UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

WATSON LABORATORIES, INC.
Petitioner

v.

UNITED THERAPEUTICS, INC.
Patent Owner

Patent No. 9,358,240
Issue Date: June 7, 2016
Title: TREPROSTINIL ADMINISTRATION BY INHALATION

Inter Partes Review No. 2017-01621

DECLARATION OF DR. AARON WAXMAN

I, Dr. Aaron Waxman, hereby declare as follows:

1. I am a pulmonary critical physician in Boston, Massachusetts. I am the Executive Director of the Center for Pulmonary and Heart Disease in the Heart and Vascular Center at Brigham and Women's Hospital in Boston, Massachusetts. I am board certified in Internal Medicine, Pulmonary Disease, and Critical Care Medicine. I have been practicing as a pulmonary and critical care doctor for over 20 years. I am a member of the American College of Chest Physicians, The American Thoracic Society, the Pulmonary Hypertension Association, and the Pulmonary Vascular Research Institute.

2. I am an Associate Professor of Medicine at Harvard Medical School and have dual appointments in the Pulmonary Critical Care and Cardiovascular Medicine divisions at the Brigham and Women's Hospital. I have previously served as assistant professor in Medicine at the Yale University School of Medicine and Tufts University School of Medicine. I have authored or co-authored more than 100 peer-reviewed journal articles, book chapters and reviews.

3. I received my Bachelor's degree from George Washington University. I received a Ph.D. in Anatomy and Neuroscience at the Albany Medical College, and an M.D. from Yale University School of Medicine. I completed my internship and residency in Internal Medicine at Yale New Haven Hospital. I also completed

a Fellowship in Pulmonary and Critical Care at the Yale School of Medicine. My *curriculum vitae* is provided as Exhibit 2041.

4. I am a paid consultant for United Therapeutics, the assignee of U.S. Patent No. 9,358,240 ("the '240 patent"), in connection with IPR2017-01621. My compensation does not depend on the content of my opinions or the disposition of this proceeding. I have been retained by United Therapeutics to provide technical expertise and my expert opinion on the '240 patent.

5. While I am neither a patent lawyer nor an expert in patent law, I have been informed of the applicable legal standards for obviousness of patent claims. I understand that the Petition brought forward by Watson Laboratories, Inc. ("Petitioner" or "Watson") challenges claims 1-9 of the '240 patent.

6. For reference, below is a list of the Exhibits that are cited herein:

Exhibit No.	Description
1001	U.S. Patent No. 9,358,240
1002	Declaration of Dr. Maureen Donovan
1003	Robert Voswinckel, et al. "Inhaled treprostinil sodium for the treatment of pulmonary hypertension" Abstract #1414, *Circulation*, 110, 17, Supplement (Oct. 2004): III-295
1005	Hossein Ardeschir Ghofrani, Robert Voswinckel, et al., "Neue Therapieoptionen in der Behandlung der pulmonalarteriellen Hypertonie," Herz, 30,4 (June 2005): 296-302
1012	WO 93/00951
1013	Declaration of Dr. Scott Bennett
1028	Olschewski H., et al., *Aerosolized Prostacyclin and Iloprost in Severe Pulmonary Hypertension*, 1996 Ann. Intern. Med. 124(9),

	820-824 (1996)
1029	Olschewski, et al., *Pharmacodynamics and Pharmacokinetics of Inhaled Iloprost, Aerosolized by Three Different Devices, in Severe Pulmonary Hypertension*, Chest J., 124(4), 1294-1304 (Oct. 2003)
1046	Voswinckel, R., et al., "Inhaled treprostinil is a potent pulmonary vasodilator in severe pulmonary hypertension," 25 European Heart Journal 22, 218 (2004)
1162	Substantive Submission filed in 12/591,200 (Nov. 9, 2015) (with accompanying Declaration of Dr. Roham T. Zamanian)
1163	Amendment and Reply filed in 12/591,200 (Feb. 2, 2016) (with accompanying Second Declaration of Dr. Roham T. Zamanian)
2002	*Oxford Dictionary of English*. 2nd ed. Revised. Oxford University Press, 2005 (excerpt).
2003	Newman, Stephen P. *Respiratory drug delivery: essential theory and practice*. Respiratory Drug Delivery Online, 2009 (excerpt).
2004	Hill, N., *Therapeutic Options for the Treatment of Pulmonary Hypertension*, Medscape Pulmonary Medicine 9(2) (2005).
2005	Exhibits Accompanying First Declaration of Dr. Roham Zamanian and Amendment and Reply filed in 12/591,200 (Nov. 9, 2015) (Ex. 1162)
2012	Orange Book Listing for Tyvaso® (Accessed October 3, 2017)
2020	Declaration of Dr. Werner Seeger
2021	Bourge *et al.*, *Cardiovascular Therapeutics* 31:38-44 (2013)
2023	*Curriculum vitae* of Dr. Lewis Rubin
2024	2002 Press Release Regarding Promotion of Robert Roscingo (accessed October 10, 2017)
2025	Shield Therapeutics Biography for Carl Sterritt (accessed October 10, 2017)
2037	Listing of Issues and Supplements of *Circulation* Accessible on *Circulation* Website (accessed April 17, 2018)
2041	*Curriculum vitae* of Dr. Aaron Waxman
2042	*Mosby's Medical Dictionary*. 7th ed. Mosby Elsevier, 2006 (excerpt).
2043	Leung, K, Louca E., & Coates, A. "Comparison of Breath-Enhanced to Breath-Actuated Nebulizers for Rate, Consistency, and Efficiency," Chest, 126(5):1619-1627 (2004)
2044	Rau, J.L., "Design Principles of Liquid Nebulization Devices Currently in Use," Respir. Care, 47(11):1257-1275 (2002)
2045	Atkins, P.J. & T.M. Crowder. "The Design and Development of Inhalation Drug Delivery Systems," Pharmaceutical Inhalation

	Aerosol Technology, 2nd Ed. (A.J. Hichey ed., CRC Press), Ch. 9 (2003)
2046	Ventavis® Patient Brochure
2047	Rau, J.L. *Respiratory Care Pharmacology*. 6th Ed. Mosby, 2002 (excerpt)

I. BACKGROUND

7. At the time of the invention, as today, pulmonary hypertension was a poorly understood, often fatal, disease with limited treatment options. Prior treatments of pulmonary hypertension with a prostacyclin analog included epoprostenol, which had significant burdens and challenges to patients. Epoprostenol can only be administered intravenously. Ex. 2004. The need for a permanent transcutaneous intravenous catheter to administer epoprostenol posed risks of infection and sepsis. *Id.* Epoprostenol patients also risk sudden occlusion of the catheter which can precipitate hemodynamic collapse because of the several minute half-life of the drug. *Id.* Moreover, epoprostenol requires daily mixing and refrigeration, thus, requiring the patient to carry a cold pack to avoid degradation at room temperature and an infusion pump to safely administer the drug.

