UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

LIQUIDIA TECHNOLOGIES, INC.,

Petitioner

v.

UNITED THERAPEUTICS CORPORATION,

Patent Owner

IPR2021-00406
U.S. Patent No. 10,716,793 B2
Issue Date: July 21, 2020

Title: Treprostinil Administration by Inhalation

PETITION FOR *INTER PARTES* REVIEW
OF U.S. Patent No. 10,716,793 B2

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1007	Voswinckel, R., et al., Abstract 218: "Inhaled treprostinil is a potent pulmonary vasodilator in severe pulmonary hypertension," *European Heart Journal* 25:22 (2004) ("Voswinckel JESC")
1008	Robert Voswinckel, Beate Enke, Andre Kreckel, Frank Reichenberger, Stefanie Krick, Henning Gall, Tobias Gessier, Thomas Schmehl, Markus G. Kohstall, Friedrich Grimminger, Hossein A. Ghofrani, Werner Seeger, and Horst Olschewski, Abstract 1414: "Inhaled Treprostinil Sodium (TRE) For the Treatment of Pulmonary Hypertension," Abstracts from the 2004 Scientific Sessions of the American Heart Association, *Circulation,* 110(17 Suppl.):III-295 (October 26, 2004) ("Voswinckel JAHA")
1009	Robert Voswinckel, Hossein A. Ghofrani, Friedrich Grimminger, and Werner Seeger, "Clinical Observations" on "Inhaled Treprostinil for Treatment of Chronic Pulmonary Arterial Hypertension," "Letters" Section of the *Annals of Internal Medicine*, 144(2):149-50 (January 2006) ("Voswinckel 2006")
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1011	First Amended Complaint filed in *United Therapeutics Corporation v. Liquidia Technologies, Inc.*, Case No. 1:20-cv-00755-RGA (D. Del.)
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1020	Clark, A.R., "Medical Aerosol Inhalers: Past, Present, and Future," *Aerosol Science and Technology*, 22:374-91 (1995) ("Clark")
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1036	Declaration of Sylvia Hall-Ellis, Ph.D. ("Hall-Ellis Decl.")
1037	English translation of OptiNeb® User Manual 2005
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1039	Frijlink, H.W. and De Boer, A.H., "Dry powder inhalers for pulmonary drug delivery," Expert Opinion on Drug Delivery, 1(1):67-86 (2004) ("Frijlink and De Boer")
1040	Chew N. and Chan H.-K., "Pharmaceutical Dry Powder Aerosol Delivery," KONA, No. 19, pp. 46-56 (2001) ("Chew and Chan")
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1042	January 27, 2020 Press Release, "Liquidia Submits New Drug Application for LIQ861 (Treprostinil) Inhalation Powder to U.S. Food And Drug Administration for the Treatment of Pulmonary Arterial Hypertension (PAH)," *available at* https://investors.liquidia.com/news-releases/news-release-

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1047	Hoeper, M.M., et al., "Long-Term Treatment of Primary Pulmonary Hypertension with Aerosolized Iloprost, a Prostacyclin Analogue," *N Engl J Med*, 342:1866-70 (2000) ("Hoeper")
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1059	Nauser, T.D., "Pulmonary Hypertension: New Perspectives," *CHF*, 9:155-62 (2003) ("Nauser 2003")
1060	Pitcairn, G., et al., "Deposition of Corticosteroid Aerosol in the Human Lung by Respimat® Soft Mist™ Inhaler Compared to Deposition by Metered Dose Inhaler or by Turbuhaler® Dry Powder Inhaler," *Journal of Aerosol Medicine*, 18(3):264-72 (2005) ("Pitcairn")
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1074	Orenitram® Label, *available at* https://www.orenitram.com/pdf/Orenitram-Prescribing-Information.pdf
1075	November 17, 2008 Press Release, "Eli Lilly and Company Licenses U.S. Rights for Tadalafil PAH Indication to United Therapeutics Corporation," *available at* https://www.fiercebiotech.com/biotech/eli-lilly-and-company-licenses-u-s-rights-for-tadalafil-pah-indication-to-united
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This is a petition for *Inter Partes* Review of claims 1-8 of U.S. Patent No. 10,716,793 B2 (EX1001) (the "'793 Patent"). The '793 Patent is directed to a method of treatment of pulmonary hypertension via inhalation of 15 to 90 micrograms of treprostinil in 1 to 3 breaths, through various inhalation devices. Treprostinil products have been on the market for almost two decades, and the initial, actually innovative patents have expired. In contrast, the '793 Patent was issued in July 2020, over 14 years after the application to which it claims priority. The '793 Patent is Patent Owner ("PO") United Therapeutics Corporation's ("UTC") latest attempt to evergreen their way into blocking fair competition, and should be invalidated based on the numerous prior art references disclosing its claim limitations before 2006.

I. MANDATORY NOTICES UNDER 37 C.F.R. § 42.8(A)(1)

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

Petitioner Liquidia Technologies, Inc. ("Liquidia") is the real party-in-interest.

B. Related Matters Under 37 C.F.R. § 42.8(b)(2)

UTC has alleged infringement of the '793 Patent by Liquidia Technologies, Inc. in *United Therapeutics Corporation v. Liquidia Technologies, Inc.*, 1:20-cv-00755-RGA, in the United States District Court for the District of Delaware.

C. Lead and Back-Up Counsel under 37 C.F.R. § 42.8(b)(3)

Petitioner provides the following designation of counsel.

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D. Service Information

The Petition is being served by FEDERAL EXPRESS to the current correspondence address for the '793 Patent, Foley & Lardner LLP, 3000 K Street N.W., Suite 600, Washington, DC 20007-5109. Petitioner may be served by e-mail

at the addresses provided above for lead and back-up counsel.

E. Power of Attorney

Filed concurrently with this petition per 37 C.F.R. § 42.10(b).

II. PAYMENT OF FEES - 37 C.F.R. § 42.103

This Petition requests review of claims 1-8 of the '793 Patent (8 claims) and is accompanied by a payment of $41,500. 37 C.F.R. § 42.15. This Petition meets the fee requirements of 35 U.S.C. § 312(a)(1). The undersigned further authorizes the United States Patent and Trademark Office, including the Patent Trial and Appeal Board, to charge any additional fee that might be due or required to Deposit Account No. 50-1283.

III. REQUIREMENTS UNDER 37 C.F.R. §§ 42.104 AND 42.108 AND CONSIDERATIONS UNDER §§ 314(A) AND 325(D)

A. Grounds for Standing Under 37 C.F.R. § 42.104(a)

Petitioner certifies that the '793 Patent is eligible for *inter partes* review, and Petitioner is not barred or estopped from requesting *inter partes* review.

B. Identification of Challenge Under 37 C.F.R. § 42.104(b) and Statement of Precise Relief Requested

Petitioner requests the Board institute *inter partes* review of claims 1-8 of the '793 Patent based on these grounds:

Ground	'793 Claim(s)	Basis for Challenge
1.	1-8	Obvious over U.S. Patent No. 6,521,212 (EX1006), Voswinckel JAHA (EX1008), and

		Voswinckel JESC (EX1007)
2.	1-8	Obvious over '212 Patent and Voswinckel JESC
3.	1	Anticipated by Ghofrani
4.	1, 3, 8	Obvious over Voswinckel JAHA and Ghofrani (EX1010)
5.	1, 3	Anticipated by Voswinckel 2006 (EX1009)
6.	2, 4-8	Obvious over Voswinckel 2006 and '212 Patent

Sections X to XV of this Petition detail why the challenged claims are invalid. This Petition is supported by accompanying Declarations of Dr. Nicholas Hill (EX1002) and Dr. Igor Gonda (EX1004), qualified experts in their fields. *See* EX1003; EX1005 (*Curriculum Vitae*).

C. Threshold Requirement for *Inter Partes* Review 37 C.F.R. § 42.108(c)

Inter partes review of claims 1-8 should be instituted because this Petition establishes a reasonable likelihood that Petitioner will prevail with respect to each of the challenged claims. 35 U.S.C. § 314(a).

D. Considerations under 35 U.S.C. § 314(a)

Petitioner diligently filed this Petition. PO asserted the '793 Patent against Petitioner for the first time on July 22, 2020 (EX1011, 15-17), and identified claims 1, 4, and 6-8 as the asserted claims in infringement contentions served October 16, 2020. This Petition is filed within three months of receiving infringement contentions and over six months before the one-year bar.

The Board should not discretionarily deny this Petition because UTC filed a motion in the district court litigation to prevent Petitioner from contesting the validity of the '793 Patent under the doctrine of assignor estoppel, based on one of the inventors, Robert Roscigno, being a former Liquidia employee. EX1013. Although the district court denied UTC's original motion (EX1014), UTC indicated it intends to further pursue its assignor estoppel allegations in district court. *See, e.g.*, EX1012, 13. Should UTC ultimately prevail on the issue of assignor estoppel in district court, Petitioner would be foreclosed from raising invalidity of the '793 Patent in that forum. Under this scenario, this Petition would be Petitioner's only available means for challenging validity of the claims, because "assignor estoppel has no place in IPR proceedings." *Arista Networks, Inc. v. Cisco Sys., Inc.*, 908 F.3d 792, 804 (Fed. Cir. 2018). Accordingly, the pending district court litigation should not be a basis for discretionary denial.

Further, the *Fintiv* factors do not weigh in favor of discretionary denial. First, this Petition includes claims not at issue in the district court litigation, namely claims 2, 3, and 5—just under half of the total claims challenged in this petition. Second, the parties have just begun claim construction proceedings in the district court litigation, have not yet taken any depositions, and have conducted only the initial minimum required discovery. Third, the merits of this Petition are strong, as exemplified by the Board's institution of petitions involving two of the references

here against similar claims in IPR2017-01621 and IPR2017-01622 (brought by a different petitioner),[1] as well as the fact that this Petition asserts five grounds to challenge independent claim 1 and at least three different grounds for each of the seven dependent claims.

Finally, previous IPRs filed on related patents 9,358,240 (IPR2017-01621) and 9,339,507 (IPR2017-01622) do not warrant discretionary denial. The prior IPRs were filed by Watson Laboratories, Inc., an unrelated party, prior to PO suing Petitioner. *Alphatec Holdings, Inc. v. Nuvasive, Inc.*, IPR2019-00361, Paper 19 at 10 (P.T.A.B. July 9, 2019). The prior IPRs were instituted, but terminated before final decision due to settlement between the parties. *Watson Labs., Inc. v. United Therapeutics, Corp.*, IPR2017-01621, Paper 64 (P.T.A.B. Aug. 27, 2018); IPR2017-01622, Paper 64 (P.T.A.B. Aug. 27, 2018).

E. Considerations under 35 U.S.C. § 325(d)

This Petition does not present a scenario in which "the same or substantially the same prior art or arguments previously were presented to the Office." 35 U.S.C. § 325(d).

[1] There is no evidence that the '793 Examiner substantively considered the institution decisions in the prior IPRs.

