

US010716793B2

(12) United States Patent

Olschewski et al.

(10) Patent No.: US 10,716,793 B2

(45) **Date of Patent:** *Jul. 21, 2020

(54) TREPROSTINIL ADMINISTRATION BY INHALATION

(71) Applicant: United Therapeutics Corporation,

Silver Spring, MD (US)

(72) Inventors: Horst Olschewski, Graz (AT); Robert

Roscigno, Chapel Hill, NC (US); Lewis J. Rubin, LaJolla, CA (US); Thomas Schmehl, Giessen (DE); Werner Seeger, Giessen (DE); Carl Sterritt, Weybridge (GB); Robert Voswinckel,

Giessen (DE)

(73) Assignee: United Therapeutics Corporation,

Silver Spring, MD (US)

(*) Notice: Subject to any disclaimer, the term of this

patent is extended or adjusted under 35

U.S.C. 154(b) by 0 days.

This patent is subject to a terminal dis-

claimer.

(21) Appl. No.: 16/778,662

(22) Filed: Jan. 31, 2020

(65) Prior Publication Data

US 2020/0171044 A1 Jun. 4, 2020

Related U.S. Application Data

- (60) Continuation of application No. 16/536,954, filed on Aug. 9, 2019, which is a continuation of application No. 15/011,999, filed on Feb. 1, 2016, now Pat. No. 10,376,525, which is a division of application No. 13/469,854, filed on May 11, 2012, now Pat. No. 9,339,507, which is a division of application No. 12/591,200, filed on Nov. 12, 2009, now Pat. No. 9,358,240, which is a continuation of application No. 11/748,205, filed on May 14, 2007, now abandoned.
- (60) Provisional application No. 60/800,016, filed on May 15, 2006.

(51) **Int. Cl.**

 A61K 31/557
 (2006.01)

 A61K 9/00
 (2006.01)

 A61K 31/192
 (2006.01)

(52) U.S. Cl.

(58) Field of Classification Search

None

See application file for complete search history.

(56) References Cited

U.S. PATENT DOCUMENTS

3,664,337 A 5/1972 Lindsey et al. 4,001,650 A 1/1977 Romain

4,306,075 A	12/1981	Aristoff
4,306,076 A	12/1981	Nelson
4,349,689 A	9/1982	Aristoff
4,473,296 A	9/1984	Shofner et al.
4,486,598 A	12/1984	Aristoff
4,495,944 A	1/1985	Brisson et al.
4,635,647 A	1/1987	Choksi
4,668,814 A	5/1987	Aristoff
4,677,975 A	7/1987	Edgar et al.
4,683,330 A	7/1987	Aristoff
4,692,464 A	9/1987	Skuballa et al.
4,708,963 A	11/1987	Skuballa et al.
4,976,259 A	12/1990	Higson et al.
4,984,158 A	1/1991	Hillsman
5,063,922 A	11/1991	Hakkinen
5,080,093 A	1/1992	Raabe et al.
5,153,222 A	10/1992	Tadepalli et al.
5,234,953 A	8/1993	Crow et al.
5,322,057 A	6/1994	Raabe et al.
5,361,989 A	11/1994	Merchat et al.
5,363,842 A	11/1994	Mishelevich et al.
5,497,763 A	3/1996	Lloyd et al.
5,551,416 A	9/1996	Stimpson et al.
5,727,542 A	3/1998	King
5,865,171 A	2/1999	Cinquin
5,881,715 A	3/1999	Shibasaki
5,908,158 A	6/1999	Cheiman
6,054,486 A	4/2000	Crow et al.
6,123,068 A	9/2000	Lloyd et al.
6,357,671 B1	3/2002	Cewers
6,521,212 B1	2/2003	Gilles et al.
6,626,843 B2	9/2003	Hillsman
6,756,033 B2	6/2004	Cloutier et al.
6,765,117 B2	7/2004	Moriarty et al.
	(Con	tinued)
	(COII	imaca,

FOREIGN PATENT DOCUMENTS

AU 1999959533 B2 2/2000 DE 19838711 C1 6/2000 (Continued)

OTHER PUBLICATIONS

Abe et al., "Effects of inhaled prostacyclin analogue on chronic hypoxic pulmonary hypertension," J. Cardiovascular Pharmacology, 2001, 37, 239 251.

Agnew JE, Bateman RM, Pavia D, Clarke SW. (1984) Radionuclide demonstration of ventilatory abnormalities in mild asthma. Clinical Science; 66: 525-531.

