70 or 80 mg/m^2 dose of liposomal irinotecan, in combination with a 200 mg/m^2 dose of the (l) form of leucovorin and a 2,400 mg/m^2 dose of 5-fluorouracil to treat the pancreatic cancer in the human patient, wherein

a. the liposomes in the diluted irinotecan injection formulation have a diameter of approximately 80-140 nm, and comprise phosphatidylcholine, cholesterol, and a polyethyleneglycol-derivatized phosphatidyl-ethanolamine; and
b. the diluted irinotecan injection formulation comprises the liposomal irinotecan in 500 mL of an injectable liquid stored at a temperature of about 2-8°C for no more than 24 hours prior to each administration.

30. (New) The method of claim 29, wherein the diluted irinotecan injection formulation comprises 500 mL of the injectable liquid and a volume of a 5 mg/mL liposomal irinotecan composition, wherein the volume is calculated to deliver the dose of liposomal irinotecan.

31. (New) The method of claim 29, wherein a 80 mg/m^2 dose of liposomal irinotecan is administered to a human patient who is not homozygous for the UGT1A1*28 allele; and the 200 mg/m^2 dose of the (l) form of leucovorin is provided by administering a 400 mg/m^2 dose of the (l+d) form of leucovorin.

32. (New) The method of claim 31, wherein the method further comprises administering an anti-emetic to the patient prior to administering the antineoplastic therapy; and the liposomal irinotecan is administered as the diluted irinotecan injection formulation as a single 90-minute infusion, the leucovorin dose is administered after the liposomal irinotecan over 30 minutes and the 5-fluorouracil dose is administered after the leucovorin over 46 hours.

33. (New) The method of claim 1, wherein the irinotecan liposomes are a unilamellar lipid bilayer vesicle that encapsulates an aqueous space which contains irinotecan in a gelated or precipitated state with sucrose octasulfate salt of irinotecan.

34. (New) The method of claim 33, wherein the injectable liquid is 5% dextrose injection.

35. (New) The method of claim 20, wherein the irinotecan liposomes are a unilamellar lipid bilayer vesicle that encapsulates an aqueous space which contains irinotecan in a gelated or precipitated state with sucrose octasulfate salt of irinotecan.

36. (New) The method of claim 35, wherein the injectable liquid is 5% dextrose injection.

37. (New) The method of claim 29, wherein the irinotecan liposomes are a unilamellar lipid bilayer vesicle that encapsulates an aqueous space which contains irinotecan in a gelated or precipitated state with sucrose octasulfate salt of irinotecan.

38. (New) The method of claim 37, wherein the injectable liquid is 5% dextrose injection.

39. (New) A method of treating metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy in a human patient who is not homozygous for the UGT1A1*28 allele, the method comprising the following steps performed once every two weeks:

a. diluting a volume of a 5 mg/mL liposomal irinotecan composition in 500 mL of an injectable liquid, to obtain a diluted irinotecan injection formulation, then
b. optionally storing the diluted irinotecan injection formulation at a temperature of about 2-8°C for no more than 24 hours prior to administration; then
c. administering an antineoplastic therapy to the human patient, the antineoplastic therapy consisting of intravenously administering to the human patient: the diluted irinotecan injection formulation providing a 80 mg/m^2 dose of liposomal irinotecan to the human patient, in combination with a 200 mg/m^2 dose of the (l) form of leucovorin and a 2,400 mg/m^2 dose of 5-fluorouracil, to treat the pancreatic cancer in the human patient;

the liposomes in the liposomal irinotecan composition having a diameter of approximately 80-140 nm, and comprising a unilamellar lipid bilayer vesicle that encapsulates an aqueous space which contains irinotecan in a gelated or precipitated state with sucrose octasulfate salt of irinotecan, the unilamellar lipid bilayer comprising phosphatidylcholine, cholesterol, and a polyethyleneglycol-derivatized phosphatidyl-ethanolamine.

40. (New) The method of claim 39, wherein the injectable liquid is 5% dextrose injection.

REMARKS

Claim Status

Currently, claims 1-4, 6-9 and 19-40 are pending in this application. Claims 5 and 10-18 have been cancelled without prejudice or disclaimer. Claims 1-3, 6-9, 19 and 20 have been amended. New claims 21-40 are added. The claim amendments and new claims are supported in the specification as filed; no new matter is added. With the claim amendments, a total of 30 claims with 4 independent claims remain pending.

The amendments to and/or cancellation of the claims are being made for the purpose of expediting prosecution and to place the application in better condition for appeal, should an appeal be necessary, and are made without prejudice or waiver.

This listing of claims will replace all prior versions and listings of claims in the application. Applicant reserves the right to present the original claims in this or a continuing application.

Claim Rejections – 35 USC § 103

The Examiner has rejected claims 1-5 as being unpatentable over Kozuch *et al.*, *The Oncologist*, 2001, 6, pp. 488-495 ("Kozuch") and Tsai *et al., Journal of Gastrointestinal Oncology*, 2011, vol. 2, no. 3, pp. 185-194 ("Tsai"), in view of American Cancer Society (ACS) (http://www.cancer.org/cancer/pancreatic-cancer-what-is-pancreatic-cancer). The Examiner acknowledges "Kozuch does not teach irinotecan in liposomal form" (Office Action at page 5), but asserts that "Tsai provides teaching that one of ordinary skill in the art would substitute the liposomal form of irinotecan and further combine the instantly claimed therapeutic agents" (Office Action at page 5) and that "ACS teaches that exocrine tumors are the most common type of pancreatic cancer; where 95% are exocrine cell adenocarcinomas. Therefore treatment that is directed towards pancreatic cancer in general refers to the most common form of exocrine pancreatic cancer" (Office Action on page 5). The Examiner asserts that "[o]ne of ordinary skill in the art would arrive at the instantly claimed invention having a reasonable expectation of success based on the combined teaching of Kozuch, Tsai and the ACS" (Office Action at page 5).

Applicant respectfully requests reconsideration and withdrawal of this rejection. Claim 5 has been cancelled, rendering the rejection moot. Claim 1 has been amended and is now directed to:

> A method of treating an exocrine pancreatic cancer, the method comprising intravenously administering an antineoplastic therapy once every two weeks to a human patient having the exocrine pancreatic cancer, the antineoplastic therapy consisting of :
> administering a 60-80 mg/m^2 dose of a liposomal irinotecan composition in a diluted irinotecan injection formulation to the human patient in a single infusion over about 90 minutes, the diluted irinotecan injection formulation comprising irinotecan liposomes in 500 mL of an injectable liquid and a volume of a 5 mg/mL liposomal irinotecan composition effective to deliver the dose of liposomal irinotecan, in combination with administering a therapeutically effective amount of leucovorin and 5-fluorouracil, to treat the exocrine pancreatic cancer in the patient, wherein the irinotecan liposome composition comprises phosphatidylcholine, cholesterol, and a polyethyleneglycol-derivatized phosphatidyl-ethanolamine, and the irinotecan liposomes in the liposomal irinotecan composition have liposome having a diameter of approximately 80-140 nm.

The Examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness with respect to independent claim 1. If the Examiner does not produce a *prima facie* case, the applicant is under no obligation to submit evidence to show nonobviousness. To reach a proper determination under 35 U.S.C. 103, the Examiner must step backward in time and into the shoes worn by the hypothetical "person of ordinary skill in the art" when the invention was unknown and just before it was made. In view of all factual information, the Examiner must then make a determination whether the claimed invention "as a whole" would have been obvious at that time to that person. Knowledge of applicant's disclosure must be put aside in reaching this determination, yet kept in mind in order to determine the "differences,"

conduct the search and evaluate the "subject matter as a whole" of the invention. The tendency to resort to "hindsight" based upon applicant's disclosure is often difficult to avoid due to the very nature of the examination process. However, impermissible hindsight must be avoided and the legal conclusion must be reached on the basis of the facts gleaned from the prior art. MPEP 2142.

The Examiner has rejected claims 6-20 as being unpatentable over Kozuch *et al.*, *The Oncologist*, 2001, 6, pp. 488-495 ("Kozuch") and Tsai *et al., Journal of Gastrointestinal Oncology*, 2011, vol. 2, no. 3, pp. 185-194 ("Tsai"), in view of American Cancer Society (ACS) (http://www.cancer.org/cancer/pancreatic-cancer-what-is-pancreatic-cancer), in further view of Yoo *et al., British Journal of Cancer,* 2009, 101, pp.1658-1663 ("Yoo"). The Examiner recognizes that the teachings of Kozuch, Tsai and ACS do "not explicitly teach the instantly claimed dosing for leucovorin and 5-FU" (Office Action at page 7), but asserts that "[o]ne of ordinary skill would arrive at the instant limitations having a reasonable expectation of success based on the combine [sic] teaching of Kozuch, Tsai, the ACS and Yoo" (Office Action at page 7). Applicant respectfully requests reconsideration and withdrawal of this rejection.

Claims 10-18 have been cancelled, rendering these rejections moot. Applicant requests reconsideration and withdrawal of these rejections.

Claims 2-4, 6-9 and 19 all depend from independent claim 1. For at least the reasons stated above, the Office Action does not provide a prima facie basis for the obviousness rejection against claim 1. Applicant requests reconsideration and withdrawal of these rejections.

As amended, independent claim 20 recites:

> A method of treating an exocrine pancreatic cancer in a human patient who has previously been treated with gemcitabine, the method comprising intravenously administering to the patient an antineoplastic therapy consisting of: a 60-80 mg/m^2 dose of liposomal irinotecan composition comprising irinotecan liposomes in a diluted irinotecan injection formulation, the diluted irinotecan injection formulation obtained by diluting a volume of the liposomal irinotecan composition containing 5 mg/mL of liposomal irinotecan into 500 mL of an injectable liquid, in combination with a 200 mg/m^2 dose of the (l) form of leucovorin and a 2,400 mg/m^2 dose of 5-fluorouracil, to treat the exocrine

pancreatic cancer in the patient, the irinotecan liposome composition comprising irinotecan sucrose octasulfate encapsulated within the irinotecan composition liposomes comprising phosphatidylcholine, cholesterol, and a polyethyleneglycol-derivatized phosphatidyl-ethanolamine, and having a diameter of approximately 80-140 nm, wherein the diluted irinotecan injection formulation, leucovorin and 5-fluorouracil are administered sequentially to the patient beginning on day 1 of a 2-week cycle.

As discussed above, the Examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness, and that burden has not been met with respect to independent claim 20.

Recitation of "60-80 mg/m^2" of MM-398 liposomal irinotecan composition and "60, 70 or 80 mg/m^2" of liposomal irinotecan refers to the amount of irinotecan hydrochloride trihydrate per m^2, and is equivalent to 50-70 mg/m^2, and 50, 60 or 70 mg/m^2, respectively, of irinotecan free base. *See* the ONIVYDE® U.S. Prescribing Information (e.g., Section 14, " The ONIVYDE dose of 70 mg/m^2 is based on irinotecan free base (equivalent to 80 mg/m^2 of irinotecan as the hydrochloride trihydrate).")(attached in Tab 1). Likewise, recitation of "5 mg/mL liposomal irinotecan composition...," and the like refers to the amount of irinotecan hydrochloride trihydrate, and is equivalent to 4.3 mg/mL of irinotecan free base.

Thus, paragraph [0060] of the present specification refers to the Prescribing Information for CAMPTOSAR® (irinotecan hydrochloride) and discusses results in 66 patients who received single agent irinotecan (350 mg/m^2 once every-3-weeks). That 350 mg/m^2 dose is based on the hydrochloride trihydrate salt of irinotecan (CAMPTOSAR® Prescribing Information, page 11, Section 5.3 and page 24, Section 11)(attached in Tab 2). Furthermore, the results reported in Figure 5 of the present specification, for example, compare pharmacokinetic results for different doses of CAMPTOSAR® and irinotecan sucrose octasulfate liposomal formulations and are reported on the basis of the hydrochloride trihydrate salt of irinotecan (*see also* paragraph [0106] of the present specification discussing the results reported in Figure 5).

Applicant notes the examiner's comment that "the liposomal irinotecan formulation is also referred to as MM-398 (see specification, p.3, Summary, para. 1)." However, "[t]hough understanding the claim language may be aided by explanations contained in the written

description, it is important not to import into a claim limitations that are not part of the claim. For example, a particular embodiment appearing in the written description may not be read into a claim when the claim language is broader than the embodiment." *Superguide Corp. v. DirecTV Enterprises, Inc.*, 358 F.3d 870, 875, 69 USPQ2d 1865, 1868 (Fed. Cir. 2004)." MPEP 2111.01.

In view of the above-mentioned amendment, applicant respectfully requests reconsideration and withdrawal of the present 35 USC 103(a) rejection of the claims.

Double Patenting

The Examiner has provisionally rejected claims 1-20 on the ground of the judicially created doctrine of non-statutory double patenting as allegedly being unpatentable over claims 1-30 of co-pending Application No. 14/844,500, over claims 24-45 of copending Application No. 14/406,776 and over claims 1-12, 14, 15 and 20-32 of allowed (but not issued) Application No. 14/812,950 (Office Action at page 11).

Terminal disclaimers in compliance with 37 C.F.R. 1.321(c) are being electronically filed herewith, along with the required fee of $160.00, rendering moot the basis for this rejection. Applicant respectfully requests reconsideration and withdrawal of this rejection.

CONCLUSION

Applicant has provided a full and complete response to the Office Action. The application is in condition for allowance. Applicant respectfully requests entry of this paper, favorable reconsideration and withdrawal of the rejections of the application, and prompt issuance of a Notice of Allowance.

Applicant believes that no further fees are required for the filing of this Response. However, if there are any additional charges or credits in direct relation to this filing please charge them to Deposit Account No.: 503145, referencing Attorney Docket No.: 239669-375516.

Respectfully submitted,

HONIGMAN MILLER SCHWARTZ AND COHN LLP

Dated: May 12, 2016

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HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all of the information needed to use ONIVYDE™ safely and effectively. See full prescribing information for ONIVYDE™

ONIVYDE™ (irinotecan liposome injection), for intravenous use
Initial U.S. Approval: 1996

WARNING: SEVERE NEUTROPENIA and SEVERE DIARRHEA
See full prescribing information for complete boxed warning

- **Fatal neutropenic sepsis occurred in 0.8% of patients receiving ONIVYDE. Severe or life-threatening neutropenic fever or sepsis occurred in 3% and severe or life-threatening neutropenia occurred in 20% of patients receiving ONIVYDE in combination with fluorouracil and leucovorin. Withhold ONIVYDE for absolute neutrophil count below 1500/mm^3 or neutropenic fever. Monitor blood cell counts periodically during treatment (2.2), (5.1).**
- **Severe diarrhea occurred in 13% of patients receiving ONIVYDE in combination with fluorouracil and leucovorin. Do not administer ONIVYDE to patients with bowel obstruction. Withhold ONIVYDE for diarrhea of Grade 2-4 severity. Administer loperamide for late diarrhea of any severity. Administer atropine, if not contraindicated, for early diarrhea of any severity (2.2), (5.2).**

INDICATIONS AND USAGE

ONIVYDE is a topoisomerase inhibitor indicated, in combination with fluorouracil and leucovorin, for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy. (1)

Limitation of Use: ONIVYDE is not indicated as a single agent for the treatment of patients with metastatic adenocarcinoma of the pancreas. (1)

DOSAGE AND ADMINISTRATION

- **Do not substitute ONIVYDE for other drugs containing irinotecan HCl. (2.3)**
- Recommended dose of ONIVYDE is 70 mg/m^2 intravenous infusion over 90 minutes every two weeks. (2.2)
- Recommended starting dose of ONIVYDE in patients homozygous for UGT1A1*28 is 50 mg/m^2 every two weeks. (2.2)
- There is no recommended dose of ONIVYDE for patients with serum bilirubin above the upper limit of normal. (2.2)
- Premedicate with a corticosteroid and an anti-emetic. 30 minutes prior to ONIVYDE. (2.2)

DOSAGE FORMS AND STRENGTHS

Injection: 43 mg/10 mL single dose vial (3)

CONTRAINDICATIONS

Severe hypersensitivity reaction to ONIVYDE or irinotecan HCl. (4, 5.4)

WARNINGS AND PRECAUTIONS

- Interstitial lung disease (ILD): Fatal ILD has occurred in patients receiving irinotecan HCl. Discontinue ONIVYDE if ILD is diagnosed. (5.3)
- Severe hypersensitivity reaction: Permanently discontinue ONIVYDE for severe hypersensitivity reactions. (5.4, 4)
- Embryo-fetal toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception. (5.5, 8.1, 8.3)

ADVERSE REACTIONS

The most common adverse reactions (≥ 20%) of ONIVYDE: diarrhea, fatigue/asthenia, vomiting, nausea, decreased appetite, stomatitis, and pyrexia. The most common laboratory abnormalities (≥ 10% Grade 3 or 4) were lymphopenia and neutropenia. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Merrimack Pharmaceuticals, Inc. at 1-844-441-6225 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Strong CYP3A4 Inducers: Avoid the use of strong CYP3A4 inducers if possible. Substitute non-enzyme inducing therapies at least 2 weeks prior to initiation of ONIVYDE. (7.1)
- Strong CYP3A4 Inhibitors: Avoid the use of strong CYP3A4 or UGT1A1 inhibitors, if possible; discontinue strong CYP3A4 inhibitors at least 1 week prior to starting therapy. (7.2)

USE IN SPECIFIC POPULATIONS

- Lactation: Do not breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 10/2015

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FULL PRESCRIBING INFORMATION

WARNING: SEVERE NEUTROPENIA and SEVERE DIARRHEA

Fatal neutropenic sepsis occurred in 0.8% of patients receiving ONIVYDE. Severe or life-threatening neutropenic fever or sepsis occurred in 3% and severe or life-threatening neutropenia occurred in 20% of patients receiving ONIVYDE in combination with fluorouracil and leucovorin. Withhold ONIVYDE for absolute neutrophil count below 1500/mm^3 or neutropenic fever. Monitor blood cell counts periodically during treatment *[see Dosage and Administration (2.2) and Warnings and Precautions (5.1)]*.

Severe diarrhea occurred in 13% of patients receiving ONIVYDE in combination with fluorouracil and leucovorin. Do not administer ONIVYDE to patients with bowel obstruction. Withhold ONIVYDE for diarrhea of Grade 2-4 severity. Administer loperamide for late diarrhea of any severity. Administer atropine, if not contraindicated, for early diarrhea of any severity *[see Dosage and Administration (2.2) and Warnings and Precautions (5.2)]*.

1 INDICATIONS AND USAGE

ONIVYDE™ is indicated, in combination with fluorouracil and leucovorin, for the treatment of patients with metastatic adenocarcinoma of the pancreas after disease progression following gemcitabine-based therapy.

Limitation of Use: ONIVYDE is not indicated as a single agent for the treatment of patients with metastatic adenocarcinoma of the pancreas *[see Clinical Studies (14)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Important Use Information

DO NOT SUBSTITUTE ONIVYDE for other drugs containing irinotecan HCl.

2.2 Recommended Dose

Administer ONIVYDE prior to leucovorin and fluorouracil *[see Clinical Studies (14)]*.

- The recommended dose of ONIVYDE is 70 mg/m^2 administered by intravenous infusion over 90 minutes every 2 weeks.
- The recommended starting dose of ONIVYDE in patients known to be homozygous for the UGT1A1*28 allele is 50 mg/m^2 administered by intravenous infusion over 90 minutes. Increase the dose of ONIVYDE to 70 mg/m^2 as tolerated in subsequent cycles.
- There is no recommended dose of ONIVYDE for patients with serum bilirubin above the upper limit of normal *[see Adverse Reactions (6.1) and Clinical Studies (14)]*.

Premedication

Administer a corticosteroid and an anti-emetic 30 minutes prior to ONIVYDE infusion.

2.3 Dose Modifications for Adverse Reactions

Table 1: Recommended Dose Modifications for ONIVYDE

Toxicity NCI CTCAE v4.0†	Occurrence	ONIVYDE adjustment in patients receiving 70 mg/m^2	Patients homozygous for UGT1A1*28 without previous increase to 70 mg/m^2
Grade 3 or 4 adverse reactions	Withhold ONIVYDE. Initiate loperamide for late onset diarrhea of any severity. Administer intravenous or subcutaneous atropine 0.25 to 1 mg (unless clinically contraindicated) for early onset diarrhea of any severity. Upon recovery to ≤ Grade 1, resume ONIVYDE at:		
	First	50 mg/m^2	43 mg/m^2
	Second	43 mg/m^2	35 mg/m^2
	Third	Discontinue ONIVYDE	Discontinue ONIVYDE
Interstitial Lung Disease	First	Discontinue ONIVYDE	Discontinue ONIVYDE
Anaphylactic Reaction	First	Discontinue ONIVYDE	Discontinue ONIVYDE

† NCI CTCAE v 4.0=National Cancer Institute Common Toxicity Criteria for Adverse Events version 4.0

For recommended dose modifications of fluorouracil (5-FU) or leucovorin (LV), refer to the Full Prescribing Information; refer to Clinical Studies (14).

2.4 Preparation and Administration

ONIVYDE is a cytotoxic drug. Follow applicable special handling and disposal procedures.[1]

Preparation

- Withdraw the calculated volume of ONIVYDE from the vial. Dilute ONIVYDE in 500 mL 5% Dextrose Injection, USP or 0.9% Sodium Chloride Injection, USP and mix diluted solution by gentle inversion.
- Protect diluted solution from light.
- Administer diluted solution within 4 hours of preparation when stored at room temperature or within 24 hours of preparation when stored under refrigerated conditions [2°C to 8°C (36°F to 46°F)]. Allow diluted solution to come to room temperature prior to administration.
- Do NOT freeze.

Administration

- Infuse diluted solution intravenously over 90 minutes. Do not use in-line filters. Discard unused portion.

3 DOSAGE FORMS AND STRENGTHS

Injection: 43 mg/10 mL irinotecan free base as a white to slightly yellow, opaque, liposomal dispersion in a single-dose vial.

4 CONTRAINDICATIONS

ONIVYDE is contraindicated in patients who have experienced a severe hypersensitivity reaction to ONIVYDE or irinotecan HCl.

5 WARNINGS AND PRECAUTIONS

5.1 Severe Neutropenia

ONIVYDE can cause severe or life-threatening neutropenia and fatal neutropenic sepsis. In Study 1, the incidence of fatal neutropenic sepsis was 0.8% among patients receiving ONIVYDE, occurring in one of 117 patients in the ONIVYDE plus fluorouracil/leucovorin (ONIVYDE/5-FU/LV) arm and one of 147 patients receiving ONIVYDE as a single agent. Severe or life-threatening neutropenia occurred in 20% of patients receiving ONIVYDE/5-FU/LV compared to 2% of patients receiving fluorouracil/leucovorin alone (5-FU/LV). Grade 3 or 4 neutropenic fever/neutropenic sepsis occurred in 3% of patients receiving ONIVYDE/5-FU/LV, and did not occur in patients receiving 5-FU/LV.

In patients receiving ONIVYDE/5-FU/LV, the incidence of Grade 3 or 4 neutropenia was higher among Asian patients [18 of 33 (55%)] compared to White patients [13 of 73 (18%)]. Neutropenic fever/neutropenic sepsis was reported in 6% of Asian patients compared to 1% of White patients *[see Clinical Pharmacology (12.3)]*.

Monitor complete blood cell counts on Days 1 and 8 of every cycle and more frequently if clinically indicated. Withhold ONIVYDE if the absolute neutrophil count (ANC) is below $1500/mm^3$ or if neutropenic fever occurs. Resume ONIVYDE when the ANC is $1500/mm^3$ or above. Reduce ONIVYDE dose for Grade 3-4 neutropenia or neutropenic fever following recovery in subsequent cycles *[see Dosage and Administration (2.2)]*.

5.2 Severe Diarrhea

ONIVYDE can cause severe and life-threatening diarrhea. Do not administer ONIVYDE to patients with bowel obstruction.

Severe or life-threatening diarrhea followed one of two patterns: late onset diarrhea (onset more than 24 hours following chemotherapy) and early onset diarrhea (onset within 24 hours of

chemotherapy, sometimes occurring with other symptoms of cholinergic reaction) *[see Cholinergic Reactions (6.1)]*. An individual patient may experience both early and late-onset diarrhea.

In Study 1, Grade 3 or 4 diarrhea occurred in 13% receiving ONIVYDE/5-FU/LV compared to 4% receiving 5-FU/LV. The incidence of Grade 3 or 4 late onset diarrhea was 9% in patients receiving ONIVYDE/5-FU/LV, compared to 4% in patients receiving 5-FU/LV. The incidence of Grade 3 or 4 early onset diarrhea was 3% in patients receiving ONIVYDE/5-FU/LV, compared to no Grade 3 or 4 early onset diarrhea in patients receiving 5-FU/LV. Of patients receiving ONIVYDE/5-FU/LV in Study 1, 34% received loperamide for late-onset diarrhea and 26% received atropine for early-onset diarrhea. Withhold ONIVYDE for Grade 2-4 diarrhea. Initiate loperamide for late onset diarrhea of any severity. Administer intravenous or subcutaneous atropine 0.25 to 1 mg (unless clinically contraindicated) for early onset diarrhea of any severity. Following recovery to Grade 1 diarrhea, resume ONIVYDE at a reduced dose *[see Dosage and Administration (2.2)]*.

5.3 Interstitial Lung Disease

Irinotecan HCl can cause severe and fatal interstitial lung disease (ILD). Withhold ONIVYDE in patients with new or progressive dyspnea, cough, and fever, pending diagnostic evaluation. Discontinue ONIVYDE in patients with a confirmed diagnosis of ILD.

5.4 Severe Hypersensitivity Reaction

Irinotecan HCl can cause severe hypersensitivity reactions, including anaphylactic reactions. Permanently discontinue ONIVYDE in patients who experience a severe hypersensitivity reaction.

5.5 Embryo-Fetal Toxicity

Based on animal data with irinotecan HCl and the mechanism of action of ONIVYDE, ONIVYDE can cause fetal harm when administered to a pregnant woman. Embryotoxicity and teratogenicity were observed following treatment with irinotecan HCl, at doses resulting in irinotecan exposures lower than those achieved with ONIVYDE 70 mg/m^2 in humans, administered to pregnant rats and rabbits during organogenesis. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with ONIVYDE and for one month following the final dose *[see Use in Specific Populations (8.1, 8.3), Clinical Pharmacology (12.1)]*.

6 ADVERSE REACTIONS

The following adverse drug reactions are discussed in greater detail in other sections of the label:

- Severe Neutropenia [see *Warnings and Precautions (5.1) and Boxed Warning]*
- Severe Diarrhea *[see Warnings and Precautions (5.2) and Boxed Warning]*
- Interstitial Lung Disease *[see Warnings and Precautions (5.3)]*

- Severe Hypersensitivity Reactions *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of ONIVYDE cannot be directly compared to rates in clinical trials of other drugs and may not reflect the rates observed in practice.

The safety data described below are derived from patients with metastatic adenocarcinoma of the pancreas previously treated with gemcitabine-based therapy who received any part of protocol-specified therapy in Study 1, an international, randomized, active-controlled, open-label trial. Protocol-specified therapy consisted of ONIVYDE 70 mg/m^2 with leucovorin 400 mg/m^2 and fluorouracil 2400 mg/m^2 over 46 hours every 2 weeks (ONIVYDE/5-FU/LV; N=117), ONIVYDE 100 mg/m^2 every 3 weeks (N=147), or leucovorin 200 mg/m^2 and fluorouracil 2000 mg/m^2 over 24 hours weekly for 4 weeks followed by 2 week rest (5-FU/LV; N=134) *[see Clinical Studies (14)]*. Serum bilirubin within the institutional normal range, albumin ≥ 3 g/dL, and Karnofsky Performance Status (KPS) ≥ 70 were required for study entry. The median duration of exposure was 9 weeks in the ONIVYDE/5-FU/LV arm, 9 weeks in the ONIVYDE monotherapy arm, and 6 weeks in the 5-FU/LV arm.

The most common adverse reactions (≥ 20%) of ONIVYDE were diarrhea, fatigue/asthenia, vomiting, nausea, decreased appetite, stomatitis, and pyrexia. The most common, severe laboratory abnormalities (≥ 10% Grade 3 or 4) were lymphopenia and neutropenia. The most common serious adverse reactions (≥ 2%) of ONIVYDE were diarrhea, vomiting, neutropenic fever or neutropenic sepsis, nausea, pyrexia, sepsis, dehydration, septic shock, pneumonia, acute renal failure, and thrombocytopenia.

Adverse reactions led to permanent discontinuation of ONIVYDE in 11% of patients receiving ONIVYDE/5-FU/LV; the most frequent adverse reactions resulting in discontinuation of ONIVYDE were diarrhea, vomiting, and sepsis. Dose reductions of ONIVYDE for adverse reactions occurred in 33% of patients receiving ONIVYDE/5-FU/LV; the most frequent adverse reactions requiring dose reductions were neutropenia, diarrhea, nausea, and anemia. ONIVYDE was withheld or delayed for adverse reactions in 62% of patients receiving ONIVYDE/5-FU/LV; the most frequent adverse reactions requiring interruption or delays were neutropenia, diarrhea, fatigue, vomiting, and thrombocytopenia.

Table 2 provides the frequency and severity of adverse reactions in Study 1 that occurred with higher incidence (≥5% difference for Grades 1-4 or ≥2% difference for Grades 3-4) in patients who received ONIVYDE/5-FU/LV compared to patients who received 5-FU/LV.

Table 2: Adverse Reactions with Higher Incidence (≥5% Difference for Grades 1-4* or ≥2% Difference for Grades 3 and 4) in the ONIVYDE/5-FU/LV Arm

Adverse Reaction	ONIVYDE/5-FU/LV N=117		5-FU/LV N=134	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Gastrointestinal disorders				
Diarrhea	59	13	26	4
Early diarrhea†	30	3	15	0
Late diarrhea‡	43	9	17	4
Vomiting	52	11	26	3
Nausea	51	8	34	4
Stomatitis§	32	4	12	1
Infections and infestations	38	17	15	10
Sepsis	4	3	2	1
Neutropenic fever/neutropenic sepsis♠	3	3	1	0
Gastroenteritis	3	3	0	0
Intravenous catheter-related infection	3	3	0	0
General disorders and administration site conditions				
Fatigue/asthenia	56	21	43	10
Pyrexia	23	2	11	1
Metabolism and nutrition disorders				
Decreased appetite	44	4	32	2
Weight loss	17	2	7	0
Dehydration	8	4	7	2
Skin and subcutaneous tissue disorders				
Alopecia	14	1	5	0

* NCI CTCAE v4.0
† Early diarrhea: onset within 24 hours of ONIVYDE administration
‡ Late diarrhea: onset >1 day after ONIVYDE administration
§ Includes stomatitis, aphthous stomatitis, mouth ulceration, mucosal inflammation.
♠ Includes febrile neutropenia

Cholinergic Reactions: ONIVYDE can cause cholinergic reactions manifesting as rhinitis, increased salivation, flushing, bradycardia, miosis, lacrimation, diaphoresis, and intestinal hyperperistalsis with abdominal cramping and early onset diarrhea. In Study 1, Grade 1 or 2 cholinergic symptoms other than early diarrhea occurred in 12 (4.5%) ONIVYDE-treated patients. Six of these 12 patients received atropine and in 1 of the 6 patients, atropine was administered for cholinergic symptoms other than diarrhea.

Infusion Reactions: Infusion reactions, consisting of rash, urticaria, periorbital edema, or pruritus, occurring on the day of ONIVYDE administration were reported in 3% of patients receiving ONIVYDE or ONIVYDE/5-FU/LV.

Laboratory abnormalities that occurred with higher incidence in the ONIVYDE/5-FU/LV arm compared to the 5-FU/LV arm (≥5% difference) are summarized in the following table.

Table 3: Laboratory Abnormalities with Higher Incidence (≥5% Difference) in the ONIVYDE/5-FU/LV Arm*#

Laboratory abnormality	ONIVYDE/5-FU/LV N=117		5-FU/LV N=134	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Hematology				
Anemia	97	6	86	5
Lymphopenia	81	27	75	17
Neutropenia	52	20	6	2
Thrombocytopenia	41	2	33	0
Hepatic				
Increased alanine aminotransferase (ALT)	51	6	37	1
Hypoalbuminemia	43	2	30	0
Metabolic				
Hypomagnesemia	35	0	21	0
Hypokalemia	32	2	19	2
Hypocalcemia	32	1	20	0
Hypophosphatemia	29	4	18	1
Hyponatremia	27	5	12	3
Renal				
Increased creatinine	18	0	13	0

* NCI CTCAE v4.0, worst grade shown.
# Percent based on number of patients with a baseline and at least one post-baseline measurement.

7 DRUG INTERACTIONS

7.1 Strong CYP3A4 Inducers

Following administration of non-liposomal irinotecan (i.e., irinotecan HCl), exposure to irinotecan or its active metabolite, SN-38, is substantially reduced in adult and pediatric patients concomitantly receiving the CYP3A4 enzyme-inducing anticonvulsants phenytoin and strong CYP3A4 inducers. Avoid the use of strong CYP3A4 inducers (e.g., rifampin, phenytoin, carbamazepine, rifabutin, rifapentine, phenobarbital, St. John's wort) if possible. Substitute non-enzyme inducing therapies at least 2 weeks prior to initiation of ONIVYDE therapy *[see Clinical Pharmacology (12.3)]*.

7.2 Strong CYP3A4 or UGT1A1 Inhibitors

Following administration of non-liposomal irinotecan (i.e., irinotecan HCl), patients receiving concomitant ketoconazole, a CYP3A4 and UGT1A1 inhibitor, have increased exposure to irinotecan and its active metabolite SN-38. Co-administration of ONIVYDE with other inhibitors of CYP3A4 (e.g., clarithromycin, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telaprevir, voriconazole) or UGT1A1 (e.g., atazanavir, gemfibrozil, indinavir) may increase systemic exposure to irinotecan or SN-38. Avoid the use of strong CYP3A4 or UGT1A1 inhibitors if possible. Discontinue strong CYP3A4 inhibitors at least 1 week prior to starting ONIVYDE therapy *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on animal data with irinotecan HCl and the mechanism of action of ONIVYDE, ONIVYDE can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. There are no available data in pregnant women. Embryotoxicity and teratogenicity were observed following treatment with irinotecan HCl, at doses resulting in irinotecan exposures lower than those achieved with ONIVYDE 70 mg/m^2 in humans, administered to pregnant rats and rabbits during organogenesis *[see Data]*. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

No animal studies have been conducted to evaluate the effect of irinotecan liposome on reproduction and fetal development; however, studies have been conducted with irinotecan HCl. Irinotecan crosses the placenta of rats following intravenous administration. Intravenous administration of irinotecan at a dose of 6 mg/kg/day to rats and rabbits during the period of organogenesis resulted in increased post-implantation loss and decreased numbers of live fetuses. In separate studies in rats, this dose resulted in an irinotecan exposure of approximately 0.002 times the exposure of irinotecan based on area under the curve (AUC) in patients administered ONIVYDE at the 70 mg/m^2 dose. Administration of irinotecan HCl resulted in structural abnormalities and growth delays in rats at doses greater than 1.2 mg/kg/day (approximately 0.0002 times the clinical exposure to irinotecan in ONIVYDE based on AUC). Teratogenic effects included a variety of external, visceral, and skeletal abnormalities. Irinotecan HCl administered to rat dams for the period following organogenesis through weaning at doses of 6 mg/kg/day caused decreased learning ability and decreased female body weights in the offspring.

8.2 Lactation

Risk Summary

There is no information regarding the presence of irinotecan liposome, irinotecan, or SN-38 (an active metabolite of irinotecan) in human milk, or the effects on the breastfed infant or on milk production. Irinotecan is present in rat milk *[see Data]*.

Because of the potential for serious adverse reactions in breastfed infants from ONIVYDE, advise a nursing woman not to breastfeed during treatment with ONIVYDE and for one month after the final dose.

Data

Radioactivity appeared in rat milk within 5 minutes of intravenous administration of radiolabeled irinotecan HCl and was concentrated up to 65-fold at 4 hours after administration relative to plasma concentrations.

8.3 Females and Males of Reproductive Potential

Contraception

Females

ONIVYDE can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment with ONIVYDE and for one month after the final dose.

Males

Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use condoms during treatment with ONIVYDE and for four months after the final dose *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

Safety and effectiveness of ONIVYDE have not been established in pediatric patients.

8.5 Geriatric Use

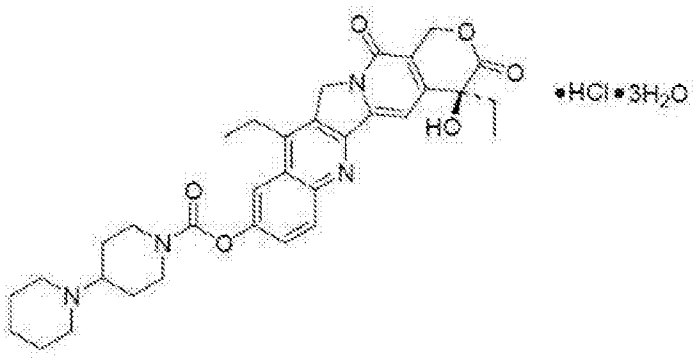
Of the 264 patients who received ONIVYDE as a single agent or in combination with 5-FU and leucovorin in Study 1, 49% were ≥ 65 years old and 13% were ≥ 75 years old. No overall differences in safety and effectiveness were observed between these patients and younger patients.

10 OVERDOSAGE

There are no treatment interventions known to be effective for management of overdosage of ONIVYDE.

11 DESCRIPTION

ONIVYDE is formulated with irinotecan hydrochloride trihydrate, a topoisomerase inhibitor, into a liposomal dispersion for intravenous use. The chemical name of irinotecan hydrochloride trihydrate is (S)-4,11-diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo1H-pyrano[3',4':6,7]-indolizino[1,2-b]quinolin-9-yl-[1,4'bipiperidine]-1'-carboxylate, monohydrochloride, trihydrate. The empirical formula is $C_{33}H_{38}N_4O_6 \cdot HCl \cdot 3H_2O$ and the molecular weight is 677.19 g/mole. The molecular structure is:



ONIVYDE is a sterile, white to slightly yellow opaque isotonic liposomal dispersion. Each 10 mL single-dose vial contains 43 mg irinotecan free base at a concentration of 4.3 mg/mL. The liposome is a unilamellar lipid bilayer vesicle, approximately 110 nm in diameter, which encapsulates an aqueous space containing irinotecan in a gelated or precipitated state as the sucrose octasulfate salt. The vesicle is composed of 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC) 6.81 mg/mL, cholesterol 2.22 mg/mL, and methoxy-terminated polyethylene glycol (MW 2000)-distearoylphosphatidyl ethanolamine (MPEG-2000-DSPE) 0.12 mg/mL. Each mL also contains 2-[4-(2-hydroxyethyl) piperazin-1-yl]ethanesulfonic acid (HEPES) as a buffer 4.05 mg/mL and sodium chloride as an isotonicity reagent 8.42 mg/mL.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Irinotecan liposome injection is a topoisomerase 1 inhibitor encapsulated in a lipid bilayer vesicle or liposome. Topoisomerase 1 relieves torsional strain in DNA by inducing single-strand breaks. Irinotecan and its active metabolite SN-38 bind reversibly to the topoisomerase 1-DNA complex and prevent re-ligation of the single-strand breaks, leading to exposure time-dependent double-strand DNA damage and cell death. In mice bearing human tumor xenografts, irinotecan liposome administered at irinotecan HCl-equivalent doses 5-fold lower than irinotecan HCl achieved similar intratumoral exposure of SN-38.

12.3 Pharmacokinetics

The plasma pharmacokinetics of total irinotecan and total SN-38 were evaluated in patients with cancer who received ONIVYDE, as a single agent or as part of combination chemotherapy, at doses between 50 and 155 mg/m^2 and 353 patients with cancer using population pharmacokinetic analysis.

The pharmacokinetic parameters of total irinotecan and total SN-38 following the administration of ONIVYDE 70 mg/m^2 as a single agent or part of combination chemotherapy are presented in Table 4.

Table 4: Summary of Mean (±Standard Deviation) Total Irinotecan and Total SN-38

Dose (mg/m^2)	Total Irinotecan					Total SN-38		
	C_{max} [µg/mL] (n=25)	$AUC_{0-\infty}$ [h·µg/mL] (n=23)	$t_{1/2}$ [h] (n=23)	CL [L/h] (n=23)	V_d [L] (n=23)	C_{max} [ng/mL] (n=25)	$AUC_{0-\infty}$ [h·ng/mL] (n=13)	$t_{1/2}$ [h] (n=13)
70	37.2 (8.8)	1364 (1048)	25.8 (15.7)	0.20 (0.17)	4.1 (1.5)	5.4 (3.4)	620 (329)	67.8 (44.5)

C_{max}: Maximum plasma concentration
$AUC_{0-\infty}$: Area under the plasma concentration curve extrapolated to time infinity
$t_{½}$: Terminal elimination half-life
CL: Clearance
V_d: Volume of distribution

Over the dose range of 50 to 155 mg/m^2, the C_{max} and AUC of total irinotecan increases with dose. Additionally, the C_{max} of total SN-38 increases proportionally with dose; however, the AUC of total SN-38 increases less than proportionally with dose.

Distribution

Direct measurement of irinotecan liposome showed that 95% of irinotecan remains liposome-encapsulated, and the ratios between total and encapsulated forms did not change with time from 0 to 169.5 hours post-dose. The mean volume of distribution is summarized in Table 4.

Plasma protein binding is <0.44% of the total irinotecan in ONIVYDE.

Elimination

Metabolism

The metabolism of irinotecan liposome has not been evaluated. Irinotecan is subject to extensive metabolic conversion by various enzyme systems, including esterases to form the active metabolite SN-38, and UGT1A1 mediating glucuronidation of SN-38 to form the inactive glucuronide metabolite SN-38G. Irinotecan can also undergo CYP3A4-mediated oxidative metabolism to several inactive oxidation products, one of which can be hydrolyzed by carboxylesterase to release SN-38. In the population pharmacokinetic analysis using the results of a subset with UGT1A1*28 genotypic testing, in which the analysis adjusted for the lower dose administered to patients homozygous for the UGT1A1*28 allele, patients homozygous (N=14) and non-homozygous (N=244) for this allele had total SN-38 average steady-state concentrations of 1.06 and 0.95 ng/mL, respectively.

Excretion

The disposition of ONIVYDE has not been elucidated in humans. Following administration of irinotecan HCl , the urinary excretion of irinotecan is 11 to 20%; SN-38, <1%; and SN-38 glucuronide, 3%. The cumulative biliary and urinary excretion of irinotecan and its metabolites (SN-38 and SN-38 glucuronide), over a period of 48 hours following administration of irinotecan HCl in two patients, ranged from approximately 25% (100 mg/m^2) to 50% (300 mg/m^2).

Specific Populations

Age, Gender, and Renal Impairment:

The population pharmacokinetic analysis suggests that age (28 to 87 years) had no clinically meaningful effect on the exposure of irinotecan and SN-38.

The population pharmacokinetic analysis suggests that gender (196 males and 157 females) had no clinically meaningful effect on the exposure of irinotecan and SN-38 after adjusting for body surface area (BSA).

In a population pharmacokinetic analysis, mild-to-moderate renal impairment had no effect on the exposure of total SN-38 after adjusting for BSA. The analysis included 68 patients with moderate (CLcr 30 - 59 mL/min) renal impairment, 147 patients with mild (CLcr 60 - 89 mL/min) renal impairment, and 135 patients with normal renal function (CLcr > 90 mL/min). There was insufficient data in patients with severe renal impairment (CLcr < 30 mL/min) to assess its effect on pharmacokinetics.

Ethnicity: The population pharmacokinetic analysis suggests that Asians (East Asians, N=150) have 56% lower total irinotecan average steady state concentration and 8% higher total SN-38 average steady state concentration than Whites (N=182).

Hepatic Impairment: The pharmacokinetics of irinotecan liposome have not been studied in patients with hepatic impairment. In a population pharmacokinetic analysis, patients with baseline bilirubin concentrations of 1-2 mg/dL (N=19) had average steady state concentrations for total SN-38 that were increased by 37% compared to patients with baseline bilirubin concentrations of <1 mg/dL (N=329); however, there was no effect of elevated ALT/AST concentrations on total SN-38 concentrations. No data are available in patients with bilirubin >2 mg/dL.

Drug Interactions

In a population pharmacokinetic analysis, the pharmacokinetics of total irinotecan and total SN-38 were not altered by the co-administration of fluorouracil/leucovorin.

Following administration of irinotecan HCl, dexamethasone, a moderate CYP3A4 inducer, does not alter the pharmacokinetics of irinotecan.

In vitro studies indicate that irinotecan, SN-38 and another metabolite, aminopentane carboxylic acid (APC), do not inhibit cytochrome P-450 isozymes.

12.5 Pharmacogenomics

Individuals who are homozygous for the UGT1A1*28 allele are at increased risk for neutropenia from irinotecan HCl. In Study 1, patients homozygous for the UGT1A1*28 allele (N=7) initiated ONIVYDE at a reduced dose of 50 mg/m^2 in combination with 5-FU/LV. The frequency of Grade 3 or 4 neutropenia in these patients [2 of 7 (28.6%)] was similar to the frequency in patients not homozygous for the UGT1A1*28 allele who received a starting dose of ONIVYDE of 70 mg/m^2 [30 of 110 (27.3%)].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been performed to assess the potential of irinotecan liposome for carcinogenicity, genotoxicity or impairment of fertility. Intravenous administration of irinotecan hydrochloride to rats once weekly for 13 weeks followed by a 91-week recovery period resulted in a significant linear trend between irinotecan HCl dosage and the incidence of combined uterine horn endometrial stromal polyps and endometrial stromal sarcomas. Irinotecan HCl was clastogenic both in vitro (chromosome aberrations in Chinese hamster ovary cells) and in vivo (micronucleus test in mice). Neither irinotecan nor its active metabolite, SN-38, was mutagenic in the in vitro Ames assay.

Dedicated fertility studies have not been performed with irinotecan liposome injection. Atrophy of male and female reproductive organs was observed in dogs receiving irinotecan liposome injection every 3 weeks at doses equal to or greater than 15 mg/kg, (approximately 3 times the clinical exposure of irinotecan following administration to ONIVYDE dosed at 70 mg/m^2) for a total of 6 doses. No significant adverse effects on fertility and general reproductive performance were observed after intravenous administration of irinotecan HCl in doses of up to 6 mg/kg/day to rats; however, atrophy of male reproductive organs was observed after multiple daily irinotecan HCl doses both in rodents at 20 mg/kg (approximately 0.007 times the clinical irinotecan exposure following ONIVYDE administration at 70 mg/m^2) and in dogs at 0.4 mg/kg (0.0007 times the clinical exposure to irinotecan following administration of ONIVYDE).

14 CLINICAL STUDIES

The efficacy of ONIVYDE was evaluated in Study 1, a three-arm, randomized, open-label trial in patients with metastatic pancreatic adenocarcinoma with documented disease progression, after gemcitabine or gemcitabine-based therapy. Key eligibility criteria included Karnofsky Performance Status (KPS) ≥70, serum bilirubin within institution limits of normal, and albumin ≥3.0 g/dL. Patients were randomized to receive ONIVYDE plus fluorouracil/leucovorin (ONIVYDE/5-FU/LV), ONIVYDE, or fluorouracil/leucovorin (5-FU/LV). Randomization was stratified by ethnicity (White vs. East Asian vs. other), KPS (70-80 vs. 90-100), and baseline albumin level (≥ 4 g/dL vs. 3.0-3.9 g/dL). Patients randomized to ONIVYDE/5-FU/LV received ONIVYDE 70 mg/m^2 as an intravenous infusion over 90 minutes, followed by leucovorin 400 mg/m^2 intravenously over 30 minutes, followed by fluorouracil 2400 mg/m^2 intravenously over 46 hours, every 2 weeks. The ONIVYDE dose of 70 mg/m^2 is based on irinotecan free base (equivalent to 80 mg/m^2 of irinotecan as the hydrochloride trihydrate). Patients randomized to ONIVYDE as a single agent received ONIVYDE 100 mg/m^2 as an intravenous infusion over 90 minutes every 3 weeks. Patients randomized to 5-FU/LV received leucovorin 200 mg/m^2 intravenously over 30 minutes, followed by fluorouracil 2000 mg/m^2 intravenously over 24 hours, administered on Days 1, 8, 15 and 22 of a 6-week cycle. Patients homozygous for the UGT1A1*28 allele initiated ONIVYDE at a reduced dose (50 mg/m^2 ONIVYDE, if given with 5-FU/LV or 70 mg/m^2 ONIVYDE as a single agent). When ONIVYDE was withheld or discontinued for adverse reactions, 5-FU was also withheld or discontinued. When the dose of

ONIVYDE was reduced for adverse reactions, the dose of 5-FU was reduced by 25%. Treatment continued until disease progression or unacceptable toxicity.

The major efficacy outcome measure was overall survival (OS) with two pair-wise comparisons: ONIVYDE versus 5-FU/LV and ONIVYDE/5-FU/LV versus 5-FU/LV. Additional efficacy outcome measures were progression-free survival (PFS) and objective response rate (ORR). Tumor status assessments were conducted at baseline and every 6 weeks thereafter. The trial was initiated as a two-arm study and amended after initiation to include a third arm (ONIVYDE/5-FU/LV). The comparisons between the ONIVYDE/5-FU/LV and the 5-FU/LV arms are limited to patients enrolled in the 5-FU/LV arm after this protocol amendment.

Four hundred seventeen patients were randomized to: ONIVYDE/5-FU/LV (N=117), ONIVYDE (N=151), or 5-FU/LV (N=149). Baseline demographics and tumor characteristics for the 236 patients randomized to ONIVYDE/5-FU/LV or 5-FU/LV (N=119) after the addition of the third arm to the study were a median age of 63 years (range 34-81 years) and with 41% $\geq$ 65 years of age; 58% were men; 63% were White, 30% were Asian, 3% were Black or African American, and 5% were other. Mean baseline albumin level was 3.97 g/dL, and baseline KPS was 90-100 in 53% of patients. Disease characteristics included liver metastasis (67%) and lung metastasis (31%). A total of 13% of patients received gemcitabine in the neoadjuvant/adjuvant setting only, 55% of patients had 1 prior line of therapy for metastatic disease, and 33% of patients had 2 or more prior lines of therapy for metastatic disease. All patients received prior gemcitabine (alone or in combination with another agent), 54% received prior gemcitabine in combination with another agent, and 13% received prior gemcitabine in combination with nab-paclitaxel.

