UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

WATSON LABORATORIES, INC.,
Petitioner,

v.

UNITED THERAPEUTICS, INC.,
Patent Owner.

Case No. IPR2017-01621
Patent No. 9,358,240

PETITION FOR INTER PARTES REVIEW OF U.S. PATENT NO. 9,358,240

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TABLE OF CONTENTS

PETITIONER'S EXHIBIT LIST

Exhibit	Description
1001	U.S. Patent No. 9,358,240
1002	Declaration of Maureen D. Donovan in Support of the Petition for Inter Partes Review of U.S. Patent No. 9,358,240
1003	Robert Voswinckel, et al. "Inhaled treprostinil sodium for the treatment of pulmonary hypertension" Abstract #1414, *Circulation*, 110, 17, Supplement (Oct. 2004): III-295 ("Voswinckel")
1004	U.S. Patent Application Publication No. 2004/0265238 A1 to Chaudry ("Chaudry")
1005	Hossein Ardeschi Ghofrani, Robert Voswinckel, et al., "Neue Therapieoptionen in der Behandlung der pulmonalarteriellen Hypertonie," Hertz, 30,4 (June 2005): 296-302 ("Ghofrani")
1006	Opti-Neb-ir® Operating Instructions, Model ON-100/2 (2005)
1007	RESERVED
1008	Venta-Neb-ir® A-I-C-I Operating Instructions, Model VN-100/4
1009	Annexes to Commission Decision C(2005)3436 of 05 September 2005, http://ec.europa.eu/health/documents/community-register/2005/2005090510259/anx_10259_en.pdf (Annex III – Ventavis® Labelling and Package Leaflet)
1010	U.S. Patent No. 6,606,989 ("Brand '989")
1011	Amendment and Reply Accompanying RCE filed in 12/591,200 (Jul. 2, 2013) (with accompanying Declaration of Lewis Rubin, M.D.)
1012	WO 93/00951 to Patton
1013	Declaration of Scott Bennett, Ph.D.
1014	Affidavit of Christopher Butler, June 15, 2017
1015	Affidavit of Christopher Butler, June 16, 2017
1016	RESERVED
1017	RESERVED
1018	U.S. Patent No. 6,521,212 ("Cloutier '212")
1019	U.S. Patent No. 4,306,075 ("Aristoff '075")
1020	U.S. Patent No. 5,190,972 ("Dumble '972")
1021	European Patent Specification 0347243 B1, published January 13, 1993
1022	U.S. Patent No. 6,261,539 ("Adjei '539")
1023	European Patent Application Publication No. EP 0372777 A2 ("Purewal EP '777")
1024	U.S. Patent No. 4,895,719 ("Radhakrishnan '719")

1025	U.S. Patent No. 5,153,222 ("Tadepalli '222")
1026	U.S. Patent No. 6,357,671 ("Cewers '671")
1027	Gessler, et al., *Ultrasonic versus Jet Nebulization of Iloprost in Severe Pulmonary Hypertension*, Eur. Respiratory J., 17:14-19 (2001)
1028	Olschewski H., et al., *Aerosolized Prostacyclin and Iloprost in Severe Pulmonary Hypertension*, 1996 Ann. Intern. Med. 124(9), 820-824 (1996) ("Olschewski 199")
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)
1030	Byron, *Drug Delivery Devices: Issues in Drug Development*, Proc. Am. Thorac. Soc., 1:321-328 (2004)
1031	U.S. Patent No. 5,544,646 ("Lloyd")
1032	Edwards D.A. et al., *Recent Advances in Pulmonary Drug Delivery Using Large Porous Inhaled Particles*, Journal of Applied Physiology, 85(2): 379-385 (1998) ("Edwards 1998")
1033	Badesch, et al., *Prostanoid Therapy for Pulmonary Arterial Hypertension*, J. of the Am. C. of Cardiology, 43(12):Suppl. S (2004)
1034	U.S. Patent No. 6,054,486 ("Crow '486")
1035	U.S. Food and Drug Administration, Drug Approval Package: Remodulin® (approved on May 21, 2002), http://www.accessdata.fda.gov/drugsatfda_docs/nda/2002/21-272_Remodulin.cfm ("Remodulin® Approval Package")
1036	Electronic Medicines Compendium, Ventavis®, http://www.medicines.org.uk/emc/medicine/13743
1037	*European Agency Approves Ventavis for Primary Pulmonary Hypertension*, P&T Community (Sep. 22, 2003), https://www.ptcommunity.com/news/2003-09-22-000000/european-agency-approves-ventavis-primary-pulmonary-hypertension
1038	EU Community Register of Medicinal Products, Homepage, http://ec.europa.eu/health/documents/community-register/html/index_en.htm
1039	EMEA Scientific Discussion, Ventavis® (2004), http://www.ema.europa.edu/docs/en_GB/document_library/EPAR_Scientific_Discussion/human/000474/WC500048688.pdf
1040	Muller et al., "Use of Inhaled Iloprost in a Case of Pulmonary Hypertension during Pediatric Congenital Heart Surgery," 99 Anesthesiology 743-747 (2003)

1041	Mueller et al., "Inhaled Iloprost in the Management of Pulmonary Hypertension in Infants Undergoing Congenital Heart Surgery," 21 Eur. J. Anaesthesiology (suppl. 33) 2-36 (2004)
1042	Commission Decision C(2005)3436 of 05 September 2005, http://ec.europa.eu/health/documents/community-register/2005/2005090510259/dec_10259_en.pdf
1043	EU Community Register of Medicinal Products for Human Use, Ventavis, http://ec.europa.eu/health/documents/community-register/html/h255.htm#
1044	Summary of Community Decisions, Official Journal of the European Union (Oct. 28, 2005) http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.C_.2005.268.01.0002.01.ENG&toc=OJ:C:2005:268:TOC (noting a modification of marketing approval for Ventavis®)
1045	Electronic Medicines Compendium, Ventavis®, http://www.medicines.org.uk/emc/history/13743#version1 (noting a change to section 4.2 – Posology and Method of Administration on September 22, 2005)
1046	Voswinckel, R., et al., "Inhaled treprostinil is a potent pulmonary vasodilator in severe pulmonary hypertension," 25 European Heart Journal 22, at 218 (2004) ("Voswinckel II")
1047	Sulica, R and Poon, M. "Medical Therapeutics for Pulmonary Arterial Hypertension From Basic Science and Clinical Trial Design to Evidence-Based Medicine." 3(2) Expert Rev. Cardiovas. Ther. 347-360 (2005)
1048	*American Heart Association's Scientific Sessions 2004 – Largest Cardiovascular Meeting Plans to 'Jazz It Up' in New Orleans*, PR Newswire (Oct. 13 2004), http://www.prnewswire.com/news-releases/american-heart-associations-scientific-sessions-2004---largest-cardiovascular-meeting-plans-to-jazz-it-up-in-new-orleans-74293197.html#
1049	EU Community Register of Medicinal Products, Frequently Asked Questions, http://ec.europa.eu/health/documents/community-register/register_faq_2015.pdf
1050	Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004, http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:136:0001:0033:en:PDF
1051	Register of Commission Documents, European Union, https://ec.europa.eu/transparency/regdoc/index.cfm?fuseaction=home

1052	Regulation (EC) No. 1049/2001 of the European Parliament and of the Council of 30 May 2001, http://www.europarl.europa.eu/RegData/PDF/r1049_en.pdf
1053	Register of the Commission Documents, European Commission, https://ec.europa.eu/transparency/regdoc/index.cfm?fuseaction=list&n=10&adv=0&coteId=&year=2005&number=3436&version=ALL&dateFrom=&dateTo=&serviceId=&documentType=&title=&titleLanguage=&titleSearch=EXACT&sortBy=NUMBER&sortOrder=DESC (search result for document search of Commission reference number '3436' for year '2005')
1054	U.S. Patent No. 5,234,953 ("Crow '953")
1055	Declaration of DeForest McDuff, Ph.D.
1056	U.S. Patent No. 9,339,507
1057	U.S. Patent No. 6,756,033
1058	Amendment and Reply filed in 12/591,200 (May 23, 2012) (with accompanying Declaration of Lewis Rubin, M.D.)
1059	Reply in 12/,591,200 (Apr. 28, 2014)
1060	William F. Ganong, Review of Medical Physiology 591-92 (17th ed. 1995)
1061	Actelion Pharmaceuticals, "Actelion Announces Full Year 2003 Financial Results" (March 2, 2004)
1062	Actelion Pharmaceuticals, "Actelion Announces Full Year 2005 Financial Results" (Feb. 23, 2006)
1063	Actelion Pharmaceuticals, Annual Report, 2002
1064	Actelion Pharmaceuticals, Annual Report, 2006
1065	Actelion Pharmaceuticals, Annual Report, 2007
1066	Actelion Pharmaceuticals, Annual Report, 2008
1067	Actelion Pharmaceuticals, Annual Report, 2010
1068	Actelion Pharmaceuticals, Annual Report, 2011
1069	Actelion Pharmaceuticals, Annual Report, 2012
1070	Actelion Pharmaceuticals, Annual Report, 2013
1071	Actelion Pharmaceuticals, Annual Report, 2014
1072	Actelion Pharmaceuticals, Annual Report, 2015
1073	Actelion Pharmaceuticals, Annual Report, 2016
1074	Adcirca, FDA Label, 5/2017
1075	Adempas, FDA Label, 10/2016
1076	Bayer, Annual Report, 2014
1077	Bayer, Annual Report, 2015

