UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CSPC PHARMACEUTICAL GROUP LIMITED,
CSPC OUYI PHARMACEUTICAL CO., LTD., AND
CONJUPRO BIOTHERAPEUTICS, INC.,
Petitioners,

v.

IPSEN BIOPHARM LTD.,
Patent Owner.

Case No. IPR2025-00505
Patent No. 11,344,552

PETITION FOR *INTER PARTES* REVIEW OF CLAIMS 1-15 OF U.S. PATENT NO. 11,344,552

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[1] https://www.cancer.gov/news-events/cancer-currents-blog/2015/irinotecan-liposome-pancreatic

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I. INTRODUCTION

CSPC Pharmaceutical Group Limited, CSPC Ouyi Pharmaceutical Co., Ltd., and Conjurpro Biotherapeutics, Inc., (herein collectively "Petitioner") request *inter partes* review of claims 1-15 ("Challenged Claims) of U.S. Patent No. 11,344,552 ("the '552 patent") (Ex. 1001), a patent assigned to Ipsen Biopharm Ltd. ("Patent Owner"). For the reasons set forth below and in the accompanying Declaration of Dr. Mark Ratain (Ex. 1002), there is a reasonable likelihood that Petitioner will prevail in establishing that at least one of the Challenged Claims is unpatentable as obvious over the prior art.

The Challenged Claims are directed to methods of treating metastatic pancreatic cancer in a human who has not previously been treated with an anti-cancer agent with a specific combination of chemotherapy drugs: (1) 60 mg/m^2 of liposomal irinotecan, (2) 60 mg/m^2 oxaliplatin, (3) 400 mg/m^2 of leucovorin, and (4) 2400 mg/m^2 of 5-fluorouracil ("5-FU"). However, Patent Owner did not invent this specific combination of drugs to treat advanced pancreatic cancer. By the time the inventors filed their patent application, the ***gold standard*** of care for treating metastatic pancreatic cancer in humans who had not received previous cancer treatment ("first-line therapy") was already irinotecan, oxaliplatin, leucovorin, and

5-FU ("FOLFIRINOX")[2], with the same claimed doses for leucovorin and 5-FU, as taught by Conroy (Ex. 1003) and Mahaseth (Ex. 1005). At best, Patent Owner merely replaced irinotecan in this established standard of care with a known form of liposomal irinotecan and slightly adjusted the dose of oxaliplatin, both of which were already taught and suggested in the prior art.

The motivation to replace irinotecan with a form of liposomal irinotecan was already well known. Indeed, Patent Owner's prior published patent application, Bayever (Ex. 1006), already reported that its form of liposomal irinotecan (MM-398) at the same claimed dose of 60 mg/m^2 along with the claimed doses of leucovorin and 5-FU of the Challenged Claims should replace non-liposomal irinotecan for treating pancreatic cancer because of alleged improved efficacy and toxicity profiles.

While Conroy and Bayever were before the Office during prosecution, the arguments raised in the Petition materially differ from those overcome by Patent Owner during prosecution for several reasons. Contrary to Patent Owner's arguments during prosecution, (i) Bayever was not limited to second-line therapy; (ii) the prior art suggested "replacing irinotecan in FOLFIRINOX [disclosed in

[2] FOLFIRINOX stands for "FOL" (folinic acid which is the same as leucovorin), "F" (5-FU), "IRIN" (irinotecan), and "OX" (oxaliplatin). (Ex. 1002, ¶116.)

Conroy and considered the gold standard at the time] with MM-398 [liposomal irinotecan];" (iii) prior art showed administering 60 mg/m^2 oxaliplatin ***administered every two weeks*** is well-tolerated ***in patients with metastatic pancreatic cancer*** and in combination ***with irinotecan***, (iv) Patent Owner's unexpected results argument is both defective and refuted by more recent studies, and (v) the claims do not require clinical efficacy in human patients but are rather only directed to the purpose of potentially bringing about a clinical benefit, thereby further undermining any unexpected results argument.

To the extent the claims are construed to require clinical efficacy, the claims would not be entitled to priority of their parent applications because these applications did not adequately describe methods using the claimed combination of drug doses to show clinical efficacy of metastatic pancreatic cancer in humans. Therefore, the claims would only have an effective filing date of November 10, 2017, which would further distinguish the arguments raised in this Petition from the prosecution by allowing even more prior art never considered by the Office in establishing that the person of skill in the art ("POSA") would be further motivated to replace liposomal irinotecan with irinotecan in FOLFIRINOX for treating patients with metastatic pancreatic cancer, including reports of Patent Owner's own clinical trial protocols and results, which by then published the claimed combination of chemotherapy drugs.

Petitioner therefore requests that this Petition be granted and that claims 1-15 be cancelled for being unpatentable.

II. MANDATORY NOTICES

A. Real Party-in-Interest (37 C.F.R. § 42.8(b)(1))

The real parties-in-interest are: CSPC Pharmaceutical Group Limited, CSPC Ouyi Pharmaceutical Co., Ltd., and Conjupro Biotherapeutics, Inc.

B. Related Matters (37 C.F.R. § 42.8(b)(1))

Petitioner is unaware of any judicial or administrative proceedings that would either affect or be affected by a decision regarding this Petition.

C. Counsel and Service Information (37 C.F.R. §§ 42.8 (b)(3) and (4))

Petitioner identifies its lead and backup counsel as shown below:

Lead Counsel	**Backup Counsel**
Luke Toft (Reg. No. 75,311) ltoft@ foxrothschild.com Fox Rothschild LLP 33 South 6th Street, Suite 3600 Minneapolis, MN 55402 Tel: (612) 607-7336 Fax: (612) 607-7100	Joe Chen (Reg. No. 70,066) joechen@foxrothschild.com Fox Rothschild LLP 212 Carnegie Center, Suite 400 Princeton, NJ 08540 Tel: (609) 844-3024 Fax: (609) 896-1469 Howard S. Suh (*pro hac vice* to be filed) hsuh@foxrothschild.com Fox Rothschild LLP 101 Park Avenue, 17th Floor New York, NY 10178 Tel: (212) 878-7914 Fax: (212) 692-0940

Petitioner consents to electronic service to the e-mail addresses above for lead and backup counsel with a copy to ipdocket@foxrothschild.com (referencing Attorney Docket No. 340008.00021).

III. PAYMENT OF FEES UNDER 37 C.F.R. § 42.103

The undersigned authorizes the Director to charge to Deposit Account No. 50-1943 (i) the fee set forth in 37 C.F.R. § 42.15(a), as required by 37 C.F.R. § 42.103, and (ii) any additional fees that might be due in connection with this Petition.

IV. CERTIFICATION OF GROUNDS FOR STANDING UNDER 37 C.F.R. § 42.103

Petitioner certifies pursuant to Rule 42.104(a) that the '552 patent is available for *inter partes* review and that Petitioner is not barred or estopped from requesting an *inter partes* review on the grounds identified in this Petition.

V. IDENTIFICATION OF CHALLENGE UNDER 37 C.F.R. § 42.104(b)

The Challenged Claims are unpatentable under 35 U.S.C. § 103.

The following is a list of prior art that renders obvious the Challenged Claims:

Exhibit	Description	Publication Date
Ex. 1003	Conroy, *et al.*, N. Engl. J. Med., 364(19):1817-25 (2011) ("Conroy")	May 12, 2011
Ex. 1004	Certified English Translation of the Protocol of Conroy, *et al*, https://www.nejm.org,[3] (2011) ("Conroy Protocol")	May 12, 2011

[3] https://www.nejm.org/doi/full/10.1056/NEJMoa1011923#APPNEJMoa1011923PRO

Exhibit	Description	Publication Date
Ex. 1005	Mahaseth, *et al.*, Pancreas, 42(8):1311-15 (2013) ("Mahaseth")	November 2013
Ex. 1006	International Publication No. WO2013/188586 A1 to Bayever ("Bayever")	December 19, 2013
Ex. 1007	Saif, Journal of the Pancreas, 15(3):278-79 (2014) ("Saif")	May 2014
Ex. 1008	Ko, *et al.*, British J. of Cancer, 109(4):920-25 (2013) ("Ko")	July 23, 2013
Ex. 1009	Cantore, *et al.*, Oncology, 67(2):93-97 (2004) ("Cantore")	September 29, 2003
Ex. 1012	Masi, *et al.*, Annals of Oncology, 15:1766-72 (2004) ("Masi")	2004
Ex. 1013	Carnevale and Ko, Future Oncology, 12(4):453-464 (2016) ("Carnevale")	December 21, 2015
Ex. 1014	Dean, *et al.*, J Clin Oncol, 34(4 Suppl.):tps482 (2016) ("Dean")	February 1, 2016
Ex. 1016	Ginocci, *et al.*, Annals of Oncology, 23(9 Suppl):ix238 (2012)	September 2012
Ex. 1017	Conroy Supplementary Appendix, N. Engl. J. Med., 364(19): 1817-25 Supplementary Appendix (2011) ("Conroy Appendix")	May 12, 2011

Petitioner requests cancellation of claims 1-15 on the following grounds:

Ground	Claims	Description
1	1, 3-6, 8-14	Obvious under 35 U.S.C. § 103 by Conroy, Conroy Protocol, Conroy Appendix and Mahaseth in combination with Bayever, Saif, Ko, and Cantore.
2	2, 7, and 15	Obvious under 35 U.S.C. § 103 by all the art identified in Ground 1 in addition to Masi and Ginocchi.
3	1-15	Obvious under 35 U.S.C. § 103 by all the art identified in Grounds 1 and 2 in addition to Carnevale, and Dean.

VI. BACKGROUND AND OVERVIEW OF THE '552 PATENT

Pancreatic cancer is one of the deadliest diseases and the fourth most common cancer-related death in the United Stated. (Ex. 1002, ¶62.) There is no cure. Many patients die within a year of being diagnosed, and the overall 5-year survival for patients with pancreatic adenocarcinoma is less than 5%. (Ex. 1041 at 3.) For patients with metastatic pancreatic cancer, removal of the tumor by surgery (surgical resection) is not an option, and therefore chemotherapy and radiation are often the only resort. *See id.*

Prior to the filings of the '552 patent, there were numerous chemotherapy options for metastatic pancreatic cancer patients who did not receive any prior anti-cancer drug treatments ("first-line therapy"), e.g., gemcitabine-based regimens. (*See* Ex. 1002, ¶¶63-64, 147-151 (citing Ex. 1003, Exs. 1033-1041; explaining development of regimens, including FOLFIRINOX and benefits to combination treatments).) At the time of the filing of the patent, the "gold standard" of first-line treatment of patients with metastatic pancreatic cancer was FOLFIRINOX, which is composed of four drugs (oxaliplatin 85 mg/m^2 over 2 h, followed by irinotecan 180 mg/m2 over 90 min and leucovorin 400 mg/m^2 over 2 h, followed by FU 400 mg/m^2 bolus and 2,400 mg/m2 46 h continuous infusion). (*See* Ex. 1002, ¶¶65-66; Ex. 1021 at 1.)

Thus, non-liposomal irinotecan (aka, free-irinotecan, CPT-11 or Camptosar) was already being used, including in standard regimens, for metastatic pancreatic cancer treatment in both the first-line setting and in the second-line setting (where patients have already undergone a treatment of anti-cancer drugs). (*See*, *e.g.*, Ex. 1002, ¶¶63, 95-98, 153-156; Ex. 1022 at 1.) However, it was already known prior to the filing of the Challenged Claims that free-irinotecan had certain pharmacologic liabilities and toxicity concerns, including rapid inactivation and clearance and substantial risk of GI injury based on being a prodrug of the more potent metabolite SN-38. (*See* Ex. 1023 at 5.)