Study 1 demonstrated a statistically significant improvement in overall survival for the ONIVYDE/5-FU/LV arm over the 5-FU/LV arm as summarized in Table 5 and Figure 1.

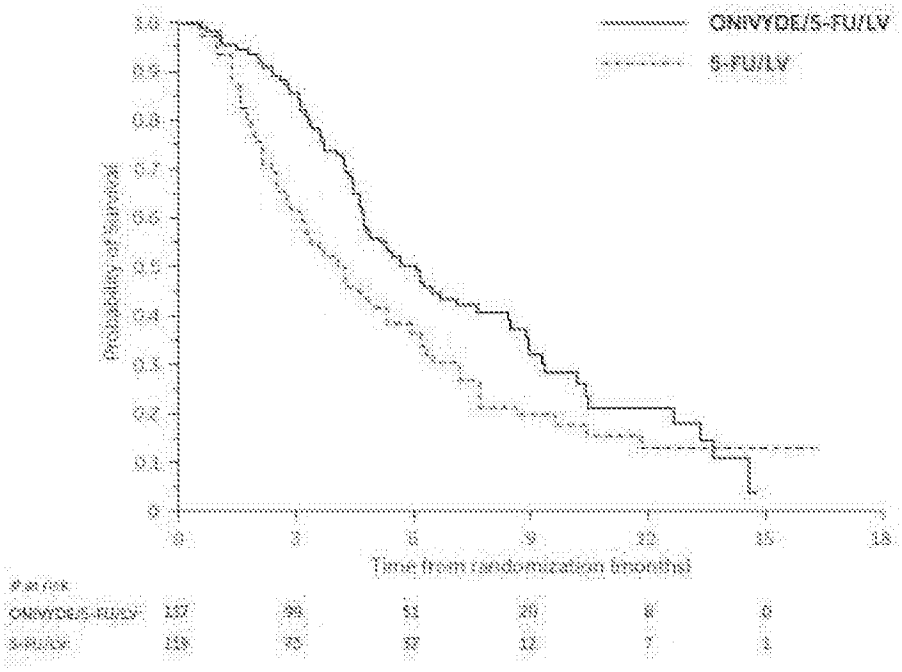
There was no improvement in overall survival for the ONIVYDE arm over the 5-FU/LV arm (hazard ratio=1.00, p-value=0.97 (two-sided log-rank test)).

Table 5: Efficacy Results from Study 1†

	ONIVYDE/5-FU/LV (N=117)	5-FU/LV (N=119)
Overall Survival		
Number of Deaths, n (%)	77 (66)	86 (72)
Median Overall Survival (months)	6.1	4.2
(95% CI)	(4.8, 8.5)	(3.3, 5.3)
Hazard Ratio (95% CI)	0.68 (0.50, 0.93)	
p-value (log-rank test)	0.014	
Progression-Free Survival		
Death or Progression, n (%)	83 (71)	94 (79)
Median Progression-Free Survival (months)	3.1	1.5
(95% CI)	(2.7, 4.2)	(1.4, 1.8)
Hazard Ratio (95% CI)	0.55 (0.41, 0.75)	
Objective Response Rate		
Confirmed Complete or Partial Response n (%)	9 (7.7%)	1 (0.8%)

† 5-FU/LV=5-fluorouracil/leucovorin; CI=confidence interval

Figure 1: Overall Survival



15 REFERENCES

1. OSHA Hazardous Drugs. *OSHA*. http://www.osha.gov/SLTC/hazardousdrugs/index.html

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

ONIVYDE is available in a single-dose vial containing 43 mg irinotecan free base at a concentration of 4.3 mg/mL

NDC: 69171-398-01

Storage and Handling

Store ONIVYDE at 2°C to 8°C (36°F to 46°F). Do NOT freeze. Protect from light.

ONIVYDE is a cytotoxic drug. Follow applicable special handling and disposal procedures.[1]

17 PATIENT COUNSELING INFORMATION

Advise patients of the following:

Severe Neutropenia
Advise patients of the risk of neutropenia leading to severe and life-threatening infections and the need for monitoring of blood counts. Instruct patients to contact their healthcare provider immediately if experiencing signs of infection, such as fever, chills, dizziness, or shortness of breath *[see Warnings and Precautions (5.1)]*.

Severe Diarrhea
Inform patients of the risk of severe diarrhea. Advise patients to contact their healthcare provider if they experience persistent vomiting or diarrhea; black or bloody stools; or symptoms of dehydration such as lightheadedness, dizziness, or faintness *[see Warnings and Precautions (5.2)]*.

Interstitial Lung Disease
Inform patients of the potential risk of ILD. Advise patients to contact their healthcare provider as soon as possible for new onset cough or dyspnea *[see Interstitial Lung Disease (5.3)]*.

Hypersensitivity to irinotecan HCl or ONIVYDE
Advise patients of the potential risk of severe hypersensitivity and that ONIVYDE is contraindicated in patients with a history of severe allergic reactions with irinotecan HCl or ONIVYDE. Instruct patients to seek immediate medical attention for signs of severe hypersensitivity reaction such as chest tightness; shortness of breath; wheezing; dizziness or faintness; or swelling of the face, eyelids, or lips *[see Contraindications (4) and Warnings and Precautions (5.4)]*.

Females and males of reproductive potential
Embryo-fetal toxicity: Inform females of reproductive potential of the potential risk to a fetus, to use effective contraception during treatment and for one month after the final dose, and to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.5), Use in Specific Populations (8.1, 8.3)]*.
Contraception: Advise male patients with female partners of reproductive potential to use condoms during treatment with ONIVYDE and for four months after the final dose *[see Females and Males of Reproductive Potential (8.3)]*.

Lactation
Advise women not to breastfeed during treatment with ONIVYDE and for one month after the final dose *[see Use in Special Populations (8.2)]*.

Manufactured for:
Merrimack Pharmaceuticals, Inc.
Cambridge, MA 02139

ONIVYDE is a trademark of Merrimack Pharmaceuticals, Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use CAMPTOSAR safely and effectively. See full prescribing information for CAMPTOSAR.

CAMPTOSAR (Irinotecan) Injection, intravenous infusion
Initial U.S. Approval: 1996

WARNING: DIARRHEA and MYELOSUPPRESSION
See full prescribing information for complete boxed warning.

- **Early and late forms of diarrhea can occur. Early diarrhea may be accompanied by cholinergic symptoms which may be prevented or ameliorated by atropine. Late diarrhea can be life threatening and should be treated promptly with loperamide. Monitor patients with diarrhea and give fluid and electrolytes as needed. Institute antibiotic therapy if patients develop ileus, fever, or severe neutropenia. Interrupt CAMPTOSAR and reduce subsequent doses if severe diarrhea occurs.**
- **Severe myelosuppression may occur.**

----------**INDICATIONS AND USAGE**----------

CAMPTOSAR is a topoisomerase inhibitor indicated for:

- First-line therapy in combination with 5-fluorouracil and leucovorin for patients with metastatic carcinoma of the colon or rectum. (1)
- Patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following initial fluorouracil-based therapy. (1)

----------**DOSAGE AND ADMINISTRATION**----------

- Colorectal cancer combination regimen 1: CAMPTOSAR 125 mg/m^2 intravenous infusion over 90 minutes on days 1, 8,15, 22 with LV 20 mg/m^2 intravenous bolus infusion on days 1, 8, 15, 22 followed by 5-FU intravenous bolus infusion on days 1, 8, 15, 22 every 6 weeks. (2.1)
- Colorectal cancer combination regimen 2: CAMPTOSAR 180 mg/m^2 intravenous infusion over 90 minutes on days 1, 15, 29 with LV 200 mg/m^2 intravenous infusion over 2 hours on days 1, 2, 15, 16, 29, 20 followed by 5-FU 400 mg/m^2 intravenous bolus infusion on days 1, 2, 15, 16, 29, 30 and 5-FU 600 mg/m^2 intravenous infusion over 22 hours on days 1, 2, 15, 16, 29, 30. (2.1)
- Colorectal cancer single agent regimen 1: CAMPTOSAR 125 mg/m^2 intravenous infusion over 90 minutes on days 1, 8, 15, 22 then 2-week rest. (2.2)
- Colorectal cancer single agent regimen 2: CAMPTOSAR 350 mg/m^2 intravenous infusion over 90 minutes on day 1 every 3 weeks. (2.2)

----------**DOSAGE FORMS AND STRENGTHS**----------

CAMPTOSAR Injection is available in three single-dose sizes:

- 2 mL-fill vial containing 40 mg irinotecan hydrochloride injection
- 5 mL-fill vial containing 100 mg irinotecan hydrochloride injection
- 15 mL-fill vial containing 300 mg irinotecan hydrochloride injection

----------**CONTRAINDICATIONS**----------

- Hypersensitivity to CAMPTOSAR or its excipients (4)

----------**WARNINGS AND PRECAUTIONS**----------

- **Diarrhea and cholinergic reactions:** Early diarrhea (occurring during or shortly after infusion of CAMPTOSAR) is usually transient and may be accompanied by cholinergic symptoms. Consider prophylactic or therapeutic administration of 0.25 mg to 1 mg of intravenous or subcutaneous atropine (unless clinically contraindicated). Late diarrhea (generally occurring more than 24 hours after administration of CAMPTOSAR) can occur. Monitor and replace fluid and electrolytes. Treat with loperamide. Use antibiotic support for ileus and fever. Interrupt CAMPTOSAR and reduce subsequent doses if severe diarrhea occurs. (5.1)
- **Myelosuppression:** Manage promptly with antibiotic support. Interrupt CAMPTOSAR and reduce subsequent doses if necessary. (5.2)
- **Patients with Reduced UGT1A1 Activity:** Individuals who are homozygous for the UGT1A1*28 allele are at increased risk for neutropenia following initiation of CAMPTOSAR treatment. (5.3)
- **Hypersensitivity:** Hypersensitivity reactions including severe anaphylactic or anaphylactoid reactions have been observed. Discontinue CAMPTOSAR if this occurs. (5.4)
- **Renal Impairment/Renal Failure:** Rare cases of renal impairment and acute renal failure have been identified, usually in patients who became volume depleted from severe vomiting and/or diarrhea. (5.5)
- **Pulmonary Toxicity:** Interstitial Pulmonary Disease (IPD)-like events, including fatalities, have occurred. Interrupt for new or progressive dysnpnea, cough, and fever pending evaluation. If IPD diagnosed, discontinue and institute appropriate treatment as needed. (5.6)
- **Toxicity of the 5 Day Regimen:** CAMPTOSAR should not be used in combination with a regimen of 5-FU/LV administered for 4-5 consecutive days every 4 weeks outside of a clinical study. (5.7)
- **Pregnancy:** CAMPTOSAR can cause fetal harm when administered to a pregnant woman. (5.9)
- **Hepatic Impairment:** In clinical trials, CAMPTOSAR has not been administered to patients with serum bilirubin > 2.0 mg/dL, or transaminases > 3 times ULN if no liver metastases, or transaminases > 5 times ULN if liver metastases. With the weekly dosage schedule, patients with total bilirubin levels 1.0-2.0 mg/dL had greater likelihood of grade 3-4 neutropenia. (5.10)

----------**ADVERSE REACTIONS**----------

Common adverse reactions (≥30%) observed in combination therapy clinical studies are: nausea, vomiting, abdominal pain, diarrhea, constipation, anorexia, mucositis, neutropenia, leukopenia (including lymphocytopenia), anemia, thrombocytopenia, asthenia, pain, fever, infection, abnormal bilirubin, alopecia. (6.1)

Common adverse reactions (≥30%) observed in single agent therapy clinical studies are: nausea, vomiting, abdominal pain, diarrhea, constipation, anorexia, neutropenia, leukopenia (including lymphocytopenia), anemia, asthenia, fever, body weight decreasing, alopecia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer Inc at 1-800-438-1985 or *www.pfizer.com* or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------**DRUG INTERACTIONS**----------

- Strong CYP3A4 Inducers: Do not administer for at least 2 weeks prior to initiation of irinotecan therapy. (7.2)
- Strong CYP3A4 Inhibitors: Discontinue at least 1 week prior to starting irinotecan therapy and do not use during irinotecan therapy. (7.3)

----------**USE IN SPECIFIC POPULATIONS**----------

- **Nursing Mothers:** Discontinue nursing when receiving therapy with CAMPTOSAR. (8.3)
- **Geriatric Use:** Closely monitor patients greater than 65 years of age because of a greater risk of early and late diarrhea in this population. (8.5)
- **Patients with Renal Impairment**: Use caution and do not use in patients on dialysis. (8.6)
- **Patients with Hepatic Impairment**: Use caution. (2.1, 5.10, 8.7, 12.3)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 07/2012

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*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: DIARRHEA AND MYELOSUPPRESSION

- **Early and late forms of diarrhea can occur. Early diarrhea may be accompanied by cholinergic symptoms which may be prevented or ameliorated by atropine. Late diarrhea can be life threatening and should be treated promptly with loperamide. Monitor patients with diarrhea and give fluid and electrolytes as needed. Institute antibiotic therapy if patients develop ileus, fever, or severe neutropenia. Interrupt CAMPTOSAR and reduce subsequent doses if severe diarrhea occurs.**
- **Severe myelosuppression may occur.**

1 INDICATIONS AND USAGE

- CAMPTOSAR Injection is indicated as a component of first-line therapy in combination with 5-fluorouracil (5-FU) and leucovorin (LV) for patients with metastatic carcinoma of the colon or rectum.

- CAMPTOSAR is indicated for patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed following initial fluorouracil-based therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Colorectal Cancer Combination Regimens 1 and 2

Administer CAMPTOSAR as a 90-minute intravenous infusion followed by LV and 5-FU. The currently recommended regimens are shown in Table 1.

A reduction in the starting dose by one dose level of CAMPTOSAR may be considered for patients with any of the following conditions: prior pelvic/abdominal radiotherapy, performance status of 2, or increased bilirubin levels. Dosing for patients with bilirubin >2 mg/dL cannot be recommended because there is insufficient information to recommend a dose in these patients.

Table 1. Combination-Agent Dosage Regimens and Dose Modifications[a]

Regimen 1 6-wk cycle with bolus 5-FU/LV (next cycle begins on day 43)	CAMPTOSAR LV 5-FU	125 mg/m^2 intravenous infusion over 90 minutes, days 1,8,15,22 20 mg/m^2 intravenous injection bolus, days 1,8,15,22 500 mg/m^2 intravenous injection bolus, days 1,8,15,22		
		Starting Dose & Modified Dose Levels (mg/m^2)		
		Starting Dose	Dose Level -1	Dose Level -2
	CAMPTOSAR	125	100	75
	LV	20	20	20
	5-FU	500	400	300
Regimen 2 6-wk cycle with infusional 5-FU/LV (next cycle begins on day 43)	CAMPTOSAR LV 5-FU Bolus 5-FU Infusion[b]	180 mg/m^2 intravenous infusion over 90 minutes, days 1,15,29 200 mg/m^2 intravenous infusion over 2 hours, days 1,2,15,16,29,30 400 mg/m^2 intravenous injection bolus, days 1,2,15,16,29,30 600 mg/m^2 intravenous infusion over 22 hours, days 1,2,15,16,29,30		
		Starting Dose & Modified Dose Levels (mg/m^2)		
		Starting Dose	Dose Level -1	Dose Level -2
	CAMPTOSAR	180	150	120
	LV	200	200	200
	5-FU Bolus	400	320	240
	5-FU Infusion[b]	600	480	360

[a]Dose reductions beyond Dose Level –2 by decrements of ≈ 20% may be warranted for patients continuing to experience toxicity. Provided intolerable toxicity does not develop, treatment with additional cycles may be continued indefinitely as long as patients continue to experience clinical benefit.
[b]Infusion follows bolus administration.

Dosing for patients with bilirubin >2 mg/dL cannot be recommended because there is insufficient information to recommend a dose in these patients *[see Warnings and Precautions (5.10), Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)]*.

Dose Modifications

Based on recommended dose levels described in Table 1, Combination Regimens of CAMPTOSAR and Dose Modifications, subsequent doses should be adjusted as suggested in Table 2, Recommended Dose Modifications for Combination Regimens. All dose modifications should be based on the worst preceding toxicity.

Table 2. Recommended Dose Modifications for CAMPTOSAR/5-Fluorouracil (5-FU)/Leucovorin (LV) Combination Schedules

Patients should return to pre-treatment bowel function without requiring antidiarrhea medications for at least 24 hours before the next chemotherapy administration. A new cycle of therapy should not begin until the granulocyte count has recovered to ≥1500/mm^3, and the platelet count has recovered to ≥100,000/mm^3, and treatment-related diarrhea is fully resolved. Treatment should be delayed 1 to 2 weeks to allow for recovery from treatment-related toxicities. If the patient has not recovered after a 2-week delay, consideration should be given to discontinuing therapy.

Toxicity NCI CTC Grade[a] (Value)	During a Cycle of Therapy	At the Start of Subsequent Cycles of Therapy[b]
No toxicity	Maintain dose level	Maintain dose level
Neutropenia		
1 (1500 to 1999/mm^3)	Maintain dose level	Maintain dose level
2 (1000 to 1499/mm^3)	↓ 1 dose level	Maintain dose level
3 (500 to 999/mm^3)	Omit dose until resolved to ≤ grade 2, then ↓ 1 dose level	↓ 1 dose level
4 (<500/mm^3)	Omit dose until resolved to ≤ grade 2, then ↓ 2 dose levels	↓ 2 dose levels
Neutropenic fever	Omit dose until resolved, then ↓ 2 dose levels	
Other hematologic toxicities	Dose modifications for leukopenia or thrombocytopenia during a cycle of therapy and at the start of subsequent cycles of therapy are also based on NCI toxicity criteria and are the same as recommended for neutropenia above.	
Diarrhea		
1 (2-3 stools/day > pretx[c])	Delay dose until resolved to baseline, then give same dose	Maintain dose level
2 (4-6 stools/day > pretx)	Omit dose until resolved to baseline, then ↓ 1 dose level	Maintain dose level
3 (7-9 stools/day > pretx)	Omit dose until resolved to baseline, then ↓ 2 dose levels	↓ 1 dose level
4 (≥10 stools/day > pretx)		↓ 2 dose levels
Other nonhematologic toxicities[d]		
1	Maintain dose level	Maintain dose level
2	Omit dose until resolved to ≤ grade 1, then ↓ 1 dose level	Maintain dose level
3	Omit dose until resolved to ≤ grade 2, then ↓ 1 dose level	↓ 1 dose level
4	Omit dose until resolved to ≤ grade 2, then ↓ 2 dose levels	↓ 2 dose levels
	For mucositis/stomatitis decrease only 5-FU, not CAMPTOSAR	*For mucositis/stomatitis decrease only 5-FU, not CAMPTOSAR.*

[a] National Cancer Institute Common Toxicity Criteria (version 1.0)
[b] Relative to the starting dose used in the previous cycle
[c] Pretreatment
[d] Excludes alopecia, anorexia, asthenia

2.2 Colorectal Single Agent Regimens 1 and 2

Administer CAMPTOSAR as a 90-minute intravenous infusion. The currently recommended regimens are shown in Table 3.

A reduction in the starting dose by one dose level of CAMPTOSAR may be considered for patients with any of the following conditions: prior pelvic/abdominal radiotherapy, performance status of 2, or increased bilirubin levels. Dosing for patients with bilirubin >2 mg/dL cannot be recommended because there is insufficient information to recommend a dose in these patients.

Table 3. Single-Agent Regimens of CAMPTOSAR and Dose Modifications

Regimen 1 (weekly)[a]	125 mg/m^2 intravenous infusion over 90 minutes, days 1,8,15,22 then 2-week rest		
	Starting Dose and Modified Dose Levels[c] (mg/m^2)		
	Starting Dose	Dose Level -1	Dose Level -2
	125	100	75
Regimen 2 (every 3 weeks)[b]	350 mg/m^2 intravenous infusion over 90 minutes, once every 3 weeks[c]		
	Starting Dose and Modified Dose Levels (mg/m^2)		
	Starting Dose	Dose Level -1	Dose Level -2
	350	300	250

[a]Subsequent doses may be adjusted as high as 150 mg/m^2 or to as low as 50 mg/m^2 in 25 to 50 mg/m^2 decrements depending upon individual patient tolerance.
[b]Subsequent doses may be adjusted as low as 200 mg/m^2 in 50 mg/m^2 decrements depending upon individual patient tolerance.
[c]Provided intolerable toxicity does not develop, treatment with additional cycles may be continued indefinitely as long as patients continue to experience clinical benefit.

Dose Modifications

Based on recommended dose-levels described in Table 3, Single-Agent Regimens of CAMPTOSAR and Dose Modifications, subsequent doses should be adjusted as suggested in Table 4, Recommended Dose Modifications for Single-Agent Schedules. All dose modifications should be based on the worst preceding toxicity.

Table 4: Recommended Dose Modifications For Single-Agent Schedules[a]

A new cycle of therapy should not begin until the granulocyte count has recovered to ≥1500/mm^3, and the platelet count has recovered to ≥100,000/mm^3, and treatment-related diarrhea is fully resolved. Treatment should be delayed 1 to 2 weeks to allow for recovery from treatment-related toxicities. If the patient has not recovered after a 2-week delay, consideration should be given to discontinuing CAMPTOSAR.

Worst Toxicity NCI Grade[b] (Value)	**During a Cycle of Therapy**	**At the Start of the Next Cycles of Therapy (After Adequate Recovery), Compared with the Starting Dose in the Previous Cycle[a]**	
	Weekly	Weekly	Once Every 3 Weeks
No toxicity	Maintain dose level	↑ 25 mg/m^2 up to a maximum dose of 150 mg/m^2	Maintain dose level
Neutropenia			
1 (1500 to 1999/mm^3)	Maintain dose level	Maintain dose level	Maintain dose level
2 (1000 to 1499/mm^3)	↓ 25 mg/m^2	Maintain dose level	Maintain dose level
3 (500 to 999/mm^3)	Omit dose until resolved to ≤ grade 2, then ↓ 25 mg/m^2	↓ 25 mg/m^2	↓ 50 mg/m^2
4 (<500/mm^3)	Omit dose until resolved to ≤ grade 2, then ↓ 50 mg/m^2	↓ 50 mg/m^2	↓ 50 mg/m^2
Neutropenic fever	Omit dose until resolved, then ↓ 50 mg/m^2 when resolved	↓ 50 mg/m^2	↓ 50 mg/m^2
Other hematologic toxicities	Dose modifications for leukopenia, thrombocytopenia, and anemia during a cycle of therapy and at the start of subsequent cycles of therapy are also based on NCI toxicity criteria and are the same as recommended for neutropenia above.		
Diarrhea			
1 (2-3 stools/day > pretx[c])	Maintain dose level	Maintain dose level	Maintain dose level
2 (4-6 stools/day > pretx)	↓ 25 mg/m^2	Maintain dose level	Maintain dose level
3 (7-9 stools/day > pretx)	Omit dose until resolved to ≤ grade 2, then ↓ 25 mg/m^2	↓ 25 mg/m^2	↓ 50 mg/m^2
4 (≥10 stools/day > pretx)	Omit dose until resolved to ≤ grade 2 then ↓ 50 mg/m^2	↓ 50 mg/m^2	↓ 50 mg/m^2
Other nonhematologic[d] toxicities			
1	Maintain dose level	Maintain dose level	Maintain dose level
2	↓ 25 mg/m^2	↓ 25 mg/m^2	↓ 50 mg/m^2
3	Omit dose until resolved to ≤ grade 2, then ↓ 25 mg/m^2	↓ 25 mg/m^2	↓ 50 mg/m^2
4	Omit dose until resolved to ≤ grade 2, then ↓ 50 mg/m^2	↓ 50 mg/m^2	↓ 50 mg/m^2

[a] All dose modifications should be based on the worst preceding toxicity
[b] National Cancer Institute Common Toxicity Criteria (version 1.0)
[c] Pretreatment
[d] Excludes alopecia, anorexia, asthenia

2.3 Dosage in Patients with Reduced UGT1A1 Activity

When administered in combination with other agents, or as a single-agent, a reduction in the starting dose by at least one level of CAMPTOSAR should be considered for patients known to be homozygous for the UGT1A1*28 allele *[see Dosage and Administration (2.1 and 2.2) and Warnings and Precautions (5.3)]*. However, the precise dose reduction in this patient

population is not known, and subsequent dose modifications should be considered based on individual patient tolerance to treatment (see Tables 1-4).

2.4 Premedication

It is recommended that patients receive premedication with antiemetic agents. In clinical studies of the weekly dosage schedule, the majority of patients received 10 mg of dexamethasone given in conjunction with another type of antiemetic agent, such as a 5-HT^3 blocker (e.g., ondansetron or granisetron). Antiemetic agents should be given on the day of treatment, starting at least 30 minutes before administration of CAMPTOSAR. Physicians should also consider providing patients with an antiemetic regimen (e.g., prochlorperazine) for subsequent use as needed. A similar antiemetic regimen should be used with Camptosar in combination therapy.

Prophylactic or therapeutic administration of atropine should be considered in patients experiencing cholinergic symptoms.

2.5 Preparation of Infusion Solution

Inspect vial contents for particulate matter and discoloration and repeat inspection when drug product is withdrawn from vial into syringe.

CAMPTOSAR Injection 20 mg/mL is intended for single use only and any unused portion should be discarded.

CAMPTOSAR Injection must be diluted prior to infusion. CAMPTOSAR should be diluted in 5% Dextrose Injection, USP, (preferred) or 0.9% Sodium Chloride Injection, USP, to a final concentration range of 0.12 mg/mL to 2.8 mg/mL. Other drugs should not be added to the infusion solution.

The solution is physically and chemically stable for up to 24 hours at room temperature and in ambient fluorescent lighting. Solutions diluted in 5% Dextrose Injection, USP, and stored at refrigerated temperatures (approximately 2° to 8°C, 36° to 46°F), and protected from light are physically and chemically stable for 48 hours. Refrigeration of admixtures using 0.9% Sodium Chloride Injection, USP, is not recommended due to a low and sporadic incidence of visible particulates. Freezing CAMPTOSAR and admixtures of CAMPTOSAR may result in precipitation of the drug and should be avoided.

The CAMPTOSAR Injection solution should be used immediately after reconstitution as it contains no antibacterial preservative. Because of possible microbial contamination during dilution, it is advisable to use the admixture prepared with 5% Dextrose Injection, USP, within 24 hours if refrigerated (2° to 8°C, 36° to 46°F). In the case of admixtures prepared with 5% Dextrose Injection, USP, or Sodium Chloride Injection, USP, the solutions should be used within 4 hours if kept at room temperature. If reconstitution and dilution are performed under strict aseptic conditions (e.g. on Laminar Air Flow bench), CAMPTOSAR

Injection solution should be used (infusion completed) within 12 hours at room temperature or 24 hours if refrigerated (2° to 8°C, 36° to 46°F).

2.6 Safe Handling

Care should be exercised in the handling and preparation of infusion solutions prepared from CAMPTOSAR Injection. The use of gloves is recommended. If a solution of CAMPTOSAR contacts the skin, wash the skin immediately and thoroughly with soap and water. If CAMPTOSAR contacts the mucous membranes, flush thoroughly with water. Several published guidelines for handling and disposal of anticancer agents are available.

2.7 Extravasation

Care should be taken to avoid extravasation, and the infusion site should be monitored for signs of inflammation. Should extravasation occur, flushing the site with sterile water and applications of ice are recommended.

3 DOSAGE FORMS AND STRENGTHS

CAMPTOSAR Injection is available in three single-dose sizes:

- 2 mL-fill vial containing 40 mg irinotecan hydrochloride
- 5 mL-fill vial containing 100 mg irinotecan hydrochloride
- 15 mL-fill vial containing 300 mg irinotecan hydrochloride

4 CONTRAINDICATIONS

- CAMPTOSAR Injection is contraindicated in patients with a known hypersensitivity to the drug or its excipients.

5 WARNINGS AND PRECAUTIONS

5.1 Diarrhea and Cholinergic Reactions

Early diarrhea (occurring during or shortly after infusion of CAMPTOSAR) is usually transient and infrequently severe. It may be accompanied by cholinergic symptoms of rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, and intestinal hyperperistalsis that can cause abdominal cramping. Bradycardia may also occur. Early diarrhea and other cholinergic symptoms may be prevented or treated. Consider prophylactic or therapeutic administration of 0.25 mg to 1 mg of intravenous or subcutaneous atropine (unless clinically contraindicated). These symptoms are expected to occur more frequently with higher irinotecan doses.

Late diarrhea (generally occurring more than 24 hours after administration of CAMPTOSAR) can be life threatening since it may be prolonged and may lead to dehydration, electrolyte imbalance, or sepsis. Grade 3-4 late diarrhea occurred in 23-31% of

patients receiving weekly dosing. In the clinical studies, the median time to the onset of late diarrhea was 5 days with 3-week dosing and 11 days with weekly dosing. Late diarrhea can be complicated by colitis, ulceration, bleeding, ileus, obstruction, and infection. Cases of megacolon and intestinal perforation have been reported. Patients should have loperamide readily available to begin treatment for late diarrhea. Begin loperamide at the first episode of poorly formed or loose stools or the earliest onset of bowel movements more frequent than normal. One dosage regimen for loperamide is 4 mg at the first onset of late diarrhea and then 2 mg every 2 hours until the patient is diarrhea-free for at least 12 hours. Loperamide is not recommended to be used for more than 48 consecutive hours at these doses, because of the risk of paralytic ileus. During the night, the patient may take 4 mg of loperamide every 4 hours. Monitor and replace fluid and electrolytes. Use antibiotic support for ileus, fever, or severe neutropenia. Subsequent weekly chemotherapy treatments should be delayed in patients until return of pretreatment bowel function for at least 24 hours without anti-diarrhea medication. Patients must not be treated with irinotecan until resolution of the bowel obstruction. If grade 2, 3, or 4 late diarrhea recurs, subsequent doses of CAMPTOSAR should be decreased *[see Dosage and Administration (2)]*.

Avoid diuretics or laxatives in patients with diarrhea.

5.2 Myelosuppression

Deaths due to sepsis following severe neutropenia have been reported in patients treated with CAMPTOSAR. In the clinical studies evaluating the weekly dosage schedule, neutropenic fever (concurrent NCI grade 4 neutropenia and fever of grade 2 or greater) occurred in 3% of the patients; 6% of patients received G-CSF for the treatment of neutropenia. Manage febrile neutropenia promptly with antibiotic support *[see Warnings and Precautions (5.2)]*. Hold CAMPTOSAR if neutropenic fever occurs or if the absolute neutrophil count drops $<1000/mm^3$. After recovery to an absolute neutrophil count $\geq 1000/mm^3$, subsequent doses of CAMPTOSAR should be reduced *[see Dosage and Administration (2)]*.

When evaluated in the trials of weekly administration, the frequency of grade 3 and 4 neutropenia was higher in patients who received previous pelvic/abdominal irradiation than in those who had not received such irradiation (48% [13/27] versus 24% [67/277]; p=0.04). Patients who have previously received pelvic/abdominal irradiation are at increased risk of severe myelosuppression following the administration of CAMPTOSAR. Based on sparse available data, the concurrent administration of CAMPTOSAR with irradiation is not recommended.

Patients with baseline serum total bilirubin levels of 1.0 mg/dL or more also had a greater likelihood of experiencing first-cycle grade 3 or 4 neutropenia than those with bilirubin levels that were less than 1.0 mg/dL (50% [19/38] versus 18% [47/266]; p<0.001). Patients with deficient glucuronidation of bilirubin, such as those with Gilbert's syndrome, may be at greater risk of myelosuppression when receiving therapy with CAMPTOSAR.

5.3 Patients With Reduced UGT1A1 Activity

Individuals who are homozygous for the UGT1A1*28 allele (UGT1A1 7/7 genotype) are at increased risk for neutropenia following initiation of CAMPTOSAR treatment.

In a study of 66 patients who received single-agent CAMPTOSAR (350 mg/m^2 once-every-3-weeks), the incidence of grade 4 neutropenia in patients homozygous for the UGT1A1*28 allele was 50%, and in patients heterozygous for this allele (UGT1A1 6/7 genotype) the incidence was 12.5%. No grade 4 neutropenia was observed in patients homozygous for the wild-type allele (UGT1A1 6/6 genotype).

In a prospective study (n=250) to investigate the role of UGT1A1*28 polymorphism in the development of toxicity in patients treated with CAMPTOSAR (180 mg/m^2) in combination with infusional 5-FU/LV, the incidence of grade 4 neutropenia in patients homozygous for the UGT1A1*28 allele was 4.5%, and in patients heterozygous for this allele the incidence was 5.3%. Grade 4 neutropenia was observed in 1.8% of patients homozygous for the wild-type allele.

In another study in which 109 patients were treated with CAMPTOSAR (100-125 mg/m^2) in combination with bolus 5-FU/LV, the incidence of grade 4 neutropenia in patients homozygous for the UGT1A1*28 allele was 18.2%, and in patients heterozygous for this allele the incidence was 11.1%. Grade 4 neutropenia was observed in 6.8% of patients homozygous for the wild-type allele.

When administered in combination with other agents or as a single-agent, a reduction in the starting dose by at least one level of CAMPTOSAR should be considered for patients known to be homozygous for the UGT1A1*28 allele. However, the precise dose reduction in this patient population is not known and subsequent dose modifications should be considered based on individual patient tolerance to treatment *[see Dosage and Administration (2)]*.

UGT1A1 Testing

A laboratory test is available to determine the UGT1A1 status of patients. Testing can detect the UGT1A1 6/6, 6/7 and 7/7 genotypes.

5. 4 Hypersensitivity

Hypersensitivity reactions including severe anaphylactic or anaphylactoid reactions have been observed. Discontinue CAMPTOSAR if anaphylactic reaction occurs.

5. 5 Renal Impairment/Renal Failure

Renal impairment and acute renal failure have been identified, usually in patients who became volume depleted from severe vomiting and/or diarrhea.

5. 6 Pulmonary Toxicity

Interstitial Pulmonary Disease (IPD)-like events, including fatalities, have occurred in patients receiving irinotecan (in combination and as monotherapy). Risk factors include pre-existing lung disease, use of pneumotoxic drugs, radiation therapy, and colony stimulating factors. Patients with risk factors should be closely monitored for respiratory symptoms before and during irinotecan therapy. In Japanese studies, a reticulonodular pattern on chest x-ray was observed in a small percentage of patients. New or progressive, dyspnea, cough, and fever should prompt interruption of chemotherapy, pending diagnostic evaluation. If IPD is diagnosed, irinotecan and other chemotherapy should be discontinued and appropriate treatment instituted as needed *[see Adverse Reactions (6.1)]*.

5.7 Toxicity of the 5 Day Regimen

Outside of a well-designed clinical study, CAMPTOSAR Injection should not be used in combination with a regimen of 5-FU/LV administered for 4-5 consecutive days every 4 weeks because of reports of increased toxicity, including toxic deaths. CAMPTOSAR should be used as recommended in Table 2 *[see Dosage and Administration (2)]*.

5.8 Increased Toxicity in Patients with Performance Status 2

In patients receiving either irinotecan/5-FU/LV or 5-FU/LV in the clinical trials, higher rates of hospitalization, neutropenic fever, thromboembolism, first-cycle treatment discontinuation, and early deaths were observed in patients with a baseline performance status of 2 than in patients with a baseline performance status of 0 or 1.

5.9 Pregnancy

CAMPTOSAR can cause fetal harm when administered to a pregnant woman. Irinotecan was embryotoxic in rats and rabbits at doses significantly lower than those administered to humans on a mg/m^2 basis. In rats, at exposures approximately 0.2 times those achieved in humans at the 125 mg/m^2 dose, irinotecan was embryotoxic and resulted in decreased learning ability and female fetal body weight in surviving pups; the drug was teratogenic at lower exposures (approximately 0.025 times the AUC in humans at the 125 mg/m^2 dose).There are no adequate and well-controlled studies of irinotecan in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with CAMPTOSAR.

5.10 Patients with Hepatic Impairment

The use of CAMPTOSAR in patients with significant hepatic impairment has not been established. In clinical trials of either dosing schedule, irinotecan was not administered to patients with serum bilirubin >2.0 mg/dL, or transaminase >3 times the upper limit of normal if no liver metastasis, or transaminase >5 times the upper limit of normal with liver metastasis. In clinical trials of the weekly dosage schedule, patients with modestly elevated baseline serum total bilirubin levels (1.0 to 2.0 mg/dL) had a significantly greater likelihood

of experiencing first-cycle, grade 3 or 4 neutropenia than those with bilirubin levels that were less than 1.0 mg/dL (50% [19/38] versus 18% [47/226]; p<0.001) *[see Dosage and Administration (2.1), Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)]*.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.
Common adverse reactions (≥30%) observed in combination therapy clinical studies are: nausea, vomiting, abdominal pain, diarrhea, constipation, anorexia, mucositis, neutropenia, leukopenia (including lymphocytopenia), anemia, thrombocytopenia, asthenia, pain, fever, infection, abnormal bilirubin, and alopecia.

Common adverse reactions (≥30%) observed in single agent therapy clinical studies are: nausea, vomiting, abdominal pain, diarrhea, constipation, anorexia, neutropenia, leukopenia (including lymphocytopenia), anemia, asthenia, fever, body weight decreasing, and alopecia.

Serious opportunistic infections have not been observed, and no complications have specifically been attributed to lymphocytopenia.

First-Line Combination Therapy

A total of 955 patients with metastatic colorectal cancer received the recommended regimens of irinotecan in combination with 5-FU/LV, 5-FU/LV alone, or irinotecan alone. In the two phase 3 studies, 370 patients received irinotecan in combination with 5-FU/LV, 362 patients received 5-FU/LV alone, and 223 patients received irinotecan alone *[see Dosage and Administration (2)]*.

In Study 1, 49 (7.3%) patients died within 30 days of last study treatment: 21 (9.3%) received irinotecan in combination with 5-FU/LV, 15 (6.8%) received 5-FU/LV alone, and 13 (5.8%) received irinotecan alone. Deaths potentially related to treatment occurred in 2 (0.9%) patients who received irinotecan in combination with 5-FU/LV (2 neutropenic fever/sepsis), 3 (1.4%) patients who received 5-FU/LV alone (1 neutropenic fever/sepsis, 1 CNS bleeding during thrombocytopenia, 1 unknown) and 2 (0.9%) patients who received irinotecan alone (2 neutropenic fever). Deaths from any cause within 60 days of first study treatment were reported for 15 (6.7%) patients who received irinotecan in combination with 5-FU/LV, 16 (7.3%) patients who received 5-FU/LV alone, and 15 (6.7%) patients who received irinotecan alone. Discontinuations due to adverse events were reported for 17 (7.6%) patients who received irinotecan in combination with 5FU/LV, 14 (6.4%) patients who received 5-FU/LV alone, and 26 (11.7%) patients who received irinotecan alone.

In Study 2, 10 (3.5%) patients died within 30 days of last study treatment: 6 (4.1%) received irinotecan in combination with 5-FU/LV and 4 (2.8%) received 5-FU/LV alone. There was one potentially treatment-related death, which occurred in a patient who received irinotecan

in combination with 5-FU/LV (0.7%, neutropenic sepsis). Deaths from any cause within 60 days of first study treatment were reported for 3 (2.1%) patients who received irinotecan in combination with 5-FU/LV and 2 (1.4%) patients who received 5-FU/LV alone. Discontinuations due to adverse events were reported for 9 (6.2%) patients who received irinotecan in combination with 5FU/LV and 1 (0.7%) patient who received 5-FU/LV alone.

The most clinically significant adverse events for patients receiving irinotecan-based therapy were diarrhea, nausea, vomiting, neutropenia, and alopecia. The most clinically significant adverse events for patients receiving 5-FU/LV therapy were diarrhea, neutropenia, neutropenic fever, and mucositis. In Study 1, grade 4 neutropenia, neutropenic fever (defined as grade 2 fever and grade 4 neutropenia), and mucositis were observed less often with weekly irinotecan/5-FU/LV than with monthly administration of 5-FU/LV.

Tables 5 and 6 list the clinically relevant adverse events reported in Studies 1 and 2, respectively.

Table 5. Study 1: Percent (%) of Patients Experiencing Clinically Relevant Adverse Events in Combination Therapies[a]

Adverse Event	Study 1					
	Irinotecan + Bolus 5-FU/LV weekly x 4 every 6 weeks N=225		Bolus 5-FU/LV daily x 5 every 4 weeks N=219		Irinotecan weekly x 4 every 6 weeks N=223	
	Grade 1-4	Grade 3&4	Grade 1-4	Grade 3&4	Grade 1-4	Grade 3&4
TOTAL Adverse Events	100	53.3	100	45.7	99.6	45.7
GASTROINTESTINAL						
Diarrhea	84.9	22.7	69.4	13.2	83.0	31.0
late	--	15.1	--	5.9	--	18.4
grade 3	--	7.6	--	7.3	--	12.6
grade 4	45.8	4.9	31.5	1.4	43.0	6.7
early						
Nausea	79.1	15.6	67.6	8.2	81.6	16.1
Abdominal pain	63.1	14.6	50.2	11.5	67.7	13.0
Vomiting	60.4	9.7	46.1	4.1	62.8	12.1
Anorexia	34.2	5.8	42.0	3.7	43.9	7.2
Constipation	41.3	3.1	31.5	1.8	32.3	0.4
Mucositis	32.4	2.2	76.3	16.9	29.6	2.2
HEMATOLOGIC						
Neutropenia	96.9	53.8	98.6	66.7	96.4	31.4
grade 3	--	29.8	--	23.7	--	19.3
grade 4	--	24.0	--	42.5	--	12.1
Leukopenia	96.9	37.8	98.6	23.3	96.4	21.5
Anemia	96.9	8.4	98.6	5.5	96.9	4.5
Neutropenic fever	--	7.1	--	14.6	--	5.8
Thrombocytopenia	96.0	2.6	98.6	2.7	96.0	1.7
Neutropenic infection	--	1.8	--	0	--	2.2
BODY AS A WHOLE						
Asthenia	70.2	19.5	64.4	11.9	69.1	13.9

Pain	30.7	3.1	26.9	3.6	22.9	2.2
Fever	42.2	1.7	32.4	3.6	43.5	0.4
Infection	22.2	0	16.0	1.4	13.9	0.4
METABOLIC & NUTRITIONAL						
Bilirubin	87.6	7.1	92.2	8.2	83.9	7.2
DERMATOLOGIC	0.9	0	3.2	0.5	0	0
Exfoliative dermatitis	19.1	0	26.5	0.9	14.3	0.4
Rash	43.1	--	26.5	--	46.1	--
Alopecia[b]						
RESPIRATORY						
Dyspnea	27.6	6.3	16.0	0.5	22.0	2.2
Cough	26.7	1.3	18.3	0	20.2	0.4
Pneumonia	6.2	2.7	1.4	1.0	3.6	1.3
NEUROLOGIC						
Dizziness	23.1	1.3	16.4	0	21.1	1.8
Somnolence	12.4	1.8	4.6	1.8	9.4	1.3
Confusion	7.1	1.8	4.1	0	2.7	0
CARDIOVASCULAR	9.3	0.9	5.0	0	9.0	0
Vasodilatation	5.8	1.3	2.3	0.5	5.8	1.7
Hypotension	9.3	--	11.4	--	5.4	--
Thromboembolic events[c]						

[a]Severity of adverse events based on NCI CTC (version 1.0)
[b]Complete hair loss = Grade 2
[c] Includes angina pectoris, arterial thrombosis, cerebral infarct, cerebrovascular accident, deep thrombophlebitis, embolus lower extremity, heart arrest, myocardial infarct, myocardial ischemia, peripheral vascular disorder, pulmonary embolus, sudden death, thrombophlebitis, thrombosis, vascular disorder.

Table 6. Study 2: Percent (%) of Patients Experiencing Clinically Relevant Adverse Events in Combination Therapies[a]

Adverse Event	Study 2			
	Irinotecan + 5-FU/LV infusional days 1&2 every 2 weeks N= 145		5-FU/LV infusional days 1&2 every 2 weeks N=143	
	Grades 1-4	Grades 3&4	Grades 1-4	Grades 3&4
TOTAL Adverse Events	100	72.4	100	39.2
GASTROINTESTINAL				
Diarrhea	72.4	14.4	44.8	6.3
late	--	10.3	--	4.2
grade 3	--	4.1	--	2.1
grade 4	28.3	1.4	0.7	0
Cholinergic syndrome[b]				
Nausea	66.9	2.1	55.2	3.5
Abdominal pain	17.2	2.1	16.8	0.7
Vomiting	44.8	3.5	32.2	2.8
Anorexia	35.2	2.1	18.9	0.7
Constipation	30.3	0.7	25.2	1.4
Mucositis	40.0	4.1	28.7	2.8
HEMATOLOGIC				
Neutropenia	82.5	46.2	47.9	13.4
grade 3	--	36.4	--	12.7
grade 4	--	9.8	--	0.7
Leukopenia	81.3	17.4	42.0	3.5
Anemia	97.2	2.1	90.9	2.1
Neutropenic fever	--	3.4	--	0.7
Thrombocytopenia	32.6	0	32.2	0
Neutropenic infection	--	2.1	--	0
BODY AS A WHOLE				
Asthenia	57.9	9.0	48.3	4.2
Pain	64.1	9.7	61.5	8.4
Fever	22.1	0.7	25.9	0.7
Infection	35.9	7.6	33.6	3.5
METABOLIC AND NUTRITIONAL				
Bilirubin	19.1	3.5	35.9	10.6
DERMATOLOGIC	10.3	0.7	12.6	0.7
Hand and foot syndrome	17.2	0.7	20.3	0
Cutaneous signs	56.6	--	16.8	--
Alopecia[c]				
RESPIRATORY				
Dyspnea	9.7	1.4	4.9	0

CARDIOVASCULAR	3.4	1.4	0.7	0
Hypotension	11.7	--	5.6	--
Thromboembolic events[d]				

[a] Severity of adverse events based on NCI CTC (version 1.0)
[b] Includes rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, abdominal cramping or diarrhea (occurring during or shortly after infusion of irinotecan)
[c] Complete hair loss = Grade 2
[d] Includes angina pectoris, arterial thrombosis, cerebral infarct, cerebrovascular accident, deep thrombophlebitis, embolus lower extremity, heart arrest, myocardial infarct, myocardial ischemia, peripheral vascular disorder, pulmonary embolus, sudden death, thrombophlebitis, thrombosis, vascular disorder.

Second-Line Single-Agent Therapy

Weekly Dosage Schedule

In three clinical studies evaluating the weekly dosage schedule, 304 patients with metastatic carcinoma of the colon or rectum that had recurred or progressed following 5-FU-based therapy were treated with CAMPTOSAR. Seventeen of the patients died within 30 days of the administration of CAMPTOSAR; in five cases (1.6%, 5/304), the deaths were potentially drug-related. One of the patients died of neutropenic sepsis without fever. Neutropenic fever occurred in nine (3.0%) other patients; these patients recovered with supportive care.

One hundred nineteen (39.1%) of the 304 patients were hospitalized because of adverse events; 81 (26.6%) patients were hospitalized for events judged to be related to administration of CAMPTOSAR. The primary reasons for drug-related hospitalization were diarrhea, with or without nausea and/or vomiting (18.4%); neutropenia/leukopenia, with or without diarrhea and/or fever (8.2%); and nausea and/or vomiting (4.9%).

The first dose of at least one cycle of CAMPTOSAR was reduced for 67% of patients who began the studies at the 125-mg/m^2 starting dose. Within-cycle dose reductions were required for 32% of the cycles initiated at the 125-mg/m^2 dose level. The most common reasons for dose reduction were late diarrhea, neutropenia, and leukopenia. Thirteen (4.3%) patients discontinued treatment with CAMPTOSAR because of adverse events. The adverse events in Table 7 are based on the experience of the 304 patients enrolled in the three studies described in *CLINICAL STUDIES (14.1).*

Table 7. Adverse Events Occurring in >10% of 304 Previously Treated Patients with Metastatic Carcinoma of the Colon or Rectum[a]

Body System & Event	% of Patients Reporting	
	NCI Grades 1-4	NCI Grades 3 & 4
GASTROINTESTINAL		
Diarrhea (late)[b]	88	31
7-9 stools/day (grade 3)	—	(16)
≥10 stools/day (grade 4)	—	(14)
Nausea	86	17
Vomiting	67	12
Anorexia	55	6
Diarrhea (early)[c]	51	8
Constipation	30	2
Flatulence	12	0
Stomatitis	12	1
Dyspepsia	10	0
HEMATOLOGIC		
Leukopenia	63	28
Anemia	60	7
Neutropenia	54	26
500 to <1000/mm^3 (grade 3)	—	(15)
<500/mm^3 (grade 4)	—	(12)
BODY AS A WHOLE		
Asthenia	76	12
Abdominal cramping/pain	57	16
Fever	45	1
Pain	24	2
Headache	17	1
Back pain	14	2
Chills	14	0
Minor infection[d]	14	0
Edema	10	1
Abdominal enlargement	10	0
METABOLIC AND NUTRITIONAL		
↓ Body weight	30	1
Dehydration	15	4
↑ Alkaline phosphatase	13	4
↑ SGOT	10	1
DERMATOLOGIC		
Alopecia	60	NA[e]
Sweating	16	0
Rash	13	1
RESPIRATORY		
Dyspnea	22	4
↑ Coughing	17	0
Rhinitis	16	0
NEUROLOGIC		
Insomnia	19	0
Dizziness	15	0
CARDIOVASCULAR		
Vasodilation (flushing)	11	0

Table 7. Adverse Events Occurring in >10% of 304 Previously Treated Patients with Metastatic Carcinoma of the Colon or Rectum[a]

[a] Severity of adverse events based on NCI CTC (version 1.0)
[b] Occurring > 24 hours after administration of CAMPTOSAR
[c] Occurring ≤24 hours after administration of CAMPTOSAR
[d] Primarily upper respiratory infections
[e] Not applicable; complete hair loss = NCI grade 2

Once-Every-3-Week Dosage Schedule

A total of 535 patients with metastatic colorectal cancer whose disease had recurred or progressed following prior 5-FU therapy participated in the two phase 3 studies: 316 received irinotecan, 129 received 5-FU, and 90 received best supportive care. Eleven (3.5%) patients treated with irinotecan died within 30 days of treatment. In three cases (1%, 3/316), the deaths were potentially related to irinotecan treatment and were attributed to neutropenic infection, grade 4 diarrhea, and asthenia, respectively. One (0.8%, 1/129) patient treated with 5-FU died within 30 days of treatment; this death was attributed to grade 4 diarrhea.

