IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Horst OLSCHEWSKI et al.
Title:	TREPROSTINIL ADMINISTRATION BY INHALATION
Appl. No.:	12/591,200
Filing Date:	11/12/2009
Examiner:	Sara Elizabeth Townsley
Art Unit:	1629
Confirmation Number:	4093

DECLARATION UNDER 37 C.F.R. § 1.132 OF DR. ROHAM T. ZAMANIAN

I, Dr. Roham T. Zamanian, hereby declare:

1. I received a Bachelor of Science and a Doctor of Medicine from the University of California, Irvine, where I also completed my internship, residency, and a fellowship in pulmonary medicine and critical care. I completed a second fellowship in pulmonary medicine and critical care at Stanford University Medical Center where I am now an Associate Professor of Medicine and Director of the Adult Pulmonary Hypertension Program.

2. I am board certified in both internal and pulmonary medicine and have served as an investigator in a number of clinical trials of pulmonary hypertension drug trials, which are listed in the attached CV. See EXHIBIT 1.

3. My research focuses on strategies for management of pulmonary hypertension, and I have a number of publications in these areas – listed in the attached CV. See EXHIBIT 1.

4. I am a paid consultant for United Therapeutics, the assignee of the above-identified patent application, in connection with this matter. My compensation does not depend on the content of my opinions or the disposition of this application.

5. Prior to consulting for United Therapeutics, I was a principal investigator in the "Aspire" registry comparing the incidence of respiratory tract adverse events in patients treated with United Therapeutics' product – Tyvaso® – with other FDA approved pulmonary hypertension therapies. Stanford University has also received compensation from United Therapeutics for my work as an investigator on the Confront and Freedom M trails.

The Cited References

6. I am familiar with the Office Action dated October 10, 2014 in U.S. Patent Application No. 12/591,200 as well as the disclosure and claims of the subject application. I am also familiar with the references cited in the Office Action.

7. I understand the claims of U.S. Patent Application No. 12/591,200 are directed to a method of treating pulmonary hypertension comprising administering by inhalation to a human in need thereof a therapeutically effective single event dose of an inhalable formulation with a pulsed ultrasonic nebulizer, wherein said therapeutically effective single event dose comprises from 15 μg to 90 μg of treprostinil or a pharmaceutically acceptable salt thereof, said therapeutically effective single event dose is inhaled in 18 or less breaths by the human

8. I have reviewed US 2004/0265238 (Chaudry) and U.S. Patent No. 6,357,671 (Cewers) cited in the Office Action, in addition to further references pertinent in the art regarding inhaled pulmonary hypertension treatment – specifically those references cited herein and attached as EXHIBITS 2-7.

9. Chaudry broadly relates to inhalable formulations for treating pulmonary hypertension and methods of using the same, see, *e.g.* title. Among the list of hypertension reducing

agents included the extensive list of paragraphs [0022]-[0027] are treprostinil and iloprost. Both compounds are cited among examples of vasodilators in paragraph [0026] that may ostensibly be used interchangeably with any other compound disclosed in the paragraph.

10. An exemplary embodiment of the claimed invention comprising treprostinil is FDA approved for use with pulmonary hypertension and available on the market as Tyvaso®. An inhalable formulation for treating pulmonary hypertension containing iloprost, Ventavis®, is also FDA approved and currently available on the market.

11. Contrary to the disclosure of Chaudry, Tyvaso® is not interchangeable with Ventavis®; rather, based on my clinical experience and the surrounding literature, Tyvaso® is preferable to Ventavis®.

I. Skepticism and long-felt need prior to Tyvaso®

12. As of May 15, 2006, the results of the Aerosolized Iloprost Randomized Study (AIR) documenting the effects of inhaled iloprost had been public about three and a half years, and Ventavis® had only been on the market for about one and a half years. *See* Olschewski et al. N Engl. J. Med. 2002;347(5):322-329 (EXHIBIT 2), FDA Listing of Priority NDA and BLA Approvals in 2004 (EXHIBIT 3); *see also* Lee et al. J. Int. Med. 2005;258:199-215 (EXHIBIT 4).

13. Clinicians were largely still of the opinion that intravenous administration of a prostacyclin analog was preferable to inhaled delivery. Thus, there was concern that the adoption Ventavis® could be happening too rapidly without a full understanding of the side effects.

14. Further, adoption of Ventavis® posed a number of issues. For instance, Ventavis® required administration 6-9 times daily, which was considered challenging for patients to implement. Moreover, clinicians remained concerned about the lack of nocturnal dosing

and physiologic impact of withdrawal during the night and early morning hours. There were concerns on how to address the interaction between the patient and the nebulizer and how to administer the therapy if the patient was either altered in mental status or intubated in the intensive care unit.

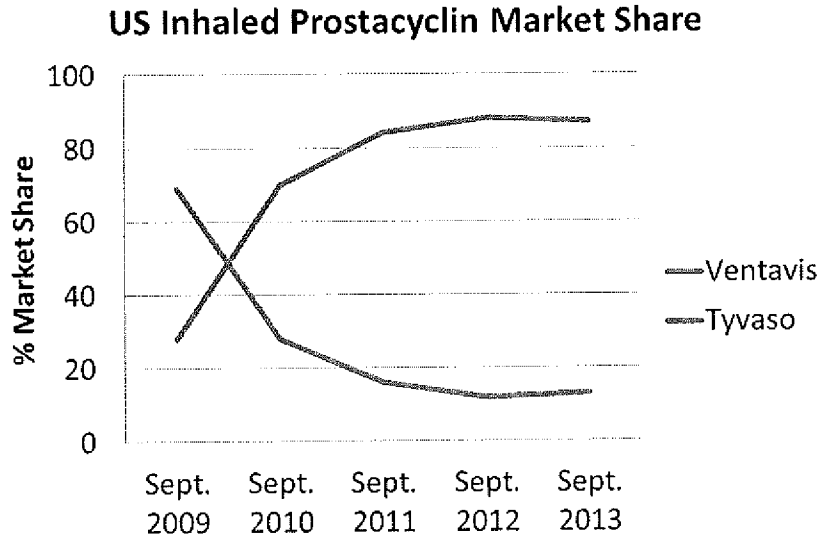
15. As of May 15, 2006, clinicians would not have arrived at a method of treatment using inhaled treprostinil according to the present claims. There was too much uncertainty as to the effects of inhaled iloprost to speculate the potential effects of another inhaled formulation comprising a prostacyclin analog. Indeed, the medical community remained convinced that intravenous administration was preferable to inhalable therapeutics.

16. Moreover, at that time, the pharmacodynamics of inhaled treprostinil would have been unpredictable; thus, precluding the ability to arrive at dosing regimens such as those claimed. Factors such as half-life, drug-drug interactions, and adverse events could not be predicted based on the then available formulations of treprostinil.

17. For at least these reasons, the benefits of inhaled treprostinil – such as those listed in the specification of the pending application at, for example, paragraphs [0081] to [0088] and in Figures 6, 10, and 11(discussed in detail below) – would not have been contemplated or expected as of May 15, 2006.

II. Commercial success of Tyvaso®

18. Interestingly, once Tyvaso® entered the market, it was clinically preferred to Ventavis®. As indicated by the graph below, after its entry onto the market, Tyvaso® rapidly increased its market share, while the share held by Ventavis® rapidly decreased.



19. I believe the tradeoff in market share results from the clinical advantages that Tyvaso® has over Ventavis®.

A. <u>Tyvaso® requires less frequent administration.</u>

20. Because of the pharmacodynamic differences between iloprost and treprostinil, Tyvaso® does not need to be administered as frequently as Ventavis®, leading to higher patient compliance.

21. Ventavis® (inhaled iloprost) has a half-life between 20-25 min. As a result, Ventavis® needs to be used 6-9 times a day, as frequent as every 2 hours.

22. In contrast, Tyvaso® (inhaled treprostinil) has a much longer half-life when inhaled by human subjects suffering from pulmonary hypertension. This allows Tyvaso® to be administered markedly less frequently – about 1 to 4 times a day.

23. In my clinical practice, I have found that patients are more likely to comply with a regimen that requires less frequent administrations; thus, Tyvaso® has been preferable.

24. Furthermore, the fact that Ventavis® has a short half-life results in periods where patients may be off-medication while asleep unless they wake up to take a dose of the drug.

Nocturnal hypoxemia is a common symptom of patients with pulmonary hypertension; thus, periods where a patient is off-medication and asleep present face less risk if Tyvaso® is prescribed instead of Ventavis®.

B. The pulsed ultrasonic nebulizer used with Tyvaso® is preferred by patients.

25. The differences in the devices used to administer each drug also results in higher patient preference and compliance with Tyvaso®.

26. Ventavis® employs an adaptive aerosol delivery (AAD) nebulizer. *See* Ventavis® Patient Brochure (EXHIBIT 5). Such a device adjusts the dose amount to the volume of the breath the patient takes in. Thus, the duration of use of the device is dependent on the patient's breathing. This can lead to the time engagement required to deliver the drug ranging from 10-20 min, depending on the AAD device. Each time the patient uses the device, the patient has to load in the drug. Once the dose is delivered, the patient has to take apart the device, remove the mesh, and then clean the mesh in distilled water. Each use of Ventavis® is, thus, a time-intensive process.

27. In contrast, Tyvaso® employs a pulsed ultrasonic nebulizer, as indicated in the pending claims. *See* Tyvaso® Patient Brochure (EXHIBIT 6). With this device, the dose is a fixed bolus dose per breath; thus, the dosing is based on breath number, e.g. 18 breaths or less as claimed. *Id*; *see also* Specification at paragraphs [0040], [0070], and [0078]. Unlike the Ventavis® device, this device is filled once a day; nothing in the way of cleaning or disassembly is done with the device until the end of the day.