8. Because of these drawbacks, epoprostenol is not suitable for treating all patients. Indeed, there are a number of patients for whom intravenous therapy is not suitable. For example, for pulmonary hypertension patients with lung disease, it is critical to maintain matched ventilation and perfusion to optimize

oxygenation and the excretion of carbon dioxide from the lung. When a patient suffers from lung disease (*e.g.* pneumonia, emphysema, or interstitial lung diseases), the lung automatically diverts blood flow away from diseased areas of the lung and toward the non-diseased portions – optimizing lung function. Since intravenous delivery of a vasodilator results in indiscriminate vasodilation, this optimization is disrupted by intravenous delivery. Similar drawbacks exist with intravenous and subcutaneous treprostinil.

9. In addition, in my clinical experience, I have found that patients prefer inhaled treatment because it is less intrusive (*i.e.* doesn't require constant infusions or a Hickman catheter) and also has less systemic side effects. The preference for inhaled treatment over intravenous administration is about 2 or 3 to 1. Thus, as a clinician considering what drug to administer a pulmonary hypertension patient, I would not compare intravenous therapeutics to inhaled therapeutics. Rather, the relevant comparison for a patient who either cannot support intravenous administration or has requested inhaled administration would be which of the two inhaled pulmonary hypertension products – Tyvaso ® or Ventavis ® - would be suitable for treatment.

10. Prior to May 15, 2006, the only FDA-approved prostacyclin-type drug that could be given in an inhalable form was iloprost, marketed as Ventavis ®. At that time, the results of an Aerosol Iloprost Randomized (AIR) Study documenting

the effects of inhaled iloprost had been public for about three-and-a-half years, and Ventavis ® had been on the market for about one-and-a-half years. Ex. 1162, 21; Ex. 2005, 1-28. As Dr. Zamanian noted in his Declaration of May 15, 2016, clinicians were concerned that the adoption of Ventavis® was happening too rapidly and were still largely of the opinion that intravenous administration of a prostacyclin analog was preferable to inhaled delivery. Ex. 1162, 21. Surprisingly, even in view of these concerns, when Tyvaso ® entered the market in 2009, there was a rapid shift from Ventavis ® to Tyvaso ®. *See* Ex. 1162, 19-39; Ex. 1163, 23-28.

II. CLAIMS OF THE '240 PATENT

11. I have reviewed the claims of the '240 patent. Provided below for reference is the language of claim 1 of the '240 patent:

> 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 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.

Ex. 1001, col. 18:2-16. I understand that this claim is an "independent claim" and that all subsequent claims, *i.e.* claims 2-9, depend from this claim – meaning that claims 2-9 require the same features or "limitations" as claim 1 but also include additional limitations. Ex. 1001, col. 18:17-37.

12. I have been informed that the terms found in the claims of a patent must be given their broadest reasonable interpretation consistent with the body text, or "specification," of the patent at issue and the statements made during prosecution of the patent, or "prosecution history," as it would be interpreted by one of ordinary skill in the art. Therefore, in this section, I provide my opinions on how a person of ordinary skill in the art ("POSA") would understand certain claim terms.

A. Person of Ordinary Skill in the Art

13. I am informed by counsel that a patent is to be interpreted from the perspective of a hypothetical person referred to as the person of ordinary skill in the art (which I will often refer to as a "POSA") to which the patent pertains. I am further informed that a determination of the level of ordinary skill is based on, among other things, the type of problems encountered in the art, prior art solutions

to those problems, rapidity with which innovations are made, sophistication of the art, and the educational level of active workers in the field.

14. The claims of the '240 patent are directed to methods for "treating pulmonary hypertension" with a specific "pulsed ultrasonic nebulizer." Ex. 1001, col. 18:2-37. I understand that several of the inventors listed on the '240 patent have post-graduate degrees in the field of medicine or drug development and all had at least several years of research, executive, and/or clinical experience in the investigation and treatment of pulmonary hypertension and in developing pharmaceutical products for the treatment of pulmonary hypertension. Ex. 2020, ¶1, 7; Ex. 1028, 1; Ex. 1029, 1; Ex. 2023; Ex. 2024; Ex. 2025.

15. Consistent with the experience of the named inventors, it is my opinion that a POSA at the time of invention would have been a person with a post-graduate degree in medicine or drug development (such as the pharmaceutical sciences) with at least two years of experience in the investigation or treatment of pulmonary hypertension. A POSA may also have had additional experience in the study, development, or use of dosage forms that had been used to treat pulmonary hypertension, such as solid oral dosage forms (e.g., tablets and capsules), injectables, and inhaled therapies. A POSA may have had a lower level of formal

education if such a person had more years of experience in the investigation or treatment of pulmonary hypertension.

16. I understand the Petitioner and its expert Dr. Donovan have offered a different interpretation of a POSA. Ex. 1002, ¶74. Even if this definition is applied, it would not affect my ultimate conclusions regarding the '240 patent discussed herein.

B. "pulsed" and "pulse"

17. Both the terms "pulse" and "pulsed" are found in claim 1. Ex. 1001, col. 18:2-16. The term "pulsed" is used as the adjective form of the word "pulse."

18. A POSA would understand the plain meaning of the term "pulse." For example, the Oxford Dictionary of English provides the following definition of the word "pulse": "[a] single vibration or short burst of sound, electric current, light, or other wave." Ex. 2002, 3. The same dictionary defines the word "wave" in the physics context as "a periodic disturbance of the particles of a substance which may be propagated without net movement of the particles, such as in the passage of undulating motion, heat, or sound." Ex. 2002, 5. A POSA would accept both dictionary definitions as providing the plain meaning of the terms "pulse" and "wave." In the scientific and medical context "pulse" is also understood to refer to rhythmic and periodic waves. *See, e.g.,* Ex. 2042, 4

(defining "pulse" as "a brief electromagnetic wave" and "a rhythmic beating or vibrating movement"; defining "pulsed Doppler" as "a type of Doppler device involving the transmission of a short-duration burst of sound into the region to be examined"; and defining "pulsed laser" as "a laser that emits short bursts of energy at fixed intervals rather than a continuous stream of energy"). In the same way, in the context of "pulsed nebulizers," pulsed has long come to be understood as meaning short periods of nebulization at fixed intervals, rather than continuous nebulization. Ex. 2043 (distinguishing pulsed nebulization versus continuous nebulization).

19. In the specification of the '240 patent, the term "pulse" is used to refer to the intermittent and periodic delivery of aerosol for a fixed duration, followed by pauses of a fixed duration in cycles. Ex. 1001, col. 13:59-60. For example, the specification identifies that "[a] pulse of aerosol was generated every 6 seconds" and that the pulsed ultrasonic nebulizer generated aerosol "in cycles consisting of 2 seconds aerosol production (pulse) and 4 seconds pause." Ex. 1001, col. 4:45-46; col. 13:58-60.

20. In the claims, each "pulse" is meant to correspond with each breath. Ex. 1001, col. 18:2-16. A similar interpretation of the term is found in Exhibit 1163, which I understand to be documents and a declaration submitted during the

prosecution of the '240 patent. Exhibit 1163 says a "pulsed" ultrasonic nebulizer produces "a 'pulse' of aerosol production followed by a pause" and that the generated pulses are "spaced apart in time that correspond to each breath inhaled by a human." Ex. 1163, 12-13.