Hospitalizations due to serious adverse events occurred at least once in 60% (188/316) of patients who received irinotecan, 63% (57/90) who received best supportive care, and 39% (50/129) who received 5-FU-based therapy. Eight percent of patients treated with irinotecan and 7% treated with 5-FU-based therapy discontinued treatment due to adverse events.

Of the 316 patients treated with irinotecan, the most clinically significant adverse events (all grades, 1-4) were diarrhea (84%), alopecia (72%), nausea (70%), vomiting (62%), cholinergic symptoms (47%), and neutropenia (30%). Table 8 lists the grade 3 and 4 adverse events reported in the patients enrolled to all treatment arms of the two studies described in *CLINICAL STUDIES (14.1)*.

Table 8: Percent Of Patients Experiencing Grade 3 & 4 Adverse Events In Comparative Studies Of Once-Every-3-Week Irinotecan Therapy[a]

	Study 1		Study 2	
Adverse Event	**Irinotecan N=189**	**BSC [b] N=90**	**Irinotecan N=127**	5-FU **N=129**
TOTAL Grade 3/4 Adverse Events	79	67	69	54
GASTROINTESTINAL				
Diarrhea	22	6	22	11
Vomiting	14	8	14	5
Nausea	14	3	11	4
Abdominal pain	14	16	9	8
Constipation	10	8	8	6
Anorexia	5	7	6	4
Mucositis	2	1	2	5
HEMATOLOGIC				
Leukopenia/Neutropenia	22	0	14	2
Anemia	7	6	6	3
Hemorrhage	5	3	1	3
Thrombocytopenia	1	0	4	2

Infection				
without grade 3/4 neutropenia	8	3	1	4
with grade 3/4 neutropenia	1	0	2	0
Fever				
without grade 3/4 neutropenia	2	1	2	0
with grade 3/4 neutropenia	2	0	4	2
BODY AS A WHOLE				
Pain	19	22	17	13
Asthenia	15	19	13	12
METABOLIC AND NUTRITIONAL				
Hepatic [c]	9	7	9	6
DERMATOLOGIC				
Hand and foot syndrome	0	0	0	5
Cutaneous signs [d]	2	0	1	3
RESPIRATORY [e]	10	8	5	7
NEUROLOGIC [f]	12	13	9	4
CARDIOVASCULAR [g]	9	3	4	2
OTHER [h]	32	28	12	14

[a] Severity of adverse events based on NCI CTC (version 1.0)
[b] BSC = best supportive care
[c] Hepatic includes events such as ascites and jaundice
[d] Cutaneous signs include events such as rash
[e] Respiratory includes events such as dyspnea and cough
[f] Neurologic includes events such as somnolence
[g] Cardiovascular includes events such as dysrhythmias, ischemia, and mechanical cardiac dysfunction
[h] Other includes events such as accidental injury, hepatomegaly, syncope, vertigo, and weight loss

The incidence of akathisia in clinical trials of the weekly dosage schedule was greater (8.5%, 4/47 patients) when prochlorperazine was administered on the same day as CAMPTOSAR than when these drugs were given on separate days (1.3%, 1/80 patients). The 8.5% incidence of akathisia, however, is within the range reported for use of prochlorperazine when given as a premedication for other chemotherapies.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post approval use of CAMPTOSAR. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Myocardial ischemic events have been observed following irinotecan therapy. Thromboembolic events have been observed in patients receiving CAMPTOSAR.

Symptomatic pancreatitis, asymptomatic pancreatic enzyme elevation have been reported. Increases in serum levels of transaminases (i.e., AST and ALT) in the absence of progressive liver metastasis have been observed.

Hyponatremia, mostly with diarrhea and vomiting, has been reported.

Transient dysarthria has been reported in patients treated with CAMPTOSAR; in some cases, the event was attributed to the cholinergic syndrome observed during or shortly after infusion of irinotecan.

Interaction between irinotecan and neuromuscular blocking agents cannot be ruled out. Irinotecan has anticholinesterase activity, which may prolong the neuromuscular blocking effects of suxamethonium and the neuromuscular blockade of non-depolarizing drugs may be antagonized.

7 DRUG INTERACTIONS

7.1 5-Fluorouracil (5-FU) and Leucovorin (LV)

In a phase 1 clinical study involving irinotecan, 5-fluorouracil (5-FU), and leucovorin (LV) in 26 patients with solid tumors, the disposition of irinotecan was not substantially altered when the drugs were co-administered. Although the C_{max} and AUC_{0-24} of SN-38, the active metabolite, were reduced (by 14% and 8%, respectively) when irinotecan was followed by 5-FU and LV administration compared with when irinotecan was given alone, this sequence of administration was used in the combination trials and is recommended *[see Dosage and Administration (2)]*. Formal *in vivo* or *in vitro* drug interaction studies to evaluate the influence of irinotecan on the disposition of 5-FU and LV have not been conducted.

7.2 Strong CYP 3A4 Inducers

Anticonvulsants and other strong inducers: Exposure to irinotecan and its active metabolite SN-38 is substantially reduced in adult and pediatric patients concomitantly receiving the CYP3A4 enzyme-inducing anticonvulsants phenytoin, phenobarbital or carbamazepine. The appropriate starting dose for patients taking these anticonvulsants or other strong inducers such as rifampin and rifabutin has not been defined. Consideration should be given to substituting non-enzyme inducing therapies at least 2 weeks prior to initiation of irinotecan therapy.

St. John's wort: Exposure to the active metabolite SN-38 is reduced in patients receiving concomitant St. John's wort. St. John's wort should be discontinued at least 2 weeks prior to the first cycle of irinotecan, and St. John's wort is contraindicated during irinotecan therapy.

Dexamethasone, a moderate CYP3A4 inducer, does not appear to alter the pharmacokinetics of irinotecan.

7.3 Strong CYP 3A4 Inhibitors

Ketoconazole is a strong inhibitor of CYP3A4 enzymes. Patients receiving concomitant ketoconazole have increased exposure to irinotecan and its active metabolite SN-38. Patients should discontinue ketoconazole at least 1 week prior to starting irinotecan therapy and ketoconazole is contraindicated during irinotecan therapy.

7.4 Atazanavir Sulfate

Coadministration of atazanavir sulfate, a CYP3A4 and UGT1A1 inhibitor has the potential to increase systemic exposure to SN-38, the active metabolite of irinotecan. Physicians should take this into consideration when co-administering these drugs.

7.5 Drug-Laboratory Test Interactions

There are no known interactions between CAMPTOSAR and laboratory tests.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D *[see Warnings and Precautions (5.9)]*

CAMPTOSAR can cause fetal harm when administered to a pregnant woman. Radioactivity related to ^{14}C-irinotecan crosses the placenta of rats following intravenous administration of 10 mg/kg (which in separate studies produced an irinotecan C_{max} and AUC about 3 and 0.5 times, respectively, the corresponding values in patients administered 125 mg/m^2). Intravenous administration of irinotecan 6 mg/kg/day to rats and rabbits during the period of organogenesis resulted in increased post-implantation loss and decreased numbers of live fetuses. In separate studies in rats, this dose produced an irinotecan C_{max} and AUC of about 2 and 0.2 times, respectively, the corresponding values in patients administered 125 mg/m^2. In rabbits, the embryotoxic dose was about one-half the recommended human weekly starting dose on a mg/m^2 basis. Irinotecan was teratogenic in rats at doses greater than 1.2 mg/kg/day and in rabbits at 6.0 mg/kg/day. In separate studies in rats, this dose produced an irinotecan C_{max} and AUC about 2/3 and 1/40th, respectively, of the corresponding values in patients administered 125 mg/m^2. In rabbits, the teratogenic dose was about one-half the recommended human weekly starting dose on a mg/m^2 basis. Teratogenic effects included a variety of external, visceral, and skeletal abnormalities. Irinotecan administered to rat dams for the period following organogenesis through weaning at doses of 6 mg/kg/day caused decreased learning ability and decreased female body weights in the offspring. There are no adequate and well-controlled studies of irinotecan in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with CAMPTOSAR.

8.3 Nursing Mothers

Radioactivity appeared in rat milk within 5 minutes of intravenous administration of radiolabeled irinotecan and was concentrated up to 65-fold at 4 hours after administration relative to plasma concentrations. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from CAMPTOSAR, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of

the drug to the mother.

8.4 Pediatric Use

The effectiveness of irinotecan in pediatric patients has not been established. Results from two open-label, single arm studies were evaluated. One hundred and seventy children with refractory solid tumors were enrolled in one phase 2 trial in which 50 mg/ m^2 of irinotecan was infused for 5 consecutive days every 3 weeks. Grade 3-4 neutropenia was experienced by 54 (31.8%) patients. Neutropenia was complicated by fever in 15 (8.8%) patients. Grade 3-4 diarrhea was observed in 35 (20.6%) patients. This adverse event profile was comparable to that observed in adults. In the second phase 2 trial of 21 children with previously untreated rhabdomyosarcoma, 20 mg/m^2 of irinotecan was infused for 5 consecutive days on weeks 0, 1, 3 and 4. This single agent therapy was followed by multimodal therapy. Accrual to the single agent irinotecan phase was halted due to the high rate (28.6%) of progressive disease and the early deaths (14%). The adverse event profile was different in this study from that observed in adults; the most significant grade 3 or 4 adverse events were dehydration experienced by 6 patients (28.6%) associated with severe hypokalemia in 5 patients (23.8%) and hyponatremia in 3 patients (14.3%); in addition Grade 3-4 infection was reported in 5 patients (23.8%) (across all courses of therapy and irrespective of causal relationship).

Pharmacokinetic parameters for irinotecan and SN-38 were determined in 2 pediatric solid-tumor trials at dose levels of 50 mg/m^2 (60-min infusion, n=48) and 125 mg/m^2 (90-min infusion, n=6). Irinotecan clearance (mean ± S.D.) was 17.3 ± 6.7 L/h/m^2 for the 50mg/m^2 dose and 16.2 ± 4.6 L/h/m^2 for the 125 mg/m^2 dose, which is comparable to that in adults. Dose-normalized SN-38 AUC values were comparable between adults and children. Minimal accumulation of irinotecan and SN-38 was observed in children on daily dosing regimens [daily x 5 every 3 weeks or (daily x 5) x 2 weeks every 3 weeks].

8.5 Geriatric Use

Patients greater than 65 years of age should be closely monitored because of a greater risk of early and late diarrhea in this population *[see Clinical Pharmacology (12.3)* and *Adverse Reactions (6.1)]*. The starting dose of CAMPTOSAR in patients 70 years and older for the once-every-3-week-dosage schedule should be 300 mg/m^2 *[see Clinical Pharmacology (12.3) and Dosage and Administration (2)]*.

The frequency of grade 3 and 4 late diarrhea by age was significantly greater in patients ≥65 years than in patients <65 years (40% [53/133] versus 23% [40/171]; p=0.002). In another study of 183 patients treated on the weekly schedule, the frequency of grade 3 or 4 late diarrhea in patients ≥65 years of age was 28.6% [26/91] and in patients <65 years of age was 23.9% [22/92].

8.6 Renal Impairment

The influence of renal impairment on the pharmacokinetics of irinotecan has not been

evaluated. Therefore, use caution in patients with impaired renal function. Irinotecan is not recommended for use in patients on dialysis.

8.7 Hepatic Impairment

Irinotecan clearance is diminished in patients with hepatic impairment while exposure to the active metabolite SN-38 is increased relative to that in patients with normal hepatic function. The magnitude of these effects is proportional to the degree of liver impairment as measured by elevations in total bilirubin and transaminase concentrations. Therefore, use caution in patients with hepatic impairment. The tolerability of irinotecan in patients with hepatic dysfunction (bilirubin greater than 2 mg/dl) has not been assessed sufficiently, and no recommendations for dosing can be made *[see Dosage and Administration (2.1), Warnings and Precautions (5.10) and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

In U.S. phase 1 trials, single doses of up to 345 mg/m^2 of irinotecan were administered to patients with various cancers. Single doses of up to 750 mg/m^2 of irinotecan have been given in non-U.S. trials. The adverse events in these patients were similar to those reported with the recommended dosage and regimen. There have been reports of overdosage at doses up to approximately twice the recommended therapeutic dose, which may be fatal. The most significant adverse reactions reported were severe neutropenia and severe diarrhea. There is no known antidote for overdosage of CAMPTOSAR. Maximum supportive care should be instituted to prevent dehydration due to diarrhea and to treat any infectious complications.

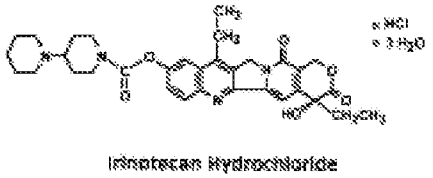
11 DESCRIPTION

CAMPTOSAR Injection (irinotecan hydrochloride injection) is an antineoplastic agent of the topoisomerase I inhibitor class.

CAMPTOSAR is supplied as a sterile, pale yellow, clear, aqueous solution. Each milliliter of solution contains 20 mg of irinotecan hydrochloride (on the basis of the trihydrate salt), 45 mg of sorbitol, NF, and 0.9 mg of lactic acid, USP. The pH of the solution has been adjusted to 3.5 (range, 3.0 to 3.8) with sodium hydroxide or hydrochloric acid. CAMPTOSAR is intended for dilution with 5% Dextrose Injection, USP (D5W), or 0.9% Sodium Chloride Injection, USP, prior to intravenous infusion. The preferred diluent is 5% Dextrose Injection, USP.

Irinotecan hydrochloride is a semisynthetic derivative of camptothecin, an alkaloid extract from plants such as *Camptotheca acuminata* or is chemically synthesized.

The chemical name is ***(S)***-4,11-diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo1***H***-pyrano[3',4':6,7]-indolizino[1,2-b]quinolin-9-yl-[1,4'bipiperidine]-1'-carboxylate, monohydrochloride, trihydrate. Its empirical formula is $C_{33}H_{38}N_4O_6 \cdot HCl \cdot 3H_2O$ and molecular weight is 677.19. It is slightly soluble in water and organic solvents. Its structural formula is as follows:



Irinotecan Hydrochloride

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Irinotecan is a derivative of camptothecin. Camptothecins interact specifically with the enzyme topoisomerase I, which relieves torsional strain in DNA by inducing reversible single-strand breaks. Irinotecan and its active metabolite SN-38 bind to the topoisomerase I-DNA complex and prevent religation of these single-strand breaks. Current research suggests that the cytotoxicity of irinotecan is due to double-strand DNA damage produced during DNA synthesis when replication enzymes interact with the ternary complex formed by topoisomerase I, DNA, and either irinotecan or SN-38. Mammalian cells cannot efficiently repair these double-strand breaks.

12.2 Pharmacodynamics

Irinotecan serves as a water-soluble precursor of the lipophilic metabolite SN-38. SN-38 is formed from irinotecan by carboxylesterase-mediated cleavage of the carbamate bond between the camptothecin moiety and the dipiperidino side chain. SN-38 is approximately 1000 times as potent as irinotecan as an inhibitor of topoisomerase I purified from human and rodent tumor cell lines. *In vitro* cytotoxicity assays show that the potency of SN-38 relative to irinotecan varies from 2- to 2000-fold; however, the plasma area under the concentration versus time curve (AUC) values for SN-38 are 2% to 8% of irinotecan and SN-38 is 95% bound to plasma proteins compared to approximately 50% bound to plasma proteins for irinotecan *[see Clinical Pharmacology (12.3)]*. The precise contribution of SN-38 to the activity of CAMPTOSAR is thus unknown. Both irinotecan and SN-38 exist in an active lactone form and an inactive hydroxy acid anion form. A pH-dependent equilibrium exists between the two forms such that an acid pH promotes the formation of the lactone, while a more basic pH favors the hydroxy acid anion form.

Administration of irinotecan has resulted in antitumor activity in mice bearing cancers of rodent origin and in human carcinoma xenografts of various histological types.

12.3 Pharmacokinetics

After intravenous infusion of irinotecan in humans, irinotecan plasma concentrations decline in a multiexponential manner, with a mean terminal elimination half-life of about 6 to 12 hours. The mean terminal elimination half-life of the active metabolite SN-38 is about 10 to

20 hours. The half-lives of the lactone (active) forms of irinotecan and SN-38 are similar to those of total irinotecan and SN-38, as the lactone and hydroxy acid forms are in equilibrium.

Over the recommended dose range of 50 to 350 mg/m^2, the AUC of irinotecan increases linearly with dose; the AUC of SN-38 increases less than proportionally with dose. Maximum concentrations of the active metabolite SN-38 are generally seen within 1 hour following the end of a 90-minute infusion of irinotecan. Pharmacokinetic parameters for irinotecan and SN-38 following a 90-minute infusion of irinotecan at dose levels of 125 and 340 mg/m^2 determined in two clinical studies in patients with solid tumors are summarized in Table 9:

Table 9. Summary of Mean (±Standard Deviation) Irinotecan and SN-38 Pharmacokinetic Parameters in Patients with Solid Tumors

Dose (mg/m^2)	Irinotecan					SN-38		
	C_{max} (ng/mL)	AUC_{0-24} (ng·h/mL)	$t_{1/2}$ (h)	V_z (L/m^2)	CL (L/h/m^2)	C_{max} (ng/mL)	AUC_{0-24} (ng·h/mL)	$t_{1/2}$ (h)
125 (N=64)	1,660 ±797	10,200 ±3,270	5.8[a] ±0.7	110 ±48.5	13.3 ±6.01	26.3 ±11.9	229 ±108	10.4[a] ±3.1
340 (N=6)	3,392 ±874	20,604 ±6,027	11.7[b] ±1.0	234 ±69.6	13.9 ±4.0	56.0 ±28.2	474 ±245	21.0[b] ±4.3

C_{max} - Maximum plasma concentration
AUC_{0-24} - Area under the plasma concentration-time curve from time 0 to 24 hours after the end of the 90-minute infusion
$t_{1/2}$ - Terminal elimination half-life
V_z - Volume of distribution of terminal elimination phase
CL - Total systemic clearance
[a] Plasma specimens collected for 24 hours following the end of the 90-minute infusion.
[b] Plasma specimens collected for 48 hours following the end of the 90-minute infusion. Because of the longer collection period, these values provide a more accurate reflection of the terminal elimination half-lives of irinotecan and SN-38.

Distribution

Irinotecan exhibits moderate plasma protein binding (30% to 68% bound). SN-38 is highly bound to human plasma proteins (approximately 95% bound). The plasma protein to which irinotecan and SN-38 predominantly binds is albumin.

Metabolism

The metabolic conversion of irinotecan to the active metabolite SN-38 is mediated by carboxylesterase enzymes and primarily occurs in the liver. *In vitro* studies indicate that irinotecan, SN-38 and another metabolite aminopentane carboxylic acid (APC), do not inhibit cytochrome P-450 isozymes. SN-38 is subsequently conjugated predominantly by the enzyme UDP-glucuronosyl transferase 1A1 (UGT1A1) to form a glucuronide metabolite. UGT1A1 activity is reduced in individuals with genetic polymorphisms that lead to reduced enzyme activity such as the UGT1A1*28 polymorphism. Approximately 10% of the North American population is homozygous for the UGT1A1*28 allele (also referred to as UGT1A1 7/7 genotype). In a prospective study, in which irinotecan was administered as a single-agent (350 mg/m^2) on a once-every-3-week schedule, patients with the UGT1A1 7/7 genotype had a higher exposure to SN-38 than patients with the wild-type UGT1A1 allele (UGT1A1 6/6 genotype) *[see Warnings and Precautions (5.3) and Dosage and Administration (2)]*. SN-38

glucuronide had 1/50 to 1/100 the activity of SN-38 in cytotoxicity assays using two cell lines *in vitro*.

Excretion

The disposition of irinotecan has not been fully elucidated in humans. The urinary excretion of irinotecan is 11% to 20%; SN-38, <1%; and SN-38 glucuronide, 3%. The cumulative biliary and urinary excretion of irinotecan and its metabolites (SN-38 and SN-38 glucuronide) over a period of 48 hours following administration of irinotecan in two patients ranged from approximately 25% (100 mg/m^2) to 50% (300 mg/m^2).

Effect of Age

The pharmacokinetics of irinotecan administered using the weekly schedule was evaluated in a study of 183 patients that was prospectively designed to investigate the effect of age on irinotecan toxicity. Results from this trial indicate that there are no differences in the pharmacokinetics of irinotecan, SN-38, and SN-38 glucuronide in patients <65 years of age compared with patients ≥65 years of age. In a study of 162 patients that was not prospectively designed to investigate the effect of age, small (less than 18%) but statistically significant differences in dose-normalized irinotecan pharmacokinetic parameters in patients <65 years of age compared to patients ≥65 years of age were observed. Although dose-normalized AUC_{0-24} for SN-38 in patients ≥65 years of age was 11% higher than in patients <65 years of age, this difference was not statistically significant. No change in the starting dose is recommended for geriatric patients receiving the weekly dosage schedule of irinotecan *[see Dosage and Administration (2)]*.

Effect of Gender

The pharmacokinetics of irinotecan do not appear to be influenced by gender.

Effect of Race

The influence of race on the pharmacokinetics of irinotecan has not been evaluated.

Effect of Hepatic Impairment

Irinotecan clearance is diminished in patients with hepatic impairment while exposure to the active metabolite SN-38 is increased relative to that in patients with normal hepatic function. The magnitude of these effects is proportional to the degree of liver impairment as measured by elevations in total bilirubin and transaminase concentrations. However, the tolerability of irinotecan in patients with hepatic dysfunction (bilirubin greater than 2 mg/dl) has not been assessed sufficiently, and no recommendations for dosing can be made *[see Dosage and Administration (2.1), Warnings and Precautions (5.10) and Use in Specific Populations (8.7)]*.

Effect of Renal Impairment

The influence of renal impairment on the pharmacokinetics of irinotecan has not been evaluated. Therefore, caution should be undertaken in patients with impaired renal function. Irinotecan is not recommended for use in patients on dialysis *[see Use in Specific Populations (8.6)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenicity studies with irinotecan were not conducted. Rats were, however, administered intravenous doses of 2 mg/kg or 25 mg/kg irinotecan once per week for 13 weeks (in separate studies, the 25 mg/kg dose produced an irinotecan C_{max} and AUC that were about 7.0 times and 1.3 times the respective values in patients administered 125 mg/m^2 weekly) and were then allowed to recover for 91 weeks. Under these conditions, there was a significant linear trend with dose for the incidence of combined uterine horn endometrial stromal polyps and endometrial stromal sarcomas. Irinotecan was clastogenic both *in vitro* (chromosome aberrations in Chinese hamster ovary cells) and *in vivo* (micronucleus test in mice). Neither irinotecan nor its active metabolite SN-38 was mutagenic in the *in vitro* Ames assay.

No significant adverse effects on fertility and general reproductive performance were observed after intravenous administration of irinotecan in doses of up to 6 mg/kg/day to rats and rabbits; however, atrophy of male reproductive organs was observed after multiple daily irinotecan doses both in rodents at 20 mg/kg and in dogs at 0.4 mg/kg. In separate studies in rodents, this dose produced an irinotecan C_{max} and AUC about 5 and 1 times, respectively, of the corresponding values in patients administered 125 mg/m^2 weekly. In dogs this dose produced an irinotecan C_{max} and AUC about one-half and 1/15th, respectively, of the corresponding values in patients administered 125 mg/m^2 weekly.

14 CLINICAL STUDIES

Irinotecan has been studied in clinical trials in combination with 5-fluorouracil (5-FU) and leucovorin (LV) and as a single agent *[see Dosage and Administration (2)]*. When given as a component of combination-agent treatment, irinotecan was either given with a weekly schedule of bolus 5-FU/LV or with an every-2-week schedule of infusional 5-FU/LV. Weekly and once-every-3-week dosage schedules were used for the single-agent irinotecan studies. Clinical studies of combination and single-agent use are described below.

14.1 Metastatic Colorectal Cancer

First Line Therapy in Combination with 5-FU/LV: Studies 1 and 2

Two phase 3, randomized, controlled, multinational clinical trials support the use of CAMPTOSAR Injection as first-line treatment of patients with metastatic carcinoma of the colon or rectum. In each study, combinations of irinotecan with 5-FU and LV were compared with 5-FU and LV alone. Study 1 compared combination irinotecan/bolus 5-FU/LV therapy given weekly with a standard bolus regimen of 5-FU/LV alone given daily for 5 days every 4 weeks; an irinotecan-alone treatment arm given on a weekly schedule was also included. Study 2 evaluated two different methods of administering infusional 5-FU/LV, with or without irinotecan. In both studies, concomitant medications such as antiemetics, atropine, and loperamide were given to patients for prophylaxis and/or management of symptoms from

treatment. In Study 2, a 7-day course of fluoroquinolone antibiotic prophylaxis was given in patients whose diarrhea persisted for greater than 24 hours despite loperamide or if they developed a fever in addition to diarrhea. Treatment with oral fluoroquinolone was also initiated in patients who developed an absolute neutrophil count (ANC) $<500/mm^3$, even in the absence of fever or diarrhea. Patients in both studies also received treatment with intravenous antibiotics if they had persistent diarrhea or fever or if ileus developed.

In both studies, the combination of irinotecan/5-FU/LV therapy resulted in significant improvements in objective tumor response rates, time to tumor progression, and survival when compared with 5-FU/LV alone. These differences in survival were observed in spite of second-line therapy in a majority of patients on both arms, including crossover to irinotecan-containing regimens in the control arm. Patient characteristics and major efficacy results are shown in Table 10.

Table 10. Combination Dosage Schedule: Study Results

	Study 1			Study 2	
	Irinotecan + Bolus 5-FU/LV weekly x 4 every 6 weeks	Bolus 5-FU/LV daily x 5 every 4 weeks	Irinotecan weekly x 4 every 6 weeks	*irinotecan* + Infusional 5-FU/LV	Infusional 5-FU/LV
Number of patients	231	226	226	198	187
Demographics and treatment administration					
Female/Male (%)	34/65	45/54	35/64	33/67	47/53
Median age in years (range)	62 (25-85)	61 (19-85)	61 (30-87)	62 (27-75)	59 (24-75)
Performance status (%)					
0	39	41	46	51	51
1	46	45	46	42	41
2	15	13	8	7	8
Primary tumor (%)					
Colon	81	85	84	55	65
Rectum	17	14	15	45	35
Median time from diagnosis to randomization (months, range)	1.9 (0-161)	1.7 (0-203)	1.8 (0.1-185)	4.5 (0-88)	2.7 (0-104)
Prior adjuvant 5-FU therapy (%)					
No	89	92	90	74	76
Yes	11	8	10	26	24
Median duration of study treatment[a] (months)	5.5	4.1	3.9	5.6	4.5
Median Relative Dose Intensity (%)[a]					
Irinotecan	72	—	75	87	—
5-FU	71	86	—	86	93
Efficacy Results					
Confirmed objective tumor response rate[b] (%)	39	21 ($p<0.0001$)[c]	18	35	22 ($p<0.005$)[c]
Median time to tumor progression[d] (months)	7.0	4.3 ($p=0.004$)[d]	4.2	6.7	4.4 ($p<0.001$)[d]
Median survival (months)	14.8	12.6 ($p<0.05$)[d]	12.0	17.4	14.1 ($p<0.05$)[d]

[a] Study 1: N=225 (irinotecan/5-FU/LV),N=219 (5-FU/LV),N=223 (irinotecan)
Study 2: N=199 (irinotecan/5-FU/LV),N=186 (5-FU/LV)
[b] Confirmed ≥ 4 to 6 weeks after first evidence of objective response
[c] Chi-square test
[d] Log-rank test

Improvement was noted with irinotecan-based combination therapy relative to 5-FU/LV when response rates and time to tumor progression were examined across the following demographic and disease-related subgroups (age, gender, ethnic origin, performance status, extent of organ involvement with cancer, time from diagnosis of cancer, prior adjuvant therapy, and baseline

laboratory abnormalities). Figures 1 and 2 illustrate the Kaplan-Meier survival curves for the comparison of irinotecan/5-FU/LV versus 5-FU/LV in Studies 1 and 2, respectively.

Figure 1. Survival
First-Line Irinotecan/5-FU/LV vs 5-FU/LV
Study 1

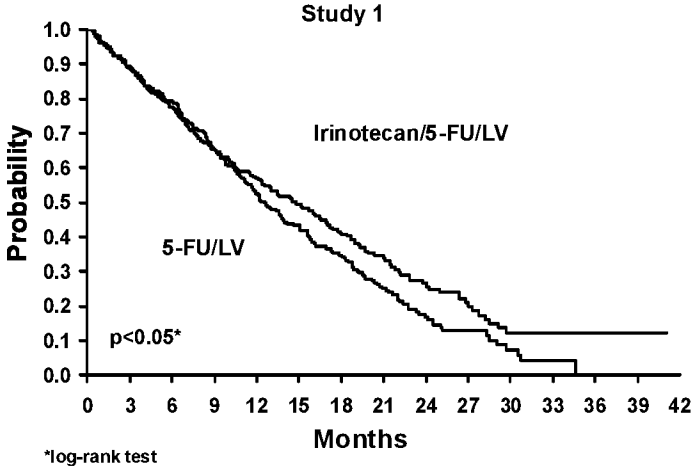
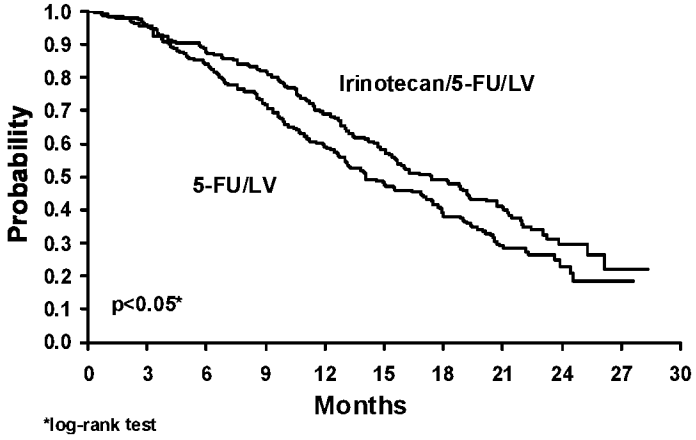


Figure 2. Survival
First-Line Irinotecan/5-FU/LV vs 5-FU/LV
Study 2



Second-Line Therapy After 5-FU-Based Treatment

4 Weekly Doses on a 6-Week Cycle: Studies 3, 4, and 5

Data from three open-label, single-agent, clinical studies, involving a total of 304 patients in 59 centers, support the use of CAMPTOSAR in the treatment of patients with metastatic cancer of the colon or rectum that has recurred or progressed following treatment with 5-FU-based therapy. These studies were designed to evaluate tumor response rate and do not provide information on effects on survival and disease-related symptoms. In each study, CAMPTOSAR was administered in repeated 6-week cycles consisting of a 90-minute intravenous infusion once weekly for 4 weeks, followed by a 2-week rest period. Starting doses of CAMPTOSAR in these trials were 100, 125, or 150 mg/m^2, but the 150-mg/m^2 dose was poorly tolerated (due to high rates of grade 4 late diarrhea and febrile neutropenia). Study 3 enrolled 48 patients and was conducted by a single investigator at several regional hospitals. Study 4 was a multicenter

study conducted by the North Central Cancer Treatment Group. All 90 patients enrolled in Study 4 received a starting dose of 125 mg/m^2. Study 5 was a multicenter study that enrolled 166 patients from 30 institutions. The initial dose in Study 5 was 125 mg/m^2 but was reduced to 100 mg/m^2 because the toxicity seen at the 125-mg/m^2 dose was perceived to be greater than that seen in previous studies. All patients in these studies had metastatic colorectal cancer, and the majority had disease that recurred or progressed following a 5-FU-based regimen administered for metastatic disease. The results of the individual studies are shown in Table 11.

Table 11. Weekly Dosage Schedule: Study Results

	Study			
	3	4	5	
Number of Patients	48	90	64	102
Starting Dose (mg/m^2/week x 4)	125[a]	125	125	100
Demographics and Treatment Administration				
Female/Male (%)	46/54	36/64	50/50	51/49
Median Age in years (range)	63 (29-78)	63 (32-81)	61 (42-84)	64 (25-84)
Ethnic Origin (%)				
White	79	96	81	91
African American	12	4	11	5
Hispanic	8	0	8	2
Oriental/Asian	0	0	0	2
Performance Status (%)				
0	60	38	59	44
1	38	48	33	51
2	2	14	8	5
Primary Tumor (%)				
Colon	100	71	89	87
Rectum	0	29	11	8
Unknown	0	0	0	5
Prior 5-FU Therapy (%)				
For Metastatic Disease	81	66	73	68
≤ 6 months after Adjuvant	15	7	27	28
> 6 months after Adjuvant	2	16	0	2
Classification Unknown	2	12	0	3
Prior Pelvic/Abdominal Irradiation (%)				
Yes	3	29	0	0
Other	0	9	2	4
None	97	62	98	96
Duration of Treatment with CAMPTOSAR (median, months)	5	4	4	3
Relative Dose Intensity[b] (median %)	74	67	73	81
Efficacy				
Confirmed Objective Response Rate (%)[c] (95% CI)	21 (9.3 - 32.3)	13 (6.3 - 20.4)	14 (5.5 - 22.6)	9 (3.3 - 14.3)
Time to Response (median, months)	2.6	1.5	2.8	2.8
Response Duration (median, months)	6.4	5.9	5.6	6.4
Survival (median, months)	10.4	8.1	10.7	9.3
1-Year Survival (%)	46	31	45	43

Table 11. Weekly Dosage Schedule: Study Results

[a] Nine patients received 150 mg/m^2 as a starting dose; two (22.2%) responded to CAMPTOSAR.

[b] Relative dose intensity for CAMPTOSAR based on planned dose intensity of 100, 83.3, and 66.7 mg/m^2/wk corresponding with 150, 125, and 100 mg/m^2 starting doses, respectively.

[c] Confirmed ≥ 4 to 6 weeks after first evidence of objective response.

In the intent-to-treat analysis of the pooled data across all three studies, 193 of the 304 patients began therapy at the recommended starting dose of 125 mg/m^2. Among these 193 patients, 2 complete and 27 partial responses were observed, for an overall response rate of 15.0% (95% Confidence Interval [CI], 10.0% to 20.1%) at this starting dose. A considerably lower response rate was seen with a starting dose of 100 mg/m^2. The majority of responses were observed within the first two cycles of therapy, but responses did occur in later cycles of treatment (one response was observed after the eighth cycle). The median response duration for patients beginning therapy at 125 mg/m^2 was 5.8 months (range, 2.6 to 15.1 months). Of the 304 patients treated in the three studies, response rates to CAMPTOSAR were similar in males and females and among patients older and younger than 65 years. Rates were also similar in patients with cancer of the colon or cancer of the rectum and in patients with single and multiple metastatic sites. The response rate was 18.5% in patients with a performance status of 0 and 8.2% in patients with a performance status of 1 or 2. Patients with a performance status of 3 or 4 have not been studied. Over half of the patients responding to CAMPTOSAR had not responded to prior 5-FU. Patients who had received previous irradiation to the pelvis responded to CAMPTOSAR at approximately the same rate as those who had not previously received irradiation.

Once-Every-3-Week Dosage Schedule

Single Arm Study: Study 6

Data from an open-label, single-agent, single-arm, multicenter, clinical study involving a total of 132 patients support a once every-3-week dosage schedule of irinotecan in the treatment of patients with metastatic cancer of the colon or rectum that recurred or progressed following treatment with 5-FU. Patients received a starting dose of 350 mg/m^2 given by 30-minute intravenous infusion once every 3 weeks. Among the 132 previously treated patients in this trial, the intent-to-treat response rate was 12.1% (95% CI, 7.0% to 18.1%).

Randomized Studies: Studies 7 and 8

Two multicenter, randomized, clinical studies further support the use of irinotecan given by the once-every-3-week dosage schedule in patients with metastatic colorectal cancer whose disease has recurred or progressed following prior 5-FU therapy. In Study 7, second-line irinotecan therapy plus best supportive care was compared with best supportive care alone. In Study 8, second-line irinotecan therapy was compared with infusional 5-FU-based therapy. In both studies, irinotecan was administered intravenously at a starting dose of 350 mg/m^2 over 90 minutes once every 3 weeks. The starting dose was 300 mg/m^2 for patients who were 70 years and older or who had a performance status of 2. The highest total dose permitted was 700 mg. Dose reductions and/or administration delays were permitted in the event of severe hematologic and/or nonhematologic toxicities while on treatment. Best supportive care was provided to patients in both arms of Study 7 and included antibiotics, analgesics, corticosteroids, transfusions, psychotherapy, or any other symptomatic therapy as clinically indicated. In both studies, concomitant medications such as antiemetics, atropine, and loperamide were given to patients for prophylaxis and/or management of symptoms from treatment. If late diarrhea

persisted for greater than 24 hours despite loperamide, a 7-day course of fluoroquinolone antibiotic prophylaxis was given. Patients in the control arm of the Study 8 received one of the following 5-FU regimens: (1) LV, 200 mg/m^2 IV over 2 hours; followed by 5-FU, 400 mg/m^2 IV bolus; followed by 5-FU, 600 mg/m^2 continuous IV infusion over 22 hours on days 1 and 2 every 2 weeks; (2) 5-FU, 250 to 300 mg/m^2/day protracted continuous IV infusion until toxicity; (3) 5-FU, 2.6 to 3 g/m^2 IV over 24 hours every week for 6 weeks with or without LV, 20 to 500 mg/m^2/day every week IV for 6 weeks with 2-week rest between cycles. Patients were to be followed every 3 to 6 weeks for 1 year.

A total of 535 patients were randomized in the two studies at 94 centers. The primary endpoint in both studies was survival. The studies demonstrated a significant overall survival advantage for irinotecan compared with best supportive care (p=0.0001) and infusional 5-FU-based therapy (p=0.035) as shown in Figures 3 and 4. In Study 7, median survival for patients treated with irinotecan was 9.2 months compared with 6.5 months for patients receiving best supportive care. In Study 8, median survival for patients treated with irinotecan was 10.8 months compared with 8.5 months for patients receiving infusional 5-FU-based therapy. Multiple regression analyses determined that patients' baseline characteristics also had a significant effect on survival. When adjusted for performance status and other baseline prognostic factors, survival among patients treated with irinotecan remained significantly longer than in the control populations (p=0.001 for Study 7 and p=0.017 for Study 8). Measurements of pain, performance status, and weight loss were collected prospectively in the two studies; however, the plan for the analysis of these data was defined retrospectively. When comparing irinotecan with best supportive care in Study 7, this analysis showed a statistically significant advantage for irinotecan, with longer time to development of pain (6.9 months versus 2.0 months), time to performance status deterioration (5.7 months versus 3.3 months), and time to > 5% weight loss (6.4 months versus 4.2 months). Additionally, 33.3% (33/99) of patients with a baseline performance status of 1 or 2 showed an improvement in performance status when treated with irinotecan versus 11.3% (7/62) of patients receiving best supportive care (p=0.002). Because of the inclusion of patients with non-measurable disease, intent-to-treat response rates could not be assessed.

Figure 3. Survival
Second-Line Irinotecan vs Best Supportive Care (BSC)
Study 7

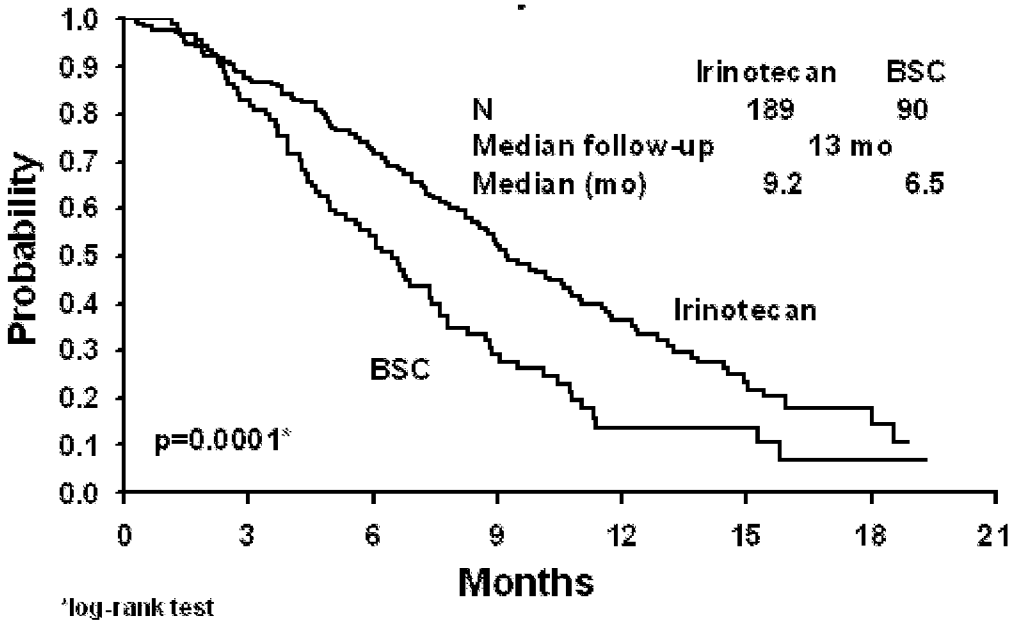


Figure 4. Survival
Second-Line Irinotecan vs Infusional 5-FU
Study 8

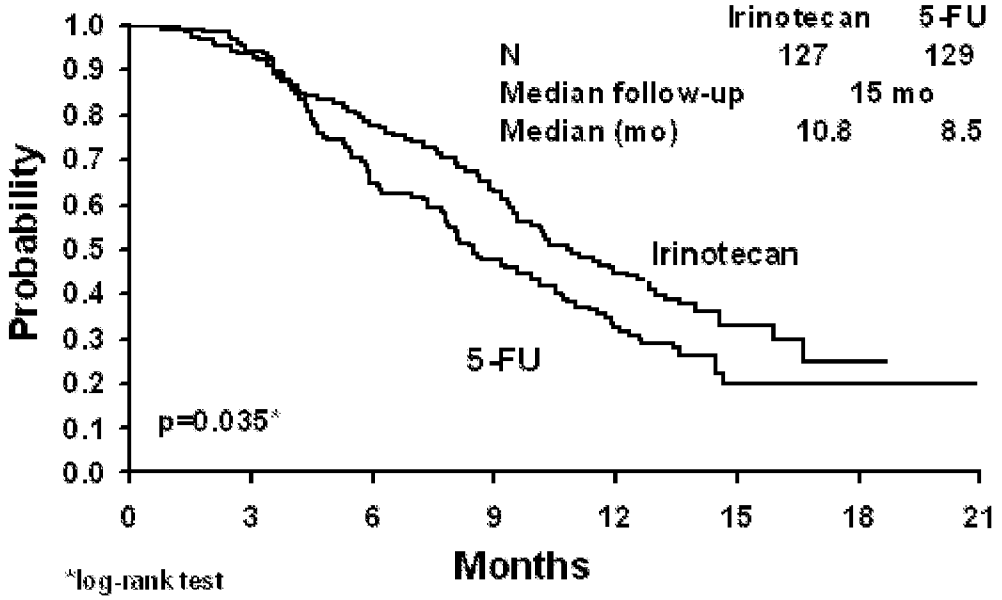


Table 12. Once-Every-3-Week Dosage Schedule: Study Results

	Study 7		Study 8	
	Irinotecan	BSC[a]	Irinotecan	5-FU
Number of patients	189	90	127	129
Demographics and treatment administration				
Female/Male (%)	32/68	42/58	43/57	35/65
Median age in years (range)	59 (22-75)	62 (34-75)	58 (30-75)	58 (25-75)
Performance status (%)				
0	47	31	58	54
1	39	46	35	43
2	14	23	8	3
Primary tumor (%)				
Colon	55	52	57	62
Rectum	45	48	43	38
Prior 5-FU therapy (%)				
For metastatic disease	70	63	58	68
As adjuvant treatment	30	37	42	32
Prior irradiation (%)	26	27	18	20
Duration of study treatment (median, months) (Log-rank test)	4.1	--	4.2 (p=0.02)	2.8
Relative dose intensity (median %)[b]	94	--	95	81-99
rvival				
Survival (median, months) (Log-rank test)	9.2 (p=0.0001)	6.5	10.8 (p=0.035)	8.5

[a] BSC = best supportive care

[b] Relative dose intensity for irinotecan based on planned dose intensity of 116.7 and 100 mg/m^2/wk corresponding with 350 and 300 mg/m^2 starting doses, respectively.

In the two randomized studies, the EORTC QLQ-C30 instrument was utilized. At the start of each cycle of therapy, patients completed a questionnaire consisting of 30 questions, such as "Did pain interfere with daily activities?" (1 = Not at All, to 4 = Very Much) and "Do you have any trouble taking a long walk?" (Yes or No). The answers from the 30 questions were converted into 15 subscales, that were scored from 0 to 100, and the global health status subscale that was derived from two questions about the patient's sense of general well being in the past week. The results as summarized in Table 13 are based on patients' worst post-baseline scores. In Study 7, a multivariate analysis and univariate analyses of the individual subscales were performed and corrected for multivariate testing. Patients receiving irinotecan reported significantly better results for the global health status, on two of five functional subscales, and on four of nine symptom subscales. As expected, patients receiving irinotecan noted significantly more diarrhea than those receiving best supportive care. In Study 8, the multivariate analysis on all 15 subscales did not indicate a statistically significant difference between irinotecan and infusional 5-FU.

Table 13. EORTC QLQ-C30: Mean Worst Post-Baseline Score[a]

QLQ-C30 Subscale	Study 7			Study 8		
	Irinotecan	BSC	p-value	Irinotecan	5-FU	p-value
Global health status	47	37	0.03	53	52	0.9
Functional scales						
Cognitive	77	68	0.07	79	83	0.9
Emotional	68	64	0.4	64	68	0.9
Social	58	47	0.06	65	67	0.9
Physical	60	40	0.0003	66	66	0.9
Role	53	35	0.02	54	57	0.9
Symptom Scales						
Fatigue	51	63	0.03	47	46	0.9
Appetite loss	37	57	0.0007	35	38	0.9
Pain assessment	41	56	0.009	38	34	0.9
Insomnia	39	47	0.3	39	33	0.9
Constipation	28	41	0.03	25	19	0.9
Dyspnea	31	40	0.2	25	24	0.9
Nausea/Vomiting	27	29	0.5	25	16	0.09
Financial impact	22	26	0.5	24	15	0.3
Diarrhea	32	19	0.01	32	22	0.2

[a] For the five functional subscales and global health status subscale, higher scores imply better functioning, whereas, on the nine symptom subscales, higher scores imply more severe symptoms. The subscale scores of each patient were collected at each visit until the patient dropped out of the study.

15 REFERENCES

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- Polovich, M., White, J. M., & Kelleher, L.O. (eds.) 2005. Chemotherapy and biotherapy guidelines and recommendations for practice (2nd. ed.) Pittsburgh, PA: Oncology Nursing Society.

16 HOW SUPPLIED/STORAGE AND HANDLING

CAMPTOSAR Injection is available in single-dose brown glass vials in the following package sizes:

2 mL NDC 0009-7529-02
5 mL NDC 0009-7529-01

CAMPTOSAR Injection is available in single-dose amber colored polypropylene CYTOSAFE® vials in the following package sizes:

2 mL NDC 0009-7529-04
5 mL NDC 0009-7529-03
15 mL NDC 0009-7529-05

Store at controlled room temperature 15° to 30°C (59° to 86°F). Protect from light. Keep the vial in the carton until the time of use.

Inspect the vial for damage and visible signs of leaks before removing from the carton. If damaged, incinerate the unopened package.

17 PATIENT COUNSELING INFORMATION

- Patients and caregivers should be informed of gastrointestinal complications, such as nausea, vomiting, abdominal cramping, and diarrhea. Patients should have loperamide readily available to begin treatment for late diarrhea (generally occurring more than 24 hours after administration of CAMPTOSAR). Begin loperamide at the first episode of poorly formed or loose stools or the earliest onset of bowel movements more frequent than normal. One dosage regimen for loperamide is 4 mg at the first onset of late diarrhea and then 2 mg every 2 hours until the patient is diarrhea-free for at least 12 hours. Loperamide is not recommended to be used for more than 48 consecutive hours at these doses, because of the risk of paralytic ileus. During the night, the patient may take 4 mg of loperamide every 4 hours. Patients should contact their physician if any of the following occur: diarrhea for the first time during treatment; black or bloody stools; symptoms of dehydration such as lightheadedness, dizziness, or faintness; inability to take fluids by mouth due to nausea or vomiting; or inability to get diarrhea under control within 24 hours.

- Patients should be warned about the potential for dizziness or visual disturbances which may occur within 24 hours following the administration of CAMPTOSAR.

- Explain the significance of routine blood cell counts. Instruct patients to monitor their temperature frequently and immediately report any occurrence of fever or infection.

- CAMPTOSAR may cause fetal harm. Advise patients to avoid becoming pregnant while receiving this drug.

- Patients should be alerted to the possibility of alopecia.

- Contains sorbitol.

This product's label may have been updated. For current full prescribing information, please visit www.pfizer.com.

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EXAMINER	
SHOMER, ISAAC	

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
08/15/2016	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No. 14/879,302	Applicant(s) HONG ET AL.	
	Examiner ISAAC SHOMER	Art Unit 1612	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *1-21* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-21* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

4) ☐ Other: _____.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

The present application is being examined under the pre-AIA first to invent provisions.