(Continued)

Primary Examiner — Jeffrey S Lundgren
Assistant Examiner — Michael J Schmitt

(74) Attorney, Agent, or Firm — Foley & Lardner LLP

(57) ABSTRACT

Treprostinil can be administered using a metered dose inhaler. Such administration provides a greater degree of autonomy to patients. Also disclosed are kits that include a metered dose inhaler containing a pharmaceutical formulation containing treprostinil.



(56) References Cited

U.S. PATENT DOCUMENTS

6,803,386	B2	10/2004	Shorr et al.
6,809,223		10/2004	Moriarty et al.
7,172,557	В1	2/2007	Parker
7,199,157		4/2007	Wade et al.
7,261,102		8/2007	Barney et al.
7,384,978		6/2008	Phares et al.
7,417,070		8/2008	Phares et al.
7,544,713	B2	6/2009	Phares et al.
7,726,303	B2	7/2010	Tyvoll et al.
9,339,507	B2 *	5/2016	Olschewski A61P 9/12
9,358,240	B2 *	6/2016	Olschewski A61P 43/00
10,376,525	B2 *	8/2019	Olschewski A61P 11/00
2003/0192532	A1	10/2003	Hopkins
2004/0063912	A1	4/2004	Blumberg et al.
2004/0105819	$\mathbf{A}1$	6/2004	Hale et al.
2004/0149282	A1	8/2004	Hickle
2004/0265238	A1	12/2004	Chaudry
2005/0165111	$\mathbf{A}1$	7/2005	Wade et al.
2005/0166913	A1	8/2005	Sexton et al.
2005/0183719	$\mathbf{A}1$	8/2005	Wuttke et al.
2005/0282901	$\mathbf{A}1$	12/2005	Phares et al.
2006/0147520	A1	7/2006	Ruegg
2006/0201500	$\mathbf{A}1$	9/2006	Von Hollen et al.
2008/0200449	$\mathbf{A}1$	8/2008	Olschewski et al.
2008/0280986	A1	11/2008	Wade et al.
2009/0036465	$\mathbf{A}1$	2/2009	Roscigno et al.
2010/0076083	$\mathbf{A}1$	3/2010	Olschewski et al.
2010/0236545	A1	9/2010	Kern
2010/0282622	$\mathbf{A}1$	11/2010	Phares
2012/0177693	A1	7/2012	Cipolla et al.

FOREIGN PATENT DOCUMENTS

	10001500 11	4 (2 2 2 4
DE	19934582 A1	1/2001
FR	2783431 A1	3/2000
JР	2003-522003 A	7/2003
JP	2004-512101 A	4/2004
JР	2005-034341 A	2/2005
WO	WO 93/00951 A1	1/1993
WO	WO 01/58514 A1	8/2001
WO	WO 01/85241 A1	11/2001
WO	WO 02/34318 A2	5/2002

OTHER PUBLICATIONS

Annals of the International Commission on Radiological Protection (ICRP) vol. 28, No. 3, 1998, Publication 80, Radiation Dose to Patients from Radiopharmaceuticals.

Aradigm Corporation news release Oct. 24, 2005, "Aradigm and United Therapeutics Sign Development and Commercialization Agreement Targeting Pulmonary Hypertension," Red Orbit News, http://www.redorbit.com/modules/news/tools.php?tool=print&id=281787, 2 pages.

Aristoff et al., "Synthesis of benzopyran prostaglandins, potent stable prostacyclin analogs, via an intermolecular mitsunobu reaction." Tetrahedron Letters, 1984, 25(36):3955-3958.

Badesch et al., "Prostanoid Therapy for Pulmonary Arterial Hypertension," Journal of the American College of Cardiology, 2004, 43(12:Suppl.S):56S-61S.

Bein et al., "Cardiovascular and pulmonary effects of aerosolized prostacyclin administration in severe respiratory failure using a ventilator nebulization system," J. Cardiovascular Pharmacology, 1996, 27, 583-586.

Benedict et al., "Evidence-based pharmacologic management of pulmonary arterial hypertension," Clinical Therapeutics, 2007, 29, 2134-2153.

Bindl et al., "Aerosolised prostacyclin for pulmonary hypertension in neonates," Archives of disease in childhood, Fetal and neonatal edition, 1994, 71(3), F214-6.

