UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

WATSON LABORATORIES, INC.

Petitioner,

v.

UNITED THERAPEUTICS CORPORATION
Patent Owner.

Case IPR2017-01621
Patents 9,358,240

EXPERT DECLARATION OF MAUREEN D. DONOVAN, PH.D.

I. INTRODUCTION

1. I, Maureen D. Donovan, Ph.D., hereby submit my expert declaration on behalf of Defendant Watson Laboratories, Inc. ("Watson").

2. I have been retained by Watson to provide technical expertise and expert opinions regarding U.S. Patent No. 9,358,240 ("the '240 patent").

3. The opinions to which I will testify at trial, if asked, are set forth in this report. My opinions in this report are based upon the information that I have received to date. They may be supplemented or modified if additional information is received. They also may be supplemented to reply to additional information or opinions provided by the parties (or witnesses retained by the parties) and issues that may arise at trial.

4. I may rely on demonstrative exhibits at trial to assist in explaining my trial testimony.

II. PERSONAL BACKGROUND AND EXPERT QUALIFICATIONS

5. I am a Professor in the Division of Pharmaceutics and Translational Therapeutics at the University of Iowa College of Pharmacy. I have more than 25 years of experience working and consulting in the field of pharmaceutics. My *curriculum vitae* is attached to this report as Exhibit A.

6. I am an expert in pharmaceutics. I received my Bachelor of Science in Pharmacy from the University of Minnesota College of Pharmacy in 1983 and my Ph.D. in Pharmaceutics from the University of Michigan in 1989.

7. My professional experience includes working as a Staff Pharmacist for Clark Professional Pharmacy from 1986 until 1989 and as a Visiting Scholar for SmithKline Beecham Pharmaceuticals in 1991. From 1989 through the present, I have held various positions at the University of Iowa College of Pharmacy. Specifically, in the Division of Pharmaceutics, I was an Assistant Professor from 1989 until 1996, and an Associate Professor from 1996 until 2008. I was promoted to the rank of Professor in 2008 in the College of Pharmacy, and I currently hold this position. From 2008 until 2013, I was the Division Head for the Division of Pharmaceutics. In 2013, I became the Associate Dean for Undergraduate Programs at the College of Pharmacy, and I currently hold this position.

8. I have over 25 years of experience in pharmaceutical research and development including actively teaching drug delivery, pharmaceutical preformulation, and compounding to pharmacy students and graduate students, and directing research programs focused on drug absorption, nasal drug delivery, and alternative routes of drug delivery and delivery systems.

9. I have published numerous articles, book chapters, and abstracts in the area of pharmaceutics, drug absorption, drug delivery, and materials

characterization. I also belong to several professional societies for pharmaceutical science and technology, including the American Association of Pharmaceutical Scientists and the Controlled Release Society.

10. I am being compensated for my work at $250 per hour for general document and background review; $400 per hour spent preparing reports; and a daily rate of $5,000 when testifying. No part of this compensation due or received is contingent upon the outcome of this matter or the pending litigation.

11. In addition to my knowledge, education, and experience in the field of pharmaceutical formulation, in forming the opinions I express in this report, I reviewed the full list of materials cited herein.

III. SUMMARY OF OPINIONS

12. As explained in detail in section VII.C., each of the asserted claims of the ’240 patent would have been obvious in light of the prior art as of May 15, 2006, which collectively teach and motivate a person of ordinary skill in the art to make a kit comprising a therapeutically effective amount of treprostinil by inhalation in an aerosol form in a pulsed ultrasonic nebulizer utilizing an opto-acoustical trigger, with instructions for use.

IV. LEGAL STANDARDS

13. While I am neither a patent lawyer nor an expert in patent law, I have been informed of the applicable legal standards for patent invalidity. I have relied

upon these legal principles, as explained to me by counsel, in forming my opinions set forth in my report.

14. I understand that clear and convincing evidence must be presented to render a patent claim invalid. I understand that evidence is sufficiently clear and convincing if it leaves the fact-finder with a definite and firm belief in the truth of a fact.

15. I understand that, even if a single prior art reference does not disclose each and every limitation of the claim, a patent claim may still be invalid as obvious. I have been informed that the standard for obviousness for the patent-in-suit, which was filed prior to the effective date of the AIA, is set out in pre-AIA version of 35 U.S.C. §103(a), which is quoted below:

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

16. I have been informed that in order for a patent claim to be considered obvious, at the time the invention was made, each and every limitation of the claim must be present within the prior art, or within the prior art in combination with the

general knowledge held by a person of ordinary skill in the art ("POSA"), and that such a person would have a reasonable expectation of success in combining these teachings to achieve the claimed invention. I also understand that the reason to select and combine features, the predictability of the results of doing so, and a reasonable expectation of success of doing so may be found in the teachings of the prior art themselves, in the nature of any need or problem in the field that was addressed by the patent, in the knowledge of a POSA in the field at the time, as well as in common sense or the level of creativity exhibited by a POSA. There need not be an express or explicit suggestion to combine references. I understand the combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.

17. I understand that an analysis of whether a claim would have been obvious to a POSA at the time of the invention requires an analysis of at least four criteria: (i) the level of ordinary skill in the art, (ii) the scope and content of the art, (iii) any differences between the prior art and the patent claims, and (iv) any objective indicia of non-obviousness. I have been informed that Plaintiff may rely on objective evidence of non-obviousness, and that I will have an opportunity to rebut any evidence that Plaintiff puts forward.

18. I understand that an analysis of whether a claim would have been obvious to a POSA at the time of the invention includes an analysis of any objective

indicia of non-obviousness. To be relevant to an obviousness analysis, I understand there must be a nexus between the secondary consideration of nonobviousness and features of the patent-in-suit that are both novel and actually claimed in the patent. In other words, evidence of a secondary consideration is only relevant if it relates to a claim element that is unique to the patents-in-suit, and not already disclosed by the prior art.

19. A prior art reference can be said to teach away when a POSA would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken in the claimed invention. The mere disclosure of more than one alternative does not constitute a teaching away from alternatives that are not disclosed when the prior art does not criticize, discredit, or otherwise discourage the solution claimed in the alleged invention. Similarly, a prior art reference that merely expresses a general preference for an alternative invention does not teach away.

20. I have relied upon this understanding of the applicable legal standards in reaching my opinions set forth in my report.

V. BACKGROUND AND TUTORIAL

21. The patent-in-suit relates to the treatment of pulmonary hypertension using a drug called treprostinil. Specifically, the treprostinil treatment is delivered by inhalation, using a nebulizer. The background below and tutorial serves as a

primer to explain the background of the development of treprostinil for therapeutic use and the background in the development of the technology used to deliver drugs via inhalation.

1. Pulmonary Hypertension

22. Pulmonary hypertension can be described as an increase in "resistance to pulmonary blood flow" and "an elevation of pulmonary arterial pressure over normal levels."[1] Other measureable hemodynamics associated with pulmonary hypertension include left atrial pressure, central venous pressure, systemic arterial pressure, heart rate, and cardiac output.[2]

23. Pulmonary hypertension "can be a manifestation of an obvious or explicable increase in resistance, such as obstruction to blood flow by pulmonary emboli, malfunction of the heart's valves or muscle in handling blood after its passage through the lungs, diminution in pulmonary vessel caliber as a reflex response to alveolar hypoxia due to lung diseases or high altitude, or a mismatch of vascular capacity and essential blood flow, such as shunting of blood in congenital abnormalities or surgical removal of lung tissue."[3]

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[1] Ex. 1001 at col. 2, ll. 6-8.

[2] Ex. 1018 at col. 7, ll. 25–33.

[3] Ex 1001 at col. 1, ll. 41-49.

24. Pulmonary hypertension may be either acute or chronic.[4] Acute pulmonary hypertension may be a reversible condition triggered by "hypoxia (as in high-altitude sickness), acidosis, inflammation, or pulmonary embolism."[5] "Chronic pulmonary hypertension is characterized by major structural changes in the pulmonary vasculature."[6] The causes for chronic pulmonary hypertension include "chronic hypoxia, thromboembolism, collagen vascular diseases, pulmonary hypercirculation due to left-to-right shunt, HIV infection, portal hypertension or a combination of genetic mutation and unknown causes."[7]

25. Life expectancy for patients with pulmonary hypertension is extremely short and death is often sudden due to failure of the right side of the heart.[8] Compounds that are effective in the treatment of pulmonary hypertension, therefore, have been the subject of significant research and development.

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[4] Ex. 1001 at Col. 2, l. 22.

[5] *Id*. at ll. 23-27.

[6] *Id*. at ll. 28-36.

[7] *Id*.

[8] Ex. 1028 at 820.

2. Early Development of Treprostinil for the Treatment of Pulmonary Hypertension

26. Treprostinil is a part of a sub-class of prostacyclin analogs called benzindene prostaglandins.[9] Prostacyclin is "an endogenously produced compound in mammalian species."[10] It is both "structurally and biosynthetically related to the prostaglandins."[11]

27. The beneficial pharmacological effects of prostaglandins have been known for decades. Prostacyclin was first synthesized in the 1970s and was discovered to act as a strong local vasodilator that inhibits the aggregation of blood platelets.[12]

28. In 1981, U.S. Patent No. 4,306,075 ("Aristoff '075") taught that benzidene prostaglandins were found to "have useful application as antithrombotic agents, anti-ulcer agents, and anti-asthma agents"[13] due to their ability to "produce

[9] Ex. 1019 at col. 1, ll. 16–24.

[10] *Id*. at col. 1, ll. 25–26.

[11] *Id*. at col. 1, ll. 26–27.

[12] *See* Ex. 1028 at 820 (noting that "[i]ntravenous prostacyclin is a potent pulmonary vasodilator in patients with primary pulmonary hypertension").

[13] Ex. 1019 at col. 12, ll. 35–37.

various pharmacological responses, such as inhibition of platelet aggregation, reduction of gastric secretion, and bronchodilation."[14] These prostacyclin analogs "produce certain prostacyclin-like pharmacological responses" and formulas containing these analogs "are used as agents in the study, prevention, control, and treatment of diseases, and other undesirable physiological conditions, in mammals, particularly humans."[15]

29. In 1989 EP 0347243 A1 taught "prostaglandins for use in the prophylaxis, treatment, or diagnosis of pulmonary hypertension."[16] EP '243 identifies treprostinil[17] as a "particularly preferred compound[]" with "exceptional pulmonary anti-hypertensive properties."[18]

30. Likewise, in 1992, U.S. Patent No. 5,153,222 ("Tadepalli '222") disclosed and claimed the use of treprostinil in the treatment of pulmonary

[14] Ex. 1020 at col. 1, ll. 22–25.

[15] *Id.* at col. 12, ll. 27–32.

[16] Ex. 1021 at 2, ll. 3-5.

[17] Identified as "9-deoxy-2',9α-methano-3-oxa-4,5,6-trinor-3,7-(1',3'-interphenylene)-13,14-dihydroprostaglandin F1."

[18] Ex. 1021 at 3, ll. 60-62.

hypertension.[19] Specifically, Tadepalli '222 disclosed the results of certain animal studies finding that treprostinil, "reduce[d] hypoxia-induced increase in pulmonary arterial pressure and pulmonary vascular resistance in a dose-related manner without appreciably affecting cardiac output or heart rate."[20] The inventors observed that "[t]he hypoxia-induced vasoconstriction did not return to its control value within 15 minutes of terminating the final infusion indicating a relatively long duration of action for [treprostinil]."[21] In another study, the inventors observed "a dose-dependent fall in systolic and diastolic pressures were observed for a period of up to 8 hours after administration indicating that [treprostinil] had good oral bioavailability."[22]

31. Tadepalli '222 explained that, like prostacyclin, treprostinil acts as a potent vasodilator that widens the blood vessels and decreases pulmonary arterial pressure. It also was found to have little effect on cardiac output and heart rate, two beneficial traits for the treatment of pulmonary hypertension.[23]

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[19] Ex. 1025 at Cover 6, ll. 27-50.

[20] *Id.* at col. 6, ll. 27–32.

[21] *Id.* at col. 6, ll. 35–39.

[22] *Id.* at col. 6, ll. 47–50.

[23] *Id.* at col. 6, ll. 30–31.