21. Based on the specification and prosecution history, it is apparent that the term pulse in the claims refers to a short burst of aerosol production. Further, the specification and prosecution are consistent with the meaning of both pulse and wave in that the pulse of aerosol must occur with a specified periodicity: in other words, a wave form with consistent time intervals between each pulse.

22. In view of the plain meaning, specification, and prosecution history, a POSA would understand the term "pulse" to refer to a period of aerosol generation and the term "pulsed" to refer to the generation of such pulses with a specified periodicity, or fixed interval.

C. "opto-acoustical trigger which allows said patient to synchronize each breath to each pulse"

23. I have been informed that United Therapeutics and Watson reached an agreement in a related litigation that the phrase "an opto-acoustical trigger" in claim 1 means "a trigger with an optical element (e.g., light) and an acoustical

element (e.g., sound)." I also understand that this agreement applies to this proceeding as well.

24. The definition above provides examples of both the optical and acoustical elements of the "opto-acoustical trigger" but no definition for the word "trigger" is provided. Therefore, a POSA would understand the word "trigger" in this phrase according its plain meaning. The Oxford Dictionary of English defines "trigger" as "an event that is the cause of a particular action, process, or situation." Ex. 2002, 4. Thus, an "opto-acoustical trigger" would be understood to require an optical element (*e.g.*, light) and an acoustical element (*e.g.*, sound) that is designed to cause a particular action, process, or situation.

25. The "opto-acoustical trigger" is required by the language of claim 1 to "allow[] said human to synchronize each breath to each pulse." The specification of the '240 patent is consistent with its description of the opto-acoustical trigger synchronizing inhalation to pulses. Ex. 1001, col.13:60-62. Therefore, in view of the plain meaning of the word and the specification, a POSA would understand the optical element (*e.g.*, light) and the acoustical element (*e.g.*, sound) are designed to "cause the particular action, process, or situation" of the synchronization of the patient's inhalation with each pulse. This synchronization of the patient's breathing to the device contrasts the claimed pulsed ultrasonic nebulizer from other

kinds of pulsed ultrasonic nebulizers, such as a breath-actuated pulsed ultrasonic nebulizer where the device adapts the pulse to the patient's individual breathing pattern, allowing the patient to control length of pulse and spacing between pulses.

26. The claimed "opto-acoustical trigger" is different from the mere combination of an optical element and an acoustical element. The "opto-acoustical trigger" is designed to cause a human to immediately inhale each aerosol pulse from the pulsed ultrasonic nebulizer as it is generated and to "synchronize the inspiration to the end of the aerosol pulse, thereby providing exact dosage." Ex. 1001, col.13:61-62. A combination of an optical element and an acoustical element that simply **provides information**, such as a signal or an alert, cannot be considered an "opto-acoustical trigger" without evidence that it is designed to cause immediate inhalation of individual aerosol pulses, as is used in this patent.

D. "single event dose"

27. Claim 1 also refers to a "single event dose" and requires that 15 to 90 micrograms of treprostinil or its salt be delivered in 1 to 18 breaths to the pulmonary hypertension patient in a "single event dose." Ex. 1001, col. 18:14-16. I further note that the patent specification gives the following supporting explanation of this term:

> Administering of treprostinil in a single event can be carried out in a limited number of breaths by a patient….
>
> The total time of a single administering event can be less than 5 minutes, or less than 1 minute, or less than 30 seconds.
>
> Treprostinil can be administered a single time per day or several times per day.

Ex. 1001, col. 7:54-62. The patent specification also presents results showing that an inhaled dose of 15 micrograms "induced pulmonary vasodilation for longer than 3 hours compared to placebo inhalation." Ex. 1001, col. 17:14-19. Claims 3 and 9 further indicate that the patient is instructed "not to repeat the single event dose for a period of at least 3 hours." Ex. 1001, col. 18:20-21, 36-37. Based on how "single event dose" is used in the patent, a POSA would understand it to mean the total time during which the pulmonary hypertension patient inhales a necessary dose of treprostinil in one sitting, which may be spaced apart from the next single event dose by several hours, and there may be more than one pulse and more than one breath corresponding to each pulse within a single event dose.

III. INSTITUTED GROUND 1

28. I have been informed that in order for a patent claim to be considered obvious, 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 POSA

at the time an invention was made, and that such a person would have a reason for and reasonable expectation of success in combining these teachings to achieve the claimed invention. I understand there may be a variety of rationales that can demonstrate the reason for and reasonable expectation of success in combining selected teachings, but, regardless of the rationale used, it must be supported by evidence.

29. I understand the Board is reviewing whether claims 1-9 are obvious over the references provided in "Ground 1" noted below.

Ground	References
Ground 1	Robert Voswinckel, et al. "Inhaled treprostinil sodium for the treatment of pulmonary hypertension" Abstract #1414, *Circulation*, 110, 17, Supplement (Oct. 2004): III-295 ("Voswinckel," Ex. 1003)
	WO 93/00951 ("Patton," Ex. 1012)
	Hossein Ardeschir Ghofrani, Robert Voswinckel, et al., "Neue Therapieoptionen in der Behandlung der pulmonalarteriellen Hypertonie," Herz, 30,4 (June 2005): 296-302 ("Ghofrani," Ex. 1005)

I further understand the Board has relied on both the references cited under "Ground 1" and Dr. Donovan's declaration (Ex. 1002) in its decision to "institute

trial" on this ground. In this section, I provide my opinions on Voswinckel (Ex. 1003), Ghofrani (Ex. 1005), and Patton (Ex. 1012) in relation to the Board's decision, Watson's arguments, and the supporting testimony provided in Dr. Donovan's declaration.

A. Voswinckel

30. Dr. Donovan's reliance on Voswinckel for showing the "safety, tolerability, and clinical efficacy" of inhaled treprostinil (Ex. 1002, ¶78) is inconsistent with how a POSA would interpret Voswinckel's findings and is premised on a fundamental misunderstanding of Voswinckel.

31. While the authors do state they are interested in evaluating the safety, tolerability and clinical efficacy in patients, they fail to disclose any information about the amount of drug per breath or spacing of breaths within an inhalation event, and the conclusions actually reflected a far more cautious conclusion. The conclusion expressly addresses efficacy only in the context of single acute dosing and only of a single measure of pulmonary hemodynamics—this cannot lead to a conclusion of clinical efficacy. Ex. 1003, 7. At best, the authors suggest long term treatment (based on 2 compassionate use patients) is "promising" and agree the results "warrant controlled studies investigating this approach in a larger series of

patients." *Id.* This invitation to investigate further is hardly the demonstration of effective and safe treatment Dr. Donovan claims.