Blanchard, J.D., Cipolla, D., Liu, K., Morishige, R., Mudumba, S.,

Interferon Gamma-1b following Inhalation via AERx® System vs. Respirgard II[™] Nebulizer Proc. ATS Annual Meeting (Abstract A373), Seattle.

Booke et al., "Prostaglandins in Patients with Pulmonary Hypertension: The Route of Administration," Anesth. Analg., 1998, 86:917, Letter to the Editor.

Boyd, B., Noymer, P., Liu, K., Okikawa, J., Hasegawa, D., Warren, S., Taylor, G., Ferguson, E., Schuster, J., Farr, S., and Gonda, I. (2004) Effect of Gender and Device Mouthpiece Shape on Bolus Insulin Aerosol Delivery Using the AERx Pulmonary Delivery System. Pharmaceutical Research. 21 (10) 1776-1782.

Byron, Peter R., "Drug Delivery Devices, Issues in Drug Development," Proc. Am. Thorac. Soc., 2004, 1:321-328.

Channick et al., "Safety and efficacy of inhaled treprostinil as add-on therapy to bosentan in pulmonary arterial hypertension," J. American College of Cardiology, 2006, 48, 1433-1437.

Colthorpe P, Taylor G, Farr SJ. (1997) A comparison of two non-invasive methods for quantifying aerosol deposition in the lungs of rabbits. J. Aerosol Med.; 10:255.

Defendant Watson Laboratories, Inc.'s Invalidity Contentions for U.S. Pat. No. 9,339,507 and 9,358,240, in The United States District Court for the District of New Jersey, Civil Action No. 3.15:cv-05723-PGS-LHG, Aug. 5, 2016, 56 pages.

Doyle et al., "Inhaled prostacyclin as a selective pulmonary vaso-dilator," Anaesthesia and Intensive Care, Aug. 1996, 24(4):514-515. Dumas et al., "Hypoxic pulmonary vasoconstriction," General Pharmacology, 1999, 33, 289-297.

Dworetz et al., "Survival of infants with persistent pulmonary hypertension without extracorporeal membrane oxygenation," Pediatrics, 1989, 84, 1-6.

EPA Integrated Risk Information System (IRIS): data sheet for 3-methylphenol (m-cresol). Accessed at http://www.epa.gov/iris/subst/0301/htm on Mar. 9, 2014.

EU Community Register, Annexes to Commission Decision C(2005)3436, Sep. 5, 2005, http://ec.europa.eu/health/documents/communityregister/2005/2005090510259/anx_10259_en.pdf (Annex III—Ventavis® Labelling and Package Leaflet), 30 pages.

Ewert et al., "Aerosolized iloprost for primary pulmonary hypertension," New England Journal of Medicine, 2000, 343, 1421-1422. Ewert et al., "Iloprost als inhalative bzw. Intravenose langzeitbehandlung von patienten mit primarer pulmonaler hypertonie," Z. Kardiol., 2000, 89, 987-999.

Farr et al., "Comparison of in vitro and in vivo efficiencies of a novel unit-dose liquid aerosol generator and a pressurized metered dose inhaler," International Journal of Pharmaceutics, 2000, 198:63-70

Final Office Action dated Oct. 10, 2014 in U.S. Appl. No. 12/591,200. Final Office Action dated Oct. 17, 2012 in U.S. Appl. No. 12/591,200. Final Office Action dated Nov. 4, 2013 in U.S. Appl. No. 12/303,877. Final Office Action dated Dec. 22, 2011 in U.S. Appl. No. 12/591,200. Final Office Action dated Jul. 2, 2013 in U.S. Appl. No. 13/120,015. Final Office Action dated Jul. 20, 2015 in U.S. Appl. No. 13/120,015. Final Office Action dated Jul. 20, 2015 in U.S. Appl. No. 13/120,015. Final Office Action dated Aug. 1, 2012 in U.S. Appl. No. 12/303,877. Findlay et al., "Radioimmunoassay for the Chemical Stable Prostacyclin Analog, 15AU81: a Preliminary Pharmacokinetics Study in the Dog," Prostaglandins Leukot. Essent. Fatty Acids, Feb. 1993, 48(2):167-174.

Fink et al., "Use of Prostacyclin and its Analogues in the Treatment of Cardiovascular Disease," Heart Disease, 1999, 1:29-40.

Gessler et al., "Ultrasonic versus jet nebulization of iloprost in severe pulmonary hypertension," Eur. Respir. J., 2001, 17, 14-19. Ghofrani et al., "Hypoxia- and non-hypoxia-related pulmonary hypertension—Established and new therapies," Cardiovascular Research, 2006, 72:30-40.