32. In 1993, U.S. Patent No. 5,234,953 ("Crow '953") disclosed that "[c]ompound A [i.e., treprostinil] was found to [be] a potent pulmonary vasodilator… [that] markedly attenuated the pulmonary vasoconstriction induced by hypoxia."[24] It further discloses other "acute beneficial hemodynamic effects" of treprostinil including "substantial reductions in pulmonary vascular resistance, pulmonary arterial pressure, systemic vascular resistance and mean arterial blood pressure and increases in cardiac output and stroke volume."[25] Crow '953 teaches the use of treprostinil in patients with congestive heart failure which is accompanied by pulmonary hypertension.

3. Drug Delivery by Inhalation

33. Delivery of drugs by inhalation has been utilized for hundreds of years. In particular, inhalation has been known and used as an effective method of drug delivery to the lungs. Since at least the early 1950s drug delivery by inhalation was considered to be "an important means of treating a variety of conditions, including such common local conditions as bronchial asthma and chronic obstructive pulmonary disease and some systemic conditions, including hormone replacement,

[24] Ex. 1054 at col. 7, ll. 19–22.

[25] Ex. 1054 at col. 7, ll. 22–28.

pain management, cystic fibrosis, etc."[26] Several advantages are associated with inhalation delivery.[27] First, inhalation allows the drug to be delivered "directly to the site of drug action."[28] Inhalation also results in "rapid onset of the therapeutic effect, compared with other routes of administration, such as intramuscular and oral routes."[29] Additionally, inhalation may be beneficial "[f]or drugs which are susceptible to breakdown in the gastrointestinal tract."[30]

34. The active drug can be formulated as a solution, suspension, or a solid. In the first case, "the drug is dissolved in a suitable solvent which can be aerosolized to form a small-particle mist."[31] By 2006, the existing devices that could aerosolize the solution included at least a pneumatic nebulizer, ultrasonic nebulizer, or "a self-contained nebulizer containing a pressurized, fluorocarbon propellant."[32] Pneumatic nebulizers—also known as jet nebulizers—are powered by compressed air or

[26] Ex. 1022 at col. 1, ll. 10-15; Ex. 1023 at p. 2, ll. 4–9.

[27] Ex. 1024 at col. 1, ll. 36–46; col. 15, ll. 39–45.

[28] *Id*. at col. 1, ll. 36–39.

[29] *Id*. at col. 1, ll. 39–41.

[30] *Id*. at col. 1, ll. 42–46.

[31] *Id*. at col. 1, ll. 49–67.

[32] *Id*.

another gas. Ultrasonic nebulizers utilize a source of ultrasound acoustically coupled to a liquid in a nebulization chamber to generate an aerosol of small liquid droplets to be delivered in controlled doses to a patient.[33]

35. To determine the optimal nebulizer, formulators would often compare jet and ultrasonic nebulizers to determine which could ideally deliver the target dose in an efficient manner.[34] These device-comparison studies showed that ultrasonic nebulizers consistently produced a higher output of drug aerosol.[35]

36. Most nebulizers operate by inserting or emptying an ampoule containing a solution of the active ingredient and optional excipients into the chamber.[36] Once the ampule is inserted into the nebulizer and it is turned on, the solution is nebulized at a certain rate. This rate is typically a constant rate, however the rate of nebulization was adjustable in some devices.[37]

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[33] Ex. 1026 at col. 1, ll. 5–26.

[34] Ex. 1027 at Abstr., 15.

[35] *Id*.

[36] Ex. 1018 at col. 8, l. 39–col. 9, l. 3.

[37] The Nebu-Tec website explains that the OptiNeb® has a nebulization rate of <0.6 mL/min. (Ex. 1014 at B-2 at 26.) In one particle size test, the output of the OptiNeb® ultrasonic nebulizer was 173±3 µL/min. (*Id*. at 31.)

37. By 2006 the delivery of a pharmaceutical product via nebulizer used at least two different methods to administer the prescribed dose—either a constant or a pulsed delivery. As opposed to a constant stream of aerosol delivery, a pulsed nebulizer only dispenses drug intermittently.[38] Because some 50% of any aerosol produced by a continuous dose nebulizer is lost while a patient is exhaling, a pulsed nebulizer offers the benefits of less drug waste and lower costs through greater efficiency.[39]

38. For example, a 2003 paper reported tests conducted with a nebulizer called "HaloLite:"

> The HaloLite is a new electronically controlled device, applying aerosol pulses only in a preset period during early inspiration, with delivery adjusted to the breathing pattern. These aerosol pulses are added up, and the device stops automatically when the target dose has been delivered. The main advantages of the system are the virtual absence of aerosol delivered to the airway dead space, the fact that the predefined drug dose will be applied irrespective of the breathing pattern, and the low volume of inhalation solution necessary for sufficient nebulization.

[38] *E.g.*, Ex. 1029 at 1301-02.

[39] *See* Ex. 1030 at 322–23.

39. While complicated and expensive devices like HaloLite used advanced computer systems to calculate the amount of drug delivered,[40] other pulsed nebulizers provided sensory cues to the patient, telling him/her when and how to breathe.[41]

4. The Development of Inhaled Treprostinil for the Treatment of Pulmonary Hypertension.

40. Because of its ability to administer drugs directly to the lungs, inhalation delivery has proven to be especially beneficial for the treatment of pulmonary conditions, including pulmonary hypertension.

41. By the early 1990s, investigators had begun researching the delivery of prostacyclin and its analogues via inhalation for the treatment of pulmonary hypertension.

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[40] *See id*.

[41] *See* Ex. 1031 at col. 34:57-35:14. ("[t]he timing device can be electrically connected with visual display signals as well as audio alarm signals. Using the timing device, the microprocessor can be programmed so as to allow for a visual or audio signal to be sent when the patient would be normally expected to administer respiratory drug.")

42. For example, Crow '953 disclosed the use of treprostinil, including in the treatment of patients with congestive heart failure that was accompanied by pulmonary hypertension.[42] Crow further disclosed that treprostinil could be delivered via pulmonary inhalation and disclosed formulations, nebulizers and droplet sizes for doing so.[43]

43. Similarly, a 1996 paper by Olschewski, et al. reported on "the effects of aerosolization of prostacyclin and its stable analog iloprost with those of nasal oxygen, inhaled nitric oxide, and intravenous prostacyclin on hemodynamics and gas exchange in patients with severe pulmonary hypertension."[44] This trial found that "[a]erosolized prostacyclin achieved the same reduction in pulmonary vascular resistance [as with intravenous prostacyclin] with a smaller increase in cardiac output but a significant decline in pulmonary artery pressure."[45] Thus, the authors concluded that aerosolized prostacyclin achieved "selectivity for the pulmonary circulation…as indicated by a substantial decrease of pulmonary artery pressure and

[42] Ex. 1054 at col. 3, l. 59–col. 4, l. 11.

[43] Ex. 1054 at col. 5, ll. 50–53.

[44] Ex. 1028 at 820.

[45] *Id*. at 822.

a smaller effect on systemic arterial pressure."[46] Olschewksi also reported that "the stable prostacyclin analog iloprost caused *nearly identical changes in hemodynamics* and gas exchange [as that of aerosolized prostacyclin]."[47] Thus, iloprost had been shown to improve survival, exercise capacity, and hemodynamics in patients with severe pulmonary hypertension.[48]

44. By the early 2000s, Cloutier disclosed and claimed the administration of a therapeutically effective amount of treprostinil by inhalation for the treatment of pulmonary hypertension.[49] The Cloutier patents included claims directed to the treatment of pulmonary hypertension in humans via aerosolized treprostinil delivery.[50]

45. Cloutier observed that aerosolized treprostinil could be given in high doses without significant non-lung effects—i.e., heart rate and cardiac output.[51] In particular, aerosolized treprostinil had no effect on systemic arterial pressure or

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[46] *Id*.

[47] *Id*. (emphasis added).

[48] Ex. 1033 at 58S.

[49] Ex. 1018 at cl. 6-8.

[50] *Id*.

[51] *Id.* at col. 10, ll. 50–57.

cardiac output.[52] Cloutier also observed that administration of treprostinil by inhalation has a much greater potency than intravascular administration:[53]

46. A number of commercial products for the treatment of pulmonary hypertension were approved in the mid-2000s as well. For example, in 2002, FDA approved Remodulin® an injectable treprostinil product (i.e., continuous subcutaneous infusion) that was indicated for the treatment of pulmonary hypertension.[54] Remodulin® is supplied in 20 mL multi-use vials in four concentrations, containing either 1.0 mg/mL, 2.5 mg/mL, 5.0 mg/mL, or 10 mg/mL of treprostinil.[55]

47. Ventavis, an inhaled iloprost product for the treatment of pulmonary hypertension, was first approved in Europe in September 2003 for marketing by Schering AG.[56] Originally, Ventavis was approved for use with two commercially available jet nebulizers, the Prodose and HaloLite.[57] Pre-approval studies, however,

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[52] *Id.* at col. 11, ll. 23–44; col. 12, ll. 28–61; figs. 4, 5, 8, 11, 12 & 15.

[53] *Id.* at col. 8, ll. 5–12.

[54] *See* Ex. 1035.

[55] *Id.* at 4.

[56] *See* Ex. 1036; Ex. 1037.

[57] *See* Ex. 1038.

were conducted using six different nebulizers, one of which was the OptiNeb® ultrasonic nebulizer and another of which was the OptiNeb-ir ultrasonic nebulizer.[58] The use of the OptiNeb® line of ultrasonic nebulizers with iloprost was also reported in 2003 in *Anesthesiology*,[59] and 2004 in the European Journal of Anaesthesiology.[60]

48. The Venta-Neb® nebulizer was also used to deliver iloprost/Ventavis as early as February 2004.[61] Indeed, the Nebu-Tec website included information about the Venta-Neb® nebulizer and its use with Ventavis as early as June 2004.[62]

49. In September 2005, Schering obtained approval to add the Venta-Neb® nebulizer to the Ventavis label in Europe.[63] After the label was approved, the Venta-Neb® nebulizer was used to deliver Ventavis to patients for the treatment of pulmonary hypertension.

50. After approval of Ventavis with Venta-Neb®, the Ventavis label included the following information about the use and characteristics of the Venta-

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[58] Ex. 1039.

[59] Ex. 1040.

[60] Ex. 1041.

[61] *See* Ex. 1007.

[62] *See* Ex. 1014 at Ex. B-3 at 42, 49.

[63] Ex. 1043; Ex. 1044; Ex. 1045; *see also* Ex. 1038.

Neb®: "Venta-Neb prompts the patient to inhale by an optical and an acoustic signal."[64] The label further instructed patients to "refer to the instruction manual of the Venta-Neb nebulizer" for additional details.[65]

51. The Venta-Neb®-ir A-I-C-I User Manual indicates that it is a "Mobile Ultrasonic Nebulizer for VENTAVIS® Inhalation."[66] The manual is directed to patients in connection with their "treatment with the VENTANEB-ir."[67] The Venta-Neb® User Manual details the functionality of the Venta-Neb® nebulizer. Specifically, it confirms that Venta-Neb® included Nebu-Tec's A-I-C-I technology, which stands for active intermittent controlled inhalation.[68] This functionality was publicly known at least as early as 2004.[69] The Venta-Neb®-ir A-I-C-I User Manual also explains that the A-I-C-I functionality includes an optical and acoustic signal to guide a patient's inhalation:[70]

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[64] Ex. 1009 at 3, 30.

[65] *Id.*

[66] Ex. 1008 at 1.

[67] *Id*. at 2.

[68] *Id*. at 32.

[69] *See e.g.* Ex. 1014 at Ex. A-1 at 4.

[70] Ex. 1008 at 32.

52. The Venta-Neb®-ir A-I-C-I User Manual also explains that "[d]ue to this to this inhalation-scheme, a more efficient and a precise dosage can be guaranteed."[71]

53. Ventavis was subsequently approved in the United States in 2004 and is indicated for the treatment of pulmonary hypertension. As the first commercially available inhalation treatment for pulmonary hypertension, Ventavis demonstrated the potential for future inhalable drugs for the treatment of pulmonary hypertension.

54. Another pulsed ultrasonic nebulizer manufactured by Nebu-Tec, known as OptiNeb®, was also known to be used to deliver inhaled treprostinil by the mid-2000s.