1078	Bayer, Annual Report, 2016
1079	*Highest paid female CEO: Race to save my daughter*, CNBC (May 19, 2015), http://www.cnbc.com/2015/05/19/highestpaidfemaleceoracetosavemydaughter.html
1080	Cowen and Company, "Biotechnology Quarterly" (Jan. 2011)
1081	Cowen and Company, "GlaxoSmithKline plc" (Sep. 14, 2015)
1082	Cowen and Company, "GlaxoSmithKline plc," (May 16, 2016)
1083	Cowen and Company, "Therapeutic Categories Outlook," Feb. 2017
1084	DiMasi, Joseph A. and Henry G. Grabowski (2012), "R&D Costs and Returns to New Drug Development: A Review of the Evidence," in Patricia Danzen and Sean Nicholson, ed., *The Oxford Handbook of the Economics of the Biopharmaceuticals Industry*, New York: Oxford University Press
1085	Approved Drug Products with Therapeutic Equivalance Evaluations ("Orange Book"), FDA (30th ed. 2010)
1086	Approved Drug Products with Therapeutic Equivalance Evaluations ("Orange Book"), FDA (37th ed. 2017)
1087	FDA Drug Details Website, Adcirca, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process (accessed 5/17/2017)
1088	FDA Drug Details Website, Adempas, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process (accessed 5/17/2017)
1089	FDA Drug Details Website, Flolan, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process (accessed 5/17/2017)
1090	FDA Drug Details Website, Letairis, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process (accessed 5/17/2017)
1091	FDA Drug Details Website, Opsumit, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process (accessed 5/17/2017)
1092	FDA Drug Details Website, Orenitram, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process (accessed 5/17/2017)
1093	FDA Drug Details Website, Remodulin, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process (accessed 5/17/2017)

1094	FDA Drug Details Website, Revatio, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process (accessed 5/17/2017)
1095	FDA Drug Details Website, Tracleer, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process (accessed 5/17/2017)
1096	FDA Drug Details Website, Tyvaso, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process (accessed 5/17/2017)
1097	FDA Drug Details Website, Uptravi, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process (accessed 5/17/2017)
1098	FDA Drug Details Website, Veletri, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process (accessed 5/17/2017)
1099	FDA Drug Details Website, Ventavis, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process (accessed 5/17/2017)
1100	Federal Reserve Website, Data Download, CHF to USD, 1998-2016, https://www.federalreserve.gov/datadownload/Preview.aspx?pi=400&rel=H10&preview=H10/ H10/RXI_N.A.SZ (accessed 4/25/2017)
1101	Federal Reserve Website, Data Download, USD to EUR, 1999-2016, https://www.federalreserve.gov/datadownload/Preview.aspx?pi=400&rel=H10&preview=H10/ H10/RXI$US_N.A.EU (accessed 4/25/2017)
1102	Federal Reserve Website, Data Download, USD to GBP, 1998-2016, https://www.federalreserve.gov/datadownload/Preview.aspx?pi=400&rel=H10&preview=H10/ H10/RXI$US_N.A.UK (accessed 4/25/2017)
1103	Flolan, FDA Label, 4/2015
1104	Gilead, Form 10-K, 2009
1105	Gilead, Form 10-K, 2010
1106	Gilead, Form 10-K, 2011
1107	Gilead, Form 10-K, 2012
1108	Gilead, Form 10-K, 2013
1109	Gilead, Form 10-K, 2014
1110	Gilead, Form 10-K, 2015
1111	Gilead, Form 10-K, 2016
1112	GlaxoWellcome, Annual Report, 1997

1113	Grabowski, Henry, John Vernon, and Joseph A. DiMasi (2002), "Returns on Research and Development for 1990s New Drug Introductions," *Pharmacoeconomics* 20(3): 11–29
1114	GSK, Annual Report, 2010
1115	GSK, Annual Report, 2011
1116	GSK, Annual Report, 2012
1117	GSK, Annual Report, 2013
1118	GSK, Annual Report, 2016
1119	Letairis, FDA Label, 10/2015
1120	Mayo Clinic Website, Pulmonary hypertension, Overview, http://www.mayoclinic.org/diseasesconditions/ pulmonary-hypertension/home/ovc-20197480 (accessed 3/22/2017)
1121	*Merck & Co. v. Teva Pharmaceuticals USA, Inc.*, 395 F.3d 1364 (Fed. Cir. 2005)
1122	NIH Website; National Heart, Lung, and Blood Institute; Types of Pulmonary Hypertension, https://www.nhlbi.nih.gov/health/health-topics/topics/pah/types (accessed 5/16/2017)
1123	Opsumit, FDA Label, 3/2017
1124	Orenitram, FDA Label, 1/2017
1125	Pfizer, Annual Report, 2005
1126	Pfizer, Annual Report, 2006
1127	Pfizer, Annual Report, 2009
1128	Pfizer, Annual Report, 2010
1129	Pfizer, Annual Report, 2011
1130	Pfizer, Annual Report, 2012
1131	Pfizer, Annual Report, 2013
1132	Pfizer, Annual Report, 2014
1133	Pfizer, Annual Report, 2015
1134	Pfizer, Annual Report, 2016
1135	RBC Capital Markets, "Untied Therapeutics Corp.," 6/13/2011
1136	Remodulin, FDA Label, 12/2014
1137	Revatio, FDA Label, 4/2015
1138	St. Louis Federal Reserve, Consumer Price Index, https://fred.stlouisfed.org/series/CPIAUCSL (accessed 5/17/2017)
1139	Tracleer, FDA Label, 10/2016
1140	Tyvaso, FDA Label, 06/2016
1141	Uptravi, FDA Label, 12/2015
1142	UTC, "Q2 2010 United Therapeutics Earnings Conference Call," 7/28/2010

1143	UTC, Form 10-K, 2000
1144	UTC, Form 10-K, 2002
1145	UTC, Form 10-K, 2003
1146	UTC, Form 10-K, 2004
1147	UTC, Form 10-K, 2005
1148	UTC, Form 10-K, 2006
1149	UTC, Form 10-K, 2007
1150	UTC, Form 10-K, 2008
1151	UTC, Form 10-K, 2009
1152	UTC, Form 10-K, 2010
1153	UTC, Form 10-K, 2011
1154	UTC, Form 10-K, 2012
1155	UTC, Form 10-K, 2013
1156	UTC, Form 10-K, 2014
1157	UTC, Form 10-K, 2015
1158	UTC, Form 10-K, 2016
1159	Veletri, FDA Label, 6/2012
1160	Ventavis, FDA Label, 11/2013
1161	Request for Review filed in 12/591,200 (Mar. 9, 2015)
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)
1164	Final Rejection of 12/591,200 (Oct. 10, 2014)

I. INTRODUCTION

This Petition seeks *inter partes* review—and ultimately the cancellation of—claims 1-9 of U.S. Patent No. 9,358,240, which relates to a method of treating pulmonary hypertension using a pulsed ultrasonic nebulizer and a formulation of a drug called treprostinil. As we show below, the '240 patent claims are invalid and should be cancelled.

On November 10, 2004, a group of researchers—including some of the named inventors on the '240 patent—presented the findings of a study that involved the aerosolized delivery of treprostinil with a pulsed ultrasonic nebulizer for the treatment of patients with pulmonary hypertension at a widely-attended American Heart Association conference in Louisiana. Abstracts of the presentations were published before the conference in a supplement to the widely-distributed periodical *Circulation*. This abstract, which we will call "Voswinckel," put the public in possession of everything needed to arrive at the claimed subject matter. Instead of promptly seeking a patent, those identifying themselves as inventors of the '240 patent waited. They waited roughly nineteen months before filing the provisional application to which the '240 patent claims priority. Under the law, they waited too long.

Allowing the '240 patent claims to stand in light of knowledge that was placed in the public domain in November 2004 is at odds with some of the most

fundamental concepts in United States patent law. As has long been the law, § 102(b) "presents a sort of statute of limitations, formerly two years, now one year, within which an inventor, even though he has made a patentable invention, must act on penalty of loss of his right to a patent." *Application of Foster*, 343 F.2d 980, 987-88 (CCPA 1965). The clock starts running when the public is placed in possession of the claimed subject matter "through the categories of the disclosure enumerated in 102(b), which include a 'printed publication' anywhere describing the invention." *Id.* at 988. Although the patent laws do not allow inventors to recapture that which they placed in the public domain more than a year before their earliest filings by making minor, obvious variations upon their public disclosures, *id.*, that's precisely what has happened here.

While Voswinckel does not expressly disclose some of the minor details of the claims, those details would have been blatantly obvious to those skilled in the art. For example,

- Using pulsed ultrasonic nebulizers having audible and visual indicators instructing the user when to breathe was well-known in the art; and
- The dosing specified by the claims was also not only specifically described by a separate printed publication discussing inhalable treprostinil, but it was readily derivable from the manual for the

OptiNeb® nebulizer described by Voswinckel based on the skill and knowledge of an ordinarily skilled artisan.

As we show below, none of the claims contribute significantly to the disclosure of Voswinckel. They recite only minor, known differences. Accordingly, they should each be cancelled as unpatentable under 35 U.S.C. § 103(a).