The art presented in this petition was listed in PO's Information Disclosure Statement, but in the absence of additional evidence of "consideration" by the Examiner, discretionary denial under § 325(d) is not warranted. *See Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH,* IPR2019-01469, Paper 6 at 7-8 (P.T.A.B Feb. 13, 2020) (precedential) (art in IDS may be considered "[p]reviously presented"); *but see, e.g.*, *Microsoft Corp. v. Parallel Networks Licensing, LLC*, IPR2015-00483, Paper 10 at 15 (P.T.A.B. July 15, 2015) ("[W]hile [a reference] was listed on a lengthy Information Disclosure Statement initialed by the Examiner, the reference was not applied against the claims and there is no evidence that the Examiner considered the particular disclosures cited . . . in the Petition."). There is no evidence in the '793 Prosecution History that the Examiner substantively considered the art or arguments presented in this Petition. The Examiner erred in not doing so, and an analysis under the *Becton* factors confirms why discretionary denial is not appropriate here.[2]

[2] The *Becton* factors are six, non-exclusive factors that are to be considered in the § 325(d) analysis: (1) the similarities and material differences between the asserted art and the prior art involved during examination; (2) the cumulative nature of the

The Patent Office only issued one substantive rejection during prosecution — for obviousness-type double patenting over U.S. Patent Nos. 10,376,525; 9,358,240; and 9,339,507. EX1015, 24-28. Because no prior art was substantively relied on during examination, under *Becton* factor 3, the "record of the [Patent] Office's previous consideration of the art is . . . silent," and the threshold for Petitioner to show the Office erred is lower: Petitioner must simply show the Office "overlook[ed] something persuasive" under *Becton* factors 5 and 6. *Advanced Bionics*, IPR2019-01469, Paper 6 at 10. As to *Becton* factor 5, Petitioner details

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asserted art and the prior art evaluated during examination; (3) the extent to which the asserted art was evaluated during examination; (4) the extent of the overlap between the arguments made during examination and the manner in which a petitioner relies on the prior art or a patent owner distinguishes the prior art; (5) whether a petitioner has pointed out sufficiently how the Office erred in evaluating the asserted prior art; and (6) the extent to which additional evidence and facts presented in the petition warrant reconsideration of the prior art or arguments. Trial Practice Guide Update (July 2019), 29-30 (citing *Becton Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 at 17–18 (P.T.A.B. Dec. 15, 2017) (informative)).

below five persuasive grounds (four based on combinations) that the Examiner overlooked even though they disclose every element of the claims and are directed to the same disease (pulmonary hypertension), drug (treprostinil), and mode of administration (inhalation). As to *Becton* factor 6, Petitioner provides two expert declarations, as well as background art not listed in the Information Disclosure Statement, demonstrating how much was already known in the art and how that art would be understood by a person of ordinary skill in the art, as additional evidence and facts that warrant reconsideration of the prior art—and consideration for the first time of arguments involving the particular grounds and combinations presented here.

Further, the prosecution histories of the patents to which the '793 Patent was terminally disclaimed (U.S. Patent Nos. 10,376,525; 9,358,240; and 9,339,507) are not applicable to this Petition, because they do not contain the arguments (i.e., the particular grounds) presented here, and any overlapping prior art was applied against different claims and combinations and/or considered by a different Examiner and cancelled.

- For the '525 patent, certain claims to a treprostinil solution and kit with a different breath disclosure were rejected over the '212 Patent under § 102(b) and Voswinckel JAHA in combination with Chaudry under § 103(a), but, tellingly, those claims were cancelled and did not issue. EX1016, 33-42. Those claims were replaced by claims requiring a "opto-acoustical" trigger on a pulsed ultrasonic nebulizer, at different

concentrations and breaths than the '793 Patent claims. *Id.*

- For the '240 patent, a different Examiner (Townsley, rather than the '793 Patent's Examiner Schmitt) considered those claims and rejected them over art in combination with the '212 patent asserted here. EX1044, 7-23. However, that rejection was overcome by an affidavit that overcame the other art (i.e., the Sandifer reference) not asserted here, and the later rejections did not involve the art presented here. *Id.*
- For the '507 patent, a different Examiner (again, Townsley, rather than Schmitt) rejected the claims to nebulizer kits over Voswinckel 2006 in combination with Chaudry, and applicants submitted an affidavit by Dr. Werner Seeger that Voswinckel 2006 was not prior art because it was not "by others" under pre-AIA § 102(a). EX1017, 50, 35-36. Despite the affidavit, the Applicant cancelled the rejected claims after conducting a telephonic interview with the Examiner and applied for new, different claims, which the Examiner allowed without rejection or addressing whether Voswinckel 2006 was proper prior art. *Id.*, 28-31.

See NRG Energy, Inc. v. Midwest Energy Emissions Corp., IPR2020-00926, Paper 19 at 20-21 (P.T.A.B. Dec. 2, 2020) (rejecting relevance of related patent's prosecution history where it did "not appear that the same or substantially the same arguments [i.e. combinations] predicated on [the prior art] were before the Office"); *Unified Patents v. B# On Demand, LLC*, IPR2020-00995, Paper 20 at 56 (P.T.A.B. Dec. 8, 2020) (finding that a related patent application's claims "shed[] little light on how the Examiner would have applied those references to the materially different" claims of the petitioned patent).

For these reasons, this Petition does not present a scenario in which discretionary denial is warranted under 35 U.S.C. § 325(d).

IV. SUMMARY OF THE '793 PATENT

A. Brief Description of the '793 Patent

The '793 Patent is entitled "Treprostinil Administration by Inhalation" and is directed to methods of treating pulmonary hypertension where a single event dose of 15 micrograms to 90 micrograms of a treprostinil formulation are delivered by inhalation in 1 to 3 breaths. EX1001, Abstract, claims 1-8. Claim 1 is the only independent claim.

Dependent claims 2, 3, and 5 claim various types of inhalers that the '793 Patent specification describes as already well-known and on the market. *See, e.g.*, *id.*, 7:15-21; 7:27-39 (listing multiple soft mist inhalers and citing to M. Hindle, The Drug Delivery Companies Report, Autumn/Winter 2004, pp. 31-34, for "a review of soft mist inhaler technology"); 12:58-59; 14:35-37 (describing use of a pulsed ultrasonic nebulizer OPTINEB® by Nebutec).

Dependent claims 4, 6, and 7 relate to the use of a dry powder (as opposed to liquid) formulation of treprostinil and a dry powder inhaler. The '793 Patent's sole description to support these claims is the following two sentences:

> The inhalation device can be also a dry powder inhaler. In such case, the respiratory drug is inhaled in solid formulation, usually in the form

> of a powder with particle size less than 10 micrometers in diameter or less than 5 micrometers in diameter.

Id., 7:22-26.

Finally, dependent claim 8 requires the absence of the preservative metacresol sometimes used in formulations. *Id.*, 15:38-41; 16:11-17; 17:36-37.

B. Summary of the Prosecution History of the '793 Patent

The '793 Patent issued July 21, 2020, ***just six months*** after application No. 16/778,662 was filed on January 31, 2020. EX1001, 1. Application No. 16/778,662 is a continuation and divisional of several patent applications, including applications that resulted in U.S. Patent Nos. 10,376,525, 9,339,507, and 9,358,240. *Id.* The patent's provisional application, No. 60/800,016, was filed on May 15, 2006. *Id.* For purposes of this Petition, Petitioner assumes the relevant priority date for the '793 Patent is May 15, 2006.

After responding to missing parts, the applicants added **Thomas Schmehl** as an inventor (*id.*, 64-65, 58), and the PTO issued one substantive rejection: obviousness-type double patenting over U.S. Patent Nos. 10,376,525; 9,358,240; and 9,339,507, which was overcome by terminal disclaimer. *Id.*, 24-30, 50-51.

V. CLAIM CONSTRUCTION UNDER 37 C.F.R. § 42.104(b)(3)

For purposes of resolving this IPR, Petitioner does not believe construction of any claim term is required. All terms should be given their plain and ordinary

meaning in the art as of May 15, 2006. *Phillips v. AWH Corp.,* 415 F.3d 1303, 1312-1313 (Fed. Cir. 2005); 37 C.F.R. § 42.100(b).

VI. OVERVIEW OF THE GROUNDS

Given the state of the art and the knowledge of a person of ordinary skill in the art as of May 15, 2006, all claims are unpatentable under 35 U.S.C. §§ 102(b) and 103. The grounds presented here rely on the '212 Patent, Voswinckel JESC, Voswinckel JAHA, Ghofrani, and Voswinckel 2006 prior art references as follows:

1. **Ground 1, Claims 1-8**: Obvious over '212 Patent and Voswinckel JESC and Voswinckel JAHA;
2. **Ground 2, Claims 1-8**: Obvious over '212 Patent and Voswinckel JESC;
3. **Ground 3, Claim 1**: Anticipated by Ghofrani;
4. **Ground 4, Claims 1, 3, and 8**: Obvious over Voswinckel JAHA and Ghofrani;
5. **Ground 5, Claims 1 and 3**: Anticipated by Voswinckel 2006; and
6. **Ground 6, Claims 2, 4-8**: Obvious over Voswinckel 2006 and the '212 Patent.

VII. PERSON OF ORDINARY SKILL IN THE ART

The challenged claims are directed to a method of treating pulmonary hypertension by administering an inhaled formulation of treprostinil. As such, the challenged claims cover multiple disciplines. With respect to the method of treating pulmonary hypertension, a person of ordinary skill in the art ("skilled artisan" or

"POSA"), at the time of the alleged invention would have a medical degree with a specialty in pulmonology or cardiology, plus at least two years of experience treating patients with pulmonary hypertension as an attending, including with inhaled therapies, or equivalent degree or experience. EX1002, ¶¶17-19. With respect to inhaled formulations used in the method to treat pulmonary hypertension, a POSA would be a Ph.D. in pharmaceutical science or a related discipline like chemistry or medicinal chemistry, plus two years of experience in pharmaceutical formulations, including inhaled products, or equivalent (*e.g.*, an M.S. in the same fields, plus 5 years of experience). EX1004, ¶¶9-11.

VIII. TECHNICAL BACKGROUND

The petitioned claims are not directed, generally, to treating pulmonary hypertension ("PH") with treprostinil, since the compound itself, and methods of using the compound to treat PH were known, patented, and FDA approved for both subcutaneous injection and intravenous administration by 2004. *See* EX1018; EX1002, ¶¶29-30; EX1004, ¶19. Rather, the claims are directed to methods of treating PH by the administration of *inhaled* treprostinil formulations, such that the relevant technical background for this Petition is the state of inhalation therapy art as of 2006.

A. History of Inhalation Therapy

Formulation POSA Dr. Gonda provides a history of inhalation therapy from ancient times to 2006, explaining that nebulizers, meter dosed inhalers ("MDI"), and dry powder inhalers ("DPI") were well-known by the mid-1990s and FDA-approved by 2006. EX1004, ¶¶21-25.

B. Inhaled Treprostinil and Its Analogues

Dr. Gonda and clinician POSA Dr. Hill also explain that treprostinil is similar to iloprost, both chemical compounds are analogues of epoprostenol, and all three compounds were known to treat patients with pulmonary arterial hypertension ("PAH") by 2006. EX1021, 392 ("Epoprostenol, a synthetic prostacyclin, and iloprost and treprostinil, synthetic prostacyclin analogues, are currently used to treat patients with PAH."); EX1004, ¶¶26-33; EX1002, ¶¶40-44. Dr. Gonda and Hill also explain that numerous patents and patent publications on inhaled epoprostenol, iloprost, and treprostinil existed by 2006. *Id.*; *see, e.g.*, EX1027, Figs. 1-5 (depicting effects of intravenous and aerosolized UT15/treprositinil and derivatives); EX1028, Abstract, [0010], [0012], [0017], [0026], [0097], Claim 44 (directed to "inhalable formulation[s] for the treatment of pulmonary hypertension" where the formulation comprises a "hypertension-reducing agent" including a "vasodilator," such as "the

prostacyclin analog **treprostinil sodium**").[3] The '212 Patent, detailed in the "Overview of the Prior Art" section below, discloses use of inhaled treprostinil for treatment of pulmonary hypertension. EX1006, Abstract, 3:1-5, 2:16-18, 2:66-3:5, 4:10-13, 4:41-54, 7:18-24.

As both Dr. Gonda and Dr. Hill explain, the benefits of inhalation over other forms of administration, such as intravenous delivery, were also well-known by 2006. EX1004, ¶¶32-33; EX1002, ¶¶31-33. For example, Chaudry disclosed that "[c]ontinuous intravenous prostacyclin is far from ideal as a treatment for pulmonary hypertension, . . . because the agent is available only in limited supply, it is very costly, and optimal management requires that the intravenous therapy with prostacyclin be started in specialized centers familiar with the technique, equipment, and dose ranging. . . . Further, because the agent is delivered systemically with only a small percentage of the agent actually absorbed by the pulmonary system, it must be administered in high dosages." EX1028, [0011]. Chaudry disclosed that "therapeutically effective amount[s] of a hypertension-reducing agent" may include various ranges, such as from "about 0.001 mg/ml to about 20 mg/ml" and provided extensive disclosure regarding the use of nebulizing devices for inhalation. *Id.*,

[3] All emphasis added unless otherwise noted.