MM-398, which is a liposomal form of irinotecan, was also known prior to filing of the patent, and had already replaced free-irinotecan in second-line therapy for metastatic pancreatic patients based on acceptable tolerability and effectiveness over prior treatments of 5-FU and leucovorin. (*See* Ex. 1002, ¶¶83-91, 139 (citing Ex. 1007 at 1; Ex. 1008 at 1).) Moreover, MM-398 had also been reported as having superior pre-clinical and pharmacological properties over free-irinotecan, including improved anti-tumor activity in cell lines, and a 50-fold higher peak serum concentration (C_{max}), a 2-3 fold higher half-life ($t_{1/2}$), and a 50-100 fold higher total exposure over one week (AUC) over free-irinotecan. (Ex. 1002, ¶¶83-91, 120-122 (describing benefits of MM-398); Ex. 1006, Examples 1-2, 5.) Based on these purported preclinical results, MM-398 received orphan drug status from the FDA on

August 1, 2011, for the treatment of pancreatic cancer, which allows a company that first obtains FDA approval for the designated orphan product for a specified rare disease to have market exclusivity for seven years. (Ex. 1025.) It is this orphan drug status of MM-398 in 2011 which currently provides Patent Owner orphan drug exclusivity of MM-398 for first-line treatment of metastatic pancreatic cancer patients until 2031. It was against this backdrop that Patent Owner filed the '552 patent.

The '552 patent describes the liposomal irinotecan as irinotecan sucrose sulfate liposome injection (otherwise termed "irinotecan sucrose octasulfate salt liposome injection" or "irinotecan sucrosofate liposome injection"). (Ex. 1002, ¶174; Ex. 1001 at 10:66-11:9.) The '552 patent states that "the formulation referred to herein as 'MM-398' (also known as PEP02, *see* U.S. Pat. No. 8,147,867) is a form of 'nanoliposomal irinotecan' (also called 'irinotecan liposome' or 'liposomal Irinotecan')," and "MM-398 is irinotecan as the irinotecan sucrose octasulfate salt encapsulated in a nanoliposome drug delivery system." (Ex. 1002, ¶174; Ex. 1001 at 11:1-9.)

Example 1 of the '552 patent describes tumor exposure of SN-38 in patients administered with free-irinotecan or MM-398, and Example 2 describes evaluation of *in vivo* tolerability and efficacy of combination therapies in an animal model. (Ex. 1002, ¶175 (citing Ex. 1001 at 19:55-21:28).) Example 3 contains a study protocol

to assess the following regimens: (1) MM-398+5-FU/LV+oxaliplatin (Arm 1), (2) MM-398+5-FU/LV (Arm 2), and (3) nab-paclitaxel+gemcitabine (Arm 3). (*Id*., (citing Ex. 1001 at 21:32-56.) The '552 patent states that in the study:

> MM-398 is administered instead of conventional irinotecan to improve the safety, tolerability, and ultimately efficacy of a FOLFIRINOX regimen, and "The addition of oxaliplatin to the NAPOLI-I regimen is included to increase DNA damage and potentiate efficacy. Further, due to the MM-398 prolonged PK properties and sustained tumor exposure, using MM-398 instead of conventional irinotecan is designed to further improve upon the efficacy of FOLFIRINOX.

(Ex. 1001 at 21:48-56.) Example 4 describes tolerability of antineoplastic therapies combining liposomal irinotecan, 5-FU/leucovorin, and oxaliplatin, and Example 5 is a description of ONIVYDE® (Irinotecan Liposome Injection) Liposomal Irinotecan. (Ex. 1002, ¶175 (citing Ex. 1001 at 43:21-46:61 and explaining a lack of recognized therapeutic benefit).)

The '552 patent has two independent claims (claims 1 and 12) and thirteen dependent claims (claims 2-11 and 13-15). These claims are recited below in Section XIII and in Appendix A.

VII. PROSECUTION OF THE '552 PATENT

Patent Owner filed U.S. Application No. 15/809,815 ("the '815 Application") that issued as the '552 patent on November 10, 2017 with 20 claims, including

independent claims 1, 16, and 19. (Ex. 1002, ¶¶192-194 (citing Ex. 1084, 60-63).) Claim 1 recited:

> A method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received an antineoplastic agent to treat the metastatic adenocarcinoma of the pancreas, the method comprising administering an antineoplastic therapy to the patient a total of once every two weeks, the antineoplastic therapy consisting of administering to the patient a total of:
>
> a. 60 mg/m^2 of liposomal irinotecan,
>
> b. 60 or 85 mg/m^2 oxaliplatin,
>
> c. 200 mg/m^2 of (l)-form of leucovorin or 400 mg/m^2 of the (l+d) racemic form of leucovorin, and
>
> d. 2,400 mg/m^2 5-fluorouracil to treat the metastatic adenocarcinoma of the pancreas in the human patient.

(Ex. 1084 at 60.)

Claims 16 and 19 were the same as claim 1 except that claim 16 was limited to 85 mg/m^2 of liposomal irinotecan and claim 19 was limited to 60 mg/m^2 of liposomal irinotecan. (*Id.* at 61-63)

A March 6, 2018 Non-final Office Action rejected the claims for, among other rejections, obviousness: Claims 1-3, 5-8, 10, 16 and 19 were rejected for obviousness over Bayever in view of Conroy; Claims 4, 9, and 18 were rejected for obviousness over Bayever in view of Conroy and Fleming; and Claims 11-15, 17, and 20 were rejected for obviousness over Bayever in view of Conroy as evidenced by Bayever

II (WO 2016/094402). (Ex. 1002, ¶¶195 (citing Ex. 1084 at 192-196; Ex. 1026).) In its August 6, 2018 response, Patent Owner eliminated the higher oxaliplatin dose through the following amendment: "60 ~~or 85~~ mg/m^2 oxaliplatin" element. (*Id*., ¶196-197 (citing Ex. 1084 at 287.)

A September 11, 2018 Final Office Action rejected the claims for, among other things, obviousness, e.g., Claims 1-3, 5-8, 10, and 19 were rejected over Bayever in view of Conroy and Alcindor et al. (Curr Oncol. 2011 Jan;18(1):18-25) (Ex. 1002, ¶198 (citing Ex. 1084 at 316.) Applicant speciously clamed in a February 11, 2019 response that its claim amendment "even more clearly recite the subject matter being claimed." (*Id*., ¶199 (citing Ex. 1084 at 380; explaining lack of clarity from amendments).)

The July 8, 2019 Non-final Office Action again rejected the claims: claims 1-3, 5-8, 10, and 19 as obviousness over Bayever in view of Conroy and Melis et at (The Society for Surgery of the Alimentary Tract; 52nd Annual Meeting Posters, May 6 - 10, 2011; ("Melis"); Claims 4, 9, 18, and 23 as obviousness over Bayever in view of Conroy, Melis, and Fleming; and Claims 11-15 and 21-22 as obviousness over Bayever in view of Conroy, Melis, and Bayever II. (*Id*., ¶200 (citing Ex. 1088 at 59-64).) Applicant's amendment consisted of the following: "200 mg/m^2 of <u>the</u> (l) form of leucovorin or 400 mg/m^2 of the (l+d) racemic form of leucovorin." (*Id*., ¶201

(citing Ex. 1091 at 350-352). Unsurprisingly, a February 27, 2020 Final Office Action maintained the rejections. (*Id*., ¶202 (citing Ex. 1097 at 190-197).)

In its January 7, 2020 response, Patent Owner amended independent claims 1 and 19 by eliminating the "a total of" and "administering to the patient a total of" language from the preamble. (*Id*., ¶203 (citing Ex. 1098 at 212, 214).

An August 26, 2021 Non-final Office Action again maintained all of its prior obviousness rejections of the claims. (*Id*., ¶204 (citing Ex. 1119 at 11-18). Patent Owner's February 25, 2022 response made no amendments and argued, among other things, that there was no motivation to combine Bayever, Conroy, and Melis, that there was no reasonable expectation of success of combining the references to achieve the claimed tolerability and efficacy of the claims, and that any *prima facie* case of obviousness of the claims is rebutted by the unexpected results of the post-filing Wainberg references. (*Id*., ¶¶205-211 (citing Ex. 1119 at 140-154, Exs. 1018-1019).)

On April 11, 2022, the Patent Office issued a Notice of Allowance that did not provide any reasons for allowance and simply indicated that claims 1, 4-13, 19, and 21-23 were allowed and claims 14, 15, and 18 were canceled. (*Id*., ¶212 (citing Ex. 1123 at 461-463.) However, as discussed in detail below, Patent Owner led the Examiner into error to the extent that the Examiner relied upon any of the arguments presented in Patent Owner's February 25, 2022 response and remarks in allowing the

claims. (*See infra* Section XI.C; *see also* Ex. 1002, ¶213 (explaining Patent Owner's reference dump).)

VIII. SUMMARY OF THE PRIOR ART

As shown herein, Conroy, the Conroy Protocol, the Conroy Appendix, Mahaseth, Bayever, Conroy 2013, Saif, Ko, Cantore, Masi, and Ginocchi are all prior art under 35 U.S.C. § 102(a)(1) because they are printed publications before the earliest possible filing date of the Challenged Claims, and none of the exceptions of 35 U.S.C. § 102(b) apply. (*See* Ex. 1002, ¶¶94, 104, 106-107, 114-115, 138, 142, 147, 152, 157; *supra* Section V.)

Carnevale and Dean are prior art under 35 U.S.C. § 102(a)(1) if the effective filing date of the Challenged Claims is deemed to be no earlier than November 10, 2017, because they are printed publications before this effective filing date, and none of the exceptions of 35 U.S.C. § 102(b) apply. (*Id*., ¶¶159, 161.)

A. Conroy

Conroy discloses the FOLFIRINOX regimen consisting of 85 mg/m^2 oxaliplatin, 180 mg/m^2 irinotecan given as a 90-minute intravenous infusion, 400 mg/m^2 leucovorin, and 5-FU, first administered as a 400 mg/m^2 bolus and then 2400 mg/m^2 5-FU infusion given as a 46-hour continuous infusion, administered every two weeks in first-line therapy in patients with metastatic pancreatic cancer. (*Id*., ¶95-96 (citing Ex. 1003 at 1-3).) Conroy compares this FOLFIRINOX regimen

against gemcitabine at a weekly dose of 1000 mg/m^2 in patients where the primary end point was overall survival. (*Id.*)

Conroy discloses most patients received less dosage, e.g., stating "[t]he median relative dose intensities of fluorouracil, irinotecan, oxaliplatin, and gemcitabine were 82%, 81%, 78%, and 100%, respectively." (Ex. 1002, ¶97 (citing Ex. 1003 at 4).) Thus, the median relative dose intensity of oxaliplatin was 78% of the 85 mg/m^2 oxaliplatin dose.

Conroy reported better overall survival in the FOLFIRINOX group compared to the gemcitabine group. (*See* Ex. 1002, ¶98; Ex. 1003 at 5-6 (stating "FOLFIRINOX was an effective first-line treatment option for patients with metastatic pancreatic adenocarcinoma" where the "median overall survival was significantly prolonged, with an increase of 4.3 months in the FOLFIRINOX group as compared with the gemcitabine group (11.1 vs. 6.8 months).".)

Conroy also reported that this FOLFIRINOX regimen was also compared with gemcitabine as a second-line therapy where there was no difference in median survival between the two groups (4.4. months in each group). (Ex. 1003 at 5.) As Dr. Ratain explains, this is not unexpected, especially given that these second-line patients had already failed a previous round of chemotherapy treatment and were more compromised because of this failed chemotherapy and a longer duration of aggressive disease. (Ex. 1002, ¶101.)

After Conroy's publication, this FOLFIRINOX regimen for first-line therapy in metastatic pancreatic cancer patients became the gold standard in this area of therapy. (Ex. 1002, ¶¶102-103; Ex. 1021 at 1-6.)

B. Conroy Protocol and Conroy Appendix

The authors of Conroy simultaneously published The Conroy Protocol (Ex. 1004) and The Conroy Appendix (Ex. 1017), to provide additional information about their work. (*See* Ex. 1003 at 3 (stating "[t]he protocol, including the statistical analysis plan, is available with the full text of this article at NEJM.org" and that "[t]he first author vouches for the fidelity of the study to the protocol."); Ex. 1017 at 1 (stating "[t]his appendix has been provided by the authors to give readers additional information about their work."); Ex. 1002, ¶¶104-106.)

Both the Conroy Protocol and the Conroy Appendix disclose that patients were to be given dose reduction of oxaliplatin from 85 mg/m^2 to 60 mg/m^2 based on various haematological toxicities, neutropenia, diarrhea, or any other grade 2 toxicities. (Ex. 1004, 16-18; Ex. 1017, 3-7.)