32. More importantly, Dr. Donovan's conclusions about Voswinckel are premised on an apparent misreading of the document. Dr. Donovan's assertion that "[t]hese 17 patients [in Voswinckel] received a three-breath inhalation treatment four times per day" is flatly incorrect. Ex. 1002, ¶109. This teaching is nowhere to be found in Voswinckel. Ex. 1003. The 17 patients very clearly received a single acute administration of treprostinil. Ex. 1003, 7. A single acute dose while the patient is catheterized is not the "treatment of pulmonary hypertension," much less the safe and therapeutically effective treatment of such. Dr. Donovan's clear misunderstanding is further highlighted where she talks about "four times per day" and "long term" treatment in the context of "single acute dosing." Ex. 1002, ¶104.

33. Voswinckel is a single-paragraph conference abstract, meaning that (1) it is not edited by a peer review panel of editors but published as-submitted following a less-stringent grading and acceptance criteria than scientific manuscripts and (2) it is not meant to be a definitive work. Ex. 1003, 1-7. Rather, such abstracts are generally submitted by researchers looking to provide their administration with a reason they should attend the meeting. To POSAs, these

abstracts are not considered publications *per se*. In fact, at Harvard, my colleagues and I are required to remove an abstract from our CVs if it has not resulted in a publication within three years. This happens quite often since conference abstracts reflect preliminary data and hypotheses which often end up being contradicted by full studies. A POSA would not rely on such preliminary data to conclude that a drug of any kind was safe, tolerable, or clinically efficacious.

34. To the extent that Voswinckel reports "promising" results with inhaled treprostinil, a POSA would view this with a degree of skepticism. A reader would review the abstract results for what they actually show. It is a huge leap for Dr. Donovan to conclude safety and efficacy from such a conference abstract that only purports to be "promising" for long-term potential – a leap a POSA would not take.

35. At best, Voswinckel sets out a study to assess "the effects of inhaled TRE [treprostinil] on pulmonary hemodynamics and gas exchange in severe pulmonary hypertension." Ex. 1003, 7. No criticality is attributed to the type of device used nor is any clarification given on how the device is used or what actual dose (in μg) is delivered. *Id.* The dose and device in Voswinckel are incidental. *Id.* It is also unclear from Voswinckel what inhalation regimen was used for the two "compassionate treatment" patients and whether they are a subset of or a

separate population from the 17 patients treated with 3 single breaths of the 600 μg/mL solution, with no information on how much drug was delivered within each breath or how the breaths were spaced apart. *Id.* The only clear teaching is that the two "compassionate treatment" patients were given four inhalations of treprostinil per day. *Id.* A POSA would not know what dose, concentration, or device was used to deliver the "compassionate treatment" based on the scant information provided. A POSA would also be cautious of results gleaned from a two-patient, uncontrolled sample size, particularly where those patients are "compassionate use" treatment.

36. I have been informed that in order for Voswinckel to be considered "prior art," for the purposes of this proceeding, it must have been "publicly accessible" and that the legal standard for accessibility was whether Voswinckel was disseminated or otherwise made available to the extent that a POSA exercising reasonable diligence can locate it. Based on this legal standard, it is my opinion that Voswinckel was not publicly accessible.

37. A POSA looking for information on treatment of pulmonary hypertension with treprostinil on or before May 15, 2006 would typically do most of his or her research online. The primary resource for online searching in the field is PubMed. A POSA typically searches PubMed using a string of search terms,

which could include the disease (*e.g.* "pulmonary hypertension" or "pulmonary arterial hypertension") and/or the active agent of interest (*e.g.*, "prostacyclin-analog" or "treprostinil"). In circumstances where a POSA is already aware of the work of a set of authors or institution, a search of PubMed of those terms might also be employed.

38. There is no PubMed entry for Voswinckel at all, much less one keyed to the authors, their institution, pulmonary hypertension, or treprostinil. Conference abstracts, like Voswinckel, are not usually indexed on PubMed because, as noted above, they are not considered peer-reviewed to the same extent as a journal publication. Therefore, a POSA exercising reasonable diligence would not have been able to locate it in the most typical and helpful way employed by a POSA.

39. In the unlikely event that no relevant resources were pulled up on PubMed, a POSA might turn to a library to locate books and peer-reviewed journals (in print) that are relevant to pulmonary hypertension. Typically, peer-reviewed journals are about 100 pages and contain an index or table of contents.

40. For a POSA to find Voswinckel through either of these methods is akin to finding a needle in a haystack. Voswinckel is one of over 2,000 abstracts in a supplement to *Circulation* providing all the abstracts for the American Heart

Association's 2004 Scientific Sessions in advance of the conference; the supplement is over 1,000 pages (an order of magnitude longer than a peer-reviewed journal). Ex. 1003, 4, 7. The version provided by Watson does not even contain a table of contents showing how the supplement is organized and/or if it could be searched. Ex. 1003.

41. I understand that Watson has relied on Dr. Bennett for the evidence that Voswinckel was publicly available. I have reviewed Dr. Bennett's declaration (Ex. 1013) and disagree with him that Voswinckel was publicly accessible. Importantly, he concludes only that "in [his] opinion, Circulation and its abstract supplements were sufficiently accessible to the public interested in the art; and an ordinarily skilled researcher, exercising reasonable diligence, would have had no difficulty finding copies of Circulation and its abstract supplements." Ex. 1013, ¶30. But the question is not whether a POSA could find *Circulation* or its supplements, but the Voswinckel reference itself. Based on Dr. Bennett's documentation –library catalog entries for the entirety of the *Circulation* periodical or all *Circulation* abstracts keyed to such terms as "cardiology" and "medicine"—a POSA would have to review thousands to hundreds of thousands of pages to locate Voswinckel—this is not reasonable diligence.

42. A POSA relying on library research would likewise be hard pressed to find the abstract. First, while a POSA might look to *Circulation* for peer-reviewed literature, a POSA would have no reason to look at non-peer reviewed literature supplements- even if it was associated with this publication. Second, even if a POSA was looking for this specific supplement to *Circulation*, Dr. Donovan and Dr. Bennett did not demonstrate how a POSA would find it in 2005 using any particular index or relevant search terms. Indeed, there is no record of this supplement on the *Circulation* website. Ex. 2037. Third, even after locating this supplement, it is not clear that a POSA could have located this specific abstract based on the evidence provided by Watson's experts.

B. Ghofrani

43. Ghofrani is a translation of a German review article, summarizing various treatment options for pulmonary hypertension. Ex. 1005. There is one portion, however, that Dr. Donovan relies on:

> Initial trials in Giessen have shown proof of efficacy of *inhaled* treprostinil for the effective reduction of the pulmonary vascular resistance (PVR) [6]. In this first study, 17 patients with severe pre-capillary pulmonary hypertension were administered inhaled treprostinil (15 mcg/inhalation). This led to a major reduction in pulmonary selective pressure and resistance with an overall duration of action of > 180 min. In direct comparison with inhaled iloprost,

> inhaled treprostinil showed a stronger pulmonary selectivity, so that it is possible to increase the dosage to up to 90 mcg (absolute inhaled dose per inhalation exercise) without adverse effects occurring [6]. Due to these unique properties (pronounced pulmonary selectivity and long duration of action after an individual inhalation), it is possible to reduce the number inhalations necessary to up to four per day; the inhalation period can be reduced to < 1 min. by selecting a suitable device. Additionally, the initial data shows that it is technically feasible for there to be only one to two breaths in an application.