[0037]-[0038], [0061]-[0066]. The '212 Patent similarly disclosed inhaled delivery was known to be more "potent" than intravenous delivery. EX1006, 8:9-17.

In fact, iloprost had already been approved for inhaled use to treat pulmonary arterial hypertension in 2004, under the brand name Ventavis®. "Ventavis is breathed (inhaled) into your lungs" and "[o]ne treatment session will usually last about 4 to 10 minutes." EX1029, 4, 15; EX1002, ¶42; EX1004, ¶33. Ventavis® (iloprost) is indicated for treatment of pulmonary arterial hypertension (EX1029 at 8) and has a maximum daily dose of 45 micrograms (*id.*, 11). *Id.*

C. Well Known Considerations for Inhalation Therapies

By 2006, it was well-known that inhalation drug particles needed to be a certain size. For example, from modern use of inhalation therapy for asthma in the 1990s, it was well known "to avoid inertial impaction in the oropharyngeal cavity and reach the lung," aerosol particles needed to be 7 micrometers or less. EX1020, 374; EX1002, ¶35; EX1004, ¶34. If those particles needed to reach the peripheral lung, they needed to be closer to 2-3 micrometers. *Id.* A 2006 Encyclopedia of Respiratory Medicine confirms that it was generally known that "inhaler devices should deliver particles smaller than approximately 5 μm in diameter in order to enter the lungs." EX1030, 58. The '212 Patent also discloses particles "preferably, less than 5 micrometers in diameter." EX1006, 5:40-41.

Similarly, by 2006, there was extensive literature on pros and cons of various inhalation devices, particularly around patient adherence concerns. *See, e.g.*, EX1031, 1313 ("Comparing clinical features of the Nebulizer, Metered-Dose Inhaler, and Dry Powder Inhaler"); EX1002, ¶¶34, 36-39; EX1004, ¶36.

Patient adherence was a recognized problem with inhaled medications. EX1002, ¶¶36-39. A 1997 article discusses the challenges of patient adherence to inhaled medications, and found that patients "on average [only] take about 50% of prescribed medication," and that adherence (or nonadherence) was linked to treatment outcome. EX1032, Abstract, 179-80. Skilled artisans understood the burden of therapy, i.e., the effort a patient needs to make to take their medication, was one of the factors impacting adherence with the prescribed dosage regimen. *See, e.g.*, EX1033, Abstract (noting that a factor "related to patient adherence" was the "complexity of the inhalation regiment (dosing frequency, number of drugs)"); EX1004, ¶40; EX1002, ¶¶36-39.

By 2006, it was well-understood that patient adherence could be improved by reducing the number of breaths and overall duration of administration required for adequate dosing with inhalation devices. *See, e.g.* EX1033 at Abstract (noting that a factor "related to patient adherence" was the "complexity of the inhalation regimens (dosing frequency, number of drugs)"); EX1034, Abstract (emphasizing the efficiency benefit of reducing the duration of therapy from 10-20 minutes on a

nebulizer to just 3 breaths from a soft mist inhaler AERx); EX1002, ¶¶ 37-38; EX1004, ¶40.

Thus, reducing the duration of the inhaled dose administration of treprostinil was a common goal by 2006, and one that had met with success. Chaudry disclosed that inhalation of its treprostinil formulation "may take about . . . 3 minutes" (EX1028, [0067]), while Voswinckel JAHA and Voswinckel 2006, detailed below, disclosed reductions in treprostinil administration duration to 3 breaths. *See also* EX1004, ¶¶40-42; EX1002, ¶39.

IX. OVERVIEW OF THE PRIOR ART

A. '212 Patent

The '212 Patent issued on February 18, 2003, and therefore is prior art to the '793 Patent under at least 35 U.S.C. §§ 102(a), (b), and (e).

The '212 Patent discloses "a method of treating pulmonary hypertension by administering an effective amount of a benzindene[4] prostaglandin" (including treprostinil, referred to as "UT-15") "by inhalation." EX1006, Abstract, 3:1-5, 2:16-18, 2:66-3:5, 4:10-13, 4:41-54, 7:18-24. A POSA in May 2006 would have known

[4] Some references spell this compound as "benzindene" and others as "benzidine." For purposes of this Petition, both spellings refer to the same compound.

that "UT-15" is synonymous with treprostinil sodium.[5] The '212 Patent discloses that an "inhaler" may be used to deliver the UT-15. *Id.*, 5:30; EX1004, ¶¶50-54; EX1002, ¶¶53-61.

The '212 Patent discloses, in the same fashion as the '793 Patent, that powder formulations may be used. *Compare* EX1006, 5:30-32, 5:37-41 ("Alternatively, solid formulations, usually in the form of a powder, may be inhaled in accordance with the present invention. In such case, the particles are preferably less than 10 micrometers in diameter, and more preferably, less than 5 micrometers in diameter."), *with* EX1001, 7:22-26. Further, claim 9 is directed to a method of treating pulmonary hypertension in a mammal, which would include humans, by the administration of an inhaled powder formulation of treprostinil. EX1006, claim 9; EX1002, ¶60.

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[5] *See, e.g.,* EX1035 ("United Therapeutics Corp (UTC) is developing treprostinil sodium (Remodulin, UT-15), a stable structural analog of prostacyclin [prostaglandin I2 or PGI_2], for the potential treatment of primary pulmonary (arterial) hypertension (PAH), peripheral vascular disease (PVD) and other cardiovascular conditions. . ."); *see also* EX1046 ("U.S. Pat No[]. 6,521,212 . . . describe[s] administration of treprostinil by inhalation for treatment of pulmonary hypertension, peripheral vascular disease and other diseases and conditions.").

As for dosage, the '212 Patent states "[i]n the case of treating peripheral vascular disease by inhalation of a benzindene prostaglandin of the present invention, the dosage for inhalation . . . should be sufficient to deliver an amount that is equivalent to a daily infusion dose in the range of 25 µg to 250 mg; typically from 0.5 tg [sic] to 2.5 mg, preferably from 7 µg to 285 µg, per day per kilogram bodyweight." EX1006, 5:54-62; *see also id.*, Figs. 16, 18.

For treating pulmonary hypertension, the '212 Patent states that aerosolized (i.e., inhaled) UT-15 "has a greater potency as compared to intravascularly administered UT-15" and teaches the "actual amount of UT-15 delivered via aerosolization delivery is only a fraction (10-50%) of the dosage delivered intravascularly." *Id.*, 8:9-17. The '212 Patent then discloses multiple examples of administering treprostinil to sheep. Sheep were "the animal model of choice" for many reasons, including, in relevant part, "sheep have been utilized for several years as an animal model of pulmonary arterial hypertension." *Id.*, 9:14-27.

The '212 Patent relies on its disclosed sheep experiments to claim treatment of mammals, including humans (*see id.*, 14:7-8, claims 5, 6, 9), and to support the overall aim of its invention—treprostinil "delivered by inhalation to a patient in need thereof in a 'therapeutically effective amount,'" where a "'therapeutically effective amount' . . . refers to that amount in which the effects from pulmonary hypertension, and particularly, pulmonary arterial pressure (PAP), are reduced towards a normal

level relative to hypertensive levels, or maintained at normal levels." *Id.*, 6:56-66. The '212 Patent then explains that POSAs can readily determine the appropriate single event dose "upon the specific circumstances of the patient being treated and the magnitude of effect desired by the patient's doctor," and "[t]itration to effect . . . to determine proper dosage." *Id.*, 6:66-7:3; EX1004, ¶35 (explaining that such titration was well-known). Such UT-15 formulations can be "given in high doses without significant non-lung effects" and are described "for human medical use." *Id.*, 10:51-57, 7:4-5.

B. Voswinckel JESC

Voswinckel JESC is an abstract presented at the European Society of Cardiology (JESC) Congress from August 28 to September 1, 2004 in Munich, Germany and published in the European Heart Journal on October 15, 2004—more than a year before May 15, 2006—and is therefore prior art to the '793 Patent under at least 35 U.S.C. § 102(b). EX1036, ¶¶ 68-75; EX1004, ¶55.

Voswinckel JESC describes a study investigating "the acute hemodynamic response to inhaled treprostinil." EX1007, Background. The study enrolled 29 patients: 8 received placebo and 21 were administered 16, 32, 48, and 64 µg/mL treprostinil solutions for 6 minutes via the OptiNeb ultrasound nebulizer, then produced by the company Nebu-tec in Germany. *Id.*, Methods. Of the 29 patients, 10 had "idiopathic PAH". *Id.*, Results. The results showed that "[t]reprostinil

inhalation results in a significant long-lasting pulmonary vasodilatation" and that, at 16 μg/mL, "near maximal pulmonary vasodilatation is achieved without adverse effects." *Id.*, Conclusion.

As Dr. Hill explains, a POSA would have expected at least 1 mL of the treprostinil solution was used over 6 minutes of inhalation, and thus would understand, therefore, at least **16, 32, 48, or 64 μg** of treprostinil were delivered to different dosing groups in this study. EX1002, ¶65. Such dosages would make sense to a POSA for patients being administered treprostinil for the first time. *Id.* This understanding is further confirmed by Dr. Gonda, who explains that the numerous nebulizers used at the time were known and expected to deliver more than 1mL of solution. EX1004, ¶56 (citing several inhalation therapies delivering 1-5mL of solution via nebulizers). In fact, a POSA would have expected the OptiNeb® device used at the time (before 2006) to nebulize (i.e., turned liquid to aerosol) at a rate of 0.6 mL of solution per minute. EX1002, ¶67 (citing EX1037, 28.) Assuming continuous administration over 6 minutes, the administered volume would have been as much as 0.6 x 6, or 3.6mL. *Id.* Thus, at 16 μg/mL, which is what Voswinckel JESC recommends as the concentration at which "near maximal pulmonary vasodilatation is achieved without adverse side effects" (EX1007, Conclusion), the administered single event dose could be as high as 0.6 mL/min x 16 μg/mL x 6 min = **57.6** μg. *Id.*

In sum, a skilled artisan would have understood at least 16, 32, 48, or 64 µg of treprostinil were delivered to patients with PAH in this study, and that understanding would have been confirmed by the volume of solution a POSA would have expected to be nebulized by the device used in the study, as well as the nebulizers known in the art. EX1002, ¶¶65-67; EX1004, ¶56.

C. Voswinckel JAHA

Voswinckel JAHA is an abstract published in the Journal of the American Heart Association on October 26, 2004—more than a year before May 15, 2006—and is therefore prior art to the '793 Patent under at least 35 U.S.C. § 102(b). EX1036, ¶¶59-67; EX1004, ¶58.

Voswinckel JAHA describes a study in which 17 patients with "severe pulmonary hypertension" received a treprostinil inhalation by use of the "pulsed OptiNeb® ultrasound nebulizer" in "3 single breaths" of a "600 µg/ml" treprostinil solution. EX1008, Methods. The study found that treprostinil "inhalation resulted in a sustained, highly pulmonary selective vasodilatation over 120 minutes," showing "strong pulmonary selective vasodilatory efficacy with a long duration of effect following single acute dosing." *Id.*, Methods, Conclusion. Voswinckel JAHA also teaches that "[t]olerability [of treprostinil] is excellent even at high drug concentrations and short inhalation times (3 breaths)" with "very promising" long term treatment effects. *Id.*, Conclusion. This description has been confirmed by the

Board in its Institution Decisions in IPR2017-01621 and IPR2017-01622. IPR2017-01621, Paper 10 at 23; IPR2017-01622, Paper 9 at 23.