Dr. Ratain explains these oxaliplatin dose reductions along with the disclosure in Conroy that the median dose intensity of oxaliplatin was 78% of the standard 85 mg/m^2 dose would indicate to a POSA that a significant portion of the patients undergoing the FOLFIRINOX trial were administered with 60 mg/m^2 based on various toxicity events. (Ex. 1002, ¶105; Ex. 1003, 4.)

C. Mahaseth

Mahaseth reported that they had modified the FOLFIRINOX regimen in both locally advanced unresectable and metastatic pancreatic cancer patients by discontinuing the 400 mg/m^2 bolus of 5-FU. (Ex. 1002, ¶¶108-110 (citing Ex. 1005 at 1; discussing motivation and attempt to address toxicity).) Patients were administered with 85 mg/m^2 oxaliplatin, 180 mg/m^2 irinotecan, 400 mg/m^2 leucovorin, and 2400 mg/m^2 5-FU for a 15-day cycle. (Ex. 1005 at 2.) This modified regimen was reported as well tolerated, with an improved safety profile over FOLFIRINOX with respect to neutropenia, fatigue, and vomiting. (Ex. 1002, ¶¶111-12 (citing Ex. 1005 at 1, 5 (stating the modified regimen has "significant activity in metastatic PC (pancreatic cancer)").) This modified regimen also maintained and improved on FOLFIRINOX's overall efficacy, with progression free survival (PFS) and overall survival (OS) of 13.7 and 17.8 months respectively. (*Id.*, ¶113 (citing Ex. 1005 at 4).)

D. Bayever

Bayever describes methods of treating pancreatic cancer in a human patient by administering a form of liposomal irinotecan (irinotecan sucrose octasulfate salt liposome injection, also referred to as "MM-398") alone or in combination of specific dosages of leucovorin and 5-FU. (*See* Ex. 1002, ¶¶116-117 (citing Ex. 1006 at 2-4; further describing concerns with then current treatments.) For example, one

of the disclosed methods describes administering 60 mg/m^2 of MM-398 to patients homozygous for the UGT1A1*28 allele, 400 mg/m^2 of leucovorin (l+d racemic form), and 2400 mg/m^2 of 5-FU every 2 weeks, which is the same doses of these drugs claimed in the Challenged Claims. (*Id.*, ¶118-119 (citing Ex. 1006 at 4, 26-27, 39-42).)

Even for patients that are not homozygous for the UGT1A1*28 allele, Bayever discloses administering 60 mg/m^2 of MM-398 along with the same doses of leucovorin and 5-FU described above in patients with certain toxicity events, such as diarrhea. (*See* Ex. 1006 at 40-42.) For example, Bayever discloses:

Table: MM-398 Dose Modifications for Diarrhea

Worst Toxicity CTCAE Grade	MM-398 Dose for Next Cycle[a]		
	Arm A: Patients Not Homozygous for UGT1A1*28	**Arm A: Patients Homozygous for UGT1A1*28[d] Arm C: Patients Not Homozygous for UGT1A1*28**	**Arm C: Patients Homozygous for UGT1A1*28[d]**
Grade 1 or 2 (2-3 stools/day > pretreatment or 4-6 stools/day > pretreatment)	100% of previous dose	100% of previous dose	100% of previous dose
Grade 3 (7-9 stools/day > pretreatment) or Grade 4 (>10 stools/day > pretreatment)	Reduce dose by 20 mg/m^2 to a minimum dose of 80 mg/m^2 [b]	Reduce dose to 60 mg/m^2 for the first occurrence and to 50 mg/m^2 for the second occurrence[e, d]	Reduce dose to 50 mg/m^2 for the first occurrence and to 40 mg/m^2 for the second occurrence [e, d]

(*Id.*, 41) (emphasis added).

Notably, Patent Owner incorrectly argued during prosecution that Bayever was limited to second-line treatments for pancreatic cancer. (Ex. 1002, ¶130 (citing Ex. 1119 at 145 (summarizing prosecution)).) However, Bayever discloses a

proposed Phase III clinical trial for second-line therapy for pancreatic cancer patients, buts its disclosure as a whole are not limited to second-line therapy.

First, Bayever suggests that its disclosed methods of treatment offers an improved version ***of existing first-line therapy of pancreatic cancer***. (Ex. 1006 at 2-4 (discussing need for better options to existing cancer treatments including the first-line FOLFIRINOX therapy, single agent gemcitabine—described as the "current standard of care in first-line treatment"—and a protein tyrosine kinase inhibitor targeted to EGFR—described as "approved for first-line use in advanced pancreatic cancer.").) Bayever also states that pancreatic cancer's high mortality rate and the limited number of treatment options created "an urgent need for improvements in, and effective alternatives to, current therapies for pancreatic cancer" and [t]he disclosed invention addresses this need and provides other benefits." (*See id.*, 3-4.) A POSA would have understood that Bayever was attempting to address concerns with known treatments, including first-line treatments, and that it in fact does "address[] this need." (Ex. 1002, ¶¶131-133 (citing Ex. 1006 at 2-4, 14-15, and claims; explaining that Bayever's disclosures teach a POSA the treatment was directed to "all pancreatic cancers," through first- and second-line therapies).)

Second, Bayever discloses dozens of embodiments (both in a summary and in the 27 claims) of various methods of treating pancreatic cancer, ***none of which*** are

limited to second-line therapy. (*Id*., ¶¶134-135 (citing Ex. 1006 at 14-15, 19-25 and claims.) Under Patient Populations (Section V), Bayever states "[t]he compositions and methods disclosed herein are useful for the treatment of ***all pancreatic cancers, including*** pancreatic cancers that are refractory or resistant to other anti-cancer treatments." (*Id*., 13.) Thus, defining the patient population as ***all pancreatic cancers*** would have conveyed to the POSA that the disclosed methods could be used in first-line therapy. (Ex. 1002, ¶132.) In Sections VI and VII, describing Combination Therapy and Treatment Protocols, Bayever describes various treatment combinations, including of MM-398, leucovorin, and 5-FU with doses that can be adjusted, but never limits the combinations to second-line therapy. (*Id*., ¶134 (citing Ex. 1006 at 14-15).) In addition, six out of seven of the working examples are not limited to second-line therapy. (Ex. 1006 at 19-25.)

Bayever's Claim 3 (one of 27 claims) states:

> A method of treating pancreatic cancer in a human patient, the method comprising co-administering to the patient an effective amount each of liposomal irinotecan, 5-fluorouracil (5-FU), and leucovorin, wherein the method comprises at least one cycle, wherein the cycle is a period of 2 weeks, and wherein for each cycle:
>
> (a) liposomal irinotecan is administered to patients not homozygous for the UGT1A1*28 allele on day 1 of each cycle at a dose of 80 mg/m and to patients homozygous for the UGT1A1*28 allele on

day 1 of cycle 1 at a dose of 60 mg/m^2 and on day 1 of each subsequent cycle at a dose of 60 mg/m^2 or 80 mg/m^2;

(b) 5-FU is administered at a dose of 2400 mg/m^2; and

(c) leucovorin is administered at a dose of 200 mg/m^2 (*l* form) or 400 mg/m (*l* + *d* racemic form).

(*Id*., 54.) Notably, this claim covers the ***same*** combination of claimed drugs at the ***same*** claimed doses as the Challenged Claims, except for the claimed oxaliplatin dose, and is not limited to second-line therapy for metastatic pancreatic cancer. (Ex. 1002, ¶135.) In fact, ***none of the 27 published claims*** limited their methods of treating pancreatic cancer in a human patient to second-line therapy. (*Id*., ¶¶135-136 (noting the related patents also don't limit to second-line therapies.)

Bayever also reports a number of purported pre-clinical benefits of MM-398 over free-irinotecan, including improved anti-tumor activity in cell lines (Examples 1-2) and better pharmacokinetics, including a 50-fold higher peak serum concentration (C_{max}), a 2-3 fold higher half-life ($t_{1/2}$), and a 50-100 fold higher total exposure over one week (AUC) over free-irinotecan. (Ex. 1002, ¶¶120-129 (citing Ex. 1006 at 5-6, 10, 13-16, 19-21, 26-27, 33, 55 (describing multiple benefits).)

E. Saif

Saif reported that the combination of MM-398 liposomal irinotecan with leucovorin and 5-FU achieved its primary endpoint in Phase III clinical trials with an overall survival of 6.1 months, which was a 1.9 month improvement over the 4.2 month survival rate demonstrated by the control group of 5-FU and leucovorin alone.

(Ex. 1002, ¶139 (citing Ex. 1007 at 1).) These results were based on a randomized large phase III clinical trial called the NAPOLI-1 study. (*Id*.) Saif discloses that this study treated patients with metastatic pancreatic cancfer who had previously received gemcitabine-based therapy. (*Id*.) Saif states that the results were "exciting, as currently FDA has approved no regimen for second-line treatment of pancreatic cancer" and "groundbreaking…in the gemcitabine-refractory setting." (*Id*., ¶140.)

Critically, Saif specifically suggests that because of these encouraging results of using MM-398 in second-line therapy, MM-398 should be further studied for potential use in first-line therapy in the FOLFIRINOX regimen. (*Id*., ¶141 (citing Ex. 1007 at 1.) For example, Saif states:

> Now that we have combination of 5-fluorouracil, oxaliplatin, irinotecan, leucovorin (FOLFIRINOX) as an option for first-line treatment too, how will this regimen fit in the algorithm of the treatment. [internal footnotes omitted].
>
> ***It seems logical to test this drug/regimen further: will it be worth replacing irinotecan in FOLFIRINOX with MM-398. However, bone marrow toxicity has to be borne in mind***.

(Ex. 1007 at 1 (emphasis added).)

F. Ko

Ko reports the results from a phase II clinical study evaluating liposomal irinotecan MM-398 monotherapy as a second-line treatment for pancreatic cancer. (Ex. 1002, ¶¶142-146.) Of the 40 patients enrolled, 75% of the patients achieved a

3-month survival rate, with median progression-free survival and overall survival of 2.4 and 5.2 months, respectively. (Ex. 1008, 1.)

Ko states that these encouraging results warrant moving forward with larger phase III clinical trials, including the NAPOLI-1 phase III trial reported by Saif. (*Id*., 5.) Ko concludes that MM-398 should be explored in the first-line therapy setting:

> Additional studies may explore this drug's potential role in the ***first-line setting*** and as part of combination regimens for APC. Moreover, given the emergence of ***FOLFIRINOX as a front-line standard in patients with good performance status***, the utility of PEP02 [MM-398] in irinotecan-pretreated patients, alone or in combination with gemcitabine, ***also merits further investigation***.

Id. (emphasis added).

G. Cantore

Cantore reported a study evaluating the clinical activity and toxicity of combination chemotherapy with irinotecan and oxaliplatin in patients with advanced metastatic pancreatic cancer that had progressed after a course of gemcitabine therapy. (Ex. 1015, 1; Ex. 1002, ¶76.) Oxaliplatin was administered at 60 mg/m^2 on days 1 and 15 and 60 mg/m^2 of irinotecan was administered on days 1, 8, and 15 every 4 weeks. (*Id*.) The results indicated that six out of the thirty patients (20%) had a clinical benefit response where the median duration was 7.2 months. (*Id.*) Cantore concludes that "[c]hemotherapy with irinotecan and oxaliplatin is an active and well-tolerated combination in patients with advanced pre-treated pancreatic cancer." (*Id.*)

Among the rationales for administering this combination therapy in second-line therapy for advanced metastatic pancreatic cancer was that irinotecan and oxaliplatin "have shown cytotoxic synergisms in vitro and in vivo, with no overlapping toxicity." (*Id.,* 4.)

H. Masi

Masi evaluated a simplified FOLFOXIRI regimen of irinotecan, oxaliplatin, leucovorin, and 5-FU that could be less myelotoxic and more easily administered in clinical practice for the first-line treatment of metastatic colorectal cancer. (Ex. 1002, ¶¶152-154; Ex. 1012 at 1-2.) This modified regimen involved a biweekly administration, with slightly reduced doses of irinotecan and oxaliplatin and continuous, rather than a chronomodulated infusion of 5-FU. (*See id.*) Masi also chose a treatment sequence of irinotecan before oxaliplatin before 5-FU because *in vitro* studies on human colon cancer cell lines showed that synergy occurs when irinotecan precedes oxaliplatin and 5-FU exposure. (Ex. 1002, ¶155; Ex. 1012 at 5.) Masi concludes that this simplified FOLFOXIRI regimen showed an improved safety profile while maintaining anti-tumor activity and efficacy. (Ex. 1002, ¶156; Ex. 1012 at 6.)