II. MANDATORY NOTICES – 37 C.F.R. § 42.8

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

Watson Laboratories, Inc. is the real party-in-interest for the purposes of this proceeding. Out of an abundance of caution, Petitioner identifies Teva Pharmaceuticals USA, Inc., Teva Parenteral Medicines, Inc., Pliva Hrvatska D.O.O., and Barr Laboratories, Inc.[1] as real parties-in-interest for the IPR requested by this Petition solely to the extent that Patent Owner contends that these separate legal entities should be named a real party-in-interest in the requested IPR, and the

[1] The following entities are parent corporations and/or publicly-held companies that own 10 percent or more of the stock of the Teva real parties-in-interest: Sicor Inc.; Teva Pharmaceuticals Holdings Cooperatieve, U.A.; IVAX LLC; Orvet UK; Teva Pharmaceuticals Europe B.V.; Teva Pharmaceuticals Industries Ltd.; Barr Pharmaceuticals, LLC; Ivax International B.V.; IVAX International GmbH; Ivax International (Luxembourg) S.a.r.l.;and IVAX Holdings GmbH.

Petitioner does so to avoid the potential expenditure of resources to resolve such a challenge. Watson Laboratories, Inc. is an indirectly-owned, wholly owned subsidiary of Teva Pharmaceuticals USA, Inc. No unnamed entity is funding, controlling, or otherwise has an opportunity to control or direct this Petition or the Petitioner's participation in any resulting IPR.

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

Patent Owner has asserted the '240 patent in the United States District Court for the District of New Jersey in case No. 3:15-cv-5723. Petitioner is the defendant in that action. Petitioner is also filing petition IPR2017-01622 related to U.S. Pat. No. 9,339,507. The '240 patent and the '507 patent share a common parent and provisional application.

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

Lead: Michael K. Nutter (Reg. No. 44,979, WINSTON & STRAWN LLP, 35 W. Wacker Dr., Chicago, IL 60601, P: 312-558-5600 / F: 312-558-5700, mnutter@winston.com). Backup: Andrew R. Sommer (Reg. No. 53,932, WINSTON & STRAWN LLP, 1700 K Street, N.W., Washington, D.C. 20006-3817, P: 202-282-5896 / F: 202-282-5100, asommer@winston.com); Kurt A. Mathas (*pro hac vice* motion to be filed, WINSTON & STRAWN LLP, 35 W. Wacker Dr., Chicago, IL 60601, P: 312-558-5600 / F: 312-558-5700, kmathas@winston.com).

D. Service Information Under 37 C.F.R. § 42.8(b)(4)

Service via hand-delivery may be made at the postal mailing address of lead and back-up counsel. Petitioner consents to service by e-mail at the following email address: IPR2017-01621@winston.com.

III. REQUIREMENTS FOR IPR – 37 C.F.R. § 42.104

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

Petitioner certifies that the ’240 patent is available for *inter partes* review (“IPR”). Petitioner is not barred or estopped from requesting this IPR. Petitioner is filing this petition within one year of being served with a complaint alleging infringement of the ’240 patent. Patent Owner filed an amended complaint asserting the ’240 patent on June 21, 2016, which was the date Watson is deemed served with the amended complaint under the Federal Rules. Dkt No. 49; Fed. R. Civ. P. 15(a)(2), (3).

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

Petitioner requests cancellation of claims 1-9 of the ’240 patent in view of the following prior art references: (1) Robert Voswinckel, et al. “Inhaled treprostinil sodium for the treatment of pulmonary hypertension” Abstract #1414, *Circulation*, 110, 17, Supplement (October 2004): III-295 (“Voswinckel”); (2) Hossein Ardeschi Ghofrani, Robert Voswinckel, et al., “Neue Therapieoptionen in der Behandlung der pulmonalarteriellen Hypertonie,” Hertz, 30,4 (June 2005): 296-302 (“Ghofrani”);

(3) WO 93/00951 to Patton ("Patton"); (4) OptiNeb®-ir Operating Instructions ("OptiNeb® User Manual"); and (5) Annexes to Commission Decision C(2005)3436 of 05 September 2005, (Annex III – Ventavis® Labelling and Package Leaflet) ("EU Community Register"). Each of these references is a prior art printed publication or patent under 35 U.S.C. § 102 (pre-AIA).

Petitioner presents the following grounds for trial:

Ground:	**Claims**	**Reference(s):**
Ground 1	1-9	Obvious over Voswinckel in view of Patton and Ghofrani
Ground 2	1-9	Obvious over Voswinckel in view of Patton and the OptiNeb® User Manual
Ground 3	1-9	Obvious over Voswinckel in view of Ghofrani and the EU Community Register.

C. Claim Construction Under 37 C.F.R. §§ 42.100(b), 42.104(b)(3)

Under 37 C.F.R. § 41.100(b), a claim of an unexpired patent is given its broadest reasonable interpretation in light of its specification. *See Cuozzo Speed Techs., LLC v. Lee*, 136 S.Ct. 2131 (2016). For the purposes of this proceeding, all terms should have their broadest reasonable interpretation when the claims are read

in light of the ’240 patent’s specification, as would have been understood by a POSA.

Consistent with an agreement reached in the district court litigation between the parties under the more restrictive *Phillips* standard for claim construction, 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).” Dkt. No. 66. 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. *See* Ex. 1001, 13:57-62 (referring to the prior art VENTA-NEB® device from Nebu-Tec as a device having an opto-acoustical trigger); Ex. 1002, ¶69.

D. How the Construed Claims are Unpatentable Under 37 C.F.R. § 42.104(b)(4)

See infra § VII.

E. Supporting Evidence Under 37 C.F.R. § 42.104(b)(5)

Each ground for trial is supported by the expert testimony of Maureen D. Donovan, Ph.D. (Ex. 1002), DeForest McDuff, Ph.D (Ex. 1055), and Scott Bennett, Ph.D (Ex. 1013) and other exhibits identified throughout this Petition and the supporting declarations.

IV. THE CHALLENGED CLAIMS

Claim 1 recites:

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,

[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.

Ex. 1001 at 18:1-38.

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

V. LEVEL OF ORDINARY SKILL IN THE ART

As of the May 2006 filing date of the provisional application that the ’507 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 drug by inhalation. Ex. 1002, ¶[74. 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. *Id.* 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. *Id.* 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. *Id.* 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. *Id.* In this Petition, reference to a POSA refers to a person with these qualifications.

VI. DETAILED EXPLANATION UNDER 37 C.F.R. § 42.104(B)

A. All References Relied Upon as Grounds for Trial Are Prior Art to the '240 Patent

1. Applicable Legal Standards

"[P]ublic accessibility' has been called the touchstone in determining whether a reference constitutes a 'printed publication' . . . ." *Suffolk Technologies, LLC v. AOL Inc.*, 752 F.3d 1358, 1364 (Fed. Cir. 2014). A reference may be publicly

accessible if other references gave the POSA a "roadmap" to the reference in question. As the Federal Circuit has said, a "given reference is 'publicly accessible' upon a satisfactory showing that such document has been disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art exercising reasonable diligence, can locate it." *Bruckelmyer v. Ground Heaters, Inc.*, 445 F.3d 1374, 1378 (Fed. Cir. 2006); *Cornell Univ. v. Hewlett–Packard Co.*, No. 01–cv–1974, 2008 WL 11274580, at *6 (N.D.N.Y. May 14, 2008) (finding that an article in a "seminal publication in the field of electrical engineering" with an explicit citation to the allegedly invalidating reference was a research aid that made the sought-after reference publicly accessible). Although distribution and indexing in a library are "helpful," they are not required. *In re Klopfenstein*, 380 F.3d 1345, 1350 (Fed. Cir. 2004).

2. Based On The Record of Proceedings Before the PTO, The Date of Invention is No Earlier than May 15, 2006

a. For Purposes of this Petition, Petitioner Assumes That Each Claim is Supported by the Provisional Application.

Without conceding that the claims are supported by the provisional application filing, 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. The Efforts to Antedate Prior Art Found In the File History Do Not Show a Date of Invention for the '240 Patent Claims Before May 15, 2006

During prosecution of the '240 patent, the applicants antedated a prior art reference to Sandifer with a declaration submitted under 37 C.F.R. § 1.131. Ex. 1011 at 14-16. That declaration, by a Dr. Lewis J. Rubin, claimed that he and the co-inventors "performed inhalation methods with pulmonary hypertension patients using treprostinil prior to September 1, 2005." Ex. 1011 at 15 ¶ 8. Those methods allegedly "included at least as much of the disclosure found in Sandifer that is cited in the Advisory Action, except that our method used human pulmonary hypertension patients rather than a sheep model." *Id.* Dr. Rubin's declaration includes a redacted clinical trial report that makes reference to an "OptiNeb device, NEBU-TEC GmbH," which he declares was a reference to an ultrasonic nebulizer, which "was used to administer pulmonary hypertension patients the indicated amounts of treprostinil . . . ." *Id.* at 15 ¶ 9.

This does not show earlier conception of the subject matter recited in the claims of the '240 patent.

There are several ways to antedate a reference. An applicant may "prove (1) a conception and reduction to practice before the filing date of [the reference] or (2) a conception before the [date of the reference] combined with diligence and reduction to practice after that date." *Tautus IP, LLC v. DaimlerChrysler Corp.*, 726

F.3d 1306, 1323 (Fed. Cir. 2013). The conception "must include ***every feature or limitation of the claimed invention***." *REG Synthetic Fuels, LLC v. Neste Oil Oyj*, 841 F.3d 954, 962 (Fed. Cir. 2016) (citing *Davis v. Reddy*, 620 F.2d 885, 889 (C.C.P.A. 1980)). Since the declaration submitted during prosecution does not describe, at least, the claimed "trigger," *see* Ex. 1001, cl. 1, it fails to establish prior invention sufficient to antedate any prior art in this proceeding. Petitioner will respond to any additional evidence of prior invention should Patent Owner submit such evidence in this proceeding.[2]

3. The Prior Art References Relied Upon Are Printed Publications

a. Voswinckel Is a Prior Art Printed Publication

Voswinckel is a prior art printed publication under § 102(b). Voswinckel appeared in a section of *Circulation* titled "Abstracts from Scientific Sessions 2004." Ex. 1003 at III-295; Ex. 1013, ¶26. *Circulation* is a journal published by the American Heart Association and is widely distributed. Ex. 1013 at ¶ 30. The

[2] The applicants cited to § 715.02 of the M.P.E.P., which indicates that when the examiner is not relying on a reference to show a particular claim limitation, but nonetheless contends it would have been obvious, the declaration under 37 C.F.R. § 1.131(a) needs only to show what the prior art references shows. Ex. 1011, 4. That provision of the MPEP is inapplicable here.

abstracts were published in a supplement in October 2006 before an American Heart Association conference in New Orleans, Louisiana held November 7-10, 2004. Ex. 1003 at cover; Ex. 1002, ¶55. The abstracts were then presented at the conference. The Voswinckel abstract specifically was presented on Wednesday November 10, 2004 in Hall I2 of the Ernest N. Morial Convention Center. Ex. 1003 at III-295.