D. Ghofrani

Ghofrani is a prior printed publication under 35 U.S.C. § 102(a) because it was published before May 15, 2006. It was published in the June 2005 issue of *Herz* and a translation, with a declaration attesting the accuracy of the translation, is provided as EX1010. *See also* EX1036, ¶¶47-55.

Ghofrani describes the use of inhaled treprostinil to treat pulmonary hypertension. EX1010, 297-98. Ghofrani states the following:

> Initial trials in Giessen have shown proof of efficacy of *inhaled* treprostinil for the effective reduction of the pulmonary vascular resistance (PVR) [6]. In this first study, 17 patients with severe pre-capillary pulmonary hypertension were administered inhaled treprostinil (***15 mcg/inhalation***). This led to a major reduction in pulmonary selective pressure and resistance with an overall duration of action of > 180 min. In direct comparison with inhaled iloprost, inhaled treprostinil showed a stronger pulmonary selectivity, so that ***it is possible to increase the dosage to up to 90 mcg (absolute inhaled dose per inhalation exercise) without adverse effects occurring*** [6]. Due to these unique properties (pronounced pulmonary selectivity and long duration of action after an individual inhalation), it is possible to reduce the number inhalations necessary to up to four per day; the inhalation period can be reduced to < 1 min. by selecting a suitable device.

> Additionally, the initial data shows that ***it is technically feasible for there to be only one to two breaths in an application***.

Id., 298.[6]

Ghofrani is prior art "by others" under judicial interpretations of pre-AIA § 102(a), because there are inventors listed on the '793 Patent that are not listed as authors on Ghofrani, and vice versa. *In re Katz*, 687 F.2d 450, 454 (C.C.P.A. 1982). The Ghofrani authors that are not '793 inventors are **Ghofrani, Reichenberger, and Grimminger**. *Compare* EX1010, 1, *with* EX1001, 1. PO encountered this issue in IPR2017-01621 and IPR2017-01622 and submitted an affidavit attesting that these authors did not contribute to the relevant portion of Ghofrani. *See* IPR2017-01621; Paper 10 at 12-14; IPR2017-01622, Paper 9 at 12-15.

But there are also individuals identified as inventors of the '793 Patent that are not included as authors of Ghofrani: **Olschewski, Roscigno, Rubin, Schmehl, and Sterritt**. EX1001, 1. In IPR2017-01621/IPR2017-01622, PO put forth a self-serving affidavit by one of the inventors, Dr. Seeger, as to how "any study that formed the basis of our discussion of inhaled treprostinil" was "performed by [him in] collaboration with Dr. Voswinckel, Olschewski, Rubin, Schmehl, Sterritt, and

[6] Quotations to Ghofrani are from the English-language translation of Ghofrani.

Roscigno." IPR2017-01621/01622, EX2098 at ¶ 8. But Dr. Seeger fails to explain why Drs. Olschewski, Rubin, Schmehl, Sterritt, and Roscigno were not listed as authors on the Ghofrani article, a concurrent fact that supports the inference that they did not make any contribution to Ghofrani's disclosure. Dr. Seeger's affidavit also does not explain if and how any inventor contributed to the use of the various inhalation devices and formulations specifically claimed in the '793 Patent. Where there are disputed facts, and Petitioner has not had a chance to depose declarant Dr. Seeger, a preliminary determination that Ghofrani is by another is appropriate,[7] and the issue should not impede institution. *Varian Med. Sys., Inc. v. William Beaumont Hosp.*, IPR2016-00163, Paper 14 at 13-15 (P.T.A.B. May 6, 2016).

E. Voswinckel 2006

Voswinckel 2006 is prior art under at least 35 U.S.C. § 102(a), because it was published in the Annals of Internal Medicine on January 17, 2006, before May 15, 2006. EX1036, ¶¶77-84.

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[7] Petitioner is entitled to a presumption that "any factual dispute created by testimonial evidence that is material to the institution decision will be resolved in favor of the petitioner . . . for purposes of determining whether to institute." 81 FR 18755 (April 1, 2016).

Voswinckel 2006 discloses a patient trial to "characterize the effects of inhaled treprostinil with special regard to safety, tolerability, and efficacy in patients with severe pulmonary arterial hypertension." EX1009 (Voswinckel 2006), 149-50. Three patients with "severe pulmonary hypertension" were given a "single 15-µg dose of treprostinil, inhaled in 3 breaths through a modified OptiNeb ultrasonic inhalation device." *Id.*, 150. One patient had a "favorable vasodilator response" and the other two patients were given "long-term inhaled treprostinil therapy . . . consisting of 4 daily 15-µg doses" over 3 months, resulting in "dramatic[]" functional improvement without side effect. *Id.* The authors concluded that treprostinil was "clinically effective, safe, and well tolerated when 15 µg was inhaled in 3 breaths 4 times daily." *Id.*

Voswinckel 2006 is "by others" under judicial interpretations of pre-AIA § 102(a). *In re Katz*, 687 F.2d at 454. Voswinckel 2006 authors **Ghofrani and Grimminger** are not listed as inventors on the '793 Patent. *Compare* EX1009, 150, *with* EX1001, 1. During prosecution of the related 9,339,507 patent, PO submitted an affidavit that these two authors "are properly listed as co-authors on the Voswinckel article because of their contributions to the Voswinckel article" but "did not contribute to conception of the presently claimed invention." EX1017, 35-36. But this affidavit fails to establish that Ghofrani and Grimminger did not contribute to the testing of the safety and efficacy of inhaled treprostinil (dosing and breaths)

used in the patient study of Voswinckel 2006 relied on in this Petition.[8] In fact, PO would be hard pressed to identify different contributions for these authors because the entire Voswinckel 2006 publication is only 1 page, all of which this Petition relies on.

Further, **Olschewski, Roscigno, Rubin, Schmehl, and Sterritt** are identified as inventors of the '793 Patent, but are not authors of Voswinckel 2006. *Compare* EX1009, 150, *with* EX1001, 1. No evidence exists in the record of the proceedings, before the Board or before the PTO, to indicate these inventors contributed to Voswinckel 2006. The fact that they are not authors on Voswinckel 2006 supports the inference they did not make any contribution to that disclosure. *Accord EmeraChem Holdings*, 859 F.3d at 1345-48. Further, PO specifically added Schmehl as inventor in February 2020, so, at the very least, PO cannot reasonably claim that Schmehl somehow contributed to the Voswinckel 2006 article published ***14 years prior***. *See* EX1015, 64-65, 58.

[8] Also, despite the affidavit, PO cancelled the rejected claims and applied for new, different claims, which the Examiner allowed without addressing whether Voswinckel 2006 was prior art. EX1017, 28-31. Thus, the issue has not been resolved or evaluated by the Patent Office for either the '507 or '793 patents.

Thus, the Voswinckel 2006 publishing entity is different than the '793 Patent inventive entity. *In re Land*, 368 F.2d at 877. In these circumstances, a preliminary determination that Voswinckel 2006 is by another is appropriate and the issue should not impede institution. *Varian Med. Sys., Inc.*, IPR2016-00163, Paper 14 at 13-15.

X. GROUND 1: CLAIMS 1-8 ARE RENDERED OBVIOUS UNDER 35 U.S.C. § 103(A) OVER THE '212 PATENT IN COMBINATION WITH VOSWINCKEL JESC AND VOSWINCKEL JAHA

A. Motivation to Combine '212 Patent with Voswinckel JESC and Voswinckel JAHA With a Reasonable Expectation of Success

A POSA would have been motivated to combine the '212 Patent with Voswinckel JESC and Voswinckel JAHA to arrive at the claims of the '793 Patent. EX1002, ¶¶75-83. All three publications are directed to solving the same problem (treatment of pulmonary hypertension) via the same means (inhaled treprostinil). *See, e.g.,* EX1006, Abstract (disclosing "[a] method of delivering benzindene prostaglandins to a patient by inhalation" for the treatment of "pulmonary hypertension"); EX1007, Background, Results (investigating "inhaled treprostinil" on patients with "idiopathic PAH"); EX1008 (titled "Inhaled Treprostinil Sodium (TRE) For the Treatment of Pulmonary Hypertension").

A POSA starting with the '212 Patent would understand that it discloses use of inhaled treprostinil sodium (UT-15, *see supra* n.5) for the treatment of pulmonary hypertension, discloses a dosage range for intravascular administration of

treprostinil for the treatment of pulmonary vascular disease, and discloses that only 10-50% of the dosage delivered intravascularly would be needed via inhalation to have the same therapeutic effect. EX1006, Abstract, 6:1-2 (disclosing "[a] method of delivering benzindene prostaglandins" "including UT-15" "to a patient by inhalation" for the treatment of "pulmonary hypertension"); 5:54-62 ("daily infusion dose in the range of 25 μg to 250 mg; typically from 0.5 tg [sic] to 2.5 mg, preferably from 7 μg to 285 μg, per day per kilogram bodyweight"), 8:9-17 (the "actual amount of UT-15 delivered via aerosolization delivery" need only be "a fraction (10-50%) of the dosage delivered intravascularly").

A POSA would also understand the '212 Patent discloses experiments in sheep and explains sheep are a model of pulmonary arterial hypertension in humans. EX1006, 9:14-27; Examples I-V and accompanying Figs. A POSA would further understand these sheep experiments were relied upon to support claims directed to treating pulmonary hypertension in mammals, which include humans, via inhaled solutions and powder formulations of treprostinil. *Id*., claims 6, 9; EX1002, ¶77. Given these teachings, a POSA would have been motivated to further investigate inhaled treprostinil as a treatment for PH in humans and would have looked to the results of Voswinckel JESC and Voswinckel JAHA, which report on this very issue. *Id.*, ¶¶78.

Voswinckel JESC, published after issuance of the ’212 Patent, confirms the results of the ’212 Patent that inhaled treprostinil is a safe and effective means for treating PH in humans. EX1002, ¶79. Voswinckel JESC discloses the effective administration of inhaled treprostinil for human patients with PAH via a nebulizer for 6 minutes. EX1007, Methods. As detailed above at Section IX.B, a POSA would understand Voswinckel JESC to disclose delivery of at least 16 to 64 μg of inhaled treprostinil to achieve this effectiveness. A POSA would have a reasonable expectation of success in combining the ’212 Patent’s disclosure with the dosage of Voswinckel JESC, because Voswinckel JESC’s results showed that “[t]reprostinil inhalation results in significant long-lasting pulmonary vasodilatation” and that “near maximal pulmonary vasodilatation is achieved without adverse effects.” *Id.*, Conclusion; EX1002, ¶79.

Having established via the ’212 Patent and Voswinckel JESC that inhaled treprostinil can be used to safely and effectively treat PH, a POSA would have been further motivated to reduce the duration of treatment to increase patient convenience and adherence—from the 6 minutes disclosed in Voswinckel JESC to 3 breaths, as disclosed in Voswinckel JAHA. EX1002, ¶80. As explained above, the problem of patient nonadherence to inhaled medications was well-understood, and a POSA in May 2006 would have readily appreciated reducing the number of breaths for drug delivery would increase patient adherence and, in turn, treatment outcome. *See*

supra, Section VIII.C.; EX1002, EX1002, ¶¶80-81. A POSA would also have understood that reducing the duration of treatment would require increasing the concentration of the administered treprostinil solution, which is confirmed by Voswinckel JAHA's use of a 600 mcg/mL solution. EX1002, ¶82 (citing EX1008, Methods).