I. Ginocchi

Ginocchi describes a modified FOLFOXIRI regimen administered to metastatic and local advanced cancer patients, where the doses of irinotecan and 5-

FU were lowered. (Ex. 1002, ¶158; Ex. 1016 at 1.) Of the 39 patients treated, no toxic deaths or febrile neutropenia were reported, and median progression-free survival was 11.5 months and median overall survival was 25.5 months. (*Id.*) The authors concluded that this modified FOLFOXIRI regimen was "quite well tolerated and it maintained its good activity in metastatic pancreatic cancer." (*Id.*)

J. Carnevale

Carnevale is a review article that discusses then recent developments of administering liposomal irinotecan MM-398 in the clinical setting. (Ex. 1002, ¶160; Ex. 1013 at 10-11.) After discussing MM-398's improved toxicity and pharmacokinetic properties over standard irinotecan and its FDA approval under the name Onivyde for use in combination with 5-FU and leucovorin for second-line treatment of pancreatic cancer patients, Carnevale concludes that:

> It is also of interest whether the optimized PK and safety profile of MM-398 over standard irinotecan would make it ***an ideal substitute*** for irinotecan in the first-line FOLFIRINOX regimen. This might represent ***a natural extension*** of MM-398's role in metastatic pancreatic cancer.

(*Id*.) (emphasis added).

K. Dean

Dean is an abstract that reports an open-label phase 2 trial to determine the efficacy and safety of liposomal irinotecan MM-398 with 5-FU, leucovorin, and oxaliplatin in first-line therapy of pancreatic cancer patients. (Ex. 1002, ¶¶161-162;

Ex. 1014, 2-3.) Dean notes that FOLFIRINOX had emerged as the standard of care for first-line treatment of metastatic pancreatic cancer. Dean also discloses the FDA clinical trial protocol number NCT02551991. (*Id*.)

IX. PERSON OF ORDINARY SKILL IN THE ART

The person of ordinary skill in the art (POSA) would have been an M.D. and/or Pharm. D who would have completed training in medical oncology, particularly in the field of gastrointestinal (GI) cancers, or a Ph.D. in clinical pharmacology, pharmaceutical sciences, pharmaceutics, and/or drug delivery, also particularly in the field of GI cancers, or their equivalents, along with at least 1-2 years of post-doctoral experience. (Ex. 1002, ¶¶44-46.) This POSA would have been part of a team of professionals with these credentials and post-doctoral experience. (*Id*.)

X. CLAIM CONSTRUCTION

The Challenged Claims are evaluated under their "ordinary and customary meaning" – that is, "the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention." *Phillips v. AWH Corp*., 415 F.3d 1303, 1312-13 (Fed. Cir. 2005). The following claim term of the Challenged Claims should be construed accordingly as shown below.

Claim term	Claim Construction	Intrinsic Evidence
"treating" and "treat," claims 1-15	"attempting to cause a therapeutic improvement but not requiring actual efficacy"	Claim 1-15, col. 2:23-25; col. 2: 27-46; col. 2:57-65, col. 18: 34-38

(*See* Ex. 1002, ¶49.)

The terms "treating" and "treat" are well-understood terms in the medical community. (Ex. 1002, ¶50.) As Dr. Ratain explains, treating a patient is always with the attempt or intent to cause a therapeutic improvement of the patient, which in the case of metastatic pancreatic cancer, could be reduced tumor growth or increased overall survival in the patient. (*Id*.) But "treatment" does not require a certain level of clinical efficacy, and often times, treating patients with this disease does not result in therapeutic improvement. (*Id*.)

The language of the claims supports this. Here, nothing in the claim language for "method of ***treating***" or "to ***treat*** the metastatic adenocarcinoma of the pancreas in the human patient" requires that "treating" brings about a particular result, such as clinical efficacy. (*Id*., ¶51.) Instead, the body of the claims define the method of treatment with structural components – administering specific combination of drugs given at specified doses, frequency (every two weeks), and conditions (patients who have not previously received an antineoplastic agent to treat the metastatic adenocarcinoma of the pancreas). (*Id*.) Construing the claims to require clinical efficacy would improperly inject non-existent functional requirements into the

claims. *See Schwing GmbH v. Putzmeister Aktiengesellschaft*, 305 F.3d 1318, 1324 (Fed. Cir. 2002) ("[W]here a claim uses clear structural language, it is generally improper to interpret it as having functional requirements."); *Novartis v. Actavis*, 2013 WL 6142747, *9 (D. Del. 2013).

The patent then states that "[a] method of treating pancreatic cancer can comprise the ***administration*** of an antineoplastic therapy of liposomal irinotecan, oxaliplatin, and 5-fluorouracil once every two weeks to the patient," without specifying clinical efficacy. (*See* Ex. 1001, 2:26-29) (emphasis added). The Summary then goes on to describe a number of different dosing options of this general method, defined solely by administration of the drugs and not by clinical efficacy. (*See id.*, 2:29-46; *see also* Ex. 1002, ¶¶52-56 (summarizing same).)

One of the further embodiments of invention states a "method of treating pancreatic cancer…the method comprising: administering to the subject ***a therapeutically effective amount*** of MM-398 liposomal irinotecan in combination" with the other claimed drugs. (*Id.*, 18:34-38) (emphasis added); *see also* Ex. 1015, ¶[0036] ("As used herein, "effective treatment" refers to treatment producing a beneficial effect, e.g., amelioration of at least one symptom of a disease or disorder."); Ex. 1002, ¶¶52-60 (citing Exs. 1015, 1028-1032; describing Patent Owner's decision to define "effective treatment" and distinguish it from "treatment," and how only the latter is used in the claims).) Thus, it is clear that the patentees

knew how to use the term "therapeutically effective" when describing a particular embodiment of their invention or define "effective treatment" in its provisional application (Ex. 1015, ¶¶ [0036], [0074]-[0076]) ***but deliberately chose to delete*** "therapeutically effective" and "effective treatment" from the claim language, which compels against injecting a therapeutic result into the Challenged Claims. (*See id*.) *See also Novartis*, 2013 WL 6142747, *10 ("The patentees could have, but did not, claim "a method of *therapeutically treating"* diseases or iron overload. That choice should be given meaning here.") (emphasis in original); *Pfizer v. Teva*, 803 F. Supp.2d 397, 407 (E.D. Va. 2011) ("Pfizer specifically deleted references in patented claims to curing or preventing ED. Those meanings cannot be read back into the patent."). (*See* Ex. 1015, ¶¶ [0036], [0074]-[0076].)

Finally, Petitioner's construction is consistent with a long line of decisions where the plain and ordinary meaning of "treating" in method of treating claims does not require any therapeutic improvement in terms of clinical efficacy but covers any attempt or purpose to provide therapeutic improvement. *See Novartis*, 2013 WL 6142747, *11 ("the Court recommends that 'treating' be construed to mean 'attempting to cause a therapeutic improvement in."); *Schering Corp. v. Mylan Pharms., Inc.,* 2011 WL 2446563,*2, *5 (D.N.J. June 15, 2011) (in construing "treating" that appears in a claim requiring "[a] method of treating ... atherosclerosis ..." of the claimed compound, "the plain meaning of 'treatment' does imply a ***goal***

of [stopping, slowing, or reversing the progression of a disease]" but "***does not necessarily imply success***") (emphasis added); *Pfizer. Teva*, 803 F. Supp.2d at 397, 401 (construing "treating erectile dysfunction" to mean "keeping [erectile dysfunction] from returning, or preventing it" would not be in line with the ordinary or customary meaning of "treating"); *Schering Corp. v. Mylan Pharmaceuticals, Inc.*, 2011 WL 2446563, *5 (D.N.J. 2011) ("treatment of" and "treating" construed to mean "***giving for the purpose*** of stopping, slowing or reversing the progression of a disease" instead of actually "stopping, slowing or reversing the progression of disease.") (emphasis added).

XI. LEGAL STANDARDS

A. Standard For Instituting IPR

The Petition must be granted if it meets the threshold requirement of demonstrating that there is a "reasonable likelihood" that Petitioner would prevail as to at least one of Challenged Claims. *See* 35 U.S.C. §314(a) (2011). The "reasonable likelihood standard is higher than mere notice pleading but "lower than the 'preponderance' standard to prevail." *Hulu, LLC v. Sound View Innovations, LLC*, IPR2018-01039, Paper 29 at 13 (PTAB Dec. 20, 2019) (precedential).

B. Standard for Obviousness under 35 U.S.C. § 103

The standard for obviousness was set forth in *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398 (2007). *KSR* emphasizes that inventions arising from ordinary innovation, ordinary skill, or common sense should not be patentable. A patent claim

may be obvious if the combination of elements was obvious to try or there existed at the time of the invention a known problem for which there was an obvious solution encompassed by the patent's claims. When a reference is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. If a person of ordinary skill can implement a predictable variation, Section 103 likely bars its patentability.

C. Standard for Discretionary Denial under 35 U.S.C. § 325(d)

When evaluating whether to exercise its discretion to deny institution of an IPR under Section 325(d), the PTAB applies a two-part test:

> 1. whether the same or substantially the same art previously was presented to the Office or whether the same or substantially the same arguments previously were presented to the Office; and
>
> 2. if either condition of the first part of the framework is satisfied, whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims.

See Advanced Bionics, LLC v. Med-El Elektromedizinische Geräte GmbH., IPR2019-01469, Paper 6, at 8 (PTAB Feb. 13, 2020). In the first step, the PTAB considers the similarities and material differences between the asserted art and the prior art involved during prosecution. *See id.*, at 9. If the first step is satisfied, the PTAB then applies the second step and considers the extent to which the prior art was the basis for rejection, whether Petitioner has pointed out sufficiently how the

Office erred in its evaluation of the prior art, and the extent to which additional evidence and facts presented in the petition justify reconsideration of the prior art or argument. *See id.* at 10-11.

Here, discretionary denial under Section 325(d) should be denied for at least the following reasons.

First, Patent Owner led the Office into error by arguing that there was no motivation to combine Conroy's first-line FOLFIRINOX regimen with the liposomal irinotecan pancreatic treatment methods of Bayever. (Ex. 1119 at 145-48.) Contrary to Patent Owner's arguments during prosecution, Bayever is not limited to second-line therapy, but its disclosure as a whole and its original claims cover first-line pancreatic cancer treatments. (*See infra* Section XIII(A)(i); Ex. 1002, ¶¶130-137.) Given that FOLFIRINOX was the gold standard of first-line treatment for metastatic pancreatic cancer patients, the POSA would have been surely motivated to replace the non-liposomal irinotecan of FOLFIRINOX with Bayever's liposomal irinotecan. (Ex. 1002, ¶¶83-91, 235-240.) Moreover, other references raised here in this Petition (which were not discussed during prosecution) clearly suggested that based on promising results of liposomal irinotecan for second-line therapy, "[i]t seems logical to test [liposomal irinotecan]" to determine whether "it will be worth replacing irinotecan in FOLFIRINOX with MM-398 [liposomal irinotecan]." (Ex. 1007 at 1; Ex. 1008 at 5.) Moreover, unlike the reference cited

during prosecution showing that oxaliplatin was tolerated at 60 mg/m^2 in cancer patients (Melis), Petitioner here relies on Cantore and Conroy Protocol, which unlike the Melis reference, suggests that 60 mg/m^2 oxaliplatin ***administered every two weeks*** is well-tolerated ***in patients with metastatic pancreatic cancer*** and in combination ***with irinotecan.*** (Ex. 1009 at 1; Ex. 1004 at 16-18.) While Patent Owner apparently distinguished Melis based on the fact that it excluded the claimed treatment of patients with metastatic disease, involved only weekly administration of oxaliplatin instead of the claimed "every two weeks" administration, and did not involve co-administration with irinotecan (Ex. 1119 at 146-48), none of these criticisms of Melis can be leveled against Cantore. Moreover, the prosecution never recognized that Conroy, the Conroy Protocol, and the Conroy Appendix disclose that FOLFIRINOX patients were administered with 60 mg/m^2 oxaliplatin. (*See* Ex. 1003, 4; Ex. 1004, 16-18; Ex. 1017, 3-7; Ex. 1002, ¶¶94-106, 241-243.)