55. Specifically, in the Fall of 2004, researchers at the University of Giessen in Germany—including Robert Voswinckel and Hossein Ghofrani—published their initial findings of a study involving the use of OptiNeb® to deliver

[71] *Id.* at 33.

treprostinil.[72] Specifically, the results were published in an October 2004 supplement to *Circulation*, naming Voswinckel as the lead author.[73] The abstract was published in advance of presentation of the study at the 2004 American Heart Association conference in New Orleans, which was held from November 7-10, 2004.[74]

56. This Voswinckel study observed the effects of inhaled treprostinil in 17 patients with severe pulmonary hypertension.[75] Using a "pulsed OptiNeb® ultrasound nebulizer," and a solution containing 600 μg/mL of treprostinil, each patient took three single breaths from the device and was observed for two hours. Voswinckel's study also observed the effects from two patients who received four of these doses per day. Voswinckel concluded that inhaled treprostinil "resulted in a sustained, highly pulmonary selective vasodilation over 120 minutes." Further, "[t]olerability is excellent even at high drug concentrations and short inhalation

[72] Ex. 1003 at 7; *see also* Ex. 1046 at 22 (disclosing the results of a test of inhaled treprostinil administered to 21 patients using an OptiNeb® ultrasonic nebulizer and measuring effects for 180 minutes).

[73] *Id*.

[74] Ex. 1048 at 1, 3.

[75] Ex. 1003 at III-295.

times (3 breaths). Long-term treatment effects are very promising." Voswinckel's findings gained immediate interest, as they were cited in a 2005 paper by Sulica and Poon in *Expert Review of Cardiovascular Therapy*.[76]

57. Voswinckel and others published a second paper in 2004 discussing the use of OptiNeb® to deliver inhaled treprostinil.[77] This study also used an "Optineb ultrasound nebulizer" but in a continuous administration mode, producing a constant stream of aerosol for six minutes.[78] This study administered treprostinil to 21 patients (8 receiving placebo), using formulations containing 16, 32, 48, or 64 µg/mL of treprostinil.[79] The patients were observed periodically for 180 minutes following inhalation, and Voswinckel similarly concluded that "[t]reprostinil inhalation results in a significant long-lasting pulmonary vasodilation."[80]

58. Some of the same researchers published another paper in June 2005, with Ghofrani as the lead author.[81] The Ghofrani paper provided an overview of

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[76] Ex. 1047 at 351.

[77] Ex. 1046 at 22.

[78] *Id*.

[79] *Id*.

[80] *Id*.

[81] Ex. 1005 at 298.

several key studies related to the treatment of pulmonary hypertension.[82] As for inhaled treprostinil, Ghofrani noted that "[t]reprostinil is a long-acting prostacyclin analog, which offers potential benefits versus [previous prostacyclin analogs] due to its long plasma half life and chemical stability in solution."[83] Ghofrani further explained that in response to observations of pain at the injection site associated with the subcutaneous administration of treprostinil, Ghofrani's research team had conducted initial trials which "have shown proof of efficacy of *inhaled* treprostinil for the effective reduction of the pulmonary vascular resistance (PVR)."[84]

59. Ghofrani explains that this proof of efficacy came from a study where 17 patients were "administered inhaled treprostinil (15 mcg/inhalation)." This dose "led to a major reduction in pulmonary selective pressure and resistance with an overall duration of action of > 180 min." Accordingly, Ghofrani concluded that inhaled treprostinil showed a stronger pulmonary selectivity than inhaled iloprost.

60. These conclusions regarding the efficacy of inhaled treprostinil also led Ghofrani to believe that the dose of inhaled treprostinil could be increased to 90 µg per dosage event, and the number of doses per day could be as few as four. Further,

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[82] *Id*.

[83] *Id*.

[84] *Id*.

Ghofrani taught that by choosing the right kind of nebulizer, it would be possible to administer this dose in just one or two breaths per event.

61. The OptiNeb® device used in Voswinckel was also well known in the art. Several of the prior art references identified Nebu-Tec as the manufacturer of OptiNeb.[85] Nebu-Tec maintained a website with many details about its nebulizer devices in the mid-2000s, including technical details and user manuals. For example, an early generation OptiNeb® device was detailed on the Nebu-Tec website by at least 2003.[86] The website included details on nebulization rates that could be achieved with OptiNeb.[87]

62. Information about a later generation OptiNeb® device, OptiNeb-ir was available on Nebu-Tec's website as of mid-2004.[88] The OptiNeb-ir User Manual, which was available for download from the website,[89] explains the functionality of this device. For example, it explains that the OptiNeb-ir is "volume controlled" and

[85] Ex. 1003 at III-295; Ex. 1040 at 744; Ex. 1041 at 3; Ex. 1046 at 22.

[86] Ex. 1014; *id*. at Ex. A-2; *id*. at Ex. B-2.

[87] *Id*. at Ex. A-2 at 3; *id*. at Ex. B-2 at 4, 31.

[88] Ex. 1014 at Ex. A-3; *id*. at Ex. B-3; *id*. at Ex. B-4.

[89] Ex. 1014 at Ex. B-4; *see* Ex. 1006 (translated).

has an output of 0.6 mL/min.[90] It also included a multifunction indicator light to tell the user when the nebulizer is on and when it is producing aerosol and made audible sounds to signal the end of an inhalation session.[91] The Optineb-ir came with six pre-set programs. Programs 1, 2, and 6 produce aerosol in pulses.[92]

63. Using audio or visual clues to signal to a user of a nebulizer when to breathe in order to obtain a pulsed dose of a drug was long-known by the mid-2000s. For example, Patton disclosed the use of such mechanisms in 1993.[93] At about the same time, Lloyd et al. disclosed a device with a microprocessor that contains a timing device with visual display signals and audio alarm signals.[94] In 2003, Brand et al. disclosed an ultrasonic vaporizer—a device that comparably creates an aerosol of drug—to deliver a predetermined volume of a pharmaceutical substance.[95] Brand's vaporizer also used a visible and or audible signal to coach the patient to

[90] Ex. 1006 at 28.

[91] *Id*. at 16.

[92] *Id*. at 17-21.

[93] Ex. 1012 at 14, ll. 3-5.

[94] Ex. 1031 at col. 34, ll. 57-62.

[95] Ex. 1010 at col. 2, ll. 3-6.

inhale the dose efficiently.[96] And as discussed above, Nebu-Tec devices also had this functionality by the mid-2000s.

VI. THE PATENT-IN-SUIT

64. I understand that United Therapeutics Corporation ("UTC") is the assignee of U.S. Patent No. 9,358,240 entitled "Treprostinil administration by inhalation," which issued on June 7, 2016 to named inventors Horst Olschewski, Robert Roscigno, Lewis J. Rubin, Thomas Schmehl, Werner Seeger, Carl Sterritt, and Robert Voswinckel.

65. The '240 patent issued from U.S. Patent Application No. 12/591,200 (the "'200 application") which was filed on November 12, 2009. The '200 application is a continuation of application No. 11/748,205, filed on May 14, 2007. The '200 application claims priority to provisional application No. 60/800,016, filed on May 15, 2006.

66. The claims of the '240 patent recite as follows:[97]

> 1. 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 from 200 to 1000

[96] *Id*. at col. 2, ll. 35-41.

[97] Ex. 1001 at cls. 1–9.

μg/ml of treprostinil or a pharmaceutically acceptable salt thereof

with a pulsed ultrasonic nebulizer that aerosolizes a fixed amount of treprostinil or a pharmaceutically acceptable salt thereof per pulse,

said pulsed ultrasonic nebulizer comprising an opto-acoustical trigger which allows said human to synchronize each breath to each pulse,

said therapeutically effective single event dose comprising from 15 μg to 90 μg of treprostinil or a pharmaceutically acceptable salt thereof delivered in 1 to 18 breaths.

2. The method of claim 1, wherein the formulation comprises 600 μg/ml of the treprostinil or its pharmaceutically acceptable salt thereof.
3. The method of claim 1, where the single event dose is not repeated for a period of at least 3 hours.
4. The method of claim 1, wherein the single event dose produces a peak plasma concentration of treprostinil about 10-15 minutes after the single event dose.
5. The method of claim 1, wherein the fixed amount of treprostinil or its pharmaceutically acceptable salt for each breath inhaled by the human comprises at least 5 μg of treprostinil or its pharmaceutically acceptable salt.
6. The method of claim 2, wherein the fixed amount of treprostinil or its pharmaceutically acceptable salt for each

breath inhaled by the human comprises at least 5 μg of treprostinil or its pharmaceutically acceptable salt.

7. The method of claim 1, wherein the single event dose is inhaled in 3-18 breaths by the human.
8. The method of claim 6, wherein the single event dose is inhaled in 3-18 breaths by the human.
9. The method of claim 6, wherein the single event dose is not repeated for a period of at least 3 hours.

A. Priority Date

67. I understand that the earliest possible effective filing date for the challenged claims is May 15, 2006—the filing date of the provisional application to which the '240 patent claims priority.

B. Meaning of Claim Terms

68. I understand that a claim of an unexpired patent is given its broadest reasonable interpretation in light of its specification in connection with an IPR proceeding. For the purposes of this proceeding, I have given all terms their broadest reasonable interpretation in light of the '240 patent's specification, as would have been understood by a POSA.

69. Consistent with an agreement reached in the district court litigation between the parties, the district court has ordered that the phrase "an opto-acoustical trigger" found in claim 1 means "a trigger with an optical element (e.g., light) and

an acoustical element (e.g., sound)."[98] Thus, the broadest reasonable interpretation of this term in light of the '240 patent specification should include at least such an interpretation, which is consistent with the specification and how a POSA would understand the term.

VII. OBVIOUSNESS OF THE '240 PATENT

70. I have been asked to opine on whether the asserted claims of the '240 patent would have been obvious to a POSA at the time of the invention, in light of the prior art. I understand the obviousness analysis takes into account four factual inquiries: (1) the level of ordinary skill in the art; (2) the scope and content of the prior art; (3) the differences between the prior art and the claimed subject matter; and (4) any objective indicia of nonobviousness. I address each of these factors below.

71. As set forth in detail below, it is my opinion that the asserted claims of the '240 patent would have been obvious to a POSA in view of the teachings of the prior art as of May 15, 2006. Specifically, in my opinion claims 1-9 of the '240 patent would have been invalid over the following combinations of prior art:

- Voswinckel in view of Patton and Ghofrani;

[98] *United Therapeutics Corp. v. Watson Labs., Inc.*, Civ. A. No. 3:15-cv-05723-PGS-LHG, at Dkt. No. 66 (Oct. 17, 2016).

- Voswinckel in view of Patton and the OptiNeb-ir® User Manual; and
- Voswinckel in view of Ghofrani and the EU Community Register.

A. The Level of Ordinary Skill in the Art

72. I understand that a POSA is a hypothetical person considered to have normal skills and knowledge in the field in which the ’240 patent relates at the time the invention was made. In this case, the earliest priority date to which the asserted claims of the ’240 patent may claim is May 15, 2006, thus a POSA would have knowledge of all the relevant art as of that time.

73. In determining the level of skill in the art, I understand that the following factors should be considered: (1) the education level of the inventor; (2) types of problems encountered in the art; (3) prior art solutions to these problems; (4) rapidity with which innovations were made; (5) sophistication of the technology; and (6) education level of active workers in the field. I have considered the above factors and drawn on my experiences with working groups in the field to make a determination as to the level of ordinary skill.

74. As of the May 2006 filing date of the provisional application that the ’240 patent claims as its effective filing date, a person having ordinary skill in the art (“POSA”) had a Ph.D. degree in pharmaceutical science or a related discipline like chemistry or medicinal chemistry, as well as at least two years of practical experience in the development of potential drug candidates, specifically in the

delivery of drugs by inhalation. The POSA could have had a lower level of formal education than a Ph.D. degree if such a person had more years of experience in the development of inhalable drugs. The POSA would regularly review literature about pharmaceutical sciences and drug delivery and would know how to carry out library research using library resources to find out more information about areas being researched. In addition, the POSA would have known how to evaluate potential drugs for their *in vitro* and *in vivo* activity and toxicity using tests disclosed in the relevant literature. Furthermore, because drug development involves a multidisciplinary approach, a POSA may interface or consult with individuals having specialized expertise, for example, a pharmacologist and/or physician with experience in the administration, dosing and efficacy of drugs for the treatment of a particular disease state. In this Petition, reference to a POSA refers to a person with these qualifications.

B. Scope and Content of the Prior Art

75. It is my understanding that an invention is patentable only if it is novel and not obvious in view of the prior art. The relevant time period for the purpose of my analysis is prior to May 15, 2006, the filing date of provisional application No. 60/800,016.