A POSA would have a reasonable expectation of success with this combination, because Voswinckel JAHA teaches that "[t]olerability is excellent even at high drug concentrations[9] and short inhalation times (3 breaths)" with "strong pulmonary selective vasodilatory efficacy with a long duration of effect following single acute dosing." EX1008, Conclusion; EX1002, ¶83. Additionally, the relevant scientific literature taught safe and effective administration of high dosages of inhaled therapeutics in short durations. *See, e.g.,* EX1010, 298 (disclosing administration of inhaled treprostinil at a dose of "15 mcg/inhalation" and that "it is possible to increase the dosage to up to 90 mcg" and that "it is technically feasible for there to be only one to two breaths in an application.");

[9] Voswinckel JAHA's results confirm the conclusions reached in the '212 Patent that "aerosolized UT-15 can be given in high doses without significant non-lung effects, i.e., heart rate, cardiac output." EX1006, 10:51-57.

EX1034, 177 (delivery 0.45mg of drug in 3 breaths). In sum, a POSA would have expected to succeed in reducing the number of breaths when delivering 15-90µg of inhaled treprostinil, due to the general state of the art regarding the safety and efficacy of such dosages of inhaled therapeutics, the known problem of patient noncompliance, and Voswinckel JAHA's explicit disclosure that administration of treprostinil was successful.

A POSA would expect Voswinckel JESC's dosage and Voswinckel JAHA's breaths to be a therapeutically effective dosing regimen for PH, and would be motivated by the '212 Patent's disclosure that "solid formulations, usually in the form of a powder" could also "be inhaled in accordance with the ['212 Patent's] invention" to create a dry powder that provided the same single event dosage as Voswinckel JESC and breath limitations of Voswinckel JAHA with a reasonable expectation of success. EX1006, 5:30-32, 5:37-41, claims 6, 9; EX1004, ¶¶78-80.

Therefore, a POSA would have been motived to and had a reasonable expectation of success in combining the teachings of the '212 Patent with the dosage of Voswinckel JESC and the breaths of Voswinckel JAHA, the combination of which renders all claims invalid, as explained below.

B. The '212 Patent in combination with Voswinckel JESC and Voswinckel JAHA renders obvious claims 1-8

1. Independent Claim 1

a. The '212 Patent discloses claim element 1[a]

1[a]	A method of treating pulmonary hypertension comprising administering by inhalation to a human suffering from pulmonary hypertension a therapeutically effective single event dose of a formulation comprising treprostinil or a pharmaceutically acceptable salt thereof

The '212 Patent describes methods of delivering a therapeutically effective amount of benzindene prostaglandin (also known as "UT-15") by inhalation to treat pulmonary hypertension in a single dose event. EX1006, Abstract, 2:16-18, 2:66-3:5, 4:10-13, 4:41-54, 7:18-24.[10] A POSA as of May 2006 would have readily

[10] Voswinckel JESC and Voswinckel JAHA additionally disclose this limitation. Voswinckel JAHA describes treating "patients with severe pulmonary hypertension" with "Inhaled Treprostinil Sodium (TRE)" with a single event dose of "3 single breaths" of "TRE solution 600 μg/ml," resulting in "strong pulmonary selective vasodilatory efficacy with a long duration of effect following single acute dosing." EX1008, Title, Methods, Conclusion. Voswinckel JESC describes a study investigating "the acute hemodynamic response to inhaled treprostinil," in which

understood that "UT-15" is synonymous with treprostinil sodium, and that treprostinil is an analog of benzindene prostaglandin.[11]

Specifically, the '212 Patent discloses and claims "a method of treating pulmonary hypertension by inhalation of a benzindene prostaglandin" (*id.*, 7:18-20) or a "pharmaceutically acceptable salt" thereof (*id.*, 4:11-12). *Id.*, claims 6, 9. The '212 Patent further states that the "benzindene prostaglandin is delivered by inhalation to a patient in need thereof in a 'therapeutically effective amount.'" *Id.*, 6:56-58. "A 'therapeutically effective amount' refers to that amount that has therapeutic effects on the condition intended to be treated or prevented." *Id.*, 6:58-61. The '212 Patent explains that "[t]he precise amount that is considered effective for a particular therapeutic purpose will, of course, depend upon the specific circumstances of the patient being treated and the magnitude of effect desired by the patient's doctor." *Id.*, 6:66-7:2. Dr. Hill confirms that a POSA would have the above

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patients with pulmonary hypertension were enrolled and administered nebulized treprostinil solution for 6 minutes, resulting in "significant long-lasting pulmonary vasodilatation" with "near maximal pulmonary vasodilatation is achieved without adverse effects." EX1007, Background, Methods, Conclusion.

[11] *See infra* note 5.

understanding. EX1002, ¶¶85-92.

b. The '212 Patent discloses claim element 1[b]

1[b]	with an inhalation device

The '212 Patent discloses that an inhaler may be used to deliver the benzindene prostaglandin. EX1006, 5:30-32 ("Preferably, a nebulizer, **inhaler**, atomizer or aerosolizer is used[,] which forms droplets from a solution or liquid containing the active ingredient(s)."). A POSA as of May 2006 would have readily understood that an inhaler is an inhalation device.[12] EX1002, ¶¶93-94.

c. Voswinckel JESC renders obvious claim element 1[c]

1[c]	wherein the therapeutically effective single event dose comprises from 15 micrograms to 90 micrograms of treprostinil or a pharmaceutically acceptable salt thereof

The '212 Patent discloses that "[i]t has been discovered that aerosolized UT-15 has both greater potency and efficacy" for "attenuating chemically induced pulmonary hypertension" as compared to intravascular delivery. EX1006, 8:5-8. The '212 Patent quantifies this potency, teaching that "aerosolized UT-15 has a

[12] Voswinckel JESC and Voswinckel JAHA additionally disclose this limitation, as both use the pulsed OptiNeb® ultrasound nebulizer as the inhalation device. EX1007, Methods; EX1008, Methods.

greater potency as compared to intravascularly administered UT-15, since the actual amount of UT-15 delivered via aerosolization delivery is only a fraction (10-50%) of the dosage delivered intravascularly." *Id.*, 8:8-12.

Given these teachings, the successful sheep data, and the claims of the '212 Patent, a POSA would have been motivated to look for data administering inhaled treprostinil in humans with PH and the doses used therein. EX1002, ¶¶96-98. A POSA would have been readily led to Voswinckel JESC, which discloses the effective administration of inhaled treprostinil for human patients with pulmonary arterial hypertension for 6 minutes on the OptiNeb® nebulizer of treprostinil solution at a concentrations of 16 to 64 μg/mL. EX1007, Methods.

As explained above at Section IX.B., a skilled artisan would have understood at least 16, 32, 48, or 64 μg of treprostinil were delivered to patients with PAH in this study, and that understanding would have been confirmed by the volume of solution a POSA would have expected to be nebulized by the OptiNeb® device used in the study, as well as the nebulizers known in the art. EX1002, ¶99; EX1004, ¶56.

This understanding is confirmed by the intravascular dosing of UT-15 to treat pulmonary hypertension approved by the FDA in 2004 for intravascular treatment of pulmonary hypertension at a dosage of 1.25 ng/kg/min. EX1018. The label provides calculations based on a 60kg and 65kg patient. *Id.*, 10. Accordingly, a POSA administering Remodulin would have known he was giving his patients a

daily treprostinil dose of 1.25ng x 60kg x (24x60)min to 1.25ng x 65kg x (24x60)min, which is to *108 to 117 micrograms*. EX1002, ¶100. A POSA would apply the '212 Patent's 10-50% adjustment between intravascular and inhaled dosing (EX1006, 8:5-12) and understand the '212 Patent to be teaching that an FDA-approvable effective dosage of aerosolized treprostinil for the treatment of pulmonary hypertension would be **10.8 to 58.5 micrograms**. *Id.* This range covers over half of the claimed 15 to 90 µg dosage.[13]

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[13] In addition, the '212 Patent discloses that "[i]n the case of treating peripheral vascular disease . . . [,] the dosage for inhalation . . . should be sufficient to deliver an amount that is equivalent to a daily [intravascular] infusion dose in the range of 25µg to 250mg." EX1006, 5:54-62; *see also id.*, Figs. 16, 18. By teaching that only 10-50% is needed for inhalation (*id.*, 8:5-12), the '212 Patent discloses that the effective dosage of inhaled treprostinil for treating peripheral vascular disease would be 2.5µg (micrograms) to 125mg (milligrams). This encompasses the full 15 to 90 micrograms claimed by the '793 Patent. Accordingly, given the fact that the '212 Patent is directed to methods of treating both pulmonary hypertension and peripheral vascular disease (*see id.*, 13:26-14:29, claims 6 and 9), a POSA would understand

Accordingly, a POSA would understand the '212 Patent in combination with Voswinckel JESC to disclose an inhaled dosage range of 15 to 90 μg of treprostinil as claimed.

d. Voswinckel JAHA discloses claim element 1[d]

1[d]	*delivered in 1 to 3 breaths.*

As explained above in Sections X.A and VIII. C., a POSA would have known to increase patient compliance and convenience, it would be desirable to reduce the number of breaths required for delivery of treprostinil by inhalation. A POSA who understood the necessary amount of dosing for aerosolized delivery of treprostinil would then look to the art for the fewest number of breaths in which that delivery could occur. EX1002, ¶102.

Voswinckel JAHA discloses a low number of breaths for the aerosolized delivery of treprostinil *specifically for treatment of pulmonary hypertension*. Thus, a POSA would understand the '212 Patent and Voswinckel JESC's dosage teachings would be readily applicable to the breath disclosure of Voswinckel JAHA. *Id.*, ¶¶102, 104 (also explaining that a "subset of the Voswinckel JESC authors"

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that an inhaled dosage of 15 to 90 micrograms of treprostinil for treatment of pulmonary hypertension would be equally possible. EX1002, ¶100n4.

published Voswinckel JAHA, additionally motivating a POSA to look at Voswinckel JAHA in combination with the '212 Patent and Voswinckel JESC).

In particular, Voswinckel JAHA states "[p]atients received a TRE [inhaled treprostinil sodium] by use of the pulsed OptiNeb® ultrasound nebulizer (**3 single breaths**, TRE solution 600 µg/ml)" and further observes that "[t]olerability is excellent even at high drug concentrations and short inhalation times (**3 breaths**)" with "strong pulmonary selective vasodilatory efficacy with a long duration of affect following single acute dosing." *See* EX1008, Methods, Conclusion. A POSA therefore would have applied the 3-breath delivery disclosure of Voswinckel JAHA to the teachings of the '212 Patent to improve patient adherence to treatment. EX1002, ¶¶103, 104.

Accordingly, a POSA reading the '212 Patent and Voswinckel JESC and applying Voswinckel JAHA's teachings to increase patient compliance and ease of use would have thought it obvious to administer treprostinil via inhalation in 3 breaths, thereby rendering 1[d] obvious.

2. Dependent Claim 2

2	The method of claim 1, wherein the inhalation device is a soft mist inhaler.

The '212 Patent discloses use of an "inhaler," (EX1006, 5:30-32), and soft mist inhalers were known as of 2004. The '793 Patent itself acknowledges that

multiple soft mist inhalers were already known in the prior art and on the market, including "the Respimat® Inhaler (Boehringer Ingelheim GmbH), the AERx® Inhaler (Aradigm Corp.), the Mystic™ Inhaler (Ventaira Pharmaceuticals, Inc) and the Aira™ Inhaler (Chrysalis Technologies Incorporated)." EX1001, 7:33-39 (also citing to M. Hindle, The Drug Delivery Companies Report, Autumn/Winter 2004, pp. 31-34, for "a review of soft mist inhaler technology"); *see also* EX1034, Abstract (demonstrating successful use of the AERx soft mist inhaler for treatment of pulmonary exacerbations in cystic fibrosis).