Ex. 1005, 3 (emphasis in original). Dr. Donovan presumes that this section is referencing "the *very same study* as Voswinckel." Ex. 1002, ¶136. Yet a POSA would not draw the same conclusion.

44. A POSA would review the references cited in the review article. The section cites to a reference "[6]," which the endnotes indicate is "Vowsinckel R, Kohstall M, Enke B, et al. Inhaled treprostinil is a potent pulmonary vasodilator in severe pulmonary hypertension. Eur Heart J 2004;25:22" ("reference [6]"). Ex. 1005, 3. I understand that this reference has been submitted by Watson as Exhibit 1046. Reference [6] reports testing inhaled treprostinil with a continuous nebulizer in more than 17 patients and does not disclose doses of 15 or 90 μg per inhalation. Ex. 1046, 5. Even in view of these discrepancies, a POSA would not conclude that Ghofrani referenced a different study – let alone the study in Voswinckel. Indeed, only reference [6] reports measurements 180 minutes after inhalation, as in

Ghofrani. Ex. 1046, 5; Ex. 1005, 3. Voswinckel, in contrast, only reports measurements 120 minutes after inhalation. Ex. 1003, 7.

45. A POSA would understand the number of patients to be a typographical error or a subset of patients of a larger study, rather than reference to a different study and paper, since this is the only aspect that is inconsistent with the disclosure of reference [6]. A POSA would understand the 15 or 90 μg per inhalation to be new information, as neither reference [6] nor Voswinckel provide a dose in micrograms per inhalation. Rather, both abstracts report a drug concentration in micrograms per milliliter. Ex. 1046, 5; Ex. 1003, 7. To calculate a microgram dose from the drug concentration would require knowledge of the diluent used, how much is aerosolized by the device, and the efficiency of the delivery of drug, but none of these parameters is provided in either abstract. *Id.* Further, since both reference [6] and Voswinckel are abstracts, a POSA would recognize both as reporting preliminary data. Since there is no basis in the cited literature for the Ghofrani's dose per inhalation and the information cited is preliminary data, a POSA would view the dose information in Ghofrani as hypothetical rather than the results of a specific study.

C. Patton

46. Contrary to the way it is depicted by Dr. Donovan (Ex. 1002, ¶124-131), Patton is not concerned with pulsed ultrasonic delivery or synchronization of breath and pulse.

47. Patton's device seems fairly inefficient, noting that at least 40% by weight of the active agent of interest should remain aerosolized. Ex. 1012, 5:4-8. Thus, in some embodiments, Patton results in waste of up to 60% of the active agent, which is a huge waste when an active agent costs upwards of $10,000. *Id.* The success of Patton is dependent on the whole amount of aerosolized active agent being inhaled as a single breath. Ex. 1012, 5:13-15. However, Patton offers no clear method for a POSA to quantify the dose of aerosolized active agent. Patton at most teaches that the amount aerosolized should be at least 40% by weight and should be smaller than the inspiratory capacity of a human, which varies greatly based on the status of the human – *e.g.*, whether they are healthy or have a disease that effects breathing, such as pulmonary hypertension. Ex. 1012, 5:15-26. Accordingly, a POSA would not be able to determine the total dose that Patton is able to deliver. It would also be difficult for a POSA to determine what if any dose would reach the patient's lungs because Patton provides a large particle size range. Ex. 1012, 9:23-26.

48. Patton also fails to describe an ultrasonic nebulizer. Ex. 1012. Rather, the device in Patton uses a gas jet or "compressor", which provides a continuous flow of air to aerosolize the drug. Ex. 1012, 12:13-25. The "light [] and/or audible signal" in Patton, identified by Dr. Donovan (Ex. 1002, ¶87), is keyed to the "operation of the compressor." Ex. 1012, 14:11-14. Patton does not teach adapting such a signal for use in a device without such a compressor, such as an ultrasonic nebulizer, much less a pulsed nebulizer. Ultrasonic nebulizers are structurally different from the device of Patton, since they use a piezoelectric element rather than a compressor to aerosolize an active agent. Ex. 2003, 26, 28. The frequency at which the piezoelectric element vibrates determines the rate and amount of nebulization. *Id.* Based on Patton – alone or in combination with any of the aforementioned references – a POSA would not have any indication on how to adapt Patton's light and sound to a structurally different device.

49. In addition, since the mist is visible to the patient in Patton, the light and audible signals are not necessary to alert the patient that the active agent is aerosolized. Ex. 1012, 14:5-6. Further, Patton does not provide any indication that it is necessary for the patient to inhale immediately after the active agent is aerosolized. Ex. 1012. In fact, one of the aims of Patton appears to be obviating the need for conscious synchronization of breath and aerosolization, as required by metered dose inhalers. Ex. 1012, 1:14-2:37.

D. Obviousness

50. I disagree with Dr. Donovan that the claims of the '240 patent are obvious over Voswinckel in view of Patton and Ghofrani.

1. The combination of Voswinckel, Patton, and Ghofrani does not teach all the elements of the '240 patent claims.

51. Dr. Donovan is incorrect that "the prior art discloses all of the elements of the claimed subject matter." Ex. 1002, ¶102. Critical requirements of the claims are not found in any of Voswinckel, Patton, or Ghofrani. Most notably, none of the references identify "a pulsed ultrasonic nebulizer that aerosolizes a fixed amount of treprostinil or a pharmaceutically acceptable salt thereof per pulse" or an opto-acoustical trigger that causes the "human [to] synchronize each breath to each pulse." In fact, both Ghofrani and Patton teach away from breath synchronization to pulsed delivery, and Voswinckel is entirely silent on the point.

52. The primary teaching in any of Voswinckel, Ghofrani, or Patton that Dr. Donovan relies on for the separate, important limitations of (1) a pulsed ultrasonic nebulizer (2) that aerosolizes a fixed amount per pulse and (3) requires synchronization of each breath to each pulse is the phrase in Voswinckel: "pulsed ultrasonic nebulizer." But this statement says nothing to a POSA about why or how the device is pulsed, whether it provides a fixed amount per pulse (or what amount), and certainly says nothing of breath synchronization. *Supra* Section

III.A. In fact, if Dr. Donovan was correct that Voswinckel and Ghofrani "describe *the very same study*," then it would be clear that even if a pulsed ultrasonic nebulizer was used in Voswinckel, it was clearly used in a continuous, not pulsed, mode. Ex. 1002, ¶136. This is because the only citation for the study in Ghofrani makes clear that patients inhaled the solution for 6 minutes using an ultrasonic nebulizer with continuous delivery. Ex. 1005; Ex. 1046; *supra* Section III.B.