28. In my clinical practice, I have found that this results in a better patient experience and, thus, higher patient compliance.

III. Unexpected Results

29. The results of the studies disclosed in the present application demonstrate that aerosolized terprostinil administered according to the instant claims has a dose dependent and longer pharmacokinetic effect than would be expected based on iloprost.

30. As noted in paragraph [0081], while the maximum effect of aerosoloized iloprost and treprostinil on pulmonary vascular resistance (PVR) was comparable, treatment with treprostinil achieved this maximum effect much sooner and lasted for a longer duration compared to treatment with iloprost. Further, while iloprost is known to reduce systemic arterial pressure (SAP), Figure 6C demonstrates that administration of treprostinil does not result in this same reduction of SAP.

31. Regardless of pulse number in which dose was administered, administration of aerosolized treprostinil resulted in no significant effect on SAP. Of particular clinical interest is the high reduction of PVR achieved in a three-pulse administration of 15 μg of treprostinil, which appears to have the most modest impact on SAP based on Figures 10 and 11.

32. These data suggest that treprostinil is far more pulmonary selective than iloprost: a result that would have been unexpected as of May 15, 2006. *See* Whittle Biochem. Pharmacol. 2012; 84:68-75 (a post-filing article describing potential mechanistic differences that may explain this difference in effect, EXHIBIT 7).

IV. Conclusion

33. Although not expected as of May 15, 2006, Tyvaso® is clinically superior to Ventavis® and preferred to Ventavis® for at least the above mentioned reasons. Further, the claimed method employing inhaled treprostinil results in unexpected benefits for treatment of pulmonary hypertension.

34. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further, that

these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed this 9th day of November, 2015.

Dr. Roham T. Zamanian

EXHIBIT 1

A. BIOGRAPHICAL INFORMATION

Roham T. Zamanian, M.D.
Division of Pulmonary & Critical Care Medicine
Stanford University Medical Center
300 Pasteur Dr, Room H3143
Stanford, CA 94305

B. ACADEMIC HISTORY

1. Colleges and Universities Attended

1989 - 1994	**Bachelor of Science**, Biological Sciences University of California, Irvine
1995 - 1999	**Doctor of Medicine** University of California, Irvine College of Medicine
1999 - 2002	**Internship and Residency, Internal Medicine** University of California, Irvine Medical Center (UCIMC)
2002 - 2003	**Pulmonary & Critical Care Fellowship** Division of Pulmonary & Critical Care Medicine University of California, Irvine Medical Center
2003 - 2005	**Pulmonary & Critical Care Fellowship** Division of Pulmonary & Critical Care Medicine Stanford University Medical Center
2004 - 2006	**eBay Advanced Fellowship in Pulmonary Vascular Disease** Vera Moulton Wall Center for Pulmonary Vascular Disease Stanford University Medical Center

2. Undergraduate and Medical School Awards and Activities

- Dean's Honor List (1990-1994)
- The Campuswide Honors Program (1990-1994)
- Howard Hughes Summer Fellow, Harvard School of Medicine (1991, 1992)
- UCI Undergraduate Excellence in Research Award (1994)
- Ralph Waldo Gerard Award for Outstanding Researcher (1994)

3. Internship, Residency, and Fellowship Training and Awards

- Intern of the year, UCIMC Dept of Medicine (1999-2000)
- Case Presentation Award, American College of Chest Physicians (2000)
- Department of Internal Medicine Research Presentation Award, UCIMC (2001)
- Fellow of the Year, UCIMC Dept of Medicine (2002-2003)
- Entelligence Young Investigator's Career Development Award (2006)
- American College of Chest Physicians Fellow (2007)
- Stanford University, Dept. of Medicine, Division of PCCM Teaching Award (2007)

4. Board Certification

- 2003 American Board of Internal Medicine - Internal Medicine
- 2006 American Board of Internal Medicine - Pulmonary

C. STANFORD UNIVERSITY EMPLOYMENT HISTORY

7/1/2006-8/1/2007	Instructor of Medicine Division of Pulmonary & Critical Care Medicine Vera Moulton Wall Center for Pulmonary Vascular Disease Stanford University School of Medicine
8/1/2007-7/1/2008	Acting Assistant Professor of Medicine Division of Pulmonary and Critical Care Medicine Vera Moulton Wall Center for Pulmonary Vascular Disease Stanford University School of Medicine
7/1/2008-11/2014	Assistant Professor of Medicine Division of Pulmonary and Critical Care Medicine Vera Moulton Wall Center for Pulmonary Vascular Disease Stanford University School of Medicine
11/2014-Present	Associate Professor of Medicine Division of Pulmonary and Critical Care Medicine Vera Moulton Wall Center for Pulmonary Vascular Disease Stanford University School of Medicine
2/1/2009-6/30/2012	Secondary Affiliation in Division of Immunology Stanford University School of Medicine
06/2006-Present	Director, Adult PH Cardiac Catheterization Laboratory Adult Pulmonary Hypertension Clinical Service Division of Pulmonary & Critical Care Medicine Vera Moulton Wall Center for Pulmonary Vascular Disease Stanford University School of Medicine
01/2007-Present	Clinical Manager, VMWC Clinical Database Vera Moulton Wall Center for Pulmonary Vascular Disease Stanford University School of Medicine
10/2007 - Present	Director, Adult Pulmonary Hypertension Clinical Service Division of Pulmonary & Critical Care Medicine Vera Moulton Wall Center for Pulmonary Vascular Disease Stanford University School of Medicine
09/2013 – 09/2018	Junior Faculty Scholar Award Vera Moulton Wall Center for Pulmonary Vascular Disease Stanford University School of Medicine

D. PUBLIC AND PROFESSIONAL SERVICE

1. Society Membership & Leadership

- Pulmonary Hypertension Association – Scientific Leadership Council
  - The PHCC Committee – Chair Task Force #2 (funding & sustainability)
  - The Insurance and Advocacy Committee (member)
- International Right Heart Failure Foundation Scientific Working Group (member).
- Pulmonary Vascular Research Institute – Fellow

- American Thoracic Society
- American College of Chest Physicians - Fellow
- International Society for Heart and Lung Transplantation

2. Editorship

American Thoracic Society Pulmonary Circulation – Pulmonary Hypertension Journal Club (2007-2011)

3. AdHoc Reviewer

- Lancet
- Circulation
- Journal of the Amercian College of Cardiology
- American Journal of Respiratory & Critical Care Medine
- European Respiratory Journal
- CHEST
- Journal of Cardiac Failure
- International Journal of Rheumatology
- Biomarkers
- Lung
- American Heart Journal

4. Clinical Trial Committee Memberships

- ASCO1 – Steering Committee Member.
  Rituximab for Scleroderma Associated Pulmonary Arterial Hypertension.
  NIH/NIAID (2010-present)

- SYMPHONY – Steering Committee Member.
  A StudY of Macitentan in Pulmonary arterial HypertensiON to validate PAH-SYMPACT.
  Actelion (2012-present)

- CMREF Ranolazine – Chair, Data and Safety Monitor Board.
  A Randomized, Double-blind, Placebo controlled, Multi-center study to Assess the Effect of Ranolazine on Outcomes and Right Heart Function in PAH.
  Cardiovascular Medical Research Education Fund & Gilead Sciences (2013-present)

- Pfizer #A1481324 – Member, Revatio Clinical Endpoint Adjudication Committee.
  A Multinational Multicenter Study to Assess the Effects of Oral Sildenafil on Mortality in Adults with PAH. (2014 – Present)

5. Grant Review / Study Sections

- Pulmonary VA Merit Grant Reviewer (2012)
- VA Merit Grant Pulmonary Board External Referee for William S. Middleton Memorial Veterans Hospital (2014)

E. GRANTS & AWARDS

Completed:

Study: The VISION Trial - A Randomized, Double-blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of the Addition of Inhaled Iloprost in Patients with Pulmonary Arterial Hypertension (PAH) Receiving Oral Sildenafil.

Role: Co-PI for a multi-site trial at Stanford (PI - Ramona Doyle)
Type: Industry-initiated multi-institutional trial
Sponsor: Industry (Actelion Pharmaceutical)
Subjects: Total 67, Stanford 2
Clinicaltrial.gov #: NCT00302211

Study: Effect of Pioglitazone versus Bosentan on Metabolic Profiles and Outcomes of Insulin Resistant Patients with Pulmonary Arterial Hypertension
Role: Senior Investigator for the overall study
Type: Investigator-initiated single institutional trial
Sponsor: Industry (Actelion Pharmaceutical)
Subjects: Stanford 2
Clinicaltrial.gov #: NCT00825266

Study: The REVEAL Registry – Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Characterization and Management
Role: Principal investigator for a multi-site trial at Stanford
Type: Industry-initiated multi-institutional trial
Sponsor: Industry (Actelion Pharmaceutical)
Subjects: Total 3500, Stanford 52
Clinicaltrial.gov #: NCT00370214

Study: Open Label Extension of the FREEDOM-C Trial - An International, Multicenter, Randomized, Double-blind, Placebo- Controlled Comparison of the Efficacy and Safety of Oral UT-15C Sustained Release Tablets in Combination with an Endothelin Receptor Antagonists and/or a Phosphodiestrase-5 Inhibitor in Subjects with Pulmonary Arterial Hypertension.
Role: Principal investigator for a multi-site trial at Stanford
Type: Industry-initiated multi-institutional trial
Sponsor: Industry (United Therapeutics Pharmaceutical)
Subjects: Total 900, Stanford 3
Clinicaltrial.gov #: NCT01027949

Study: The PROSPECT Registry – Registry to Evaluate Room Temperature Stable Epoprostenol.
Role: Principal investigator for a multi-site trial at Stanford
Type: Industry-initiated multi-institutional trial
Sponsor: Industry (Actelion Pharmaceutical)
Subjects: Total 200, Stanford 7
Clinicaltrial.gov #: Pending

Current:

Grant: Proteomics of Inflammation, Immunity and Pulmonary Arterial Hypertension
Source: National Institutes of Health / The National Heart, Lung, and Blood Institute
Dates: 08/2010 – 08/2015; Enrolling.
Role: Human Core Director, (PI – Gary Nolan)

Grant: Elafin Therapy for Lung Diseases
Source: National Institutes of Health / National Heart Lung and Blood Institute (PAR-09-185)
Dates: 08/2011 – 08/2015; Enrolling.