Circulation is a periodical held by more than a thousand different libraries. Ex. 1013, ¶30. Libraries catalog or index *Circulation* by subject, and some libraries separately index the supplements to *Circulation*, such as the supplement in which Voswinckel is found. *Id.* These supplements are also cataloged by their subject matter. *Id.* *Circulation*—and the articles in it—would have been sufficiently accessible to the interested public such that the various volumes and issues of the publication could be found by a POSA exercising reasonable diligence and without difficulty. *Id.*

A copy of Voswinckel (and the volume containing it) is located in the British Library. Ex. 1013, ¶31. That copy bears a stamp from the British Library and bears a date of November 22, 2004, indicating that this was when the volume was processed by the British Library.[3] *Id.* Initially, the volume was available in the

[3] There are two copies of Voswinckel in the record because the date stamp was cut off when the first copy was made. Both copies are identical in substance.

reading room until May 22, 2005. *Id.*; Ex. 1003 at cover. As an indication that other researchers were familiar with Voswinckel, a March 2005 article by Sulica and Poon cites to Voswinckel. *Id.*, ¶33 & Attachment 1f.

Given the foregoing, Voswinckel was publicly available to a POSA by no later than December 2004, *id.*, ¶32, and likely earlier. Because Voswinckel was publicly available more than a year before May 15, 2006, it is a printed publication under § 102(b).

b. Ghofrani Is a Prior Art Printed Publication

i. Ghofrani Was Publicly Accessible More Than 1 Year Before the Earliest Possible Filing Date

Ghofrani is a prior art printed publication under § 102(a). Ghofrani was published in the June 2005 issue of *Herz*.[4] *Herz* is a journal that is held by 97 libraries world-wide, and is cataloged in those libraries by subject matter. Ex. 1013, ¶ 41.

[4] Ghofrani was published in German. In accordance with 37 C.F.R. § 42.63(b), a declaration attesting to the accuracy of the translation has been provided herewith. All citations and quotations in the Petition are based on the English translation of Ghofrani. Ex. 1005.

A copy of Ghofrani can be found at the University of California at Los Angeles's Biomedical Library.[5] Ex. 1013, ¶ 36, 42. The volume in which Ghofrani appears was stamped by the Biomedical Library as being received on June 22, 2005. Ex. 1013, ¶ 42. Ghofrani would have been on the library shelves no later than early July 2005. Id., ¶ 43.

Given the foregoing, Ghofrani was publicly available to a POSA no later than July 2005, which was well before the May 15, 2006 earliest possible effective filing date of the '507 patent claims. Therefore, Ghofrani is a prior art printed publication under § 102(a).

ii. Ghofrani Is "By Another"

Consistent with judicial interpretations of § 102(a), Ghofrani is a publication "by another." *In re Katz,* 687 F.2d 450, 454 (CCPA 1982). Ghofrani identifies as authors the following people that are not listed as inventors on the '240 patent: Hossein Ardeschir Ghofrani, Frank Reichenberger, and Fredrich Grimminger. Ex. 1005, 1. There are also individuals identified as inventors of the '240 patent that are not included as authors of Ghofrani, *i.e.*, Horst Olschewski, Robert Roscigno, Lewis Rubin, Thomas Schmehl, and Carl Sterritt. Ex. 1001, cover. Thus, the publishing

[5] It is also available online, and is accessible from SpringerLink by using keyword searches.

entity is different than the inventive entity. *In re Land*, 368 F.2d 866, 877 (CCPA 1966). There is no evidence in the record of the proceedings before the PTO to indicate that the disclosed subject matter in Ghofrani is not bound by another. *Accord Emerachem Holdings, LLC v. Volkswagen Group of Am., Inc.*, --F.3d --, 2017 WL 2587462, at*3-5 (Fed. Cir. Jun. 15, 2017). In these circumstances, a preliminary determination that Ghofrani is by another is appropriate and this issue should be no impediment to institution. *Varian Med. Sys., Inc. v. William Beaumont Hosp.*, IPR2016-00163, Paper 16, at 13-15 (May 6, 2016).

c. Patton Is a Prior Art Printed Publication

Patton is a publication under the Patent Cooperation Treaty. Ex. 1012. It was published on January 21, 1993, more than one year before the earliest possible effective filing date of May 15, 2006. *Id.*, cover. Patton is thus a prior art printed publication under § 102(b).

d. The OptiNeb® User Manual Is a Printed Publication

The OptiNeb® User Manual is a prior art printed publication under § 102(b). OptiNeb® was a familiar brand name of a nebulizer made by German company Nebu-Tec. Ex. 1002, ¶61. More than a year before the earliest possible effective filing date, OptiNeb® was referred to in the Voswinckel abstract, among other references. Ex. 1003, III-295; Ex. 1002, ¶61. Thus, the OptiNeb® nebulizer was not a well-kept secret unknown to POSAs. A POSA would have been led to seek

out literature further describing the OptiNeb® nebulizer based on these references in the literature.

POSAs interested in learning more about pharmaceutical dosing using equipment like nebulizers were in the practice of seeking more information from the manufacturer of equipment. Ex. 1002, ¶169. A POSA interested in learning about the OptiNeb® nebulizer would have been led to seek out Nebu-Tec's website on the Internet, and would have found Nebu-Tec to be located at www.nebu-tec.de--an obvious location on the web for Nebu-Tec's location on the Internet since it is a German company. Ex. 1014 Exhibit A-3. Once there, a POSA would have found information on the OptiNeb® nebulizer by clicking on the "Optineb-ir" tab. *Id.* Exhibit A-3, B-3. There, the POSA would have found further information about the commercially available OptiNeb-ir device. A POSA would further have found Nebu-Tec's OptiNeb® user manual included with this Petition as Exhibit 1006[6] as of 2004 by clicking on the Support page and then clicking on the OptiNeb® Instruction Guide. *Id*. Exhibit A-1, A-3, B-1, B-3, B-4. There was no password on

[6] Ex. 1006 is a translation of Ex. 1014 Exhibit B-4.

the PDF and it was freely available for download as indicated from the fact that it can be readily retrieved from the Internet Archive.[7] *Id.*

In light of the foregoing, the OptiNeb® User Manual is a prior art printed publication because it was readily accessible to a POSA exercising reasonable diligence. A POSA would have been naturally led based on known published works to Nebu-Tec's website where that POSA would have found the OptiNeb® User Manual was freely available for download and viewing. Because the OptiNeb® User Manual was publicly accessible at least as of June 2004, it is prior art under 35 U.S.C. § 102(b).

e. EU Community Register Is a Printed Publication

The EU Community Register is a prior art printed publication under § 102(a). Ventavis® is a commercial drug product that was first approved for sale in Europe in 2003. Ex. 1002, ¶47. The active ingredient in Ventavis® is iloprost, which like treprostinil is a stable prostacyclin analogue. *Id.*, ¶47, 215. Ventavis® was the first product indicated for the treatment of pulmonary hypertension that was delivered via inhalation by a nebulizer. *Id.*, ¶214. Accordingly, a POSA who was seeking to deliver another prostacyclin analogue by inhalation for the treatment of pulmonary

[7] If the manual was not accessible at the time of the crawl, it could not have been captured by the Internet Archive.

hypertension—such as treprostinil—would have been aware of Ventavis®, and would have been aware of and have investigated the capabilities of the nebulizers used to deliver Ventavis®, including regulatory filings in United States and Europe. *Id.*, ¶102-104.

In September 2005, Schering AG, the company that marketed Ventavis® in Europe, obtained approval to add the Venta-Neb nebulizer to the Ventavis® label in Europe. *Id.*, ¶49. This amendment to the labeling was made in Annex III to Commission Decision C(2005)3436 of 05 September 2005 (the "Decision"). Ex. 1009; Ex. 1002, ¶49, 102. The Decision, including Annex III, were available to the public through the EU Community Register of Medicinal Products (the "Community Register"), which "contains the centrally, for all EU Member States, by the European Commission since 1995 authorised products." Ex. 1049; *see also* Ex. 1038; Ex. 1002, ¶[102-108. Commission Decisions are published by the Community Register once notification of the decision has been received by whom the decision is addressed, which will "generally be done the first working day after proof of notification is received." Ex. 1049. Here, the Community Register page for Ventavis identifies the Decision in an entry titled "Centralised Variation," with a "closed date procedure" of September 8, 2005. Ex. 1043; Ex. 1002, ¶ 106-107.