53. Indeed, on the "fixed amount per pulse" requirement, Dr. Donovan admits that "Voswinckel does not expressly state that the nebulizer generated a fixed amount per pulse." Ex. 1002, ¶121. Without identifying any other reference where this limitation is found, she simply concludes that "a POSA would find this requirement to be "obvious" or "straight-forward." Ex. 1002, ¶121-123.

54. To the extent Dr. Donovan asserts that the requirement of a pulsed ultrasonic nebulizer aerosolizing a fixed amount of treprostinil per pulse is found in Patton, that is incorrect. Ex. 1002, ¶124. Patton does not deal with a pulsed ultrasonic nebulizer (or an ultrasonic nebulizer at all, much less one that delivers a fixed amount of treprostinil), but deals with compressed air from a compressor in a jet nebulizer. *Supra* Section III.C. Nor does Patton teach "pulsed" delivery within the meaning of the claim. *Id.* Patton's sole mention of the word pulse is in connection with a single pressure pulse produced to fluidize powder in a jet

nebulizer. Ex. 1012, 10:34. Patton does not employ a repeated and periodic (pulsed versus continuous) nebulization intended to synchronize to a patient's consecutive breaths.

55. With respect to the claim requirement that "said pulsed nebulizer compris[e] an opto-acoustical trigger which allows said human to synchronize each breath to each pulse," it is my opinion that this is not taught anywhere in Voswinckel, Ghofrani, or Patton. Dr. Donovan argues that a pulsed ultrasonic nebulizer necessarily creates aerosol during the inhalation cycle and necessarily has the primary purpose of avoiding waste of aerosolization during exhaling and that the patient "must synchronize their breath to the pulse of drug being delivered," and that therefore an opto-acoustical trigger follows "by necessity." Ex. 1002, ¶127-128. But none of these assumptions or features are found in any of the three references considered. *Supra* Section III.A-C. Nor does Dr. Donovan cite to authority that they are necessary or required, apart from the conclusory statement that they are "obvious." Ex. 1002.

56. Dr. Donovan admits that Voswinckel does not disclose an opto-acoustical trigger, does not identify the dose delivered, and that "Voswinckel does not expressly state that the nebulizer generated a fixed amount per pulse." Ex. 1002, ¶105, 106, 121. But Dr. Donovan fails to acknowledge that Voswinckel also

does not teach a pulsed ultrasonic nebulizer that allows a human to synchronize each breath to each pulse. Dr. Donovan appears to bypass this entirely as a requirement of the claims. As I discussed above, Voswinckel also does not disclose a method for long-term treatment of pulmonary hypertension where it was concerned primarily with single acute dosing. *Supra* Section III.A.

57. The sole prior art reference that Dr. Donovan relies on for the requirement of an opto-acoustical trigger which allows synchronizing each breath to each pulse is Patton, which she says "would have made this limitation obvious" (not that Patton contains the limitation explicitly). *See*, *e.g.*, Ex. 1002, ¶130 (where Dr. Donovan argues that "combining Voswinckel with the teachings of Patton would have made this limitation obvious," versus making the claim obvious or teaching this limitation.). Dr. Donovan concludes that "Patton teaches that the opto-acoustical trigger is utilized before each and every breath." Dr. Donovan's assertions about Patton are incorrect. Ex. 1002, ¶131; Ex. 1012, 5:23-25.

58. First, Patton does not teach an opto-acoustical trigger used before "each and every breath." Ex. 1002, ¶ 131. Rather, Patton teaches a sequence whereby a patient readies the device by operating the puff size button, presses a button to energize the compressor, which delivers air for mixing and forming a puff to fill a holding chamber, and after the chamber is filled the signals are

activated for several seconds to signal that a patient may take a single breath to empty the chamber. If the patient wishes another dose, he must repeat the entire process: he must ready himself for another inhalation, ready the device to the extent it needs additional drug or puff size setting, press the button to energize the compressor, wait for the compressor to deliver air for mixing with the drug into the holding chamber, look for the light or sound signal that indicates that the puff is ready in the chamber, and take a breath while the holding chamber holds the medicine. There is no teaching in Patton that suggests that this entire process is so quick that it can happen for "each breath" as required by the '240 patent. Rather, it is likely that the patient will have to take several breaks to ready himself or the device before he is able to take another dose. Contrary to Dr. Donovan's conclusions, Patton does not provide a trigger before "each and every" one of the patient's breaths, but only those that the patients decides he is ready for. In other words, the device and timing in Patton is patient-driven whereas the dose timing in the claims of the '240 patent is device-driven. The claims of the '240 patent require the patient to coordinate his breathing to the timing of the device, which is an aspect discouraged and reversed in Patton

59. Since the patient controls the delivery of aerosol, the light and/or sound signals will not occur before "each and every breath" but, rather, only the breaths where the patient chooses to start inhaling. In addition, the signals in

Patton "are activated for several seconds by the timer function," and the holding chamber is intended to "hold" and avoid loss of the puff, permitting the patient some amount of time before they choose to inhale. Ex. 1012, 17:22-24. This allows for the patient to take non-dosed breaths while the signal is activated.

60. Patton does not teach that the "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." Ex. 1002, ¶ 131. Rather, the light and/or audible signal in Patton for several seconds merely "will alert the user that puff is ready to be withdrawn from chamber 42" for the **single** breath necessary to draw out the **single** "puff" from the holding chamber. Ex. 1012, 14:4. The patient can then take any number of breaths without medication until he wishes to repeat a dose. It is not even possible for the device to be configured to deliver a pulse (much less trigger synchronization) of "each breath" as required by the claims. By the same logic, Patton does not **trigger** the patient to immediately breathe to synchronize breathing to pulsing.

61. Second, Patton does not "only create[] aerosol during (at least part) of the inhalation cycle," as Dr. Donovan contends is necessary for her opinion. Ex. 1002, ¶ 127. Rather, Patton generates a "puff" to be held in a holding chamber, and only once the aerosol generation is complete is the patient alerted that they

may inhale. That is, aerosol generation does not occur during an inhalation cycle, but before it.

62. Third, Patton does not require "a human to synchronize each breath to each pulse," as required by the claims of the '240 patent. The '240 patent claims and specification make clear this synchronization requires consecutive timed cycles ("pulsed") of aerosol production and pause such that each consecutive pulse is synchronized with each consecutive breath. *Supra* Section II.B.; Ex. 1001, col. 4:45-46; col. 13:58-60. Patton does not provide for consecutive timed cycles (pulses) to coordinate with consecutive breaths. The only repetition allowed for in Patton is that "[t]he patient will continue activating puffs with button 13b until the prescribed number of puffs have been taken." Ex. 1012, 11:32-34.

63. Dr. Donovan even touts the benefit of the patient simply generating another pulse when they wish to resume if, for example, they are interrupted during an inhalation with a fit of coughing or an urgent phone call. Ex. 1002, ¶ 198. However, Patton explicitly highlights the "inconvenien[ce]" and limitations of "requir[ing] that the patient maintain a constantly rhythmic breathing pattern." Ex. 1012, 3:21-22. Patton also seeks to escape the problem of many patients being incapable of the coordination between activation and inhalation required by

devices such as MDIs. Ex. 1012, 1:32-34. Thus not only does Patton not teach this limitation, it discourages, and teaches away from it.