In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

Note Regarding Declarations Under 37 C.F.R. 1.132

The following information may be relevant to applicant during the course of prosecution:

Affidavits or declarations, such as those submitted under 37 CFR 1.130, 1.131 and 1.132, filed during the prosecution of the prior application do not automatically become a part of this application. Where it is desired to rely on an earlier-filed affidavit or declaration, the applicant should make the remarks of record in this application and include a copy of the original affidavit or declaration filed in the prior application.

Claim Rejections - 35 USC § 112(b) – Indefiniteness

The following is a quotation of 35 U.S.C. 112(b):

> (b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:
> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-21 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.

The instant claims recite the language “a patient in need thereof.” It is unclear what is meant by the phrase "a patient in need thereof" as the skilled artisan would not have been able to determine the scope of which patients are in need of the claimed treatment and which are not in need of the claimed treatment.

For the purposes of examination under prior art, the phrase “a patient in need thereof” is understood to refer to a patient suffering from cancer, as irinotecan is known to treat cancer.

Claim Rejections - 35 USC § 103 – Obviousness

The following is a quotation of pre-AIA 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject

matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under pre-AIA 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under pre-AIA 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of pre-AIA 35 U.S.C. 103(c) and potential pre-AIA 35 U.S.C. 102(e), (f) or (g) prior art under pre-AIA 35 U.S.C. 103(a).

Claim 1-21 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Chou et al. (Journal of Bioscience and Bioengineering, Vol. 95 No. 4, 2003, pages 405-408) in view of Schlessinger et al. (US Patent 5,783,568).

Chou et al. (hereafter referred to as Chou) is drawn to a liposomal irinotecan formulation, as of Chou, page 405, title and abstract. This composition includes irinotecan along with lipids, as of Chou, page 405, abstract. This composition is intended for cancer treatment, as of Chou, page 405, left column, first paragraph.

Chou does not teach sucrose octasulfate.

Schlessinger et al. (hereafter referred to as Schlessinger) is drawn to the treatment of cancer, as of Schlessinger, title and abstract. Schlessinger teaches that sucrose octasulfate has the ability to treat cancer or an angiogenic abnormality as it prevents oligomerization of heparin growth factor, as of Schlessinger, column 27 lines 19-26. Schlessinger teaches intravenous administration, as of Schlessinger, column 11 line 46.

Schlessinger does not teach irinotecan.

It would have been prima facie obvious for one of ordinary skill in the art to have included sucrose octasulfate, as of Schlessinger, into the liposome of Chou. Chou is drawn to a liposome comprising irinotecan, which is intended for use in treating cancer. As sucrose octasulfate is also used for treating cancer, as taught by Schlessinger, the skilled artisan would have been motivated to have included the sucrose octasulfate of Schlessinger into the liposome of Chou. Generally, it is prima facie obvious to combine two compositions (liposomal irinotecan, as of Chou, and sucrose octasulfate, as of Schlessinger), each of which is taught by the prior art to be useful for same purpose (treating cancer), in order to form a third composition to be used for the very same purpose. The idea for combining them flows logically from their having been individually

taught in the prior art. See MPEP 2144.06. Moreover, where it would have been obvious to have combined individually known ingredients, evidence must be provided establishing that appellant's combination of agents is in some way more effective or in some way different than any single member of that combination in order to rebut that prima facie case. See In re Dial, 140 USPQ 244 (C.C.P.A. 1964).

As to claims 1 and 2, the intravenous administration of Schlessinger, column 11 line 46, reads on the requirement of this claim.

As to claims 3-7, these claims modify the amount of irinotecan per the amount of lipid, which is recited in various units in these claims. Chou teaches a specific amount of irinotecan, as of Chou, page 405, right column, first full paragraph, and a specific amount of phospholipids and total liposome lipids, as of Chou, legend in figure 1 on page 406, right column of Chou, as well as elsewhere in the reference. The examiner notes that generally, differences in concentration (e.g. of drug and of lipid) will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating that such concentration is critical. See MPEP 2144.05(II)(A). As such evidence has not been presented, this rejection applies to claims 3-7.

As to claim 8, Chou teaches DSPC and cholesterol, as of Chou, page 405, right column, first full paragraph.

As to claim 9, Chou teaches a ratio of DSPC:cholesterol:PEG200 (apparently DSPE-PEG-2000) of 100:30:5, as of Chou, page 406, right column, figure 1. While this differs slightly from the recited amount, such differences in concentration do not generally support the patentability of subject matter encompassed by the prior art

unless there is evidence indicating that such concentration is critical. See MPEP 2144.05(II)(A). As such evidence has not been presented, this rejection applies to claim 9.

As to claim 10, Chou teaches liposome sizes from as little as 88 nm to as about 165 nm, as of Chou, page 406, left column, table 1 at top of column. This overlaps with the claimed range of 110-120 nm. While the prior art does not disclose the exact claimed values, but does overlap: in such instances even a slight overlap in range establishes a *prima facie* case of obviousness. See MPEP 2144.05(I).

As to claim 11, this claim is rejected for the same reason that claims 3-7 are rejected.

As to claim 12, part (a) of this claim is rejected for the same reason that claim 2 is rejected.

As to claim 13, this claim is rejected for the same reason that claim 9 is rejected.

As to claim 14, this is an independent claim reciting parenteral administration of an irinotecan liposome formulation. Specific lipids and amounts thereof are recited. The specific lipids are taught by Chou, page 405, right column, first full paragraph below abstract, teaching DSPC, cholesterol, and DSPE-PEG. Amounts of these ingredients are taught as of Chou, page 406, right column, caption of Figure 1. While the amounts in the prior art and claims differ, it is nevertheless the case that this claim is rejected for the same reason that claim 10 is rejected.

As to claim 15, this claim is rejected for the same reason that claims 3-7 are rejected.

As to claim 16, Chou teaches an encapsulation efficiency of 97-99%, as of Chou, page 406, left column, bottom paragraph.

As to claim 17, this claim is rejected for the same reason that claims 3-7 are rejected.

As to claim 18, part (a), this claim is rejected for the same reason that claim 2 is rejected.

As to claim 19, this is an independent claim requiring essentially the same subject matter as independent claim 14, expect with intravenous administration instead of parenteral administration. Intravenous administration is also required by claim 2. As such, this claim is rejected for the same reason that claims 2 and 14 are rejected.

As to claim 20, Chou teaches an encapsulation efficiency of 97-99%, as of Chou, page 406, left column, bottom paragraph.

As to claim 21, this claim is rejected for the same reason that claim 10 is rejected.

Non-Statutory Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference

claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(1) - 706.02(l)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For

more information about eTerminal Disclaimers, refer to

www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

Prior to setting forth the grounds of rejection, the examiner has provided the following summaries of the copending and conflicting cases.

Table of Conflicting Patents

Instant Case	**Conflicting Patent**	**Double Patenting?**
14/879,302	8,147,867	Yes
14/879,302	8,329,213	Yes
14/879,302	8,703,181	Yes
14/879,302	8,992,970	Yes
14/879,302	8,658,203	Yes, but not on instant claims 2 and 19-21 because conflicting claims do not teach intravenous administration

Table of Copending Applications

Instant Case	Copending Case	Double Patenting?
14/879,302	14/632,422	Yes
14/879,302	14/151,632	Yes, but not on instant claims 2 and 19-21 because conflicting claims do not teach intravenous administration
14/879,302	15/213,127	Yes
14/879,302	14/879,302	No (same case)
14/879,302	14/879,358	Yes
14/879,302	14/964,239	No because copending claims do not teach sucrose octasulfate and teach inositol hexaphosphate instead
14/879,302	14/965,140	Yes
14/879,302	14/966,458	Yes
14/879,302	14/979,666	No, because copending claims do not teach irinotecan and teach docetaxel instead
14/879,302	14/181,583	Yes

Non-Statutory Double Patenting (Grounds of Rejection)

Claims 1-21 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-35 of U.S. Patent No. 8,147,867. Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons:

The instant claims are drawn to a method for parenteral administration of a composition comprising irinotecan and sucrose octasulfate.

The conflicting claims are drawn to a composition comprising irinotecan and sucrose octasulfate, and optionally including a substituted ammonium compound. Conflicting claim 13 recites parenteral administration and conflicting claims 8 and 33 recite intravenous bolus administration.

The instant and conflicting claims differ because the conflicting claims are composition claims, whereas the instant claims are method claims. Nevertheless, as the conflicting claims recite both parenteral administration and intravenous administration, it would have been prima facie obvious to have administered the composition of the conflicting claims in this manner for predictable administration of irinotecan with a reasonable expectation of success.

Claims 1-21 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-17 of U.S. Patent No. 8,329,213 by itself or in view of Leue et al. (US 2002/0045756 A1).

The instant claims are drawn to a method for parenteral administration of a composition comprising irinotecan and sucrose octasulfate.

The conflicting claims are drawn to a composition comprising a liposome with irinotecan and sucrose octasulfate. Conflicting claim 14 recites parenteral administration.

The instant and conflicting claims differ because the conflicting claims are composition claims, whereas the instant claims are method claims. Nevertheless, as the conflicting claims recite both parenteral administration and intravenous administration, it would have been prima facie obvious to have administered the composition of the conflicting claims in this manner for predictable administration of irinotecan with a reasonable expectation of success.

As to claim 2, the conflicting claims do not teach intravenous administration.

Leue et al. (hereafter referred to as Leue) is drawn to camptothecin and its derivatives. Leue teaches that irinotecan can be administered in solution by intravenous injection, as of Leue, paragraph 0062.

It would have been prima facie obvious for one of ordinary skill in the art to have administered the composition of the conflicting claims by intravenous injection. This is because the composition of the conflicting claims includes irinotecan and is used for therapeutic purposes. As intravenous injection is a known method of administering irinotecan, the skilled artisan would have been motivated to have administered irinotecan by intravenous injection for predictable insertion of irinotecan into the body of a subject with a reasonable expectation of success.

Claims 1-21 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-17 of U.S. Patent No. 8,703,181 by itself or in view of Leue et al. (US 2002/0045756 A1). Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons:

The instant claims are drawn to a method for parenteral administration of a composition comprising irinotecan and sucrose octasulfate.

Conflicting claim 13 is drawn to a method of delivering irinotecan to a tumor comprising injection of a composition that is a liposome having irinotecan and sucrose octasulfate. Injection is understood to be a form of parenteral administration.

The instant and conflicting claims differ because conflicting claim 13 recites various limitations regarding the location of the irinotecan and sucrose octasulfate in the liposome, e.g. that both are in the interior aqueous space and not the bilayer. Nevertheless, the subject of the conflicting claims is within the scope of that of instant claim 1, and effectively anticipates instant claim 1. This results in a prima facie case of anticipatory-type non-statutory double patenting with regard to claim 1.

As to claim 2, the conflicting claims do not teach intravenous administration.

Leue et al. (hereafter referred to as Leue) is drawn to camptothecin and its derivatives. Leue teaches that irinotecan can be administered in solution by intravenous injection, as of Leue, paragraph 0062.

It would have been prima facie obvious for one of ordinary skill in the art to have administered the composition of the conflicting claims by intravenous injection. This is because the method of the conflicting claims includes administration irinotecan by injection, but does not specify the method by which irinotecan is injected. As intravenous injection is a known method of administering irinotecan, the skilled artisan would have been motivated to have administered irinotecan by intravenous injection for predictable insertion of irinotecan into the body of a subject with a reasonable expectation of success.

Claims 1-21 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 8,992,970 by itself or in view of Leue et al. (US 2002/0045756 A1).

The instant claims are drawn to a method for parenteral administration of a composition comprising irinotecan and sucrose octasulfate.

The conflicting claims are drawn to a liposome composition comprising irinotecan and sucrose octasulfate, and optionally a substituted ammonium compound. Confliting claim 8 teaches parenteral administration.

The instant and conflicting claims differ because the conflicting claims are composition claims, whereas the instant claims are method claims. Nevertheless, as the conflicting claims recite both parenteral administration and intravenous administration, it would have been prima facie obvious to have administered the composition of the

conflicting claims in this manner for predictable administration of irinotecan with a reasonable expectation of success.

As to claim 2, the conflicting claims do not teach intravenous administration.

Leue et al. (hereafter referred to as Leue) is drawn to camptothecin and its derivatives. Leue teaches that irinotecan can be administered in solution by intravenous injection, as of Leue, paragraph 0062.

It would have been prima facie obvious for one of ordinary skill in the art to have administered the composition of the conflicting claims by intravenous injection. This is because the composition of the conflicting claims includes irinotecan and is used for therapeutic purposes. As intravenous injection is a known method of administering irinotecan, the skilled artisan would have been motivated to have administered irinotecan by intravenous injection for predictable insertion of irinotecan into the body of a subject with a reasonable expectation of success.

Claims 1 and 3-18 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-22 of U.S. Patent No. 8,658,203. Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons:

The instant claims are drawn to a method for parenteral administration of a composition comprising irinotecan and sucrose octasulfate.

The conflicting claims are drawn to a method for treating a brain tumor in a mammal. The method comprises providing a liposomal formulation comprising sucrose

octasulfate and irinotecan, and administering said liposomal formulation to the mammal via a conduit placed in the brain tissue of the mammal.

As best understood by the examiner, the term “parenteral” refers to a route of administration that is not enteral and avoids the gastrointestinal tract. As such, the skilled artisan would have understood that the method of the conflicting claims is a parenteral method as the recited conduit would not have been present in the gastrointestinal tract. As such, the method of the conflicting claims appears to be within the scope of that of instant claim 1, and therefore effectively anticipates instant claim 1. This results in a prima facie case of anticipatory-type non-statutory double patenting.

However, this rejection does not apply to claims 2 and 19-21 as the conduit of the conflicting claims does not appear to be intravenous, and there would have been no motivation for the skilled artisan to have used intravenous administration instead of the conduit of the conflicting claims.

Claims 1-21 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 21-23 of copending Application No. 14/632,422 (reference application) in view of Leue et al. (US 2002/0045756 A1).

The instant claims are drawn to a method for parenteral administration of a composition comprising irinotecan and sucrose octasulfate.

The copending claims are drawn to a liposomal composition comprising sucrose octasulfate and a cationic antineoplastic agent made by a specific method. The cationic antineoplastic agent may be irinotecan, as of copending claim 11.

The instant claims and copending claims differ because copending claims 21-23 are composition claims, whereas the instant claims are drawn to a method of treatment.

Leue et al. (hereafter referred to as Leue) is drawn to camptothecin and its derivatives. Leue teaches that irinotecan can be administered in solution by intravenous injection, as of Leue, paragraph 0062. The camptothecin derivatives (of which irinotecan is one) are anticancer agents, as of Leue, paragraph 0003.

It would have been prima facie obvious for one of ordinary skill in the art to have administered the composition of the copending claims by intravenous injection. This is because the composition of the copending claims includes irinotecan and is used for therapeutic purposes. As intravenous injection is a known method of administering irinotecan, the skilled artisan would have been motivated to have administered irinotecan by intravenous injection for predictable insertion of irinotecan into the body of a subject with a reasonable expectation of success.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Claims 1 and 3-18 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-12 of copending

Application No. 14/151,632 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons:

The instant claims are drawn to a method for parenteral administration of a composition comprising irinotecan and sucrose octasulfate.

The copending claims are drawn to a fluid conduit comprising a liposome which includes sucrose octasulfate and a cationic antineoplastic agent. The cationic antineoplastic agent may be irinotecan, as of conflicting claim 6.

The instant and copending claims differ because the instant claims are drawn to a device, whereas the copending claims are drawn to a method for administering a composition. However, the skilled artisan would have understood the term “parenternal”, as of the instant claims, to refer to forms of administration that avoid the gastrointestinal tract. As the administration by fluid conduit or infusion catheter intended by the copending claims would appear to avoid the digestive tract, it is understood to be a form of parenteral administration. As such, the skilled artisan would have been motivated to have administered the composition of the copending claims using the device of the copending claims in a manner that is parenteral.

This rejection does not apply to instant claims 2 and 19-21 because the methods of administration of the copending claims are not intravenous, which is what is recited by instant claims 2 and 19-21. The skilled artisan would not have been motivated to have administered the composition comprising a cationic antineoplastic agent of the

copending claims in a manner that is intravenous because a different form of administration is recited in the copending claims.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Claims 1-21 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claim 1 of copending Application No. 15/213,127 by itself or in view of Leue et al. (US 2002/0045756 A1).

The instant claims are drawn to a method for parenteral administration of a composition comprising irinotecan and sucrose octasulfate.

The copending claim is drawn to an injectable composition comprising irinotecan and sucrose octasulfate encapsulated in a liposome.

The instant and copending claims differ because the copending claims are drawn to a composition whereas the instant claims are drawn to a method. Nevertheless, the composition of the copending claims is recited as an injectable composition. As such, the skilled artisan would have been motivated to have administered this composition by injection. Said injection is understood to read on the required parenteral administration because injection avoids the gastrointestinal tract and is therefore not enteral.

The copending claim does not teach intravenous administration, as required by instant claim 2.

Leue et al. (hereafter referred to as Leue) is drawn to camptothecin and its derivatives. Leue teaches that irinotecan can be administered in solution by intravenous

injection, as of Leue, paragraph 0062. The camptothecin derivatives (of which irinotecan is one) are anticancer agents, as of Leue, paragraph 0003.

It would have been prima facie obvious for one of ordinary skill in the art to have administered the composition of the copending claims by intravenous injection. This is because the composition of the copending claims includes irinotecan and is used for therapeutic purposes. As intravenous injection is a known method of administering irinotecan, the skilled artisan would have been motivated to have administered irinotecan by intravenous injection for predictable insertion of irinotecan into the body of a subject with a reasonable expectation of success.

This is a provisional nonstatutory double patenting rejection.

Claims 1-21 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1, 7-10, 12, 14-17, 19, 23, 24, 26, and 28-34 of copending Application No. 14/879,358 in view of Leue et al. (US 2002/0045756 A1).

The instant claims are drawn to a method for parenteral administration of a composition comprising irinotecan and sucrose octasulfate.

The copending claims are drawn to a composition comprising irinotecan and sucrose octasulfate encapsulated in a liposome.

The instant and copending claims differ because the copending claims are drawn to a composition whereas the instant claims are drawn to a method. As such, the copending claims do not teach the required parenteral or intravenous administration.

Leue et al. (hereafter referred to as Leue) is drawn to camptothecin and its derivatives. Leue teaches that irinotecan can be administered in solution by intravenous injection, as of Leue, paragraph 0062. The camptothecin derivatives (of which irinotecan is one) are anticancer agents, as of Leue, paragraph 0003.

It would have been prima facie obvious for one of ordinary skill in the art to have administered the composition of the copending claims by intravenous injection. This is because the composition of the copending claims includes irinotecan and is used for therapeutic purposes. As intravenous injection is a known method of administering irinotecan, the skilled artisan would have been motivated to have administered irinotecan by intravenous injection for predictable insertion of irinotecan into the body of a subject with a reasonable expectation of success.

This is a provisional nonstatutory double patenting rejection.

Claims 1-21 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1, 4-8, 13, 14, and 23-44 of copending Application No. 14/965,140 in view of Leue et al. (US 2002/0045756 A1).

The instant claims are drawn to a method for parenteral administration of a composition comprising irinotecan and sucrose octasulfate.

The copending claims are drawn to a composition comprising irinotecan and sucrose octasulfate encapsulated in a liposome.

The instant and copending claims differ because the copending claims are drawn to a composition whereas the instant claims are drawn to a method. As such, the copending claims do not teach the required parenteral or intravenous administration.

Leue et al. (hereafter referred to as Leue) is drawn to camptothecin and its derivatives. Leue teaches that irinotecan can be administered in solution by intravenous injection, as of Leue, paragraph 0062. The camptothecin derivatives (of which irinotecan is one) are anticancer agents, as of Leue, paragraph 0003.

It would have been prima facie obvious for one of ordinary skill in the art to have administered the composition of the copending claims by intravenous injection. This is because the composition of the copending claims includes irinotecan and is used for therapeutic purposes. As intravenous injection is a known method of administering irinotecan, the skilled artisan would have been motivated to have administered irinotecan by intravenous injection for predictable insertion of irinotecan into the body of a subject with a reasonable expectation of success.

This is a provisional nonstatutory double patenting rejection.

Claims 1-21 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-16 of copending Application No. 14/966,458 in view of Leue et al. (US 2002/0045756 A1).

The instant claims are drawn to a method for parenteral administration of a composition comprising irinotecan and sucrose octasulfate.

The copending claims are drawn to an irinotecan liposome comprising a sulfated sugar. Said sulfated sugar may be sucrose octasulfate, as of copending claim 5.

The instant and copending claims differ because the copending claims are drawn to a composition whereas the instant claims are drawn to a method. As such, the copending claims do not teach the required parenteral or intravenous administration.

Leue et al. (hereafter referred to as Leue) is drawn to camptothecin and its derivatives. Leue teaches that irinotecan can be administered in solution by intravenous injection, as of Leue, paragraph 0062. The camptothecin derivatives (of which irinotecan is one) are anticancer agents, as of Leue, paragraph 0003.

It would have been prima facie obvious for one of ordinary skill in the art to have administered the composition of the copending claims by intravenous injection. This is because the composition of the copending claims includes irinotecan and is used for therapeutic purposes. As intravenous injection is a known method of administering irinotecan, the skilled artisan would have been motivated to have administered irinotecan by intravenous injection for predictable insertion of irinotecan into the body of a subject with a reasonable expectation of success.

This is a provisional nonstatutory double patenting rejection.

Claims 1-21 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 15 and 16 of copending Application No. 14/181,583 (reference application) by itself or in view of Leue et al. (US 2002/0045756 A1) and Allen et al. (US 2001/0038851 A1).

The instant claims are drawn to a method for parenteral administration of a composition comprising irinotecan and sucrose octasulfate.

The conflicting claims are drawn to a method of imaging and treatment. Conflicting claims 15 and 16 are drawn to a method of injecting irinotecan sucrose octasulfate in a liposome.

The instant and conflicting claims differ because the conflicting claims include imaging steps that are absent from the instant claims. Nevertheless, the conflicting claims teach injecting a liposomal composition of irinotecan and sucrose octasulfate. As such, the subject matter of the conflicting claims effectively anticipates that of the instant claims, resulting in a prima facie case of anticipatory-type non-statutory double patenting.

While the instant claims teach injection, the instant claims do not teach parenteral injection.

Leue et al. (hereafter referred to as Leue) is drawn to camptothecin and its derivatives. Leue teaches that irinotecan can be administered in solution by intravenous injection, as of Leue, paragraph 0062. The camptothecin derivatives (of which irinotecan is one) are anticancer agents, as of Leue, paragraph 0003.

It would have been prima facie obvious for one of ordinary skill in the art to have administered the composition of the copending claims by intravenous injection. This is because the composition of the copending claims includes irinotecan and is used for therapeutic purposes. As intravenous injection is a known method of administering irinotecan, the skilled artisan would have been motivated to have administered

irinotecan by intravenous injection for predictable insertion of irinotecan into the body of a subject with a reasonable expectation of success.

The copending claims do not teach DSPC, cholesterol, and PEG-DSPE as liposome lipids.

Allen et al. (hereafter referred to as Allen) is drawn to a therapeutic liposome, as of Allen, title and abstract. Said liposome may deliver irinotecan, as of Allen, paragraph 0021. Liposomes of Allen include DSPC, as of Allen, paragraph 0061, and cholesterol, as of Allen, paragraph 0058. The molar ratio of phosphatidylcholine to cholesterol appears to be about 55:40, as of Allen, paragraph 0095 - this is about a 2.75:2 molar ratio. Allen teaches DSPE-PEG, optionally linked to an additional ingredient, as of Allen, paragraphs 0035, 0036, 0094, and 0095.

Allen does not teach sucrose octasulfate.

It would have been prima facie obvious for one of ordinary skill in the art to have included DSPC and cholesterol as lipids in the liposome used in the method of the conflicting claims. The method of the conflicting claims utilizes a liposome comprising irinotecan, but is silent as to the lipid composition of the liposome. As DSPC, cholesterol, and DSPE-PEG are well known lipids used in liposomes that deliver irinotecan, the skilled artisan would have been motivated to have used DSPC and cholesterol in the liposome used in the method of the conflicting claims to predictably deliver irinotecan with a reasonable expectation of success. Generally, it is *prima facie* obvious to select a known material (DSPC and cholesterol) for incorporation into a composition (that which is used in the method of the conflicting claims), based on its

recognized suitability for its intended use (to produce structure in a liposome). See MPEP 2144.07.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ISAAC SHOMER whose telephone number is (571)270-7671. The examiner can normally be reached on 8:00 AM - 5:00 PM Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick F. Krass can be reached on (571)272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/ISAAC SHOMER/
Primary Examiner, Art Unit 1612

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/879,302	10/09/2015	Keelung Hong	239669-378794/100.1130US1	5912

133156 7590 12/15/2016

Honigman Miller Schwartz and Cohn LLP
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EXAMINER	
SHOMER, ISAAC	

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
12/15/2016	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@honigman.com
arhoades@honigman.com
lbroecker@honigman.com

Office Action Summary	Application No. 14/879,302	Applicant(s) HONG ET AL.	
	Examiner ISAAC SHOMER	Art Unit 1612	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 November 2016*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *1-10 and 12-21* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-10 and 12-21* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

4) ☐ Other: _____.

DETAILED ACTION

Applicants' arguments, filed 15 November 2016, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

The present application is being examined under the pre-AIA first to invent provisions.

Non-Statutory Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(1) - 706.02(l)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

Claims 1-10 and 12-21 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claim 1 of copending Application No. 15/296,536 (reference application) by itself or in view of Berge et

al. (Journal of Pharmaceutical Sciences, Vol. 66 No. 1, January 1977, pages 1-19).

Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons:

Instant claim 1 is drawn to a method of treatment comprising parenteral administration of a liposomal irinotecan composition comprising irinotecan sucrose octasulfate and phospholipids, with a total of 150-550 mg of irinotecan per total liposome phospholipid.

Copending claim 1 is drawn to an injectable liquid pharmaceutical composition. Said composition comprises irinotecan sucrose octasulfate encapsulated within liposomes. An amount of 500-550 mg of irinotecan per mmol of total liposome phospholipids is taught by the copending claim. The size of the liposome and the potency of the composition is also taught.

The instant and copending claims differ because the instant claims are method of treatment claims, whereas the copending claims are drawn to a composition. However, the composition of the copending claims is an injectable liquid composition. As injection is a form of parenteral administration, the skilled artisan would have been motivated to have conducted the method of parenteral administration using the composition of the copending claims.

Instant claim 1 differs from the copending claims because instant claim 1 recites a total amount of 150 to 550 mg of irinotecan per mmol of liposome phospholipids, whereas the copending claims recite 500-550 mg of irinotecan per mmol of total liposome phospholipids. Nevertheless, the recitation of the conflicting claims is within

the scope of the instant claims, resulting in a prima facie case of non-statutory double patenting.

The examiner takes the position that copending claim 1 appears to be within the scope of instant claim 1. Nevertheless, purely *en arguendo*, the examiner will proceed as if the copending claims differ from the instant claims because the copending claims are drawn to irinotecan hydrochloride, whereas the instant claims are drawn to irinotecan base.

Berge et al. (hereafter referred to as Berge) is drawn to pharmaceutical salts. Berge teaches that any compound that exhibits acid or base characteristics may (but not must) participate in salt formation, as of Berge, page 2, left column, first paragraph in section entitled "Potentially Useful Salts." Berge teaches both chloride and hydrochloride as anions used in pharmaceutically acceptable salts, as of Berge, page 2, Table I.

It would have been prima facie obvious for one of ordinary skill in the art to have substituted irinotecan in the base form in place of irinotecan in the hydrochloride salt form. Berge teaches that while hydrochloride salts are a form of salt used in pharmaceutical compositions, a basic moiety on a therapeutic agent may be in the form of a free base, as of Berge, page 2, left column, first paragraph in section entitled "Potentially Useful Salts" as well as page 7, left column, first full paragraph. As such, the skilled artisan would have been motivated to have altered irinotecan from being in the form of a hydrochloride salt to being in the form of a free base for predictable administration with therapeutic effects with a reasonable expectation of success.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Claims 1-10 and 12-21 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-20 of copending Application No. 15/227,631 (reference application) in view of Rahman et al. (WO 2003/030864 A1). Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons:

Instant claim 1 is drawn to a method of treatment comprising parenteral administration of a liposomal irinotecan composition comprising irinotecan sucrose octasulfate and phospholipids, with a total of 150-550 mg of irinotecan per total liposome phospholipid.

Copending claim 1 is drawn to a pharmaceutical composition comprising irinotecan sucrose octasulfate precipitated in a matrix. This composition appears to be in the form of a liposome, as of copending claim 2. The liposome has a specific size and a specific amount of irinotecan of 500-550 mg of irinotecan per mmol of total phospholipids.

The instant and copending claims differ because the copending claims are drawn to a composition, whereas the instant claims are drawn to a method of parenteral administration. The copending claims do not teach the required method of administration.

Rahman et al. (hereafter referred to as Rahman) is drawn to a liposomal formulation of irinotecan, as of Rahman, title and abstract. The liposomal formulation of Rahman can be administered in a variety of methods including parenterally and intravenously, as of Rahman, page 6 lines 20-22.

Rahman does not teach sucrose octasulfate.

It would have been prima facie obvious for one of ordinary skill in the art to have administered the liposome of the copending claims parenterally, including intravenously, as taught by Rahman. The copending claims are drawn to a liposome comprising irinotecan as the active agent. As Rahman teaches that irinotecan can be administered intravenously, the skilled artisan would have been motivated to have administered the liposome of the copending claims intravenously for predictable delivery of irinotecan with a reasonable expectation of success.

Instant claim 1 differs from the copending claims because instant claim 1 recites a total amount of 150 to 550 mg of irinotecan per mmol of liposome phospholipids, whereas the copending claims recite 500-550 mg of irinotecan per mmol of total liposome phospholipids. Nevertheless, the recitation of the conflicting claims is within the scope of the instant claims, resulting in a prima facie case of non-statutory double patenting.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Claims 1-10 and 12-21 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-20 of copending Application No. 15/227,561 (reference application) in view of Rahman et al. (WO 2003/030864 A1) and as evidenced by Israelachvili et al. (Quarterly Reviews of Biophysics, Vol. 13 No. 2, 1980, pages 121-200). Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons:

Instant claim 1 is drawn to a method of treatment comprising parenteral administration of a liposomal irinotecan composition comprising irinotecan sucrose octasulfate and phospholipids, with a total of 150-550 mg of irinotecan per total liposome phospholipid.

Copending claim 1 is drawn to a pharmaceutical composition comprising irinotecan sucrose octasulfate precipitated in a matrix. The liposome has a specific size and a specific amount of irinotecan of 500 mg of irinotecan per mmol of total phospholipids. While the copending claims do not appear to recite a liposome, the skilled artisan would have expected that the lipids of copending claim 7; namely DSPC, cholesterol, and PEG-DSPE are vesicle-forming lipids and would have formed a liposome.

The instant and copending claims differ because the copending claims are drawn to a composition, whereas the instant claims are drawn to a method of parenteral administration. The copending claims do not teach the required method of administration.

Rahman et al. (hereafter referred to as Rahman) is drawn to a liposomal formulation of irinotecan, as of Rahman, title and abstract. The liposomal formulation of Rahman can be administered in a variety of methods including parenterally and intravenously, as of Rahman, page 6 lines 20-22.

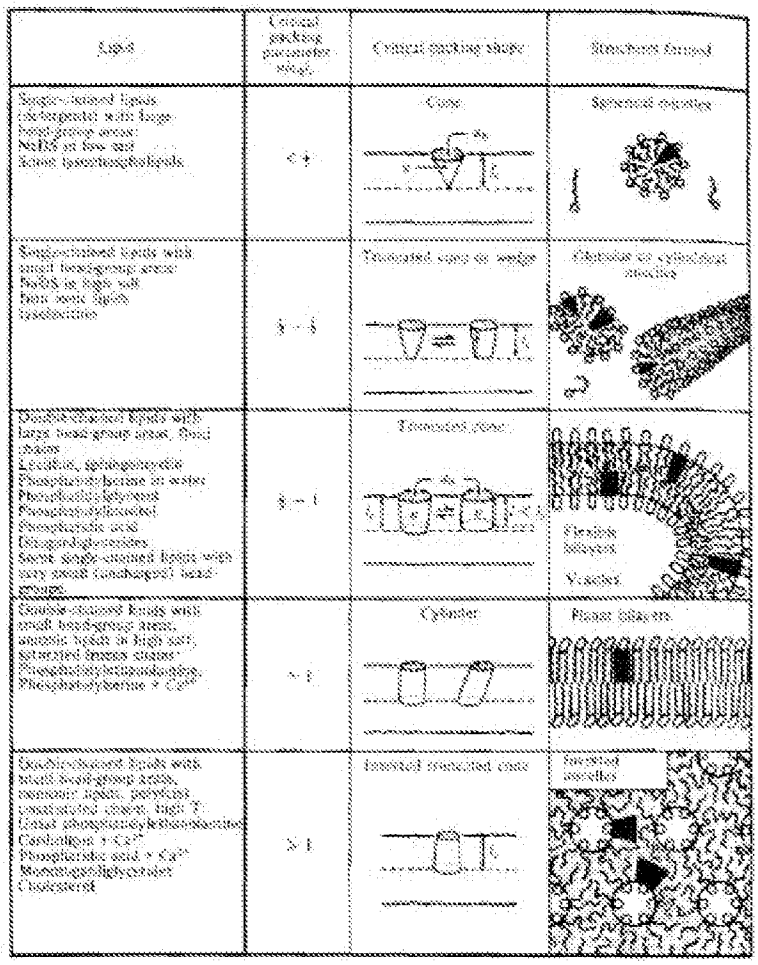
Rahman does not teach sucrose octasulfate.

It would have been prima facie obvious for one of ordinary skill in the art to have administered the liposome of the copending claims parenterally, including intravenously, as taught by Rahman. The copending claims are drawn to a liposome comprising irinotecan as the active agent. As Rahman teaches that irinotecan can be administered intravenously, the skilled artisan would have been motivated to have administered the liposome of the copending claims intravenously for predictable delivery of irinotecan with a reasonable expectation of success.

Instant claim 1 differs from the copending claims because instant claim 1 recites a total amount of 150 to 550 mg of irinotecan per mmol of liposome phospholipids, whereas the copending claims recite 500 mg of irinotecan per mmol of total liposome phospholipids. Nevertheless, the recitation of the conflicting claims is within the scope of the instant claims, resulting in a prima facie case of non-statutory double patenting.

The instant claims recite that the composition to be administered in the method of the instant claims is a liposome. The copending claims recite a “composition” and do not specify a liposome. Nevertheless, the copending claims recite that the lipid formulation has DSPC, cholesterol, and PEG-DSPE in a specific molar ratio, as of copending claim

7, which appears to be the same molar ratio in instant claim 9. Additionally, the skilled artisan would have understood that the lipids of the copending claims include a preponderance of a phosphatidylcholine. The skilled artisan would have understood that phosphatidylcholine (i.e. lecithin) forms flexible lipid bilayers, which are the structure of liposomes. As evidence for this, the examiner cites Israelachvili et al. (hereafter referred to as Israelachvili). Israelachvili provides a table as of page 158, which shows which lipids form which structures. This table shows that lecithin (i.e. phosphatidylcholine) forms flexible bilayers and vesicles, which is the structure of a liposome.



This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Additional Note Regarding Double Patenting

MPEP 804(I)(B)(1) discloses the following:

> If a "provisional" nonstatutory double patenting rejection is the only rejection remaining in an application having the earliest effective U.S. filing date (including any benefit claimed under 35 U.S.C. 120, 121, 365(c) [but not 35 U.S.C. 119(e)], or 386(c)) compared to the reference application(s), the examiner should withdraw the rejection in the application having the earliest effective U.S. filing date and permit that application to issue as a patent, thereby converting the "provisional" nonstatutory double patenting rejection in the other application(s) into a nonstatutory double patenting rejection when the application with the earliest U.S. effective filing date issues as a patent.

The examiner notes that both the instant application, as well as copending applications 15/296536, 15/227631, and 15/227561, over which the instant claims have been rejected, claim benefit through 35 U.S.C. 120 to instant application 11/121,294, filed on 2 May 2005.

As such, for this purpose, the instant application and the above-rejected copending applications are understood to have the same effective U.S. filing date. As such, the provision that the provisional nonstatutory double patenting rejection should be withdrawn prior to allowance is not applicable with regard to the non-statutory double patenting rejections listed above. This is because the instant application is not “the

application with the earliest effective U.S. filing date" because the instant and copending applications have the same effective U.S. filing date.

Additional Copending Applications

As additional relevant copending applications, the examiner cites the following applications:

15/364,021;

15/363,761;

15/363,923; and

15/363,978.

These applications are drawn to liposomal formulations of irinotecan. However, the liposomal formulations recited in these claims do not include sucrose octasulfate, which is required by the instant claims. As such, the instant claims are not rejected over the claims of the above-cited application on the grounds of provisional non-statutory double patenting.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ISAAC SHOMER whose telephone number is (571)270-7671. The examiner can normally be reached on 8:00 AM - 5:00 PM Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick F. Krass can be reached on (571)272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/ISAAC SHOMER/
Primary Examiner, Art Unit 1612

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/879,358	10/09/2015	Keelung Hong	239669-378837/1001130US12	8093

133156 7590 12/28/2015

Honigman Miller Schwartz and Cohn LLP
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EXAMINER	
SHOMER, ISAAC	

ART UNIT	PAPER NUMBER
1612	

MAIL DATE	DELIVERY MODE
12/28/2015	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 14/879,358	Applicant(s) HONG ET AL.	
	Examiner ISAAC SHOMER	Art Unit 1612	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
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Status

1)☐ Responsive to communication(s) filed on _____.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) 1-20 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) 1-20 is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

4) ☐ Other: _____.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

The present application is being examined under the pre-AIA first to invent provisions.

In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

Claim Rejections - 35 USC § 103 – Obviousness

The following is a quotation of pre-AIA 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under pre-AIA 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under pre-AIA 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of pre-AIA 35 U.S.C. 103(c) and potential pre-AIA 35 U.S.C. 102(e), (f) or (g) prior art under pre-AIA 35 U.S.C. 103(a).

Claims 1-20 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Chou et al. (Journal of Bioscience and Bioengineering, Vol. 95, No. 4, 2003, pages 405-408) in view of Schlessinger et al. (US Patent 5,783,568).

Chou et al. (hereafter referred to as Chou) is drawn to a liposomal irinotecan formulation, as of Chou, page 405, title and abstract. This composition includes irinotecan along with lipids, as of Chou, page 405, abstract. This composition is intended for cancer treatment, as of Chou, page 405, left column, first paragraph.

Chou does not teach sucrose octasulfate.

Schlessinger et al. (hereafter referred to as Schlessinger) is drawn to the treatment of cancer, as of Schlessinger, title and abstract. Schlessinger teaches that sucrose octasulfate has the ability to treat cancer or an angiogenic abnormality as it

prevents oligomerization of heparin growth factor, as of Schlessinger, column 27 lines 19-26.

Schlessinger does not teach irinotecan.

It would have been prima facie obvious for one of ordinary skill in the art to have included the sucrose octasulfate into the liposome of Chou. Chou is drawn to a liposome comprising irinotecan, which is intended for use in treating cancer. As sucrose octasulfate is also used for treating cancer, as taught by Schlessinger, the skilled artisan would have been motivated to have included the sucrose octasulfate of Schlessinger into the liposome of Chou. Generally, it is prima facie obvious to combine two compositions (liposomal irinotecan, as of Chou, and sucrose octasulfate, as of Schlessinger), each of which is taught by the prior art to be useful for same purpose (treating cancer), in order to form a third composition to be used for the very same purpose. The idea for combining them flows logically from their having been individually taught in the prior art. See MPEP 2144.06. Moreover, where it would have been obvious to have combined individually known ingredients, evidence must be provided establishing that appellant's combination of agents is in some way more effective or in some way different than any single member of that combination in order to rebut that prima facie case. See In re Dial, 140 USPQ 244 (C.C.P.A. 1964).

As to claim 2, Chou teaches adding 1 mg of irinotecan to 1 mL of liposomes at a lipid concentration of 5 mM (i.e. 5 mmol per liter), as of Chou, page 406, left column, first paragraph below Table 1. As such, this appears to be the following concentration, given a molecular weight of irinotecan of 586.678 Daltons:

$$\frac{1\ mg\ irinotecan}{1\ mL\ liposome} \times \frac{1\ mmol\ Irinotecan}{586\ mg\ Irinotecan} \times \frac{1\ L\ liposome}{5\ mmol\ lipid} \times \frac{1000\ mL\ liposome}{1\ L\ liposome}$$

This is equivalent to about 0.34 mol of irinotecan per mol of lipid, which is within the required range.

As to claim 3, the examiner notes the calculated value of 0.34 mol of irinotecan per mol of lipid. While it is unclear what the molecular weight of the lipid is, the examiner will assume a molecular weight of about 790 Daltons, as that is the molecular weight of distearoylphosphatidylcholine (DSPC), though the examiner acknowledges that there are lipids with a molecular weight that is higher (e.g. DSPE-PEG) or lower (e.g. cholesterol). As such, the examiner presents the following calculation:

$$\frac{1\ mg\ irinotecan}{1\ mL\ liposome} \times \frac{1\ L\ liposome}{5\ mmol\ lipid} \times \frac{1\ mmol\ lipid}{790\ mg\ lipid} \times \frac{1000\ mL\ liposome}{1\ L\ liposome}$$

This is a ratio of about 0.25 mg irinotecan per mg of lipid. While this is lower than the claimed amount, the skilled artisan would have been motivated to have increased the amount of irinotecan in order to have predictably increased the anti-cancer properties with a reasonable expectation of success. Additionally, it is noted that generally, differences in concentration between the claimed invention and prior art will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating that such concentration is critical. See MPEP 2144.05(II)(A). In the absence of such evidence, this claim is rejected.

As to claim 4, this claim is rejected for the same reason that claim 2 is rejected.

As to claim 5, the examiner presents the following calculation, with the same molecular weight assumptions as above:

$$\frac{1\ mg\ irinotecan}{1\ mL\ liposome} \times \frac{1\ mmol\ irinotecan}{586\ mg\ irinotecan} \times \frac{1\ L\ liposome}{5\ mmol\ lipid} \times \frac{1000\ mL\ liposome}{1\ L\ liposome}$$

$$\times \frac{1\ mmol\ lipid}{790\ mg\ lipid} \times \frac{1000\ \ mg}{1\ gram}$$

This is a value of about 0.43 mmol of irinotecan per gram of lipid. While this is lower than the claimed amount, the skilled artisan would have been motivated to have increased the amount of irinotecan in order to have predictably increased the anti-cancer properties with a reasonable expectation of success. Additionally, it is noted that generally, differences in concentration between the claimed invention and prior art will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating that such concentration is critical. See MPEP 2144.05(II)(A). In the absence of such evidence, this claim is rejected.

As to claim 6, the examiner presents the following calculation:

$$\frac{1\ mg\ irinotecan}{1\ mL\ liposome} \times \frac{1\ L\ liposome}{5\ mmol\ lipid} \times \frac{1000\ mL\ lipid}{1\ L\ lipid}$$

This is about 200 mg of irinotecan per mmol of lipid. While this is lower than the claimed amount, the skilled artisan would have been motivated to have increased the amount of irinotecan in order to have predictably increased the anti-cancer properties with a reasonable expectation of success.

As to claim 7, Chou teaches DSPC and cholesterol, as of Chou, page 406, right column, first full paragraph.

As to claim 8, Chou teaches a ratio of DSPC/chol/PEG of 100:30:5, as of Chou, page 406, right column, Figure 1. While this appears to be mass ratio, an ensuing molar ratio would appear to be 0.12:0.078:0.0025, based on molecular weights of DSPC ≈

790, cholesterol ≈ 387, and DSPE-PEG ≈ 2000. This is about a ratio of about 3:1.95:0.0625. While this is not necessarily the same as the size that is claimed, it is noted that generally, differences in concentration between the claimed invention and prior art will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating that such concentration is critical. See MPEP 2144.05(II)(A). In the absence of such evidence, this claim is rejected.

As to claim 9, Chou teaches particle sizes of 75-765 nm, as of Chou, page 406, right column, Table 2. This overlaps with the claimed size range. While the prior art does not disclose the exact claimed values, but does overlap: in such instances even a slight overlap in range establishes a *prima facie* case of obviousness. See MPEP 2144.05(I).

As to claim 10, this claim is rejected for the same reason that claims 2-9 are rejected.

As to claim 11, this is an independent claim requiring irinotecan and sucrose octasulfate encapsulated in a liposome with DSPC and cholesterol in a molar ratio of 3:2. The examiner calculated a molar ratio of DSPC:cholesterol of 3:1.95, as of claim 8, rejected above. This is understood to be sufficiently close to the 3:2 required molar ratio to read on the subject matter of claim 11. Generally, differences in concentration between the claimed invention and prior art will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating that such concentration is critical. See MPEP 2144.05(II)(A). In the absence of such evidence, this claim is rejected.

As to claim 12, this claim is rejected for the same reason that claim 8 is rejected.

As to claim 13, this claim is rejected for the same reasons that claims 2-6 are rejected.

As to claim 14, this claim is rejected for the same reason that claim 9 is rejected.

As to claim 15, this is an independent claim requiring irinotecan and sucrose octasulfate in a liposome, wherein at least 90% of the irinotecan in the pharmaceutical composition is encapsulated by the liposome. Chou teaches an encapsulation efficiency of about 97-99%, as of Chou, page 406, left column, bottom paragraph.

As to claim 16, this claim is rejected for the same reason that both claims 2 and claim 8 are rejected.

As to claim 17, this claim is rejected for the same reason that claims 14 and 9 are rejected.

As to claim 18, this claim is rejected for the same reason that claims 3 and 6 are rejected.

As to claim 19, this claim is rejected for the same reasons that claims 17, 14, and 9 are rejected.

As to claim 20, this claim is rejected for the same reason that claim 6 is rejected.

Note Regarding Reference Date: Chou was published online on 27 August 2003. This is less than a year older than the oldest claimed priority date of 3 May 2004, which is the filing date of provisional application 60/567,921. As such, Chou is prior art at least under 35 U.S.C. 102(a).

Non-Statutory Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the claims at issue are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the reference application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(1) - 706.02(l)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/forms/. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to http://www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

Non-Statutory Double Patenting – Patent 8,147,867

Claims 1-20 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-35 of U.S. Patent No. 8,147,867. Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons:

Instant claim 1 is drawn to a liposome comprising irinotecan and sucrose octasulfate encapsulated in one or more lipids.

Confliting claim 1 is drawn to a liposomal irinotecan composition comprising sucrose octasulfate, along with phospholipids and optionally a substituted ammonium compound. Said composition has a specific release rate.

Instant claim 1 differs from conflicting claim 1 because conflicting claim 1 recites various limitations regarding a substituted ammonium compound and release rate that are not recited by the instant claims. Nevertheless, the subject matter of conflicting

claim 1 appears to be within the scope of instant claim 1. This results in a prima facie case of anticipatory-type non-statutory double patenting.

As to instant claims 2-20, these claims further limit claim 1 by reciting specific ratios of specific lipids and irinotecan. The examiner notes that conflicting claims 14 and 15 teach molar ratios of irinotecan to total lipids of 1.0 and 1.76 mol irinotecan per mole lipid as of conflicting claims 14 and 15, which is understood to read on the required ratios. The subject matter of conflicting claim 24 also appears to read on the subject matter of instant claim 6. Also, conflicting claim 29 teaches lecithin and cholesterol at a 3:2 molar ratio, which reads on the ratio required by instant claim 16, and PEG-DSPE is taught, as of conflicting claim 31.

Non-Statutory Double Patenting – Patent 8,329,213

Claims 1-6, 9, 10, and 15-20 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-5 and 8-17 of U.S. Patent No. 8,329,213. Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons:

Instant claim 1 is drawn to a liposome comprising irinotecan and sucrose octasulfate encapsulated in one or more lipids.

Conflicting claim 1 is drawn to a liposome comprising sucrose octasulfate and a cationic antineoplastic agent in the form of a salt. Conflicting claim 11 teaches irinotecan as the cationic antineoplastic agent.

The instant and conflicting claims differ because conflicting claim 11 recites that the irinotecan is in the form of a salt of sucrose octasulfate. This is not required by the instant claims. Nevertheless, the subject matter of conflicting claim 11 appears to be within the scope of instant claim 1. This results of a prima facie case of anticipatory-type non-statutory double patenting.

As to instant claims 2-6, 9, 10, and 15-20, these claims further modify the proportions of lipid and irinotecan in the liposome. Conflicting claims 12 and 13 recite such values in terms of a molar ratio. Nevertheless, the examiner notes that differences in concentration will generally not support the patentability of subject matter encompassed by the prior art (in this case conflicting claims) unless there is evidence indicating that such concentration is critical. See MPEP 2144.05(II)(A). Absent such evidence, these claims are rejected.

Claims 7, 8, and 11-14 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-5 and 8-17 of U.S. Patent No. 8,329,213 in view of Lim et al. (US Patent 5,858,397).

Instant claim 1 is drawn to a liposome comprising irinotecan and sucrose octasulfate encapsulated in one or more lipids. The claims rejected here further modify claim 1 to require that the specific lipids DSPC, cholesterol, and DSPE-PEG are present, with some claims requiring these elements to be present in specific proportions.

Conflicting claim 1 is drawn to a liposome comprising sucrose octasulfate and a cationic antineoplastic agent in the form of a salt. Conflicting claim 11 teaches irinotecan as the cationic antineoplastic agent.

The conflicting claims do not recite DSPC, cholesterol, or PEG-DSPE.

Lim et al. (hereafter referred to as Lim) is drawn to a liposomal formula of mitoxantrone, which is used for cancer treatment, as of Lim, title and abstract. Lipids used in this liposome include cholesterol, DSPC, and PEG-DSPE, as of Lim, column 2 lines 49-59, as well as column 8 line 43 and column 14 line 8.

Lim does not teach irinotecan or sucrose octasulfate.