Role: Human Core Co-Director, (PI – Marlene Rabinovitch)

Grant: iPSC Derived Endothelial Cells as Surrogates using Pulmonary Hypertension as a Prototype Disease
Source: NIH / National Heart Lung and Blood Institute (1U01HL107393-01)
Dates: 07/2011 – 06/2016; Enrolling.
Role: Co-Investigator, (PI – Marlene Rabinovitch)

Grant: Stanford PAH Transplant and Preparation Center
Source: Continuing Medical Research and Education Fund (CMREF UL1RR024986)
Dates: 04/2006 – 03/2015; Enrolling.
Role: CO-PI, (PI – Marlene Rabinovitch)

Study: Treatment of Systemic Sclerosis-Associated Pulmonary Arterial Hypertension with a Monoclonal Antibody to CD20 (Rituximab)
Role: Co-investigator for the overall study
Type: Cooperative group clinical trial
Sponsor: National Institutes of Child Health and Human Development – (U19 AI 056362)
Subjects: Total 27, Stanford 6 (Goal 80)
Clinicaltrial.gov #: NCT01086540

Study: CONFRONT PAH – A 48-week Study of the Effect of Dual Therapy (Inhaled Treprostinil and Tadafafil) Versus Mono-therapy (Tadalafil), 2 FDA Approved Pulmonary Hypertension Medications.
Role: Senior Investigator for the overall study
Type: Investigator-initiated multi-institutional trial
Sponsor: Industry (United Therapeutics Pharmaceutical)
Subjects: Total 21, Stanford 11 (Goal 30)
Clinicaltrial.gov #: NCT01305252

Study: Study of Incidence of Respiratory Tract Adverse Events in Patients Treated With Tyvaso® Compared to Other FDA Approved Pulmonary Arterial Hypertension (PAH) Therapies (Aspire)
Role: Principal investigator for a multi-site trial at Stanford
Type: Industry-initiated multi-institutional trial
Sponsor: Industry (United Therapeutics Pharmaceutical)
Subjects: Total 1320, Stanford 42
Clinicaltrial.gov #: NCT01266265

Study: TrANsFoRM PAH – Phase II Study of Safety, Tolerability, and Efficacy of FK-506 (Tacrolimus) in Pulmonary Arterial Hypertension.
Role: Co-Senior Investigator for the overall study
Type: Investigator-initiated single-center trial
Sponsor: University (Vera Moulton Wall Center & SPARK @ Stanford University)
Subjects: Total 24, Goal 40
Clinicaltrial.gov #: NCT01647945

Study: SYMPHONY – A multi-center, open-label, single-arm, Phase 3b study of macitentan in patients with Pulmonary Arterial Hypertension to psychometrically validate the PAH-SYMPACT instrument
Role: Investigator & Steering Committee Member
Type: Investigator-initiated single-center trial
Sponsor: Actelion Pharmaceuticals US, Inc.
Subjects: Total 275, Stanford (pending)

Clinicaltrial.gov #: NCT01841762

F. PUBLICATIONS [53 total: 47 published; 2 in press; 4 submitted]

Peer-Reviewed [51 total; 45 published; 2 in press; 4 submitted]

1. J Sechrist, MA Nieto, **RT Zamanian**, M Bronner-Fraser. Regulative Response of the Cranial Neural Tube after Neural Fold Ablation: Spatiotemporal Nature of Neural Crest Regeneration and up-regulation of *Slug*. *Development* 1995 121, 4103-4115 (1995).

2. J Olsson, **RT Zamanian.** Toxicity of Local Anesthetics in the Emergency Department. emedicine (Emergency Medicine) Online. 2005 ***www.emedicine.com***

3. J Olsson, **RT Zamanian,** JA Feinstein, RL Doyle. Surgical Strategies for Management of Pulmonary Arterial Hypertension. *Semin Respir Crit Care Med.* 2005 Aug; 26(4):417-28.

4. E Ketchum, **RT Zamanian,** D Fleischmann. CT-Angiography of Pulmonary Artery Thrombi and Aneurysms in Hughes-Stovin Syndrome. *Am J Roentgenol.* 2005 Aug; 185(2):330-2.

5. **RT Zamanian**, F Haddad, RL Doyle, A Weinacker. Management Strategies for Patients with Pulmonary Hypertension in the Intensive Care Unit. *Critical Care Medicine*, 2007 Sep; 35(9):2037-50.

6. CI Zoumalan, **RT Zamanian**, RL Doyle, MF Marmor. ERG evaluation of daily, high-dose sildenafil usage. *Doc Ophthalmol,* 2009 Jun;118(3):225-31. Epub 2008 Sept 26.

7. GS Horng, E Ashley, L Balsam, B Reitz, **RT Zamanian**. Progressive dyspnea after CABG: Complication of Retained Epicardial Pacing Wires. *Ann Thorac Surg*, 2008 Oct;86(4):1352-4.

8. **RT Zamanian,** M Gould. Effectiveness and cost effectiveness of thrombolysis in patients with acute pulmonary embolism. *Curr Opin Pulm Med,* 2008 Sep;14(5):422-6.

9. CE Ventetuolo, RL Benza, AJ Peacock, **RT Zamanian**, DB Badesch, SM Kawut. Surrogate and combined end points in pulmonary arterial hypertension. *Proc Am Thorac Soc.* 2008 Jul 15;5(5):617-22.

10. **RT Zamanian**, G Hansmann, S Snook, D Lilienfeld, K Rappaport, M Rabinovitch, G Reaven, RL Doyle. Insulin Resistance in Pulmonary Arterial Hypertension. *Eur Respir J.* 2009 Feb;33(2):318-24. Epub 2008 Dec 1.

11. VA de Jesus Perez, F Haddad, RH Vagelos, W Fearon, J Feinstein, **RT Zamanian.** Angina associated with left main coronary artery compression in pulmonary hypertension. *J Heart Lung Transplant.* 2009 May;28(5):527-30. Epub 2009 Feb 20.

12. Haddad F, **Zamanian RT**, Beraud AS, Schnittger I, Feinstein J, Peterson T, Yang P, Doyle RL, Rosenthal D. A Novel Non-Invasive Method of Estimating Pulmonary Vascular Resistance in Patients With Pulmonary Arterial Hypertension. *J Am Soc Echocardiogr* 2009;22:523-529.

13. G Hansmann, **RT Zamanian**. PPARγ Activation: A Novel Treatment for Pulmonary Arterial Hypertensions. *Sci Transl Med.* 2009 Dec 23;1(12):12ps14..

14. Chung L, Liu J, Parsons L, Hassoun PM, McGoon M, Badesch DB, Miller DP, Nicolls MR, **Zamanian RT**. Characterization of connective tissue disease-associated pulmonary arterial hypertension from REVEAL: identifying systemic sclerosis as a unique phenotype. *Chest.* 2010 Dec;138(6):1383-94. Epub 2010 May 27.

15. Elliott CG, Barst RJ, Seeger W, Porres-Aguilar M, Brown LM, **Zamanian RT**, Rubin LJ. Worldwide physician education and training in pulmonary hypertension: pulmonary vascular disease: the global perspective. *Chest.* 2010 Jun;137(6 Suppl):85S-94S.

16. Kudelko KT, Nadeau K, Leung AN, Liu J, Haddad F, **Zamanian RT**, De Jesus Perez V. Epoprostenol-associated pneumonitis: diagnostic use of a T-cell proliferation assay. *J Heart Lung Transplant.* 2010 Sep;29(9):1071-5. Epub 2010 Jun 8.

17. Banerjee D, Haddad F, **Zamanian RT**, Nagendran J. Right ventricular failure: a novel era of targeted therapy. *Curr Heart Fail Rep.* 2010 Dec;7(4):202-11.

18. Kao L, Myer P, Nguyen L, **Zamanian RT**, Chung L. Colonic ulceration as an unusual manifestation of vasculopathy in systemic sclerosis. *Rheumatology* (Oxford). 2011 Mar;50(3):626-8. Epub 2010 Dec 20.

19. de Jesus Perez V, Kudelko K, Snook S, **Zamanian RT**. Drugs and toxins-associated pulmonary arterial hypertension: lessons learned and challenges ahead. *Int J Clin Pract* Suppl. 2011 Jan;(169):8-10. doi: 10.1111/j.1742-1241.2010.02606.

20. Chandra SM, Razavi H, Kim J, Agrawal R, Kundu RK, de Jesus Perez V, **Zamanian RT**, Quertermous T, Chun HJ. Disruption of the apelin-APJ system worsens hypoxia-induced pulmonary hypertension. *Arterioscler Thromb Vasc Biol.* 2011 Apr;31(4):814-20. Epub 2011 Jan 13.

21. Perez VA, **Zamanian RT**. Chronic thromboembolic pulmonary hypertension. *N Engl J Med.* 2011 Apr 28;364(17):1677.

22. Haddad F, Fuh E, Peterson T, Skhiri M, Kudelko KT, De Jesus Perez V, Winkelmayer WC, Doyle RL, Chertow GM, **Zamanian RT**. Incidence, correlates, and consequences of acute kidney injury in patients with pulmonary arterial hypertension hospitalized with acute right-side heart failure. *J Card Fail.* 2011 Jul;17(7):533-9. Epub 2011 Apr 22.