A POSA would find it obvious that the treprostinil disclosed in the '212 Patent could be used in such soft mist inhalers and be motivated to do so. EX1002, ¶¶106-110; EX1004, ¶¶66-71. As Dr. Gonda explains, a POSA would have known that the aqueous solution described in the '212 Patent would be suitable for soft mist inhalation in 3 breaths, and would have been motivated to develop/found it obvious to try using a soft mist inhaler because "soft mist inhalers were known to offer numerous advantages," particularly "repeatable and consistent" drug delivery "regardless of ambient temperature (T = 15-30°C), pressure, or humidity" without the use of propellants. EX1004, ¶¶68-69 (citing EX1069, 932). A POSA would have a reasonable expectation of success in delivering 15 to 90 micrograms of treprostinil in 1 to 3 breaths with a soft mist inhaler, because Voswinckel JAHA successfully delivered treprostinil in 3 breaths and because soft mist inhalers

approved for market use were well characterized as suitable for inhaled delivery of drugs at similar dosages in one or a small number of breaths. *Id.*, ¶70.

Accordingly, to a POSA, the '212 Patent in combination with Voswinckel JESC and Voswinckel JAHA renders this claim obvious.

3. Dependent Claim 3

3	The method of claim 1, wherein the inhalation device is a pulsed ultrasonic nebulizer.

The '212 Patent discloses use of an ultrasonic nebulizer, teaching that "[o]ne preferred nebulizer is the AM-601 MEDICATOR AEROSOL DELIVERY SYSTEM™ (a nebulizer manufactured by Healthline Medical in Baldwin Park, Calif.)." EX1006, 5:33-36. Voswinckel JESC discloses use of the "OptiNeb ultrasound nebulizer", and Voswinckel JAHA use of the "pulsed OptiNeb® ultrasound nebulizer." EX1007, Methods; EX1008, Methods. Also, pulsed ultrasonic nebulizers were well-known and already on the market by 2006. *See, e.g.*, EX1001, 12:58-59, 14:35-37 (describing use of a pulsed ultrasonic nebulizer OPTINEB® by Nebutec). Thus, to a POSA, the '212 Patent in combination with Voswinckel JESC and Voswinckel JAHA renders this claim obvious. EX1002, ¶¶112-114; EX104, ¶¶73-75.

4. Dependent Claim 4

4	The method of claim 1, wherein the inhalation device is a dry powder

	inhaler.

Claim 4 is disclosed in the ’212 Patent, which discloses an “inhaler” may be used to deliver the benzindene prostaglandin. EX1006, 5:30-32. The ’212 Patent further states “solid formulations, usually in the form of a powder, may be inhaled in accordance with the present invention.” *Id.*, 5:37-39. And finally, claim 9 of the ’212 Patent is specifically directed to an inhaled powder formulation of treprostinil. Accordingly, a POSA would have readily understood the “inhaler” disclosed in the ’212 Patent could be used as a “dry powder inhaler,” as claimed, to deliver powder formulations. EX1004, ¶¶77-80; EX1002, ¶¶116-117. Such dry powder inhalers were well known and “widely accepted” as of 2006. *See id.*; EX1038, 1311 (October 2005 “Dry Powder Inhalers: An Overview”).

5. Dependent Claim 5

5	The method of claim 1, wherein the inhalation device is a pressurized metered dose inhaler.

The ’793 Patent defines a pressurized metered dose inhaler as “a device which produces the aerosol clouds for inhalation from solutions and/or suspensions of respiratory drugs in chlorofluorocarbon (CFC) and/or hydrofluoroalkane (HFA) solutions.” EX1001, 7:17-21. The ’212 Patent discloses use of an “inhaler,” (EX1006, 5:30-32), and pressurized metered dose inhalers were well-known as of 2004, offered the advantage of being “reasonably efficient” while being “inherently

portable and very convenient to use" and were readily available, well understood, and offered for "[n]early all major respiratory drugs. *See* EX1004, ¶¶82-85 (citing EX1020, 379; EX1019, 29, 32); EX1002, ¶119.

6. Dependent Claim 6

6	The method of claim 4, wherein the formulation is a powder.

Claim 6 is disclosed in the '212 Patent, which discloses and specifically claims that powder formulations may be used to treat pulmonary hypertension. EX1006, 5:37-39 ("Alternatively, solid formulations, usually in the form of a powder, may be inhaled in accordance with the present invention."), claim 9.

7. Dependent Claim 7

7	The method of claim 6, wherein the powder comprises particles less than 5 micrometers in diameter.

Claim 7 is disclosed in the '212 Patent, which expressly discloses and claims that "the particles are preferably less than 10 micrometers in diameter, and more preferably, less than 5 micrometers in diameter." EX1006, 5:39-41, claim 9.

8. Dependent Claim 8

8	The method of claim 1, wherein the formulation contains no metacresol.

Claim 8 is disclosed in the '212 Patent, which has no disclosure requiring the presence of metacresol in the described formulation. EX1006, 5:25-29 (disclosing formulation of a "more preferred solution" that does not include metacresol), 8:39-

44 (disclosing steps of formulating treprostinil inhalation solution that do not include metacresol). A POSA would thus understand the '212 Patent to disclose a formulation of UT-15 (*i.e.*, treprostinil) that contains no metacresol. EX1004, ¶¶92-93 (explaining that "use of preservatives in inhalation products was strongly discouraged by 2006").

Voswinckel JAHA also specifically states that a "preservative free solution of inhaled TRE" was used (Voswinckel JAHA at Methods), which a POSA would understand to mean that the solution contained no metacresol, because metacresol was known in 2006 to be a preservative. EX1004, ¶94; *see also* EX1001, 15:40-41 (referring to a "metacresol preservative" in "treprostinil solution").

Accordingly, a POSA would have understood the combination of the '212 Patent, Voswinckel JESC, and Voswinckel JAHA to render this claim obvious. EX1002, ¶123.

XI. GROUND 2: CLAIMS 1-8 ARE RENDERED OBVIOUS UNDER 35 U.S.C. § 103(a) OVER THE '212 PATENT IN COMBINATION WITH VOSWINCKEL JESC

A. Motivation to Combine With a Reasonable Expectation of Success

A POSA would have been motivated to combine the '212 Patent with Voswinckel JESC, because both disclose use of the same drug (treprostinil/UT-15) for the same disease (pulmonary arterial hypertension) through the same route of administration (inhalation of solution of treprostinil). The first four paragraphs of

Section X.A. explain why a POSA would have been motivated to combine these references with a reasonable expectation of success.

B. The '212 Patent in combination with Voswinckel JESC renders obvious claims 1-8

1. Independent Claim 1

a. The '212 Patent in combination with Voswinckel JESC renders obvious claim elements 1[a], 1[b], and 1[c]

1[a]	A method of treating pulmonary hypertension comprising administering by inhalation to a human suffering from pulmonary hypertension a therapeutically effective single event dose of a formulation comprising treprostinil or a pharmaceutically acceptable salt thereof
1[b]	with an inhalation device
1[c]	wherein the therapeutically effective single event dose comprises from 15 micrograms to 90 micrograms of treprostinil or a pharmaceutically acceptable salt thereof

As explained above at Sections X.B.1.a to X.B.1.c, the '212 Patent discloses elements 1[a] and 1[b], and the '212 Patent in combination with Voswinckel JESC discloses element 1[c].

b. Claim element 1[d] is obvious via routine optimization

1[d]	delivered in 1 to 3 breaths.

Element 1[d] would have been obvious over the '212 Patent and Voswinckel JESC in view of a POSA's general knowledge in the field and/or by applying routine optimization.

A POSA reading the '212 Patent and Voswinckel JESC would have been motivated to minimize the number of breaths required for administration of treprostinil by inhalation, to increase patient compliance and convenience. *See* EX1002, ¶¶128, 130. In addition, by May 2006, the general state of the art had established the safety and efficacy of high dosages of inhaled therapeutics delivered over a small number of breaths. *See, e.g., id.*, ¶129; EX1034, 177 (delivery of 0.45mg of drug in 3 breaths); EX1010, 298 ("[I]t is technically feasible for there to be only one to two breaths in an application."); EX1008, Methods (administration of 600 µg/mL treprostinil in 3 breaths); EX1009, 150 (administration of 15µg treprostinil in 3 breaths). Further, claim 9 of the '212 Patent is specifically directed to an inhaled powder formulation of treprostinil, which is commonly delivered by dry powder inhalers. EX1006, claim 9. Dry powder inhalers are breath-actuated as opposed to delivering doses over a set period of time. EX1039, 81 ("Advantages such as the potential ability to generate high FPFs and a relatively high lung deposition, fast and easy administration, the ability to prepare stable formulations (compared with solutions), and the fact that DPIs are breath-actuated and easily portable, justify their existence."). Therefore, a POSA would have been encouraged to and found it obvious to modify the teachings of the '212 Patent and Voswinckel JESC to deliver inhaled treprostinil in 1 to 3 breaths. EX1002, ¶¶126-131.

Relying on the '212 Patent and Voswinckel JESC to deliver inhaled

treprostinil in 1 to 3 breaths would have amounted to mere routine optimization. *See, e.g., Genzyme Therapeutic Prods. L.P. v. Biomarin Pharm. Inc.*, 825 F.3d 1360, 1365, 1373 (Fed. Cir. 2016) (affirming decision finding dosing claims obvious when "the claimed dosing schedule would have been arrived at by routine optimization"); *see also Hoffmann-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1329-31 (Fed. Cir. 2014) (affirming decision finding dosing claims obvious because "[a] relatively infrequent dosing schedule has long been viewed as a potential solution to the problem of patient compliance"); *see also Merck & Co., Inc. v. Teva Pharms. USA, Inc.,* 395 F.3d 1364, 1373 (Fed. Cir. 2005) (reversing decision to find claims obvious that covered slightly different dosages from those of the prior art). In fact, the '212 Patent itself contemplates dose optimization as a matter of routine. EX1006, 6:56-7:3 ("Titration to effect may be used to determine proper dosage."), 7:25-33; *see also generally id.*, 1:10-2:64. Such titration to effect was well known in similar aerosolized prostacyclin therapy. EX1004, ¶35 (citing EX1047, EX1048); EX1002, ¶127, 130. A POSA therefore would have understood the benzindene prostaglandin (*i.e.*, treprostinil) disclosed in the '212 Patent and Voswinckel JESC could be "delivered in 1 to 3 breaths."

2. Dependent Claims 2-8

2	The method of claim 1, wherein the inhalation device is a soft mist inhaler.

3	The method of claim 1, wherein the inhalation device is a pulsed ultrasonic nebulizer.
4	The method of claim 1, wherein the inhalation device is a dry powder inhaler.
5	The method of claim 1, wherein the inhalation device is a pressurized metered dose inhaler.
6	The method of claim 4, wherein the formulation is a powder.
7	The method of claim 6, wherein the powder comprises particles less than 5 micrometers in diameter.
8	The method of claim 1, wherein the formulation contains no metacresol.

The additional limitations of dependent claims 2-8 are disclosed in the '212 Patent, as explained above in Sections X.B.2 to X.B.8. Further, for claim 3, Voswinckel JESC specifically teaches use of the "OptiNeb® ultrasound nebulizer," which the '793 patent confirms is pulsed. EX1007, Methods; EX1001, 14:35-37.

XII. GROUND 3: CLAIM 1 IS ANTICIPATED BY GHOFRANI

Ghofrani explicitly discloses every element of claim 1.

A. Ghofrani Discloses Claim Element 1[a]

1[a]	A method of treating pulmonary hypertension, comprising administering by inhalation to a human suffering from pulmonary hypertension a therapeutically effective single event dose of a formulation comprising treprostinil or a pharmaceutically acceptable salt thereof

Element 1[a] is disclosed by Ghofrani, which teaches the recited method of treating pulmonary hypertension. Ghofrani, in relevant part, discloses the efficacy

of "inhaled treprostinil" for 17 patients with "pulmonary hypertension" at a dosage of "15mcg/inhalation" for total dosage of "up to 90mcg . . . without adverse effects occurring." EX1010, 298; EX1002, ¶¶136-138. Ghofrani further discloses that "initial data shows that it is technically feasible for there to be only one to two breaths in an application." EX1010, 298.