It would have been prima facie obvious for one of ordinary skill in the art to have included the lipids of Lim in the liposome of the conflicting claims. The conflicting claims teach a liposome, but do not specify the types of lipids included in the liposome. As DSPC, cholesterol, and PEG-DSPE are lipids known to be included a liposome, the skilled artisan would have been motivated to have used these lipids in the composition of the conflicting claims to have predictably formed a liposome with a reasonable expectation of success. Generally, it is *prima facie* obvious to select a known material (DSPC, cholesterol, and/or PEG-DSPE) for incorporation into a composition (a liposome), based on its recognized suitability for its intended use (as liposome lipids). See MPEP 2144.07.

The instant claims require specific proportions of each lipid. While the proportions of the instant claims do not appear to be taught either by the conflicting claims or by Lim, the examiner notes that differences in concentration will generally not support the

patentability of subject matter encompassed by the prior art (in this case conflicting claims) unless there is evidence indicating that such concentration is critical. See MPEP 2144.05(II)(A). Absent such evidence, these claims are rejected.

Non-Statutory Double Patenting – Patent 8,703,181

Claims 1-6, 9, and 15-20 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-17 of U.S. Patent No. 8,703,181.

Claims 7, 8, and 11-14 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-177 of U.S. Patent No. 8,703,181 in view of Lim et al. (US Patent 5,858,397).

Instant claim 1 is drawn to a liposome comprising irinotecan and sucrose octasulfate encapsulated in one or more lipids.

Conflicting claim 11 is drawn to a method of delivering irinotecan to a tumor through a liposome comprising a sucrose octasulfate salt of irinotecan, as of conflicting claim 11.

The instant and conflicting claims differ because the instant claims are composition claims whereas the conflicting claims are method claims. Nevertheless, the composition delivered by conflicting claim 11 has all the required features of the composition recited by instant claim 1. This results in a prima facie case of anticipatory-type non-statutory double patenting.

As to instant claims 2-20, these claims further modify the proportions of lipid and irinotecan in the liposome, or modify proportions of lipids such as DSPC, cholesterol, and PEG-DSPE. Conflicting claims 12 and 13 teach specific molar ratios of irinotecan to lipids. Nevertheless, the examiner notes that differences in concentration (e.g. as between the instantly claimed and conflicting compositions) will generally not support the patentability of subject matter encompassed by the prior art (in this case conflicting claims) unless there is evidence indicating that such concentration is critical. See MPEP 2144.05(II)(A). Absent such evidence, these claims are rejected.

Non-Statutory Double Patenting – Patent 8,992,970

Claims 1-20 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 8,992,970

Instant claim 1 is drawn to a liposome comprising irinotecan and sucrose octasulfate encapsulated in one or more lipids.

Conflicting claim 1 is drawn to liposomes having sucrose octasulfate and irinotecan, along with specific lipids such as DSPC, cholesterol, and PEG-DSPE.

The instant and conflicting claims differ because conflicting claim 1 recites lipids that are not recited in instant claim 1. Also, conflicting claim 1 appears to require a "supersaturation" type limitation, which is not required by instant claim 1. Nevertheless, the subject matter of conflicting claim 1 is within the scope of that of instant claim 1, resulting in the subject matter of the conflicting claims effectively anticipation that of the

instant claims. This results in a prima facie case of anticipatory-type non-statutory double patenting.

As to instant claims 2-20, these claims modify proportions of lipids, and ratios of therapeutic agent to lipid. For example, conflicting claim 6 recites a specific ratio of DSPC/cholesterol/DSPE-PEG, which appears to be essentially the same as that recited by confliting claim 8. While the ratios of irinotecan to lipids do not appear to be explicitly recited to be the same in the conflicting claims as in the instant claims, the examiner notes that differences in concentration (e.g. as between the instantly claimed and conflicting compositions) will generally not support the patentability of subject matter encompassed by the prior art (in this case conflicting claims) unless there is evidence indicating that such concentration is critical. See MPEP 2144.05(II)(A). Absent such evidence, these claims are rejected.

Provisional Non-Statutory Double Patenting – 14/632,422

Claims 1-20 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-23 of copending Application No. 14/632,422 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons:

Instant claim 1 is drawn to a liposome comprising irinotecan and sucrose octasulfate encapsulated in one or more lipids.

Copending claim 22 is drawn to a liposome comprising sucrose octasulfate and irinotecan encapsulated in an aqueous interior space.

The instant and conflicting claims differ because the conflicting claims require that the composition be able to be prepared by a specific method, which is not required by the instant claims. Nevertheless, the composition of the conflicting claims appears to be within the scope of instant claim 1, resulting in a prima facie case of anticipatory-type non-statutory double patenting.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Provisional Non-Statutory Double Patenting – Application 14/879,302

Claims 1-20 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-21 of copending Application No. 14/879,302 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons:

Instant claim 1 is drawn to a liposome comprising irinotecan and sucrose octasulfate encapsulated in one or more lipids.

Copending claim 1 is drawn to a method of treatment comprising the parenteral administration of a liposome comprising irinotecan and sucrose octasulfate encapsulated in one or more lipids.

The instant and copending claims differ because the copending claims are method claims, whereas the instant claims are composition claims. Nevertheless, the method of the copending claims utilizes the composition of the instant claims as part of its method, which thereby effectively anticipates the composition of the instant claims, resulting in a prima facie case of anticipatory-type non-statutory double patenting.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ISAAC SHOMER whose telephone number is (571)270-7671. The examiner can normally be reached on 8:00 AM - 5:00 PM Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick F. Krass can be reached on (571)272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/ISAAC SHOMER/
Primary Examiner, Art Unit 1612

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14/879,358	10/09/2015	Keelung Hong	239669-378837/1001130US12	8093

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EXAMINER	
SHOMER, ISAAC	

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
07/12/2016	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@honigman.com
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Office Action Summary	Application No. 14/879,358	Applicant(s) HONG ET AL.	
	Examiner ISAAC SHOMER	Art Unit 1612	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 May 2016*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *1,7-10,12,14-17,19,23,24,26 and 28-34* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1,7,9,10,14,15,17,23,26,28,29 and 31-34* is/are rejected.

8)☒ Claim(s) *8,12,16,19,24 and 30* is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

4) ☐ Other: _____.

DETAILED ACTION

Applicants' arguments, filed 23 May 2016, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

The present application is being examined under the pre-AIA first to invent provisions.

Non-Statutory Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the claims at issue are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the reference application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(1) - 706.02(l)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/forms/. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to http://www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

Claims 1, 15, 23, 26, 33, and 34 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-22 of U.S. Patent No. 8,658,203 in view of Berge et al. (Journal of Pharmaceutical Sciences, Vol. 66 No. 1, January 1977, pages 1-19).

Instant claim 1 is drawn to a liposome composition comprising irinotecan and sucrose octasulfate encapsulated in a liposome comprising one or more phospholipids. The liposome includes a total amount of about 500 mg of irinotecan hydrochloride per mmol of phospholipid.

Conflicting claim 1 is drawn to a method for treating a brain tumor. This method involves the step of providing a liposome comprising phospholipids. Said liposome may comprise irinotecan and sucrose octasulfate, as of part "1" of conflicting claim 1, along with a possible substituted ammonium compound, as of part "2" of conflicting claim 1. The liposome may comprise irinotecan entrapped in the liposome at 500 grams of irinotecan per mol of phospholipids, as of conflicting claim 3, which is the same as 500 mg irinotecan per mmol of phospholipid.

Conflicting claim 1 does not specify irinotecan hydrochloride.

Berge et al. (hereafter referred to as Berge) is drawn to pharmaceutical salts. Berge teaches that hydrochloride is a common counter-anion of cationic drugs, as of Berge, Table I, reproduced below.

Table I—FDA-Approved Commercially Marketed Salts

Anion	Percent*	Anion	Percent*
Acetate	1.26	Iodide	3.02
Benzenesulfonate	0.25	Isethionate[1]	0.88
Benzoate	0.51	Lactate	0.76
Bicarbonate	0.13	Lactobionate	0.13
Bitartrate	0.63	Malate	0.13
Bromide	4.68	Maleate	3.02
Calcium edetate	0.25	Mandelate	0.38
Camsylate[2]	0.25	Mesylate	2.02
Carbonate	0.38	Methylbromide	0.76
Chloride	4.17	Methylnitrate	0.38
Citrate	3.03	Methylsulfate	0.88
Dihydrochloride	0.51	Mucate	0.13
Edetate	0.25	Napsylate	0.25
Edisylate[3]	0.88	Nitrate	0.64
Estolate[4]	0.13	Pamoate (Embonate)	1.01
Esylate[5]	0.13	Pantothenate	0.25
Fumarate	0.25	Phosphate/diphosphate	3.16
Gluceptate[6]	0.38	Polygalacturonate	0.13
Gluconate	0.51	Salicylate	0.88
Glutamate	0.25	Stearate	0.25
Glycollylarsanilate[7]	0.13	Subacetate	0.38
Hexylresorcinate	0.13	Succinate	0.38
Hydrabamine[8]	0.25	Sulfate	2.40
Hydrobromide	1.36	Tannate	0.88
Hydrochloride	42.38	Tartrate	3.54
Hydroxynaphthoate	0.25	Teoclate[9]	0.13
		Triethiodide	0.13

It would have been prima facie obvious for one of ordinary skill in the art to have used hydrochloride as the counter-ion to irinotecan in the composition used in the method of the conflicting claims. The conflicting claims are drawn to a method of using a liposome comprising irinotecan and sucrose octasulfate. The skilled artisan would have been aware that irinotecan is a drug that includes a cationic moiety. As hydrochloride is a common FDA-approved counter-ion for an active agent that comprises a cationic moiety, the skilled artisan would have been motivated to have used hydrochloride as the counter-ion to irinotecan for predictable administration as a therapeutic active agent with a reasonable expectation of success.

As to claim 1, the examiner notes that the instant claims are drawn to a composition, whereas the conflicting claims are drawn to a method. However, the method of the conflicting claims utilizes a composition that renders the instant claims obvious, for the reasons set forth above.

As to instant claim 15, it is noted that conflicting claim 1 recites that the irinotecan and sucrose octasulfate are entrapped in the liposome. For this purpose, entrapped is understood to have the same meaning as encapsulated, and the subject matter of the conflicting claims is understood to read on instant claim 15.

As to instant claim 23, the subject matter of the conflicting claims reads on this claim for the same reason as is the case regarding claims 1 and 15.

As to claim 26, the skilled artisan would have expected that the entirety of the irinotecan would have been encapsulated in the liposome of the conflicting claims as irinotecan is taught to be encapsulated in a liposome.

As to claim 33, the conflicting claims teach triethylammonium, as of conflicting claim 9. As triethylammonium is cationic and sucrose octasulfate anionic, the skilled artisan would have expected that these components would have combined to form sucrose octasulfate triethylammonium as required by the claims.

As to claim 34, the skilled artisan would have expected that the combination of triethylammonium and sucrose octasulfate would have resulted in precipitation.

Claims 7, 9, 10, 14, 17, 28, 29, 31, and 32 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-22 of U.S. Patent No. 8,658,203 in view of Berge et al. (Journal of Pharmaceutical Sciences, Vol. 66 No. 1, January 1977, pages 1-19), the combination further in view of Boulikas (US Patent 6,511,676).

Instant claim 1 is drawn to a liposome composition comprising irinotecan and sucrose octasulfate encapsulated in a liposome comprising one or more phospholipids. The liposome includes a total amount of about 500 mg of irinotecan hydrochloride per mmol of phospholipid. Instant claim 7 further recites that the liposome includes DSPC and cholesterol.

Conflicting claim 1 is drawn to a method for treating a brain tumor. This method involves the step of providing a liposome comprising phospholipids. Said liposome may comprise irinotecan and sucrose octasulfate, as of part "1" of conflicting claim 1, along with a possible substituted ammonium compound, as of part "2" of conflicting claim 1. The liposome may comprise irinotecan entrapped in the liposome at 500 grams of irinotecan per mol of phospholipids, as of conflicting claim 3, which is the same as 500 mg irinotecan per mmol of phospholipid. Berge teaches hydrochloride as a couter-ion. See the rejection of claim 1 above over the conflicting claims in view of Berge.

Boulikas is drawn to a liposome comprising cisplatin for the treatment of cancer, as of Boulikas, title and abstract. Boulikas teaches that liposomes include phosphatidylcholine, cholesterol, and PEG-DSPE, as of Boulikas, column 17 lines 16-42. The phosphatidylcholine comprises hydrocarbons with a chain length in the range of 14-22 carbons which may be saturated – the 18 carbon saturated phosphatidylcholine is DSPC. PEG in DSPE-PEG may have a molecular weight from 1000 to 5000 Daltons, as of Boulikas, column 17 lines 16-42. Liposomes may be sized from 100 nm to 160 nm, as of Boulikas, column 20 lines 62-65.

It would have been prima facie obvious for one of ordinary skill in the art to have made the liposome of the conflicting claims from DSPC, cholesterol, and PEG2000-DSPE. The conflicting claims teach a liposome comprising phospholipids, as of conflicting claim 1. As DSPC, cholesterol, and PEG2000-DSPE are well known ingredients for a liposome used to carry an anti-cancer drug, the skilled artisan would have been motivated to have included these ingredients to have predictably formed a liposome of the conflicting claims in the manner that it can deliver irinotecan with a reasonable expectation of success.

Additionally, the skilled artisan would have been aware that a size range of 100 nm to 160 nm is a known size for a liposome to deliver an anti-cancer agent, as this size range is taught by Boulikas. This size range overlaps with the claimed size range of 110 nm to 120 nm. While the prior art does not disclose the exact claimed values, but does overlap: in such instances even a slight overlap in range establishes a *prima facie* case of obviousness. See MPEP 2144.05(I).

As to claim 7, the teachings of Boulikas of a saturated 18 carbon phosphatidylcholine and cholesterol read on this claim.

As to claim 9, the teachings of Boulikas regarding liposome size read on this claim.

As to claim 10, this claim is rejected for the same reason as both claims 7 and 9.

As to claim 14, this claim is rejected for the same reason that claim 9 is rejected.

As to claim 17, this claim is rejected for the same reason that claims 9 and 14 are rejected.

As to claim 28, this claim is rejected for the same reason that claim 9 is rejected.

As to independent claim 29, this claim is rejected for the same reason that claims 1, 7, and 9 are rejected.

As to instant claims 31 and 32, the examiner notes that the conflicting claims teach at least 500 grams of irinotecan per mole of phospholipid, as of conflicting claim 3. As DSPC is a well known phospholipid for use in liposomes, as of Boulikas, the skilled artisan would have expected that the ratio taught by the conflicting claims would have resulted in at least 500 grams of irinotecan per mole of DSPC and PEG2000-DSPE after combination with Boulikas.

Allowable Subject Matter

Claims 8, 12, 16, 19, 24, and 30 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

This double patenting rejection does not apply to the claims that require a specific ratio of DSPC to cholesterol to PEG-DSPE (or PEG2000-DSPE) of 3:2:0.015 as this highly specific ratio is not taught by the conflicting claims or by Berge or Boulikas.

Table of Issued Patents With Common Inventors

Instant Case	**Patent**	**Is There Double Patenting?**	**TD Filed?**
14/879,358	8,147,867	T.D. Already Filed	yes
14/879,358	8,329,213	T.D. Already Filed	yes
14/879,358	**8,658,203**	**Yes – See below**	**no**
14/879,358	8,703,181	T.D. Already Filed	yes
14/879,358	8,992,870	T.D. Already Filed	yes

Table of Copending Applications With Common Inventors

Instant Case	Application	Is There Double Patenting?	TD Filed?
14/879,358	14/151,632	No (different subject matter)	no
14/879,358	14/632,422	T.D. Already Filed	yes
14/879,358	14/879,302	T.D. Already Filed	yes
14/879,358	14/879,358	No – this is the instant app.	no
14/879,358	14/964,239	No – Copending Case drawn to polyphosphorylated polyol, not sucrose octasulfate	no
14/879,358	14/965,140	T.D. Already Filed	yes
14/879,358	14/966,458	T.D. Already Filed	yes
14/879,358	14/979,666	No – Copending Case drawn to docetaxel, not irinotecan	no

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ISAAC SHOMER whose telephone number is (571)270-7671. The examiner can normally be reached on 8:00 AM - 5:00 PM Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick F. Krass can be reached on (571)272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/ISAAC SHOMER/
Primary Examiner, Art Unit 1612

Examiner-Initiated Interview Summary	Application No.	Applicant(s)	
	14/879,358	HONG ET AL.	
	Examiner	Art Unit	
	ISAAC SHOMER	1612	

All participants (applicant, applicant's representative, PTO personnel):

(1) *ISAAC SHOMER*. (3)_____.

(2) *Meghan Klaric*. (4)_____.

Date of Interview: *16 June 2016*.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☒ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☐102 ☐103 ☒Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: *1,7-10,12,14-17,19,23,24,26 and 28-34*.

Identification of prior art discussed: *Patent 8,658,203*.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

Examiner contacted representative of applicant to request a terminal disclaimer for patent 8,658,203. No previous double patenting rejection had been written rejecting the instant claims over the claims of the '203 patent. As no response has been forthcoming 3 weeks after contacting representative of applicant regarding this matter, the examiner has gone ahead and written a non-final office action rejecting the instant claims over the claims of the '203 patent on the grounds of non-statutory double patenting. As such, this interview summary has been attached to a non-final office action.

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☒ Attachment

/ISAAC SHOMER/
Primary Examiner, Art Unit 1612

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/964,239	12/09/2015	Keelung Hong	239669-373914/1001130US09	3785

133156 7590 11/04/2016

Honigman Miller Schwartz and Cohn LLP
350 East Michigan Avenue
Suite 300
Kalamazoo, MI 49007

EXAMINER	
SHOMER, ISAAC	

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
11/04/2016	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@honigman.com
fhunter@honigman.com

Office Action Summary	Application No. 14/964,239	Applicant(s) HONG ET AL.	
	Examiner ISAAC SHOMER	Art Unit 1612	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *1-20* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-20* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

4) ☐ Other: _____.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

The present application is being examined under the pre-AIA first to invent provisions.

In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

Claim Rejections - 35 USC § 112(b) – Indefiniteness

The following is a quotation of 35 U.S.C. 112(b):
(b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 19 is rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.

Claim 19 recites “polyphosphorylated polyol” in claim 8. There is no antecedent basis for this term. For the purpose of examination under prior art, the term "polyphosphorylated polyol" will be interpreted as if it recites "inositol polyphosphate."

Claim Rejections - 35 USC § 103 – Obviousness

The following is a quotation of pre-AIA 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under pre-AIA 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under pre-AIA 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of pre-AIA 35 U.S.C. 103(c) and potential pre-AIA 35 U.S.C. 102(e), (f) or (g) prior art under pre-AIA 35 U.S.C. 103(a).

Claim 1-3, 5-10, and 14-20 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Chou et al. (Journal of Bioscience and Bioengineering, Vol. 95 No. 4, 2003, pages 405-408) in view of Vucenik et al. (Journal of Nutrition, Vol. 133, 2003, pages 3778S-3784S) and Hu et al. (US 2004/0156889 A1).

Chou et al. (hereafter referred to as Chou) is drawn to irinotecan in a liposome, as of Chou, page 405, title and abstract. Said irinotecan is added to the liposome using a gradient method, as of Chou, page 405, abstract. Irinotecan exhibits antitumor activity, as of Chou, page 405, left column.

Chou does not teach a phosphorylated polyol. Chou also does not teach using **substituted** ammonium compounds for liposome gradient loading.

Vucenik et al. (hereafter referred to as Vucenik) is drawn to inositol hexaphosphate for cancer inhibition, as of Vucenik, page 3778S, title and abstract. Said inositol hexaphosphate destroys tumor cells and enhances conventional chemotherapy, as of Vucenik, page 3778S.

It would have been prima facie obvious for one of ordinary skill in the art to have included inositol hexaphosphate, as of Vucenik, in the liposome of Chou. Chou is drawn to a liposome comprising irinotecan, which is a drug used to treat cancer. As inositol hexaphosphate is also used to treat cancer, as taught by Vucenik, the skilled artisan

would have been motivated to have combined the inositol hexaphosphate of Vucenik with the irinotecan of Chou in order to have predictably achieved an additive effect at treating cancer with a reasonable expectation of success. Generally, it is prima facie obvious to combine two compositions (iriontecan and inositol hexaphosphate), each of which is taught by the prior art to be useful for same purpose (treating cancer), in order to form a third composition to be used for the very same purpose. The idea for combining them flows logically from their having been individually taught in the prior art. See MPEP 2144.06. Moreover, where it would have been obvious to have combined individually known ingredients, evidence must be provided establishing that appellant's combination of agents is in some way more effective or in some way different than any single member of that combination in order to rebut that prima facie case. See In re Dial, 140 USPQ 244 (C.C.P.A. 1964).

While Chou teaches pH gradient loading of liposomes, Chou does not teach diethylammonium and triethylammonium for said pH gradient loading.

Hu et al. (hereafter referred to as Hu) is drawn to loading drugs into liposome via gradients, as of Hu, title and abstract. Hu teaches achieving the pH gradient using ammonium salts, as of Hu, paragraph 0048. Alkylamine derivatives of ammonium salts are also taught as of Hu, including diethylamine, as of Hu, paragraph 0048.

It would have been prima facie obvious for one of ordinary skill in the art to have substituted diethylamine, which is used as of Hu, in place of ammonium, which is suggested as of Chou, page 408, left column, end of first full paragraph, for pH gradient loading of liposomes. Chou is drawn to an irinotecan liposome loaded by pH gradient,

and suggests ammonium for the purpose of causing such pH gradient loading. Hu teaches that both ammonium and alkyl derivatives of ammonium such as diethylamine are useful for pH gradient loading of liposomes, as of Hu, paragraph 0048. As such, the skilled artisan would have been motivated to have substituted diethylamine in place of ammonium for predictable pH gradient loading of liposomes with a reasonable expectation of success. The simple substitution of one element (diethylamine) in place of another (ammonium) in order to achieve predictable results (pH gradient loading of liposomes) is prima facie obvious. See MPEP 2143, Exemplary Rationale B.

As to claim 1, the claim requires that a specific amount of irinotecan be loaded into the vesicle. This limitation appears to further limit the process by which the claimed product is prepared, and not the claimed product itself. Product-by-process claims are not limited to the manipulations of the recited steps (e.g. that 85% of irinotecan is loaded at a temperature above the phase transition), only the structure implied by the steps (e.g. a liposome comprising irinotecan, a phosphorylated polyol, and substituted ammonium compounds).

As to claim 2, the inositol hexaphosphate of Vucenik is understood to have a pKa in the required range as it is a phosphate monoester. See pages 20-21, paragraph 0079 for evidence that a phosphate ester would have a pKa in the required range.

As to claim 3, Chou teaches DSPC and cholesterol in a liposome, as of Chou, page 406, right column, first full paragraph. These are present in a 100:30 mass ratio, as of Chou, page 406, right column, figure 1. DSPC has a molecular weight of about 790 Daltons, and cholesterol of about 387 Daltons. As such, this is:

$$\frac{100\ g\ DSPC}{30\ g\ cholesterol} \times \frac{387\ g\ cholesterol}{1\ mol\ cholesterol} \times \frac{1\ mol\ DSPC}{790\ g\ DSPC}$$

Which is a molar ratio of about 1.63 mole of DSPC per mole of cholesterol, or about 3.2 mole of DSPC per 2 mole of cholesterol. This slightly exceeds the required 3:2 molar ratio. Nevertheless, differences in concentration between the prior art and the claimed invention do not generally support the patentability claimed invention unless there is evidence that the claimed concentration is critical. See MPEP 2144.05(II)(A). In this case, applicant has not presented evidence that a 3:2 molar ratio of DSPC:cholesterol is critical as compared with a 3.2:2 ratio of these ingredients. Additionally, there is motivation to optimize result-effective variables, as of MPEP 2144.05(II)(B), and both DSPC and cholesterol are result-effective because they are both structural lipids that form the bilayers of the liposome.

As to claims 5-7, inositol hexaphosphate, as of Vucenik, reads on the requirements of claims 5-7.

As to claim 8, this claim is an independent claim reciting essentially the same subject matter as claim 1 except requiring an inositol phosphate as opposed to a polyphosphorylated polyol. Nevertheless, inositol hexaphosphate, as of Vucenik, reads on the required inositol phosphate. As such, claim 8 is thereby rejected for essentially the same reason that claim 1 is rejected.

As to claim 9, this claim is rejected for the same reason that claim 2 is rejected.

As to claim 10, this claim is rejected for essentially the same reason that claim 3 is rejected.

As to claim 14, this claim is rejected for essentially the same reason that claim 7 is rejected.

As to claim 15, Vucenik teaches inositol hexaphosphate at 0.4% and 2.0%, as of Vucenik, page 3780S, left column, third paragraph. Inositol hexaphosphate has a molecular weight of about 660 Daltons. Assuming a density of 1 g/mL, this is the following molar concentration at maximum:

$$\frac{2\ g\ IP6}{100\ g\ total} \times \frac{1\ mol\ IP6}{660\ g\ IPC} \times \frac{1\ g\ total}{1\ mL\ total} \times \frac{1000\ mL}{1L}$$

This is about a concentration of 0.03 M. As best understood by the examiner, the unit "N" refers to *normality* and in this case is the molarity of phosphate, which would be six times that of inositol hexaphosphate itself because there are 6 phosphate groups per molecule. This is about 0.18 M. As such, while the concentration of inositol hexaphosphate differs between the claimed invention and the prior art, such differences in concentration do not support the patentability of the claimed subject matter unless there is evidence that such concentration is critical. See MPEP 2144.05(II)(A). As such evidence of criticality has not been presented, the cited prior art applies to claim 15. In addition, there is motivation to optimize result-effective variables, as of MPEP 2144.05(II)(B), and inositol hexaphosphate is result effective because it has the result of treating cancer, as taught by Vucenik.

As to claim 16, this claim requires substituted ammonium compounds in an amount of 0.55-0.65 M (550-650 mM). Hu teaches ammonium in an amount of about 60 mM, as of Hu, paragraph 0043. The amount taught by the prior art is about an order of magnitude lower than that of the claimed invention. As such, while the concentration of

ammonium (or substituted ammonium) differs between the claimed invention and the prior art, such differences in concentration do not support the patentability of the claimed subject matter unless there is evidence that such concentration is critical. See MPEP 2144.05(II)(A). As such evidence of criticality has not been presented, the cited prior art applies to claim 15. In addition, there is motivation to optimize result-effective variables, as of MPEP 2144.05(II)(B), and ammonium (or substituted ammonium) is result effective because it has the result of gradient loading the liposome.

As to claim 17, this claim is rejected for the same reason that claim 7 is rejected.

As to claim 18, this claim is rejected for the same reason that claim 15 is rejected.

As to claim 19, this claim is rejected for essentially the same reasons that claims 15 and/or 16 are rejected.

As to claim 20, this is an independent claim requiring irinotecan and an inositol polyphosphate encapsulated in a lipid vesicle. The steps by which the vesicle is made are recited by the claim, including specific concentrations of the inositol polyphosphate, the substituted ammonium, and a specific ratio of DSPC:cholesterol:PEG-DSPE. As such, the recited material in this claim with the exception of the PEG-DSPE has been recited in instant claims 1, 6, 8, 15, and 16, and this claim is rejected for the same reasons that these claims have been rejected. PEG-DSPE is taught by Chou, as of Chou, page 406, right column, and appears to be present in a mass ratio of about 5% of that of DSPC or about 16.7% of that of cholesterol. Chou teaches that PEG in this context has a molecular weight of about 2000, and as such, the DSPE-PEG would have

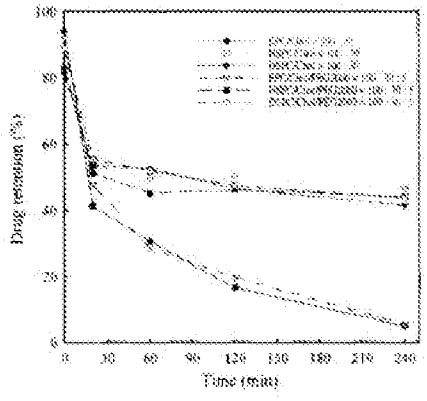
been expected to have a molecular weight of about 2750. As such, the following molar ratio of DSPE-PEG to cholesterol can be calculated:

$$\frac{16.7\ g\ DSPEPEG}{100-16.7\ g\ chol}\times\frac{1\ mol\ DSPEPEG}{2750\ g\ DSPEPEG}\times\frac{387\ g\ chol}{1\ mol\ chol}$$

This is about 0.02 moles of DSPE-PEG per mole of cholesterol, or about 0.04 moles of DSPE-PEG per 2 moles of cholesterol. This is slightly higher than the recited ratio of 0.015 moles of DSPE-PEG per 2 moles of cholesterol. Nevertheless, while the molar amount of DSPE-PEG differs between the claimed invention and the prior art, such differences in concentration do not support the patentability of the claimed subject matter unless there is evidence that such concentration is critical. See MPEP 2144.05(II)(A). As such evidence of criticality has not been presented, the cited prior art applies to claim 15. In addition, there is motivation to optimize result-effective variables, as of MPEP 2144.05(II)(B), and DSPE-PEG is result effective because it has the result of preventing mononuclear phagocytic system uptake in vivo (preventing the immune system from removing the liposome), as of Chou, page 408, left column, top paragraph.

Note Regarding Reference Date: The Hu reference has a filing date of 26 November 2003 and an effective filing date of 26 November 2002. These dates are earlier than the earliest effective filing date of the instant application of 3 May 2004. As such, Hu is prior art under 35 U.S.C. 102(e).

Note Regarding Non-Rejected Claims: As best understood by the examiner, Chou teaches that the liposomes retain at most about 50% irinotecan after 4 hours, as of Chou, page 406, right column, Figure 1, reproduced below.



This is less than the required amount of 70% retention after 8 hours in vivo in claims 4 and 11. As such, this rejection does not apply to claims 4, 11, and those claims which depend thereon.

Claim Rejections - 35 USC § 112(a) – Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112(a):

> (a) IN GENERAL.—The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor or joint inventor of carrying out the invention.

The following is a quotation of the first paragraph of pre-AIA 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

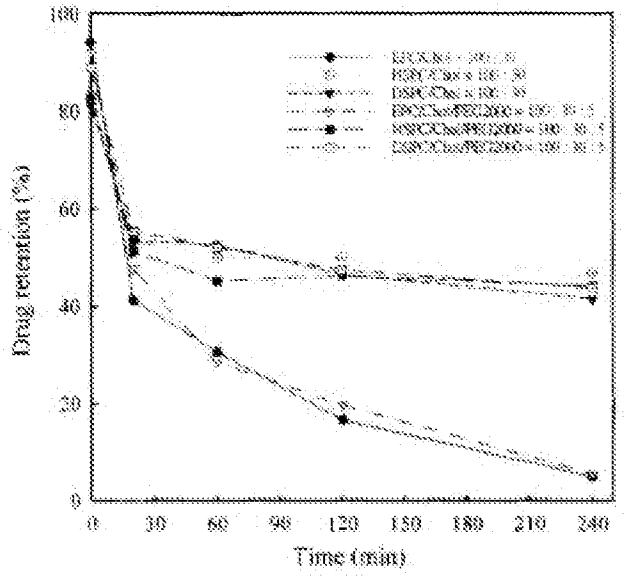
Claims 4 and 11-13 are rejected under 35 U.S.C. 112(a) or 35 U.S.C. 112 (pre-AIA), first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in

such a way as to reasonably convey to one skilled in the relevant art that the inventor or a joint inventor, or for pre-AIA the inventor(s), at the time the application was filed, had possession of the claimed invention.

Introduction: To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. An adequate written description of a chemical invention also requires a precise definition, such as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed. See, e.g., Univ. of Rochester v. G.D. Searle & Co., 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004). See also Ariad Pharmaceuticals Inc. v. Eli Lilly & Co. 94 USPQ2d 1161, 1176-77 (Fed. Cir. 2010). When there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. See *Enzo Biochem*, 323 F.3d at 966, 63 USPQ2d at 1615; *Noelle v. Lederman*, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004). See also MPEP 2163.

State of the Art: In this case, the claimed subject matter relates to an irinotecan liposome that retains at least 70% of the irinotecan after 8 hours in the bloodstream. As representative of the state of the art, the examiner cites Chou et al. (Journal of Bioscience and Bioengineering, Vol. 95 No. 4, 2003, pages 405-408), which was cited in the obviousness rejection above. Chou et al. (hereafter referred to as Chou) is drawn to a liposome comprising irinotecan, as of Chou, title and abstract. However, said

liposome retained only about 40-50% of active agent at maximum after 4 hours (240 minutes), as of Chou, page 406, right column, figure 1, reproduced below.



As such, the state of the art regarding irinotecan liposomes that retain 70% of drug after 8 hours in vivo is poorly developed because Chou teaches specifically that irinotecan liposomes retain 50% or less drug after 4 hours. As such, the retention of 70% of irinotecan after 8 hours in vivo is highly unpredictable based on the teachings of Chou.

Instant Disclosure: The instant specification is an extensive specification including a large number of examples, tables, and graphs. Nevertheless, few of the disclosed examples appear to relate to the claimed subject matter of a liposome including a polyphosphorylated polyol. (In contrast, a great deal of examples relate to a liposome including a polysulfated sugar such as sucrose octasulfate). In one such example, applicant discloses what appears to be a breakdown of about 24.9% of liposome in vivo after 8 hours, as of page 52, Table 7, reproduced below.

Liposome-entrapped salt	Drug/lipid ratio, % of pre-injection value	Liposome lipid, % I.D. in the blood
TMA citrate	80.2 ± 7.8	18.8 ± 3.4
TMA sulfate	70.1 ± 4.8	23.6 ± 1.8
TMA pyrophosphate	67.3 ± 9.2	23.2 ± 3.1
TMA triphosphate	70.6 ± 6.0	24.9 ± 8.2
TMA polyphosphate	107.5 ± 8.9	24.3 ± 3.4
TEA sulfate	76.6 ± 13.1	23.6 ± 0.1

However, this appears to be specific to trimethylammonium triphosphate.

Elsewhere in the specification, a disclosure of from about 54.6% to 85.2% of drug remaining in the liposome after 8 hours is disclosed, as of page 62, Table 8, reproduced below.

Drug/lipid ratio, mg/mmol phospholipid			Drug remaining in the liposomes, % of pre-injection value	
Input	Output	% loaded	After 8 hours	After 24 hours
200	208.4	104.2	54.6±9.9	9.72±2.23
300	286.3	95.4	85.2±14.3	14.52±2.51
400	348.8	87.2	84.5±18.3	17.31±6.34
500	518.9	103.8	66.8±19.6	13.47±1.83

The above-reproduced data appears to be specific to irinotecan "TEA-Pn" (triethylammonium polyphosphate) liposomes. Data relating to a topotecan liposome with TEA-Pn is disclosed on page 76, Table 16.

As such, the specification discloses/reduces to practice only a limited number of liposomes comprising a polyphosphate and which retain at least about 70% of active agent after 8 hours in vivo. These species are not viewed as being reasonably representative of the genus in its claimed scope of “polyphosphorylated polyol” of claim 1 and “inositol polyphosphate” of claim 8. This is because no readily apparent combination of identifying characteristics is provided (e.g. identifying which

polyphosphates are capable of achieving the claimed retention), other than the disclosure of those specific species as examples of the claimed genus.

Conclusion to Written Description Rejection: Accordingly, the specification does not appear to adequately describe the claimed genus of liposomes comprising irinotecan, lipids, and a polyphosphorylated polyol or an inositol polyphosphate that retain 70% of the irinotecan after 8 hours in vivo.

Non-Statutory Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory

double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(1) - 706.02(l)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

Claims 1, 2, 4-9, 11, and 14-19 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-22 of U.S. Patent No. 8,658,203. Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons:

The instant claims are drawn to an irinotecan liposome comprising irinotecan, a polyphosphorylated polyol, and a substituted ammonium compound encapsulated in a lipid vesicle.

Conflicting claim 1 is drawn to a method of treating a brain tumor comprising using a liposome made from irinotecan and inositol hexaphosphate as well as a substituted ammonium compound. Conflicting claim 10 recites triethylammonium as the substituted ammonium compound.

The instant and conflicting claims differ because the conflicting claims are method claims, whereas the instant claims are composition claims. Nevertheless, the liposome used in the method of conflicting claim 10 appears to be within the scope of instant claim 1. As such, there appears to be a prima facie case of anticipatory-type non-statutory double patenting with respect to claim 1.

As to claim 2, the skilled artisan would have expected that inositol hexaphosphate would have had the required pKa.

As to claim 4, as the liposome of the conflicting claims is the same as that of the instant claims, the skilled artisan would have expected that it would have the same release time. Also, the subject matter of these claims appears to be taught by confliting claims 12 and 13.

As to claims 5-7, inositol hexaphosphate, as of the conflicting claims, is understood to read on this requirement.

As to claim 8, this is an independent claim reciting essentially the same subject matter as claim 1 except reciting an inositol polyphosphate instead of the

polyphoshporylated polyol of claim 1. As such, claim 8 is rejected for essentially the same reason as claim 1.

As to claim 9, this is rejected for the same reason as claim 2.

As to claim 11, this is rejected for the same reason as claim 4.

As to claim 14, this is rejected for the same reason as claim 7.

As to claims 15 and 16, while the conflicting claims do not specifically recite the amount of the particular agent, this does not appear to overcome the prima facie case of non-statutory double patenting. Generally, differences in concentration will not support the patentability of subject matter encompassed by the prior art (in this case conflicting claims) unless there is evidence indicating that such concentration is critical, and in this case, no such evidence has been provided. See MPEP 2144.05(II)(A), which was cited in the obviousness rejections above.

As to claim 17, this claim is rejected for the same reason that claim 7 is rejected.

As to claims 18 and 19, these are rejected for the same reason that claims 15 and 16 are rejected.

Claims 3, 10, 12, 13, and 20 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-22 of U.S. Patent No. 8,658,203 in view of Chou et al. (Journal of Bioscience and Bioengineering, Vol. 95 No. 4, 2003, pages 405-408).

The instant claims are drawn to an irinotecan liposome comprising irinotecan, a polyphosphorylated polyol, and a substituted ammonium compound encapsulated in a

lipid vesicle. Instant claim 3 recites a liposome with cholesterol, and instant claim 20 also recites PEG-DSPE.

Conflicting claim 1 is drawn to a method of treating a brain tumor comprising using a liposome made from irinotecan and inositol hexaphosphate as well as a substituted ammonium compound. Conflicting claim 10 recites triethylammonium as the substituted ammonium compound.

The conflicting claims do not recite DSPC, cholesterol and PEG-DSPE.

Chou et al. (hereafter referred to as Chou) is drawn to a liposome comprising irinotecan and inositol hexaphosphate. See the obviousness rejection above which includes the Chou reference. Chou teaches that the liposome may comprise DSPC, cholesterol, and PEG-DSPE, as of Chou, page 406, right column. PEG-DSPE is useful to prevent phagocytic uptake in vivo, as of Chou, page 408, left column, top paragraph.

It would have been prima facie obvious for one of ordinary skill in the art to have included the cholesterol and PEG-DSPE of Chou in the liposome of the conflicting claims. This is because cholesterol and PEG-DSPE are known lipids to be used in liposomes. As such, the skilled artisan would have been motivated to have used the lipids of Chou in the liposome of the conflicting claims to have predictably formed a liposome capable of being used in the method of the conflicting claims of treating a brain tumor with a reasonable expectation of success.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ISAAC SHOMER whose telephone number is (571)270-7671. The examiner can normally be reached on 8:00 AM - 5:00 PM Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick F. Krass can be reached on (571)272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/ISAAC SHOMER/
Primary Examiner, Art Unit 1612

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/964,239	12/09/2015	Keelung Hong	239669-373914/1001130US09	3785

133156 7590 04/26/2017

Honigman Miller Schwartz and Cohn LLP
Merrimack
350 East Michigan Avenue
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Kalamazoo, MI 49007

EXAMINER
SHOMER, ISAAC

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
04/26/2017	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Examiner-Initiated Interview Summary	Application No.	Applicant(s)		
	14/964,239	HONG ET AL.		
	Examiner	Art Unit	AIA (First Inventor to File) Status	Page
	ISAAC SHOMER	1612	No	1 of 1

All participants (applicant, applicant's representative, PTO personnel):

1. ISAAC SHOMER (Primary Examiner); Telephonic 2. Meghan Klaric (Attorney of Record); Telephonic

Date of Interview: 21 April 2017

Claim(s) discussed: 24, 26

Issues Discussed:

Item(s) under 35 U.S.C. 112:
Examiner contacted representative of applicant to ask about an issue surrounding claims 24 and 26. Namely, it appeared to the examiner from reading these claims that the relevant test to determine encapsulated irinotecan recited in these claims requires a radioactive label, though this was not entirely clear to the examiner. However, the claims upon which claims 24 and 26 depend do not appear to recite a radioactive compound in the claimed liposome composition. As such, the examiner requested that representative of applicant clarify the issue of whether claims 24 and 26 have appropriate antecendent basis. In response, represntative of applicant expressed the intention to provide a supplemental amendment to address this issue. No agreement was reached at this time.

/ISAAC SHOMER/ Primary Examiner, Art Unit 1612	

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of the interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

Applicant is reminded that a complete written statement as to the substance of the interview must be made of record in the application file. It is the applicant's responsibility to provide the written statement, unless the interview was initiated by the Examiner and the Examiner has indicated that a written summary will be provided. See MPEP 713.04

Please further see:

MPEP 713.04
Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews, paragraph (b)
37 CFR § 1.2 Business to be transacted in writing

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14/964,239	12/09/2015	Keelung Hong	263266-411994	3785

139696 7590 06/21/2017

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EXAMINER
SHOMER, ISAAC

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
06/21/2017	ELECTRONIC

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The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@honigman.com
lzerby@honigman.com
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Office Action Summary	Application No. 14/964,239	Applicant(s) HONG ET AL.	
	Examiner ISAAC SHOMER	Art Unit 1612	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *2 May 2017*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *1,3,4,8,10,11 and 21-27* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1,3,4,8,10,11 and 21-27* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

4) ☐ Other: _____.

DETAILED ACTION

Applicants' arguments, filed 6 March and 2 May 2017, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

The present application is being examined under the pre-AIA first to invent provisions.

Claim Rejections - 35 USC § 112(b) – Indefiniteness

The following is a quotation of 35 U.S.C. 112(b):
(b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3, 4, 8, 10, and 11 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.

Claim 1, second line, recites that the irinotecan liposome comprises inositol hexaphosphate. However, claim 1, fourth line, recites that the liposome comprises a polyphophorylated polyol. This appears to be an issue of a broad and a narrow

recitation in the same claim, with the broad recitation being the polyphosphorylated polyol and the narrower recitation being inositol hexaphosphate.

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 1 recites the broad recitation a polyphosphorylated polyol, and the claim also recites inositol hexaphosphate, which is the narrower statement of the range/limitation.

A similar issue exists with regard to claim 8, with the fourth line of claim 8 reciting "inositol polyphosphate" and the second line of claim 8 reciting "inositol hexaphosphate."

For the purposes of examination under prior art, the instant claims will be examined as if the broader recitation is limiting.

Claim Rejections - 35 USC § 103 – Obviousness

The following is a quotation of pre-AIA 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under pre-AIA 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under pre-AIA 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of pre-AIA 35 U.S.C. 103(c) and potential pre-AIA 35 U.S.C. 102(e), (f) or (g) prior art under pre-AIA 35 U.S.C. 103(a).

Claim 21 and 22 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Chou et al. (Journal of Bioscience and Bioengineering, Vol. 95 No. 4, 2003, pages 405-408) in view of Vucenik et al. (Journal of Nutrition, Vol. 133, 2003, pages 3778S-3784S).

Chou et al. (hereafter referred to as Chou) is drawn to irinotecan in a liposome, as of Chou, page 405, title and abstract. Said irinotecan is added to the liposome using a gradient method, as of Chou, page 405, abstract. Irinotecan exhibits antitumor activity, as of Chou, page 405, left column.

Chou does not teach a phosphorylated polyol.

Vucenik et al. (hereafter referred to as Vucenik) is drawn to inositol hexaphosphate for cancer inhibition, as of Vucenik, page 3778S, title and abstract. Said inositol hexaphosphate destroys tumor cells and enhances conventional chemotherapy, as of Vucenik, page 3778S.

It would have been prima facie obvious for one of ordinary skill in the art to have included inositol hexaphosphate, as of Vucenik, in the liposome of Chou. Chou is drawn to a liposome comprising irinotecan, which is a drug used to treat cancer. As inositol hexaphosphate is also used to treat cancer, as taught by Vucenik, the skilled artisan would have been motivated to have combined the inositol hexaphosphate of Vucenik with the irinotecan of Chou in order to have predictably achieved an additive effect at treating cancer with a reasonable expectation of success. Generally, it is prima facie obvious to combine two compositions (iriontecan and inositol hexaphosphate), each of which is taught by the prior art to be useful for same purpose (treating cancer), in order

to form a third composition to be used for the very same purpose. The idea for combining them flows logically from their having been individually taught in the prior art. See MPEP 2144.06. Moreover, where it would have been obvious to have combined individually known ingredients, evidence must be provided establishing that appellant's combination of agents is in some way more effective or in some way different than any single member of that combination in order to rebut that prima facie case. See In re Dial, 140 USPQ 244 (C.C.P.A. 1964).

As to claim 21, the combination of Chou with Vucenik and Hu includes a liposome, irinotecan, and inositol hexaphosphate.

As to claim 22, this claim is rejected for the same reasons that claims 3 and 10 are rejected.

Note Regarding Reference Date: The Hu reference has a filing date of 26 November 2003 and an effective filing date of 26 November 2002. These dates are earlier than the earliest effective filing date of the instant application of 3 May 2004. As such, Hu is prior art under 35 U.S.C. 102(e).

Claim 1, 3, 8, and 10 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Chou et al. (Journal of Bioscience and Bioengineering, Vol. 95 No. 4, 2003, pages 405-408) in view of Vucenik et al. (Journal of Nutrition, Vol. 133, 2003, pages 3778S-3784S) and Hu et al. (US 2004/0156889 A1).

Chou is drawn to an irinotecan liposome. Vucenik is drawn to inositol hexaphosphate. See the rejection above over Chou in view of Vucenik by themselves.

While Chou teaches pH gradient loading of liposomes, Chou does not teach diethylammonium and triethylammonium for said pH gradient loading.

Hu et al. (hereafter referred to as Hu) is drawn to loading drugs into liposome via gradients, as of Hu, title and abstract. Hu teaches achieving the pH gradient using ammonium salts, as of Hu, paragraph 0048. Alkylamine derivatives of ammonium salts are also taught as of Hu, including diethylamine, as of Hu, paragraph 0048.

It would have been prima facie obvious for one of ordinary skill in the art to have substituted diethylamine, which is used as of Hu, in place of ammonium, which is suggested as of Chou, page 408, left column, end of first full paragraph, for pH gradient loading of liposomes. Chou is drawn to an irinotecan liposome loaded by pH gradient, and suggests ammonium for the purpose of causing such pH gradient loading. Hu teaches that both ammonium and alkyl derivatives of ammonium such as diethylamine are useful for pH gradient loading of liposomes, as of Hu, paragraph 0048. As such, the skilled artisan would have been motivated to have substituted diethylamine in place of ammonium for predictable pH gradient loading of liposomes with a reasonable expectation of success. The simple substitution of one element (diethylamine) in place of another (ammonium) in order to achieve predictable results (pH gradient loading of liposomes) is prima facie obvious. See MPEP 2143, Exemplary Rationale B.

As to claim 1, the claim requires that a specific amount of irinotecan be loaded into the vesicle. This limitation appears to further limit the process by which the claimed

product is prepared, and not the claimed product itself. Product-by-process claims are not limited to the manipulations of the recited steps (e.g. that 85% of irinotecan is loaded at a temperature above the phase transition), only the structure implied by the steps (e.g. a liposome comprising irinotecan, a phosphorylated polyol, and substituted ammonium compounds).

As to claim 3, Chou teaches DSPC and cholesterol in a liposome, as of Chou, page 406, right column, first full paragraph. These are present in a 100:30 mass ratio, as of Chou, page 406, right column, figure 1. DSPC has a molecular weight of about 790 Daltons, and cholesterol of about 387 Daltons. As such, this is:

$$\frac{100\ g\ DSPC}{30\ g\ cholesterol} \times \frac{387\ g\ cholesterol}{1\ mol\ cholesterol} \times \frac{1\ mol\ DSPC}{790\ g\ DSPC}$$

Which is a molar ratio of about 1.63 mole of DSPC per mole of cholesterol, or about 3.2 mole of DSPC per 2 mole of cholesterol. This slightly exceeds the required 3:2 molar ratio. Nevertheless, differences in concentration between the prior art and the claimed invention do not generally support the patentability claimed invention unless there is evidence that the claimed concentration is critical. See MPEP 2144.05(II)(A). In this case, applicant has not presented evidence that a 3:2 molar ratio of DSPC:cholesterol is critical as compared with a 3.2:2 ratio of these ingredients. Additionally, there is motivation to optimize result-effective variables, as of MPEP 2144.05(II)(B), and both DSPC and cholesterol are result-effective because they are both structural lipids that form the bilayers of the liposome.

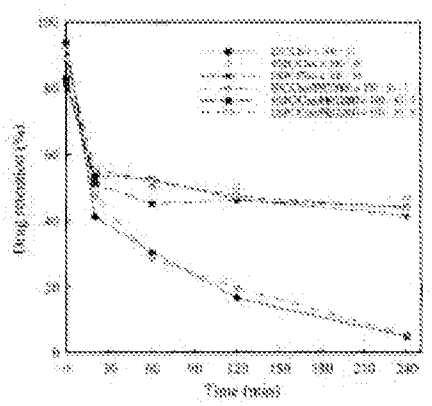
As to claim 8, this claim is an independent claim reciting essentially the same subject matter as claim 1 except requiring an inositol phosphate as opposed to a

polyphosphorylated polyol. Nevertheless, inositol hexaphosphate, as of Vucenik, reads on the required inositol phosphate. As such, claim 8 is thereby rejected for essentially the same reason that claim 1 is rejected.

As to claim 10, this claim is rejected for essentially the same reason that claim 3 is rejected.