76. The use of treprostinil to treat pulmonary hypertension is not a new discovery. The '240 patent concedes that the prior art teaches the "administration of treprostinil by inhalation for the treatment of pulmonary hypertension."[99]

77. As illustrated by the following prior art references, it was well-known in the art before May 2006 that treprostinil could be used in the treatment of pulmonary hypertension. Indeed, formulations of treprostinil had already been developed and were described in detail. Moreover, several studies showing the efficacy of treprostinil in the treatment of pulmonary hypertension had been conducted and published by that time. The specific prior art references discussed below, which form the grounds for this IPR petition, would have been available to and known by a POSA. In addition, a person with ordinary skill in the art would also be knowledgeable of all of the background teachings of the prior art discussed above.

1. Voswinckel

78. Voswinckel is a 2004 abstract published in *Circulation*, which discloses the treatment of pulmonary hypertension with inhaled treprostinil.[100] The purpose of the study was to evaluate the effects of inhaled treprostinil on pulmonary

[99] Ex. 1001 at col. 5, ll. 41–45.

[100] Ex. 1003 at III-295.

hemodynamics and gas exchange in severe pulmonary hypertension and to assess safety, tolerability, and clinical efficacy in patients with severe pulmonary hypertension. In this study, 17 human patients with severe pulmonary hypertension were treated with inhaled treprostinil, which resulted in "a sustained, highly pulmonary selective vasodilation over 120 minutes."

79. In addition, Voswinckel teaches that beneficial effects were observed with 3 single breaths of treprostinil administered four times per day with a 600 µg/mL solution in a pulsed Optineb® ultrasonic nebulizer.[101] The beneficial effects lasted for over 120 minutes.

80. I understand that the October 2004 issue of *Circulation* in which Voswinckel was published was made available in libraries by at least December 2004.[102] Thus, this would have been included in the literature of which a POSA would have been aware before May 2006. As I mentioned above, this abstract was originally presented to the public at the American Heart Association's Science Sessions 2004 Meeting in New Orleans, and materials were given to all attendees after the conference.[103]

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[101] *Id*.

[102] Ex. 1013 at ¶¶ 30-32.

[103] *See* ¶ 53, *supra*; Ex. 1048 at 3.

2. Ghofrani

81. Ghofrani is an article published in *Herz* in June 2005.[104] Ghofrani teaches that "[i]nhaled treprostinil can potentially have benefits over the already approved inhaled iloprost, related to its higher pulmonary selectivity as well as to the longer biological half-life."[105] Further, Ghofrani explains "[i]nitial trials in Giessen have shown proof of efficacy of *inhaled* treprostinil for effective" treatment.[106]

82. Ghofrani discloses a study in which patients "were administered inhaled treprostinil (15 mcg/inhalation)."[107] In such a dose, Ghofrani discloses that "it is technically feasible for there to be only one to two breaths in an application."[108]

83. 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." Thus, a POSA would have understood that on the low end (a single

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[104] Ex. 1005 at 298.

[105] *Id*. at 296, Abstr.

[106] *Id*. at 298.

[107] A POSA would have understood that both "mcg" and μg refer to the same unit of measurement: micrograms.

[108] *Id*.

breath application) Ghofrani was disclosing a 15 µg single event dose, and on the high end—*i.e.* the "absolute inhaled dose per inhalation exercise"—a 90 µg dose.

84. The study discussed in Ghofrani is either very similar or identical to the study discussed in Voswinckel in that both include 17 patients who "were administered inhaled treprostinil (15 mcg/inhalation)."[109] Notably, Ghofrani is also listed as an author on the Voswinckel paper, and vice versa.[110]

85. I understand that the June 2005 issue of *Herz* in which Ghofrani was published and was made available in libraries and online by at least July 2005.[111] Thus, this would have been included in the literature of which a POSA would have been aware before May 2006.

3. Patton

86. Patton is an international patent application published in January 1993 entitled "Method and Device for Delivering Aerosolized Medicaments."[112] Patton teaches a "device for accurately delivering aerosolized doses of a medicament [by dispersing] a measured amount of drug (40) in a measured volume of carrier gas . . .

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[109] *Id*.

[110] *Compare id. with* Ex. 1003 at III-295.

[111] Ex. 1013 at ¶¶ 42-23.

[112] Ex. 1012 at Cover.

The apparatus optimally includes a dose regulator (13a), a counter (13c), a clock (13e), a dose memory (30), and a signal (32) to indicate when a dose is ready by inhalation."[113]

87. Based on the title and abstract, a POSA interested in inhaled drug delivery would have known about Patton. In addition to Patton's teaching about devices used to deliver medicaments to the lungs, a POSA also would have learned that a "light [] and/or an audible signal [] will alert the user that a puff is ready to be withdrawn from the chamber. . . ."[114] Further, "[t]his sequence is repeated for each bolus."[115] Thus, a POSA would have learned about the use of a light and/or audible signal to alert the user prior to each inhalation.

88. Indeed, Patton teaches that "[t]he signals [] are set to begin immediately after operation of the compressor [] ceases. The cessation of the compressor sound will also alert the patient that bolus formation is complete."[116] Thus, Patton teaches a POSA that after the aerosol pulse is generated, the patient should inhale and be prompted to do so with a signal.

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[113] *Id*. at Abstr.

[114] *Id*. at 14, ll. 3-4.

[115] *Id*. at 14, ll. 14-15.

[116] *Id*. at 14, ll. 11-14.

89. Patton's device "is of a type that will nebulize or mix a ***defined amount*** of medicant with the preselected amount of compressed air received from [the] compressor []. The defined amount, referred to as a dosage or bolus, flows into a chamber [] via the conduit."[117]

90. Patton teaches a system that generates aerosol using gas—i.e. a jet nebulizer.[118] Nevertheless, a POSA would understand that Patton's teachings about the use of lights and sounds to prompt the user could apply equally to an ultrasonic nebulizer.

91. In other words, Patton's Unit 40 teaches a fixed pulse of drug from a nebulizer that uses lights and sounds to signal a patient to inhale the dose.

4. OptiNeb®-ir User Manual

92. As explained above, OptiNeb® was a pulsed ultrasonic nebulizer used to deliver inhaled medicines.[119] The Optineb®-ir User Manual provides technical details about the operation of this device. It is "volume controlled" and has an output of 0.6 mL/min, a fixed rate of nebulization.[120] The User Manual explains that this

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[117] *Id.* at 13, ll. 3-7 (emphasis added).

[118] *Id*. at 10, ll. 6-10.

[119] *See* ¶ 52, *supra*.

[120] Ex. 1006 at 28.

nebulizer came with six pre-set programs. Including Programs 1, 2, and 6, which produce aerosol in pulses.[121] Indeed, under programs 1 and 2, the User Manual provides that "[t]he aerosol is intermittently generated (no continuous aerosol production)."[122]

93. Program 6 is described as "Intermittent operating mode." The program allows for individual programming of the "active phase," i.e. the time during which the nebulizer generates an aerosol of drug to inhale.[123] Importantly, the time of the active phase cannot be longer than the time of the passive phase. Thus, a patient cannot inhale for longer than they exhale. The OptiNeb® is configured with safety protocols that prevent this from occurring.[124]

94. The OptiNeb®-ir User Manual explains that that OptiNeb®-ir "is equipped with a multifunction lamp."[125] The lamp "lights up yellow" when the nebulizer is turned on, but not producing any aerosol; and the lamp "lights up green"

[121] Ex. 1006 at 17-21.

[122] *Id*. at 18.

[123] *Id*. at 20-21.

[124] *Id*. at 21.

[125] *Id*. at 16.

when nebulization is occurring.[126] The device also has "an acoustic signal," which "sounds when the device is switched off."[127]

5. EU Community Register

95. As explained above, in September 2005, Schering obtained approval to add the Venta-Neb® nebulizer to the Ventavis label in Europe.[128] I understand that this label was made publicly available by being published by the European Union's ("EU") regulatory agencies. Similar to the FDA, the EU publishes information about approved drug products, including changes in labeling on their website, in what is known as the EU Community Register of Medicinal Products (the "Community Register").

96. When formulating an inhaled treprostinil product, a POSA would certainly have had the motivation to look at the other inhalable drugs from the same class—i.e. Ventavis, the inhalable iloprost solution. From the label, a POSA could learn about dosing regimen, concentration of drug in solution, length of treatment, volume administered, and other important formulation parameters. This is

[126] *Id*.

[127] *Id*.

[128] *See* ¶ 47, *supra*.

especially true in pulmonary drug delivery where the label will contain information on the functionality of the device approved to deliver the drug.

97. Just as a POSA would have a strong incentive to look at all available information on iloprost in the U.S., a POSA would be motivated to look to other countries in which the drug had been approved and any useful teachings or issues that arose under the laws of those countries. Thus, a POSA would have looked to the Community Register in the same manner and for the same reasons as the POSA would have looked at publications from FDA.

98. Much like the FDA website, the EU lists approved drugs by their brand name and includes the Commission's decisions since the drug was approved. I understand that this September 2005 Ventavis label was made available by the Community Register as well as the Register of Commission Documents, which I understand provides public access to the documents of the European Parliament, the Council and the Commission.

99. I obtained a copy of the Ventavis label as amended to include VentaNeb in September 2005 on the EU Community Register website. First, I went to the Community Register home page at http://ec.europa.eu/health/documents/community-register/. I then clicked on "Access to the Community Register." Under the "Community register of medicinal products for human use" heading, in the "Active" ingredient row I clicked on "Alphabetical" which took me to an

alphabetical listing of products. I scrolled down and selected Ventavis, which took me to Ventavis' Community Register page—http://ec.europa.eu/health/documents/community-register/html/h255.htm. This page provides a record of commission decisions for Ventavis. One of the entries for Ventavis, indicates a "Centralised Variation," with a "closed date procedure" of September 8, 2005. By accessing the English language dropdown for that entry, I was able to access the summary publication in the EU Journal ("summary publ" dropdown)[129] [Ex 1043] as well as the Commission Decision dated September 5, 2005 ("decision docs" dropdown)[130] as well as the attached Annexes, which included the newly-approved label ("annex" dropdown).[131]

100. I also searched the European Commission's Register of Commission Documents, which I understand provides public access to the documents of the Parliament, the Council, and the Commission[132] by going to https://ec.europa.eu/transparency/regdoc/index.cfm?fuseaction=home. Using the 'document search' feature, I searched for "Ventavis" and selected the radio button

[129] Ex. 1043.

[130] Ex. 1043.

[131] Ex. 1043.

[132] Ex. 1051.

to search 'all versions.' By searching for Commission Decisions for Ventavis, I reached a page from which a POSA could request the Commission Decision, including the September 5, 2005 Commission Decision adding Venta-Neb® to the Ventavis label. When the same search is conducted but searching 'final versions only,' the Commission Decision of September 5, 2005 is not found. This suggests that the Commission Decision was not a final version, and thus why it includes the notation "Not for Publication" on its face. However, the Register of Commission Documents page indicates that the Community Decision had a "date of publication" of September 5, 2005.[133]

101. The Ventavis label contained in the EU Community Register included several teachings about the use and characteristics of the Venta-Neb®. First, "Venta-Neb prompts the patient to inhale by an optical and an acoustic signal."[134] Second, Venta-Neb® can be operated in two different modes: P1, which delivers 5 µg of iloprost in 25 inhalation cycles; and P2, which delivers 2.5 µg in 10 inhalation cycles.[135] In other words, the Venta-Neb® measured the dose over the course of either 25 or 10 breaths. A POSA would understand that a breath-by-breath

[133] Ex. 1053.

[134] Ex. 1043 at 3, 30.

[135] *Id*.

measurement of the delivered dose means that each breath contains an equal amount of drug. This is particularly true in combination with the optical and acoustic signals that prompt the patient.[136] Thus, P1 delivers 0.2 μg of treprostinil per breath for 25 breaths, and P2 delivers 0.25 μg of treprostinil per breath for 10 breaths. These instructions teach a patient how to use the Venta-Neb® nebulizer and were included with the Ventavis® prescription drug product.

C. The Differences Between the Prior Art and the Claimed Subject Matter Would Have Been Obvious

102. In my opinion, there are no inventive differences between the prior art and the claimed subject matter of the ’240 patent. The prior art discloses all of the elements of the claimed subject matter. A POSA would have followed the clear motivation in the art to combine these elements with a reasonable expectation of success in doing so. Therefore, in light of the teachings of the prior art and the knowledge of those of skill in the art, it is my opinion that each of the asserted claims of the ’240 patent are obvious.