B. Ghofrani Discloses Claim Element 1[b]

1[b]	with an inhalation device

Element 1[b] is disclosed by Ghofrani, which states patients were administered "inhaled treprostinil," which would require an inhalation device. EX1010, 298. Ghofrani further discloses that "it is possible to reduce the number [of] inhalations necessary to up to four per day; the inhalation period can be reduced to <1min. by selecting **a suitable device**." *Id*. A POSA as of May 2006 would have readily understood such a "suitable device" to be an inhalation device. EX1002, ¶139.

C. Ghofrani Discloses Element 1[c]

1[c]	wherein the therapeutically effective single event dose comprises from 15 micrograms to 90 micrograms of treprostinil or a pharmaceutically acceptable salt thereof

Ghofrani discloses a study in which patients "were administered [a single

event dose of] inhaled treprostinil (15 mcg[14]/inhalation)." EX1010 (Ghofrani), 298. That dose "led to a major reduction in pulmonary selective pressure and resistance with an overall duration of action of >180 min." *Id*. Ghofrani further discloses "it is possible to increase the dosage to up to 90 mcg (absolute inhaled dose per inhalation exercise) without adverse effects occurring." *Id.* Ghofrani thus discloses a per inhalation exercise (i.e., single event dose) that covers the claimed dosage range. EX1002, ¶140.

D. Ghofrani Discloses Claim Element 1[d]

1[d]	delivered in 1 to 3 breaths.

Ghofrani discloses that "it is technically feasible for there to be only one to two breaths in an application" of the claimed dosage, disclosing element 1[d] to a POSA. EX1010, 298; EX1002, ¶141-142.

XIII. GROUND 4: CLAIMS 1, 3, AND 8 ARE RENDERED OBVIOUS UNDER 35 U.S.C. § 103(A) OVER VOSWINCKEL JAHA IN COMBINATION WITH GHOFRANI

A. Motivation to Combine With A Reasonable Expectation of Success

The Board has found that "Voswinckel [2004] references a 17 patient study that appears to be the same as the 17 patent study discussed in the relevant portions of Ghofrani." IPR2017-01621, Paper 10 at 14. Dr. Hill agrees and explains why a

[14] A POSA would have understood that "mcg" and "μg" refer to micrograms.

POSA would have expected the disclosures of Ghofrani to apply to Voswinckel JAHA. EX1002, ¶¶143-144.

Even if not the same study, every author of Ghofrani is also an author of Voswinckel JAHA, motivating a POSA to look at Ghofrani for additional details after reviewing the Voswinckel JAHA Abstract. *Compare* EX1010, with EX1008; EX1002, ¶145. Since Voswinckel JAHA does not expressly provide the total dose administered in its single event dose of 1 to 3 breaths, a POSA would have been motivated to look to Ghofrani for the optimal dosing range in Voswinckel JAHA's breath range. Ghofrani discloses a study in which patients "were administered inhaled treprostinil (15 mcg/inhalation)," teaches that "it is possible to increase the dosage to up to 90 mcg (absolute inhaled dose per inhalation exercise) without adverse effects occurring," and discloses that "it is technically feasible for there to be only one to two breaths in an application" with these dose ranges. EX1010, 298. Thus, a POSA would have been motivated to combine Voswinckel JAHA with the 15-90 mcg dosage disclosure of Ghofrani. EX1002, ¶145.

A POSA would have had a reasonable expectation of success in combining the two, because both references teach successful safety and efficacy of inhaled treprostinil at their respective breath and dosage levels. EX1002, ¶145. Voswinckel JAHA teaches that its "inhalation resulted in a sustained, highly pulmonary selective vasodilatation over 120 minutes," showing "strong pulmonary selective vasodilatory

efficacy with a long duration of effect following single acute dosing" with "[n]o side effects." EX1008, Methods, Conclusion. Ghofrani teaches that its dosing "led to a major reduction in pulmonary selective pressure and resistance with an overall duration of action of >180 min . . . without adverse effects occurring." EX1010, 298.

B. Voswinckel JAHA in combination with Ghofrani renders obvious claims 1, 3, and 8

1. Independent Claim 1

a. Voswinckel JAHA and Ghofrani disclose claim element 1[a]

1[a]	A method of treating pulmonary hypertension comprising administering by inhalation to a human suffering from pulmonary hypertension a therapeutically effective single event dose of a formulation comprising treprostinil or a pharmaceutically acceptable salt thereof

Element 1[a] is disclosed by Voswinckel JAHA, which teaches the recited method of treating pulmonary hypertension. Voswinckel JAHA describes treating "17 patients with severe pulmonary hypertension" with "Inhaled Treprostinil Sodium (TRE)." EX1008, Title, Methods. Voswinckel JAHA also describes a single event dose of "3 single breaths" of "TRE solution 600 μg/ml" having "strong pulmonary selective vasodilatory efficacy with a long duration of effect following single acute dosing." *Id.*, Methods, Conclusion.

Ghofrani also discloses element 1[a]. *See supra* Section XII.A.

b. Voswinckel JAHA and Ghofrani disclose claim element 1[b]

1[b]	with an inhalation device

Element 1[b] is disclosed by Voswinckel JAHA, which expressly discloses "inhaled TRE" through the "use of the pulsed OptiNeb® ultrasound nebulizer." *Id.*, Methods. A POSA as of May 2006 would have readily understood that this nebulizer is an inhalation device. EX1002, ¶150.

Ghofrani also discloses element 1[b]. *See supra* Section XII.B.

c. Voswinckel in combination with Ghofrani discloses element 1[c]

1[c]	wherein the therapeutically effective single event dose comprises from 15 micrograms to 90 micrograms of treprostinil or a pharmaceutically acceptable salt thereof

Element 1[c] would have been obvious over Voswinckel JAHA in combination with Ghofrani. Because Voswinckel does not expressly provide the total dose administered in its single event dose, a POSA would have looked to Ghofrani to fill in the optimal single event dosing range, since "both references disclose that inhaled administration of treprostinil at these doses in 1-3 breaths was an effective treatment for pulmonary hypertension." EX1002, ¶155. In Ghofrani, patients "were administered inhaled treprostinil (15 mcg/inhalation)." EX1010, 298. Ghofrani further discloses that "it is possible to increase the dosage to up to 90 mcg (absolute inhaled dose per inhalation exercise) without adverse effects occurring."

Id. Ghofrani further discloses that "it is technically feasible for there to be only one to two breaths in an application." *Id.* Thus, a POSA would have understood that Ghofrani was disclosing a 15 to 90 μg single event dose—the entire claimed range—in the same 1-3 breath range as Voswinckel JAHA. EX1002, ¶154. A POSA administering treprostinil in accordance with the teachings of Voswinckel JAHA would have been motivated to use the range of doses disclosed by Ghofrani because such doses "led to a major reduction in pulmonary selective pressure and resistance with an overall duration of action of > 180 min . . . without adverse effects occurring," i.e. a POSA would understand that this dose was therapeutically effective and safe. EX1010, 298; EX1002, ¶¶153-154.

d. Voswinckel JAHA and Ghofrani disclose claim element 1[d]

1[d]	delivered in 1 to 3 breaths.

Element 1[d] is disclosed by Voswinckel JAHA, which discloses treating patients with a single event dose of "3 single breaths." EX1008, Methods. Ghofrani further discloses that "it is technically feasible for there to be only one to two breaths in an application" of the claimed dosage. EX1010, 298. Thus, both Voswinckel JAHA and Ghofrani disclose element 1[d].

2. Dependent Claim 3

3	The method of claim 1, wherein the inhalation device is a pulsed ultrasonic nebulizer.

The limitation of claim 3 is disclosed by Voswinckel JAHA, which specifically teaches use of the "pulsed OptiNeb® ultrasound nebulizer." EX1008, Methods.

3. Dependent Claim 8

8	The method of claim 1, wherein the formulation contains no metacresol.

The limitation of claim 8 is disclosed by Voswinckel JAHA, which states that a "preservative free solution of inhaled TRE" was used (EX1008, Methods), which a POSA would understand to mean that the solution contained no metacresol, because metacresol was known in 2006 to be a preservative. EX1004, ¶¶94, 104; *see also* EX1001, 15:40-41 (referring to a "metacresol preservative" in "treprostinil solution").

XIV. GROUND 5: CLAIMS 1 AND 3 ARE ANTICIPATED BY VOSWINCKEL 2006

A. Independent Claim 1

1. Voswinckel 2006 discloses claim element 1[a]

1[a]	A method of treating pulmonary hypertension comprising administering by inhalation to a human suffering from pulmonary hypertension a therapeutically effective single event dose of a formulation comprising treprostinil or a pharmaceutically acceptable salt thereof

Element 1[a] is disclosed in Voswinckel 2006, which teaches the recited method of treating pulmonary hypertension. Voswinckel 2006 describes treating

"three patients with severe pulmonary hypertension" with "inhaled treprostinil." EX1009, 150. Voswinckel 2006 also describes "**a single** 15-µg **dose** of treprostinil, inhaled in 3 breaths" inducing "highly pulmonary selective and sustained vasodilatation" proving that "[t]he drug was clinically effective" at the dosage and number of breaths. *Id.*

2. Voswinckel 2006 discloses claim element 1[b]

1[b]	with an inhalation device,

Element 1[b] is disclosed in Voswinckel 2006, which expressly discloses "inhaled treprostinil" administered "through a modified OptiNeb ultrasonic **inhalation device**." *Id.*

3. Voswinckel 2006 discloses claim element 1[c]

1[c]	wherein the therapeutically effective single event dose comprises from 15 micrograms to 90 micrograms of treprostinil or a pharmaceutically acceptable salt thereof

Element 1[c] is disclosed in Voswinckel 2006, which teaches that "a single 15-µg dose of treprostinil" was inhaled by patients "through a modified OptiNeb ultrasonic inhalation device." *Id.*

4. Voswinckel 2006 discloses claim element 1[d]

1[d]	delivered in 1 to 3 breaths.

Element 1[d] is disclosed in Voswinckel 2006 which teaches that "15-µg dose of treprostinil" was inhaled by patients "in **3 breaths** through a modified OptiNeb ultrasonic inhalation device." *Id.*

B. Claim 3

3	The method of claim 1, wherein the inhalation device is a pulsed ultrasonic nebulizer.

Voswinckel 2006 discloses use of a "modified OptiNeb ultrasonic inhalation device" (EX1009 (Voswinckel 2006), 150), which was a known pulsed ultrasonic nebulizer as of May 2006. EX1004, ¶108; EX1002, ¶172; EX1001, 14:35-37 (describing use of a "pulsed ultrasonic nebulizer" OPTINEB® by Nebutec).

XV. GROUND 6: CLAIMS 2 AND 4-8 ARE OBVIOUS OVER VOSWINCKEL 2006 IN COMBINATION WITH THE '212 PATENT

As explained above, Claim 1 is anticipated by Voswinckel 2006. The additional limitations of claims 2 and 4-8 are obvious over Voswinckel 2006 in view of the '212 Patent.

A. Motivation to Combine With a Reasonable Expectation of Success

Both the '212 Patent and Voswinckel 2006 are directed to the use of inhaled treprostinil (also known as benzindene prostaglandin UT-15), for the treatment of pulmonary hypertension. *See, e.g.,* EX1006, Abstract (disclosing "[a] method of delivering benzindene prostaglandins to a patient by inhalation" for the treatment of "pulmonary hypertension"); *see also* EX1009 (Voswinckel 2006), 149 (titled

"Inhaled Treprostinil for Treatment of Chronic Pulmonary Arterial Hypertension"). Indeed, Voswinckel 2006, like Voswinckel JESC and Voswinckel JAHA, puts into clinical practice the express teachings of the '212 Patent, with success. But Voswinckel 2006 is limited to one form of inhalation delivery, and other forms were well-known by 2006. Each form had various advantages and disadvantages that made it useful for different patients and scenarios. *See, e.g.*, EX1031 ("Comparing Clinical Features of the Nebulizer, Metered-Dose Inhaler, and Dry Powder Inhaler"). As Dr. Gonda and Dr. Hill explain, a POSA would have been motivated to apply the '212 Patent's teachings as to various forms of inhalers and dry powder formulations, while maintaining the dosage and breath limitations of Voswinckel 2006, with a reasonable expectation of success because Voswinckel 2006 had shown that treprostinil was "clinically effective, safe, and well tolerated" at the dosage and breath of "15 μg … inhaled in 3 breaths." *See* EX1009, 150; EX1004, ¶110-113; EX1002, ¶¶173-176.