Note Regarding Non-Rejected Claims

As best understood by the examiner, Chou teaches that the liposomes retain at most about 50% irinotecan after 4 hours, as of Chou, page 406, right column, Figure 1, reproduced below.



This is less than the required amount of 70% retention after 8 hours in vivo in claims 4 and 11. As such, this rejection does not apply to claims 4, 11, and those claims which depend thereon. This rationale also applies to claims 23-27.

Response to Arguments

In applicant's response on 6 March 2017, applicant contends that neither Chou, Vucenik, nor Hu disclose various properties pertaining to a liposome comprising inositol hexaphosphate and irinotecan. In applicant's response on 6 March 2017, pages 6 and 7, applicant cites Examples 9, 12, and 73 of the instant specification, as well as Table 8 and Figure 2 of the instant specification, as providing evidence that the claimed composition provides unexpectedly superior results as compared with what would have been expected in the prior art.

Upon review of the instant application, the examiner notes that table 8, the specification discloses the following, wherein the term "Pn" is an abbreviation for inositol hexaphosphate and "CPT-11" refers to irinotecan.

Table 8. The effect of drug/lipid ratio on the drug loading and *in vivo* drug retention in irinotecan TEA-Pn liposomes (average ± standard deviation)

Drug/lipid ratio, mg/mmol phospholipid			Drug remaining in the liposomes, % of pre-injection value	
Input	Output	% loaded	After 8 hours	After 24 hours
200	208.4	104.2	54.6±9.0	9.72±2.25
300	286.3	95.4	85.2±14.3	14.22±2.51
400	348.8	87.2	81.5±18.3	17.31±6.14
500	519.9	103.8	66.8±19.6	15.47±1.44

As such, the specification clearly discloses examples whereby irinotecan liposomes have over 70% of irinotecan remaining in the liposomes 8-hours post-injection. In contrast, Chou teaches that the liposomes retain at most about 50% irinotecan after 4 hours, as of Chou, page 406, right column, Figure 1, above. As such, applicant has discovered that the inclusion of inositol hexaphosphate in a liposome

comprising irinotecan results in greater retention of the irinotecan in the liposome as compared with a liposome comprising irinotecan but lacking inositol hexaphosphate.

Nevertheless, applicant's results are not commensurate in scope with the rejected claims. See MPEP 716.02(d). Claim 1 is drawn to a polyphosphorylated polyol, and claim 8 is drawn to inositol polyphosphate. Applicant's results are drawn to inositol hexaphosphate and irinotecan. There is no indication that the superior irinotecan retention obtained by applicant with the use of an irinotecan/inositol hexaphosphate liposome would have been applicable to the broad scope of an irinotecan/inositol polyphosphate liposome, let alone an irinotecan/polyphosphorylated polyol liposome.

Also with this regard, the examiner notes that beneficial results appear to have been achieved only at a concentration of inositol hexaphosphate of 0.65 N and irinotecan concentrations of 200-500 mg per mmol of phosphatolipids, e.g. as of page 61, paragraph 0166. The skilled artisan would not have expected the beneficial results obtained at these concentrations to have been applicable over the broad range of irinotecan and inositol hexaphosphate concentrations. As such, applicant's results are not commensurate in scope with the rejected claims. See MPEP 716.02(d).

Non-Statutory Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent

and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(1) - 706.02(l)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26,

PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

Claims 1, 3, 4, 8, 10, 11, and 21-27 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-19 of copending Application No. 15/363,923 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons:

The instant claims are drawn to a liposomal composition encapsulating irinotecan and inositol hexaphosphate, as of instant claim 21.

Copending claim 1 is drawn to pharmaceutical composition comprising irinotecan liposomes encapsulating irinotecan and inositol hexaphosphate, with a specific mole ratio.

The instant and copending claims differ because copending claim 1 recites a specific mole ratio which is not recited by the instant claims. Nevertheless, the subject matter of copending claim 1 is within the scope of instant claim 1. This is understood by the examiner to result in a prima facie case of anticipatory-type non-statutory double patenting.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ISAAC SHOMER whose telephone number is (571)270-7671. The examiner can normally be reached on 8:00 AM - 5:00 PM Monday-Friday.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick F. Krass can be reached on (571)272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/ISAAC SHOMER/
Primary Examiner, Art Unit 1612

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/964,239	12/09/2015	Keelung Hong	263266-411994	3785

139696 7590 12/11/2017

Honigman Miller Schwartz and Cohn LLP/Ipsen
350 East Michigan Avenue, Suite 300
Kalamazoo, MI 49007

EXAMINER	
SHOMER, ISAAC	

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
12/11/2017	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@honigman.com
lzerby@honigman.com
arhoades@honigman.com

Office Action Summary	Application No. 14/964,239	Applicant(s) Hong et al.	
	Examiner ISAAC SHOMER	Art Unit 1612	AIA Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 21 November 2017 .

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____ .

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 8,10-11 and 21-27 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 8,10-11 and 21-27 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

DETAILED CORRESPONDENCE

Applicants' arguments, filed 21 November 2017, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

The present application is being examined under the pre-AIA first to invent provisions.

Status of Claims

Claims 8, 10, 11, and 21-27 are pending and subject to substantive examination.

Claim Rejections - 35 USC § 103 – Obviousness

The following is a quotation of pre-AIA 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

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This application currently names joint inventors. In considering patentability of the claims under pre-AIA 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of pre-AIA 35 U.S.C. 103(c) and potential pre-AIA 35 U.S.C. 102(e), (f) or (g) prior art under pre-AIA 35 U.S.C. 103(a).

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inositol hexaphosphate destroys tumor cells and enhances conventional chemotherapy, as of Vucenik, page 3778S.

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As to claim 21, the combination of Chou with Vucenik and Hu includes a liposome, irinotecan, and inositol hexaphosphate.

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While Chou teaches pH gradient loading of liposomes, Chou does not teach diethylammonium and triethylammonium for said pH gradient loading.

Hu et al. (hereafter referred to as Hu) is drawn to loading drugs into liposome via gradients, as of Hu, title and abstract. Hu teaches using diethylamine as a weak base, as of Hu, paragraph 0113. Said weak base is used to provide a gradient, as of Hu, paragraph 0019.

It would have been prima facie obvious for one of ordinary skill in the art to have substituted diethylamine, which is used as of Hu, in place of ammonium, which is suggested as of Chou, page 408, left column, end of first full paragraph, for pH gradient loading of liposomes. Chou is drawn to an irinotecan liposome loaded by pH gradient, and suggests ammonium for the purpose of causing such pH gradient loading. Hu teaches that both ammonium and alkyl derivatives of ammonium such as diethylamine are useful for pH gradient loading of liposomes, as of Hu, paragraph 0113. As such, the skilled artisan would have been motivated to have substituted diethylamine in place of ammonium for predictable pH gradient loading of liposomes with a reasonable

expectation of success. The simple substitution of one element (diethylamine) in place of another (ammonium) in order to achieve predictable results (pH gradient loading of liposomes) is prima facie obvious. See MPEP 2143, Exemplary Rationale B.

As to claim 8, the claim requires that a specific amount of irinotecan be loaded into the vesicle. This limitation appears to further limit the process by which the claimed product is prepared, and not the claimed product itself. Product-by-process claims are not limited to the manipulations of the recited steps (e.g. that 85% of irinotecan is loaded at a temperature above the phase transition), only the structure implied by the steps (e.g. a liposome comprising irinotecan, a phosphorylated polyol, and substituted ammonium compounds). See MPEP 2113.

As to claim 10, Chou teaches DSPC and cholesterol in a liposome, as of Chou, page 406, right column, first full paragraph. These are present in a 100:30 mass ratio, as of Chou, page 406, right column, figure 1. DSPC has a molecular weight of about 790 Daltons, and cholesterol of about 387 Daltons. As such, this is:

$$\frac{100\ g\ DSPC}{30\ g\ cholesterol} \times \frac{387\ g\ cholesterol}{1\ mol\ cholesterol} \times \frac{1\ mol\ DSPC}{790\ g\ DSPC}$$

Which is a molar ratio of about 1.63 mole of DSPC per mole of cholesterol, or about 3.2 mole of DSPC per 2 mole of cholesterol. This slightly exceeds the required 3:2 molar ratio. Nevertheless, differences in concentration between the prior art and the claimed invention do not generally support the patentability claimed invention unless there is evidence that the claimed concentration is critical. See MPEP 2144.05(II)(A). In this case, applicant has not presented evidence that a 3:2 molar ratio of DSPC:cholesterol is critical as compared with a 3.2:2 ratio of these ingredients. Additionally, there is motivation to optimize result-effective variables, as of MPEP

2144.05(II)(B), and both DSPC and cholesterol are result-effective because they are both structural lipids that form the bilayers of the liposome.

Note Regarding Reference Date of Hu Reference: The Hu reference has a filing date of 26 November 2003 and an effective filing date of 26 November 2002. These dates are earlier than the earliest effective filing date of the instant application of 3 May 2004. As such, Hu is prior art under 35 U.S.C. 102(e).

Response to Arguments Regarding Obviousness Rejections

Applicant provides arguments regarding the applied rejections, as of applicant's response on 21 November 2017 (hereafter referred to as applicant's response). These arguments are addressed below.

Applicant argues that there is no motivation for the skilled artisan to have combined irinotecan with inositol hexaphosphate alone, as of applicant's response, page 5, heading of section.

This is not persuasive, at least because Vucenik teaches that inositol hexaphosphate (abbreviated as IP_6) is a broad spectrum antineoplastic agent, as of Vucenik, page 3779S, right column, section entitled "Anticancer action of IP_6." As such, the skilled artisan would have expected that inositol hexaphosphate would have had anti-cancer activity by itself.

Additionally, even if, purely *en arguendo*, it were the case that Vucenik teaches that inositol hexaphosphate would not have been effective alone, this would not have been sufficient to overcome the applied rejection. This is because the instant claims recite the phrase "comprising", which does not exclude additional unrecited elements.

See MPEP 2111.03, second paragraph. As such, these arguments appear to be insufficient to overcome the applied rejection given that the instant claims do not exclude additional unrecited elements.

Applicant then argues that there would have been no motivation for the skilled artisan to use inositol hexaphosphate inside a liposome, as of applicant's response, page 6.

This is not persuasive. The Chou reference describes various benefits of liposomes, especially polyethylene glycol derivatized liposomes, which include increasing anti-tumor activity, decreasing toxicity, and preserving the active form of the drug, as of Chou, page 405, left column, first and second paragraphs. As such, the skilled artisan would have understood that there would have been a benefit to encapsulating an active substance in a liposome. As inositol hexaphosphate, as of Vucenik, is an active substance, the skilled artisan would have been motivated to have encapsulated inositol hexaphosphate into a liposome. In addition, the examiner notes MPEP 2145(III), which states that "the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference.... Rather, the test is what the combined teachings of those references would have suggested to those of ordinary skill in the art." This appears to be relevant here.

Applicant then argues that the encapsulation of inositol hexaphosphate in a liposome would not have been technically feasible, as of applicant's response, page 6, end of second to last paragraph. This is not persuasive, for the reasons set forth below.

After making the statement that inositol hexaphosphate encapsulation in a liposome would not have been technically feasible, applicant makes various points, as

of page 6, bottom paragraph and page 7. These points mostly concern the dosage of inositol hexaphosphate used in Vucenik, as compared with the dosages of irinotecan. Applicant then goes on to assert, on page 7, last full paragraph, that the skilled artisan would have immediately recognized that it would not be technically possible to generate a liposome with inositol hexaphosphate and irinotecan inside the liposome at a ratio of almost 100:1. No explanation is provided for why the skilled artisan would have readily understood that this is not technically possible. As such, this argument is not persuasive for at least this reason.

To the extent that applicant is arguing that the dosage of inositol hexaphosphate in the prior art differs from that of the claimed invention, this argument is not persuasive at least because the instant claims do not recite a specific dosage of inositol hexaphosphate or a specific ratio of inositol hexaphosphate to irinotecan. Arguments regarding limitations that are not claimed are not persuasive. See MPEP 2145(VI). Even if applicant were to amend the claims to recite such specific amounts or ratios, applicant should bear in mind the MPEP guidance regarding overlap and optimization of ranges in MPEP 2144.05.

With regard to the Hu reference, applicant takes the position that paragraph 0048 of Hu is drawn to the use of diethylamine as a membrane permeable base following the loading of pharmaceutical agents, as of applicant's response, page 8.

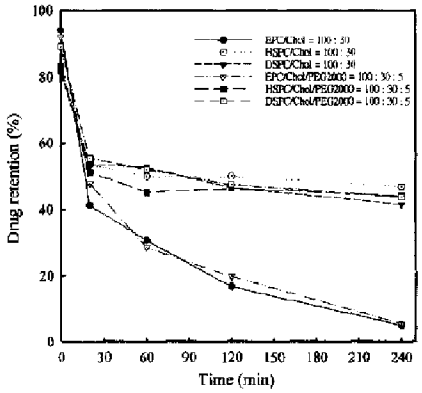
In response, the examiner notes that Hu teaches diethylamine (referred to as "diethyl amine") as a weak base, as of Hu, paragraph 0113, wherein said weak base is used to provide a gradient, as of Hu, paragraph 0019. As such, the teachings of Hu

encompass using diethylamine to provide a gradient. Said diethylamine would have been protonated to have formed the diethylammonium cation.

In the previous office action the examiner erred in citing the incorrect portion of the Hu document, as the examiner cited paragraph 0048 of Hu when the examiner should have cited paragraph 0113 of Hu. As such, this office action is made NON-FINAL.

Note Regarding Non-Rejected Claims over Prior Art

As best understood by the examiner, Chou teaches that the liposomes retain at most about 50% irinotecan after 4 hours, as of Chou, page 406, right column, Figure 1, reproduced below.



This is less than the required amount of 70% retention after 8 hours in vivo in claim 11. As such, this rejection does not apply to claim 11, and those claims which depend thereon. This rationale also applies to claims 23-27.

Non-Statutory Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(1) - 706.02(l)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

Claims 8, 10, 11, and 21-27 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-19 of copending Application No. 15/363,923 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons:

The instant claims are drawn to a liposomal composition encapsulating irinotecan and inositol hexaphosphate, as of instant claim 21.

Copending claim 1 is drawn to pharmaceutical composition comprising irinotecan liposomes encapsulating irinotecan and inositol hexaphosphate, with a specific mole ratio.

The instant and copending claims differ because copending claim 1 recites a specific mole ratio which is not recited by the instant claims. Nevertheless, the subject matter of copending claim 1 is within the scope of instant claim 1. This is understood by

the examiner to result in a prima facie case of anticipatory-type non-statutory double patenting.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Response to Arguments: Applicant has requested that the examiner hold this rejection in abeyance until all other rejections are overcome, as of applicant's response, page 8, bottom paragraph.

As such, as no arguments have been provided regarding this double patenting rejection, the rejection has been maintained.

Terminal Disclaimer

The terminal disclaimer filed on 6 March 2017 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of US Patent 8,658,203 has been reviewed and is accepted. The terminal disclaimer has been recorded.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ISAAC SHOMER whose telephone number is (571)270-7671. The examiner can normally be reached on 7:30 AM to 5:00 PM Monday Through Friday.

Examiner interviews are available via telephone, in-person, and video conferencing using a USPTO supplied web-based collaboration tool. To schedule an interview, applicant is encouraged to use the USPTO Automated Interview Request (AIR) at http://www.uspto.gov/interviewpractice.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick F Krass can be reached on (571)272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

ISAAC . SHOMER
Primary Examiner
Art Unit 1612

/ISAAC SHOMER/
Primary Examiner, Art Unit 1612

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/964,571	12/09/2015	ELIEL BAYEVER	239669-381296	1063

133156 7590 02/13/2017

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EXAMINER	
BAEK, BONG-SOOK	

ART UNIT	PAPER NUMBER
1621	

NOTIFICATION DATE	DELIVERY MODE
02/13/2017	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No. 14/964,571	Applicant(s) BAYEVER ET AL.	
	Examiner BONG-SOOK BAEK	Art Unit 1621	AIA (First Inventor to File) Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *1-6* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-6* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

4) ☐ Other: _____.

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

DETAILED ACTION

Status of claims

Claims 1-6 are under examination in the instant office action.

Claim Rejections - 35 USC § 112 (b)

The following is a quotation of 35 U.S.C. 112(b):

(B) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention. All the dependent claims are included.

It is unclear to whom the claimed irinotecan is being administered. While the preamble of the claims recites a method of treating cancer in a patient having a tumor lesion with a ferumoxytol tumor lesion uptake of at least 32.6 mcg/mL one hour after intravenous administration of 5 mg/kg intravenous ferumoxytol up to a maximum dose of 510 mg total ferumoxytol, the active method step of the claims does not require administration to such patient.

Rather, the active method step appears to only require administering irinotecan in a MM-398 irinotecan liposome without reciting to whom the irinotecan is administered. Thus, it is vague and unclear as to whether the preamble, which recites cancer treatment, or the active step which only requires administering irinotecan in a MM-398 irinotecan liposome without limiting the patient population to a patient having cancer, controls the metes and bounds of the claimed method. This rejection might be overcome by amending instant claim 1 to recite "the method comprising intravenous administration of irinotecan in a MM-398 irinotecan liposome to the patient, provided there is support in the disclosure for such an amendment.

Also, the scope of the patient population to be treated is of indeterminate scope even if it is intended to recite "the method comprising intravenous administration of irinotecan in a MM-398 irinotecan liposome to the patient". The preamble of Claim 1 recites "a patient having a tumor lesion with a ferumoxytol tumor lesion uptake of at least 32.6 mcg/mL one hour after intravenous administration of 5 mg/kg intravenous ferumoxytol up to a maximum dose of 510 mg total ferumoxytol", but the active method step does not recite administration of ferumoxytol. Thus, it is unclear whether the target patient population is limited to a patient who has already received intravenous administration of ferumoxytol before one hour and is having a tumor lesion with a ferumoxytol tumor lesion uptake of at least 32.6 mcg/mL after intravenous administration of ferumoxytol, or the target patient population encompasses any patients who can have a tumor lesion with a ferumoxytol tumor lesion uptake of at least 32.6 mcg/mL one hour after intravenous administration of ferumoxytol if ferumoxytol is administered, thus not requiring intravenous administration of ferumoxytol before administration of irinotecan as an active step. In addition, dependent claim 2 further makes the scope unclear because it recites that "the cancer

comprises a tumor retaining ferumoxytol". If the target patient population is a patient who has already received intravenous administration of ferumoxytol before one hour and is having a tumor lesion with a ferumoxytol tumor lesion uptake of at least 32.6 mcg/mL after intravenous administration of ferumoxytol as stated in the first interpretation, the cancer necessarily comprises a tumor retaining ferumoxytol since claim 1 recites the patient has "a tumor lesion with a ferumoxytol tumor lesion uptake". Thus, claim 2 does not further limit the scope of claim 1. Accordingly, one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the subject matter for which Applicant seek patent protection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a)(1) the claimed invention was patented, described in a printed publication, or in public use, on sale or otherwise available to the public before the effective filing date of the claimed invention.

Claims 1-6 are rejected under 35 U.S.C. 102(a)(1) as being anticipated by US 2014/0170075.

As stated above in the rejection under 35 U.S.C. 112(b), the active method step appears to only require administering irinotecan in a MM-398 irinotecan liposome without reciting to whom the irinotecan is administered. Thus, the statements in the preamble reciting the purpose or intended use of the claimed invention does not change a structural difference and does not limit the claims. Accordingly, as long as the prior art teaches administering irinotecan in a MM-398 irinotecan liposome in the same amount as claimed, it reads on the instant claims.

US 2014/0170075 teaches a method for selecting and providing pharmaceutical treatment to a patient for a localized infectious, inflammatory, or neoplastic condition, the method comprising identifying one or more locations of infection, inflammation or neoplasia in a patient, and subsequently, obtaining at least one contrast-enhanced MRI image of a first location of the one or more locations, and subsequently, selecting an anti-infective, anti-inflammatory, or anti-neoplastic pharmaceutical agent and treating the patient with the selected pharmaceutical agent, wherein the contrast agent is ferumoxytol (FMX) which is intravenously administered at 5 mg/kg up to 510 mg/kg and wherein the pharmaceutical agent is a liposomal anti-neoplastic agent (abstract, [0019], [0020]claims 8-13). US 2014/0170075 also teaches that the liposomal therapeutic agent is MM-398 (irinotecan sucroseoctasulfate liposome injection) and the tumor is a non-small cell lung cancer (NSCLC) tumor, a triple negative breast cancer (TNBC) tumor, a colorectal cancer (CRC) tumor, a pancreatic cancer tumor, a small cell lung cancer tumor, a gastric cancer tumor, a cervical cancer tumor, or Ewing's sarcoma (claims 14-16). The reference specifically discloses a working examples wherein patients with advanced solid tumors and multiple metastases were injected with FMX at 5 mg/kg and then were infused with 80 mg/m^2 MM-398 and shows that the patents have tumor lesion with FMX uptake (see Examples 9-10 and Figs. 6-8), which means the tumor retains FMX. The reference further discloses the measured FMX levels at day 2 (24 h) and day 4 (72 h) after FMX injection together with the calculated volumes of four liver lesions at treatment start ("Screening") and after four weeks or two treatment cycles wherein the level of FMX 24 hours after the intravenous administration of FMX is 38.98, 28, 04, 39.94, and 37.35 mcg/ml in lesions 1-4, respectively (Example 10 and table).

Also, it discloses that the change in the volume of liver tumor lesion is greater in lesion 1, 3, and 4 (Example 10 and table). Since the patient has a tumor lesion with FMX tumor lesion uptake of 38.98, 39.94, and 37.35 mcg/ml after 24 hours after the intravenous administration, it inherently discloses that "a FMX tumor lesion uptake is "at least 32.6 mcg/ml one hour after the intravenous administration of 5 mg/kg FMX" as evidenced by Fig. 6B (the FMX uptake level is lower after 24 hrs than after one hour). In addition, US 2014/0170075 teaches that as FMX has been demonstrated to be safe for intravenous administration to patients and is shown herein not to interfere with nanoliposome therapies if used as an imaging agent, even within 1-4 hours prior to administration of nanoliposomal therapeutics, these results indicate that FMX MRI allows for selection patients who will (or will not) benefit from nanoliposomal therapy ([0105]). Furthermore, US 2014/0170075 teaches that patients identified as having sites of pathology that are predicted to exhibit nanoparticle accumulation would be considered more likely to respond to nanoparticulate therapeutic agents and patients identified as having sites of pathology that are predicted not to exhibit nanoparticle accumulation would be considered less likely to respond to nanoparticulate therapeutic agents and treating patients in accordance with such identifications would avoid the administration of sub-optimal therapeutic treatments to patients in need of therapy ([0011]).

As to claim 6, it further recites that the patient has Her2 positive breast cancer and the ferumoxytol is present in an additional, metastatic lesion. The recitation only limits the preamble, but it still does not further limit the active step of the method because the active method step does not recite to whom irinotecan is administered as stated above. Accordingly, the teachings of

administering irinotecan in a MM-398 irinotecan liposome in the same amount as claimed in US 2014/0170075 also reads on claim 6.

As such, the prior art anticipates the instant claims.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BONG-SOOK BAEK whose telephone number is 571-270-5863. The examiner can normally be reached 9:00AM-6:00PM Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Wu-Cheng Shen can be reached on 571-272-3157. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/BONG-SOOK BAEK/

Primary Examiner, Art Unit 1621

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/964,571	12/09/2015	ELIEL BAYEVER	263266-411575	1063

139696 7590 11/01/2017

Honigman Miller Schwartz and Cohn LLP/Ipsen
350 East Michigan Avenue, Suite 300
Kalamazoo, MI 49007

EXAMINER	
BAEK, BONG-SOOK	

ART UNIT	PAPER NUMBER
1621	

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11/01/2017	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No. 14/964,571	Applicant(s) BAYEVER et al.	
	Examiner BONG-SOOK BAEK	Art Unit 1621	AIA Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 7/13/2017 .

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____ .

2a)☑ This action is **FINAL**. 2b) ☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☑ Claim(s) 1 and 4-14 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☑ Claim(s) 1 and 4-14 is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)

2) ☑ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____ .

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____

4) ☐ Other: _____ .

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

DETAILED ACTION

Status of claims

The amendment filed on July 13, 2017 is acknowledged. Claims 2-3 have been canceled and new claims 7-14 have been added. Claims 1 and 4-14 are under examination in the instant office action.

Applicants' arguments, filed on July 13, 2017, have been fully considered but they are moot in view of new grounds of rejection necessitated by the amendments (i.e., adding new limitations and new claims). Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application. Responses are limited to Applicants' arguments relevant to either reiterated or newly applied rejections.

Claim Objections

Claims 8 and 10 are objected because of the following informalities: typographical errors. The recitation, "the group consisting of HER2 negative breast cancer, HER2 negative metastatic breast cancer, and HER2 negative or HER2 positive and is metastatic breast cancer with at least one brain lesion" in lines 8-10 of claim 8 should be corrected to -- the group consisting of a) HER2 negative breast cancer, c) HER2 negative metastatic breast cancer, and c) HER2 negative or HER2 positive metastatic breast cancer with at least one brain lesion".

The recitation, "the group consisting of breast cancer with active brain metastasis, HER2 negative breast cancer, HER2 negative metastatic breast cancer, and HER2 negative or HER2 positive and is metastatic breast cancer with at least one brain lesion" in lines 1-4 of claim 10 should be corrected to -- the group consisting of a) breast cancer with active brain metastasis, b) HER2 negative breast cancer, c) HER2 negative metastatic breast cancer, and d) HER2 negative or HER2 positive metastatic breast cancer with at least one brain lesion".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a)(1) the claimed invention was patented, described in a printed publication, or in public use, on sale or otherwise available to the public before the effective filing date of the claimed invention.

Claims 8, 10, and 11-12 are rejected under 35 U.S.C. 102(a)(1) as being anticipated by US 2014/0170075 as evidenced by Merrimack Pharmaceuticals, Inc. Pilot study (ClinicalTrials.gov Identifier: NCT01770353, August 9, 2013, cited in the IDS filed on 7/14/2017).

US 2014/0170075 teaches a method for selecting and providing pharmaceutical treatment to a patient for a localized infectious, inflammatory, or neoplastic condition, the method comprising identifying one or more locations of infection, inflammation or neoplasia in a patient, and subsequently, obtaining at least one contrast-enhanced MRI image of a first location of the one or more locations, and subsequently, selecting an anti-infective, anti-inflammatory, or anti-neoplastic pharmaceutical agent and treating the patient with the selected pharmaceutical agent, wherein the contrast agent is ferumoxytol (FMX) which is intravenously administered at 5 mg/kg

up to 510 mg/kg and wherein the pharmaceutical agent is a liposomal anti-neoplastic agent (abstract, [0019], [0020]claims 8-13). US 2014/0170075 also teaches that the liposomal therapeutic agent is MM-398 (irinotecan sucroseoctasulfate liposome injection) and the tumor is a non-small cell lung cancer (NSCLC) tumor, a triple negative breast cancer (TNBC) tumor (HER2 negative breast cancer), a colorectal cancer (CRC) tumor, a pancreatic cancer tumor, a small cell lung cancer tumor, a gastric cancer tumor, a cervical cancer tumor, or Ewing's sarcoma (claims 14-16). US 2014/0170075 teaches that as FMX has been demonstrated to be safe for intravenous administration to patients and is shown herein not to interfere with nanoliposome therapies if used as an imaging agent, even within 1-4 hours prior to administration of nanoliposomal therapeutics, these results indicate that FMX MRI allows for selection patients who will (or will not) benefit from nanoliposomal therapy ([0105]). US 2014/0170075 further teaches that patients identified as having sites of pathology that are predicted to exhibit nanoparticle accumulation would be considered more likely to respond to nanoparticulate therapeutic agents and patients identified as having sites of pathology that are predicted not to exhibit nanoparticle accumulation would be considered less likely to respond to nanoparticulate therapeutic agents and treating patients in accordance with such identifications would avoid the administration of sub-optimal therapeutic treatments to patients in need of therapy ([0011]).

The reference specifically discloses a human clinical trial (ClinicalTrials.gov Identifier: NCT01770353) wherein patients with advanced solid tumors and multiple metastases were injected with FMX at 5 mg/kg and then were infused with 80 mg/m^2 MM-398 and shows that the patents have tumor lesion with FMX uptake (see[0135], [0139], and Examples 9-10 and Figs. 6-8). As evidenced by the clinical trial (ClinicalTrials.gov Identifier: NCT01770353), the solid tumor includes ER/PR positive breast cancer and triple negative breast cancer (HER2 negative)

and MM-398 80 mg/m^2 was administered once every two weeks) (see Condition, Arms, and Criteria sections). The reference further discloses the measured FMX levels at day 2 (24 h) and day 4 (72 h) after FMX injection together with the calculated volumes of four liver lesions at treatment start ("Screening") and after four weeks or two treatment cycles wherein the level of FMX 24 hours after the intravenous administration of FMX is 38.98, 28, 04, 39.94, and 37.35 mcg/ml in lesions 1-4, respectively (Example 10 and table). Also, it discloses that the change in the volume of liver tumor lesion is greater in lesion 1, 3, and 4 (Example 10 and table). Since the patient has a tumor lesion with FMX tumor lesion uptake of 38.98, 39.94, and 37.35 mcg/ml after 24 hours after the intravenous administration, it inherently discloses that "a FMX tumor lesion uptake is "at least 32.6 mcg/ml one hour after the intravenous administration of 5 mg/kg FMX" as evidenced by Fig. 6B (the FMX uptake level is lower after 24 hrs than after one hour). Thus, US 2014/0170075 teaches a method of treating breast cancer such as Her2 negative breast cancer (e.g., a triple negative breast cancer) and Her2 negative breast metastatic cancer, which comprises administering to the patient 5 mg/kg intravenous ferumoxyltol up to a maximum dose of 510 mg total ferumoxytol; b. identifying a tumor lesion in the patient having a ferumoxytol tumor lesion uptake of at least 32.6 mcg/mL one hour after intravenous administration the ferumoxytol; and c. administering irinotecan in a MM-398 irinotecan liposome in an amount effective to administer the amount of irinotecan present in a 80 mg/m2 dose of irinotecan hydrochloride trihydrate as claimed.

As such, the instant claims are anticipated by US 2014/0170075.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102 of this title, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103 are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1. 4-5, 8, and 10-12 are rejected under 35 U.S.C. 103 as being unpatentable over US 2014/0170075 as evidenced by Merrimack Pharmaceuticals, Inc. Pilot study (ClinicalTrials.gov Identifier: NCT01770353, August 9, 2013, cited in the IDS filed on 7/14/2017) in view of Noble *et al.* (Cancer Res. 66(5): 2801-2806, 2006, cited in the IDS filed on 7/14/2017).

US 2014/0170075 teaches a method for selecting and providing pharmaceutical treatment to a patient for a localized infectious, inflammatory, or neoplastic condition, the method comprising identifying one or more locations of infection, inflammation or neoplasia in a patient, and subsequently, obtaining at least one contrast-enhanced MRI image of a first location of the one or more locations, and subsequently, selecting an anti-infective, anti-inflammatory, or anti-

neoplastic pharmaceutical agent and treating the patient with the selected pharmaceutical agent, wherein the contrast agent is ferumoxytol (FMX) which is intravenously administered at 5 mg/kg up to 510 mg/kg and wherein the pharmaceutical agent is a liposomal anti-neoplastic agent (abstract, [0019], [0020]claims 8-13). US 2014/0170075 also teaches that the liposomal therapeutic agent is MM-398 (irinotecan sucroseoctasulfate liposome injection) and the tumor is a non-small cell lung cancer (NSCLC) tumor, a triple negative breast cancer (TNBC) tumor, a colorectal cancer (CRC) tumor, a pancreatic cancer tumor, a small cell lung cancer tumor, a gastric cancer tumor, a cervical cancer tumor, or Ewing's sarcoma ([0068] and claims 14-16). US 2014/0170075 teaches that as FMX has been demonstrated to be safe for intravenous administration to patients and is shown herein not to interfere with nanoliposome therapies if used as an imaging agent, even within 1-4 hours prior to administration of nanoliposomal therapeutics, these results indicate that FMX MRI allows for selection patients who will (or will not) benefit from nanoliposomal therapy ([0105]). US 2014/0170075 further teaches that patients identified as having sites of pathology that are predicted to exhibit nanoparticle accumulation would be considered more likely to respond to nanoparticulate therapeutic agents and patients identified as having sites of pathology that are predicted not to exhibit nanoparticle accumulation would be considered less likely to respond to nanoparticulate therapeutic agents and treating patients in accordance with such identifications would avoid the administration of sub-optimal therapeutic treatments to patients in need of therapy ([0011]).

The reference specifically discloses a human clinical trial (ClinicalTrials.gov Identifier: NCT01770353) wherein patients with advanced solid tumors and multiple metastases were injected with FMX at 5 mg/kg and then were infused with 80 mg/m^2 MM-398 and shows that the patents have tumor lesion with FMX uptake (see[0135], [0139], and Examples 9-10 and Figs. 6-

8). As evidenced by the clinical trial (ClinicalTrials.gov Identifier: NCT01770353), the solid tumor includes ER/PR positive breast cancer and triple negative breast cancer (HER2 negative) and MM-398 80 mg/m^2 was administered once every two weeks) (see Condition, Arms, and Criteria sections). The reference further discloses the measured FMX levels at day 2 (24 h) and day 4 (72 h) after FMX injection together with the calculated volumes of four liver lesions at treatment start ("Screening") and after four weeks or two treatment cycles wherein the level of FMX 24 hours after the intravenous administration of FMX is 38.98, 28, 04, 39.94, and 37.35 mcg/ml in lesions 1-4, respectively (Example 10 and table). Also, it discloses that the change in the volume of liver tumor lesion is greater in lesion 1, 3, and 4 (Example 10 and table). Since the patient has a tumor lesion with FMX tumor lesion uptake of 38.98, 39.94, and 37.35 mcg/ml after 24 hours after the intravenous administration, it inherently discloses that "a FMX tumor lesion uptake is "at least 32.6 mcg/ml one hour after the intravenous administration of 5 mg/kg FMX" as evidenced by Fig. 6B (the FMX uptake level is lower after 24 hrs than after one hour).

The reference does not specifically disclose the treatment of breast cancer with active brain metastasis.

Noble *et al.* teaches that convection-enhanced delivery of nanoliposomal CPT-11 (irinotecan) greatly prolonged tissue residence while also substantially reducing toxicity, resulting in a highly effective treatment strategy in preclinical brain tumor models (abstract).

It would have been prima facie obvious to one of ordinary skill in the art before the effective filing date of the claimed invention to use nanoliposomal irinotecan such as MM-398 for treating breast cancer with active brain metastasis because of the following reasons. As stated above, nanoliposomal irinotecan such as MM-398 was known to be effective for treating breast cancer with active metastatic lesion and a head and neck cancer as evidenced by US 2014/0170075.

Also, Noble *et al.* teaches that irinotecan in a nanoliposome is suitable for treating brain tumor. Thus, one of ordinary skill in the art would have been motivated to use the nanoliposomal irinotecan such as MM-398 taught by US 2014/0170075 in the treatment of breast cancer with active brain metastasis on the reasonable expectation that it would effectively treat both breast and brain tumor lesions.

Claims 1-6, 8, and 10-13 are rejected under 35 U.S.C. 103 as being unpatentable over US 2014/0170075 as evidenced by Merrimack Pharmaceuticals, Inc. Pilot study (ClinicalTrials.gov Identifier: NCT01770353, August 9, 2013, cited in the IDS filed on 7/14/2017) in view of US2013/0274281.

US 2014/0170075, Merrimack Pharmaceuticals, Inc. Pilot study (ClinicalTrials.gov Identifier: NCT01770353, August 9, 2013, cited in the IDS filed on 7/14/2017) as applied *supra* are herein applied for the same teachings in their entirety.

The reference does not specifically disclose the treatment of breast cancer with active brain metastasis or HER2 positive breast cancer.

US2013/0274281 teaches the use of irinotecan in combination with 4-iodo-3-nitrobenzamide for the treatment of locally advanced or metastatic breast cancer or breast cancer with brain metastases wherein the breast cancer can be HER2 positive or negative (abstract and claims 4-6).

It would have been prima facie obvious to one of ordinary skill in the art before the effective filing date of the claimed invention to use the nanoliposomal irinotecan such as MM-398 taught by US 2014/0170075 in the treatment of breast cancer with active brain metastasis or HER2 positive breast cancer because US 2014/0170075 already teaches that the nanoliposomal

irinotecan such as MM-398 is useful for treating breast cancer with active metastatic lesion and irinotecan was also known to be suitable for treating breast cancer with active brain metastasis, HER2 positive breast cancer, and HER2 negative breast cancer as evidenced by US2013/0274281. One of ordinary skill in the art would have reasonably expected that the nanoliposomal irinotecan such as MM-398, which is generally useful for treating breast cancer as evidenced by US 2014/0170075, would also be useful for treating subtypes of breast cancer including breast cancer with active brain metastasis, HER2 positive breast cancer, and HER2 negative breast cancer in the absence of evidence to the contrary.

Claims 7, 9, and 14 are rejected under 35 U.S.C. 103 as being unpatentable over US 2014/0170075 as evidenced by Merrimack Pharmaceuticals, Inc. Pilot study (ClinicalTrials.gov Identifier: NCT01770353, August 9, 2013, cited in the IDS filed on 7/14/2017) in view of Noble *et al.* (Cancer Res. 66(5): 2801-2806, 2005, cited in the IDS filed on 7/14/2017) in further view of Pfizer Background Document on the UGT1A1 Polymorphisms and Irinotecan Toxicity (ACPS November 3, 2004 Advisory Committee Meeting).

US 2014/0170075, Merrimack Pharmaceuticals, Inc. Pilot study (ClinicalTrials.gov Identifier: NCT01770353, August 9, 2013, cited in the IDS filed on 7/14/2017), and Noble *et al.* as applied *supra* are herein applied for the same teachings in their entirety.

The references do not specify that the patient is not homozygous for the UGT1A1*28 allele. However, it was well-known in the art that patients who are homozygous for the UGT1A1*28 allele are at greater risk for irinotecan-induced severe diarrhea or neutropenia as evidenced by Pfizer Background Document (see p3, para 5). Thus, it would have been prima facie obvious to one of ordinary skill in the art before the effective filing date of the claimed

invention to use the nanoliposomal irinotecan such as MM-398 taught by US 2014/0170075 in the treatment of patients with breast cancer who is not homozygous for UGT1A1*28 allele for avoiding the risk for irinotecan-induced severe diarrhea or neutropenia.

Claims 7, 9, and 14 are rejected under 35 U.S.C. 103 as being unpatentable over US 2014/0170075 as evidenced by Merrimack Pharmaceuticals, Inc. Pilot study (ClinicalTrials.gov Identifier: NCT01770353, August 9, 2013, cited in the IDS filed on 7/14/2017) in view of US2013/0274281 in further view of Pfizer Background Document on the UGT1A1 Polymorphisms and Irinotecan Toxicity (ACPS November 3, 2004 Advisory Committee Meeting).

US 2014/0170075, Merrimack Pharmaceuticals, Inc. Pilot study (ClinicalTrials.gov Identifier: NCT01770353, August 9, 2013, cited in the IDS filed on 7/14/2017), and US2013/0274281 as applied *supra* are herein applied for the same teachings in their entirety.

The references do not specify that the patient is not homozygous for the UGT1A1*28 allele. However, it was well-known in the art that patients who are homozygous for the UGT1A1*28 allele are at greater risk for irinotecan-induced severe diarrhea or neutropenia as evidenced by Pfizer Background Document (see p3, para 5). Thus, it would have been prima facie obvious to one of ordinary skill in the art before the effective filing date of the claimed invention to use the nanoliposomal irinotecan such as MM-398 taught by US 2014/0170075 in the treatment of patients with breast cancer who is not homozygous for UGT1A1*28 allele for avoiding the risk for irinotecan-induced severe diarrhea or neutropenia.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Also, Applicant's submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on July 14, 2017 prompted the new ground(s) of rejection presented in this Office action.

Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BONG-SOOK BAEK whose telephone number is 571-270-5863. The examiner can normally be reached 9:00AM-6:00PM Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Wu-Cheng Shen can be reached on 571-272-3157. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications

may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/BONG-SOOK BAEK/
Primary Examiner, Art Unit 1621

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/964,571	12/09/2015	ELIEL BAYEVER	263266-411575	1063

153749 7590 09/25/2018

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EXAMINER	
BAEK, BONG-SOOK	

ART UNIT	PAPER NUMBER
1621	

NOTIFICATION DATE	DELIVERY MODE
09/25/2018	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docketing@mcneillbaur.com
eofficeaction@appcoll.com
patents.us@ipsen.com

Office Action Summary	Application No. 14/964,571	Applicant(s) BAYEVER et al.	
	Examiner BONG-SOOK BAEK	Art Unit 1621	AIA Status Yes

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on 01 May 2018.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL.** 2b) ☑ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5) ☑ Claim(s) 1 and 4-14 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6) ☐ Claim(s) _____ is/are allowed.

7) ☑ Claim(s) 1 and 4-14 is/are rejected.

8) ☐ Claim(s) _____ is/are objected to.

9) ☐ Claim(s) _____ are subject to restriction and/or election requirement

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov.**

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.

4) ☐ Other: _____.

Notice of Pre-AIA or AIA Status

The present application, filed on or after March 16, 2013, is being examined under the first inventor to file provisions of the AIA.

DETAILED ACTION

A request for continued examination under 37 C.F.R. 1.114, including the fee set forth in 37 C.F.R. 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 C.F.R. 1.114, and the fee set forth in 37 C.F.R. 1.17(e) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 C.F.R. 1.114. Applicant's submission filed May 1, 2018 has been received and entered into the present application.

Status of claims

The amendment filed on May 1, 2018 is acknowledged. Claims 1 and 4-14 are under examination in the instant office action.

Applicants' arguments, filed on May 1, 2018, have been fully considered but they are moot in view of new grounds of rejection necessitated by the amendments (i.e., changing the dose of irinotecan). Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102 of this title, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103 are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 4-5, 8, and 10-12 are rejected under 35 U.S.C. 103 as being unpatentable over US 2014/0170075 as evidenced by Merrimack Pharmaceuticals, Inc. Pilot study (ClinicalTrials.gov Identifier: NCT01770353, August 9, 2013, cited in the IDS filed on 7/14/2017) in view of Noble *et al.* (Cancer Res. 66(5): 2801-2806, 2006, cited in the IDS filed on 7/14/2017) in further in view of US 2004/0002505.

US 2014/0170075 teaches a method for selecting and providing pharmaceutical treatment to a patient for a localized infectious, inflammatory, or neoplastic condition, the method comprising identifying one or more locations of infection, inflammation or neoplasia in a patient, and subsequently, obtaining at least one contrast-enhanced MRI image of a first location of the one or more locations, and subsequently, selecting an anti-infective, anti-inflammatory, or anti-

neoplastic pharmaceutical agent and treating the patient with the selected pharmaceutical agent, wherein the contrast agent is ferumoxytol (FMX) which is intravenously administered at 5 mg/kg up to 510 mg/kg and wherein the pharmaceutical agent is a liposomal anti-neoplastic agent (abstract, [0019], [0020]claims 8-13). US 2014/0170075 also teaches that the liposomal therapeutic agent is MM-398 (irinotecan sucroseoctasulfate liposome injection) and the tumor is a non-small cell lung cancer (NSCLC) tumor, a triple negative breast cancer (TNBC) tumor, a colorectal cancer (CRC) tumor, a pancreatic cancer tumor, a small cell lung cancer tumor, a gastric cancer tumor, a cervical cancer tumor, or Ewing's sarcoma ([0068] and claims 14-16). US 2014/0170075 teaches that as FMX has been demonstrated to be safe for intravenous administration to patients and is shown herein not to interfere with nanoliposome therapies if used as an imaging agent, even within 1-4 hours prior to administration of nanoliposomal therapeutics, these results indicate that FMX MRI allows for selection patients who will (or will not) benefit from nanoliposomal therapy ([0105]). US 2014/0170075 further teaches that patients identified as having sites of pathology that are predicted to exhibit nanoparticle accumulation would be considered more likely to respond to nanoparticulate therapeutic agents and patients identified as having sites of pathology that are predicted not to exhibit nanoparticle accumulation would be considered less likely to respond to nanoparticulate therapeutic agents and treating patients in accordance with such identifications would avoid the administration of sub-optimal therapeutic treatments to patients in need of therapy ([0011]).

The reference specifically discloses a human clinical trial (ClinicalTrials.gov Identifier: NCT01770353) wherein patients with advanced solid tumors and multiple metastases were injected with FMX at 5 mg/kg and then were infused with 80 mg/m^2 MM-398 and shows that the patents have tumor lesion with FMX uptake (see[0135], [0139], and Examples 9-10 and Figs. 6-

8). As evidenced by the clinical trial (ClinicalTrials.gov Identifier: NCT01770353), the solid tumor includes ER/PR positive breast cancer and triple negative breast cancer (HER2 negative) and MM-398 80 mg/m^2 was administered once every two weeks) (see Condition, Arms, and Criteria sections). The reference further discloses the measured FMX levels at day 2 (24 h) and day 4 (72 h) after FMX injection together with the calculated volumes of four liver lesions at treatment start ("Screening") and after four weeks or two treatment cycles wherein the level of FMX 24 hours after the intravenous administration of FMX is 38.98, 28, 04, 39.94, and 37.35 mcg/ml in lesions 1-4, respectively (Example 10 and table). Also, it discloses that the change in the volume of liver tumor lesion is greater in lesion 1, 3, and 4 (Example 10 and table). Since the patient has a tumor lesion with FMX tumor lesion uptake of 38.98, 39.94, and 37.35 mcg/ml after 24 hours after the intravenous administration, it inherently discloses that "a FMX tumor lesion uptake is "at least 32.6 mcg/ml one hour after the intravenous administration of 5 mg/kg FMX" as evidenced by Fig. 6B (the FMX uptake level is lower after 24 hrs than after one hour).

The reference does not specifically disclose the treatment of breast cancer with active brain metastasis.

Noble *et al.* teaches that convection-enhanced delivery of nanoliposomal CPT-11 (irinotecan) greatly prolonged tissue residence while also substantially reducing toxicity, resulting in a highly effective treatment strategy in preclinical brain tumor models (abstract).

It would have been prima facie obvious to one of ordinary skill in the art before the effective filing date of the claimed invention to use nanoliposomal irinotecan such as MM-398 for treating breast cancer with active brain metastasis because of the following reasons. As stated above, nanoliposomal irinotecan such as MM-398 was known to be effective for treating breast cancer with active metastatic lesion and a head and neck cancer as evidenced by US 2014/0170075.

Also, Noble *et al.* teaches that irinotecan in a nanoliposome is suitable for treating brain tumor. Thus, one of ordinary skill in the art would have been motivated to use the nanoliposomal irinotecan such as MM-398 taught by US 2014/0170075 in the treatment of breast cancer with active brain metastasis on the reasonable expectation that it would effectively treat both breast and brain tumor lesions.

While the example of US 2014/0170075 disclose administering 80 mg/m2 MM-398, the reference does not specifically disclose 60 mg/m^2 dose of irinotecan hydrochloride trihydrate as amended.

However, it was known in the art that the daily dose of irinotecan hydrochloride trihydrate range from 40 to 150 mg/m2 as evidenced by US 2004/0002505 ([0090]). Thus, it would have been prima facie obvious to one of ordinary skill in the art before the effective filing date of the claimed invention to optimize the dosage for getting desired effects based on known daily effective dosage. Also, the claimed range falls within the range disclose in the prior art. In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a prima facie case of obviousness exists. *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976). Furthermore, "[A] prior art reference that discloses a range encompassing a somewhat narrower claimed range is sufficient to establish a prima facie case of obviousness." *In re Peterson*, 315 F.3d 1325, 1330, 65 USPQ2d 1379, 1382-83 (Fed. Cir. 2003). In addition, it is well-established that merely selecting proportions and ranges is not patentable absent a showing of criticality. *In re Becket*, 33 USPQ 33; *In re Russell*, 169 USPQ 426. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire

of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages.")

Claims 1-6, 8, and 10-13 are rejected under 35 U.S.C. 103 as being unpatentable over US 2014/0170075 as evidenced by Merrimack Pharmaceuticals, Inc. Pilot study (ClinicalTrials.gov Identifier: NCT01770353, August 9, 2013, cited in the IDS filed on 7/14/2017) in view of US2013/0274281 in further in view of US 2004/0002505.

US 2014/0170075, Merrimack Pharmaceuticals, Inc. Pilot study as applied *supra* are herein applied for the same teachings in their entirety.

The reference does not specifically disclose the treatment of breast cancer with active brain metastasis or HER2 positive breast cancer.

US2013/0274281 teaches the use of irinotecan in combination with 4-iodo-3-nitrobenzamide for the treatment of locally advanced or metastatic breast cancer or breast cancer with brain metastases wherein the breast cancer can be HER2 positive or negative (abstract and claims 4-6).

It would have been prima facie obvious to one of ordinary skill in the art before the effective filing date of the claimed invention to use the nanoliposomal irinotecan such as MM-398 taught by US 2014/0170075 in the treatment of breast cancer with active brain metastasis or HER2 positive breast cancer because US 2014/0170075 already teaches that the nanoliposomal irinotecan such as MM-398 is useful for treating breast cancer with active metastatic lesion and irinotecan was also known to be suitable for treating breast cancer with active brain metastasis, HER2 positive breast cancer, and HER2 negative breast cancer as evidenced by

US2013/0274281. One of ordinary skill in the art would have reasonably expected that the nanoliposomal irinotecan such as MM-398, which is generally useful for treating breast cancer as evidenced by US 2014/0170075, would also be useful for treating subtypes of breast cancer including breast cancer with active brain metastasis, HER2 positive breast cancer, and HER2 negative breast cancer in the absence of evidence to the contrary.

While the example of US 2014/0170075 disclose administering 80 mg/m2 MM-398, the reference does not specifically disclose 60 mg/m^2 dose of irinotecan hydrochloride trihydrate as amended.