23. Hansmann G, Plouffe BD, Hatch A, von Gise A, Sallmon H, **Zamanian RT**, Murthy SK. Design and validation of an endothelial progenitor cell capture chip and its application in patients with pulmonary arterial hypertension. *J Mol Med (Berl).* 2011 Jul 7.

24. Haddad F, Kudelko K, Mercier O, Vrtovec B, **Zamanian RT**, de Jesus Perez V. Pulmonary hypertension associated with left heart disease: characteristics, emerging concepts, and treatment strategies. *Prog Cardiovasc Dis.* 2011 Sep-Oct;54(2):154-67.

25. Haddad F, Peterson T, Fuh E, Kudelko K, de Jesus Perez V, Skhiri M, Vagelos R, Schnittger I, Denault AY, David R, Doyle R, **Zamanian RT**. Characteristics and Outcome following Hospitalization for Acute Right Heart Failure in patients with Pulmonary Arterial Hypertension. *Circ Heart Fail* 2011 Nov;4(6):692-9. Epub 2011 Sep 9.

26. Ayala E, Kudelko KT, Haddad F, **Zamanian RT**, De Jesus Perez V. The Intersection of Genes and Environment: Development of Pulmonary Arterial Hypertension in a patient with Hereditary Hemorrhagic Telangiectasia and Stimulant Exposure. *CHEST 2012* Jun;141(6):1598-600.

27. Maxwell BG, Pearl RG, Kudelko KT, **Zamanian RT**, Hill CC. Airway Management and Perioperative Decision Making in the Patient With Severe Pulmonary Hypertension Who Requires Emergency Noncardiac Surgery. *J Cardiothorac Vasc Anesth.* 2012 Oct;26(5):940-4.

28. Perez VA, Rosenzweig E, Rubin LJ, Poch D, Bajwa A, Park M, Jain M, Bourge RC, Kudelko K, Spiekerkoetter E, Liu J, Hsi A, **Zamanian RT**. Safety and Efficacy of Transition from Systemic Prostanoids to Inhaled Treprostinil in Pulmonary Arterial Hypertension. *Am J Cardiol.* 2012 Nov 15;110(10):1546-50. [Epub ahead of print]

29. Perez VA, Haddad F, **Zamanian RT**. Diagnosis and management of pulmonary hypertension associated with left ventricular diastolic dysfunction. *Pulm Circ.* 2012 Apr;2(2):163-9.

30. Barst RJ, Chung L, **Zamanian RT**, Turner M, McGoon M. Functional Class Improvement and Three-Year Survival Outcomes in Patients With Pulmonary Arterial Hypertension in the REVEAL Registry. *CHEST* 2013 Jul;144(1):160-8.

31. Waxman AB, **Zamanian RT**. Pulmonary Arterial Hypertension: New insights into the optimal role of current and emerging prostacyclin therapies. *Am J Cardiol.* 2013 Mar4;111(5Suppl):1A-16A.

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49. Kudelko K, Snook S, Tannenbaum CE, Spiekerkoetter E, De Jesus Perez V, Liu J, Haddad F, Doyle RL, Kawut SM, **Zamanian RT**. Characterization of Patients with Drugs and Toxins Associated Pulmonary Arterial Hypertension: A Clinical and Outcomes Perspective. *Am J Respir Crit Care Med (In Submission)*

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51. Maron BA, Maddox TM, Hess E, Opotowsky AR, Tedford RJ, Lahm T, Joynt KE, Kass DJ, Stephens T, Stanislawski MA, Swenson ER, Goldstein RH, Leopold JA, **Zamanian RT**, M.D.,10 Elwing JM, Plomondon ME, Grunwald GK, Barón AE, Rumsfeld J, Choudhary G. Association of Subclinical Pulmonary Hypertension with Mortality and Hospitalization: Insights from the VA-CART Program. *NEJM (In Submission)*

Non-Peer Reviewed (2 published)

1. **RT Zamanian.** Nosocomial Infections in the Intensive Care Unit. *Respiratory Therapy International*, 1996 Vol 5 (1), 87-89.

2. **RT Zamanian.** Double Lung Transplantation in Cystic Fibrosis Patients. *Respiratory Therapy International*, 1996 Vol 5 (1), 39-40.

Book Chapters (3 published)

1. M Brenner, M Safani, G Heal, F Mazdisnian, R Klein, **R Zamanian**, S Gallacher, H Poggemeyer, G Foster, F Daneschvar, M Krutzik, A Wilson. Current Clinical Strategies: Manual of Critical Care Medicine. 2002-2003 Edition. CCS Publishing.

2. DV Daniels, SG Rockson, R Vagelos. Concise Cardiolog: An Evidence-Based Handbook – Chapter 10: Pulmonary Hypertension. F Haddad, RL Doyle, JC Liu, **RT Zamanian**. Lippincott Williams & Wilkins 2008.

3. O Distler et al. Scleroderma – modern aspects of pathogenesis, diagnosis, and therapy. Chapter 4: PAH in Systemic Sclerosis. L Chung & **RT Zamanian**. Auflage – Bermen: UNI-MED, 2009.

G. Lectureships and Selected Presentations

International

- "Methamphetamine Associated Pulmonary Arterial Hypertension"
  Stanford CV Institute – Gachon University Collaborative, July 2014

Incheon, Korea

- "Methamphetamine Associated Pulmonary Arterial Hypertension"
  European Respiratory Society, September 2013
  Barcelona, Spain

- "An Update on Insulin Resistance in Pulmonary Arterial Hypertension"
  International Society for Heart & Lung Transplantation Society, April 2013
  Montreal, Canada

- "Novel Future Therapeutics in Pulmonary Arterial Hypertension"
  Asia Pacific Cardiology Conference, February 2013
  Pattaya, Thailand

- "Refining Views of Co-morbidities and Vascular Responsiveness in Pulmonary Arterial Hypertension"
  Pulmonary Vascular Medicine Grand Rounds, September 2011
  Sheffield University, UK

- "Insulin Resistance in Pulmonary Arterial Hypertension"
  European Respiratory Society, September 2010
  Barcelona, Spain

- "Role of PPAR-gamma in PAH"
  Clinical trial debate organizer
  Pulmonary Vascular Research Institute Annual Meeting, January 2009
  Mexico City, Mexico

United States

- "The New Era in Chronic Obstructive Pulmonary Disease"
  Medicine Ground Rounds, October 2004
  Doctor's Medical Center, Modesto, CA

- "An Update on Pulmonary Arterial Hypertension"
  Medicine Ground Rounds, December 2004
  St. Luke's Hospital, San Francisco, CA

- "Management Strategies in Pulmonary Arterial Hypertension"
  Medicine Ground Rounds, January 2005
  Highland Hospital, Oakland, CA

- "Current Research & Future Therapies for Pulmonary Arterial Hypertension"
  Pulmonary Hypertension Association - California PH Forum
  Burlingame, CA, June 2005

- "Diagnosis and Treatment of Pulmonary Arterial Hypertension"
  Medicine Grand Rounds, July 2006
  St. Rose Hospital, Hayward, CA

- "Insulin Resistance in Pulmonary Arterial Hypertension"
  Pulmonary Medicine Grand Rounds, February 2007

University of Rochester, Rochester, NY

- "Novel Biomarkers and Disease Modifiers in Pulmonary Arterial Hypertension"
  Vascular Biology Seminar, March 2007
  National Institutes of Health, Washington DC

- "Insulin Resistance in Pulmonary Arterial Hypertension"
  Pulmonary & Critical Care Medicine Grand Rounds, June 2007
  Columbia University Medical Center, New York, NY

- "An Update on the Management of Pulmonary Arterial Hypertension"
  Medicine Grand Rounds, June 2007
  Sequoia Hospital, Redwood City, CA

- "Diagnosis and Management of Pulmonary Arterial Hypertension"
  Medicine Grand Rounds, June 2010
  Eden Medical Center, Castro Valley, CA

- "Discovering Novel Biomarkers, Risk Factors, and Etiologies – A New Wave of Clinical Research in Pulmonary Arterial Hypertension"
  Pulmonary & Critical Care Medicine Grand Rounds, May 2010
  University of California, San Diego, CA

- "Controversies in Management of Pulmonary Arterial Hypertension"
  Medicine Grand Rounds, July 2011
  John Muir Medical Center, Concord, CA

- "Guide to Diagnosis and Treatment of Pulmonary Arterial Hypertension"
  Primary Care Medicine Grand Rounds, November 2011
  St. Joseph Medical Center, Phoenix, AZ

- "Refining Views of Co-morbidities and Vascular Responsiveness in Pulmonary Arterial Hypertension"
  Pulmonary & Critical Care Grand Rounds, December 2011
  Baylor College of Medicine, Houston, TX

- "New Concepts and Controversies in Pulmonary Arterial Hypertension"
  Cardiology Grand Rounds, April 2012
  Allegheny General Hospital, Pittsburgh, PA

- "Impact of Insulin Resistance in Pulmonary Hypertension"
  American Thoracic Society International Conference, May 2012
  San Francisco, CA

- "Breathing Better – Oxygen supplementation and Pulmonary Rehabilitation in PAH"
  Pulmonary Hypertension Association International Conference, June 2012
  Orlando, FL

- "Refining Views of Co-morbidities and Vascular Responsiveness in Pulmonary Arterial Hypertension"
  Pulmonary & Critical Care Grand Rounds, October 2012

University of California, Irvine College of Medicine, Orange, CA

- "Prognostic Utility of Combined Biomarkers in PAH"
  Clinical Research Lecture Series, November 2012
  Genentech, South San Francisco, CA