Ghofrani et al., "New therapies in the treatment of pulmonary hypertension," Herz (Heart), 2005, 4:296-302, with English translation

Hallioglu et al., "Comparison of Acute Hemodynamic Effects of Aerosolized and Intravenous *Iloprost* in Secondary Pulmonary



(56) References Cited

OTHER PUBLICATIONS

Haraldsson et al., "Comparison of inhaled nitric oxide and inhaled aerosolized prostacyclin in the evaluation of heart transplant candidates with elevated pulmonary vascular resistance," Chest, 1998, 114–780-786

Hoeper et al., "A comparison of the acute hemodynamic effects of inhaled nitric oxide and aerosolized iloprost in primary hypertension," J. American College of Cardiology, 2000, 35, 176-182.

Hoeper et al., "Effects of inhaled nitric oxide and aerosolized iloprost in pulmonary veno-occlusive disease," Respiratory Medicine, 1999, 93, 62-70.

Hoeper et al., "Long term treatment of primary pulmonary hypertension with aerosolized iloprost, a prostacyclin analogue," New England Journal of Medicine, 2000, 342, 1866-1870.

Horn et al., "Treprostinil therapy for pulmonary artery hypertension," Expert Opinion on Investigational Drugs, 2002, 11(11):1615-1622.

Howarth, P.H., "Why particle size should affect clinical response to inhaled therapy," Journal of Aerosol Medicine, 2001, 14 Supp. 1, S-27-S-34.

Ichida et al., "Additive effects of beraprost on pulmonary vasodilation by inhaled nitric oxide in children with pulmonary hypertension," American Journal of Cardiology, 1997, 80, 662-664.

Konorza et al., "Klinisch-pharmakologische Austestung bei pulmonaler Hypertonie zur Therapiefuehrung," Herz, 2005, 30:286-295, English abstract on first page.

Krause et al., "Pharmacokinetics and pharmacodynamics of the prostacyclin analogue iloprost in man," Eur. J. Clin. Pharmacol., 1986, 30, 61-68.

Labiris et al., "Pulmonary drug delivery. Part II: The role of inhalant delivery devices and drug formulations in therapeutic effectiveness of aerosolized medications," Br. J. Clin. Pharmacol., 2003, 56(6):600-612

Lee et al., "Current strategies for pulmonary arterial hypertension," J. Internal Medicine, 2005, 258, 199-215.

Martin, John C., "Inhaled Form of Remodulin in the Pipeline," http://www.phneighborhood.com/content/in_the_news/archive_2320,aspx, ph Neighborhood, Oct. 28, 2005, 2 pages.

Max et al., "Inhaled prostacyclin in the treatment of pulmonary hypertension," Eur. J. Pediatr., 1999, 158 Suppl 1, S23-S26.

McNulty et al., "The Pharmacokinetics and Pharmacodynamics of the Prostacyclin Analog 15AU81 in the Anesthetized Beagle Dog," Prostaglandins Leukot. Essent. Fatty Acids, Feb. 1993, 48(2):159-166

Miller et al., "Standardisation of spirometry. Series ATS/ERS Task Force: Standardisation of Lung Function Testing" Eur Respir J 2005; 26: 319-338.

Mueller et al., "Inhaled iloprost in the management of pulmonary hypertension in infants undergoing congenital heart surgery," European Journal of Anaesthesiology, Jun. 2004, 21(Suppl.33):3, Abstract No. 084.

National Radiological Protection Board. Doses to Patients from Medical Radiological Examinations in Great Britain. (1986) Radiological Protection Bulletin No. 77.

Nebu-Tec med. Produkte Eike Kern GmbH, VENTA-NEB®-ir A-I-C-I® Operating Instrutions, Sep. 2005.

Non-Final Office Action dated Jan. 29, 2015 in U.S. Appl. No. 13/120,015.

Non-Final Office Action dated Oct. 11, 2011 in U.S. Appl. No. 12/303,877.

Non-Final Office Action dated Oct. 31, 2012 in U.S. Appl. No. 13/120,015.

Non-Final Office Action dated Dec. 30, 2014 in U.S. Appl. No. 12/303,877.

Non-Final Office Action dated Mar. 15, 2013 in U.S. Appl. No. 12/303.877.

Non-Final Office Action dated Mar. 9, 2014 in U.S. Appl. No. 12/591,200.