However, it was known in the art that the daily dose of irinotecan hydrochloride trihydrate range from 40 to 150 mg/m2 as evidenced by US 2004/0002505 ([0090]). Thus, it would have been prima facie obvious to one of ordinary skill in the art before the effective filing date of the claimed invention to optimize the dosage for getting desired effects based on known daily effective dosage. Also, the claimed range falls within the range disclose in the prior art. In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a prima facie case of obviousness exists. *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976). Furthermore, "[A] prior art reference that discloses a range encompassing a somewhat narrower claimed range is sufficient to establish a prima facie case of obviousness." *In re Peterson*, 315 F.3d 1325, 1330, 65 USPQ2d 1379, 1382-83 (Fed. Cir. 2003). In addition, it is well-established that merely selecting proportions and ranges is not patentable absent a showing of criticality. *In re Becket*, 33 USPQ 33; *In re Russell*, 169 USPQ 426. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire

of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages.")

Claims 7, 9, and 14 are rejected under 35 U.S.C. 103 as being unpatentable over US 2014/0170075 as evidenced by Merrimack Pharmaceuticals, Inc. Pilot study (ClinicalTrials.gov Identifier: NCT01770353, August 9, 2013, cited in the IDS filed on 7/14/2017) in view of Noble *et al.* (Cancer Res. 66(5): 2801-2806, 2005, cited in the IDS filed on 7/14/2017) and US 2004/0002505, in further view of Pfizer Background Document on the UGT1A1 Polymorphisms and Irinotecan Toxicity (ACPS November 3, 2004 Advisory Committee Meeting).

US 2014/0170075, Merrimack Pharmaceuticals, Inc. Pilot study, Noble *et al.* and US 2004/0002505 as applied *supra* are herein applied for the same teachings in their entirety.

The references do not specify that the patient is not homozygous for the UGT1A1*28 allele. However, it was well-known in the art that patients who are homozygous for the UGT1A1*28 allele are at greater risk for irinotecan-induced severe diarrhea or neutropenia as evidenced by Pfizer Background Document (see p3, para 5). Thus, it would have been prima facie obvious to one of ordinary skill in the art before the effective filing date of the claimed invention to use the nanoliposomal irinotecan such as MM-398 taught by US 2014/0170075 in the treatment of patients with breast cancer who is not homozygous for UGT1A1*28 allele for avoiding the risk for irinotecan-induced severe diarrhea or neutropenia.

Claims 7, 9, and 14 are rejected under 35 U.S.C. 103 as being unpatentable over US 2014/0170075 as evidenced by Merrimack Pharmaceuticals, Inc. Pilot study (ClinicalTrials.gov

Identifier: NCT01770353, August 9, 2013, cited in the IDS filed on 7/14/2017) in view of US2013/0274281 and US 2004/0002505, in further view of Pfizer Background Document on the UGT1A1 Polymorphisms and Irinotecan Toxicity (ACPS November 3, 2004 Advisory Committee Meeting).

US 2014/0170075, Merrimack Pharmaceuticals, Inc. Pilot study, US2013/0274281, and US 2004/0002505 as applied *supra* are herein applied for the same teachings in their entirety.

The references do not specify that the patient is not homozygous for the UGT1A1*28 allele. However, it was well-known in the art that patients who are homozygous for the UGT1A1*28 allele are at greater risk for irinotecan-induced severe diarrhea or neutropenia as evidenced by Pfizer Background Document (see p3, para 5). Thus, it would have been prima facie obvious to one of ordinary skill in the art before the effective filing date of the claimed invention to use the nanoliposomal irinotecan such as MM-398 taught by US 2014/0170075 in the treatment of patients with breast cancer who is not homozygous for UGT1A1*28 allele for avoiding the risk for irinotecan-induced severe diarrhea or neutropenia.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BONG-SOOK BAEK whose telephone number is 571-270-5863. The examiner can normally be reached 9:00AM-6:00PM Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Melenie Gordon can be reached on 571-272-8037. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/BONG-SOOK BAEK/
Primary Examiner, Art Unit 1621

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EXAMINER	
SHOMER, ISAAC	

ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 14/965,140	Applicant(s) HONG ET AL.	
	Examiner ISAAC SHOMER	Art Unit 1612	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) 1-20 is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) 1-20 is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

4) ☐ Other: _____.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

The present application is being examined under the pre-AIA first to invent provisions.

In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

Note Regarding Claim Interpretation

Prior to setting forth the relevant grounds of rejection, the examiner takes the following position regarding the interpretation of the instant claims.

As an initial matter, the instant claims are product-by-process claims. Such product-by-process claims are not limited to the manipulations of the recited steps, only to the structure implied by the steps. See MPEP 2113.

Additionally, the instant claims are understood to recite a liposome composition comprising irinotecan and sucrose octasulfate. Although a sulfate ammonium cation is recited in the claim, it is best understood as an item that is used in the process of making the claimed composition, but need not be present in the composition required by the instant claims. This is because the claims appear to recite a composition in which

said substituted ammonium cation is used in the preparation of the claimed composition but removed prior to finishing the forming of the claimed composition, as well as a composition in which this cation is present in the final composition. The term "comprising" is open ended and does not exclude additional unrecited elements or method steps; see MPEP 2111.03, second paragraph.

Note Regarding Declarations Under 37 C.F.R. 1.132

The following information may be relevant to applicant during the course of prosecution:

Affidavits or declarations, such as those submitted under 37 CFR 1.130, 1.131 and 1.132, filed during the prosecution of the prior application do not automatically become a part of this application. Where it is desired to rely on an earlier-filed affidavit or declaration, the applicant should make the remarks of record in this application and include a copy of the original affidavit or declaration filed in the prior application.

Substantial Duplicate Claims - Warning

Applicant is advised that should claim 17 be found allowable, claim 18 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof.

Applicant is advised that should claim 7 be found allowable, claim 20 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof.

When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

With regard to claims 7 and 20, the examiner notes that claim 7 depends upon claim 6, which depends upon claim 4, whereas claim 20 depends directly upon claim 4. Nevertheless, the scope of claims 7 and 20 is the same because claim 6 does not exclude anything additional from the scope of claim 4 as compared with what is already excluded by the limitations of claims 7 and 20.

Claim Rejections - 35 USC § 112(b) – Indefiniteness

The following is a quotation of 35 U.S.C. 112(b):
(b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-20 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.

Independent claims 1, 4, 13, and 15, all require the step of “forming” in step (a) of these claims. This does not appear to be a positive process step. This is because the

step of forming appears to limit only the product formed by the step, and not the process by which the intermediate product of this step is formed. As such, it is unclear if the word “forming” is to be understood as “providing”, or whether there is additional delineation of how the method occurs due to the recited “forming" step.

Claim Rejections - 35 USC § 112(d) – Failure to Limit Parent Claim

The following is a quotation of 35 U.S.C. 112(d):

> (d) REFERENCE IN DEPENDENT FORMS.—Subject to subsection (e), a claim in dependent form shall contain a reference to a claim previously set forth and then specify a further limitation of the subject matter claimed. A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), fourth paragraph:

> Subject to the [fifth paragraph of 35 U.S.C. 112 (pre-AIA)], a claim in dependent form shall contain a reference to a claim previously set forth and then specify a further limitation of the subject matter claimed. A claim in dependent form shall be construed to incorporate by reference all the limitations of the claim to which it refers.

Claims 18-20 are rejected under 35 U.S.C. 112(d) or pre-AIA 35 U.S.C. 112, 4th paragraph, as being of improper dependent form for failing to further limit the subject matter of the claim upon which it depends, or for failing to include all the limitations of the claim upon which it depends. Claim 18 depends from claim 17, but appears to recite the same limitations as claim 17. Applicant may cancel the claim(s), amend the claim(s) to place the claim(s) in proper dependent form, rewrite the claim(s) in independent form, or present a sufficient showing that the dependent claim(s) complies with the statutory requirements.

Claim Rejections - 35 USC § 103 – Obviousness

The following is a quotation of pre-AIA 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under pre-AIA 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under pre-AIA 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of pre-AIA 35 U.S.C. 103(c) and potential pre-AIA 35 U.S.C. 102(e), (f) or (g) prior art under pre-AIA 35 U.S.C. 103(a).

Claims 1-20 are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Chou et al. (Journal of Bioscience and Bioengineering, Vol. 95, No. 4, 2003, pages 405-408) in view of Schlessinger et al. (US Patent 5,783,568).

Chou et al. (hereafter referred to as Chou) is drawn to a liposomal irinotecan formulation, as of Chou, page 405, title and abstract. This composition includes irinotecan along with lipids, as of Chou, page 405, abstract. This composition is intended for cancer treatment, as of Chou, page 405, left column, first paragraph.

Chou does not teach sucrose octasulfate.

Schlessinger et al. (hereafter referred to as Schlessinger) is drawn to the treatment of cancer, as of Schlessinger, title and abstract. Schlessinger teaches that sucrose octasulfate has the ability to treat cancer or an angiogenic abnormality as it prevents oligomerization of heparin growth factor, as of Schlessinger, column 27 lines 19-26.

Schlessinger does not teach irinotecan.

It would have been prima facie obvious for one of ordinary skill in the art to have included sucrose octasulfate, as of Schlessinger, into the liposome of Chou. Chou is drawn to a liposome comprising irinotecan, which is intended for use in treating cancer. As sucrose octasulfate is also used for treating cancer, as taught by Schlessinger, the skilled artisan would have been motivated to have included the sucrose octasulfate of Schlessinger into the liposome of Chou. Generally, it is prima facie obvious to combine two compositions (liposomal irinotecan, as of Chou, and sucrose octasulfate, as of

Schlessinger), each of which is taught by the prior art to be useful for same purpose (treating cancer), in order to form a third composition to be used for the very same purpose. The idea for combining them flows logically from their having been individually taught in the prior art. See MPEP 2144.06. Moreover, where it would have been obvious to have combined individually known ingredients, evidence must be provided establishing that appellant's combination of agents is in some way more effective or in some way different than any single member of that combination in order to rebut that prima facie case. See In re Dial, 140 USPQ 244 (C.C.P.A. 1964).

As to claims 1, 4, 13, and 15, these are all independent claims that recite that the claimed product be made by a specific process. Neither Chou nor Schlessinger teach a specific process by which the product is to be made. Nevertheless, the instant claims are product-by-process claims, and these claims are not limited to the manipulations of the recited steps, only to the structure implied by the steps. See MPEP 2113. The structure implied by the steps of the instant claims is a liposome comprising irinotecan, as is the structure of the composition of Chou in view of Schlessinger. As such, the composition of Chou in view of Schlessinger is understood to render the claimed product obvious even though neither Chou nor Schlessinger teach the process by which the claimed product is made.

As to claims 2, 3, 5-10, 12, and 16-20, these claims further modify the substituted ammonium used in the claimed process. However, as best understood by the examiner, the substituted ammonium salt is part of the process used to prepare the claimed liposome, but not part of the claimed liposomes themselves. As such, these claims are

understood as further modifying the process by which the claimed product is made, but not further modifying the claimed product itself. As such, these claims are rejected for the same reason that claims 1, 4, 13, and 15 are rejected.

As to claims 11 and 14, these claims recite a specific concentration of sucrose octasulfate. No such specific concentration is taught by Schlessinger. Nevertheless, differences in concentration between the prior art and the instant claims will generally not support patentability of the instant claims in the absence of evidence of criticality or unexpected results of the claimed range. As no such evidence of criticality or unexpected results of the claimed range has been presented, claim 10 has been rejected over the conflicting claims. See MPEP 2144.05(II)(A).

Note Regarding Reference Date: The examiner has obtained an abstract of the Chou document which shows that Chou was published online on 27 August 2003. This is less than a year prior to the earliest effective filing date of 3 May 2004. As such, Chou is understood to be prior art at least under pre-AIA 35 U.S.C. 102(a).

Non-Statutory Double Patenting – Legal Information

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the claims at issue are not identical, but at least

one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the reference application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(1) - 706.02(l)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/forms/. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more

information about eTerminal Disclaimers, refer to

http://www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

Non-Statutory Double Patenting – Patent 8,147,867

Claims 1-20 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-35 of U.S. Patent No. 8,147,867. Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons:

Instant claim 1 is drawn to a liposomal irinotecan composition comprising irinotecan and sucrose octasulfate encapsulated in a lipid vesicle. A process by which the claimed vesicle is made is recited by instant claim 1. This process includes a substituted ammonium cation, though there is no apparent requirement that the substituted ammonium cation be included in the final lipid vesicle.

Conflicting claim 1 is drawn to a liposomal irinotecan composition comprising liposomes, sucrose octasulfate, and optionally a substituted ammonium compound.

As such, both the subject matter of instant and conflicting claim 1 is drawn to a liposomal irinotecan composition comprising sucrose octasulfate. As such, the subject matter of conflicting claim 1 effectively anticipates that of instant claim 1, resulting in a prima facie case of anticipatory-type non-statutory double patenting.

Instant claim 1 differs from conflicting claim 1 in that instant claim 1 recites a process by which the claimed composition is prepared in the form of a product-by-process type claim. This process is not recited by the conflicting claims. Nevertheless,

the structure of the conflicting claim appears to anticipate that of the instant claim even though the product of the conflicting claim may have been made in a different manner. Product-by-process claims are not limited to the manipulations of the recited steps, only to the structure implied by the steps. See MPEP 2113.

As to instant claims 2 and 3, conflicting claim 10 teaches various ammonium salts which read on those required by instant claims 2 and 3. The examiner notes that, e.g. triethylammonium of the conflicting claims reads on triethylamine of the instant claims.

As to instant claim 4, this is an independent claim reciting a product comprising the same elements as instant claim 1 (liposome with irinotecan and sucrose octasulfate) but prepared by a different method. As such, claim 4 is a product-by-process claim like claim 1, but the process appears to be slightly different as compared with that of claim 1. As such, this claim is effectively anticipated by the conflicting claims for the same reason that claim 1 is effective anticipated by the conflicting claims, resulting in a prima facie case of anticipatory-type non-statutory double patenting.

As to instant claims 5-7, conflicting claim 10 teaches various ammonium salts which read on those required by instant claims 5-7. The examiner notes that, e.g. triethylammonium of the conflicting claims reads on triethylamine of the instant claims.

As to instant claim 8, the skilled artisan would have understood that the ammonium cation or mono, di, or tri substituted ammonium cations with substituted alkyl groups generally have a pKa in the range of about 9-11. This is within the claimed range. [In contrast, aromatic ammoniums such as protonated aniline or pyridine have a

lower pKa, and quaternary ammoniums do not have a pKa in aqueous solution as they do not include a proton directly bonded to a nitrogen which can be deprotonated].

As to instant claim 9, this claim further limits the process by which the claimed composition is prepared, but not the composition itself. As such, this claim is rejected for the same reason that claims 1 and 4 are rejected. Also see MPEP 2113.

As to instant claim 10, this claim is interpreted as requiring a specific concentration of substituted ammonium compound in the final product. Conflicting claim 1 recites substituted ammonium compound that may be included in the final product, but the conflicting claims are silent to the molar concentration of such substituted ammonium compound. Nevertheless, differences in concentration between the prior art (in this case conflicting claims) and the instant claims will generally not support patentability of the instant claims in the absence of evidence of criticality or unexpected results of the claimed range. As no such evidence of criticality or unexpected results of the claimed range has been presented, claim 10 has been rejected over the conflicting claims. See MPEP 2144.05(II)(A). Also, there is motivation to optimize a result effective variable, and the conflicting claims indicate that the substituted ammonium is result effective in that it is used to cause the result of irinotecan being loaded into the liposome. See MPEP 2144.05(II)(B).

As to instant claim 11, this claim is drawn to an amount of sucrose octasulfate. Although the conflicting claims do not explicitly teach the claimed amount, the teachings of the conflicting claims would have rendered the instant claims obvious for essentially the same reason as in instant claim 10.

As to instant claim 12, this is rejected for the same reason that instant claim 10 is rejected.

As to instant claim 13, this is an independent claim that, similar to claim 4, recites an irinotecan liposome comprising sucrose octasulfate made by a specific process, and is a product-by-process claim. As such, claim 13 is a product-by-process claim like claim 1, but the process appears to be slightly different as compared with that of claim 1. As such, this claim is effectively anticipated by the conflicting claims for the same reason that claim 1 is effective anticipated by the conflicting claims, resulting in a prima facie case of anticipatory-type non-statutory double patenting.

As to instant claim 14, this claim is rejected for the same reason that instant claims 10-12 are rejected.

As to instant claim 15, this is an independent claim comprising a liposome comprising irinotecan and sucrose octasulfate, which is a product-by-process claim. This claim is rejected for the same reason that claims 13, 4, and 1 are rejected, as well as the reasons that claims 2 and 6 are rejected.

As to instant claim 16, this claim is rejected for the same reason that instant claim 9 is rejected.

As to claim 17-20, this claim is rejected for the same reason that claims 3 and 7 are rejected.

Non-Statutory Double Patenting – Patent 8,329,213

Claims 1-20 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-17 of U.S. Patent No. 8,329,213. Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons:

The instant claims are drawn to a liposomal irinotecan composition comprising irinotecan and sucrose octasulfate encapsulated in a lipid vesicle. A process by which the claimed vesicle is made is recited by instant claim 1. This process includes a substituted ammonium cation, though there is no apparent requirement that the substituted ammonium cation be included in the final lipid vesicle.

Conflicting claim 1 is drawn to a liposome comprising sucrose octasulfate and a cationic antineoplastic agent. Said antineoplastic agent is irinotecan, as of conflicting claim 12. As such, the conflicting claims recite a liposome comprising sucrose octasulfate and irinotecan.

As such, both the subject matter of instant and conflicting claim 1 is drawn to a liposomal irinotecan composition comprising sucrose octasulfate. As such, the subject matter of conflicting claim 1 effectively anticipates that of instant claim 1, resulting in a prima facie case of anticipatory-type non-statutory double patenting.

Instant claim 1 differs from conflicting claim 1 in that instant claim 1 recites a process by which the claimed composition is prepared in the form of a product-by-process type claim. This process is not recited by the conflicting claims. Nevertheless, the structure of the conflicting claim appears to anticipate that of the instant claim even though the product of the conflicting claim may have been made in a different manner.

Product-by-process claims are not limited to the manipulations of the recited steps, only to the structure implied by the steps. See MPEP 2113.

Non-Statutory Double Patenting – Patent 8,703,181

Claims 1-20 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-17 of U.S. Patent No. 8,703,181. Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons:

The instant claims are drawn to a liposomal irinotecan composition comprising irinotecan and sucrose octasulfate encapsulated in a lipid vesicle. A process by which the claimed vesicle is made is recited by instant claim 1. This process includes a substituted ammonium cation, though there is no apparent requirement that the substituted ammonium cation be included in the final lipid vesicle.

While the claimed scope of the instant and conflicting claims includes a liposome with irinotecan and sucrose octasulfate, the instant and conflicting claims differ for the following reasons:

(a) the instant claims are drawn to a composition, whereas the conflicting claims are drawn to a method for delivering an antineoplastic agent to a tumor; and

(b) the instant claims recite that the liposome is prepared in a specific manner, which is not recited by the conflicting claims.

With regard to part (a) above, the composition used in the method of the conflicting claims appears to include the same elements as that of the instant claims (i.e. a liposome comprising irinotecan and sucrose octasulfate). In view of this, there appears to be a case of anticipatory-type non-statutory double patenting.

With regard to part (b) above, instant claim 1 differs from conflicting claim 1 in that instant claim 1 recites a process by which the claimed composition is prepared in the form of a product-by-process type claim. This process is not recited by the conflicting claims. Nevertheless, the structure of the conflicting claim appears to anticipate that of the instant claim even though the product of the conflicting claim may have been made in a different manner. Product-by-process claims are not limited to the manipulations of the recited steps, only to the structure implied by the steps. See MPEP 2113.

Non-Statutory Double Patenting – Patent 8,992,970

Claims 1-20 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 8,992,970. Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons:

The instant claims are drawn to a liposomal irinotecan composition comprising irinotecan and sucrose octasulfate encapsulated in a lipid vesicle. A process by which the claimed vesicle is made is recited by instant claim 1. This process includes a

substituted ammonium cation, though there is no apparent requirement that the substituted ammonium cation be included in the final lipid vesicle.

The conflicting claims are drawn to a liposomal composition comprising irinotecan and sucrose octasulfate, and optionally a substituted ammonium compound, as of conflicting claim 1.

The instant claims and conflicting claims differ because the conflicting claims specify various lipids to be present in the liposome, which is not specified by the instant claims. Nevertheless, the conflicting claims appear to delineate the claimed subject matter in greater detail than the instant claims. As such, the subject matter of the conflicting claims is within the scope of that of the instant claims, resulting in a prima facie case of anticipatory-type non-statutory double patenting.

The instant and conflicting claims differ in that instant claim 1 recites a process by which the claimed composition is prepared in the form of a product-by-process type claim. This process is not recited by the conflicting claims. Nevertheless, the structure of the conflicting claim appears to anticipate that of the instant claim even though the product of the conflicting claim may have been made in a different manner. Product-by-process claims are not limited to the manipulations of the recited steps, only to the structure implied by the steps. See MPEP 2113.

Provisional Non-Statutory Double Patenting – Application 14/632,422

Claims 1-20 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-23 of copending Application No. 14/632,422 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons:

The instant claims are drawn to a liposomal irinotecan composition comprising irinotecan and sucrose octasulfate encapsulated in a lipid vesicle. A process by which the claimed vesicle is made is recited by instant claim 1. This process includes a substituted ammonium cation, though there is no apparent requirement that the substituted ammonium cation be included in the final lipid vesicle.

The copending claims 1-20 are drawn to a method for preparing a liposome comprising a cationic antineoplastic agent. This agent may be irinotecan, as of copending claims 11 and 12.

As best understood, while the process of the copending claims and that recited in the instant claims are not necessarily the same process. Nevertheless, the liposome of instant claim 1 appears to be the same as the liposome prepared by the method of copending claim 12. As such, the structure made by the method of the copending claim appears to anticipate that of the instant claim even though the product of the copending claim may have been made in a different manner. Product-by-process claims are not limited to the manipulations of the recited steps, only to the structure implied by the steps. See MPEP 2113.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Provisional Non-Statutory Double Patenting – Application 14/879,358

Claims 1-20 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-20 of copending Application No. 14/879,358 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons:

The instant claims are drawn to a liposomal irinotecan composition comprising irinotecan and sucrose octasulfate encapsulated in a lipid vesicle. A process by which the claimed vesicle is made is recited by instant claim 1. This process includes a substituted ammonium cation, though there is no apparent requirement that the substituted ammonium cation be included in the final lipid vesicle.

The copending claims are drawn to a liposome comprising irinotecan and sucrose octasulfate.

The instant and copending claims differ because the instant claims are product-by-process claims reciting the process by which the claimed composition is formed, whereas the copending claims do not recite such a process. Nevertheless, the liposome of instant claim 1 appears to be the same as the liposome prepared by the method of copending claim 12. As such, the structure made by the method of the copending claim

appears to anticipate that of the instant claim even though the product of the copending claim may have been made in a different manner, resulting in a prima facie case of anticipatory-type non-statutory double patenting. Product-by-process claims are not limited to the manipulations of the recited steps, only to the structure implied by the steps. See MPEP 2113.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Provisional Non-Statutory Double Patenting – Application 14/966,458

Claims 1-20 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-16 of copending Application No. 14/966,458 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons:

The instant claims are drawn to a liposomal irinotecan composition comprising irinotecan and sucrose octasulfate encapsulated in a lipid vesicle. A process by which the claimed vesicle is made is recited by instant claim 1. This process includes a substituted ammonium cation, though there is no apparent requirement that the substituted ammonium cation be included in the final lipid vesicle.

Copending claim 1 is also a product-by-process claim, drawn to an irinotecan liposome comprising a sulfate sugar made by a specific process.

The process used to make the composition of instant claim 1 appears to be the same as the process used to make the composition of copending claim 1.

The instant and copending claims differ because instant claim 1 recites sucrose octasulfate, whereas copending claim 1 recites a sulfate sugar, which is a class of molecules that includes a sucrose octasulfate. However, copending claim 5 recites sucrose octasulfate specifically as one of a choice of various sulfated sugars. As such, copending claim 1 appears to effectively anticipate instant claim 1, resulting in a prima facie case of anticipatory-type non-statutory double patenting.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ISAAC SHOMER whose telephone number is (571)270-7671. The examiner can normally be reached on 8:00 AM - 5:00 PM Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick F. Krass can be reached on (571)272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/ISAAC SHOMER/
Primary Examiner, Art Unit 1612

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/965,140	12/10/2015	Keelung Hong	239669-373915/1001130US10	8650

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Honigman Miller Schwartz and Cohn LLP
350 East Michigan Avenue
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EXAMINER	
SHOMER, ISAAC	

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
07/13/2016	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@honigman.com
fhunter@honigman.com

Examiner-Initiated Interview Summary	Application No.	Applicant(s)	
	14/965,140	HONG ET AL.	
	Examiner	Art Unit	
	ISAAC SHOMER	1612	

All participants (applicant, applicant's representative, PTO personnel):

(1) *ISAAC SHOMER*. (3)_____.

(2) *Meghan Klaric*. (4)_____.

Date of Interview: *16 June 2016*.

Type: ☒ Telephonic ☐ Video Conference
☐ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☒ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☐102 ☐103 ☒Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: *1-9,13,14 and 21-30*.

Identification of prior art discussed: *US Patent 8,658,203*.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

Examiner contacted representative of applicant to request that a terminal disclaimer be filed over the claims of US Patent 8,658,203. This is because the examiner took the position that there is a double patenting rejection is appropriate over the claims of this patent. As no such terminal disclaimer has been filed after 3 weeks, the examiner has issued a non-final office action setting forth the double patneting rejection over the claims of US patent 8,658,203. As such, this interview summary has been attached to a non-final office action.

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☒ Attachment

/ISAAC SHOMER/
Primary Examiner, Art Unit 1612

Office Action Summary	Application No. 14/965,140	Applicant(s) HONG ET AL.	
	Examiner ISAAC SHOMER	Art Unit 1612	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *1 June 2016*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *1-9,13,14 and 21-30* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-9,13,14 and 21-30* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

4) ☐ Other: _____.

DETAILED ACTION

Applicants' arguments, filed 1 June 2016, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

The present application is being examined under the pre-AIA first to invent provisions.

Claim Objections

Claim 2 is objected to because of the following informalities: Claim 2 includes a list of various amines. However, this list includes extra unnecessary commas (e.g. as of the 6th line of the claim). This appears to be grammatically incorrect.

Claim Rejections - 35 USC § 112(b) – Indefiniteness

The following is a quotation of 35 U.S.C. 112(b):
(b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 22, 24, and 26 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and

distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.

Claims 22, 24, and 26 recite “about 500-550 irinotecan base.” This is indefinite because there are no units after “about 500-550 irinotecan base” so it is unclear how these numbers further limit the scope of the claim. For the purpose of examination under prior art, the examiner assumes that the claim recites about 500-550 mg of irinotecan per mmol of phospholipid (or 500-550 grams of irinotecan per gram of phospholipid) as this is recited in claim 1.

Non-Statutory Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(1) - 706.02(l)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

Claims 1-3, 9, 13, 14, and 27-30 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-22 of U.S. Patent No. 8,658,203.

Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons:

Instant claim 1 is drawn to an irinotecan liposome comprising irinotecan base, sucrose octasulfate, and a substituted ammonium cation. Irinotecan is present in an amount of 150-550 mg of irinotecan base per mmol of total vesicle phospholipids.

Conflicting claim 1 is drawn to a method of treating a brain tumor by administering a liposomal formulation. Said liposomal formulation may include irinotecan, sucrose octasulfate, and a substituted ammonium compound, as of part “2” of conflicting claim 1. Said irinotecan is entrapped in an amount of 500 grams per mol of phospholipid, which is the same as 500 mg irinotecan per mmol of phospholipid.

The instant and conflicting claims differ because the instant claims are composition claims, whereas the conflicting claims are method claims. Nevertheless, the composition used in the method of the conflicting claims includes the same elements as the composition of the instant claims. As such, the composition used in the method of the conflicting claims appears to effectively anticipate that of the instant claims, resulting in a prima facie case of non-statutory double patenting.

As to instant claim 1, the examiner notes that this claim is a product-by-process claim. The conflicting claims are drawn to a method of using a composition, and do not recite specific process steps drawn to how the composition is made. Nevertheless, the composition used in the method of the conflicting claims appears to include the same elements as that of the instant claims, resulting in a prima facie case of non-statutory double patenting. See MPEP 2113 regarding product by process claims.

As to instant claim 1, the claim requires that at least 85% of the irinotecan is loaded into the lipid vesicle. This is understood to further limit a process step by which the claimed composition is made, and not the composition itself. As such, the reasoning regarding product-by-process claims applies with regard to this limitation.

As to instant claim 1, the claim recites irinotecan base. In contrast, the conflicting application recites "irinotecan." However, irinotecan itself is understood to be basic. As the conflicting claims recite “irinotecan” instead of protonated irinotecan, the composition used in the method of the conflicting claims is understood to include irinotecan in the form of a base.

As to instant claim 2, the claim recites various substituted ammonium salts, which are recited in conflicting claim 9.

As to instant claim 3, triethylammonium (e.g. the ammonium cation of trimethylamine) is recited by conflicting claim 10.

As to instant claim 9, the reasoning regarding product-by-process claims set forth above regarding claim 1 also applies to claim 9.

As to instant claims 13 and 14, the reasoning regarding product-by-process claims set forth above regarding claim 1 also applies to claims 13 and 14.

As to instant claim 27, the reasoning regarding product-by-process claims set forth above regarding claim 1 also applies to claims 27

As to instant claims 28 and 29, conflicting claims 9 and 10 teach the required ammonium cation of triethylammonium (which is the cationic salt of trimethylamine).

As to instant claim 30, this claim is rejected for the same reason that claims 1 and 27 are rejected.

Claims 4-8 and 21-26 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-22 of U.S. Patent No. 8,658,203 in view of Allen et al. (US 2001/0038851 A1).

Instant claim 1 is drawn to an irinotecan liposome comprising irinotecan base, sucrose octasulfate, and a substituted ammonium cation. Irinotecan is present in an amount of 150-550 mg of irinotecan base per mmol of total vesicle phospholipids. Instant claim 4 further requires the lipids distearoyl phosphatidylcholine (DSPC) and cholesterol to be present in a 3:2 molar ratio.

The conflicting claims are drawn to a method of using a liposome comprising irinotecan, sucrose octasulfate, and a substituted ammonium compound.

The conflicting claims do not teach DSPC and cholesterol as liposome lipids.

Allen et al. (hereafter referred to as Allen) is drawn to a therapeutic liposome, as of Allen, title and abstract. Said liposome may deliver irinotecan, as of Allen, paragraph 0021. Liposomes of Allen include DSPC, as of Allen, paragraph 0061, and cholesterol, as of Allen, paragraph 0058. The molar ratio of phosphatidylcholine to cholesterol appears to be about 55:40, as of Allen, paragraph 0095 - this is about a 2.75:2 molar ratio.

Allen does not teach sucrose octasulfate.

It would have been prima facie obvious for one of ordinary skill in the art to have included DSPC and cholesterol as lipids in the liposome used in the method of the conflicting claims. The method of the conflicting claims utilizes a liposome comprising irinotecan, but is silent as to the lipid composition of the liposome. As DSPC and cholesterol are well known lipids used in liposomes that deliver irinotecan, the skilled artisan would have been motivated to have used DSPC and cholesterol in the liposome used in the method of the conflicting claims to predictably deliver irinotecan with a reasonable expectation of success. Generally, it is *prima facie* obvious to select a known material (DSPC and cholesterol) for incorporation into a composition (that which is used in the method of the conflicting claims), based on its recognized suitability for its intended use (to produce structure in a liposome). See MPEP 2144.07.

As to instant claim 4, the claim requires a 3:2 molar ratio of DSCP to cholesterol. The ratio of the conflicting claims is slightly different at 55:40, which is 2.75:2. Nevertheless, this difference fails to overcome the case of obviousness-type non-statutory double patenting. Generally, differences in concentration will not support patentability of subject matter encompassed by the prior art unless there is evidence that such concentration is critical, and in this case, such evidence does not appear to be present. See MPEP 2144.05(II)(A).

As to instant claims 5-8, the ammonium salts of conflicting claims 9 and 10 are understood to read on the additional requirement of these claims.

As to instant claim 21, while the conflicting claims are silent with respect to the liposome size, Allen teaches liposomes sized from 92-111 nm, as of Allen, paragraph

0127. This overlaps with the claimed size range, resulting in a prima facie case of obviousness, and therefore, a prima facie case of obviousness-type non-statutory double patenting. See MPEP 2144.05(I).

As to claim 22, conflicting claim 3 recites 500 grams of irinotecan per mole of phospholipid, which is understood to read on the additional requirement of this claim.

As to instant claim 23, this claim is rejected for the same reason that claim 21 is rejected.

As to instant claim 24, this claim is rejected for the same reason that claim 22 is rejected.

As to instant claim 25, this claim is rejected for the same reason that claim 21 is rejected.

As to instant claim 26, this claim is rejected for the same reason that claim 22 is rejected.

Table of Conflicting Issued Patents

Instant Case	Patent	Double Patenting?	TD Filed?
14/965,140	8,147,867	T.D. Already Filed	yes
14/965,140	8,329,213	T.D. Already Filed	yes
14/965,140	**8,658,203**	**Yes – see rejection above**	**no**
14/965,140	8,703,181	T.D. Already Filed	yes
14/965,140	8,992,870	T.D. Already Filed	yes

Table of Copending Applications – Case 14/965,140

Instant Case	Application	Double Patenting?	TD Filed?
14/965,140	14/151,632	No – Copending Claims are drawn to catheter	
14/965,140	14/632,422	T.D. Already Filed	yes
14/965,140	14/879,302	No- copending claims do not require substituted ammonium cation	
14/965,140	14/879,358	T.D. Already Filed	yes
14/965,140	14/964,239	No – Case drawn to polyphosphorylated polyol, not sucrose octasulfate	
14/965,140	14/965,140	No – same case	
14/965,140	14/966,458	T.D. Already Filed	yes
14/965,140	14/979,666	No – Case drawn to docetaxel, not irinotecan	

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ISAAC SHOMER whose telephone number is (571)270-7671. The examiner can normally be reached on 8:00 AM - 5:00 PM Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick F. Krass can be reached on (571)272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/ISAAC SHOMER/
Primary Examiner, Art Unit 1612

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/965,140	12/10/2015	Keelung Hong	239669-373915/1001130US10	8650

133156 7590 12/19/2016

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EXAMINER	
SHOMER, ISAAC	

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
12/19/2016	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No. 14/965,140	Applicant(s) HONG ET AL.	
	Examiner ISAAC SHOMER	Art Unit 1612	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *6 December 2016*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *1* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

4) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after allowance or after an Office action under *Ex Parte Quayle*, 25 USPQ 74, 453 O.G. 213 (Comm'r Pat. 1935). Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, prosecution in this application has been reopened pursuant to 37 CFR 1.114.

Applicant's submission filed on 6 December 2016 has been entered, and the arguments presented therein have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

The present application is being examined under the pre-AIA first to invent provisions.

Information Disclosure Statement

The information disclosure statement submitted with the RCE on 6 December 2016 has been considered. In the case of non-patent literature references #4 and #5, these references are not in English with the apparent exception of the abstract. As such, the examiner has marked on the reference that only the English abstract has been considered.

Non-Statutory Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(1) - 706.02(l)(3) for applications not subject to examination under the first inventor to file

provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

Claim 1 is provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claim 1 of copending Application No. 15/296,536 (reference application) in view of Berge et al. (Journal of Pharmaceutical Sciences, Vol. 66 No. 1, January 1977, pages 1-19).

Instant claim 1 is drawn to an irinotecan liposome comprising irinotecan and sucrose octasulfate with a specific concentration of irinotecan being encapsulated of 150-550 mg per mmol of liposome phospholipids.

Copending claim 1 is drawn to an injectable pharmaceutical composition comprising irinotecan sucrose octasulfate encapsulated in a liposome at a concentration of 500-550 mg of irinotecan hydrochloride per mmol of vesicle phospholipids.

The instant and copending claims differ because the instant claims are drawn to irinotecan base whereas the copending claims are drawn to irinotecan hydrochloride.

Berge et al. (hereafter referred to as Berge) is a review article drawn to pharmaceutical salts, as of Berge, page 1. Berge teaches that compounds that exhibit acid or base characteristics can participate in salt formation, as of Berge, page 2, left column, first paragraph in section entitled "potentially useful salts." Berge teaches that hydrochloride is a well-known anion for pharmaceutical salts, as of Berge, page 2, Table I. Berge teaches the existence of a hydrochloride salt and free base as of Berge, page 7, left column, first full paragraph.

It would have been prima facie obvious for one of ordinary skill in the art to have substituted irinotecan free base in place of the irinotecan hydrochloride used in the copending claims. Berge teaches that both a hydrochloride salt and a free base form are known forms of basic pharmaceuticals. As such, the skilled artisan would have been motivated to have substituted irinotecan in the free base form in place of irinotecan in the hydrochloride salt form for predictable administration for pharmaceutical purposes with a reasonable expectation of success. The simple substitution of one known element (irinotecan free base) in place of another (irinotecan hydrochloride) to achieve predictable results (the pharmaceutical effect of irinotecan) is prima facie obvious. See MPEP 2143, Exemplary Rationale B.

Copending claim 1 includes specific recitations not included in instant claim 1, such as specific liposome lipids and a more specific ratio of iriontecan per liposome lipids. Nevertheless, the recitations of copending claim 1 are within the scope of those

of instant claim 1 with the exception of the difference between irinotecan hydrochloride and irinotecan free base discussed above. As such, the limitations of instant claim 1 are rendered obvious by those of copending claim 1 after the modification of Berge has been made.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

The examiner further notes that MPEP 804(I)(B)(1) states the following:

> If a "provisional" nonstatutory double patenting rejection is the only rejection remaining in an application having the earliest effective U.S. filing date (including any benefit claimed under 35 U.S.C. 120, 121, 365(c), or 386(c)) [but not provisional applications under 35 U.S.C. 119(e)] compared to the reference application(s), the examiner should withdraw the rejection in the application having the earliest effective U.S. filing date and permit that application to issue as a patent, thereby converting the "provisional" nonstatutory double patenting rejection in the other application(s) into a nonstatutory double patenting rejection when the application with the earliest U.S. effective filing date issues as a patent.

However, this section of the MPEP also states the following:

> If a "provisional" nonstatutory double patenting rejection is the only rejection remaining in an application, and that application has an effective U.S. filing date (including any benefit claimed under 35 U.S.C. 120, 121, 365(c), or 386(c)) that is later than, or the same as, the effective U.S. filing date of at least one of the reference application(s), the rejection should be maintained until applicant overcomes the rejection. In accordance with 37 CFR 1.111(b), applicant's reply must present arguments pointing out the specific distinctions believed to render the claims, including any newly presented claims, patentable over any applied references. Alternatively, a reply that includes the filing of a compliant terminal disclaimer in the later-filed application under 37 CFR 1.321 will overcome a nonstatutory double patenting rejection and is a sufficient reply pursuant to 37 CFR 1.111(b).

> Upon the filing of a compliant terminal disclaimer in a pending application, the nonstatutory double patenting rejection will be withdrawn in that application.

In this case, both instant and copending applications claim benefit back to prior application 11/121,294. As such, both the instant and copending claims are understood to have the same effective filing date. As such, this double patenting rejection applied herein is not withdrawn.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ISAAC SHOMER whose telephone number is (571)270-7671. The examiner can normally be reached on 8:00 AM - 5:00 PM Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick F. Krass can be reached on (571)272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/ISAAC SHOMER/
Primary Examiner, Art Unit 1612

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/966,458	12/11/2015	Keelung Hong	239669-379238/1001130US14	6467

133156 7590 12/06/2016

Honigman Miller Schwartz and Cohn LLP
350 East Michigan Avenue
Suite 300
Kalamazoo, MI 49007

EXAMINER	
SHOMER, ISAAC	

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
12/06/2016	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@honigman.com
arhoades@honigman.com

Office Action Summary	Application No. 14/966,458	Applicant(s) HONG ET AL.	
	Examiner ISAAC SHOMER	Art Unit 1612	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *1-16* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-16* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

4) ☐ Other: _____.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

The present application is being examined under the pre-AIA first to invent provisions.

In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

Note Regarding Claim Interpretation

Instant claim 1 is drawn to a composition comprising an irinotecan liposome with a sulfated sugar. The examiner makes the following two points regarding interpretation of claim 1.

Sulfated Sugar: As best understood by the examiner, the term “sulfated sugar” refers to both sulfated monosaccharides and sulfated polysaccharides, and will be interpreted in this manner.

Product-by-Process: The instant claims are composition claims but recite a method by which the claimed invention is made. This method includes the use of diethylammonium or triethylammonium. As best understood by the examiner, diethylammonium or triethylammonium appear to be used as vehicles to help load the composition, but the claim does not clearly indicate that these components are present

in the final composition. As such, the claims will be examined as if these components are not required to be present in the final composition.

Claim Rejections - 35 USC § 102(a) – Anticipation

The following is a quotation of the appropriate paragraphs of pre-AIA 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claim(s) 1 and 2 is/are rejected under pre-AIA 35 U.S.C. 102(a) as being anticipated by Chou et al. (Journal of Bioscience and Bioengineering, Vol. 95, No. 4, 2003, pages 405-408).

Chou et al. (hereafter referred to as Chou) is drawn to liposomal irinotecan prepared by pH gradient loading, as of Chou, page 405, title and abstract. Liposome lipids include distearoyl phosphatidyl choline (DSPC), soy phosphatidylcholine, and dextran sulfate, which reads on the required sulfated sugar. Chou teaches uptake ratios of over 90% in some embodiments, as of Chou, page 406, left column, Table 1.

As to claim 1, instant claim 1 recites a specific process by which the instantly claimed composition is made. Chou teaches that the claimed composition is made by a process that includes gradient loading, as of Chou, page 405, title and abstract. While Chou does not explicitly teach loading with diethylammonium or triethylammonium, the examiner takes the position that these compounds are part of the process by which the claimed product was made, but not part of the claimed product itself. As such, the

composition of Chou includes all of the elements recited by the instant claims as part of the final product. Product-by-process claims are not limited to the manipulations of the recited steps (e.g. loading with diethylammonium or triethylammonium), only to the structure implied by the steps. See MPEP 2113(I).

As to claim 2, dextran sulfate is understood to have a pKa of 3 or less.

This rejection does not apply to claim 4 because Chou appears to show retention of only about a maximum of 30% or 40% of active agent after 2 hours, as of Chou, page 407, right column, Figure 4. This is less than 70% retention of active agent after 8 hours.

Claim Rejections - 35 USC § 103 – Obviousness

The following is a quotation of pre-AIA 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under pre-AIA 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under pre-AIA 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of pre-AIA 35 U.S.C. 103(c) and potential pre-AIA 35 U.S.C. 102(e), (f) or (g) prior art under pre-AIA 35 U.S.C. 103(a).

Claims 1-3 and 12-14 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Chou et al. (Journal of Bioscience and Bioengineering, Vol. 95, No. 4, 2003, pages 405-408) in view of Hu et al. (WO 2004/047801 A2).

Chou et al. (hereafter referred to as Chou) is drawn to liposomal irinotecan prepared by pH gradient loading, as of Chou, page 405, title and abstract. Liposome lipids include distearoyl phosphatidyl choline (DSPC), soy phosphatidylcholine, and dextran sulfate, which reads on the required sulfated sugar.

For the purposes of this rejection, it is understood that Chou does not teach diethylammonium and/or triethylammonium.

Hu et al. (hereafter referred to as Hu) is drawn to a method of loading drug into a liposome by gradient, as of Hu, title and abstract. Hu teaches the use of ammonium salts of citrate and sulfate to make the gradient, as of Hu, page 6, lines 1-9. Elsewhere in the document, Hu teaches diethylamine and salts thereof for making a gradient, as of Hu, page 15, line 16. The salts of diethylamine are understood to be diethylammonium salts.

While Hu teaches ammonium sulfate, Hu does not teach a sulfate sugar.

It would have been prima facie obvious for one of ordinary skill in the art to have loaded the liposome of Chou using the diethylammonium gradients of Hu. Chou is drawn to an irinotecan liposome that is loaded by a gradient. As Hu teaches that diethylammonium (referred to as diethylamine) is a known way to load a liposome, the skilled artisan would have been motivated to have loaded the liposome of Chou using the gradient system of Hu for predictable loading of an active agent such as irinotecan with a reasonable expectation of success. Generally, it is *prima facie* obvious to select a known material (diethylamine or diethylammonium) for incorporation into a composition (the liposome of Chou), based on its recognized suitability for its intended use (gradient loading of liposomes). See MPEP 2144.07.

As to claim 2, dextran sulfate is understood to have a pKa of 3 or less.

As to claim 3, Chou teaches a ratio of DSPC to cholesterol of 100:30, as of Chou, page 407, left column, figure 2. As best understood by the examiner, this is mass ratio. DSPC has a molecular weight of about 790 Daltons, and cholesterol has a molecular weight of about 386.5 Daltons. As such, a mass ratio of 100:30 (3.33) is

understood to be a molar ratio of about 1.63:1 of DSPC to cholesterol. This is slightly greater than the required 3:2 ratio (1.5:1) of DSPC to cholesterol. Nevertheless, generally, differences in concentration (e.g. of DSPC and cholesterol) will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating that such concentration is critical. See MPEP 2144.05(II)(A). As no evidence has been presented so far that a molar ratio difference between 1.5:1 and 1.63:1 of DSPC to cholesterol is critical, this rejection applies to claim 3. Additionally, the concentrations of DSPC and cholesterol and understood to be result-effective variables because these components effect the results of structural stability of the liposome, as they are the primary structural components of the liposome's bilayers.

As to claims 12-14, Chou does not teach the explicit recited concentration of dextran sulfate, nor does Hu teach the explicit recited concentration of diethylammonium. Nevertheless, generally, differences in concentration (e.g. of DSPC and cholesterol) will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating that such concentration is critical. See MPEP 2144.05(II)(A). As no evidence has been presented so far of criticality of these concentrations, this rejection is applied to claims 12 and 13. Dextran sulfate is understood to be a result-effective variable as it affects the result of drug retention, as of Chou, page 405, last sentence of abstract. Diethylamine (i.e. diethylammonium) is understood to be a result-effective variable as the presence of an ammonium salt or substituted ammonium salt affects loading of a drug into the liposome, as taught by Hu.

This rejection does not apply to claim 4 because Chou appears to show retention of only about a maximum of 30% or 40% of active agent after 2 hours, as of Chou, page 407, right column, Figure 4. This is less than 70% retention of active agent after 8 hours. Nothing taught by Hu indicates that a longer retention would have been expected from using diethylamine to load the liposome.

Note Regarding Reference Date: The instant application has an earliest effective filing date of 3 May 2004. Hu was published on 10 June 2004, which is later than the earliest effective filing date. Nevertheless, Hu is an international patent application that is written in English after 29 November 2000 and designates the United States. As such, the filing date of Hu is relevant regarding 35 U.S.C. 102(e). See MPEP 2136.03(II)(A). Hu has an international filing date of 26 November 2003 and claims benefit of provisional application 60/429,122, filed on 26 November 2002, both of which are earlier than the instant filing date. As Hu does not have the same inventive entity as the instant application, Hu is therefore understood to be prior art under 35 U.S.C. 102(e).

Non-Statutory Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double

patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(1) - 706.02(l)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may

be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

Prior to setting forth the grounds of rejection, the examiner has provided the following table regarding the conflicting patents and relevant copending applications.

Table of Conflicting Patents and Allowed Applications

Instant Case	**Conflicting Patent**	**Double Patenting?**
14/966,458	8,147,867	Yes
14/966,458	8,329,213	Yes
14/966,458	8,703,181	Yes
14/966,458	8,992,970	Yes
14/966,458	8,658,203	Yes
14/966,458	14/879,358 (allowed)	Yes
14/966,458	14/965,140 (allowed)	Yes

Table of Copending Applications

Instant Case	**Copending Case**	**Double Patenting?**
14/966,458	14/632,422	Yes
14/966,458	14/151,632	Yes
14/966,458	15/213,127	Yes
14/966,458	14/879,302	Yes
14/966,458	14/964,239	No because copending claims do not teach sulfated sugar and teach a polyphosphorylated polyol instead
14/966,458	14/966,458	No (same case)
14/966,458	14/979,666	No, because copending claims do not teach irinotecan and teach docetaxel instead
14/966,458	14/181,583	Yes (copending claim 16)
14/966,458	15/227,631	Yes
14/966,458	15/227,561	Yes
14/996,458	15/296,536	Yes

Claims 1-16 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-35 of U.S. Patent No. 8,147,867. Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons:

Instant claim 1 is drawn to an irinotecan liposome composition comprising irinotecan and a sulfated sugar. A specific product by process is recited in the instant claims. A substituted ammonium is included in the process of making the product but not necessarily in the product itself. Instant claim 6 recites that the sulfated sugar is sucrose octasulfate.

Conflicting claim 1 is drawn to a liposomal irinotecan composition comprising a liposome with irinotecan, sucrose octasulfate, and optionally a substituted ammonium compound.

The conflicting claims differ from instant claim 1 because the conflicting claims recite sucrose octasulfate, whereas instant claim 1 is drawn to a sulfated sugar. Nevertheless, sucrose octasulfate is within the scope of the required sulfated sugar. As such, the embodiment of conflicting claim 1 is within the scope of that of instant claim 1, resulting in a prima facie case of anticipatory-type non-statutory double patenting.

The conflicting claims differ from instant claim 1 because the conflicting claims do not recite the product-by-process of the instant claims. Nevertheless, when it comes to product-by-process limitations, the instant claims are not limited to the manipulations of the recited steps, only to the structure implied by the steps. As the compositions of the

instant and conflicting claims both include a liposome comprising irinotecan and sucrose octasulfate, this composition of the conflicting claim is understood to be within the scope of the instantly claimed composition.

Claims 1-16 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-17 of U.S. Patent No. 8,329,213. Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons:

Instant claim 1 is drawn to an irinotecan liposome composition comprising irinotecan and a sulfated sugar. A specific product by process is recited in the instant claims. A substituted ammonium is included in the process of making the product but not necessarily in the product itself. Instant claim 6 recites that the sulfated sugar is sucrose octasulfate.