- "Alterations in Glucose Metabolism and PAH"
  American Thoracic Society International Conference, May 2013
  Philadelphia, PA

- "Tacrolimus for pulmonary hypertension - approaching the disease using high throughput screening of BMPR2 mutant animal"
  Pulmonary Hypertension Drug Discovery and Development Symposium, July 2014
  US-FDA, Washington DC

- "Dual Upfront Therapy for Pulmonary Arterial Hypertension"
  National Jewish Hospital, September 2014
  Denver, CO

H. Prior & Current Mentees

Name	Year	Current Position
Francois Haddad, MD	2006-2008	Assistant Clinical Professor of Medicine Division of Cardiovascular Medicine Stanford University
Kristina Kudelko, MD	2008-2009	Assistant Clinical Professor of Medicine Division of Pulmonary & Critical Care Medicine Stanford University
David Poch, MD	2009-2010	Assistant Clinical Professor of Medicine Division of Pulmonary & Critical Care Medicine University of California, San Diego
Shigeki Saito, MD	2010-2011	Assistant Professor of Medicine Division of Pulm & Critical Care Medicine Toulane University
Lana Melendres-Groves, MD	2011-2012	Assistant Professor of Medicine Division of Pulm & Critical Care Medicine University of New Mexico
Nathan Brunner, MD	2012-2013	Assistant Professor of Medicine Division of Cardiology University of British Columbia, Vancouver.
Krithika Ramachandran, MD	2012-2013	Pulmonary & Critical Care Medicine Washington.
Olga Fortenko, MD	2012-2014	Fellow in Division of Pulmonary & Critical Care Medicine Stanford University Medical Center
Mona Selej, MD	2013-2014	eBay Pulmonary Vascular Fellow Division of Pulmonary & Critical Care Medicine Vera Moulton Wall Center for Pulmonary Vascular Disease Stanford University School of Medicine
Jennifer Hellawell, MD	2014-03/2015	eBay Pulmonary Vascular Fellow Division of Pulmonary & Critical Care Medicine Vera Moulton Wall Center for Pulmonary Vascular Disease Stanford University School of Medicine

The New England Journal of Medicine

INHALED ILOPROST FOR SEVERE PULMONARY HYPERTENSION

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ABSTRACT

Background Uncontrolled studies suggested that aerosolized iloprost, a stable analogue of prostacyclin, causes selective pulmonary vasodilatation and improves hemodynamics and exercise capacity in patients with pulmonary hypertension.

Methods We compared repeated daily inhalations of 2.5 or 5.0 μg of iloprost (six or nine times per day; median inhaled dose, 30 μg per day) with inhalation of placebo. A total of 203 patients with selected forms of severe pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension (New York Heart Association [NYHA] functional class III or IV) were included. The primary end point was met if, after week 12, the NYHA class and distance walked in six minutes were improved by at least one class and at least 10 percent, respectively, in the absence of clinical deterioration according to predefined criteria and death.

Results The combined clinical end point was met by 16.8 percent of the patients receiving iloprost, as compared with 4.9 percent of the patients receiving placebo (P=0.007). There were increases in the distance walked in six minutes of 36.4 m in the iloprost group as a whole (P=0.004) and of 58.8 m in the subgroup of patients with primary pulmonary hypertension. Overall, 4.0 percent of patients in the iloprost group (including one who died) and 13.7 percent of those in the placebo group (including four who died) did not complete the study (P=0.024); the most common reason for withdrawal was clinical deterioration. As compared with base-line values, hemodynamic values were significantly improved at 12 weeks when measured after iloprost inhalation (P<0.001), were largely unchanged when measured before iloprost inhalation, and were significantly worse in the placebo group. Further significant beneficial effects of iloprost treatment included an improvement in the NYHA class (P=0.03), dyspnea (P=0.015), and quality of life (P=0.026). Syncope occurred with similar frequency in the two groups but was more frequently rated as serious in the iloprost group, although this adverse effect was not associated with clinical deterioration.

Conclusions Inhaled iloprost is an effective therapy for patients with severe pulmonary hypertension. (N Engl J Med 2002;347:322-9.)

A CONTINUOUS infusion of prostacyclin was the first therapy shown to reduce mortality in a controlled study of patients with severe pulmonary hypertension.[1] However, its use is associated with a number of serious drawbacks. The lack of pulmonary selectivity results in systemic side effects, tolerance leads to progressive increases in the dose, and there may be recurrent infections of the intravenous catheter.[2] As an alternative, inhaled nitric oxide possesses pulmonary selectivity, but it is less potent than prostacyclin in the pulmonary vasculature.[3,4] Moreover, an interruption in the inhalation of continuous nitric oxide may cause rebound pulmonary hypertension.[5,6] Designed to combine the beneficial effects of prostacyclin with those of an inhalational application, aerosolized prostacyclin was found to be a potent pulmonary vasodilator in patients with acute respiratory failure, exerting preferential vasodilatation in well-ventilated lung regions.[7-10] Similar results were obtained in spontaneously breathing patients who had lung fibrosis and severe pulmonary hypertension.[11]

Iloprost is a stable analogue of prostacyclin that is associated with a longer duration of vasodilatation.[12] When administered during a short aerosolization ma-

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*The other members of the Aerosolized Iloprost Randomized (AIR) study group are listed in the Appendix.

neuver to patients with pulmonary hypertension, its pulmonary vasodilative potency was similar to that of prostacyclin, but its effects lasted for 30 to 90 minutes, as compared with 15 minutes.[4,11,13-15] Several open-label, uncontrolled studies of patients with severe pulmonary hypertension suggested that long-term use of aerosolized iloprost results in substantial clinical improvement.[11,13,16-20] Our objective in this trial was to evaluate the effects of inhaled iloprost using a rigorous end point of clinical efficacy.

METHODS

Selection of Patients

Patients with primary pulmonary hypertension and selected forms of nonprimary pulmonary hypertension were candidates for the study. The forms of nonprimary pulmonary hypertension included appetite-suppressant–associated and scleroderma-associated pulmonary hypertension as well as inoperable chronic thromboembolic pulmonary hypertension. The inclusion criteria were a mean pulmonary-artery pressure greater than 30 mm Hg, the ability to cover between 50 and 500 m without encouragement on a six-minute walk test,[21] and a New York Heart Association (NYHA) functional class of III or IV[22] despite the use of standard conventional therapy (anticoagulants, diuretics, digitalis, calcium-channel blockers, and supplemental oxygen). Patients who were taking investigational drugs, prostanoids, or beta-blockers were excluded. The doses of calcium-channel blockers had to be constant for more than six weeks before study entry. Exclusion criteria were a pulmonary-artery wedge pressure at rest of more than 15 mm Hg, a cardiac index at rest of less than 1.5 or more than 4 liters per minute per square meter of body-surface area, bleeding disorders, a bilirubin level of more than 3 mg per deciliter (51 μmol per liter), creatinine clearance below 30 ml per minute, a forced vital capacity below 50 percent, a forced expiratory volume in one second that was less than the mean normal value minus twice the standard deviation, and clinical instability.

Study Design

A total of 203 patients participated after giving written informed consent and after the study had been approved by the local ethics committees at 37 European specialist centers. Patients were randomly assigned to receive iloprost (Ilomedin, Schering) or placebo after stratification according to NYHA functional class (III or IV) and type of pulmonary hypertension (primary or nonprimary) by an independent committee whose members were unaware of patients' identities. A total of 101 patients were randomly assigned to the iloprost group, and 102 were assigned to the placebo group.

For inhalation, iloprost or placebo was diluted with saline to a concentration of 10 μg per milliliter, and 2 ml was added to a nebulizer (HaloLite, MedicAid). This device delivered short pulses of aerosolized particles (geometric median [±SD] aerodynamic diameter of particles, 4.3±0.05 μm)[23] during the first part of each inspiration until a predefined total inhaled dose of 2.5 μg had been dispensed. The inhalation was then stopped or repeated once, to achieve a total dose of 5.0 μg, depending on how well the patient tolerated the treatment. After each inhalation, the residual volume in the nebulizer was discarded. This maneuver was repeated six or nine times daily, with an overnight break. The frequency of inhalation and the dose were individually determined within the first eight days of therapy according to a predefined dosing algorithm.

Right-heart catheterization was performed in all patients at base line and after 12 weeks. The acute effects of inhaled iloprost were evaluated after 12 weeks in all patients, but not at base line, to avert unblinding. At base line and after 4, 8, and 12 weeks, patients completed a six-minute walk test, the Mahler Dyspnea Index questionnaire,[24] the EuroQol questionnaire,[25] and the 12-item Medical Outcomes Study Short-Form General Health Survey.[26]

Patients were removed from the study if they met two or more of the following predefined criteria for a deterioration in their condition: refractory systolic arterial hypotension (blood pressure, less than 85 mm Hg); worsening right ventricular failure (e.g., as indicated by the development of refractory edema or ascites); rapidly progressing cardiogenic, hepatic, or renal failure; a decrease of at least 30 percent in the distance walked in six minutes; and a decline in measures of hemodynamic function, such as central venous pressure and mixed venous oxygen saturation.