Administration of Radioactive Substances Advisory Committee (ARSAC) (Mar. 2006). ARSAC Secretariat, Chilton, Didcot, Oxon. OX11 0RQ.

Notice of Allowance dated Jun. 11, 2015 in U.S. Appl. No. 12/303,877.

Olschewski et al. For the German PPH Study Group, "Inhaled iloprost to treat severe pulmonary hypertension—An uncontrolled trial," Annals of Internal Medicine, 2000, 132, 435-443.

Olschewski et al., Aerosolized prostacyclin and iloprost in severe pulmonary hypertension,: Annals of Internal Medicine, 1996, 124, 820 824.

Olschewski et al., "Inhaled Iloprost for Severe Pulmonary Hypertension," N. Eng. J. Med., Aug. 1, 2002, 347(5):322-329.

Olschewski et al., "Inhaled prostacyclin and iloprost in severe pulmonary hypertension secondary to lung fibrosis," Am. Respir. Crit. Care Med., 1999, 160, 600-607.

Olschewski et al., "Pharmacodynamics and pharmacokinetics of inhaled iloprost, aerosolized by three different devices, in severe pulmonary hypertension," Chest, 2003, 124, 1294-1304.

Olschewski et al., "Prostacyclin and its analogues in the treatment of pulmonary hypertension," Pharmacology and Therapeutics, 2004, 102, 139-153.

Olschewski et al., "Recovery from circulatory shock in severe primary pulmonary hypertension (PPH) with aerosolization of iloprost," Intensive Care Med., 1998, 24, 631-634.

Olschewski, Horst, "Therapie der pulmonalen Hypertonie," Pneumologe, 2004. 1:95-101.

OPTINEB®-ir Operating Instructions, Unit Type ON-100/2-2.4 MHz, 2005, 33 pages, verified English translation.

Pappert et al., "Aerosolized Prostacyclin Versus Inhaled Nitric Oxide in Children with Severe Acute Respiratory Distress Syndrome," Anesthesiology, Jun. 1995, 82(6):1507-1511.

Publications of the International Commission on Radiological Protection (ICRP) (1977) Recommendations of the International Commission on Radiological Protection 26.

Pulmonary Delivery, ONdrugDelivery, 2006, 5 pages.

Rigby, Jonathan, Aradigm Corporation, "Technological advances for success: Product pipeline in targeted pulmonary delivery," Pulmonary Delivery Innovative Technologies Breathing New Life into Inhalable Therapeutics, ONdrugDelivery, http://www.ondrugdelivery.com/publications/Pulmonary.pdf, 2006, 17-19.

Rubin et al., "Pulmonary Arterial Hypertension: A Look to the Future," Journal of the American College of Cardiology, Jun. 18, 2004, 43(12,Suppl.S):89S-90S.

Saini et al., "Effect of Electrostatic Charge and Size Distributions on Respirable Aerosol Deposition in Lung Model," Industry Applications Conference, 2004, 39th IAS Annual Meeting, Conference Record of the 2004 IEEE Seattle, WA, Oct. 3-7, 2004, 2:948-952. Sandifer et al., "Effects of Aerosol vs IV UT-15 on Prostaglandin H₂ Analog-Induced Pulmonary Hypertension in Sheep," Chest, 2005, 128:616S.

Sandifer et al., "Potent effects of aerosol compared with intravenous treprostinil on the pulmonary circulation," J. Appl. Physiol., 2005, 99:2363-2368.

Santak et al., "Prostacyclin aerosol in an infant with pulmonary hypertension," Eur. J. Pediatr., 1995, 154, 233-235.

Scientific discussion for the approval of Ventavis, European Medicines Agency (EMEA), Oct. 20, 2004, 30 pages.

Soditt et al., "Improvement of oxygenation induced by aerosolized prostacyclin in a preterm infant with persistent pulmonary hypertension of the newborn," Intensive Care Med., 1997, 23, 1275-1278. Steffen et al., "The Effects of 15AU81, a Chemically Stable Prostacyclin Analog, on the Cardiovascular and Renin-Angiotensis Systems of Anesthetized Dogs," Prostaglandins, Leukotrienes and Essential Fatty Acids, 1991, 43:277-286.

Stricker et al., "Sustained improvement of performance and haemodynamics with long-term aerosolized prostacyclin therapy in severe pulmonary hypertension," Schweiz Med. Wochenschr., 1999, 129, 923-927.