64. Ghofrani does not fill these gaps in the teaching of Voswinckel and Patton. Ghofrani does not teach chronic treatment of pulmonary hypertension, administering a therapeutically effective single event dose of a formulation comprising 200 to 1000 mcg/ml of treprostinil, a pulsed ultrasonic nebulizer, aerosolization of a fixed amount of treprostinil per pulse, an opto-acoustical trigger, or synchronization of each breath to each pulse. Ex. 1005. Moreover, as I discussed above, Ghofrani does not teach, as Dr. Donovan suggests, that the doses delivered in Voswinckel were 15mcg to 90 mcg. *Supra* Section III.B.

65. Dr. Donovan does not cite to any prior art reference that discloses the dependent claim limitation of claim 4 that "the single event dose produces a peak plasma concentration of treprostinil about 10-15 minutes after the single event dose." Instead, she argues that this limitation is "inherent" to treatment with treprostinil. Ex. 1002, ¶147. Her sole reference for the argument of this limitation is the specification of the '240 patent itself. She cites to nothing outside the '240 patent specification that demonstrates that a POSA would have known or caused the peak plasma concentration of 10-15 minutes following a single event dose.

2. A POSA would not have a motivation to combine Voswinckel, Patton, and Ghofrani with a reasonable expectation of success.

66. Dr. Donovan also talks about a "clear motivation in the art to combine these elements with a reasonable expectation of success in doing so." Ex. 1002, ¶102. Dr. Donovan makes the following arguments regarding motivations to combine the teachings of Voswinckel and Patton:

- A POSA would be motivated to combine Patton's teaching of strategies to deliver a pulsed dose precisely and efficiently with the therapeutically efficacious treatment with treprostinil disclosed by Voswinckel. Ex. 1002, ¶ 105.

- 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, with a reasonable expectation of success because it simply seeks to improve upon the successful treatment already achieved. Ex. 1002, ¶ 125.

- 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." Ex. 1002, ¶ 132.

67. Every motivation Dr. Donovan alleges to combine the teachings of Patton and Voswinckel relies on the strategies of reliability, precision, and efficiency allegedly reflected by the parameters and configurations implemented in Patton's device. However, the device in Patton is not an ultrasonic nebulizer, let alone a pulsed ultrasonic nebulizer or a nebulizer that requires synchronizing each breath to each pulse. *Supra* Section III.C.

68. Dr. Donovan touts the accurate measurement and delivery of single breath doses on simple and reliable equipment in Patton, but these features are taught only with respect to the device in Patton, which uses a compressor. Ex. 1002, ¶124. Therefore, a POSA looking at Patton would be lead to using the relatively simple compressor-based device in Patton to administer a drug, not the far more complex pulsed ultrasonic nebulizer of the claims. Ex. 2003, 26, 28. In further view of Voswinckel, a POSA might, at best, attempt to administer treprostinil via the device disclosed in Patton. This device is not a pulsed ultrasonic nebulizer, does not deliver periodic pulses of aerosolization, and does not require (and in fact discourages) breath synchronization.

69. Looking at all three of Voswinckel, Ghofrani, and Patton as relevant reference, a POSA would not, in 2006, be motivated to decide on a pulsed ultrasonic nebulizer with unknown and undisclosed characteristics against the multiple other options of jet nebulizers, metered dose inhalers, breath actuated devices, and continuous nebulizers presented in those references as successful. In fact, the only approved inhaled prostacyclin treatment in the U.S., Ventavis, used a jet nebulizer, the Prodose® ADD® System. Ex. 2046, 6.

70. A POSA would appreciate that ultrasonic nebulizers were known to have limitations. For example, it was known that not every drug can be adapted for use in an ultrasonic nebulizer because "[u]ltrasonic nebulizers…may cause drug degradation," among other reasons. Ex. 2044, 1. Additionally, while ultrasonic nebulizers may have a higher output rate than jet nebulizers, they often retain a higher dead volume and produce a coarser aerosol than air jet nebulizers. Ex. 2045, 7.

71. Under Dr. Donovan's reasoning and reliance on Patton, the significant detail provided in Patton on a successful device would lead a POSA to that device, a jet nebulizer with patient-driven dosing and a holding chamber to guide dosing, over a pulsed ultrasonic nebulizer, particularly one with the requirements of breath synchronization, which is expressly discouraged in Patton.

72. Another reason a POSA would not have had a reasonable expectation that the claimed dosing regimen would have succeeded using treprostinil in a pulsed ultrasonic nebulizer would have been the unknown pharmacodynamics of inhaled treprostinil in such a method. Dr. Donovan mistakenly appears to believe that the claimed dosing regimen is expected from treprostinil's known properties as an intravenous/subcutaneous drug, stating:

> 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.

Ex. 1002, ¶213. Her conclusion that the benefits of inhaled treprostinil are based on stability and "half-life" which have been "known for years", presumably a reference to properties of the known subcutaneous and intravenous treprostinil products, illustrates a basic misunderstanding of how inhaled prostacyclin drugs exert their effects in pulmonary hypertension patients, as well as a failure to understand pharmacodynamics of inhaled therapies. Circulatory half-life and stability are only part of the considerations. When a prostacyclin like treprostinil is administered in inhaled form, some of the inhaled drug exerts its biological effect locally after passing into the diseased pulmonary vasculature – therefore the

circulatory half-life has nothing to do with this portion of an inhaled therapy's duration of action. Dr. Donovan's view is contradicted by Ex. 2047, 5 (noting "[t]he general rationale for aerosolized drug delivery to the airways for treating respiratory disease is the local delivery of the drug to the target organ, with reduced or minimal body exposure to the drug and hopefully reduced prevalence or severity of possible side effects"). Also, how much drug is inhaled in each breath and the time between pulses/breaths will affect the extent to which any of the inhaled drug spills over into circulation. In addition, some aerosolized solutions of drug transit more quickly or slowly across the membranes of the lungs and into the blood vessels as they interact with "secretions in the lumen, nerve endings, cells (e.g., mast cells), or bronchial smooth muscle in the airway wall," which will also affect duration of activity in pulmonary hypertension patients. Ex. 2047, 13. By using a fixed amount of drug in each pulse and spacing apart the pulses with an opto-acoustical trigger that synchronizes the patient's breaths to each pulse, this can prevent excessive spill-over into circulation, which could otherwise cause unacceptable side effects that interfere with patient compliance. Similarly, the type of inhalation device can have an impact on duration of action. Ex. 2047, 13 (noting "the exact percentage [of inhaled drug reaching the targeted part of the lungs] can vary with different delivery devices or techniques of patient use from 10% to 30%"). Aerosolized drug will be distributed in the throat and lungs in a

different way depending on the device used, which further impacts duration of action by affecting the balance between locally deposited drug in the lungs and systemic drug that enters the circulation. Ex. 2047, 11-17. For these reasons, I disagree with Dr. Donovan's conclusion that a POSA would have predicted the success of the claimed methods simply by knowing treprostinil's circulatory half-life and stability.