In addition, the Decision, and its Annexes, were available to the public through the European Commission's Register of Commission Documents, which

provides public access to the documents of the European Parliament, the Council and the Commission pursuant to Regulation (EC) No 1049/2001. Ex. 1051. Regulation (EC) No. 1049/2001 further requires the institutions to make a register of documents available online. Ex. 1052. In particular, Article 11 mandates the institutions establish a register by June 2002, and Article 12 states that the institutions shall as far as possible make documents directly accessible to the public in electronic form. *Id.* The Register of Commission of Documents indicates that the date of publication for the Decision was "05/09/2005" or September 5, 2005 according to the EC date convention. Ex. 1053; Ex. 1002, ¶ 107. Therefore, through either source—the Community Register or the Register of Commission Documents—the amended Ventavis label in Annex III was available and accessible to the public as of September 2005.

The Ventavis® label in the EU Community Register is a prior art printed publication because it was readily accessible to a POSA exercising reasonable diligence. A POSA would have been led to the Ventavis® label because it was the only commercially approved inhalable product for the treatment of pulmonary hypertension in a time period where alternatives were being heavily researched. Ex. 1002 ¶215. The Ventavis® label was freely available for download from the EU regulatory agency. *Id.*, ¶105-106.

Because the EU Community Register was publicly accessible at least as of September 2005, it is prior art under 35 U.S.C. § 102(a).

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

More than a year before the earliest filing date of the '240 patent, Voswinckel disclosed a study that "assess[ed] the safety, tolerability, and clinical efficacy" of inhaled treprostinil "in patients with severe" pulmonary hypertension. Ex. 1003 at III-295. The study disclosed that "[p]atients received a TRE inhalation by use of the pulsed OptiNeb® ultrasound nebulizer (3 single breaths, TRE solution 600 µg/ml)." *Id.* The study revealed that "[i]nhaled [treprostinil] show[ed] strong pulmonary selective vasodilatory efficacy with a long duration of effect following single acute dosing." *Id.* Although the study did not disclose the precise dose of inhaled treprostinil that was delivered to treat pulmonary hypertension, another reference did.

The POSA, wishing to treat pulmonary hypertension, would have been motivated to make minor, obvious modifications to this method. For instance, it would have been obvious to modify the nebulizer to use a light and sound in order to instruct the patient when to breathe. This would allow for the patient to receive a more precise dose. There is nothing patentable here. Ex. 1002 ¶ 104-166.

1. Claim 1 Would Have Been Obvious Over Voswinckel in View of Patton and Ghofrani

a. Preamble: "A method of treating pulmonary hypertension"

Even if the preamble limits claim 1, the recited feature is expressly disclosed in Voswinckel.

Voswinckel discloses a method for treating pulmonary hypertension. Ex. 1003, III-295 ("objective" was to "evaluate the effects of inhaled TRE on pulmonary hemodynamics and gas exchange in severe pulmonary hypertension (PH) and to assess . . . efficacy in patients with severe PH."); Ex. 1002, ¶109. Voswinckel is titled "Inhaled Treprostinil Sodium (TRE) For the Treatment of Pulmonary Hypertension," and appears under the category of, "Pulmonary Arterial Hypertension: New Therapies." Ex. 1003, III-295. Voswinckel thus plainly relates to treating pulmonary hypertension. Ex. 1002, ¶109. Voswinckel also discloses a pharmaceutical formulation (treprostinil) and a device for administering that formulation (a pulsed OptiNeb® ultrasound nebulizer). Ex. 1003, III-295. Therefore, even if the preamble of claim 1 is a limitation, it would have been obvious to a POSA.

i. Limitation [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"

This limitation is disclosed in Voswinckel.

Voswinckel teaches that the OptiNeb® nebulizer is configured to "deliver by inhalation a therapeutically effective single event dose of said formulation." Voswinckel's disclosure of the administration of treprostinil using the OptiNeb® nebulizer would have been understood by a POSA to disclose a "single event dose" because it discloses "a TRE inhalation" of "3 single breaths," which it also describes as a "short inhalation time[]." Ex. 1003, III-295. A POSA would have understood that the description of a 3-breath dose followed by 120 minutes of monitoring constitutes a "single event dose." Ex. 1002, ¶115. This conclusion is further confirmed by "short inhalation time," which further suggests a single event to a POSA. Indeed, this conclusion is consistent with the specification of the '240 patent, which describes a "single event" dosing as including "a limited number of breaths" such as 3 breaths, and the single event dosing can be "less than 5 minutes." Ex. 1001, 7:50-60. Voswinckel further discloses the compassionate treatment of two individuals who were treated "with 4 inhalations of TRE per day." A POSA would understand each of those "inhalations" to be a "single event dose."

Voswinckel further discloses "a formulation comprising 200 to 1000 µg/ml of treprostinil or a pharmaceutically acceptable salt thereof." Ex. 1002, ¶ 114. Voswinckel explains that "inhaled TRE was applied to 17 patients with severe pulmonary hypertension." Ex. 1003, III-295. As reflected by Voswinckel's title, "TRE" stands for "treprostinil sodium," *id.*, which a POSA would have understood to be "treprostinil or a pharmaceutically acceptable salt thereof." Ex. 1002, ¶ 114. Voswinckel teaches that the patients were dosed with a treprostinil "solution [of] 600 µg/ml," which is within—indeed centered on—the claimed range. Ex. 1003, III-295; Ex. 1002, ¶ 114.

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

[B]: "[W]ith a pulsed ultrasonic nebulizer . . . ." Voswinckel teaches "a pulsed ultrasonic nebulizer" as required by claim 1. Ex. 1001, 18:9; Ex. 1002, ¶ 119. Voswinckel teaches that "[p]atients received a [treprostinil] inhalation by use of the pulsed OptiNeb® ultrasound nebulizer." Ex. 1003, III-295.

[B1] A nebulizer that "aerosolizes a fixed amount of treprostinil or a pharmaceutically acceptable salt thereof per pulse."

As explained above, Voswinckel teaches the administration of "treprostinil or a pharmaceutically acceptable salt thereof." *Supra* § VI.B.i.2. Voswinckel's nebulizer would have been readily understood to aerosolize the drug to be

administered—in Voswinckel's case treprostinil or a pharmaceutically acceptable salt thereof. Yet, Voswinckel does not expressly state that the nebulizer created "a fixed amount" of the formulation "per pulse." Nevertheless, aerosolizing a fixed amount per pulse would have been obvious to a POSA.

Patton teaches a "unit 40" that "is of a type that will nebulize or mix a ***defined amount of medicant*** with the preselected amount of compressed air from compressor," to form "a dosage or bolus" so that it can be inhaled by the patient when prompted to do so by the use of a "light 50 and/or an audible signal 52." Ex. 1012, 13:2-7; Ex. 14:3-20; Ex. 1002, ¶ 124.

It would have been obvious to a POSA to ensure that Voswinckel's pulsed ultrasonic nebulizer aerosolized "a fixed amount" of treprostinil (or pharmaceutically acceptable salt thereof) per pulse. Ex. 1002, ¶ 121. A POSA would appreciate that a fixed amount per pulse is a straight-forward way to design a method of administration with a nebulizer. *Id.*, ¶ 122. A fixed amount of treprostinil per pulse would allow a physician prescribing a drug via a nebulizer to a patient the ability to titrate up or down depending on variables like a patient's tolerance for the drug (or lack thereof) or size by simply increasing or decreasing inhalation time or breaths. *Id.* Thus, rather than a complicated scheme where the drug is delivered in varying amounts, a fixed dose per pulse allows the prescriber to instruct the patient to take more or less breaths as needed. *Id.* The point of using a pulsed nebulizer is

to precisely and efficiently deliver drug to a patient, thus this simple configuration is the well-suited. *Id.*, ¶ 123. This ensures that the patient will receive the desired therapeutically effective dose during each administration without the inefficiency or side effects of delivering more drug then the patient needs. *Id.*

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

Voswinckel teaches "a pulsed ultrasonic nebulizer" as required by claim 1. Ex. 1001, 18:9; Ex. 1002, ¶ 119. Voswinckel teaches that "[p]atients received a [treprostinil] inhalation by use of the pulsed OptiNeb® ultrasound nebulizer." Ex. 1003, III-295. Voswinckel does not expressly state that the disclosed OptiNeb® nebulizer included the claimed "opto-acoustical trigger" as construed in the district court proceedings to mean "a trigger with an optical element (*e.g.*, light) and an acoustical element (*e.g.*, sound)." *Supra* § IV. Nevertheless, this feature would have been obvious over Voswinckel in view of Patton.

Patton teaches a system for delivering medicants via inhalation, including through the use of a nebulizer. Ex. 1012, 10:6-10. "[U]nit 40" described by Patton "is of a type that will nebulize or mix a defined amount of medicant with the preselected amount of compressed air received from compressor 22. The defined amount, referred to as a dosage or bolus, flows into a chamber 42 via" a conduit. *Id.*, 13:3-7. The apparatus further includes a "light 50 and/or an audible signal 52"

that "will alert the user that a puff is ready to be withdrawn from chamber 42 when the compressor 22 shuts down." *Id.*, 14:3-5. These two signals (50, 52) "are set to begin immediately after operation of the compressor 22 ceases," and indicate that the formation of the bolus is complete. *Id.*, 14:3-20. This process repeats for each breath. *Id.*; Ex. 1002, ¶ 131. Therefore, Patton teaches an "opto-acoustical trigger," as required by claim 1.

Patton further demonstrates that the known triggers allowed the patient to synchronize each breath to each pulse, as claim 1 requires. Ex. 1002, ¶ 131. Put another way, Patton demonstrates that such triggers were known as indicators for patients to begin to inhale aerosolized medications administered using a nebulizer.