B. Voswinckel 2006 in combination with the '212 Patent renders obvious claims 2 and 4-8

1. Dependent Claim 2

2	The method of claim 1, wherein the inhalation device is a soft mist inhaler.

As explained above at Sections X.B.2 and XV.A., a POSA would understand the '212 Patent's teachings to apply to soft mist inhalers, and expect Voswinckel

2006's dosage and breath disclosures to be realizable via a soft mist inhaler. EX1004, ¶115-116. Thus, Voswinckel 2006 in combination with the '212 Patent render obvious "wherein the inhalation device is a soft mist inhaler."

2. Dependent Claim 4

4	The method of claim 1, wherein the inhalation device is a dry powder inhaler.

The '212 Patent discloses this element, as detailed above at Section X.B.4. *See also* EX1002, ¶180; EX1004, ¶118. A POSA would have readily understood that "inhaled treprostinil" dosage and breath disclosure of Voswinckel 2006 could be utilized as a powder delivered in a "dry powder inhaler" as disclosed and claimed by the '212 Patent. EX1004, ¶119. A POSA would have been motivated to do so because dry powder inhalers were well-known to be very portable and quick to use, breath-actuated, could be designed as single-dose or multi-dose devices, provided the "lowest cost dose," and were easier for patients (especially children) to use than the pulsed ultrasonic nebulizer disclosed in Voswinckel 2006. *Id.*; EX1030, 58, 61-62, 63; EX1031, 1316-17; *see also* EX1039, 81 ("Advantages such as the potential ability to generate high FPFs and a relatively high lung deposition, fast and easy administration, the ability to prepare stable formulations (compared with solutions), and the fact that DPIs are breath-actuated and easily portable, justify their existence."). A POSA would thus have had a reasonable expectation of success that

the "inhaled treprostinil" described in Voswinckel 2006 could be delivered using a dry powder inhaler. EX1004, ¶119.

3. Dependent Claim 5

5	The method of claim 1, wherein the inhalation device is a pressurized metered dose inhaler.

The '793 Patent defines a pressurized metered dose inhaler (pMDI) as "a device which produces the aerosol clouds for inhalation from solutions and/or suspensions of respiratory drugs in chlorofluorocarbon (CFC) and/or hydrofluoroalkane (HFA) solutions. EX1001, 7:17-21. The '212 Patent discloses use of an "inhaler," (EX1006, 5:30-32) and pMDIs were well-known inhalers as of 2004. *See* EX1004, ¶121; EX1002, ¶183.

A POSA would have been motivated to deliver the "inhaled treprostinil" described in Voswinckel 2006 using pMDIs with a reasonable expectation of success. As Dr. Gonda explains, pMDIs were known to be "efficient" while being "inherently portable and very convenient to use" (EX1020 at 379), which would motivate a POSA to deliver the "inhaled treprostinil" using a pMDI, because patient adherence was a known problem that could be eased by portability and convenience. EX1004, ¶122. And a POSA would have had a reasonable expectation that the "inhaled treprostinil" disclosed in Voswinckel 2006 could be delivered using a pMDI, because they were readily available, well understood, and offered for

"[n]early all major respiratory drugs." *Id*.

Thus, a POSA would have understood the combination of Voswinckel 2006 and the '212 Patent to render claim 5 obvious. EX1002, ¶184.

4. Dependent Claim 6

6	The method of claim 1, wherein the formulation is a powder.

Claim 6 would have been obvious over Voswinckel 2006 in combination with the '212 Patent, which discloses and claims that powder formulations may be used to treat pulmonary hypertension. EX1006, 5:37-39 ("Alternatively, solid formulations, usually in the form of a powder, may be inhaled in accordance with the present invention."), claims 6 and 9. A POSA would have been motivated to convert Voswinckel 2006's treprostinil solution to a powder because powders were known to be more stable formulations than solutions by May 2006, and the '212 Patent specifically claims such powder formulations for the same indication as Voswinckel 2006. *See* EX1004, ¶125; EX1039, 81; EX1006, claim 9. A POSA would have had a reasonable expectation of success in doing so because converting a solution to dry powder was well known by 2006, and the '212 Patent discloses and claims that treprostinil can be formulated as a powder for delivery by inhalation. *See, e.g.*, EX1004, ¶125; EX1040, 51-53 ("Preparation of Powders" section).

5. Dependent Claim 7

7	The method of claim 1, wherein the powder comprises particles less than 5 micrometers in diameter.

Claim 7 would have been obvious over Voswinckel 2006 in combination with the '212 patent, which discloses that "the particles are preferably less than 10 micrometers in diameter, and more preferably, less than 5 micrometers in diameter." EX1006, 5:39-41.

6. Dependent Claim 8

8	The method of claim 1, wherein the formulation contains no metacresol.

Claim 8 is disclosed in Voswinckel 2006 and the '212 Patent. Voswinckel 2006 does not disclose the presence of metacresol in the described formulation of "inhaled treprostinil," and the '212 Patent discloses formulations without metacresol. *See generally* EX1009; EX1006, 5:25-29 (disclosing formulation of a "more preferred solution" that does not include metacresol), 8:39-44 (disclosing steps of formulating treprostinil inhalation solution that do not include metacresol). Voswinckel 2006 in combination with the '212 Patent therefore discloses a formulation of treprostinil that contains no metacresol. EX1004, ¶130-131.

XVI. NO SECONDARY CONSIDERATIONS OF NON-OBVIOUSNESS EXIST

No secondary considerations of non-obviousness were presented to the PTO.

To the extent PO argues, similar to their arguments in IPR2017-01621 and IPR2017-01622 and in the '793 Patent, that the claims recite unexpected results, address a long-felt but unmet need, have been copied, and have been commercially successful, those considerations do not preserve validity, particularly because PO cannot establish a nexus between those considerations and the claims.

First, the fact that treprostinil by inhalation was safe and effective at the dosage range claimed by the '793 patent was not **an unexpected result** by 2006. This result was already disclosed by the prior art discussed in this Petition (*see, e.g.*, EXS1007-1010. Thus, the success of administering 15 to 90 micrograms of treprostinil in 1 to 3 breaths was entirely *expected* as of May 2006. EX1004, ¶133.

Second, no **long-felt, but unmet need** for a "treatment for pulmonary hypertension that can be administered using a compact inhalation device" (EX1001, 2:60-62) existed in 2006, such that it was allegedly addressed by PO's Tyvaso® (treprostinil) inhalation solution. By 2006, pulmonary hypertension treatment with a compact inhalation device, like a nebulizer, could be achieved in more breaths, lower concentrations, and by iloprost. *See supra*, Sections VIII.B-C. These treatments meet the articulated "long-felt need," regardless of whether they practice the '793 Patent claims—exemplifying why there is no nexus between the '793 Patent's treprostinil, dosage, or breath claim limitations and the purported need. In addition, treprostinil was already available for subcutaneous and intravenous

administration well before Tyvaso® (*see, e.g.*, EX1018), and there are disadvantages to oral inhalation, such that even today, doctors prescribe subcutaneous or intravenous dosing of treprostinil over inhaled treprostinil. *See* EX1002, ¶¶189-190; EX1004, ¶135. So, more accurately, Tyvaso® was approved by the FDA as another option, useful in certain circumstances, for an already met need.[15] EX1004, ¶137. To the extent there was any need for the other claimed, non-nebulizer inhalation devices, PO actively gave up on those paths and instead pursued minor advancements in its nebulizer and non-inhaled routes like oral delivery. *See* EX1004, ¶136. PO simply claimed use of the other devices without producing a product for the market, because they did not believe they met a long-felt need worth pursuing and instead wanted to force out companies, like Petitioner, who developed dry powder formulations and inhalers. *Id.*

Third, as for **copying**, PO cannot show evidence of copying simply because

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[15] Further, as Dr. Gonda explains, a POSA would have known that pulmonary hypertension treatment with compact inhalation devices, like a soft mist inhaler or a dry powder inhaler, could be achieved in a smaller number of breaths using a higher concentration of the drug, and the safety, tolerability, and efficacy of such formulations was tested in patients. EX1004, ¶134.

they have accused Petitioner of infringing the '793 Patent claims. As Dr. Gonda explains, a POSA would not consider Liquidia' s product "copying," because PO UTC never developed a dry powder formulation or inhaler. EX1004, ¶138. Further, considering the '793 Patent issued *after* Liquidia developed LIQ861 and submitted its NDA, a skilled artisan would not consider Liquidia's product a "copy" of the alleged claimed invention. *Compare* EX1001 (issued July 21, 2020), *with* EX1042 (announcing Liquidia's NDA submission in January 27, 2020 Press Release); EX1049 (announcing FDA acceptance of LIQ861 NDA on April 8, 2020.)

PO may argue, as they have in district court, that because inventor Roscigno is a former employee of the Petitioner, Petitioner must have copied the claimed invention. But any inference that Roscigno's involvement resulted in any alleged "copying" is unsupported speculation by the PO, and is belied by the fact that Roscigno had been working at Liquidia since 2015, years before the application for the '793 Patent was even filed in 2020.

Finally, PO has not produced evidence that Tyvaso®'s market share is tied to the '793 Patent claims. In fact, while the Tyvaso® label recommends an initial dosage of 3 breaths, it expressly instructs increasing the dosage by "an additional 3 breaths per session" every "1-2 week[s]" as tolerated. *See* EX1043, 1 (Dosage and Administration). All but the initial dosing usage of Tyvaso® would not practice the '793 Patent claims, which are limited to a single event dose of 1 to 3 breaths. In

addition, Tyvaso®, a solution of treprostinil, is approved for oral inhalation through a pulsed ultrasonic delivery device, and therefore does not practice any claims directed to a soft mist inhaler, dry powder, DPI or MDI. *Id.*, 2 (Section 2.1). In sum, any evidence of Tyvaso®'s **commercial success** lacks the required nexus to the claims.

Accordingly, the secondary considerations of non-obviousness do not warrant a finding that the Petitioned Claims are patentable.

XVII. CONCLUSION

Petitioner respectfully requests that the Board institute *inter partes* review of claims 1–8 of the '793 Patent.

Respectfully submitted,

Dated: January 7, 2021

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CERTIFICATE OF COMPLIANCE WITH WORD COUNT

Pursuant to 37 C.F.R. § 42.24(d), I certify that this preliminary response complies with the type-volume limits of 37 C.F.R. § 42.24(c)(1) because it contains 13,689 words, according to the word-processing system used to prepare this petition, excluding the parts of this preliminary response that are exempted by 37 C.F.R. § 42.24(c) (including the table of contents, a table of authorities, an exhibits list, a listing of facts, a certificate of service or this certificate of word count, or appendix of exhibits).

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CERTIFICATE OF SERVICE

I hereby certify, pursuant to 37 C.F.R. §§ 42.6(e) and 42.105(b), that a complete and entire copy of this **PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 10,716,793** including all exhibits (**Nos. 1001-1079**) and related documents, were served via FEDERAL EXPRESS on the 7th day of January, 2021, the same day as the filing of the above-identified document in the United States Patent and Trademark Office/Patent Trial and Appeal Board, upon the Patent Owner by serving the correspondence address of record with the USPTO as follows:

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And, via FEDERAL EXPRESS upon counsel of record for Patent Owner in the litigation pending before the U.S. District Court for the District of Delaware entitled *United Therapeutics Corporation v. Liquidia Technologies, Inc.*, Case No. 1:20-cv-00755-RGA as follows:

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