Outcome Measures

The primary end point of the study consisted of an increase of at least 10 percent in the distance walked in six minutes and an

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.*

CHARACTERISTIC	ILOPROST GROUP (N=101)	PLACEBO GROUP (N=102)
Age — yr	51.2±13.2	52.8±12.0
Weight — kg	71.3±14.6	72.6±13.9
Sex — %		
Male	31.7	33.3
Female	68.3	66.7
Underlying disease — no. (%)		
Primary pulmonary hypertension	51 (50.5)	51 (50.0)
Nonprimary pulmonary hypertension	50 (49.5)	51 (50.0)
Appetite suppressants	4 (4.0)	5 (4.9)
Collagen vascular disease	13 (12.9)	22 (21.6)
Chronic thromboembolic pulmonary hypertension	33 (32.7)	24 (23.5)
Oral vasodilator therapy — no. (%)	52 (51.5)	58 (56.9)
NYHA functional class — no. (%)		
III	60 (59.4)	59 (57.8)
IV	41 (40.6)	43 (42.2)
Mahler Dyspnea Index†	4.14±1.8	4.27±1.8
6-Minute walk distance — m	332±93	315±96
Hemodynamic variables‡		
Pulmonary-artery pressure — mm Hg	52.8±11.5	53.8±14.1
Cardiac output — liters/min	3.8±1.1	3.8±0.9
Pulmonary vascular resistance — dyn·sec·cm^{-5}	1029±390	1041±493
Systemic vascular resistance — dyn·sec·cm^{-5}	1872±673	1827±503
Central venous pressure — mm Hg	9.2±5.3	8.2±5.0
Pulmonary-artery wedge pressure — mm Hg	7.5±3.3	7.6±3.9
Arterial oxygen saturation — %	92.6±4.4	92.2±5.0
Mixed venous oxygen saturation — %	60.4±7.5	60.5±8.2
Heart rate — beats/min	83.9±12.2	81.8±15.4

*Plus–minus values are means ±SD. NYHA denotes New York Heart Association. There were no significant differences between the iloprost and the placebo groups. Data on all variables were available for all patients except in the following categories: pulmonary-artery pressure, 1 patient in each group; cardiac output, 1 patient in the iloprost group and 6 in the placebo group; pulmonary vascular resistance, 10 and 6, respectively; systemic vascular resistance, 11 and 14; central venous pressure, 5 and 7; pulmonary-artery wedge pressure, 8 and 3; arterial oxygen saturation, 35 and 31; mixed venous oxygen saturation, 16 and 18; and heart rate, 2 and 3.

†On this 12-point scale, higher scores indicate less dyspnea.

‡Patients who were receiving long-term oxygen therapy received nasal oxygen during the measurement of base-line hemodynamic variables.

improvement in the NYHA functional class in the absence of a deterioration in the clinical condition or death during the 12 weeks of the study. Secondary efficacy variables were changes in the values for the six-minute walk test, the NYHA class, Mahler Dyspnea Index scores, hemodynamic variables, and the quality of life; clinical deterioration; death; and the need for transplantation.

Statistical Analysis

The primary evaluation of efficacy included all randomized patients. Data are presented as means ±SD, unless otherwise stated. We included data on patients who prematurely discontinued the study using a last-observation-carried-forward analysis for the six-minute walk test. Patients who died were assigned a value of 0 m. All statistical tests for efficacy variables were two-tailed, with an alpha level of 0.05.

To analyze the primary efficacy end point and the improvement criteria, we used the Mantel–Haenszel test,[27] stratified according to the type of pulmonary hypertension (primary or nonprimary) and NYHA class (III or IV). Patients with missing data on the primary end point at week 12 were considered not to have had a response.

Changes in the results of the six-minute walk were evaluated with use of nonparametric analysis of covariance stratified according to the type of pulmonary hypertension (primary or nonprimary) and the NYHA class (III or IV), with use of the base-line value as the covariate (analysis of covariance), and the Wilcoxon signed-rank test.

Changes from base line in hemodynamic values were analyzed with t-statistics. The investigators had full access to the data and performed the analyses independently of the sponsor.

RESULTS

Base-line demographic and hemodynamic data are given in Table 1. The mean frequency of inhalation was 7.5 times per day. Ninety-one percent of patients received 5.0 μg per inhalation, and 9 percent received 2.5 μg, corresponding to a median inhaled dose of 30 μg per day.

Primary Efficacy End Point

For the primary end point, we found a significant effect of treatment in favor of iloprost (P=0.007) (Fig. 1). The estimated odds of an effect in the iloprost group, as compared with the placebo group, were 3.97 (95 percent confidence interval, 1.47 to 10.75, by the Mantel–Haenszel test), with no significant heterogeneity among the four subgroups categorized according to type of pulmonary hypertension and NYHA class at base line (P=0.79 by the Breslow–Day test). The secondary analysis of the primary end point was a logistic-regression model that included treatment assignment, demographic data, and base-line characteristics. Only treatment assignment (P=0.01) contributed significantly to the probability of a response.

Secondary End Points

Six-Minute Walk Test

The percentage of patients who had an increase of at least 10 percent in the distance walked in six minutes at week 12 was slightly, but not significantly, higher in the iloprost group than in the placebo group (P=0.06) (Table 2). The type of pulmonary hypertension had no significant effect on the outcome in either group (P=0.90). A higher percentage of patients in the placebo group than in the iloprost group had a decrease in the distance walked of at least 10 percent or did not complete the study (Table 2).

The absolute change in the distance walked in six minutes was significantly larger (by 36.4 m) in the

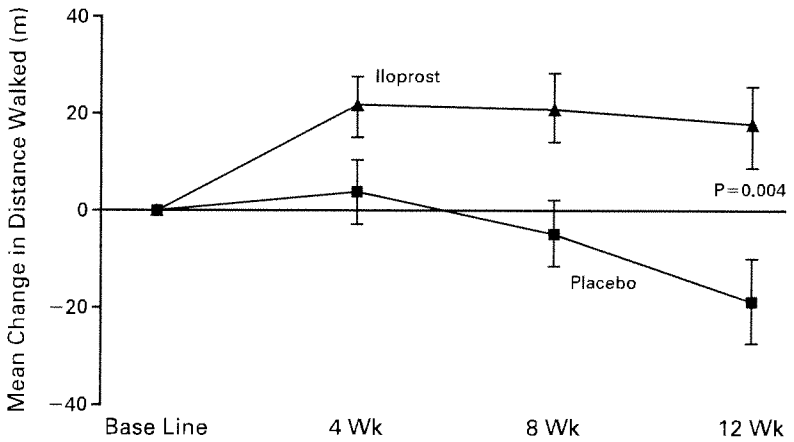

Figure 1. Effect of Inhaled Iloprost and Placebo on the Mean (±SE) Change from Base Line in the Distance Walked in Six Minutes, According to an Intention-to-Treat Analysis.

The P value was obtained with Wilcoxon's test for two independent samples.

iloprost group than in the placebo group ($P=0.004$) (Fig. 1): 58.8 m among those with primary pulmonary hypertension and 12 m among those with nonprimary pulmonary hypertension. A parametric analysis of covariance, which included the absolute value on the six-minute walk test at week 12 as a dependent variable and the treatment assignment ($P=0.02$), type of pulmonary hypertension ($P=0.06$), and distance walked at base line ($P<0.001$) did not show a statistically significant interaction between treatment and type of pulmonary hypertension ($P=0.09$).

NYHA Class

More patients in the iloprost group than in the placebo group had an improvement in the severity of heart failure, as assessed by the NYHA class ($P=0.03$) (Table 2). The type of pulmonary hypertension had no effect on the outcome in either group ($P=0.39$). The percentage of patients with a deterioration in NYHA class did not differ significantly between the groups, but the analysis did not include patients who left the study early owing to death or other reasons. A larger proportion of patients in the placebo group than in the iloprost group did not complete the study (Table 2 and Fig. 2). Reasons included death, discontinuation of study medication, and withdrawal of consent, mostly owing to clinical deterioration, insufficient clinical benefit, or both.

Hemodynamics and Gas Exchange

In the placebo group, cardiac output, systemic arterial oxygen saturation, and mixed venous oxygen saturation decreased significantly after 12 weeks and pulmonary vascular resistance and right atrial pressure increased significantly (Table 3). In the iloprost group, values assessed at 12 weeks, before the first morning dose of inhaled iloprost, were largely unchanged from base line, whereas values assessed after inhalation were significantly decreased (in the case of pulmonary-artery pressure, pulmonary vascular resistance, systemic arterial pressure, and systemic arterial oxygen saturation) or increased (in the case of carbon monoxide and pulmonary-artery wedge pressure). At the completion of the 12-week study, acute hemodynamic responsiveness to inhaled iloprost was equivalent in the placebo group and the iloprost group, though the latter group had been exposed to daily iloprost inhalation for three months (data not shown).

Mahler Dyspnea Index

The mean Mahler Dyspnea Index transition score was significantly better at week 12 in the iloprost

TABLE 2. EFFECTS OF 12 WEEKS OF THERAPY WITH INHALED ILOPROST OR PLACEBO ON THE NEW YORK HEART ASSOCIATION (NYHA) CLASS AND THE SIX-MINUTE WALK TEST.

VARIABLE	ILOPROST GROUP			PLACEBO GROUP		
	ALL PATIENTS	PATIENTS WITH PRIMARY PULMONARY HYPERTENSION	PATIENTS WITH NONPRIMARY PULMONARY HYPERTENSION	ALL PATIENTS	PATIENTS WITH PRIMARY PULMONARY HYPERTENSION	PATIENTS WITH NONPRIMARY PULMONARY HYPERTENSION
	percentage of patients					
Change in NYHA class						
Improved by 2 classes	1.0*	1.9	0.0	0.0	0.0	0.0
Improved by 1 class	23.8*	22.6	25.0	12.7	7.3	19.1
Unchanged	64.4	66.0	62.5	65.7	69.1	61.7
Worsened	5.9	3.8	8.3	7.8	10.9	4.3
Data missing	1.0	1.9	0.0	0.0	0.0	0.0
Noncompletion of study	4.0	3.8	4.2	13.7	12.7	14.9
Death	1.0	1.9	0.0	3.9	3.6	4.3
Other	3.0†	1.9	4.2	9.8‡	9.1	10.6
Change in 6-minute walk distance						
≥10% increase	37.6§	49.1	25.0	25.5	30.9	19.1
<10% increase to <10% decrease	42.6	37.7	47.9	32.4	20.0	46.8
≥10% decrease	13.9	5.7	22.9	25.5	32.7	17.0
Data missing	5.9	7.5	4.2	16.7	16.4	17.0
Combined end point	16.8¶	20.8	12.5	4.9	5.5	4.3

*$P=0.03$ for the comparison of rates of improvement (by one or two classes) with the placebo group.