Assuming that Voswinckel's OptiNeb® pulsed nebulizer did not include an opto-acoustical trigger that allows the patient to synchronize each breath to each pulse, it would have been obvious to add such a feature to the nebulizer. Ex. 1002, ¶ 127, 131. A POSA would have understood that a pulsed nebulizer delivers the drug to be administered in discrete pulses and the patient receives the drug when the patient inhales. *Id.*, ¶ 127. A POSA would have further understood that the timing of the inhalation was important to ensure efficient delivery of the drug: without some sort of trigger, the patient would be unable to synchronize their breathing to the distribution of drug, and the efficiency gains from a pulse function are wasted. *Id.* ¶ 128.

Audible and visual prompts are commonplace, and that is no exception in the field of nebulizers. Providing audible and visual triggers to a patient appeals to a combination of senses that are commonly appealed to (e.g., stop lights and a traffic cop's whistle appeal both to sight and sound). Ex. 1002 ¶ 129. Appealing to these same senses on a nebulizer such as the OptiNeb® nebulizer disclosed in Voswinckel would have applied a known technique to coordinate inhalation with the delivery of medication and would have done nothing more than yield predictable results. Ex. 1002, ¶ 202. 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. *Id.*, ¶ 129, 203. Accordingly, a POSA would have been motivated to ensure that Voswinckel's OptiNeb® nebulizer included the claimed "opto-acoustical trigger which allows said human to synchronize each breath to each pulse."

iv. Limitation [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."

Voswinckel discloses the administration of treprostinil or a pharmaceutically acceptable salt thereof," as discussed above. *Supra* § VI.B.i.2. Moreover, Voswinckel discloses that the single event dose is delivered in 3 breaths, which is within the range of 1 to 18 breaths. Ex. 1003, III-295 ("Patients received a TRE

inhalation by use of the pulsed OptiNeb® ultrasound nebulizer (3 single breaths, TRE solution 600 µg/ml).”). Voswinckel does not provide an express discussion of the total dose administered in the single event dose. Nevertheless, at the time of the earliest effective filing date, those skilled in the art would have understood that such a dosing of between 15 µg to 90 µg was an optimal dosing range based on the teachings of Ghofrani.

Ghofrani discloses a study in which patients “were administered inhaled treprostinil (15 mcg/inhalation).”[8] Ex. 1005, 298.[9] Ghofrani further discloses that “it is possible to increase the dosage to up to 90 mcg (absolute inhaled dose per inhalation exercise) without adverse effects occurring.” *Id.* Ghofrani further discloses that “it is technically feasible for there to be only one to two breaths in an application.” Ex. 1005, 298. Thus, a POSA would have understood that on the low end (a single inhalation) 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. Based on these teachings, a POSA would have understood that Ghofrani thus

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

[9] Quotations to Ghofrani are from the English-language translation of Ghofrani. Ex. 1005.

disclosed the entire claimed dosage range. Ex. 1002, ¶ 135. A POSA administering treprostinil in accordance with the teachings of Voswinckel would have been motivated to use the range of doses disclosed by Ghofrani because such doses "led to a major reduction in pulmonary selective pressure and resistance with an overall duration of action of > 180 min." Ex. 1005, 298; Ex. 1002, ¶ 135. In other words, this dose was therapeutically effective. Ex. 1002, ¶ 116-117. A POSA would have further understood that 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)." Ex. 1005, 298; Ex. 1002, ¶ 136. Notably, Ghofrani is also listed as an author on the Voswinckel paper. Ex. 1003, III-295. So too are other authors.

2. Claim 2 Would Have Been Obvious Over Voswinckel in view of Patton and Ghofrani

Claim 2 depends from claim 1 and further requires "the formulation comprises 600 µg/ml of the treprostinil or its pharmaceutically acceptable salt thereof." Ex. 1001, 18:18-20. Voswinckel teaches that "[p]atients received a TRE inhalation" from a "TRE solution 600 µg/ml." Ex. 1003, III-295. As such, Voswinckel teaches the additional requirements of claim 2. Ex. 1002, ¶ 139. Thus, claim 2 would have been obvious over Voswinckel in view of Patton and Ghofrani as applied to claim 1, above.

3. Claim 3 Would Have Been Obvious Over Voswinckel in view of Patton and Ghofrani

Claim 3 depends from claim 1, and further requires "the single event dose is not repeated for a period of at least 3 hours." Ex. 1001, 18:20-21. Voswinckel discloses a study in which two patients "received compassionate treatment with 4 inhalations of TRE per day after the acute test." Ex. 1003, III-295. A POSA would have understood that four inhalations per day corresponds to one inhalation every six hours, or one inhalation every four hours during waking hours (assuming eight hours of sleep per day). Ex. 1002, ¶ 142. Voswinckel teaches therapeutically effective results from this dosing schedule, which would teach a POSA that the single event dose need not be repeated for a period of at least 3 hours.

Further, based on the teachings of Ghofrani, a POSA would have found this lower bound obvious. Ghofrani explains that "it is possible to reduce the number inhalations necessary to up to four per day," Ex. 1005, 298. Moreover, Ghofrani acknowledges that the administration of inhaled treprostinil within the range of doses recited in claim 1 "led to a major reduction in pulmonary selective pressure and resistance with an overall duration of action of > 180 min." *Id.* A POSA would have understood that this statement in Ghofrani teaches that the overall duration of a dose of inhaled treprostinil would have a duration of action of more than 3 hours—180 minutes. Ex. 1002, ¶ 143. A POSA would have further understood, therefore, that this three-hour period would have provided the upper bound for the frequency

of dosing of the therapy discussed by Voswinckel. Dosing more frequently than this would be unnecessary given the duration of action of treprostinil disclosed by Ghofrani, Ex. 1002, ¶ 143.

4. Claim 4 Would Have Been Obvious Over Voswinckel in view of Patton, and Ghofrani

Claim 4 depends from claim 1, and further requires that "the single event dose produces a peak plasma concentration of treprostinil about 10-15 minutes after the single event dose." Ex. 1001, 18:22-24. The peak plasma condition recited by this claim would have been the necessary result of administering treprostinil in the manner contemplated by Voswinckel and Ghofrani, as is evident from the disclosure of the '240 patent. A POSA would have appreciated that 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. *Id.*, ¶ 147. When treprostinil is administered as recited in claim 1, it will inherently reach its peak plasma concentration about 10-15 minutes after the single event dose. *Id.* Specifically, the '240 patent states that "study ii" resulted in peak plasma concentrations of treprostinil that "were found 10-15 minutes after inhalation." Ex. 1001, 16:17-19. This was the case regardless of whether the dose was administered in one breath, or over six minutes. Ex. 1002, ¶ 148. A POSA would understand that the three breath treatment regimen used by Voswinckel could and would be delivered in less than six minutes. *Id.*, ¶ 149. Similarly, Ghofrani teaches both a treatment in one inhalation and administration of

a single event dose is less than one minute. *Id.* Thus, according to the conclusions in the specification, both treatment regimen would result in a peak plasma concentration within 10-15 minutes of administration of the dose. *Id.*

5. Claim 5 Would Have Been Obvious Over Voswinckel in view of Patton and Ghofrani

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." Ex. 1001, 18:25-28. Voswinckel discloses that "[p]atients received a [treprostinil] inhalation" in "3 single breaths." Ex. 1003 at III-295. As explained in connection with claim 1, a POSA would have found it obvious to administer a dose of between 15 µg and 90 µg. *Supra* § VI.B.i.5.

A POSA would have understood that each breath was to administer an equal amount of the dose. Indeed, as we have explained, it would have been obvious for the POSA to configure the nebulizer to deliver a fixed amount per pulse, as required by claim 1. *Supra* § VI.B.i.3. As we have also explained, the purpose of the opto-acoustical trigger was to coordinate a patient's breath to the pulse of the device. *Supra* § VI.B.i.4. Accordingly, a dose of 15 µg or greater administered in three equal breaths would result in the inhalation of "at least 5 µg" per breath, as the claim requires.

6. Claim 6 Would Have Been Obvious Over Voswinckel in view of Patton and Ghofrani

Claim 6 depends from claim 2, 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." Ex. 1001, 18:29-32. We have already shown how Voswinckel discloses the limitation of claim 2 and how Voswinckel in view of Patton, and Ghofrani would have rendered claim 1 obvious. Voswinckel and Ghofrani render this limitation obvious for the same reasons as described in connection with claim 5. Ex. 1002, ¶ 156.

7. Claim 7 Would Have Been Obvious Over Voswinckel in view of Patton and Ghofrani

Claim 7 depends from claim 1, and further requires that "the single event dose is inhaled in 3-18 breaths by the human." Ex. 1001, 18:33-34. Voswinckel teaches that "[p]atients received a [treprostinil] inhalation by use of the pulsed OptiNeb® ultrasound nebulizer" in "3 single breaths," which is "in 3-18 breaths by the human" as required by claim 7. Ex. 1003, III-295; Ex. 1002, ¶ 160.

8. Claim 8 Would Have Been Obvious Over Voswinckel in view of Patton, and Ghofrani

Claim 8 depends from claim 6, and requires that "the single event dose is inhaled in 3-18 breaths by the human." Ex. 1001, 18:35-36. As we have discussed above, Voswinckel in combination with Ghofrani disclose the subject matter of

claim 6, and claim 1 would have been obvious over the combined teachings of Voswinckel, Patton, and Ghofrani.

Voswinckel teaches that "[p]atients received a [treprostinil] inhalation by use of the pulsed OptiNeb® ultrasound nebulizer" in "3 single breaths," which is "in 3-18 breaths by the human" as required by claim 8. Ex. 1003, III-295; Ex. 1002, ¶ 163.