Second, while no reason was provided by the Examiner in allowing the Challenged Claims, it is likely that he was persuaded in particular with Patent Owner's unexpected results arguments, which were emphasized in Patent Owner's last remarks in response to the last Office Action before allowance. (Ex. 1119 at 151-54.) There, Patent Owner relied upon post-filing art in the form of the Wainberg references, (Exs. 1018-1019), to argue that the claimed 60 mg/m^2 of liposomal irinotecan co-administered with 60 mg/m^2 of oxaliplatin had better tolerability than

combinations with higher doses of oxaliplatin (85 mg/m^2) and that this improved tolerated dose resulted in superior efficacy over the gold standard FOLFIRINOX regimen. (Ex. 1119 at 151-52.) Patent Owner claimed that these post-filing "unexpected results" rebutted the *prima facie* case of obviousness. (*Id.*, 154.) However, Patent Owner's unexpected results argument is defective because rather than being unexpected, the POSA would have fully expected that administering a lower dose of oxaliplatin with liposomal irinotecan would result in lower toxicity because it was commonly known that lower amounts of chemotherapy drugs correlate to fewer side effects. (Ex. 1002, ¶¶254-261.) As to Patent Owner's argument that its claimed combination of liposomal irinotecan and oxaliplatin had superior efficacy over FOLFIRINOX, the Wainberg article cautions that the two therapies reported at the time "cannot be reliably compared," and that "direct comparisons" between the two studies "cannot be made," especially in view of the "[l]imitations inherent in [Wainberg's] study design includ[ing] the small number of patients, which limits the precision of efficacy parameter estimates; the lack of an efficacy hypothesis; the non-randomised design; and the absence of a control group." (*Id*., ¶255-257; Ex. 1019 at 8.) Moreover, other more recent post-filing publications, which do not suffer from Wainberg's inherent limitations, have refuted Patent Owner's unexpected results argument by concluding that the claimed therapy and

the gold standard FOLFIRINOX therapy showed ***identical*** efficacy.[4] (Ex. 1002, ¶¶164-170 (explaining how these larger studies have found a lack clinically or statistically significant differences); Ex. 1010 at 1-10; Ex. 1011 at 1-2.)

Third, while the Patent Owner argued that the Challenged Claims are directed to clinical efficacy in a human suffering metastatic pancreatic cancer, (Ex. 1119 at 153), the '552 patent makes clear that the method of treatment claims are only directed for the ***purpose*** of potentially bringing about a clinical benefit but that clinical efficacy is not required. (Ex. 1002, ¶49.) After all, the '552 patent has no data showing that the claimed dosing regimen of drugs shows any actual efficacy over baseline results in human patients. (*See generally* Ex. 1001.) While the Examiner may have been misled by the Patent Owner in believing that the Challenged Claims should be granted because they demonstrated unexpected results in the form of superior efficacy, a proper claim construction of "method of treatment" does not require clinical efficacy in a human patient, and thus Patent Owner's lack of reasonable expectation of success and unexpected results arguments during prosecution should be further discounted.

[4] *See* Nichetti, *et al*., JAMA Network Open, 7(1):1-13 (2024) ("Nichetti") (Ex. 1010, 1-2); Nevala-Plagemann and Garrido-Laguna, Nature Reviews Clinical Oncology, 21(8):567-68 (2024) ("Nevala-Plagemann") (Ex. 1011, 1.)

Other material differences and errors in the prosecution of the '552 Patent are further described *infra* Section XIII(A)(i).

XII. EFFECTIVE FILING DATE

Grounds 1 and 2 are premised on a claim construction of "treating" and "treat" of the Challenged Claims to mean "attempting to cause a therapeutic improvement but not requiring actual efficacy." (*See supra* Section X). Under this claim construction, the Challenged Claims would have an effective filing date of August 21, 2015, the filing date of the '552 patent's earliest provisional application.

However, if the Board adopts a claim construction of "treating" and "treat" to require a showing of clinical efficacy, then the effective filing date of the Challenged Claims must be November 10, 2017, the actual filing date of the '552 patent. (Ex. 1002, ¶¶216-227.) Specifically, because no parent application provides an adequate written description of the claims under 35 U.S.C. § 112, the Challenged Claims would only be entitled to an effective filing date of their actual application. *See* 35 U.S.C. §§ 100(i)(1)(A)-(B), 120. "For a claim in a later-filed application to be entitled to the filing date of an earlier application under 35 U.S.C. § 120 (1994), the earlier application must comply with the written description requirement of 35 U.S.C. § 112(a)." *Tronzo v. Biomet, Inc.,* 156 F.3d 1154, 1158 (Fed. Cir. 1998). The earlier applications, therefore, must "contain a written description of the invention, and of the manner and process of making and using it." *Id.* A disclosure in any parent

application that merely renders the later-claimed invention obvious is not sufficient to meet the written description requirement; it must describe the claimed invention with all its limitations. *See id.*

Here, if the Challenged Claims are construed such that the method of treatment requires clinical efficacy, then none of the parent applications would adequately describe the claims. As detailed by Dr. Ratain, none of these applications demonstrate that the inventors were in possession of a method of treatment that actually results in any clinical efficacy to patients with metastatic pancreatic cancer. (Ex. 1002, ¶¶216-226.) Further, a POSA would understand the specifications to be directed to "administration" of an antineoplastic therapy of the claimed chemotherapy drugs. (*Id*., ¶¶56-59 (citing Ex. 1015, ¶[0007]; Exs. 1028-1032).) These disclosures also say the invention is based "on several pre-clinical discoveries" in non-patient cell line experiments and mouse studies involving anti-tumor activity and improved tumor growth inhibition. (*See*, *e.g*., Ex. 1020, ¶[0008].) Finally, the invention is allegedly also based on the discovery that the claimed doses and combination of drugs "provide for the administration of a human tolerated antineoplastic therapy." (Ex. 1020, ¶[0009].) The claimed therapy provides for less side effects but does not show that the inventors knew that its method of treatment would provide clinical efficacy.

The disclosures of the parent applications contain 12 figures with subparts. (Ex. 1020.) Figures 1-11 involve pre-clinical studies of cell lines and animal models but none involve the treatment of human patients. (*Id.*, FIGS. 1-11.) Only Figure 12 shows a schematic of proposed human clinical trials, but there are no results of these clinical trials described in these specifications. (*Id*., FIG. 12.) In fact, the Detailed Description Sections discuss these preclinical cell line and animal tests along with a laundry list of different dosing combinations among the claimed chemotherapy drugs without providing any data regarding clinical efficacy. (Ex. 1001, 5:50 – 18:17; Ex. 1020, [0035]-[0075].)

None of the working examples in the parent applications demonstrate that the inventors possessed a method of treating metastatic pancreatic cancer patients with clinical efficacy. (*See* Ex. 1002, ¶¶225-226.)

Based on this limited disclosure, the POSA would not have recognized that the inventors were in possession of a method that would result in clinical efficacy, and as a result, the parent applications do not show "that the inventors *actually invented* the invention claimed." *Centocor Ortho Biotech, Inc. v. Abbott Labs.,* 636 F.3d 1341, 1348 (Fed. Cir. 2011); *see also* Ex. 1002, ¶227. While it may have been the inventors' goal to demonstrate actual efficacy through their description of the clinical protocol, "[p]atents are not rewarded for mere searches, but are intended to compensate their successful completion." *Novo Pharmaceuticals v. Dr. Reddy's*

Labs., 923 F.3d 1368, 1381 (2019). Moreover, "[a] 'mere wish or plan' for obtaining the claimed invention is not adequate written description," *Centocor,* 636 F.3d at 1348.

To the extent Patent Owner later established clinical efficacy of the claimed methods through the results of clinical trials not disclosed in the '552 patent, this "is of no import," since written description must be evaluated at the time of the filing of the disclosure, which was well before the results of the Phase III trials. *Biogen International GmbH v. Mylan Pharmaceuticals Inc.*, 18 F.4th 1333, 1343-44 (Fed. Cir. 2021). As a result, these parent applications lack written description of the Challenged Claims if these claims are construed to require clinical efficacy. *See Nuvo*, 923 F. 3d at 1384 (patents held invalid "for lack of an adequate written description given that the shared specification does not adequately describe the claimed effectiveness of uncoated PPI [proton pump inhibitors]."); *Biogen*, 18 F.4th at 1345 (Fed. Cir. 2021).

XIII. DETAILED EXPLANATION OF GROUNDS FOR UNPATENTABILITY

A. Ground 1: There is a reasonable likelihood that at least Claims 1, 3-6, 8-14 are obvious under 35 U.S.C. § 103 by Conroy, Conroy Protocol, Conroy Appendix and Mahaseth in combination with Bayever, Saif, Ko, and Cantore in view of Nichetti and Nevala-Plagemann

(i) Claim 1

The obviousness of claim 1 is demonstrated below in the following claim

chart.

Claim 1 of the ’552 patent	**Prior Art**
A method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received an antineoplastic agent to treat the metastatic adenocarcinoma of the pancreas, the method comprising administering an antineoplastic therapy to the patient once every two weeks, the antineoplastic therapy consisting of: a. 60 mg/m^2 of liposomal irinotecan, b. 60 mg/m^2 oxaliplatin, c. 200 mg/m^2 of the (1)-form of leucovorin or 400 mg/m^2 of the (l+d) racemic form of leucovorin, and d. 2,400 mg/m^2 5-fluorouracil; to treat the metastatic adenocarcinoma of the pancreas in the human patient.	Conroy, Conroy Protocol, Conroy Appendix and Mahaseth disclose: The FOLFIRINOX method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received an antineoplastic agent to treat the metastatic adenocarcinoma of the pancreas (Ex. 1003, 1; Ex. 1004, 4; Ex. 1017, 1; Ex. 1005, 1), the method comprising administering an antineoplastic therapy to the patient once every two weeks (Ex. 1003, 1; Ex. 1004, 5; Ex. 1005, 1), the antineoplastic therapy consisting of: • 60 mg/m^2 oxaliplatin (Ex. 1003, 4; Ex. 1004, 16-18; Ex. 1017, 3-7), • 400 mg/m^2 of the (l+d) racemic form of leucovorin (Ex. 1003, 1; Ex. 1004, 14, 40; Ex. 1005, 2; Ex. 1017, 3), and • 2,400 mg/m^2 5-fluorouracil (Ex. 1003, 1; Ex. 1004, 5; Ex. 1005, 2); to treat the metastatic adenocarcinoma of the pancreas in the human patient. (Ex. 1003, 1; Ex. 1004, 4; Ex. 1005, 1; Ex. 1017, 1) **Bayever** discloses: A method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received an antineoplastic agent to treat the metastatic adenocarcinoma of the pancreas (Ex. 1006, 2-4), the method comprising administering an antineoplastic therapy to the patient once every two weeks (i*d.*, 4, 6), the antineoplastic therapy consisting of: • 60 mg/m^2 of liposomal irinotecan (*id.*, 4, 39-42), • 400 mg/m^2 of the (l+d) racemic form of leucovorin (*See*, *e.g.*, *id.,* 4, 6, 14), and

Claim 1 of the ’552 patent	Prior Art
	• 2,400 mg/m^2 5-fluorouracil (*See id.*); to treat the metastatic adenocarcinoma of the pancreas in the human patient. (*Id.,* 3-4.) **Saif** and **Ko** disclose that MM-398 liposomal irinotecan should be further evaluated to replace free-irinotecan in FOLFIRINOX in first-line therapy for metastatic pancreatic cancer. (Ex. 1007, 1; Ex. 1008, 5.) **Cantore**, the **Conroy Protocol**, and the **Conroy Appendix** disclose that 60 mg/m^2 oxaliplatin was safe and effective in treating metastatic pancreatic cancer when administered with irinotecan every two weeks. (Ex. 1003, 1; Ex. 1004, 16-18; Ex. 1017, 3-7.)

(*See also* Ex. 1002, ¶¶228-307.)