†Treatment was discontinued in all three patients.

‡Treatment was discontinued in seven patients, and three patients withdrew their consent.

§$P=0.06$ for the comparison with the placebo group.

¶$P=0.007$ for the comparison with the placebo group.

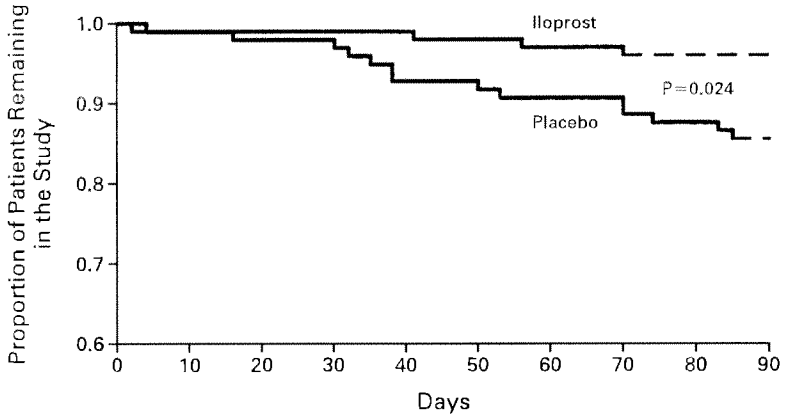

Figure 2. Kaplan–Meier Estimates of the Likelihood of Completing the 12-Week Study.
Reasons for not completing the study included death, discontinuation of study medication, and withdrawal of consent (see Table 2).

TABLE 3. MEAN (±SD) CHANGE FROM BASE LINE IN HEMODYNAMIC VALUES DURING 12 WEEKS OF THERAPY WITH INHALED ILOPROST OR PLACEBO.*

VARIABLE	PLACEBO GROUP	ILOPROST GROUP	
		BEFORE INHALATION	AFTER INHALATION
	mean ±SD		
Pulmonary-artery pressure (mm Hg)	−0.2±6.9	−0.1±7.3	−4.6±9.3†
Cardiac output (liters/min)	−0.19±0.81‡	+0.05±0.86	+0.55±1.1†
Pulmonary vascular resistance (dyn·sec·cm^{-5})	+96±322‡	−9±275§	−239±279†
Systemic arterial pressure (mm Hg)	−0.2±12.4	−1.7±12.8	−4.3±13.6¶
Right arterial pressure (mm Hg)	+1.4±4.8‡	+0.5±4.6	−0.8±4.6
Pulmonary-artery wedge pressure (mm Hg)	+0.7±3.6	+1.1±4.7‡	+1.8±5.3¶
Arterial oxygen saturation (%)	−1.6±4.4‡	−0.4±3.7	−1.4±3.7‡
Mixed venous oxygen saturation (%)	−3.2±6.7†	−1.1±7.6	+1.8±8.3
Heart rate (beats/min)	−1.2±9.5	−1.8±12.4	−2.25±12.6

*For the iloprost group, both preinhalation and postinhalation values after 12 weeks are compared with the base-line values at study entry.

†P<0.001 for the difference from base-line values.

‡P<0.05 for the difference from base-line values.

§P<0.01 for the comparison with the placebo group.

¶P<0.01 for the difference from base-line values.

group than in the placebo group (change, +1.42±2.59 vs. +0.30±2.45; P=0.015). The type of pulmonary hypertension had no effect on this outcome.

Quality of Life

Mean scores on the EuroQol visual-analogue scale improved significantly (from 46.9±15.9 to 52.8±19.1) in the iloprost group but were virtually unchanged in the placebo group (dropping from 48.6±16.9 to 47.4±21.1, P=0.026 by analysis of covariance). The EuroQol health-state score improved from 0.49±0.28 to 0.58±0.27 in the iloprost group and was unchanged in the placebo group (0.56±0.29 to 0.56±0.31, P=0.11 by analysis of covariance). None of the other measures of the quality of life were significantly different between the groups.

Clinical Deterioration and Death

One patient died in the iloprost group during the 12-week study, as compared with four patients in the placebo group ($P=0.37$) (Table 2). Criteria for clinical deterioration were met in 4.9 percent of patients in the iloprost group and 8.8 percent of those in the placebo group ($P=0.41$). This indicated that fewer patients either died or deteriorated in the iloprost group than in the placebo group (4.9 percent vs. 11.8 percent, $P=0.09$). The type of pulmonary hypertension had no effect on the outcome. During the study period, none of the patients received a lung transplant.

Safety

The total number of patients who had serious adverse events did not differ significantly between the groups (Table 4). Right ventricular failure and edema were more than twice as frequent in the placebo group as in the iloprost group. The total number of syncopal events in each of the two groups was similar (eight in the iloprost group and five in the placebo group), but these events were more often considered serious in the iloprost group. Syncope was not associated with clinical deterioration or premature withdrawal from the study. Syncopal events occurred more than two hours after the last inhalation (often after an overnight break), were exercise-induced in two patients, were induced by bradycardia in two patients (associated with gastroenteritis in one patient and with verapamil therapy in the other), and resulted in head trauma in one patient. Flushing and jaw pain were more common in the iloprost group, but these adverse effects were mostly transient and mild and were not considered to be serious in any patient.

DISCUSSION

The results of this clinical trial demonstrate that long-term inhaled administration of aerosolized iloprost, a stable analogue of prostacyclin, improves a clinically important combined end point consisting of exercise capacity, NYHA class, and clinical deterioration in patients with selected forms of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension. Moreover, iloprost improved several secondary end points.

Since intravenous epoprostenol was shown to improve survival among the most severely ill patients with primary pulmonary hypertension, it has been unethical to perform randomized clinical trials among patients with pulmonary hypertension in which survival is used as an end point. We chose a combined rather than a single end point (e.g., the distance walked in six minutes) in order to make a more rigorous determination of whether inhaled iloprost was efficacious. Nearly 40 percent of all patients who were treated with iloprost increased their six-minute walking distance by at least 10 percent. However, only half as many patients also had improvement in the NYHA class; conversely, not all patients with an improvement in NYHA class had an increase of at least 10 percent in the distance walked in six minutes. Thus, although only 17 percent of patients in the iloprost group reached the combined end point, a substantial number of the remaining patients met less strict criteria for clinical improvement that would warrant continued therapy. Furthermore, significantly fewer patients in the iloprost group than in the placebo group prematurely discontinued the study as a result of lack of efficacy or other reasons, suggesting that even when iloprost therapy does not produce substantial improvement, it may stabilize the clinical condition.

The mean inhaled dose of iloprost corresponded to 0.37 ng per kilogram of body weight per minute, which is considerably lower than an effective intravenous or subcutaneous dose.[2,28] Thus, targeted delivery of prostanoids to the pulmonary vasculature by means of inhalation may substantially reduce the drug requirements.

TABLE 4. INCIDENCE OF SERIOUS AND OTHER ADVERSE EVENTS.*

VARIABLE	ILOPROST GROUP (N=101)	PLACEBO GROUP (N=102)	P VALUE
	no. of patients (%)		
Serious adverse event			
Any event	28 (27.7)	25 (24.5)	0.63
Right ventricular failure and edema	4 (4.0)	10 (9.8)	0.16
Syncope	5 (5.0)	0	0.03
Other†	33 (32.7)	35 (34.3)	0.88
Adverse event‡			
Any event	91 (90.1)	90 (89.2)	0.82
Increased cough	39 (38.6)	26 (25.5)	0.05
Headache	30 (29.7)	20 (19.6)	0.11
Flushing	27 (26.7)	9 (8.8)	0.001
Influenza-like syndrome	14 (13.9)	10 (9.8)	0.39
Peripheral edema	13 (12.9)	16 (15.7)	0.69
Nausea	13 (12.9)	8 (7.8)	0.26
Jaw pain	12 (11.9)	3 (2.9)	0.02
Hypotension	11 (10.9)	6 (5.9)	0.22
Diarrhea	9 (8.9)	11 (10.8)	0.81
Vertigo	7 (6.9)	11 (10.8)	0.46
Syncope	8 (7.9)	5 (4.9)	0.41
Other adverse events§	296	277	

*The most common adverse events are listed.

†These events included an aggravation reaction (an event causing concern about possible deterioration) in four patients in the iloprost group and five patients in the placebo group, hypoxemia in two patients in the placebo group, pneumonia in two patients in the iloprost group, tachycardia in two patients in the iloprost group and one in the placebo group, laboratory-test abnormalities in two patients in the iloprost group, chest pain in two patients in each group, and dyspnea in two patients in each group.

‡Data were available for 101 patients in the placebo group.

§The number is the total number of other adverse events.