9. Claim 9 Would Have Been Obvious Over Voswinckel in view of Patton and Ghofrani

Claim 9 depends from claim 6, and further requires that "the single event dose is not repeated for a period of at least 3 hours." As we have discussed above, Voswinckel in combination with Ghofrani disclose the subject matter of claim 6, and claim 1 would have been obvious over the combined teachings of Voswinckel, Patton, and Ghofrani. The text of claim 9 is identical to the text of claim 3, with the exception of its changed dependency. Our analysis of the additional limitation imposed by claim 3 is equally applicable to the limitation of claim 9.

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

Even without looking to Ghofrani, the POSA still would have found it obvious to practice the claimed method. Voswinckel and Patton render obvious the administration of treprostinil via a pulsed nebulizer (with an opto-acoustical trigger) to treat pulmonary hypertension. Indeed, Voswinckel discloses a specific nebulizer:

OptiNeb®. The OptiNeb® User Manual teaches OptiNeb®'s capabilities. A POSA considering both the OptiNeb® User Manual and Voswinckel would have understood that OptiNeb® would deliver a dose within the claimed range using the solution and breath parameters disclosed in Voswinckel. Ex. 1002. ¶ 167-185.

1. Claim 1 Would Have Been Obvious Over Voswinckel in view of Patton and the OptiNeb® User Manual

As explained in connection with Ground 1, the preamble and limitations [A], [B], and [C] would have been obvious in view of Voswinckel. That analysis is equally applicable here. We address limitation [D] below, in view of Patton and the OptiNeb® User Manual.

i. Limitation [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."

Voswinckel discloses the administration of treprostinil or a pharmaceutically acceptable salt thereof," as discussed above. *Supra* § VI.B.i.2. Moreover, Voswinckel discloses that the single event dose is delivered in 3 breaths, which is within the range of 1 to 18 breaths. Ex. 1003, III-295. Voswinckel does not provide an express discussion of the total dose administered in the single event dose. Nevertheless, at the time of the earliest effective filing date, those skilled in the art would have been able to derive the single event dose administered in Voswinckel by looking to the information in Voswinckel in view of the OptiNeb® User Manual.

Ex. 1002, ¶ 173-179 The POSA would have been motivated to look to the OptiNeb® User Manual because Voswinckel discloses the use of an OptiNeb® to administer treprostinil. *Id.*, ¶ 169, 179. The POSA seeking to perform this method would have wanted to be familiar with the properties of OptiNeb®. *Id.*.

Based on these two references, the POSA would have known:

- Voswinckel discloses that patients were administered a "TRE solution 600 µg/ml" in "3 single breaths." Ex. 1003 at III-295.
- The OptiNeb® User Manual discloses that the OptiNeb® could nebulize (that is, produce aerosol) at a rate of 0.6 ml/min. Ex. 1006 at 28.
- A typical inhalation of a therapeutic agent would be 2-3 seconds long. Ex. 1002, ¶[174.

Based on these well-known facts, the POSA would have used his undergraduate-level mathematics skills to calculate the dose of treprostinil that could be delivered in three breaths (per Voswinckel) using the solution from Voswinckel (600 µg/ml) and the capabilities of the OptiNeb®-ir nebulizer (nebulization at 0.6 ml/min) as follows:

(600 µg/ml) * (0.6 ml/min) = 360 µg/min

(360 µg/min) / (60 seconds/min) = 6 µg/second.

(6 µg/second) * (2-3 seconds/breath) = 12-18 µg/breath

(12-15 µg/breath) * (3 breaths) = 36-54 µg

Accordingly, the POSA would have known that the OptiNeb® (as used in Voswinckel) could produce drug at a rate of up to 36-54 µg in 3 breaths. Ex. 1002, at ¶174. An ordinarily skilled artisan would recognize that this is the maximum dose that could be achieved with the OptiNeb's nebulization rate, but would also know that the nebulization rate, concentration of solution or number of breaths could all be routinely optimized. *Id.*, ¶ 177. At a minimum, the POSA would have known that a dose of 36-54 µg of treprostinil could be delivered using the solution and number of breaths from Voswinckel with the maximum capabilities of the OptiNeb device. *Id.*, ¶ 174, 179. That is within the claimed range.

Further, the particular dose and breath limitations are variables that a POSA could routinely optimize in order to meet a therapeutic target. Ex. 1002, ¶177-178 A POSA would know to adjust the concentration of drug in the formulation or the rate of nebulization to adjust the dose delivered. *Id.* at 177. 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. *Id.* Again, as I explained above, a POSA could easily calculate the dose nebulized per second, determine the number of seconds for the patient to inhale, and derive the dose. *Id.*

2. Claims 2, 3, 7, and 8 Would Have Been Obvious Over Voswinckel in view of Patton, and the OptiNeb® User Manual.

As explained in connection with Ground 1, Voswinckel teaches the required additional limitations of claims 2, 3, 7 and 8, and 9

3. Claim 4 Would Have Been Obvious Over Voswinckel in view of Patton and the OptiNeb® User Manual

Claim 4 depends from claim 1, and further requires that "the single event dose produces a peak plasma concentration of treprostinil about 10-15 minutes after the single event dose." Ex. 1001, 18:22-24 The peak plasma condition recited by this claim would have been the necessary result of administering treprostinil in the range that was rendered obvious by Voswinckel in view of the OptiNeb® User Manual. A POSA would have appreciated that 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 in an amount of 36-45 µg, as it would have been using the maximum nebulization rate for OptiNeb®-ir (based on the OptiNeb® User Manual), it will inherently reach its peak plasma concentration about 10-15 minutes after the single event dose. Specifically, the '240 patent states that "study ii" resulted in peak plasma concentrations of treprostinil "10-15 minutes after inhalation." Ex. 1001, 16:45-47. This was the case regardless of whether the dose was administered in one breath, or over six minutes. Tellingly, the '240 patent provides no other disclosure about how to achieve the claimed peak plasma

concentrations other than to dose in a manner consistent with that taught by Voswinckel and the OptiNeb® User Manual. Therefore, the administration of between 36-45 µg of treprostinil (as taught by the prior art) necessarily results in a single event dose that produces the claimed peak plasma concentrations within the time period recited by claim 4.

4. Claim 5 Would Have Been Obvious Over Voswinckel in view of Patton, and the OptiNeb® User Manual.

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." Ex. 1001, 18:25-28. Voswinckel discloses that "[p]atients received a [treprostinil] inhalation" in "3 single breaths." Ex. 1003 at III-295. As we explained in connection with claim 1, a POSA would have found it obvious to use the method of Voswinckel to administer a dose of up to 36-54 µg with OptiNeb®. *Supra* § VI.C.i.1.

It would have been obvious for a POSA to administer an equal amount of the dose in each breath. Indeed, as we have explained, it would have been obvious for the POSA to configure the nebulizer to deliver a fixed amount per pulse (if it was not already so configured), as required by claim 1. *Supra* § VI.B.i.3. A POSA would appreciate that a fixed amount per pulse is the most straight-forward way to design a method of administration with a nebulizer. Ex. 1002, ¶ 122 A fixed amount of

treprostinil per pulse allows the prescriber the ability to titrate up or down depending on variables like a patient's tolerance for the drug (or lack thereof) or size. *Id.* Thus, rather than a complicated scheme where the drug is delivered in varying amounts, a fixed dose per pulse allows the prescriber to instruct the patient to take more or less breaths as needed. *Id.* The point of using a pulsed nebulizer is to precisely and efficiently deliver drug to a patient, thus this simple configuration is the well-suited. *Id.*, ¶ 123. This ensures that the patient will receive the desired therapeutically effective dose during each administration without the inefficiency or side effects of delivering more drug then the patient needs. *Id.*

As we have also explained, it would have been obvious to use the opto-acoustical trigger to coordinate a patient's breath to the pulse of the device.

A dose of greater than 15 µg (such as 36 µg) administered in three equal breaths would result in the inhalation of "at least 5 µg" per breath, as the claim requires.

5. Claim 6 Would Have Been Obvious Over Voswinckel in view of Patton, and the OptiNeb® User Manual

Claim 6 depends from claim 2, 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." Ex. 1001, 18:29-32. We have already shown how Voswinckel discloses the limitation of claim 2 and how Voswinckel in view of Chaudry, Patton, and the

OptiNeb® User Manual would have rendered claim 1 obvious. Voswinckel and the OptiNeb® User Manual render this limitation obvious for the same reasons as described in connection with claim 5.

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

As we have explained above, a POSA would have found it obvious to practice the claimed method: (1) administering a formulation comprising 200-1000 µg/ml of treprostinil, (2) at a dose of 15-90 µg over between 1 and 18 breaths, (3) with a pulsed ultrasonic nebulizer. As we have also explained, these three references do not expressly disclose the claimed "opto-acoustical trigger" in connection with the disclosed pulsed ultrasonic nebulizer. As we show further below, pulsed ultrasonic nebulizers with opto-acoustical triggers were known in the art for administering inhalable forms of drugs for the treatment of pulmonary hypertension based on the EU Community Register. And, it would have been obvious to include such a feature on the ultrasonic nebulizer used to practice the claimed method. Ex. 1002, ¶ 186-204.

1. Claim 1 Would Have Been Obvious Over Voswinckel in view of Ghofrani and the EU Community Register

As explained in connection with Ground 1 above, the preamble and limitations [A], [C], and [D] would have been obvious to a POSA in view of Voswinckel and Ghofrani. The discussions of these limitations are equally

applicable here. We address limitation [B] and [D] below, in view of the EU Community Register.