Claim 1 is obvious over the prior art because the claimed method of treatment merely substituted a liposomal irinotecan with non-liposomal irinotecan in an already established gold-standard FOLFIRINOX regimen that disclosed the same claimed combination of drugs. (Ex. 1002, ¶¶231-264; *but see id.*, ¶¶67-72, 92-93 (FOLFIRINOX had drawbacks and others had tried to modify).) As discussed above, Conroy, the Conroy Protocol, the Conroy Appendix, and Mahaseth disclosed every feature of this claim, including the claimed 60 mg/m^2 oxaliplatin, except that they used free irinotecan instead of liposomal irinotecan. (Supra Sections VII.A-C.) As Dr. Ratain explains, the POSA reviewing the results of Conroy stating that the

median dose intensity of oxaliplatin was 78% and the fact that the Conroy Protocol and Appendix disclosed numerous dose reductions of oxaliplatin to 60 mg/m^2 oxaliplatin in the event of certain toxicity incidents, would have concluded that a significant portion of FOLFIRINOX patients were administered with 60 mg/m^2 oxaliplatin. (Ex. 1002, ¶¶105, 241-243 (explaining the toxicity concerns and the obvious range and/or dose of 60 mg/m^2 oxaliplatin was known).)

Moreover, the POSA would have been motivated to replace free-irinotecan with liposomal irinotecan in view of Bayever, which by then had already disclosed a method of treating metastatic pancreatic cancer with the same liposomal irinotecan composition of the Challenged Claims along with the exact same claimed doses of leucovorin and 5-FU. (Ex. 1002, ¶¶235-240 (explaining the prior arts' motivations to substitute MM-398 for the free irinotecan and the obviousness of arriving at the claimed dose, which was taught by the art).) This is further supported by Saif and Ko—not discussed during prosecution—which both suggested evaluating MM-398 liposomal irinotecan in first-line therapy. Ko states that MM-398 should be explored in additional studies "in the first-line setting," and then specifically references "FOLFIRINOX as a front-line standard in patients with good performance status." (Ex. 1008, 5.) Saif goes even further: first by asking that "[n]ow that we have…FOLFIRINOX as an option for first-line treatment, how will this [MM-398] regimen fit in the algorithm of the treatment," and then answering "[i[t seems logical

to test this [MM-398] drug/regimen further" to determine "replacing irinotecan in FOLFIRINOX with MM-398." (Ex. 1007, 1.) Thus, contrary to Patent Owner's arguments during prosecution, the prior art clearly provided motivation to combine the MM-398 liposomal irinotecan of Bayever with the gold-standard first-line therapy of FOLFIRINOX.

This combination also traverses other arguments raised by Patent Owner during prosecution.

First, while Patent Owner argued during prosecution that Conroy disclosed a higher dose of 5-FU because of the addition of 400 mg/m^2 bolus, (Ex. 1119 at 145), Mahaseth (not discussed during prosecution) teaches a modified FOLFIRINOX regimen that eliminates the 400 mg/m^2 bolus while still maintaining an acceptable toxicity profile and superior efficacy over other first-line therapies. (Ex. 1002, ¶244 (citing Ex. 1005 at 1-4).) Thus, Mahaseth's modified FOLFIRINOX regimen discloses the same claimed dose of 5-FU (2400 mg/m^2) and leucovorin (400 mg/m^2) as the Challenged Claims. (*Id*., ¶¶110-113).)

Second, Patent Owner incorrectly argued that Conroy only disclosed the higher 85 mg/m^2 instead of the claimed 60 mg/m^2 dose of oxaliplatin. (*See*, *e.g*., Ex. 119 at 145.) But the Examiner failed to appreciate that Conroy disclosed that the median dose intensity of oxaliplatin was 78%, and that the Conroy Protocol and Appendix disclosed numerous instances of oxaliplatin dose reductions to 60

mg/m^2 based on various toxicity events, which a POSA would have readily understood. (Ex. 1003, 4; Ex. 1004, 16-18; Ex. 1017, 3-7; Ex. 1002, ¶¶97, 105-106, 241-242.)

Third, Patent Owner argued there would have been no motivation to combine Conroy's FOLFIRINOX regimen with Bayever by incorrectly maintaining that Bayever is strictly limited to second-line treatment of pancreatic cancer and a POSA would not combine teachings related to first-line treatments with second-line treatments. (Ex. 1119 at 146; Ex. 1002, ¶¶130-137 (summarizing argument and explaining POSA's understanding that Bayever would be understood to be directed to both lines of treatment).) However, not only was Bayever not limited to second-line treatments of metastatic pancreatic cancer, Patent Owner's attempt to equate Bayever with FDA's approval of ONIVYDE® for second-line treatment to suggest otherwise is specious, especially considering that this FDA approval was not in the prior art. (*See* Ex. 1061.) Instead, Bayever discloses purported improvements upon prior first-line therapy, such as FOLFIRINOX, gemcitabine, and a protein tyrosine kinase inhibitor targeted to EGFR. (*See* Ex. 1002, ¶¶131-137 (citing Ex. 1006 and explaining disclosures).) This is borne out in the Summary, Detailed Description, including Patent Populations, Combination Therapy, and Treatment Protocols, and six out of the seven working examples of the disclosure where the invention is never limited to second-line therapy. (*Id*.) Indeed, ***all 27 of the published claims*** never

limit the invention to second-line therapy, which further underscores Bayever's disclosure as covering first-line therapy. (*Id*.) *See In re Rasmussen,* 650 F.2d 1212, 1214 (CCPA 1981) (claims as filed in the original specification are part of the disclosure). Thus, to the extent that the Office was misled by Patent Owner in believing that Bayever was limited to second-line therapy of pancreatic cancer, this was an error that materially affected the patentability of the Challenged Claims. After all, when read properly as ***not*** being limited to second-line therapy, but actually covering first-line therapy, Bayever clearly provided the motivation to combine its liposomal irinotecan therapy with the established gold-standard first-line therapy of FOLFIRINOX, as taught by Conroy and Mahaseth. (Ex. 1002, ¶¶137, 236-240.) This would have especially been the case since Bayever discloses a number of purported benefits of its liposomal irinotecan over free-irinotecan, including improved pharmacokinetic and toxicity profiles. (*See id*.; Ex. 1006 at 5-6, 10-15, 20-33, Figs. 1-6, Examples 1-6.)

Moreover, even assuming for the sake of argument that Bayever is limited to second-line therapy (it is not), Patent Owner was incorrect in arguing that the POSA would not combine teachings regarding first-line and second-line cancer therapies. As Dr. Ratain explains, the prior art was replete with examples of numerous drugs that were used or suggested for use in both first-line and second-line cancer therapies, foremost being irinotecan itself, since it was being used in established

first-line and second-line therapies for pancreatic cancer. (*See*, *e.g.*, Ex. 1002, ¶¶131-137, 141, 153, 160.)

Fourth, Petitioner's reliance on Cantore and other prior art renders Patent Owner's arguments related to Melis (relied upon by the Examiner) moot. Cantore discloses that 60 mg/m^2 oxaliplatin with irinotecan "shows evidence of being therapeutically beneficial, in patients with progressive metastatic pancreatic cancer," and no patients were ever reported in Cantore to have to resort to higher doses of oxaliplatin, like the 85 mg/m^2 of Melis. (Ex. 1009 at 5.) Other criticisms of Melis—that it excluded patients with metastatic pancreatic disease and only involved weekly and not bi-weekly administrations (Ex. 1119 at 147-48 (emphasis in original))—do not apply to Cantore. Thus. Cantore is substantially different from Melis and Patent Owner's arguments in trying to overcome Melis cannot be applied to Cantore.

Moreover, the Office steadfastly maintained throughout prosecution that lowering the dose of oxaliplatin from 85 mg/m^2 in FOLFIRINOX to the claimed 60 mg/m^2 was a "result effective variable" that rendered the claims obvious. (*See*, *e.g.*, Ex. 1097 at 194; Ex. 1119 at 12-13.) To the extent Patent Owner reversed the Office's determination by arguing that it was not known that adjusting oxaliplatin's dose would lead to fewer side effects, this too was an error that was material to the patentability of the Challenged Claims. Contrary to Patent Owner's arguments, POSA would have known that varying the amount of oxaliplatin, as with other

chemotherapy drugs, would result in differences in toxicity and effectiveness. (Ex. 1002, ¶¶69-72, 77-82 (explaining dose reductions for such purposes was a routine practice).) As Dr. Ratain explains, administering oxaliplatin was a standard prior art regimen in treating numerous cancers, including metastatic pancreatic cancer, and methods of determining a tolerable and effective dose of oxaliplatin were already established in gold-standard first-line therapies like FOLFIRINOX. (*Id*.) As Dr. Ratain further explains, it would have been fully expected that given what was known about MM-398 liposomal irinotecan's pre-clinical profile to remain at the tumor site longer than free-irinotecan (as disclosed in Bayever), lowering the dose of oxaliplatin from 85 mg/m^2 to the claimed 60 mg/m^2 would have been routine optimization. (*Id*.¶241.) In fact, as discussed above, Conroy discloses a median relative dose intensity of oxaliplatin of 78% of the 85 mg/m^2, and the Conroy Protocol and Appendix teach that there should be a dose reduction of oxaliplatin to 60 mg/m^2 based on certain toxicity events. (*Id*.) This clearly demonstrates that the POSA recognized that adjusting the dose of oxaliplatin was a result effective variable subject to routine optimization, ***a critical point not appreciated by the Examiner or Patent Owner during prosecution.*** Thus, the POSA certainly would have had the motivation to use routine and conventional methods to slightly adjust this dose to the claimed oxaliplatin dose. (Ex. 1002, ¶¶77-82, 241-242.)

Notably, Patent Owner's reliance on *OSI Pharmaceuticals, LLC v. Apotex, Inc.*, during prosecution to rebut the obviousness of optimizing the dose of oxaliplatin, (*see* Ex. 1119 at 150-51), is inapposite because this case did not even involve whether adjusting the doses of prior known compounds was routine. *See* 939 F.3d 1375 (Fed. Cir. 2019). The claims at issue in *OSI* were not dosing claims, but broadly claimed methods of treating various non-small cell lung cancers ("NSCLC") with an effective amount of erlotinib. *Id*. at 1378-79. The Federal Circuit reversed the PTAB's decision of obviousness because it found that the prior art references did not show any suggestion that erlotinib could be used to treat NSCLC, not that dosing claims could be arrived at from the prior art based on routine optimization. *Id.* at 1384-1386.

In sharp contrast to Patent Owner's reliance on *OSI*, Courts have routinely held dosing claims (such as the Challenged Claimed) invalid for being obvious "when the optimization of a range or other variable within the claims [] flows form the 'normal desire of scientists or artisans to improve upon what is already generally well known.'" *Pfizer v. Apotex*, 480 F.3d 1348, 1368 (Fed. Cir. 2007) ("our predecessor court set forth the rule that the discovery of an optimum value of a variable in a known process is usually obvious."); *Genentech, Inc. v. Sandoz Inc.*, 55 F.4th 1368 (Fed. Cir. 2022) ("varying doses in response to the occurrence of side effects would seem to be a well-established, hence obvious, practice."); *Amgen Inc.*

v. Sandoz Inc., 66 F.4th 952, 968 (Fed. Cir. 2023) ("Varying dose in response to the occurrence of side effects is well-known and obvious to the skilled artisan."); *ImmunoGen, Inc. v. Vidal*, 653 F. Supp. 3d 258, 294 (E.D. Va. 2023).

Fifth, Patent Owner erroneously maintained throughout prosecution that the method of treatment claims required clinical efficacy when it argued that the prior art did not show a reasonable expectation of success. (*See*, *e.g.,* Ex. 1119 at 148 ("there would have been no reasonable expectation that including oxaliplatin from a first-line treatment regimen (e.g., as disclosed in Conroy) into a second-line treatment regimen (e.g., as disclosed in Bayever) would yield an ***effective*** and tolerable first-line treatment pursuant to the claims.") (emphasis added).) Under a proper claim construction, the Challenged Claims do not require any clinical efficacy. (Section X.) These method of treatment claims only require that the claimed cocktail of chemotherapy drugs be administered ***for the purpose*** of providing an effective treatment of metastatic pancreatic cancer. (*See id.*)

To the extent that the Office was misguided by Patent Owner that a reasonable expectation of success of practicing the Challenged Claims required evidence of clinical efficacy, this also was an error that materially affected the patentability of those claims. By not requiring a clinical efficacy threshold, the bar to proving obviousness of the Challenged Claims is much lower since the POSA would only need to combine the prior art to arrive at a first-line treatment regimen administered

for the purpose of treating metastatic pancreatic cancer, and not with the expectation that the regimen would have superior clinical efficacy over the gemcitabine/nab-paclitaxel control arm. As Dr. Ratain explains, methods of treating metastatic pancreatic cancer are always with the hope that the patient will live longer, but that is often not the case. (Ex. 1002, ¶¶49-50.) However, these are still valid methods of treatment because they are administered for the ***purpose*** of trying to extend and improve life, not a guarantee that they will. (*Id*.)