IV. OBJECTIVE INDICIA

73. The '240 patent is listed in the Orange Book for the product Tyvaso® (treprostinil) Inhalation Solution, a drug-device combination for delivery of treprostinil by inhalation. Ex. 2012.

74. The use of the Tyvaso®, in the intended manner and as taught by United Therapeutics' label and package insert practices claims 1-9 of the '240 patent. Indeed, Tyvaso®, the only form of approved inhaled treprostinil, requires use of a pulsed ultrasonic nebulizer with an opto-acoustical trigger to deliver therapeutically effective amounts via inhalation. As provided in Tyvaso's Instructions for Use, the Tyvaso® contains a pulsed ultrasonic nebulizer comprising an opto-acoustical trigger. The Tyvaso® Prescribing Information explicitly describes the nebulizer as "an ultrasonic, pulsed delivery device." Pulsed indicates that the nebulizer intermittently generates aerosol rather than continuously generating aerosol. Ultrasonic indicates that the device uses vibration of a piezoelectric element to generate drug containing droplets.

75. The device uses light and sound to trigger each time the patient must inhale through the mouthpiece in successive breaths, with the intent of triggering inhalation at the same time as a bolus of aerosol is being generated. The optical component takes the form of a green flashing inhalation indicator light and the

acoustical component takes the form of a single short beep. This opto-acoustical trigger is the mechanism by which the patient is prompted to synchronize each inhalation to each pulse of aerosol generation.

76. The unique features of the claimed nebulizer (*e.g.*, the combination of visible and audible signals designed to prompt the correct number of inhalations, and inhalations coordinated with aerosol generation), together with its more convenient dosing regimen, are critical to the device's ability to deliver precise drug doses that balance safety and efficacy. These features also contribute to higher patient compliance.

77. In the United States, there are only two inhaled prostacyclins approved for the treatment of pulmonary hypertension: Tyvaso ® (inhaled treprostinil) and Ventavis ® (inhaled iloprost). Ventavis® differs from Tyvaso® in terms of active agent and in the dose and device with which it is administered. When inhaled therapeutics were first being developed for pulmonary hypertension, it was believed that inhaled iloprost would be superior to inhaled treprostinil because iloprost was considered a "more potent" prostanoid. Because of the focus in the art on inhaled iloprost, Ventavis® entered the market five years before Tyvaso ®. Despite the fact that Ventavis® was the first of the two products to

market, clinicians such as myself rapidly switched to prescribing Tyvaso® after its approval. Ex. 1162, 22-23. A number of factors contributed to this shift.

78. First, Tyvaso® required less frequent administration (1-4 times a day) because of its high dose – from 15 μg to 90 μg – and relatively short time of administration – 1 to 18 breaths. *See also* Ex. 1162, 23-24; Ex. 1163, 26-27. Ventavis®, on the other hand, cannot be provided at high doses and needs to be used 6-9 times a day, as frequent as every 2 hours. Ex. 1162, 23. This property is tied to the unexpected pharmacodynamic properties between inhaled treprostinil and iloprost, leading to a longer duration of action for inhaled treprostinil. *Id.*

79. Second, both patients and clinicians preferred the device with which Tyvaso® was administered – a pulsed ultrasonic nebulizer with an opto-acoustical trigger. Ventavis® employs a breath-actuated nebulizer, which adjusts the dose amount to the volume of the breath a patient takes in. Ex. 2005, 36.

80. From a patient standpoint, the Ventavis® device is disfavored because the time of engagement with the device is dependent on the patient's breathing pattern. *Id.* This means that the time of engagement can range up to 10-20 min. In addition, each time the patient uses the device, the patient must load the drug, use the device, take apart the device, remove the mesh, and then clean the device, making each use a time-intensive process. *Id.* My patients, for example, reported

that they disliked the device, the frequency of use, and the side effects and, hence, had poor compliance when prescribed Ventavis®. I saw minimal improvement, if at all, in pulmonary hypertension patients prescribed Ventavis®. In contrast, patients prescribed Tyvaso® found its device easy to use. The device requires a minimal effort on their end to take in the dose with a breath, since the opto-acoustical trigger informs them when to breathe in.

81. From a clinician standpoint, the Ventavis® device is disfavored because it does not provide a clear idea of what dose is being delivered – both due to the breath-actuated delivery and the lack of patient compliance. Since patients use the device between 6-9 times a day with a variable number of breaths, it is difficult for a clinician to determine what dose is being delivered to the patient on each administration. Further, due to issues with compliance, even a dose based on estimated breath number per engagement with device could be incorrect, since the patient may not actually be using the device with the correct frequency. In contrast, the Tyvaso® device provides a clear dose per breath, which in turn can be titrated by a clinician so each patient gets a set dose. With controlled titration, the

dose can be adapted to minimize side effects that a patient might experience with inhaled treprostinil.[1]

82. Studies have shown a statistically significant improvement in quality of life reported by pulmonary hypertension patients who switched from inhaled iloprost to inhaled treprostinil. This difference is directly related to the beneficial claim limitations of the single event dosing, including the numbers of breaths, concentration, dose, Tmax, time between single event doses, and ease of use of the device. Ex. 2021, 5. Additionally, "the transition from inhaled iloprost to inhaled treprostinil resulted in a time savings of approximately 1.4 h per day." *Id.* Patients transitioning from inhaled iloprost to inhaled treprostinil had improved six-minute walk distances (a common metric to assess pulmonary hypertension), improved patient satisfaction, and improved quality of life. Ex. 2021, 5-6.

83. Taking into account the aforementioned considerations, I have not used Ventavis® in clinical practice for a number of years, and I have heard few, if any,

[1] It should be noted that, unexpectedly, at high doses inhaled treprostinil has fewer side effects compared to inhaled iloprost. However, the use of the pulsed ultrasonic nebulizer with opto-acoustical trigger allows for the further advantage of minimizing these side effects in a manner unrelated to the properties of the different drugs.

complaints regarding the use of Tyvaso®. I have reviewed both declarations submitted during the prosecution of the '240 patents in which Dr. Zamanian reports similar conclusions. Ex. 1162, 19-39; Ex. 1163, 23-28. I agree with the conclusions he drew in these declarations and find they are consistent with my clinical experience. Specifically, I agree that there is a nexus between the claimed features of the '240 patent and the success of Tyvaso given the advantages described above.

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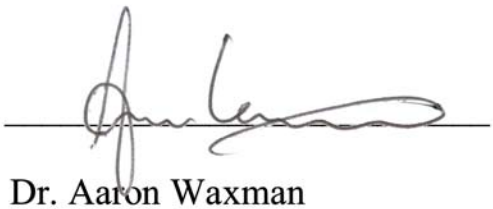
V. CONCLUSION

84. I hereby declare that all statements made herein of my 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 false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code.

Date: April 26, 2018



Dr. Aaron Waxman