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

[B]: "[W]ith a pulsed ultrasonic nebulizer . . . ." Voswinckel teaches "a pulsed ultrasonic nebulizer" as required by claim 1. Ex. 1001, 18:9; Ex. 1002, ¶ 192. Voswinckel teaches that "[p]atients received a [treprostinil] inhalation by use of the pulsed OptiNeb® ultrasound nebulizer." Ex. 1003, III-295.

[B1]: A nebulizer that "aerosolizes a fixed amount of treprostinil per pulse." Voswinckel teaches the administration of "treprostinil or a pharmaceutically acceptable salt thereof." *Supra* § VI.B.i.2. Voswinckel's nebulizer would have been understood to aerosolize the drug to be administered—in Voswinckel's case treproistinil or a pharmaceutically acceptable salt thereof. Yet, Voswinckel does not expressly state that the nebulizer created "a fixed amount" of the formulation "per pulse." Nevertheless, aerosolizing a fixed amount per pulse would have been obvious to a POSA.

The EU Community Register teaches "a portable ultrasonic battery-powered nebuliser," called Venta-Neb, which was "suitable for the administration of Ventavis," an approved drug. Ex. 1009 at 3. The Venta-Neb operated on two programs; the patient's doctor was to choose which program was right for each

patient. Ex. 1009 at 25-26. Each program administered a certain amount of drug over a certain number of inhalation cycles. P1 was to administer 5.0 µg over 25 cycles; P2 was to administer 2.5 µg over 10 inhalation cycles. Ex. 1009 at 3, 26. A POSA would have appreciated that the administration of an approved drug requires the ability to administer a fixed dose of an amount certain. Ex. 1002 at ¶ 197. Therefore, the POSA would have understood that ultrasonic nebulizers could be used to administer a fixed dose. *Id.* When the dose is expressed in a specific number of breaths, a POSA would understand that each breath is intended to give an equal amount of drug per breath. *Id.* Thus, 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.

In view of the EU Community Register, a POSA would expect that the Venta-Neb delivered the constant amount of drug each cycle, or each "pulse." Ex. 1002, ¶[197. Therefore, the POSA would have understood that ultrasonic nebulizers could be used to administer a fixed dose.

Further, using a fixed amount (concentration of drug) per pulse would have been obvious because it is reliable and repeatable. Ex. 1002, ¶ 198. If a patient were to be interrupted during an inhalation, an inconsistent dose would make it difficult to resume treatment. *Id.* 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. *Id.* 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. *Id.*

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. Ex. 1002 at ¶ 199. The Ventavis label does not express the dose in a number of breaths for these two devices. *Id.* Rather, the label explains that "HaloLite and Prodose are dosimetric systems. *Id.* They stop automatically after the pre-set dose has been delivered. *Id.* The inhalation time depends on the patient's breathing pattern." *Id.* Thus, these devices do not deliver a fixed amount of drug per pulse, but rather vary the amount per breath based on the patient. *Id.* 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. *Id.*

ii. <u>Limitation [C]: "said pulsed ultrasonic nebulizer comprising an opto-acoustical trigger which allows said human to synchronize each breath to each pulse"</u>

Voswinckel teaches "a pulsed ultrasonic nebulizer" as required by claim 1. Ex. 1001, 18:15; Ex. 1002, ¶ 192. Voswinckel teaches that "[p]atients received a

[treprostinil] inhalation by use of the pulsed OptiNeb® ultrasound nebulizer." Ex. 1003, III-295. Voswinckel does not expressly state that the disclosed OptiNeb® nebulizer included the claimed "opto-acoustical trigger," *i.e.*, "a trigger with an optical element (*e.g.*, light) and an acoustical element (*e.g.*, sound)." *Supra* § IV. This feature would have been obvious over Voswinckel in view of the EU Community Register.

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. Ex. 1002, ¶ 201. 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. *Id.*, ¶ 202. 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. *Id.*, ¶ 203. 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." *Id.*, ¶ 204.

Accordingly, a POSA would have been motivated to ensure that Voswinckel's OptiNeb® nebulizer included the claimed "opto-acoustical trigger," which "allow[ed]" a patient "to synchronize each breath to each pulse."

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

As discussed in connection with Ground 1 above, Voswinckel and Ghofrani teach or render obvious the additional limitations of claims 2-9. The application of those references to dependent claims 2-9 applies equally with respect to this ground. Thus, claims 2-9 would have been obvious over Voswinckel in view of Ghofrani, Patton and the EU Community Register.

a. Alleged Evidence Regarding Secondary Considerations Does Not Render the Claimed Subject Matter Non-Obvious

During prosecution of the '240 patent, the patentee asserted that various secondary considerations rendered the '240 patent non-obvious. These arguments are not persuasive—particularly in view of the compelling and interrelated teachings of Voswinckel and Ghofrani, which were not among the prior art considered during prosecution.

First, the patentee submitted a declaration of Dr. Lewis Rubin, who argued that "[t]he fact that one breath of 15 micrograms of treprostinil could provide such a long duration of action in a pulmonary hypertension patient was unexpected." Ex. 1058, 20 ¶15. But a POSA, familiar with Voswinckel and Ghofrani, would not have been surprised. Voswinckel disclosed that patients received "compassionate treatment with 4 inhalations of TRE per day." Ex. 1003, III-295. As explained above, 4 inhalations per day corresponds to 1 inhalation every 4-6 hours. Moreover, Ghofrani taught that "it is possible to reduce the number of inhalations necessary to up to four per day," and that a dose could include a single inhalation of 15mcg/inhalation. Ex. 1005, 298. According to Ghofrani, this led to a "major reduction in pulmonary selective pressure." *Id.* Because Voswinckel and Ghofrani were in the prior art, the result championed as surprising during prosecution was no surprise at all.

Second, Dr. Rubin argued that it was surprising that "such high concentrations of treprostinil [up to 90 µg] were so well tolerated by pulmonary hypertension patients." Ex. 1058, 20-21 ¶16. Again, a POSA familiar with Voswinckel and Ghofrani would not have been surprised. As explained in connection with Ground 2, Voswinckel (when read in view of the OptiNeb® User Manual) rendered obvious a dose of 45 µg, which is within the claimed range. Ghofrani disclosed that "it is

possible to increase the dosage up to 90 µg (absolute inhaled dose per inhalation exercise) without adverse effects occurring." Ex. 1005, 298.

Third, Dr. Rubin stated that he "did not expect that the higher single event doses of treprostinil . . . would lead to a marked improvement in quality of patient life as shown by the patient responses while still maintaining an acceptable level of side effects as judged by patients." Ex. 1058, 22 ¶19. But as just explained, Voswinckel and Ghofrani disclosed that treprostinil could be dosed as claimed, safely and effectively. A POSA would not have been surprised.

Applicants further argued that it was unexpected that "treprostinil can be administered with a pulsed ultrasonic nebulizer so that its therapeutically effective single event dose is inhaled in 18 or less breaths by a human and has been approved by the FDA for such an administration regimen." Ex. 1059, 6. But Voswinckel discloses the "use of the pulsed OptiNeb® ultrasonic nebulizer" to administer a TRE solution in "3 single breaths." Ex. 1003, III-295.

Finally, Applicants pointed to the alleged commercial success of United Therapeutics's Tyvaso® product. Ex. 1059, 7-8. But the patentee attributed that success to "more convenient dosing," *id.*, 9, which, as we have shown above, was found in the prior art and was not new at all. "[C]ommercial success without invention will not make patentability." *Great Atl. & Pac. Tea. Co. v. Supermarket Equip. Corp.*, 340 U.S. 147, 153 (1950). And, it does not do so here either.

VII. CONCLUSION

For the reasons set forth above, the challenged claims 1-9 of the ’240 patent are unpatentable. Petitioner therefore requests that an *inter partes* review of these claims be instituted and that the challenged claims be canceled.

Respectfully submitted,

Dated: June 21, 2017

/*Michael K. Nutter*/
Michael K. Nutter, Lead Counsel
Reg. No. 44,979
Drew R. Sommer, Back-Up Counsel
Reg. No. 53,932
Kurt A. Mathas, Back-Up Counsel
WINSTON & STRAWN LLP

I. CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(d), the undersigned certifies that this Petition complies with the type-volume limitation of 37 C.F.R. § 42.24(a). The word count application of the word processing program used to prepare this Petition indicates that the Petition contains 10,858 words, excluding the parts of the brief exempted by 37 C.F.R. § 42.24(a).

Respectfully,

Dated: June 21, 2017

/*Michael K. Nutter*/
Michael K. Nutter, Lead Counsel
Reg. No. 44,979

II. PAYMENT OF FEES UNDER 37 C.F.R. §§ 42.15(a) AND 42.103

The required fees are submitted herewith. If any additional fees are due at any time during this proceeding, the Office is authorized to charge such fees to Deposit Account No. 50-1814.

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105(a), this is to certify that I caused to be served a true and correct copy of the foregoing Petition for *Inter Partes* review of U.S. Patent No. 9,358,240 (and accompanying electronic Exhibits EX1001 – EX1164) by overnight courier, on this 21st day of June, 2017, on the Patent Owner at the correspondence address of the Patent Owner as follows:

Foley & Lardner LLP
3000 K Street N.W.
Suite 600
Washington, D.C. 20007-5109

and at other addresses also likely to effect service:

Douglas Carsten
Wilson Sonsini Goodrich & Rosati
12235 El Camino Real
San Diego, CA 92130

Respectfully submitted,

Dated: June 21, 2017

/*Michael K. Nutter*/
Michael K. Nutter, Lead Counsel
Reg. No. 44,979