Sixth, Patent Owner's unexpected results arguments are completely flawed. Patent Owner relied upon post-filing art in the form of the Wainberg references to try to rebut the *prima facie* case of obviousness. (*See* Ex. 1119 at 151-54.) Patent Owner argued that Wainberg showed the unexpected result that the claimed dose of 60 mg/m^2 liposomal irinotecan and 60 mg/m^2 oxaliplatin (60/60) was more tolerable than regimens with higher doses of either liposomal irinotecan or oxaliplatin. (*Id.*, 152.) Patent Owner then argued that this claimed 60/60 regimen "unexpectedly resulted in primary efficacy outcomes ***higher*** than that of the currently preferred FOLFIRINOX regimen as reported in Conroy." (*Id.*, 153) (emphasis added). Patent Owner then concluded that "[t]hese improvements are tangible benefits that demonstrate an improvement in efficacy of the claimed dosage regimens over the Conroy FOLFIRINOX regimen." (*Id.*)

However, this is hardly unexpected, since it has been universally accepted now and in the prior art that providing lower doses of these chemotherapy drugs results in fewer side effects. (Ex. 1002, ¶¶69-82 (explaining dose reduction to reduce side effects), 253-262 (explaining expected results).)

In addition, Patent Owner's arguments regarding superior efficacy are misleading. The Wainberg article itself cautions the public that such comparisons "cannot be made" between its results and those of FOLFIRINOX because of the "limitations inherent" in its study. (*Id*., ¶¶252-257 (citing Ex 1019 at 8.) Wainberg highlights that "important differences between the study populations include the proportions of patients with metastatic disease at study entry…, the proportions with liver metastases…, and the median ages," where the FOLFIRINOX patients were older and had a higher proportion of metastatic disease. (*Id.*) Patent Owner never disclosed these clear warnings made by Wainberg to the Office, but instead touted these findings as "tangible benefits" of "improved efficacy" over the prior art. (Ex 1119 at 153.)

Critically, more recent publications, which compared large scale clinical trial data between the Patent Owner's ONIVYDE® product against FOLFIRINOX in first-line therapy for pancreatic cancer patients, completely refute Patent Owner's unexpected results of clinical superiority. (Ex. 1002, ¶¶258-260.) Nichetti reported that there was ***no difference*** observed in overall survival between NALIRIFOX (the

regimen of the Challenged Claims) (11.1 months) and the prior art FOLFIRINOX (11.7 months) regimen, and FOLFIRINOX actually yielded better survival rates although not found to be statistically significant. (Ex. 1010, 1.) This compelled Nichetti to conclude that the "data do not suggest a preference between NALIRIFOX and FOLFIRINOX…". (*Id.*, 10.) Likewise, Nevala-Plagemann states that the "median OS [overall survivability] of patients receiving NALIRIFOX in NAPOLI 3 is ***identical*** to that of those who received FOLFIRINOX in PRODIGE 4 (11.1 months)." (Ex. 1011, 1) (emphasis added).

Notably, Nichetti and Nevala-Plagemann do not suffer from the inherent limitations of Wainberg because they compared randomized clinical trials involving a large number of patients, each with established efficacy hypotheses and control groups. (Ex. 1002, ¶260.) Nichetti and Nevala-Plagemann clearly establish that the regimen of the Challenged Claims confers ***no unexpected results*** because it yields the ***same efficacy*** to the prior art FOLFIRINOX first-line therapy, thus supporting the obviousness of the Challenged Claims because they offer ***no benefit*** over the prior art. (*See id*., ¶¶258-262.)

Thus, to the extent that the Office allowed the claims based on Patent Owner's erroneous unexpected results arguments to rebut the *prima facie* case of obviousness, this again was a material error which precludes the application of Section 325(d) discretion to deny the Petition. (*See* Section XI.C.)

(ii) **Claim 3:** The method of claim 1, wherein the 5-fluorouracil is administered as an infusion over 46 hours.

Claim 3 is also obvious based on the discussion above regarding claim 1 and the fact that both Conroy and Mahaseth disclose that 5-FU is administered as an infusion over 46 hours. (*See* Ex. 1003 at 1; Ex. 1005 at 2; Ex. 1002, ¶¶265-267 (explaining how both references teach limitation).)

(iii) **Claim 4:** The method of claim 1, wherein the leucovorin is administered immediately prior to the 5-fluorouracil.

Claim 4 is also obvious based on the discussion above regarding claim 1 and the fact that Conroy, Mahaseth, and Bayever all disclose that the leucovorin is administered immediately prior to 5-FU. (*See* Ex. 1003 at 1; Ex. 1005 at 2; Ex. 1006 at 27 ("leucovorin should always be administered prior to 5-FU."), 53; Ex. 1002, ¶¶268-270 (explaining same).)

(iv) **Claim 5:** The method of claim 1, wherein the liposomal irinotecan, oxaliplatin and leucovorin are administered on days 1 and 15 of a 28-day treatment cycle.

Claim 5 is also obvious based on the discussion above regarding claim 1 and the fact that Conroy discloses that irinotecan, oxaliplatin, and leucovorin were administered every two weeks, which corresponds to days 1 and 15, and that six months of chemotherapy was recommended for patients who had a response, which

constitutes at least one 28-day treatment cycle. (*See* Ex. 1003 at 3.) Bayever also discloses that liposomal irinotecan MM-398 and leucovorin were also administered every 2 weeks, which corresponds to days 1 and 15, and that patients were to be treated "until disease progression (radiological or clinical deterioration), intolerable toxicity or by other reasons for study termination. (*See* Ex. 1006 at 26-27.) Taken together, the POSA would have understood that the claimed method of claim one would be administered on days 1 and 15 of a 28-day treatment cycle. (Ex. 1002, ¶¶271-273 (explaining same).)

(v) **Claim 6:** The method of claim 1, wherein the liposomal irinotecan is administered as an infusion over about 90 minutes.

Claim 6 is also obvious based on the discussion above regarding claim 1 and the fact that Bayever discloses that MM-398 is administered as an infusion over 90 minutes. (*See* Ex. 1006 at 26-27, 33; Ex. 1002, ¶¶274-276 (explaining same).)

(vi) Claim 8: The method of claim 1, wherein the liposomal irinotecan comprises irinotecan sucrose octasulfate encapsulated in liposomes.

Claim 8 is also obvious based on the discussion above regarding claim 1 and the fact that Bayever discloses irinotecan sucrose octasulfate encapsulated in liposomes. (*See* Ex. 1006 at 4-6; Ex. 1002, ¶¶277-279 (explaining same).)

(vii) Claim 9: The method of claim 1, wherein the liposomal irinotecan comprises irinotecan encapsulated in liposomes comprising 1,2-

distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, and a N-(carbonylmethoxypolyethlyeneglycol-2000)-1,23-phosphoethanolamine (MPEG-2000-DSPE).

(viii) **Claim 10:** The method of claim 1, wherein the liposomal irinotecan comprises irinotecan sucrose octasulfate encapsulated in liposomes comprising 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, and a N-(carbonylmethoxypolyethlyene glycol-2000)-1,2-distearoly-sn-glycero-3-phosphoethanolamine (MPEG-2000-DSPE).

Claims 9 and 10 are also obvious based on the discussion above regarding claim 1 and the fact that Bayever discloses liposomal irinotecan comprising this claimed composition. Bayever cites to U.S. Patent No. 8,147,867 ("the '867 patent") (Ex. 1024) when referring to MM-398 liposomal irinotecan. A POSA would have found this obvious in view of Bayever. (Ex. 1002, ¶¶280-285 (citing Exs. 1006 at 9, 1024 at 27:46-51; 91:13-18 and claim 31).) The '867 patent describes a liposomal irinotecan comprising irinotecan sucrose octasulfate comprising 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, and a N-(carbonylmethoxy polyethlyeneglycol-2000)-1,2-distearoly-sn-glycero-3-phosphoethanolamine (MPEG-2000-DSPE). (*See* Ex. 1024, Claim 31.)

(ix) **Claim 11:** The method of claim 10, wherein the liposomal irinotecan, oxaliplatin, leucovorin, and 5-fluorouracil are administered beginning

on days 1 and 15 of a 28-day treatment cycle; each administration of the liposomal irinotecan is administered prior to each administration of the leucovorin; each administration of the leucovorin is administered immediately prior to each administration of the 5-fluorouracil; and each administration of the 5-fluorouracil is administered as an infusion over 46 hours.

Claim 11 is also obvious based on the discussion above with respect to claims 1, 3, 5, and 10 and the fact Conroy, Mahaseth, and Bayever disclose that liposomal irinotecan is administered prior to leucovorin and leucovorin is administered prior to 5-FU and over 46 hours. (*See* Ex. 1002, ¶¶286-291 (citing Ex. 1003 at 3; Ex. 1006 at 6, 13-15, 26-33; Ex. 1005 at 2).)

(x) **Claim 12:** A method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received gemcitabine to treat the metastatic adenocarcinoma of the pancreas, the method comprising administering an antineoplastic therapy to the patient once every two weeks, the antineoplastic therapy consisting of: (a) 60 mg/m^2 of liposomal irinotecan, (b) 60 mg/m^2 oxaliplatin, (c) 200 mg/m^2 of the (1)-form of leucovorin or 400 mg/m^2 of the (l+d) racemic form of leucovorin, and (d) 2,400 mg/m^2 5-fluorouracil; to treat the metastatic adenocarcinoma of the pancreas in the human patient.

Claim 12 is also obvious based on the discussion above with respect to claim 1 because gemcitabine is an antineoplastic agent, and the FOLFIRINOX regimen of Conroy and Mahaseth was administered as first-line therapy in patients who had not been previously treated with gemcitabine. (*See supra* claim 1; Ex. 1002, ¶¶292-294 (citing Ex. 1003 at 1; Ex. 1005 at 1.)

(xi) **Claim 13:** The method of claim 1, wherein the liposomal irinotecan, oxaliplatin, leucovorin, and 5-fluorouracil are administered beginning on days 1 and 15 of a 28-day treatment cycle; each administration of the liposomal irinotecan is administered prior to each administration of the leucovorin; each administration of the leucovorin is administered prior to each administration of the 5-fluorouracil; and each administration of the 5-fluorouracil is administered as an infusion over 46 hours.

Claim 13 is also obvious based on the discussion above with respect to claims 1, 3, 10, and 11. (Ex. 1002, ¶¶295-301 (explaining the prior art, including Conroy, Mahaseth, and Bayever, disclosed such administration).)

(xii) **Claim 14:** The method of claim 12, wherein the liposomal irinotecan, oxaliplatin, leucovorin, and 5-fluorouracil are administered beginning on days 1 and 15 of a 28-day treatment cycle; each administration of the liposomal irinotecan is administered prior to each administration of

the leucovorin; each administration of the leucovorin is administered prior to each administration of the 5-fluorouracil; and each administration of the 5-fluorouracil is administered as an infusion over 46 hours.

Claim 14 is also obvious based on the discussion above with respect to claims 1, 3, 12, and 13. (Ex. 1002, ¶¶302-307 (explaining that Conroy, Mahaseth, and Bayever teach or suggest such an administration).)

B. Ground 2: There is a reasonable likelihood that Claims 2, 7, and 15 are obvious under 35 U.S.C. § 103 based on the prior art disclosed in Ground 1 in combination with Masi and Ginocchi

(i) Claim 2: The method of claim 1, wherein each administration of the oxaliplatin begins 2 hours after completing each administration of the liposomal irinotecan**.**

Claim 2 is also obvious based on the discussion above with respect to claim 1 in Ground 1 and the fact that Bayever discloses that liposomal irinotecan MM-398 should be administered first before any other drugs, and that Masi discloses that irinotecan should be administered prior to oxaliplatin in chemotherapy treatment for metastatic colorectal cancer based on the FOLFOXIRI regimen. (Ex. 1012, 5.) Ginocchi applied a modified FOLFOXIRI regimen (which administers the irinotecan before the oxaliplatin) to metastatic pancreatic patients which was shown to be well tolerated with good efficacy. (*See* Ex. 1016, 1.)