Conflicting claim 1 is drawn to a liposome comprising sucrose octasulfate and a cationic antineoplastic agent. The cationic antineoplastic agent may be sucrose octasulfate, as of conflicting claim 11.

The conflicting claims differ from instant claim 1 because the conflicting claims recite sucrose octasulfate, whereas instant claim 1 is drawn to a sulfated sugar. Nevertheless, sucrose octasulfate is within the scope of the required sulfated sugar. As such, the embodiment of conflicting claim 1 is within the scope of that of instant claim 1, resulting in a prima facie case of anticipatory-type non-statutory double patenting.

The conflicting claims differ from instant claim 1 because the conflicting claims do not recite the product-by-process of the instant claims. Nevertheless, when it comes to product-by-process limitations, the instant claims are not limited to the manipulations of the recited steps, only to the structure implied by the steps. As the compositions of the instant and conflicting claims both include a liposome comprising irinotecan and sucrose octasulfate, this composition of the conflicting claim is understood to be within the scope of the instantly claimed composition.

Claims 1-16 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-17 of U.S. Patent No. 8,703,181. Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons:

Instant claim 1 is drawn to an irinotecan liposome composition comprising irinotecan and a sulfated sugar. A specific product by process is recited in the instant claims. A substituted ammonium is included in the process of making the product but not necessarily in the product itself. Instant claim 6 recites that the sulfated sugar is sucrose octasulfate.

Conflicting claim 1 is drawn to a method of delivering an antineoplastic agent to a tumor, wherein the antineoplastic agent is cationic and is in a liposome with sucrose octasulfate. The antineoplastic agent may be irinotecan, as of conflicting claim 11.

The conflicting claims differ from instant claim 1 because the conflicting claims recite sucrose octasulfate, whereas instant claim 1 is drawn to a sulfated sugar. Nevertheless, sucrose octasulfate is within the scope of the required sulfated sugar. As such, the embodiment of conflicting claim 1 is within the scope of that of instant claim 1, resulting in a prima facie case of anticipatory-type non-statutory double patenting.

The conflicting claims differ from the instant claims because the conflicting claims are drawn to method of use claims, whereas the instant claims are composition claims. Nevertheless, the composition used in the method of the conflicting claims is a liposome comprising sucrose octasulfate and irinotecan, which is the same product as that of the instant claims. As such, this difference between composition and method claims is insufficient to overcome the applied rejection.

The conflicting claims differ from instant claim 1 because the conflicting claims do not recite the product-by-process of the instant claims. Nevertheless, when it comes to product-by-process limitations, the instant claims are not limited to the manipulations of the recited steps, only to the structure implied by the steps. As the compositions of the instant and conflicting claims both include a liposome comprising irinotecan and sucrose octasulfate, this composition of the conflicting claim is understood to be within the scope of the instantly claimed composition.

Claims 1-16 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 8,992,970. Although the

claims at issue are not identical, they are not patentably distinct from each other because of the following reasons:

Instant claim 1 is drawn to an irinotecan liposome composition comprising irinotecan and a sulfated sugar. A specific product by process is recited in the instant claims. A substituted ammonium is included in the process of making the product but not necessarily in the product itself. Instant claim 6 recites that the sulfated sugar is sucrose octasulfate.

Conflicting claim 1 is drawn to a liposome comprising irinotecan and sucrose octasulfate. Specific lipids are recited such as phosphatidylcholine and phosphatidylethanolamine, which are well known lipids used in liposomes.

The conflicting claims differ from instant claim 1 because the conflicting claims recite sucrose octasulfate, whereas instant claim 1 is drawn to a sulfated sugar. Nevertheless, sucrose octasulfate is within the scope of the required sulfated sugar. As such, the embodiment of conflicting claim 1 is within the scope of that of instant claim 1, resulting in a prima facie case of anticipatory-type non-statutory double patenting.

The conflicting claims differ from instant claim 1 because the conflicting claims do not recite the product-by-process of the instant claims. Nevertheless, when it comes to product-by-process limitations, the instant claims are not limited to the manipulations of the recited steps, only to the structure implied by the steps. As the compositions of the instant and conflicting claims both include a liposome comprising irinotecan and sucrose octasulfate, this composition of the conflicting claim is understood to be within the scope of the instantly claimed composition.

Claims 1-16 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-22 of U.S. Patent No. 8,658,203. Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons:

Instant claim 1 is drawn to an irinotecan liposome composition comprising irinotecan and a sulfated sugar. A specific product by process is recited in the instant claims. A substituted ammonium is included in the process of making the product but not necessarily in the product itself. Instant claim 6 recites that the sulfated sugar is sucrose octasulfate.

Conflicting claim 1 is drawn to a method of treating a brain tumor. The method of the conflicting claims utilizes a liposome with sucrose octasulfate.

The conflicting claims differ from instant claim 1 because the conflicting claims recite sucrose octasulfate, whereas instant claim 1 is drawn to a sulfated sugar. Nevertheless, sucrose octasulfate is within the scope of the required sulfated sugar. As such, the embodiment of conflicting claim 1 is within the scope of that of instant claim 1, resulting in a prima facie case of anticipatory-type non-statutory double patenting.

The conflicting claims differ from the instant claims because the conflicting claims are drawn to method of use claims, whereas the instant claims are composition claims. Nevertheless, the composition used in the method of the conflicting claims is a liposome comprising sucrose octasulfate and irinotecan, which is the same product as that of the

instant claims. As such, this difference between composition and method claims is insufficient to overcome the applied rejection.

The conflicting claims differ from instant claim 1 because the conflicting claims do not recite the product-by-process of the instant claims. Nevertheless, when it comes to product-by-process limitations, the instant claims are not limited to the manipulations of the recited steps, only to the structure implied by the steps. As the compositions of the instant and conflicting claims both include a liposome comprising irinotecan and sucrose octasulfate, this composition of the conflicting claim is understood to be within the scope of the instantly claimed composition.

Claims 1-16 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1, 7-10, 12, 14-17, 19, 23, 24, 26, and 28-34 of copending Application No. 14/879,358 (reference application – currently allowed). Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons:

Instant claim 1 is drawn to an irinotecan liposome composition comprising irinotecan and a sulfated sugar. A specific product by process is recited in the instant claims. A substituted ammonium is included in the process of making the product but not necessarily in the product itself. Instant claim 6 recites that the sulfated sugar is sucrose octasulfate.

Copending claim 1 is drawn to a composition comprising irinotecan and sucrose octasulfate in a liposome, with a specific amount of irinotecan encapsulated.

The copending claims differ from instant claim 1 because the copending claims recite sucrose octasulfate, whereas instant claim 1 is drawn to a sulfated sugar. Nevertheless, sucrose octasulfate is within the scope of the required sulfated sugar. As such, the embodiment of copending claim 1 is within the scope of that of instant claim 1, resulting in a prima facie case of anticipatory-type non-statutory double patenting.

The copending claims differ from instant claim 1 because the copending claims do not recite the product-by-process of the instant claims. Nevertheless, when it comes to product-by-process limitations, the instant claims are not limited to the manipulations of the recited steps, only to the structure implied by the steps. As the compositions of the instant and copending claims both include a liposome comprising irinotecan and sucrose octasulfate, this composition of the copending claim is understood to be within the scope of the instantly claimed composition.

Claims 1-16 are rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1, 4-8, 13, 14, and 23-44 of copending Application No. 14/965,140 (reference application – currently allowed). Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons:

Instant claim 1 is drawn to an irinotecan liposome composition comprising irinotecan and a sulfated sugar. A specific product by process is recited in the instant claims. A substituted ammonium is included in the process of making the product but

not necessarily in the product itself. Instant claim 6 recites that the sulfated sugar is sucrose octasulfate.

Copending claim 1 is drawn to a composition comprising irinotecan and sucrose octasulfate in a liposome, with a specific amount of irinotecan encapsulated.

The copending claims differ from instant claim 1 because the copending claims recite sucrose octasulfate, whereas instant claim 1 is drawn to a sulfated sugar. Nevertheless, sucrose octasulfate is within the scope of the required sulfated sugar. As such, the embodiment of copending claim 1 is within the scope of that of instant claim 1, resulting in a prima facie case of anticipatory-type non-statutory double patenting.

The copending claims differ from instant claim 1 because the copending claims do not recite the product-by-process of the instant claims. Nevertheless, when it comes to product-by-process limitations, the instant claims are not limited to the manipulations of the recited steps, only to the structure implied by the steps. As the compositions of the instant and copending claims both include a liposome comprising irinotecan and sucrose octasulfate, this composition of the copending claim is understood to be within the scope of the instantly claimed composition.

Claims 1-16 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-5, 13, 14, and 24-36 of copending Application No. 14/632,422 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons:

Instant claim 1 is drawn to an irinotecan liposome composition comprising irinotecan and a sulfated sugar. A specific product by process is recited in the instant claims. A substituted ammonium is included in the process of making the product but not necessarily in the product itself, wherein the substituted ammonium compound is diethylammonium or triethylammonium. Instant claim 6 recites that the sulfated sugar is sucrose octasulfate.

Copending claim 1 is drawn to a method of preparing a liposomal irinotecan composition comprising contacting a liposome comprising sucrose octasulfate with a substituted ammonium compound. The substituted ammonium compound may be diethylammonium or triethylammonium, as of copending claim 3.

The copending claims differ from instant claim 1 because the copending claims recite sucrose octasulfate, whereas instant claim 1 is drawn to a sulfated sugar. Nevertheless, sucrose octasulfate is within the scope of the required sulfated sugar. As such, the embodiment of copending claim 1 is within the scope of that of instant claim 1, resulting in a prima facie case of anticipatory-type non-statutory double patenting.

The copending claims differ from the instant claims because the copending claims are drawn to a method of making a composition, whereas the instant claims are drawn to a composition itself. Nevertheless, it appears that the method of making the composition of the copending claims appears to be essentially the same as the method recited in the instant product-by-process claims. As such, the method of the copending claims would have been expected to have produced the composition of the instant claims, resulting in a prima facie case of non-statutory double patenting.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Claims 1-16 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-12 of copending Application No. 14/151,632 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons:

Instant claim 1 is drawn to an irinotecan liposome composition comprising irinotecan and a sulfated sugar. A specific product by process is recited in the instant claims. A substituted ammonium is included in the process of making the product but not necessarily in the product itself. Instant claim 6 recites that the sulfated sugar is sucrose octasulfate.

The copending claims are drawn to a fluid conduit comprising sucrose octasulfate and a cationic antineoplastic agent, as of copending claim 1. Said cationic antineoplastic agent may be irinotecan, as of copending claim 6.

The copending claims differ from instant claim 1 because the copending claims recite sucrose octasulfate, whereas instant claim 1 is drawn to a sulfated sugar. Nevertheless, sucrose octasulfate is within the scope of the required sulfated sugar. As such, the embodiment of copending claim 1 is within the scope of that of instant claim 1, resulting in a prima facie case of anticipatory-type non-statutory double patenting.

The copending claims differ from the instant claims because the copending claims are drawn to a fluid conduit, which is not required by the instant claims. Nevertheless, the composition of the copending claims includes irinotecan and sucrose octasulfate encapsulated in a liposome, which are essentially the same ingredients as that of the instant claims. As such, although the composition of the copending claims includes ingredients not explicitly recited by the instant claims, the composition of the copending claims is within the scope of that of the instant claims, resulting in a prima facie case of anticipatory-type non-statutory double patenting.

The copending claims differ from instant claim 1 because the copending claims do not recite the product-by-process of the instant claims. Nevertheless, when it comes to product-by-process limitations, the instant claims are not limited to the manipulations of the recited steps, only to the structure implied by the steps. As the compositions of the instant and copending claims both include a liposome comprising irinotecan and sucrose octasulfate, this composition of the copending claim is understood to be within the scope of the instantly claimed composition.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Claims 1-16 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1 of copending Application No. 15/213,127 and 15/296,536 (reference applications). Although the claims at issue

are not identical, they are not patentably distinct from each other because of the following reasons:

Instant claim 1 is drawn to an irinotecan liposome composition comprising irinotecan and a sulfated sugar. A specific product by process is recited in the instant claims. A substituted ammonium is included in the process of making the product but not necessarily in the product itself. Instant claim 6 recites that the sulfated sugar is sucrose octasulfate.

Copending claim 1 of both copending applications is drawn to an irinotecan and sucrose octasulfate encapsulated within liposomes. Various other ingredients and properties are taught, including the liposome lipids and concentration of irinotecan.

The copending claim differs from instant claim 1 because the copending claims recite sucrose octasulfate, whereas instant claim 1 is drawn to a sulfated sugar. Nevertheless, sucrose octasulfate is within the scope of the required sulfated sugar. As such, the embodiment of copending claim 1 is within the scope of that of instant claim 1, resulting in a prima facie case of anticipatory-type non-statutory double patenting.

The copending claims differ from instant claim 1 because the copending claims do not recite the product-by-process of the instant claims. Nevertheless, when it comes to product-by-process limitations, the instant claims are not limited to the manipulations of the recited steps, only to the structure implied by the steps. As the compositions of the instant and copending claims both include a liposome comprising irinotecan and sucrose octasulfate, this composition of the copending claim is understood to be within the scope of the instantly claimed composition.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Claims 1-16 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-10 and 12-21 of copending Application No. 14/879,302 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons:

Instant claim 1 is drawn to an irinotecan liposome composition comprising irinotecan and a sulfated sugar. A specific product by process is recited in the instant claims. A substituted ammonium is included in the process of making the product but not necessarily in the product itself. Instant claim 6 recites that the sulfated sugar is sucrose octasulfate.

Copending claim 1 is drawn to a method of treatment comprising administering a composition comprising liposomal irinotecan and sucrose octasulfate.

The copending claims differ from instant claim 1 because the copending claims recite sucrose octasulfate, whereas instant claim 1 is drawn to a sulfated sugar. Nevertheless, sucrose octasulfate is within the scope of the required sulfated sugar. As such, the embodiment of copending claim 1 is within the scope of that of instant claim 1, resulting in a prima facie case of anticipatory-type non-statutory double patenting.

The copending claims differ from the instant claims because the copending claims are drawn to method of treatment claims, whereas the instant claims are

composition claims. Nevertheless, the composition used in the method of the copending claims is a liposome comprising sucrose octasulfate and irinotecan, which is the same product as that of the instant claims. As such, this difference between composition and method claims is insufficient to overcome the applied rejection.

The copending claims differ from instant claim 1 because the copending claims do not recite the product-by-process of the instant claims. Nevertheless, when it comes to product-by-process limitations, the instant claims are not limited to the manipulations of the recited steps, only to the structure implied by the steps. As the compositions of the instant and copending claims both include a liposome comprising irinotecan and sucrose octasulfate, this composition of the copending claim is understood to be within the scope of the instantly claimed composition.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Claims 1, 2, and 5-8 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claim 16 of copending Application No. 14/181,583 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons:

Instant claim 1 is drawn to an irinotecan liposome composition comprising irinotecan and a sulfated sugar. A specific product by process is recited in the instant claims. A substituted ammonium is included in the process of making the product but

not necessarily in the product itself. Instant claim 6 recites that the sulfated sugar is sucrose octasulfate.

Copending claim 16 is drawn to a method of treating a tumor with an irinotecan sucrose octasulfate liposome injection.

The copending claims differ from instant claim 1 because the copending claims recite sucrose octasulfate, whereas instant claim 1 is drawn to a sulfated sugar. Nevertheless, sucrose octasulfate is within the scope of the required sulfated sugar. As such, the embodiment of copending claim 1 is within the scope of that of instant claim 1, resulting in a prima facie case of anticipatory-type non-statutory double patenting.

The copending claims differ from the instant claims because the copending claims are drawn to method of treatment claims, whereas the instant claims are composition claims. Nevertheless, the composition used in the method of the copending claims is a liposome comprising sucrose octasulfate and irinotecan, which is the same product as that of the instant claims. As such, this difference between composition and method claims is insufficient to overcome the applied rejection.

The copending claims differ from instant claim 1 because the copending claims do not recite the product-by-process of the instant claims. Nevertheless, when it comes to product-by-process limitations, the instant claims are not limited to the manipulations of the recited steps, only to the structure implied by the steps. As the compositions of the instant and copending claims both include a liposome comprising irinotecan and sucrose octasulfate, this composition of the copending claim is understood to be within the scope of the instantly claimed composition.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Claims 1-16 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claim 1-20 of copending Application No. 15/227,631 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons:

Instant claim 1 is drawn to an irinotecan liposome composition comprising irinotecan and a sulfated sugar. A specific product by process is recited in the instant claims. A substituted ammonium is included in the process of making the product but not necessarily in the product itself. Instant claim 6 recites that the sulfated sugar is sucrose octasulfate.

Copending claim 1 is drawn to a pharmaceutical composition comprising irinotecan and sucrose octasulfate with a specific size and a specific amount of irinotecan.

The copending claims differ from instant claim 1 because the copending claims recite sucrose octasulfate, whereas instant claim 1 is drawn to a sulfated sugar. Nevertheless, sucrose octasulfate is within the scope of the required sulfated sugar. As such, the embodiment of copending claim 1 is within the scope of that of instant claim 1, resulting in a prima facie case of anticipatory-type non-statutory double patenting.

The copending claims differ from instant claim 1 because the copending claims do not recite the product-by-process of the instant claims. Nevertheless, when it comes

to product-by-process limitations, the instant claims are not limited to the manipulations of the recited steps, only to the structure implied by the steps. As the compositions of the instant and copending claims both include a liposome comprising irinotecan and sucrose octasulfate, this composition of the copending claim is understood to be within the scope of the instantly claimed composition.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Claims 1-16 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claim 1-20 of copending Application No. 15/227,561 (reference application). Although the claims at issue are not identical, they are not patentably distinct from each other because of the following reasons:

Instant claim 1 is drawn to an irinotecan liposome composition comprising irinotecan and a sulfated sugar. A specific product by process is recited in the instant claims. A substituted ammonium is included in the process of making the product but not necessarily in the product itself. Instant claim 6 recites that the sulfated sugar is sucrose octasulfate.

Copending claim 1 is drawn to a pharmaceutical composition comprising irinotecan and sucrose octasulfate with a specific size and a specific amount of irinotecan.

The copending claims differ from instant claim 1 because the copending claims recite sucrose octasulfate, whereas instant claim 1 is drawn to a sulfated sugar.

Nevertheless, sucrose octasulfate is within the scope of the required sulfated sugar. As such, the embodiment of copending claim 1 is within the scope of that of instant claim 1, resulting in a prima facie case of anticipatory-type non-statutory double patenting.

The copending claims differ from instant claim 1 because the copending claims do not recite the product-by-process of the instant claims. Nevertheless, when it comes to product-by-process limitations, the instant claims are not limited to the manipulations of the recited steps, only to the structure implied by the steps. As the compositions of the instant and copending claims both include a liposome comprising irinotecan and sucrose octasulfate, this composition of the copending claim is understood to be within the scope of the instantly claimed composition.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Cited Prior Art

As relevant prior art, the examiner cites Schlessinger et al. (US Patent 5,783,568). Schlessinger et al. (hereafter referred to as Schlessinger) teaches that sucrose octasulfate has anticancer activity, as of Schlessinger, column 27 lines 19-26. Nevertheless, no rejection has been written over Chou in view of Schlessinger. This is because applicant has shown unexpected results relating to the combination of sucrose octasulfate with irinotecan in a liposome. See e.g. applicant's response on 28 March 2016 in related application 14/879,358 (over which a double patenting rejection has been made above). In this response, applicant has pointed to the instant specification,

specifically example 14 of the instant specification, which show that sucrose octasulfate in combination with irinotecan in a liposome results in a drug retention half-life of 56.8 hours, which exceeds that of Chou by 15 times. See page 8, second to last paragraph of applicant's response on 28 March 2016 in related application 14/879,358. In view of these unexpected and significant results, no rejection has been written over Chou in view of Schlessinger.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ISAAC SHOMER whose telephone number is (571)270-7671. The examiner can normally be reached on 8:00 AM - 5:00 PM Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick F. Krass can be reached on (571)272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/ISAAC SHOMER/
Primary Examiner, Art Unit 1612

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/966,458	12/11/2015	Keelung Hong	239669-379238/1001130US14	6467

133156 7590 04/27/2017

Honigman Miller Schwartz and Cohn LLP
Merrimack
350 East Michigan Avenue
Suite 300
Kalamazoo, MI 49007

EXAMINER	
SHOMER, ISAAC	

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
04/27/2017	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@honigman.com
lbroecker@honigman.com
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Examiner-Initiated Interview Summary	Application No. 14/966,458	Applicant(s) HONG ET AL.		
	Examiner ISAAC SHOMER	Art Unit 1612	AIA (First Inventor to File) Status No	Page 1 of 1

All participants (applicant, applicant's representative, PTO personnel):

1. ISAAC SHOMER (Primary Examiner); Telephonic 2. Meghan Klaric (Attorney of Record); Telephonic

Date of Interview: 21 April 2017

Claim(s) discussed: 18, 23

Issues Discussed:

Item(s) under 35 U.S.C. 112:
Examiner contacted representative of applicant to ask about an issue surrounding claims 18 and 23. Namely, it appeared to the examiner from reading these claims that the relevant test to determine encapsulated irinotecan recited in these claims requires a radioactive label, though this was not entirely clear to the examiner. However, the claims upon which claims 18 and 23 depend do not appear to recite a radioactive compound in the claimed liposome composition. As such, the examiner requested that representative of applicant clarify the issue of whether claims 18 and 23 have appropriate antecendent basis.
In response, represntative of applicant expressed the intention to provide a supplemental amendment to address this issue. No agreement was reached at this time.

/ISAAC SHOMER/ Primary Examiner, Art Unit 1612	

Applicant recordation instructions: It is not necessary for applicant to provide a separate record of the substance of the interview.

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

Applicant is reminded that a complete written statement as to the substance of the interview must be made of record in the application file. It is the applicant's responsibility to provide the written statement, unless the interview was initiated by the Examiner and the Examiner has indicated that a written summary will be provided. See MPEP 713.04

Please further see:

MPEP 713.04
Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews, paragraph (b)
37 CFR § 1.2 Business to be transacted in writing

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
14/979,666	12/28/2015	Keelung Hong	239669-379239/1001130US15	5182

133156 7590 12/09/2016

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EXAMINER	
SHOMER, ISAAC	

ART UNIT	PAPER NUMBER
1612	

NOTIFICATION DATE	DELIVERY MODE
12/09/2016	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No. 14/979,666	Applicant(s) HONG ET AL.	
	Examiner ISAAC SHOMER	Art Unit 1612	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 December 2015*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *1-21* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-21* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

4) ☐ Other: _____.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

The present application is being examined under the pre-AIA first to invent provisions.

In the event the determination of the status of the application as subject to AIA 35 U.S.C. 102 and 103 (or as subject to pre-AIA 35 U.S.C. 102 and 103) is incorrect, any correction of the statutory basis for the rejection will not be considered a new ground of rejection if the prior art relied upon, and the rationale supporting the rejection, would be the same under either status.

Claim Rejections - 35 USC § 112(b) – Indefiniteness

The following is a quotation of 35 U.S.C. 112(b):
(b) CONCLUSION.—The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the inventor or a joint inventor regards as the invention.

The following is a quotation of 35 U.S.C. 112 (pre-AIA), second paragraph:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 9-13 are rejected under 35 U.S.C. 112(b) or 35 U.S.C. 112 (pre-AIA), second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the inventor or a joint inventor, or for pre-AIA the applicant regards as the invention.

Claim 9 recites sucrose octasulfate polyanion in the form of an acid or a salt of a taxane. Said taxane may be docetaxel. It is unclear how sucrose octasulfate can be present in the form of a salt of docetaxel since docetaxel does not include a cationic

group such as an amine group that can be protonated to balance the negative charge from sucrose octasulfate. As such, this claim is indefininte because it is unclear how the terms "salt", "sucrose octasulfate", and/or "docetaxel" are interpreted in view of this language.

For the purposes of examination under prior art, claim 9 will be understood to be drawn to cationic derivatives of docetaxel, including but not limited to those recited in instant claim 1.

Claim Rejections - 35 USC § 103 – Obviousness

The following is a quotation of pre-AIA 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under pre-AIA 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.

3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

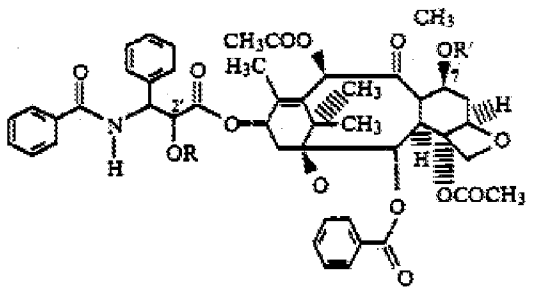
This application currently names joint inventors. In considering patentability of the claims under pre-AIA 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of pre-AIA 35 U.S.C. 103(c) and potential pre-AIA 35 U.S.C. 102(e), (f) or (g) prior art under pre-AIA 35 U.S.C. 103(a).

Claims 20 and 21 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Webb et al. (US Patent 5,741,516) in view of Stella et al. (US Patent 4,960,790), Li et al. (US 2001/0034363 A1).

Webb et al. (hereafter referred to as Webb) is drawn to a liposome comprised of sphingomyelin and cholesterol, as of Webb, title and abstract. The liposome of Webb may be used to deliver a drug useful to treat a tumor, as of Webb, column 3 lines 25-30. Further inclusion of "PEG-PE" is taught as of Webb, column 4 lines 31-35, wherein "PEG-PE" refers to phosphatidylethanolamine derivatized with polyethylene glycol.

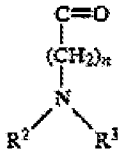
Webb does not teach a docetaxel prodrug or sucrose octasulfate.

Stella et al. (hereafter referred to as Stella) is drawn to derivatives of taxol (i.e. paclitaxel) having the formula



(II)

Wherein at least one of the "R" groups in the above-reproduced structure has the formula



Wherein n is from 1-3, and R^2 and R^3 are either hydrogen or an alkyl radical having 1 to 3 carbons, as of Stella, abstract. The compounds of Stella have excellent antitumor activity.

It would have been prima facie obvious for one of ordinary skill in the art to have used the compound of Stella as the active antitumor agent in the liposome composition of Webb. Webb is drawn to a liposome intended for delivery of an anti-cancer agent, as of Webb, column 3 lines 25-30. As the derivatives of taxol of Stella have anti-cancer (i.e. anti-tumor) activity, the skilled artisan would have been motivated to have used the compound of Stella in the composition of Webb. Generally, it is *prima facie* obvious to select a known material (the taxol derivative of Stella) for incorporation into a composition (the liposome of Webb), based on its recognized suitability for its intended use (an active agent to treat cancer). See MPEP 2144.07.

In the alternative, the skilled artisan would have been motivated to have substituted one active anti-cancer agent (the taxol derivative of Stella) in place of another (vincristine, which is taught as an anti-cancer agent as of the abstract of Webb) for predictable treatment of cancer with a reasonable expectation of success. The simple substitution of one known element (the taxol derivative of Stella) in place of another (vincristine, as of Webb) in order to achieve predictable results (treatment of cancer) is prima facie obvious. See MPEP 2143, Exemplary Rationale B.

Neither Webb nor Stella teach a derivative of docetaxel, as Stella is drawn to a derivative of paclitaxel.

Li et al. (hereafter referred to as Li) is drawn to water-soluble compositions of paclitaxel and docetaxel formed by conjugating paclitaxel or docetaxel to a water-soluble polymer, as of Li, title and abstract. The chemical conjugation is shown in figures 1A and 1B of Li, and includes conjugation at the 2' and 7 position of the taxoid. Li teaches that the conjugation taught by Li can apply to paclitaxel, docetaxel or another taxoid, as of Li, paragraph 0018. In addition, docetaxel has therapeutic effectiveness against cancer, as of Li, paragraph 0004.

Li teaches chemical derivatization in a manner that differs from what is required by the instant claims, in that Li teaches forming a polymer, which is not taught by the instant claims.

It would have been prima facie obvious for one of ordinary skill in the art to have derivatized docetaxel, as of Li, in the manner taught by Stella. Li teaches that both paclitaxel and docetaxel are used for treating cancer, and can be derivatized at their 2'

or 7 positions to form a therapeutic agent that treats cancer. Stella is drawn to a form of derivitization at the 2' or 7 position of a taxoid intended to render the taxoid water-soluble. As such, the skilled artisan would have been motivated to derivatized docetaxel, as of Li, in the manner taught by Stella, for predictable use of the thus-derivatized docetaxel as an anti-cancer drug in the composition of Webb with a reasonable expectation that the thus-derivatized docetaxel would have been capable of treating cancer. The simple substitution of one known element (derivatized docetaxel) in place of another (derivatized paclitaxel) to achieve predictable results (treatment of cancer by the derivatized form is prima facie obvious. See MPEP 2143, Exemplary Rationale B.

As to claims 20 and 21, the claim recites administering docetaxel to a patient in need thereof. Li teaches administration by injection, as of Li, paragraph 0087. The skilled artisan would have been motivated to have administered derivatized docetaxel to a patient suffering from cancer, as taught by Li. This derivatized docetaxel would have acted as a prodrug by breaking down in vivo, as of Stella, column 1 lines 60-65. As such, the skilled artisan would have expected that at least a portion of the derivatized docetaxel would have been converted to docetaxel outside the liposome, as of the last three lines of claim 20, as well as the additional limitations of claim 21.

As to claim 20, the claim requires cholesterol and a phospholipid. Spingomyelin, as of Webb, is understood to read on the required phospholipid.

As to claim 20, Webb teaches that in the present composition, the liposomal interior has a pH less than that of the liposome exterior, as of Webb, column 2 lines 26-

35 – this function appears to be an effect of using the sphingomyelin-cholesterol combination. Webb teaches a liposome interior pH of about 2-5, as of Webb, column 2 lines 52-54. While Webb appears to be silent as to the pH of the exterior component, the skilled artisan would have expected it to have been greater than about 5, up to close to neutral or slightly higher than neutral in some embodiments (e.g. 7.0-7.5), as of Webb, column 7 lines 20-25. As such, the skilled artisan would have been motivated to have optimized the external pH to have been in a range of about 5-7.5, which overlaps with the required pH range.

Claims 1, 2, 9, 10, 14-16, and 19 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Webb et al. (US Patent 5,741,516) in view of Stella et al. (US Patent 4,960,790), Li et al. (US 2001/0034363 A1), the combination further in view of Schlessinger et al. (US Patent 5,783,568).

Webb is drawn to a sphingomyelin-cholesterol liposome. Stella is drawn to an aminoacyl derivative of paclitaxel, and Li is drawn to derivitization of docetaxel. See the above rejections over Webb in view of Stella and Li.

None of the above references teach sucrose octasulfate.

Schlessinger et al. (hereafter referred to as Schlessinger) is drawn to a method of treating cancer, as of Schlessinger, title and abstract. Schlessinger teaches administration of sucrose octasulfate to treat cancer, as of Schlessinger, column 27 lines 18-26.

Schlessinger does not teach a liposome or docetaxel.

It would have been prima facie obvious for one of ordinary skill in the art to have included sucrose octasulfate in the liposome of Webb. Webb is drawn to a liposome comprising sphingomyelin and cholesterol for the treatment of cancer which comprises an anti-cancer drug. As sucrose octasulfate has effectiveness in treating cancer, as of Schlessinger, column 27 lines 18-26, the skilled artisan would have been motivated to have added sucrose octasulfate to the liposome of Webb to have predictably treated cancer with a reasonable expectation of success. Generally, it is prima facie obvious to combine two components (the anti-cancer drug in the liposome of Webb and sucrose octasulfate, of Schlessinger), each of which is taught by the prior art to be useful for same purpose (treating cancer), in order to form a third composition to be used for the very same purpose. The idea for combining them flows logically from their having been individually taught in the prior art. See MPEP 2144.06. Moreover, where it would have been obvious to have combined individually known ingredients, evidence must be provided establishing that appellant's combination of agents is in some way more effective or in some way different than any single member of that combination in order to rebut that prima facie case. See In re Dial, 140 USPQ 244 (C.C.P.A. 1964).

As to claim 2, Stella teaches 2'(N,N-diethylaminopropionyl)taxol, as of Stella, column 2, line 62. Upon substituting docetaxel in place of taxol (paclitaxel), this would have resulted in the required docetaxel prodrug.

As to claim 9, this is an independent claim reciting a liposome having an interior aqueous space separated from the aqueous medium by a lipid membrane. This

liposome comprises sucrose octasulfate and either docetaxel or a 2'(diethylamino)ester aminoacyl prodrug of docetaxel. As such, claim 9 is rejected for essentially the same reason that claim 1 is rejected. Webb teaches a liposome, Li teaches docetaxel, and Schlessinger teaches sucrose octasulfate, as explained in the above rejection of claim 1.

As to claim 10, nothing in the art indicates that there is a micelle-forming surfactant, a cyclodextrin, or a hydrophilic polymer moiety. The examiner notes that although Li does teach derivatizing docetaxel with a hydrophilic polymer moiety, Li is cited only to show the equivalency between docetaxel and that derivatizing the taxoid with a hydrophilic polymer moiety is not part of the applied rejection.

As to claim 14, this is an independent claim reciting a 2'-(diethylamino) ester aminoacyl docetaxel prodrug encapsulated within a liposome, wherein at least 90% of the docetaxel prodrug is encapsulated within the liposome. This claim is rejected for essentially the same reason that claim 1 is rejected. Webb teaches a liposome, Schlessinger teaches sucrose octasulfate, and Li/Stella teach docetaxel. The limitation of claim 14 reciting that at least 90% of the docetaxel prodrug is encapsulated in the liposome appears to be a product-by-process limitation in that it recites that at least 90% of the prodrug used in the beginning of the process is found in the liposome at the end of the process, and as such, further limits the process by which the claimed liposome is formed and not the claimed liposome itself. Product-by-process claims are not limited to the manipulations of the recited steps (e.g. placing a specific percentage

of starting active agent in the liposome), only the structure implied by the steps (e.g. a liposome comprising sucrose octasulfate and the required docetaxel prodrug).

As to claim 15, Webb teaches a specific amount of drug included in the liposome, as of Webb, column 3 lines 20-25. While Webb does not appear to clearly teach the required amount of drug in the units of moles of drug per moles of lipid, the examiner notes that generally, differences in concentration between the prior art and the claimed invention will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating that such concentration is critical. See MPEP 2144.05(II)(A). As no such evidence of a critical concentration has been provided, the required concentration of docetaxel prodrug is understood to be prima facie obvious. In addition, there is motivation to optimize result-effective variables. See MPEP 2144.05(II)(B). Both the docetaxel prodrug and total lipids are understood to be result-effective variables as the docetaxel prodrug is effective to treat cancer and the lipids are effective to form the liposome of Webb.

As to claim 16, this claim is rejected for essentially the same reasons that claim 15 is rejected. The primary difference between these claims is that claim 16 recites the lipid:drug ratio in the form of a molar ratio, whereas claim 15 recites the lipid:drug ratio on the form of a mass ratio.

As to claim 19, Webb teaches that in the present composition, the liposomal interior has a pH less than that of the liposome exterior, As of Webb, column 2 lines 26-35 – this function appears to be an effect of using the sphingomyelin-cholesterol combination. Webb teaches a liposome interior pH of about 2-5, as of Webb, column 2

lines 52-54. While Webb appears to be silent as to the pH of the exterior component, the skilled artisan would have expected it to have been greater than about 5, up to close to neutral or slightly higher than neutral in some embodiments (e.g. 7.0-7.5), as of Webb, column 7 lines 20-25. As such, the skilled artisan would have been motivated to have optimized the external pH to have been in a range of about 5-7.5, which overlaps with the required pH range. With regard to the amount of docetaxel prodrug, claim 19 is rejected for essentially the same reason that claim 16 has been rejected.

Claims 3-8, 11-13, and 18 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Webb et al. (US Patent 5,741,516) in view of Stella et al. (US Patent 4,960,790), Li et al. (US 2001/0034363 A1) and Schlessinger et al. (US Patent 5,783,568), the combination further in view of MacLachlan et al. (US 2004/0142025 A1).

Webb is drawn to a sphingomyelin/cholesterol liposome encapsulating an anti-cancer drug. Stella and Li teach a docetaxel prodrug. Schlessinger teaches sucrose octasulfate. See the above rejection over Webb, Stella, Li, and Schlessinger in combination. Webb also teaches a pegylated lipid PEG-PE, as of Webb, column 4 lines 5-10.

Webb does not teach PEG-DSG.

MacLachlan et al. (hereafter referred to as MacLachlan) is drawn to liposomes and a method and apparatus for producing the liposomes, as of MacLachlan, title and

abstract. The liposome of MacLachlan utilizes PEG-DSG as the PEG-lipid in the liposome, as of MacLachlan, paragraph 0052.

It would have been prima facie obvious for one of ordinary skill in the art to have substituted PEG-DSG, as of MacLachlan, in place of PEG-PE, as of Webb, in the liposome of Webb. The liposome of Webb includes a pegylated lipid, as of Webb, column 4 lines 5-10. PEG-DSG, as of MacLachlan, is also a pegylated lipid that is used in liposomes. As such, the skilled artisan would have been motivated to have substituted PEG-DSG, as of MacLachlan, in place of PEG-PE in the liposome of Webb to have formed a sphingomyelin/cholesterol liposome comprising PEG-DSG for predictable delivery of active agents with a reasonable expectation of success. The simple substitution on one known element (PEG-DSG) in place of another (PEG-PE) to achieve predictable results (formation of a liposome with a pegylated lipid) is prima facie obvious.

As to claim 3, the PEG-DSG of MacLachlan reads on the additional requirements of this claim.

As to claim 4, Webb teaches sphingomyelin and cholesterol, and MacLachlan teaches PEG-DSG. The above references do not appear to clearly teach the required amount of lipid components in the units of molar concentration or molar ratio. Nevertheless, such differences in concentration between the prior art and the claimed invention does not generally support the patentability of subject matter encompassed by the prior art unless there is evidence indicating that the claimed concentration is critical. See MPEP 2144.05(II)(A). As no such evidence of criticality has been provided, the

required concentration of docetaxel prodrug is understood to be prima facie obvious. In addition, there is motivation to optimize result-effective variables. See MPEP 2144.05(II)(B). The sphingomyelin, cholesterol, and pegylated lipid are all liposome forming lipids, and as such, their presence affects the result of forming a stable liposome to encapsulate a drug.

As to claim 5, the combination of these references is a liposome including sphingomyelin and cholesterol (Webb), PEG-DSG (MacLachlan), sucrose octasulfate (Schlessinger), and doctetaxel prodrug (Stella and Li).

As to claim 6, the skilled artisan would have been motivated to have optimized the concentrations of the sphingomyelin, cholesterol, and PEG-DSPE for essentially the same reasons as set forth in the rejection of claim 4 above.

As to claim 7, the skilled artisan would have been motivated to have encapsulated the therapeutic agents inside the liposome as this is taught by Webb. As both docetaxel prodrug and sucrose octasulfate are therapeutic agents, the skilled artisan would have been motivated to have encapsulated these active agents in the interior aqueous space in the liposome. In addition, the examiner notes that the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference. See MPEP 2145(III). Also, a difference in whether one prior art component (e.g. docetaxel) is integral to or not integral to another component does not affect whether it is prima facie obvious. See MPEP 2144.04(V)(B & C). In addition, Webb teaches unilamellar liposomes, as of Webb, column 3 lines 30-35.

As to claim 8, Webb teaches a liposome interior pH of about 2-5, as of Webb, column 2 lines 52-54. While Webb appears to be silent as to the pH of the exterior component, the skilled artisan would have expected it to have been greater than about 5, up to close to neutral or slightly higher than neutral in some embodiments (e.g. 7.0-7.5), as of Webb, column 7 lines 20-25. As such, the required pH of part (a) of claim 8 would have been prima facie obvious. In addition, with regard to parts (b) and (c) of claim 8, the differences between concentrations in the prior art and claimed invention would not appear to overcome the prima facie case of obviousness in the absence of evidence of criticality. See MPEP 2144.05(II)(A & B), e.g. as in the rejection of claim 4 above.

As to claim 11, this claim is rejected for essentially the same reason that claim 3 was rejected above.

As to claims 12 and 13, these claims are rejected for essentially the same reason that claims 4 and 6 were rejected above.

As to claim 18, this is rejected for the same reason that claims 13 and 6 were rejected above.

Note Regarding Reference Date: The instant application has an earliest effective filing date on 3 May 2004. MacLachlan was published on 22 July 2004, which is later than the instant effective filing date. However, MacLachlan was filed on 30 June 2003, and claims benefit from a provisional application filed in 2002. As such, MacLachlan is prior art under 35 U.S.C. 102(e).

Claims 17 is/are rejected under pre-AIA 35 U.S.C. 103(a) as being unpatentable over Webb et al. (US Patent 5,741,516) in view of Stella et al. (US Patent 4,960,790), Li et al. (US 2001/0034363 A1) and Schlessinger et al. (US Patent 5,783,568), the combination further in view of Zadi (US 2003/0138481 A1).

Webb is drawn to a sphingomyelin/cholesterol liposome encapsulating an anti-cancer drug. Stella and Li teach a docetaxel prodrug. Schlessinger teaches sucrose octasulfate. See the above rejection over Webb, Stella, Li, and Schlessinger in combination. Webb also teaches a pegylated lipid PEG-PE, as of Webb, column 4 lines 5-10.

Webb does not teach DSPC and PEG-DSPE.

Zadi is drawn to a liposome comprising a lipophilic active ingredient, as of Zadi, title and abstract. The liposome of Zadi includes distearoyl phosphatidylcholine (DSPC) and PEG-DSPE (pegylated distearoyl phosphatidylethanolamine), as of Zadi, paragraphs 0035 and 0036. DSPE-PEG of Zadi is understood to be the same structure as PEG-DSPE of the instant claims.

It would have been prima facie obvious for one of ordinary skill in the art to have included the lipids of Zadi in the liposome of Webb. Zadi is drawn to a liposome, and teaches the inclusion of various lipids into that liposome. Webb is also drawn to the formation of a liposome. As the lipids of Zadi are useful for forming a liposome, the skilled artisan would have been motivated to have included the lipids of Zadi in the liposome of Webb for predictable formation of a liposome with a reasonable expectation

of success. Generally, it is *prima facie* obvious to select a known material (DSPC and PEG-DSPE, as of Zadi) for incorporation into a composition (that of Webb), based on its recognized suitability for its intended use (forming a liposome). See MPEP 2144.07.

As to claim 17, the claim requires specific concentrations of DSPC, cholesterol, and PEG-DSPE. The prior art does not appear to teach explicitly teach these concentrations or ratios. Nevertheless, differences in concentration between the prior art and the claimed invention will not generally support the patentability of subject matter encompassed by the prior art unless there is evidence indicating that such concentration is critical. See MPEP 2144.05(II)(A). As no such evidence of criticality has been provided, this combination of references applies to claim 17. In addition, there is motivation to optimize result-effective variables. See MPEP 2144.05(II)(B). The concentration of liposome lipids is understood to be result-effective because the presence of such lipids achieves the result of forming the liposomal structure.

Cited Art

As a relevant case, the examiner cites US Patent 8,147,867. The ‘867 patent has the same inventors as the instant application and is part of the continuity chain of the instant application. Nevertheless, no double patenting rejections have been written over the claims of the ‘867 patent for the following reasons.

The instant claims are drawn to a liposome comprising sucrose octasulfate and a specific cationic prodrug of docetaxel. Some instant claims such as claim 1 also recite sphingomyelin and cholesterol as liposome lipids.

Claim 1 of the ‘867 patent is drawn to a liposome comprising sucrose octasulfate. However, this liposome includes irinotecan as the drug. It would not have been prima facie obvious for one of ordinary skill in the art to have substituted the recited cationic prodrug of docetaxel in place of irinotecan. Also, it would not have been prima facie obvious for the skilled artisan to have made the liposome of the claims of the '867 patent out of sphingomyelin. This is at least because the ‘867 patent uses a phosphatidylcholine as the liposome lipid, as of claims 20 and 21 of the ‘867 patent. As such, no double patenting rejection has been written over the claims of the '867 patent.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ISAAC SHOMER whose telephone number is (571)270-7671. The examiner can normally be reached on 8:00 AM - 5:00 PM Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner’s supervisor, Frederick F. Krass can be reached on (571)272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/ISAAC SHOMER/
Primary Examiner, Art Unit 1612

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
15/059,640	03/03/2016	Eliel Bayever	239669-389679	1056

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EXAMINER
STRONG, TORI

ART UNIT	PAPER NUMBER
1629	

NOTIFICATION DATE	DELIVERY MODE
12/02/2016	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patents@honigman.com
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Office Action Summary	Application No. 15/059,640	Applicant(s) BAYEVER ET AL.	
	Examiner TORI M. STRONG	Art Unit 1629	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 November 2016*.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *1,3-5 and 18* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1,3-5 and 18* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☒ The drawing(s) filed on *25 April 2016* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

4) ☐ Other: _____.

DETAILED ACTION

Notice of Pre-AIA or AIA Status

The present application is being examined under the pre-AIA first to invent provisions.

Status of Claims

Claims 1, 3-5 and 18 are pending in the instant application; claims 2, 6-17 and 19-22 are previously cancelled prior to examination; claims 1, 3 and 18 are amended prior to examination; claims 1, 3-5 and 18 are the subject of the Office Action below.

Information Disclosure Statement

The information disclosure statements (IDSs) submitted on March 3, 2016 were filed on the mailing date of the application. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. Enclosed with this Office Action are return copies of Form PTO/SB/08B with the Examiner's initials and signature indicating those references that have been considered.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of pre-AIA 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 3-5 and 18 are rejected under pre-AIA 35 U.S.C. 102(a) as being anticipated by Tsai *et al.* (*Journal of Gastrointestinal Oncology*, 2011, Vol.2, No.3, pp.185-194; cited in IDS).

Applicant's invention, according to **claim 1**, is directed to a method of treating pancreatic cancer comprising intravenously administering, once every three weeks, a single administration of 120 mg/m^2 of irinotecan encapsulated in a liposome wherein no other antineoplastic agent is administered during that three weeks.

Tsai teaches nanovector-based therapies in advanced pancreatic cancer exploring various antineoplastic agents (abs). Tsai explicitly teaches liposomal irinotecan, referred to as nanoliposomal CPT-11, nLs-CPT-11, PEP02 or MM-398 (p.188, col.2, para.2). Tsai teaches treatment of patients with pancreatic cancer where nanoliposomal CPT-11 was delivered for 90 minutes, once every three weeks where 120 mg/m^2 was the maximum dose tolerated (p.189, col.2, para.2). The instant claim directly reads on the art of Tsai. Therefore the instant claim is anticipated.

Applicant's invention, according to **claim 3**, limits claim 1 and requires the administration as an intravenous infusion over 90 minutes.

Tsai teaches intravenous delivery of nanoliposomal CPT-11 over 90 minutes, as stated *supra*. The instant limitation directly reads on the art of Tsai and thus is anticipated.

Applicant's invention, according to **claim 4**, limits claim 1 and requires the pancreatic cancer to have progressed after treatment with gemcitabine-based therapy prior to administration.

Tsai explicitly teaches administration of nanoliposomal CPT-11 with gemcitabine-refractory patients; where positive results were demonstrated in a trial and increase in survival (p.189-190, bridging para.). The instant limitation directly reads on the art of Tsai and thus is anticipated.

Applicant's invention, according to **claim 5**, limits claim 1 and requires the therapy to be administered for at least six weeks.

Tsai teaches, as indicated *supra*, a treatment cycle is three weeks. Tsai further teaches a mean cycle of treatment was 5.4 cycles, thus meaning on average 16.2 weeks. Tsai teaches treatment that is at least six weeks. The instant limitation directly reads on the art of Tsai and thus is anticipated.

Applicant's invention, according to **claim 18**, limits claim 1 and requires the pancreatic cancer to be metastatic adenocarcinoma of the pancreas that has progressed after treatment with gemcitabine-based therapy prior to administration.

Tsai teaches the effectiveness and potent antitumor activity of nanoliposomal CPT-11 against COLO357 (p.189, col.2, para.1), which a metastatic adenocarcinoma of the pancreas cell line as evidenced by Morgan *et al.* (*Int. J. Cancer*, 1980, 25(5), pp.591-598; see abstract). Tsai teaches the COLO357 cells were grafted into nude mice to form an orthotopic tumor xenograft, and intravenous administration of nanoliposomal CPT-11 had antitumor activity without systemic toxicity. The instant limitation reads on the art of Tsai and therefore is anticipated.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on nonstatutory double patenting provided the reference application or patent either is shown to be commonly owned with the examined application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. See MPEP § 717.02 for applications subject to examination under the first inventor to file provisions of the AIA as explained in MPEP § 2159. See MPEP §§ 706.02(l)(1) - 706.02(l)(3) for applications not subject to examination under the first inventor to file provisions of the AIA. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO Internet website contains terminal disclaimer forms which may be used. Please visit www.uspto.gov/patent/patents-forms. The filing date of the application in which the form is filed determines what form (e.g., PTO/SB/25, PTO/SB/26, PTO/AIA/25, or PTO/AIA/26) should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

Claim 1, 3-5 and 18 are provisionally rejected on the ground of nonstatutory double patenting as being unpatentable over claims 1-20 of copending Application No. 15/341,377 and claims 1-20 of copending Application No. 15/341,619. Although the

claims at issue are not identical, they are not patentably distinct from each other because each application sets out to claim a method of treatment of pancreatic cancer, either explicitly claimed or explicitly expressed, through intravenous administration of liposomal irinotecan. Each disclosure claims a dose of, or a range that encompasses, 120 mg/m^2 of liposomal irinotecan. The applications claim inventions that are obvious variants and thus the nonstatutory double patenting rejection is applied.

This is a provisional nonstatutory double patenting rejection because the patentably indistinct claims have not in fact been patented.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TORI M. STRONG whose telephone number is (571)272-6333. The examiner can normally be reached on Monday-Friday 8am-5pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Lundgren can be reached on 571-272-5541. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/TORI M STRONG/
Examiner, Art Unit 1629

/JEFFREY S. LUNDGREN/
Supervisory Patent Examiner, Art Unit 1629