Van Heerden et al., "Inhaled aerosolized prostacyclin as a selective



(56) References Cited

OTHER PUBLICATIONS

Van Heerden et al., "Re: Delivery of inhaled aerosolized prostacyclin (IAP)," Anaesthesia and Intensive Care, 1996, 24, 624-625.

Voswinckel et al., "Acute effects of the combination of sildenafil and inhaled treprostinil on haemodynamics and gas exchange in pulmonary hypertension," Pulmonary Pharmacology & Therapeutics, 2008, 21, 824-832.

Voswinckel et al., "Favorable Effects of Inhaled Treprostinil in Severe Pulmonary Hypertension," Journal of the American College of Cardiology, 2006, 48(8):1672-1681.

Voswinckel et al., "Inhaled Treprostinil for Treatment of Chronic Pulmonary Arterial Hypertension," Annals of Internal Medicine, Jan. 17, 2006, 144(2):149-150.

Voswinckel et al., "Inhaled treprostinil is a potent pulmonary vasodilator in severe pulmonary hypertension," European Heart Journal, Journal of the European Society of Cardiology, ESC Congress, Aug. 28-Sep. 1, 2004, Munich, Germany, p. 22, abstract 218.

Voswinckel et al., "Inhaled Treprostinil Sodium (TRE) for the Treatment of Pulmonary Hypertension," Circulation, Oct. 2004, Abstract 1414, 110, 17 Supplement.

Voswinckel et al., "Inhaled Treprostinil Sodium (TRE) for the Treatment of Pulmonary Hypertension," Circulation, Oct. 26, 2004, Supplement, 110(17):295, abstract 1414.

Walmrath et al., "Effects of inhaled versus intravenous vasodilators in experimental pulmonary hypertension," Eur. Respir. J., 1997, 10, 1084-1092.

Wasserman et al., "Bronchodilator effects of prostacyclin (PGI2) in dogs and guinea pigs," European Journal of Pharmacology, 1980, 66, 53-63

Watson Laboratories, Inc. (Petitioner) v. United Therapeutics Corp. (Patent Owner), Decision Granting Institute of Inter Partes Review 37 C.F.R. 42.108, IRP2017-01621, U.S. Pat. No. 9,358,240, Jan. 11, 2018.

Watson Laboratories, Inc. (Petitioner) v. United Therapeutics Corp. (Patent Owner), Decision Granting Institute of Inter Partes Review 37 C.F.R. 42.108, IRP2017-01622, U.S. Pat. No. 9,339,507, Jan. 11, 2018.

Watson Laboratories, Inc. (Petitioner) v. United Therapeutics Corp. (Patent Owner), Petition for Inter Partes Review, IRP2017-01622, U.S. Pat. No. 9,339,507, with all Exhibits on exhibit list.

Watson Laboratories, Inc. (Petitioner) v. United Therapeutics Corp. (Patent Owner), Petition for Inter Partes Review, IRP2017-01621, U.S. Pat. No. 9,358,240, with only Exhibits 1002, 1059, 1161 and 1164 and not including exhibits already provide with C2.

Webb et al., "The use of inhaled aerosolized prostacyclin (IAP) in the treatment of pulmonary hypertension secondary to pulmonary embolism," Intensive Care Med., 1996, 22, 353-355.

Wensel et al., "Effects of iloprost inhalation on exercise capacity and ventilator efficiency in patients with primary pulmonary hypertension," Circulation, 2000, 101, 2388-2392.

Wetzel, R.C., "Aerosolized prostacyclin: in search of the ideal pulmonary vasodilator," Anesthesiology, 1995, 82, 1315-1317.

Wittwer et al., "Inhalative Pre-Treatment of Donor Lungs Using the Aerosolized Prostacyclin Analog Iliprost Ameliorates Reperfusion Injury," J. Heart Lung Transplant, 2005, 24:1673-1679.

Zanen et al., "Optimal particle size for beta 2 agonist and anticholinergic aerosols in patients with severe airflow obstruction," Thorax, 1996, 51, 977-980.

Zanen et al., "The optimal particle size for β -adrenergic aerosols in mild asthmatics," International Journal of Pharmaceutics, 1994, 107, 211-217.

* cited by examiner



time [min] time [min] PVR SVR FIGURE 1 <u>ş</u> 30µg Treprostinil (n=12)
45µg Treprostinil (n=9)
60µg Treprostinil (n=20) time [min] time [min] PAP SAP Placebo (n=4) 두 % of baseline values % of baseline values

DOCKET

Explore Litigation Insights



Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time** alerts and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.