While these references do not explicitly mention that oxaliplatin be administered 2 hours after liposomal irinotecan, this would have been merely routine optimization to determine this variable. Thus, when Masi and Ginocchi are combined with the fact that Bayever teaches that liposomal irinotecan MM-398 should be the first drug administered in therapy, this renders claim 2 obvious. (Ex. 1006, Claim 4.)

(ii) **Claim 7:** The method of claim 1, wherein the liposomal irinotecan is administered, followed by administering the oxaliplatin, followed by administering the leucovorin, followed by administering the 5-fluorouracil.

Claim 7 is also obvious based on the discussion above regarding claim 1 in Ground 1, claim 2 of Ground 2, and by the fact that Conroy and Mahaseth both disclose that 5-FU is administered last in the FOLFIRINOX regimen with leucovorin immediately preceding it and that Bayever also discloses that 5-FU is administered last with leucovorin immediately preceding it. (*See* Ex. 1002, ¶¶308-309; Ex.1003 at 1-3; Ex. 1005 at 2; Ex. 1006 at Claims 4, 13-15.) Moreover, as discussed above with respect to claim 2, this claimed sequence of drugs is the same as FOLFOXIRI, which was shown to be safe and effective in metastatic pancreatic cancer patients. (*See* Ex. 1016 at 1.)

(iii) **Claim 15:** The method of claim 1, wherein each administration of the oxaliplatin begins after completing each administration of the liposomal irinotecan, and the method further comprises administering a corticosteroid and an anti-emetic to the patient prior to the antineoplastic therapy.

Claim 15 is also obvious based on the discussion above with respect to claim 1 of Ground 1, claim 2 of Ground 2, and the fact that Bayever discloses administering dexamethasone, which is a corticosteroid, and an anti-emetic to the patient prior to the antineoplastic therapy. (*See* Ex. 1002, ¶¶310-311; Ex. 1006 at 4-6, 33-35 Claims 9, 18.)

C. Ground 3: There is a reasonable likelihood that Claims 1-15 are obvious under 35 U.S.C. § 103 based on the prior art disclosed in Grounds 1 and 2 and Carnevale and Dean.

Under Ground 3, the Challenged Claims are obvious based on an effective filing date of November 10, 2017. (Ex. 1002, ¶¶312-330.) Under this priority date, the Challenged Claims are obvious based on additional prior art not discussed during prosecution. Even if the Challenged Claims are construed to require clinical efficacy under Ground 3, this would still render the claims obvious since prior art that establishes obviousness is not sufficient to satisfy an adequate written description of the claims. *See Tronzo*¸ 156 F.3d at 1158.

(i) Claim 1

Claim 1 is obvious for all the reasons set forth above with respect to claim 1 of Ground 1 and based on the further disclosure of Carnevale and Dean. Carnevale discloses that based on the optimized pharmacokinetics and safety profile of MM-398, it suggests that MM-398 liposomal irinotecan would "make ***an ideal substitute*** for irinotecan in the first-line FOLFIRINOX regimen" and that this might represent ***a natural extension*** of MM-398's role in metastatic pancreatic cancer." (Ex. 1002, ¶¶313-314; Ex. 1013 at 11) (emphasis added).

Dean discloses a phase 2 clinical trial that evaluates the safety and efficacy of liposomal irinotecan MM-398 with 5-FU, leucovorin, and oxaliplatin in first-line therapy of pancreatic cancer patients. (Ex. 1002, ¶315; Ex. 1014, 1-3.)

Therefore, Carnevale and Dean provide even more motivation to the POSA to substitute free irinotecan with MM-398 liposomal irinotecan in the established gold-standard FOLFIRINOX regimen at the claimed doses and frequency. (*Id*., ¶316.)

(ii) Claim 2

Claim 2 is obvious for all the reasons discussed above with respect to claim 1 of Ground 1 and 3 and claim 2 of Ground 2.

(iii) Claim 3

Claim 3 is obvious for all the reasons set forth above with respect to claims 1 and 3 of Ground 1 and claim 1 of Ground 3. (*Id*., ¶318.)

(iv) Claim 4

Claim 4 is obvious for all the reasons set forth above with respect to claims 1 and 4 of Ground 1 and claim 1 of Ground 3. (*Id*., ¶319.)

(v) Claim 5

Claim 5 is obvious for all the reasons set forth above with respect to claims 1 and 5 of Ground 1 and claim 1 of Ground 3. (*Id*., ¶320.)

(vi) Claim 6

Claim 6 is obvious for all the reasons set forth above with respect to claims 1 and 6 of Ground 1 and claim 1 of Ground 3. (*Id*., ¶321.)

(vii) Claim 7

Claim 7 is obvious for all the reasons set forth above with respect to claim 1 of Ground 1, claim 7 of Ground 2, and claim 1 of Ground 3. (*Id*., ¶322.)

(viii) Claim 8

Claim 8 is obvious for all the reasons set forth above with respect to claims 1 and 8 of Ground 1 and claim 1 of Ground 3. (*Id*., ¶323.)

(ix) Claim 9

Claim 9 is obvious for all the reasons set forth above with respect to claims 1 and 9 of Ground 1 and claim 1 of Ground 3. (*Id*., ¶324.)

(x) Claim 10

Claim 10 is obvious for all the reasons set forth above with respect to claims 1 and 19 of Ground 1 and claim 1 of Ground 3. (*Id*., ¶325.)

(xi) Claim 11

Claim 11 is obvious for all the reasons set forth above with respect to claims 1, 3, 10, and 11 of Ground 1 and Claim 1 in Ground 3. (*Id*., ¶326.)

(xii) Claim 12

Claim 12 is obvious for all the reasons set forth above with respect to claims 1 and 12 of Ground 1 and claim 1 of Ground 3. (*Id*., ¶327.)

(xiii) Claim 13

Claim 13 is obvious for all the reasons set forth above with respect to claims 1, 3, and 13 of Ground 1 and claim 1 of Ground 3. (*Id*., ¶328.)

(xiv) Claim 14

Claim 13 is obvious for all the reasons set forth above with respect to claims 1, 3, 12, 13, and 14 of Ground 1 and claim 1 of Ground 3. (*Id*., ¶329.)

(xv) Claim 15

Claim 15 is obvious for all the reasons set forth above with respect to claims 1 of Ground 1, claims 2 and 15 of Ground 2, and claim 1 of Ground 3. (*Id*., ¶330.)

XIV. CONCLUSION

Based on the foregoing, Petitioner requests institution of IPR for claims 1-15 of the ’552 patent based on the grounds specified in the Petition.

By: / Lukas Toft /
Lukas Toft
Reg. No. 75,311
Counsel for Petitioners

Dated: January 17, 2025

CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(d), the undersigned certifies that the foregoing Petition for *Inter Partes* Review of Claims 1–15 of U.S. Patent No. 11,344,552 contains, as measured by the word-processing system used to prepare this paper, 13,734 words. This word count does not include the items excluded by 37 C.F.R. § 42.24 as not counting towards the word limit.

By: / Lukas Toft /
Lukas Toft
Reg. No. 75,311
Counsel for Petitioners

Dated: January 17, 2025

CERTIFICATE OF SERVICE

I hereby certify that on January 17, 2025, I caused a true and correct copy of the foregoing Petition for *Inter Partes* Review of Claims 1–15 of U.S. Patent No. 11,344,552 to be served by Federal Express on the Patent Owner at the following correspondence address of record as listed on the USPTO's Patent Center website:

153749 - McNeil PLLC/Ipsen
Ipsen Bioscience, Inc.
245 First Street, 18th Floor
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A courtesy copy was also sent by electronic mail to the Patent Owner's litigation counsel at the following address:

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By: / Lukas Toft /
Lukas Toft
Reg. No. 75,311
Counsel for Petitioners

Dated: January 17, 2025

Appendix A

Claims of U.S. Patent No. 11,344,552

1. A method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received an antineoplastic agent to treat the metastatic adenocarcinoma of the pancreas, the method comprising administering an antineoplastic therapy to the patient once every two weeks, the antineoplastic therapy consisting of:

a. 60 mg/m^2 of liposomal irinotecan,

b. 60 mg/m^2 oxaliplatin,

c. 200 mg/m^2 of the (l)-form of leucovorin or 400 mg/m^2 of the (l+d) racemic form of leucovorin, and

d. 2,400 mg/m^2 5-fluorouracil;

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

2. The method of claim 1, wherein each administration of the oxaliplatin begins 2 hours after completing each administration of the liposomal irinotecan.

3. The method of claim 1, wherein the 5-fluorouracil is administered as an infusion over 46 hours.

4. The method of claim 1, wherein the leucovorin is administered immediately prior to the 5-fluorouracil.

5. The method of claim 1, wherein the liposomal irinotecan, oxaliplatin and leucovorin are administered on days 1 and 15 of a 28-day treatment cycle.

6. The method of claim 1, wherein the liposomal irinotecan is administered as an infusion over about 90 minutes.

7. The method of claim 1, wherein the liposomal irinotecan is administered, followed by administering the oxaliplatin, followed by administering the leucovorin, followed by administering the 5-fluorouracil.

8. The method of claim 1, wherein the liposomal irinotecan comprises irinotecan sucrose octasulfate encapsulated in liposomes.

9. The method of claim 1, wherein the liposomal irinotecan comprises irinotecan encapsulated in liposomes comprising 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, and a N-(carbonylmethoxypolyethlyene glycol-2000)-1,2-distearoly-sn-glycero-3-phosphoethanolamine (MPEG-2000-DSPE).

10. The method of claim 1, wherein the liposomal irinotecan comprises irinotecan sucrose octasulfate encapsulated in liposomes comprising 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), cholesterol, and a N-(carbonylmethoxypolyethlyene glycol-2000)-1,2-distearoly-sn-glycero-3-phosphoethanolamine(MPEG-2000-DSPE).

11. The method of claim 10, wherein the liposomal irinotecan, oxaliplatin, leucovorin, and 5-fluorouracil are administered beginning on days 1 and 15 of a 28-

day treatment cycle; each administration of the liposomal irinotecan is administered prior to each administration of the leucovorin; each administration of the leucovorin is administered immediately prior to each administration of the 5-fluorouracil; and each administration of the 5-fluorouracil is administered as an infusion over 46 hours.

12. A method of treating metastatic adenocarcinoma of the pancreas in a human patient who has not previously received gemcitabine to treat the metastatic adenocarcinoma of the pancreas, the method comprising administering an antineoplastic therapy to the patient once every two weeks, the antineoplastic therapy consisting of:

a. 60 mg/m^2 of liposomal irinotecan,

b. 60 mg/m^2 oxaliplatin,

c. 200 mg/m^2 of the (1)-form of leucovorin or 400 mg/m^2 of the (l+d) racemic form of leucovorin, and

d. 2,400 mg/m^2 5-fluorouracil;

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

13. The method of claim 1, wherein the liposomal irinotecan, oxaliplatin, leucovorin, and 5-fluorouracil are administered beginning on days 1 and 15 of a 28-day treatment cycle; each administration of the liposomal irinotecan is administered prior to each administration of the leucovorin; each administration of the leucovorin

is administered prior to each administration of the 5-fluorouracil; and each administration of the 5-fluorouracil is administered as an infusion over 46 hours.

14. The method of claim 12, wherein the liposomal irinotecan, oxaliplatin, leucovorin, and 5-fluorouracil are administered beginning on days 1 and 15 of a 28-day treatment cycle; each administration of the liposomal irinotecan is administered prior to each administration of the leucovorin; each administration of the leucovorin is administered prior to each administration of the 5-fluorouracil; and each administration of the 5-fluorouracil is administered as an infusion over 46 hours.

15. The method of claim 1, wherein each administration of the oxaliplatin begins after completing each administration of the liposomal irinotecan, and the method further comprises administering a corticosteroid and an anti-emetic to the patient prior to the antineoplastic therapy.