103. Specifically, in my opinion claims 1-9 of the ’240 patent would have been invalid over the following combinations of prior art:

- Combination 1: Voswinckel in view of Patton and Ghofrani;

[136] *See id*.

- Combination 2: Voswinckel in view of Patton and the OptiNeb®-ir User Manual; and
- Combination 3: Voswinckel in view of Ghofrani and the EU Community Register.

1. Combination 1: Claims 1-9 are Invalid as Obvious Under § 103(a) Over Voswinckel in view of Patton and Ghofrani

104. In 2004, Voswinckel disclosed a study that taught the safe and effective administration of inhaled treprostinil using an ultrasonic nebulizer to deliver treprostinil aerosolized from a solution containing 600 µg/mL of treprostinil in an OptiNeb® device in 3 distinct pulses (breaths).[137] Voswinckel's reported efficacy of the treatment after two hours of observation led him to conclude that the results were promising for the long-term potential of a treprostinil inhalation treatment for pulmonary hypertension.[138] Indeed, Voswinckel taught that by delivering this treatment four times per day, "[i]nhaled [treprostinil] show[ed] strong pulmonary selective vasodilatory efficacy with a long duration of effect following single acute dosing."[139] Importantly, Voswinckel reported that "[n]o side effects have been

[137] Ex. 1003 at III-295.

[138] *Id*.

[139] *Id*.

observed by the patients during long-term treatment" and "[t]olerability is excellent even at high drug concentrations."[140]

105. Voswinckel does not specify whether the OptiNeb® device comprised an opto-acoustical trigger.[141] Nevertheless, this aspect of the claims of the '240 patent would have been obvious to a POSA who would understand that a pulsed nebulizer could include a prompt to the patient so that the patient would know that the drug has been aerosolized and inhalation should begin. Beyond this basic logical step that would have been obvious to a POSA, a POSA could combine the teachings of Voswinckel with Patton, which expressly teaches the need and function of such a trigger.[142] Since Patton teaches strategies to deliver a pulsed dose precisely and efficiently, a POSA would be motivated to combine it with the therapeutically efficacious treatment with treprostinil disclosed by Voswinckel.

106. Finally, Voswinckel does not expressly identify the dose that was delivered with three breaths of treprostinil solution, but Ghofrani—Voswinckel's

[140] *Id*.

[141] *See id*.

[142] Ex. 1012 at 14, ll. 3-5.

co-author—teaches that this dose was 15 µg, but could go as high as 90 µg per single event dose, and be administered four times per day.[143]

107. As explained below this combination of references demonstrates that all of the claims of the ’240 would have been obvious.

a. Claim 1 of the ’240 Patent

Claim 1 recites:[144]

A method of treating pulmonary hypertension comprising:

[A] administering by inhalation to a human suffering from pulmonary hypertension a therapeutically effective single event dose of a formulation comprising from 200 to 1000 µg/ml of treprostinil or a pharmaceutically acceptable salt thereof

[B] with a pulsed ultrasonic nebulizer **[B1]** that aerosolizes a fixed amount of treprostinil or a pharmaceutically acceptable salt thereof per pulse,

[C] said pulsed ultrasonic nebulizer comprising an opto-acoustical trigger which allows said human to synchronize each breath to each pulse,

[143] Ex. 1005 at 298.

[144] Ex. 1001 at cls. 1-9.

[D] said therapeutically effective single event dose comprising from 15 µg to 90 µg of treprostinil or a pharmaceutically acceptable salt thereof delivered in 1 to 18 breaths.

Dependent claims 2-9 add further features to this independent claim, as discussed in more detail below.

i. Claim 1: Preamble

108. Claim 1 is directed to "a method for treating pulmonary hypertension."

109. Voswinckel discloses a method of treatment as required by claim 1. Indeed, Voswinckel administered a three-breath inhalation treatment of treprostinil to 17 patients with severe pulmonary hypertension.[145] These 17 patients received a three-breath inhalation treatment four times per day using a pulsed ultrasonic nebulizer from Nebu-Tec and a formulation comprising 600 µg/mL of treprostinil. This formulation and device are used in combination to treat pulmonary hypertension.

110. At the conclusion of this study, Voswinckel observed that inhaled treprostinil "resulted in a sustained, highly pulmonary selective vasodilation over 120 minutes." Further, "[t]olerability is excellent even at high drug concentrations and short inhalation times (3 breaths). Long-term treatment effects are very

[145] Ex. 1003 at III-295.

promising." Thus, Voswinckel did actually teach a treatment for pulmonary hypertension.

ii. Claim 1: Limitation [A]

111. Limitation [A] requires "administering by inhalation to a human suffering from pulmonary hypertension a therapeutically effective single event dose of a formulation comprising from 200 to 1000 μg/ml of treprostinil or a pharmaceutically acceptable salt thereof."

112. Given that the POSA wished to treat pulmonary hypertension, it would have been obvious to deliver a therapeutically effective single event dose of treprostinil for the treatment of pulmonary hypertension to a human suffering from pulmonary hypertension. A POSA would appreciate that there is no point in administering a dose that is not therapeutically effective. Similarly, a POSA would understand that an administration by inhalation—such as a nebulization treatment—is intended to be of a limited duration. It is not practical for a patient to spend an entire day breathing in and out of a nebulizer. If the inhaled drug could not sustain beneficial effects for a substantial period of time, a POSA would appreciate that another route of administration may be more appropriate.

113. As I explained above, Voswinckel did, in fact, administer an inhalation treatment to 17 humans suffering from pulmonary hypertension and observed the resulting beneficial effects from this treatment for up to two hours.[146]

114. During this study, Voswinckel administered a formulation containing 600 µg/mL of treprostinil, an amount that is directly within the range in claim 1.[147]

115. Moreover, Voswinckel clearly teaches a single event dose where three breaths of treprostinil taken from a pulsed ultrasonic nebulizer are delivered in "4 inhalations of TRE per day."[148] Voswinckel described a q.i.d. dosing regimen where the drug is delivered in four distinct "events" over the course of the day. Accordingly, Voswinckel teaches that this single event dose resulted in delivery of a therapeutically effective dose of treprostinil for the treatment of pulmonary hypertension.[149]

116. Similarly, Ghofrani teaches that early trials administering inhaled treprostinil suggested that the duration of action was over 180 minutes, meaning that

[146] Ex. 1003 at III-295.

[147] Ex. 1003 at III-295.

[148] Ex. 1003 at III-295.

[149] *Id*.

a patient would only need four doses per day in inhalation periods that can be less than one minute.[150]

117. The teachings of Voswinckel and Ghofrani clearly indicate a therapeutically effective single event dose to a POSA. Rather than a continuous administration of drug, a patient following the methods in Voswinckel and/or Ghofrani would know that they could receive a full day of pulmonary hypertension treatment with a total of 12 breaths (Voswinckel), or even as low as four breaths in view of Ghofrani's teaching that "it is technically feasible for there to be only one to two breaths in an application."[151]

iii. Claim 1: Limitation [B]

118. Limitation [B] requires a "with a pulsed ultrasonic nebulizer **[B1]** that aerosolizes a fixed amount of treprostinil or a pharmaceutically acceptable salt thereof per pulse."

119. As I explained above, Voswinckel is an abstract describing a study where "[p]atients received a [treprostinil] inhalation by use of the pulsed OptiNeb® ultrasound nebulizer." Thus, there can be no doubt that this limitation is expressly disclosed by Voswinckel and therefore would have been obvious to a POSA.

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[150] Ex. 1005 at 298.

[151] *Id.*; Ex. 1003 at III-295.

(A) Claim 1: Limitation [B1]

120. Limitation [B1] requires the nebulizer to be "configured to (a) aerosolize a fixed amount of treprostinil per pulse."

121. As explained above, Voswinckel reports using a "pulsed OptiNeb® ultrasonic nebulizer."[152] Although, Voswinckel does not expressly state that the nebulizer generated a fixed amount per pulse, a POSA would find this requirement to be obvious.

122. First, a POSA would appreciate that a fixed amount per pulse is a straight-forward way to design a method of administration with a nebulizer. A fixed amount of treprostinil per pulse allows the prescriber the ability to titrate the number of breaths up or down depending on variables like a patient's tolerance for the drug (or lack thereof) to achieve a desired dose. A patient may also need to adjust the duration of breaths depending on their condition. Thus, rather than a complicated scheme where the drug is delivered in varying amounts, a fixed dose per pulse allows

[152] Ex. 1003, III-295.

the prescriber to instruct the patient to make a simple adjustment to the device or the treatment regimen.[153]

123. Second, the reason for using a pulsed nebulizer is to achieve a precise and efficient delivery of drug to a patient. Thus, using a fixed breath per pulse would have been obvious because it is reliable and repeatable. If a patient were to be interrupted during an inhalation, an inconsistent dose would make it difficult to resume treatment. For example, if a patient were about to inhale but cannot because of a fit of coughing or an urgent phone call, a fixed amount of drug per pulse would allow the patient to simply generate another pulse when able to resume. This ensures that the patient will receive the desired therapeutically effective dose during each administration without the inefficiency or side effects of delivering more (or less) drug then the patient needs.

124. Even if this limitation were not obvious based on the general knowledge of a POSA, Patton teaches a nebulizer that generates "a ***defined amount of medicant*** with the preselected amount of compressed air from compressor."[154] Here, the

[153] *See* Ex. 1012 at 8, ll. 11-14 ("Further advantages of the present invention include the ability to vary the total dosage delivered, either by controlling the number of breaths taken or by controlling the amount of medicament in each breath.").

[154] *Id*. at 13, ll. 2-7; 14, ll. 3-20.

preselected amount of compressed air from the nebulizer in Patton teaches that the duration of the pulse is set in advance and is intended to nebulize a specific amount of the drug-containing solution.[155] By setting a predetermined dose and using an opto-acoustical trigger, Patton teaches that a device can achieve "a very accurate measurement and delivery of the doses, while employing relatively simple and reliable equipment."[156] Patton found that the accuracy and simplicity of the method and device proved "particularly effective for delivering high value drugs . . . with minimal loss of drug in the device."[157]

125. As explained above, a POSA would be motivated to combine Voswinckel's teaching of a therapeutically efficacious treatment using a pulsed nebulizer with Patton's teachings on reliability, precision, and efficiency. A POSA would have a reasonable expectation of success with such a combination because it simply seeks to improve upon the successful treatment already achieved.

[155] *Id*. at 13, ll. 3-7.

[156] *Id*. at 8, ll. 8-11.

[157] *Id*. at 8, ll. 5-8.

iv. Claim 1: Limitation [C]

126. Limitation [C] requires "said pulsed ultrasonic nebulizer comprising an opto-acoustical trigger which allows said human to synchronize each breath to each pulse."

127. Including an opto-acoustical trigger with the pulsed nebulizer disclosed in Voswinckel would have been obvious to a POSA. A POSA would know that as opposed to a continuous administration, the pulsed nebulizer only creates aerosol during (at least part) of the inhalation cycle. The primary purpose of using a pulsed nebulizer is to avoid wasting the drug that gets aerosolized while the patient is exhaling. Thus, the patient must synchronize their breath to the pulse of drug that is being delivered. Avoiding this waste makes the nebulizer more cost-effective.

128. A POSA would therefore appreciate that when using a pulsed nebulizer, the patient needs to know when the drug is ready to be inhaled, otherwise the efficiency gains from the pulsed nebulizer would be lost. Thus, by necessity, a POSA would implement some sort of signal to demonstrate to the patient that the device is generating aerosol and is ready for the patient to inhale. Without this sort of trigger, the patient would be unable to synchronize their breathing to the distribution of drug, and the pulsed nebulizer would not function as intended.

129. To create an effective signal, a POSA would appreciate that sensory clues such as light and sound would provide the most effective cues. These types of

signals are commonly used in everyday life (e.g a visual signal from a traffic light or the honk of a car horn), and thus would have been obvious for any POSA to implement. A combination of lights and sounds would have been just as obvious to a POSA (e.g. when a cell phone lights up and rings), understanding that the more triggers provided, the easier it is for the patient to synchronize (i.e. why cell phones also vibrate while ringing and lighting up).[158]

130. To the extent that the use of audio and visual cues would not have been obvious to a POSA, combining Voswinckel with the teachings of Patton would have made this limitation obvious.

131. Patton's Unit 40 creates a "dosage or bolus" by creating a preselected amount of aerosolized drug.[159] Once the aerosol is ready, a "light [] and/or an audible signal [] will alert the user that a puff is ready to be withdrawn from the

[158] Since an ultrasonic nebulizer turns an aqueous solution of drug into aerosol using the vibrations of a piezoelectric crystal, adding vibrations would not be helpful in a pulsed ultrasonic nebulizer. Similarly, signals using taste or smell would not be preferred because the patient would need to ensure that they do not start inhaling until the drug is being produced, rather than tasting or smelling the drug, exhaling, and then beginning the treatment. Such a signal would not avoid waste.

[159] *Id*. at 13 3-7.

chamber."[160] Furthermore, "[t]he signals [] are set to begin immediately after the operation of the compressor [] ceases."[161] Thus, the Patton device is configured so that before each breath, the device will create a pulse of aerosol, then make an audible trigger to "alert the patient" that it is time to inhale.[162] Thus, Patton's teaching of signals with light and sound is an opto-acoustical trigger that allows a human to synchronize each breath to each pulse. Indeed, Patton teaches that the opto-acoustical trigger is utilized before each and every breath.

132. A POSA would be motivated to combine Patton and Voswinckel because Patton teaches the parameters and configurations that can be implemented in a nebulizer, specifically ways in which a nebulizer can accurately and efficiently deliver a target dose.[163] In particular, a POSA with the knowledge of Voswinckel's finding of therapeutic efficacy with inhaled treprostinil would be motivated to find ways to ensure the drug is delivered efficiently to keep costs down and delivered precisely to ensure the reliability of the future studies that Voswinckel recommends.

[160] *Id*. at 14, 3-5.

[161] *Id*. at 14, 11-12.

[162] *Id*. at 14, 12-15.

[163] Ex. 1012 at Abstr.

v. Claim 1: Limitation [D]

133. Limitation [D] requires "said single event dose comprising from 15 μg to 90 μg of treprostinil or a pharmaceutically acceptable salt thereof delivered in 1 to 18 breaths." This limitation would have been obvious to a POSA.

134. In forming my opinions in this matter I reviewed the file history of the '240 patent. During this review I agreed with the examiner's findings that the particular dose and breath limitations are variables that a POSA could routinely optimize in order to meet a preset target.[164] As I explained above, a POSA would know to adjust the concentration of drug in the formulation or the rate of nebulization to adjust the dose delivered. Since the formulation is expressed in μg/mL or mg/mL, and the rate of nebulization is expressed in mL/min, a POSA could easily calculate the amount of drug that could be nebulized in a given period of time. A POSA could easily calculate the dose nebulized per second, determine the number of seconds for the patient to inhale, and derive the dose.

135. Furthermore, Ghofrani discloses the entire claimed dosage range.[165] A POSA performing the method of Voswinckel would be motivated to use a dose

[164] Ex. 1164 at 4-5.

[165] Ex. 1005 at 298.

disclosed in Ghofrani because such doses "led to a major reduction in pulmonary selective pressure and resistance with an overall duration of action of > 180 min."[166]

136. Ghofrani further appears to describe *the very same study* as Voswinckel. Ghofrani discloses that at "[i]nitial trials in Giessen," 17 patients "were administered inhaled treprostinil (15 mcg/inhalation)."[167] The Voswinckel study was conducted in Giessen, and 17 patients were administered inhaled treprostinil.[168] Additionally, Ghofrani is listed as an author of Voswinckel, and vice versa.[169] Thus, Ghofrani shows that the Voswinckel study actually administered a dose within the claimed range, and Voswinckel itself discloses that the dose was administered in "3 single breaths."[170]

[166] *Id*.

[167] *Id*.

[168] Ex. 1003 at III-295.

[169] *Compare* Ex. 1005 at 297 *with* Ex. 1003 at III-295.

[170] Ex. 1003 at III-295.

b. Claim 2: "[F]ormulation comprises 600 µg/ml"

137. Claim 2 of the '240 patent recites as follows:

> The method of claim 1, wherein the formulation comprises 600 µg/ml of the treprostinil or its pharmaceutically acceptable salt thereof.

138. Claim 2 is a dependent claim of the '240 patent. In my opinion, claim 2 of the '240 patent is invalid as obvious. First, "the method of claim 1" is obvious for the reasons stated above. Second, the only added limitation in claim 2 is a formulation with 600 µg/mL of treprostinil. This limitation narrows from claim 1, which teaches a range from 200–1000 µg/mL.

139. As I explained above, Voswinckel explicitly teaches a formulation of treprostinil with 600 µg/mL used in a therapeutically effective single dose event of inhaled treprostinil. Thus, there is nothing novel about this limitation. Based on this teaching, a POSA would have reasonably expected to succeed with a formulation comprising 600 µg/mL of treprostinil.

c. Claim 3: "[S]ingle event dose is not repeated for a period of at least 3 hours"

140. Claim 3 of the ' 240 patent recites as follows:

> The method of claim 1, wherein the single event dose is not repeated for a period of at least 3 hours.

141. Claim 3 depends from claim 1. In my opinion, claim 3 of the '240 patent is invalid as obvious. First, "the method of claim 1" is obvious for the reasons stated above. Second, the only added limitation in claim 3 is that a second dose is not given within three hours of the first dose. This limitation is also obvious based on the prior art and the knowledge of a POSA.

142. Voswinckel discloses a study in which two patients "received compassionate treatment with 4 inhalations of TRE per day after the acute test." A POSA would understand that four inhalations per day corresponds to one inhalation every six hours (24 hours per day / 4 doses), or one inhalation every four waking hours (assuming eight hours of sleep per day, so 16 hours per day / 4 doses). In other words, in Voswinckel, the single event dose is not repeated for a period of "at least 3" hours.

143. Ghofrani also discloses that "it is possible to reduce the number inhalations necessary to up to four per day,"[171] and thus renders this limitation obvious for the same reasons as Voswinckel. Moreover, Ghofrani teaches that beneficial effects lasted for at least 180 minutes, thus suggesting that a POSA would not see any reason to provide a subsequent dose for three hours—while the first dose is still working.

[171] Ex. 1005 at 298.

144. It would have been obvious for a POSA to follow the method disclosed in Voswinckel and to dose no more frequently then every 3 hours.

d. Claim 4: "[P]roduces a peak plasma concentration of treprostinil about 10-15 minutes after the single event dose"

145. Claim 4 of the ' 240 patent recites as follows:

> The method of claim 1, wherein the single event dose produces a peak plasma concentration of treprostinil about 10-15 minutes after the single event dose.

146. Claim 4 depends from claim 1. In my opinion, claim 4 of the '240 patent is invalid as obvious. First, "the method of claim 1" is obvious for the reasons stated above. Second, the only added limitation in claim 4 is that the "single event dose produces a peak plasma concentration of treprostinil about 10–15 minutes after the single event dose."

147. The time to reach the peak plasma concentration is a function of the properties of the drug, and the manner in which it is administered. When treprostinil is administered as claimed, or, for example, as taught in Voswinckel and Ghofrani, it will inherently reach its peak plasma concentration about 10-15 minutes after the single event dose. This is confirmed by the disclosures in the specification of the '240 patent.

148. The only discussion of peak plasma time in the specification of the '240 patent provides that in "study ii," peak plasma concentrations of treprostinil were

found 10-15 minutes after inhalation.[172] "Study ii" administered inhaled placebo or inhaled treprostinil to 31 patients.[173] The '240 patent then states that "each patient received one inhalation"[174] but also that "[i]nhalation time was 6 minutes in all groups."[175] Of these patients, 8 received a placebo, 8 received a dose of 30 μg of treprostinil (from a formulation containing 16 μg/mL of treprostinil), 6 received 60 μg of treprostinil (from a formulation containing 32 μg/mL of treprostinil), 6 received 90 μg of treprostinil (from a formulation containing 48 μg/mL of treprostinil), and 3 received 120 μg of treprostinil (from a formulation containing 64 μg/mL of treprostinil).[176] The specification teaches that these treatment regimens would have resulted in peak plasma concentrations within 10-15 minutes.

149. A POSA would understand that the three breath treatment regimen used by Voswinckel could and would be delivered in less than six minutes.[177] Similarly, Ghofrani teaches ***both*** a treatment in one inhalation ***and*** administration of a single

[172] Ex. 1001 at Col. 16, ll. 17-19.

[173] *Id*. at col. 13, ll. 38-43.

[174] *Id*. at col. 13, ll. 42-44.

[175] *Id*. at col. 13, ll. 49.

[176] *Id*. at col. 14, ll. 38-48.

[177] Ex. 1003 at III-295.

event dose in less than one minute.[178] Thus, according to the conclusions in the specification, this treatment regimen would result in a peak plasma concentration within about 10-15 minutes of administration of the dose.

e. Claim 5: "[E]ach breath inhaled by the human comprises at least 5 µg of treprostinil"

150. Claim 5 of the '240 patent recites as follows:

> The method of claim 1, wherein the fixed amount of treprostinil or its pharmaceutically acceptable salt for each breath inhaled by the human comprises at least 5 µg of treprostinil or its pharmaceutically acceptable salt.

151. Claim 5 depends from claim 1. In my opinion, claim 5 of the '240 patent is invalid as obvious. First, "the method of claim 1" is obvious for the reasons stated above. Second, the only added limitation in claim 5 is that the amount of treprostinil per breath is at least 5 µg.

152. A POSA would appreciate that 5 µg is the lowest possible dose per breath at the respective ends of the claimed dose—i.e., that 3 breaths can deliver 15 µg and 18 breaths can deliver 90 µg of treprostinil. In other words, 15 µg / 3 breaths = 5 µg / breath and 90 µg / 18 breaths = 5 µg / breath. Thus, this is not a unique

[178] Ex. 1005 at 298 (teaching "15 mcg/inhalation" and "the inhalation period can be reduced to <1 min. by selecting a suitable device.").

claim limitation, but a mathematical relationship between dependent variables (dose and breath).

153. Furthermore, Ghofrani teaches that patients were administered "15 mcg/inhalation" which could be increased up to 90 µg, and that "the initial data shows that it is technically feasible for there to be only one or two breaths in an application." This suggests that the 15 µg could have been delivered in 3 breaths or less, and thus teaches at least 5 µg per breath. Similarly, a 15 µg dose in 1-2 breaths would be 15 µg or 7.5 µg per breath, respectively. The same "at least 5 µg per breath" would also be achieved by delivering and dose between 15 and 90 µg in 1-2 breaths.

154. Voswinckel teaches that "[p]atients received a [treprostinil] inhalation" in "3 single breaths." To deliver the dose taught by Ghofrani (15 µg) in 3 breaths requires 5 µg per breath. Since Voswinckel already disclosed a therapeutically effective dosing regimen, it would have been obvious to combine with the similar findings of Ghofrani.

f. Claim 6: "[E]ach breath inhaled by the human comprises at least 5 µg of treprostinil"

155. Claim 6 of the '240 patent recites as follows:

> The method of claim 2, wherein the fixed amount of treprostinil or its pharmaceutically acceptable salt for each breath inhaled by the human comprises at least 5 ng of treprostinil or its pharmaceutically acceptable salt.

156. Claim 6 depends from claim 2. In my opinion, claim 6 of the '240 patent is invalid as obvious. Claim 2 depends from claim 1, but limits that method to a formulation of 600 μg/mL. As I have explained above, claims 1 and 2 would have been obvious to a POSA. Moreover, claim 6 would have been obvious for the same reasons I just explained above in my discussion of claim 5.

g. Claim 7: "[S]ingle event dose is inhaled in 3-18 breaths by the human"

157. Claim 7 of the '240 patent recites as follows:

> The method of claim 1, wherein the single event dose is inhaled in 3 to 18 breaths by the human.

158. Claim 7 depends from claim 1. In my opinion, claim 7 of the '240 patent is invalid as obvious. As I explained above, claim 1 is obvious. Claim 7 depends from claim 1, providing only one new limitation—narrowing the number of breaths from 1–18 to 3–18. This narrowed limitation is also obvious in light of the prior art.

159. First, 3-18 is a subset of 1-18, and the specification provides no explanation for why this subset is substantially different from 1-18.

160. Second, Voswinckel specifically teaches a therapeutically efficacious dose in 3 breaths.[179] Thus a POSA would have reasonably expected to succeed with a single event dose delivered in 3 to 18 breaths.

h. Claim 8: "[S]ingle event dose is inhaled in 3-18 breaths by the human"

161. Claim 8 of the '240 patent recites as follows:

> The method of claim 6, wherein the single event dose is inhaled in 3 to 18 breaths by the human.

162. Claim 8 depends from claim 6. In my opinion, claim 8 of the '240 patent is invalid as obvious. Claim 8 merely takes the method of claim 6 and narrows the number of breaths limitation in the same manner as in claim 7. For the same reasons that I found claims 6 and 7 to be obvious, I also find claim 8 to be obvious.

163. Voswinckel discloses this limitation for the same reasons given in connection with claim 7. Namely, in Voswinckel, "[p]atients received a [treprostinil] inhalation by use of the pulsed OptiNeb® ultrasound nebulizer" in "3 single breaths." Voswinckel also discloses the use of a 600 μg/mL solution required by claim 6.

[179] Ex. 1003 at III-295.

i. Claim 9: "[S]ingle event dose is not repeated for a period of at least 3 hours"

164. Claim 9 of the '240 patent recites as follows:

> The method of claim 6, wherein the single event dose is not repeated for a period of at least 3 hours.

165. Claim 9 depends from claim 6. In my opinion, claim 9 of the '240 patent is invalid as obvious. Claim 9 simply combines the limitations of claims 3 and 6 and is thus obvious for the same reasons as claims 3 and 6 as I opined above. Voswinckel renders this limitation obvious for the same reasons given in connection with claim 3. Voswinckel also discloses the use of a 600 µg/mL solution required by claim 6.

166. There is nothing novel about combining the dose per breath limitations of claim 3 with the frequency of administration limitation in claim 3—i.e., not repeating a dose for 3 hours. Rather, this is a function of the half-life of the drug.

2. Combination 2: Claims 1-9 are Invalid as Obvious Under § 103(a) Over Voswinckel in view of Patton and the OptiNeb®-ir User Manual

167. As I explained above, claims 1-9 of the '240 patent are obvious over Voswinckel, in view of Ghofrani and Patton. I have also found that claims 1-9 are obvious over Voswinckel in view of Patton and the OptiNeb®-ir User Manual. This opinion is offered as an alternative to the reasons I explained above, and is in no way intended to waive, contradict, or undermine those opinions.

168. This alternate opinion is similar to the opinions I listed above in that—to the extent they are not already obvious in view of the general knowledge of a POSA—claims 1-9 are obvious over the various teachings of Voswinckel regarding the efficacious administration of treprostinil to treat pulmonary hypertension using an OptiNeb® pulsed ultrasonic nebulizer in three breaths. Again, the teachings of Voswinckel can be combined with the precision and efficiency teachings of Patton to render the asserted claims obvious. The OptiNeb®-ir User Manual relied on in this combination further supports Patton's teachings regarding an opto-acoustic trigger and delivering a fixed dose. For example, it explains that the OptiNeb®-ir is "volume controlled" and has an output of 0.6 mL/min.[180] It also included a multifunction indicator light to tell the user when the nebulizer is on and when it is producing aerosol and made audible sounds to signal the end of an inhalation session.[181]

169. In this section, however, instead of using the teachings of Ghofrani, I will explain how the limitations of claims 1-9 would have been obvious to a POSA based upon the properties of the OptiNeb® device that was commercially available at the time. Descriptions of these properties were publicly available as they were

[180] Ex. 1006 at 28.

[181] *Id*. at 16.

displayed in the User Manual, which was posted on the manufacturer's website (Nebu-Tec). A POSA would have gone to the Nebu-Tec website in light of the several publications that specifically tested treatments for pulmonary hypertension using OptiNeb® and referenced the German manufacturer, Nebu-Tec. Indeed, this information is provided in Voswinckel itself. Thus, a POSA seeking to formulate an inhalable treprostinil formulation would be motivated to examine the capabilities of the device to derive the information that Voswinckel did not disclose, such as the administered dose.

a. Claim 1 of the '240 patent

170. As explained above, the preamble and limitations [A], [B], [B1], and [C] would have been obvious over Voswinckel in view of Patton. It would have been obvious use a pulsed ultrasonic nebulizer that aerosolizes a fixed amount of treprostinil per pulse wherein said pulsed ultrasonic nebulizer comprises an opto-acoustical trigger which allows said human to synchronize each breath to each pulse.

171. I have been asked to alternately consider whether limitation [D] would have been obvious in reference to the OptiNeb®-ir User Manual in place of Ghofrani. As explained below, I have concluded that limitation [D] would have been obvious over Voswinckel, in view of Patton, and the OptiNeb®-ir User Manual.

i. Claim 1: Limitation [D]

172. Limitation [D] requires "said single event dose comprising from 15 μg to 90 μg of treprostinil or a pharmaceutically acceptable salt thereof delivered in 1 to 18 breaths."

173. Voswinckel discloses that patients were administered a "TRE solution 600 μg/ml" in "3 single breaths" using an OptiNeb® pulsed ultrasonic nebulizer.[182] The OptiNeb®-ir User Manual discloses that the OptiNeb®-ir could nebulize (that is, produce aerosols) at a rate of 0.6 mL/min.[183] A 600 μg/mL formulation in a nebulizer capable of aerosolizing 0.6 mL/min would generate 360 μg of treprostinil aerosol per minute (i.e. 6 μg of treprostinil per second).

174. A POSA would also know that a normal human breathes at a rate of 12-15 times per minute.[184] This means that a typical inhalation cycle (inhale and exhale) takes somewhere between 4 seconds (60 seconds / 15 breaths) and 5 seconds (60 seconds / 12 breaths). Thus, a patient may inhale from somewhere between 2-3 seconds. A POSA could then do the math:

- ((600 μg/mL X 0.6 mL/min) / 60 seconds) X 2 seconds = 12 μg

[182] Ex. 1003 at III-295.

[183] Ex. 1006 at 28.

[184] Ex. 1060.

- ((600 µg/mL X 0.6 mL/min) / 60 seconds) X 3 seconds = 18 µg

Thus, a POSA would calculate that Voswinckel delivered between 12-18 µg of drug per breath for a total of 36-54 µg over 3 breaths.

175. The Nebu-Tec website also reported that an earlier OptiNeb device could nebulize at a rate of up to 0.6 mL/min, but could be configured to generate an output of 0.173 mL/min.[185] A POSA would understand that 0.173 mL/min with a 600 µg/mL formulation would generate 103.8 µg of treprostinil per minute, or 1.73 µg per second. Using the same breathing instructions, a POSA would understand that:

- ((600 µg/mL X 0.173 mL/min) / 60 seconds) X 2 seconds = 3.46 µg
- ((600 µg/mL X 0.173 mL/min) / 60 seconds) X 3 seconds = 5.19 µg

176. A POSA would have understood that the Nebu-Tec device could be programmed to achieve different rates of nebulization that were at least somewhere between 0.173 – 0.6 mL/min. This is consistent with the User Manual teaching that the output could be increased as in P3. Accordingly a POSA would be able to calculate the dose for one breath:

- 2 second breath: 3.46-12 µg per breath
- 3 second breath: 5.19-18 µg per breath

And for the 3-breath regimen in Voswinckel:

[185] Ex. 1014 at B-2 at 31.

- 2 second breath: 10.38-36 µg per 3 breaths
- 3 second breath: 15.57-54 µg per 3 breaths

177. To a POSA, meeting a target dose is simply a product of choosing the desired rate of nebulization and solution concentration with a knowledge of the intended inhalation pattern. By adjusting these three variables a POSA can configure a nebulizer to release a target dose over a target number of breaths (target period of time). By routinely optimizing these parameter a POSA can increase the dose per breath by increasing the formulation concentration, the rate of nebulization, and/or the duration of the breath. Any one of these parameters can be routinely optimized by adjusting the others. This can be understood by a simple formula:

Drug Concentration (µg/mL) X Nebulization Rate (mL/min) = Dose (µg/min)

Thus, if a POSA knows two of the three pieces of information (i.e. rate of nebulization and dose), then the third can be easily calculated. . Moreover, a POSA would have known that effective doses of treprostinil could be delivered by varying combinations of formulation and time/breaths. For example, another Voswinckel abstract discloses lower solutions concentrations (16, 32, 48, and 64 µg/mL) over a longer inhalation time of 6 minutes using OptiNeb also achieved "significant long-lasting pulmonary vasodilation."[186]

[186] Ex. 1046 at 22.

178. Thus, this simple math that was well-known to a POSA would motivate a POSA to combine the teachings of Voswinckel with the OptiNeb®-ir User Manual. The User Manual's teaching of OptiNeb®-ir combined with Voswinckel render this limitation obvious.

179. Since Voswinckel teaches that a therapeutically efficacious treatment was obtained using the OptiNeb® ultrasonic nebulizer, a POSA would be motivated to look at the specifications of that device when formulating treprostinil for inhalation. Voswinckel's success would teach a POSA that the OptiNeb® device is capable of producing a therapeutically effective aerosol of treprostinil.

b. Claims 2-9 Would Have Been Obvious Over Voswinckel in view of Patton and the OptiNeb®-ir User Manual

180. As explained in connection with Combination 1, Voswinckel alone teaches the required additional limitations of claims 2, 7 and 8.

181. Also as explained in connection with Combination 1, a POSA would have known from Voswinckel that it would have been obvious to wait at least 3 hours before providing a second dose of treprostinil. Voswinckel teaches four doses a day, thus it would be obvious to space them apart, rather than repeat a dose too soon. Thus, claims 3 and 9 would have been obvious.

182. Furthermore, as explained in Combination 1 with regard to claim 4, a peak plasma concentration of treprostinil is attained within 10-15 minutes of

administration when the treatment time is less than 6 minutes. Since it does not take more than 6 minutes to administer the 3-breath regimen taught in Voswinckel, claim 4 would have been obvious for the same reasons.

c. Claim 5 Would Have Been Obvious Over Voswinckel, Patton, and the OptiNeb®-ir User Manual.

183. Claim 5 depends from claim 1, and further requires that "the fixed amount of treprostinil or its pharmaceutically [acceptable] salt for each breath inhaled by the human comprises at least 5 μg of treprostinil or its pharmaceutically acceptable salt."[187] This limitation is rendered obvious over Voswinckel combined with the OptiNeb®-ir User Manual. Given the fact that Voswinckel used a formulation containing 600 μg/mL of treprostinil and OptiNeb® was known to have a nebulization rate of 0.6 mL/min, a POSA would understand that over the course of 3 breaths, Voswinckel would have delivered over 5 μg per breath. Thus, administering at least 5 μg per breath would have been obvious to a POSA.

d. Claim 6 Would Have Been Obvious Over Voswinckel, Patton, and the OptiNeb®-ir User Manual

184. Claim 6 depends from claim 2, and further requires that "the fixed amount of treprostinil or its pharmaceutically [acceptable] salt for each breath

[187] Ex. 1001, 18:29-32.

inhaled by the human comprises at least 5 μg of treprostinil or its pharmaceutically acceptable salt."[188]

185. I explained how Voswinckel discloses the limitation of claim 2 and how Voswinckel in view of Patton and the OptiNeb®-ir User Manual would have rendered claim 1 obvious. Voswinckel and the OptiNeb®-ir User Manual render this limitation obvious for the same reasons as described in connection with claim 5.

3. Combination 3: Claims 1-9 are Invalid as Obvious Under § 103(a) Over Voswinckel in view of Ghofrani and the EU Community Register

186. As I explained above, claims 1-9 of the '240 patent are obvious over Voswinckel, in view of Ghofrani and Patton. I also explained that claims 1-9 are obvious over Voswinckel in view of Patton and the OptiNeb®-ir User Manual. I have also found that claims 1-9 are obvious over Voswinckel in view of Ghofrani and the EU Community Register. This opinion is offered as an alternative to the two combinations I explained above, and is in no way intended to waive, contradict, or undermine those opinions.

187. This alternate opinion is similar to the opinions I listed above in that—to the extent they are not already obvious in view of the general knowledge of a POSA—claims 1-9 are obvious over the various teachings of Voswinckel regarding

[188] Ex. 1001, 18:29-32.

the efficacious administration of treprostinil to treat pulmonary hypertension using an OptiNeb® pulsed ultrasonic nebulizer in three breaths. Again, the teachings of Voswinckel can be combined with the information regarding the Venta-Neb® device that was approved for use in Europe with Ventavis and published in the EU Community Register. In May 2006, the only inhalable pulmonary hypertension treatment that was commercially sold was Ventavis®, a nebulized therapy containing iloprost. As I explained above, iloprost is a part of the same class of drug as treprostinil, prostacyclin-like prostaglandins. A POSA would be motivated to look for information on the devices used to administer Ventavis®—the brand name of its closest competitor and of the same therapeutic class of drug. The Ventavis label was published in the EU Community Register prior to the filing of the provisional application leading to the '240 patent.

188. As I explained in connection with Combination 1, Voswinckel and Ghofrani render obvious a method for the administration of an inhalable treprostinil formulation containing 200-1000 μg/mL treprostinil in a therapeutically effective single event dose of 15-90 μg, via a pulsed nebulizer ultrasonic nebulizer to treat a human suffering from pulmonary hypertension.

189. As explained below, the EU Community Register disclosed an ultrasonic nebulizer with an opto-acoustical trigger that administered a fixed amount

of drug per breath. Thus, it would have been obvious to modify the OptiNeb® nebulizer used in Voswinckel to include an opto-acoustical trigger.

a. Claim 1 of the '240 patent

190. As explained in connection with Combination 1 above, the preamble and limitations [A], and [D] would have been obvious to a POSA in view of Voswinckel and Ghofrani. Below, I address limitation [B], [B1], and [C] in view of the EU Community Register.

i. Claim 1: Limitation [B]

191. Limitation [B] requires **[B]** with a pulsed ultrasonic nebulizer **[B1]** that aerosolizes a fixed amount of treprostinil or a pharmaceutically acceptable salt thereof per pulse.

192. As I explained above, Voswinckel teaches "a pulsed ultrasonic nebulizer" as required by claim 1.[189] Voswinckel teaches that "[p]atients received a [treprostinil] inhalation by use of the pulsed OptiNeb® ultrasound nebulizer."[190]

193. The EU Community Register provides information about Ventavis®, the commercially sold inhalable iloprost product for the treatment of pulmonary

[189] *See* Ex. 1001 at col. 18, ll. 8-13.

[190] Ex. 1003, III-295.

hypertension.[191] It discloses that "Venta-Neb®, a portable ultrasonic battery-powered nebuliser, has been shown to be suitable for the administration of Ventavis."[192] The Community Register also suggests that Venta-Neb® is a pulsed nebulizer. Indeed the Ventavis package insert teaches that Venta-Neb® can be operated in two different modes: P1, which deliver 5 µg of iloprost in 25 inhalation cycles; and P2, which delivers 2.5 µg in 10 inhalation cycles. A POSA would understand that an "inhalation cycle" means an inhalation and an exhalation. Thus, just like the pulsed OptiNeb® devices and claims 1-9 of the '240 patent, Venta-Neb® measures the dose by the number of breaths.

(A) Limitation [B1]

194. Limitation [B1] requires the nebulizer to be "configured to (a) aerosolize a fixed amount of treprostinil per pulse."

195. As I explained several times above, Voswinckel's reported OptiNeb® nebulizer is a "pulsed ultrasonic nebulizer," as required by claim 1.[193] Voswinckel's reported nebulizer would have been readily understood to aerosolize the drug to be

[191] Ex. 1009 at 2.

[192] Ex. 1009 at 3.

[193] Ex. 1001 at col. 18, ll. 8–13

administered—in Voswinckel's case treprostinil or a pharmaceutically acceptable salt thereof.

196. The EU Community Register teaches that Ventavis was administered with Venta-Neb®. The Ventavis package insert teaches that Venta-Neb® can be operated in two different modes: P1, which delivers 5 µg of iloprost in 25 inhalation cycles; and P2, which delivers 2.5 µg in 10 inhalation cycles.

197. A POSA would have appreciated that the administration of an approved drug requires the ability to administer a fixed dose. Therefore, the POSA would have understood that ultrasonic nebulizers could be used to administer a fixed dose. Moreover, by measuring the dose in a specific number of breaths, a POSA would understand that each breath is intended to give an equal amount of drug per breath. In other words, a POSA would understand that in P1, 5 µg is administered in 25 inhalation cycles, with each one delivering 0.2 µg per breath. P2 delivers 2.5 µg in 10 breaths, i.e. 0.25 µg per breath.

198. As I explained above, using a fixed amount (concentration of drug) per pulse would have been obvious because it is reliable and repeatable. If a patient were to be interrupted during an inhalation, an inconsistent dose would make it difficult to resume treatment. For example, if a patient were about to inhale but cannot because of a fit of coughing or an urgent phone call, a fixed amount of drug per pulse would allow the patient to simply generate another pulse when able to

resume. This ensures that the patient will receive the desired therapeutically effective dose during each administration without the inefficiency or side effects of delivering more (or less) drug then the patient needs.

199. This understanding is further confirmed by the EU Community Register, which, in addition to explaining the functionality of Venta-Neb®, teaches about two jet nebulizer systems that have also been approved for Ventavis, the HaloLite and Prodose. The Ventavis label ***does not*** express the dose in a number of breaths for these two devices. Rather, the label explains that "HaloLite and Prodose are dosimetric systems. They stop automatically after the pre-set dose has been delivered. The inhalation time depends on the patient's breathing pattern." Thus, these devices do not deliver a fixed amount of drug per pulse, but rather vary the amount per breath based on the patient. Thus, instead of explaining that the dose can be measured in 10 or 25 breaths, the Ventavis label explains that HaloLite and Prodose take 4-5 minutes to deliver 2.5 µg and 8-10 minutes to deliver 5 µg.

ii. Claim 1: Limitation [C]

200. Limitation [C] requires "said pulsed ultrasonic nebulizer comprising an opto-acoustical trigger which allows said human to synchronize each breath to each pulse."

201. The EU Community Register expressly discloses this limitation as it states: "Venta-Neb prompts the patient to inhale by an optical and an acoustic

signal." Even if Voswinckel's OptiNeb® pulsed ultrasonic nebulizer and the EU Community Register's Venta-Neb® did not include such an opto-acoustical trigger, it would have been obvious to add such a feature to the nebulizer. Audible and visual prompts are commonplace, as I explained above.

202. Appealing to these same senses using a nebulizer such as the OptiNeb® nebulizer disclosed in Voswinckel would have simply applied a known technique to coordinate inhalation with the delivery of medication and would have done nothing more than yield predictable results.

203. Moreover, incorporating both an optical and acoustical element as a trigger would have been understood to provide even more accurate and efficient dosing—a key consideration for using a pulsed nebulizer—because the signal would help the patient inhale the precise dose.

204. Here a POSA would have been motivated to combine the OptiNeb® nebulizer from Voswinckel with the features of the Venta-Neb® nebulizer disclosed in the EU Community Register because both nebulizers were manufactured by the same company, Nebu-Tec. This would also have provided the POSA with a reasonable expectation of successfully incorporating the opto-acoustical

functionality into Voswinckel's reported OptiNeb® device. "Venta-Neb prompts the patient to inhale by an optical and an acoustic signal."[194]

b. Claims 2-9 Would Have Been Obvious Over Voswinckel in view of Ghofrani and the EU Community Register.

As discussed in connection with Combination 1 above, Voswinckel and Ghofrani teach or render obvious the additional limitations of claims 2-9. Therefore, claims 2-9 would have been obvious over Voswinckel in view of Ghofrani and the EU Community Register.

4. Objective Indicia of Nonobviousness Do Not Overcome the Strong Showing of Obviousness

205. During prosecution of the '240 patent, the patentee asserted that various secondary considerations of nonobviousness suggested that the asserted claims of the '240 patent were not obvious over the prior art before the USPTO. I disagree that the evidence of secondary considerations of record support the nonobviousness of the claims. I reserve the right to address any additional grounds that may be raised.

206. Importantly, these secondary considerations arguments were made without putting Voswinckel and Ghofrani before the USPTO during prosecution. As I have explained in detail, these references in the combinations disclosed above

[194] Ex. 1009 at 3.

show that each one of the limitations in claims 1-9 of the ’240 patent were obvious to a POSA.

207. Assuming the myriad teachings of Voswinckel and Ghofrani are overcome, the evidence of secondary considerations presented during the prosecution of the ’240 patent does not change my opinions.

a. Unexpected Results

208. ***First***, the patentee argued that it was surprising that “treprostinil solution can be successfully administered with an ultrasonic nebulizer.”[195] Since I explained in the background and the scope and content of the prior art the numerous teachings of successful administration of drugs with ultrasonic nebulizers, this result is not surprising either. Voswinckel literally disclosed the administration of “TRE inhalation by use of the pulsed OptiNeb® ultrasound nebulizer” and that he observed the beneficial effects for up to two hours.[196]

209. Furthermore, the benefits that patients have experienced from Tyvaso cannot be attributed to the specific nebulizer. Here, the device is just a means to deliver the target dose of a well-known drug (treprostinil) treating the condition for which it was known to treat (pulmonary hypertension). In fact, the specification of

[195] Ex. 1058 at 9.

[196] Ex. 1003 at III-295.

the ’240 patent claims that the same beneficial effects were observed when administering inhaled treprostinil in two puffs of a soft mist inhaler.

210. ***Second***, I understand that Dr. Lewis Rubin argued that the duration of effect from a single breath delivering 15 µg of treprostinil and the tolerance of up to 90 µg was surprising or unexpected. This cannot be true, however, since Ghofrani taught the same exact method of administration showing effects that lasted for 180 minutes.[197] Indeed, an inhalation of 15 µg was reported in Ghofrani and led him to conclude that a patient could tolerate up to 90 µg without side effect. Thus, Rubin was arguing the exact opposite of what was known from Ghofrani.

211. Similarly, the patentee’s argument that they did not expect their treprostinil concentration range to work falls flat in light of Voswinckel. Since Voswinckel successfully administered a formulation with 600 µg/mL of treprostinil, it is not surprising that various ranges that encompass Voswinckel’s formulation would have been effective.

212. Finally, the patentee pointed to the alleged commercial success of United Therapeutics’ Tyvaso® product.[198] Even the patentee admits, however, that

[197] Ex. 1005 at 298.

[198] Ex. 1058 at 9.

alleged success is attributable to "more convenient dosing," a feature that is not claimed.[199]

213. I understand that the Examiner rejected each and every one of these secondary considerations arguments, and I agree, especially in light of the teachings of Voswinckel and Ghofrani. What is clear, however, is that the benefits of treprostinil stem from the compound itself, which is more stable and has a longer half-life than other prostacyclins; these benefits are not dependent on delivery in 1-18 breaths or the fact that a pulsed ultrasonic nebulizer was used. Rather, these are the inherent effects of treprostinil—which have been known for years.

214. Even if there were evidence of secondary considerations of nonobviousness, and they were found to overcome the teachings of the prior art referenced above, this supposed evidence would not have a nexus to claims 1-9 of the '240 patent. There can be no connection because a POSA would have been blocked by UTC from commercializing an inhaled treprostinil product. The Cloutier patents—*i.e.*, the '212 and '033 patents—broadly claim the right to any aerosolized treatment using treprostinil.[200] These patents effectively blocked anyone outside UTC from pursuing an inhalable drug product containing treprostinil.

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[199] Ex. 1059 at 10.

[200] Ex. 1018 at cls. 6-8; Ex. 1057 at cls. 1-3.

215. But even before the Cloutier patents, a POSA would have been blocked from commercializing ***any*** formulation of treprostinil since the issuance of the Aristoff '075 patent in March 1980.[201] The Aristoff '075 patent covers the composition and production of treprostinil.[202] In 1988 the Tadepalli '222 patent was issued, which covers the use of treprostinil for the treatment of pulmonary hypertension.[203] Thus, without a license to these patents, a POSA would have been unable to commercialize the inhaled treprostinil product claimed in the '240 patent.

VIII. SUPPLEMENTATION AND REBUTTAL

216. I may also testify in rebuttal to testimony or opinions offered by other witnesses. I reserve my right to supplement or amend this report in light of any additional information or documents, in response to any critique of my report or alternative opinions advanced by or on behalf of United Therapeutics Corp.

IX. CONCLUSION

217. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful

[201] Ex. 1019 at cls. 1-13.

[202] *Id*.

[203] Ex. 1025 at cls. 1-2.

false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon. If called to testify as to the truth of the matters stated herein, I could and would testify competently.

218. I understand that this declaration is to be filed as evidence in a contested case before the Patent Trial and Appeal Board of the United States Patent and Trademark Office. I acknowledge that I may be subject to cross examination in the case and that cross examination will take place within the United States. If cross examination is required of me, I will appear for cross examination within the United States during the time allotted for cross examination.

I declare under penalty of perjury that the foregoing is true and correct.

Executed on this 21st day of June 2017, in Iowa City, Iowa.

Date: Maureen D Donovan

Maureen D. Donovan, Ph.D.