Like other investigators, we found that the benefit was greatest among patients with primary pulmonary hypertension and was similar to that of epoprostenol[1] and bosentan.[29] Although patients with nonprimary pulmonary hypertension had improvement in the scores for the Mahler Dyspnea Index and quality-of-life measures that were similar to those achieved in patients with primary pulmonary hypertension, fewer such patients reached the combined end point, and they also had a smaller absolute change in the distance walked in six minutes. Similar results have been obtained with the use of other drugs for pulmonary hypertension, including epoprostenol,[30] beraprost,[31] and treprostinil.[28]

Hemodynamic assessments of preinhalation values showed that values stabilized in the iloprost group, whereas they deteriorated in the placebo group. The degree of deterioration may be underestimated, since patients who discontinued treatment prematurely did not undergo follow-up hemodynamic examination. Postinhalation assessments of hemodynamic variables demonstrated a significant improvement in the iloprost group, as was anticipated on the basis of previous reports.[4,11,13,16] Since the acute hemodynamic response did not differ between the groups, it appears unlikely that tolerance developed over the 12-week course of iloprost treatment. During long-term treatment, the patients' hemodynamic status is somewhere between preinhalation and postinhalation values. In comparison, continuous intravenous therapy may result in a more sustained hemodynamic improvement[32]; however, continuous intravenous therapy also poses considerable risks, including relapse after the interruption of therapy and complications, and is difficult to administer.

With respect to adverse events, flushing was more common in the iloprost group, but the frequency of most of the other inhalation-associated side effects was similar. There were more syncopal episodes in the iloprost group than in the placebo group (eight vs. five), and these episodes were more frequently defined as serious adverse events, but they were not associated with clinical deterioration. Since syncope occurred a relatively long time (two to nine hours) after the last inhalation, the loss of an effect of iloprost may have caused these events. However, the same side effect was observed with bosentan therapy, suggesting that these drugs may have a more pronounced effect on blood pressure during exercise. Alternatively, patients who had clinical improvement with therapy may have become more physically active, challenging the limits of their cardiac reserve. We would advise patients to increase their physical activity gradually after the initiation of therapy for pulmonary hypertension.

The inhalation device that we used provided accurate doses of iloprost. However, it is not battery-driven, and inhalation commonly required 10 minutes. Different techniques of administering aerosolized iloprost result in similar acute hemodynamic effects as long as identical doses are delivered to the respiratory tract in a particle size suitable for alveolar deposition.[14,33] With other techniques, the duration of inhalation may be shortened considerably.[14]

In conclusion, this large, placebo-controlled trial demonstrates the efficacy and safety of inhaled iloprost for the treatment of severe primary pulmonary hypertension and selected forms of pulmonary arterial and chronic thromboembolic pulmonary hypertension. The advantages of intermittent inhaled therapy over intravenous therapy, coupled with the improvement in a number of clinically meaningful variables, suggest that inhaled iloprost therapy is effective. It may be a suitable alternative to continuous intravenous prostacyclin, especially in patients who do not derive a clear survival benefit with intravenous therapy.

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APPENDIX

The members of the AIR study group were as follows: *Steering Committee* — W. Seeger (chair), N. Galiè, T. Higenbottam, S. Nikkho, R. Naeije, H. Olschewski, L.J. Rubin, G. Simonneau; *Other Investigators* — H. Fabel and E. Spiekerkötter (Medizinische Hochschule, Hannover, Germany); F. Grimminger and R. Wiedemann (University Clinic, Giessen, Germany); H. Leuchte (University Clinic Großhadern, Munich, Germany); M. Aquilina (Università di Bologna, Bologna, Italy); K. Amsha and R. Lawson (Royal Hallamshire Hospital, Sheffield, United Kingdom); R. Alcock (Freeman Hospital, Newcastle-upon-Tyne, United Kingdom); A. Pförte (Universitätsklinik Eppendorf, Hamburg, Germany); J. Schauer (Medizinische Klinik und Poliklinik Universitätsklinik, Leipzig, Germany); W. Budts (Gasthuisberg University Clinic, Leuven, Belgium); P. Escribano and M. Lázaro (Hospital 12 de Octubre, Madrid); E. Huchalla (Hôpital Claude-Huriez, Lille, France); M. Borst (Ludolf-Krehl-Klinik, Heidelberg, Germany); C.M. Black (Royal Free Hospital, London); C. Bravo, A. Román, and V. Monforte (Centro Sanitario, Vall d'Hebron, Barcelona, Spain); A. Peacock (West Infirmary, Glasgow, United Kingdom); A. Boonstra (Academic Hospital, Free University, Amsterdam); C. Fracchia (Fondazione Salvatore Maugeri, Montescano, Italy); C. Marini (Istituto di Fisiologia Clinica Consiglio Nazionale della Ricerche, Pisa, Italy); L. Nicod (Hôpital Cantonal Universitaire, Geneva); J. Pepke-Zaba (Papworth Hospital, Cambridge University, Cambridge, United Kingdom); G. Sybrecht and H. Wilkens (Pneumologie Uniklinik, Homburg, Germany); A. Torbicki (National Institute of Tuberculosis and Lung Disease, Warsaw, Poland); P. Diot (Hôpital Bretonneau, Tours, France); T. Mota (Hospital de Pulido Valente, Lisbon, Portugal); J.L. Pennaforte (Centre Hospitalier Universitaire [CHU] Reims, Reims, France); T. Perez and F. Radenne (CHU Lille, Lille, France); C. Pison (CHU Hôpital Nord, Grenoble, France); J.L. Vachiery (Hôpital Erasme, Brussels, Belgium); P. Hallgren (Kardiologkliniken, Goteborg, Sweden); F-X. Kleber (Unfallkrankenhaus, Berlin, Germany); L. Providencia (Hospitais de Universidade de Coimbra, Coimbra, Portugal); V.R.G. Ribeiro (Vila Nova de Caia, Portugal); M. Soler (Kantonsspital, Basel, Switzerland); and H. Stricker (Ospedale Regionale di Locarno La Caritá, Locarno, Switzerland).

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EXHIBIT 3

Drugs

Priority NDA and BLA Approvals in 2004

Priority New Drug Application (NDA) Approvals:

NDA Number	ProprietaryName	Established Name	Applicant	Chemical Type	Review Classification	Approval Date	Indication
N021539	Acetadote	Acetylcysteine	Cumberland Pharms	3	P, O	23-Jan-04	Acetadote is indicated to be administered intravenously within 8 to 10 hours after ingestion of a potentially hepatotoxic quantity of acetaminophen, to prevent or lessen hepatic injury.
N021462	Alimta	Pemetrexed Disodium	Eli Lilly	1	P, O	04-Feb-04	Alimta is indicated in the treatment of patients with malignant pleural mesothelioma whose disease is either unresectable or who are otherwise not candidates for curative surgery.
N021688	Sensipar	Cinacalcet Hydrochloride	Amgen	1	P	08-Mar-04	Sensipar is indicated for the treatment of secondary hyperparathyroidism in patients with chronic kidney disease on dialysis, and the treatment of hypercalcemia in patients with parathyroid carcinoma.
N021256	Human Secretin	Human Secretin	Chirhoclin	1	P, O	09-Apr-04	Human Secretin is indicated for (1) Stimulation of pancreatic secretions, including bicarbonate, to aid in the diagnosis of pancreatic exocrine dysfunction, (2) Stimulation of gastrin secretion to aid in the diagnosis of gastrinoma, and (3) Stimulation of pancreatic secretions to facilitate the identification of the ampulla of Vater and accessory papilla during endoscopic retrograde cholangiopancreatography (ERCP).
N021264	Apokyn	Apomorphine Hydrochloride	Bertek	1	P	20-Apr-04	Apokyn is indicated for the acute, intermittent treatment of hypomobility, "off" episodes ("end-of-dose wearing off" and unpredictable "on/off" episodes) associated with advanced Parkinson's disease.
N021640	Vitrase	Ovine Hyaluronidase	Ista Pharms	1	P	05-May-04	Vitrase is indicated as an adjuvant to increase the absorption and dispersion of other injected drugs; for hypodermoclysis; and as an adjunct in subcutaneous urography for improving resorption of radiopaque agents.
N050794	Vidaza	Azacitidine	Pharmion	1	P, O	19-May-04	Vidaza is indicated for the treatment of patients with the following myelodysplastic syndrome subtypes: refractory anemia or refractory anemia with ringed sideroblasts (if accompanied by neutropenia or thrombocytopenia and requiring transfusions), refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and chronic myelomonocytic leukemia.
N021497	Alinia	Nitazoxanide	Romark	3	P	21-Jul-04	Alinia is indicated for the treatment of diarrhea caused by Giardia Lamblia in patients 12 years and older.
N021431	Campral	Acamprosate Calcium	Lipha	1	P	29-Jul-04	Campral is indicated for the maintenance of abstinence from alcohol in patients with alcohol dependence who are abstinent at treatment initiation.
N021752	Truvada	Emtricitabine; Tenofovir Disoproxil Fumarate	Gilead Sciences	4	P	02-Aug-04	Truvada is indicated in combination with other antiretroviral agents (such as non-nucleoside reverse transcriptase inhibitors or protease inhibitors) for the treatment of HIV-1 infection in adults.
N021749	Pentetate Calcium Trisodium	Pentetate Calcium Trisodium	Pharma Hameln GmbH	1	P	11-Aug-04	Pentetate Calcium Trisodium is indicated for the treatment of internal contamination with plutonium, americium or curium to increase the rates of elimination.
N021751	Pentetate Zinc Trisodium	Pentetate Zinc Trisodium	Pharma Hameln GmbH	1	P	11-Aug-04	Pentetate Zinc Trisodium is indicated for the treatment of internal contamination with plutonium, americium or curium to increase the rates of elimination.

N021563	Clarinex	Desloratadine	Schering	3	P	01-Sep-04	Clarinex is indicated for the relief of the nasal and non-nasal symptoms of perennial allergic rhinitis, and the symptomatic relief of pruritus, reduction in the number of hives, and size of hives, in patients with chronic idiopathic urticaria in children 6 months to 2 years of age.
N021683	Manoplex	Insoluble Prussian Blue	Degussa Limited	5	P	14-Oct-04*	Manoplex is indicated for the treatment of patients with known or suspected internal contamination with radioactive cesium and/or radioactive or non-radioactive thallium to increase their rates of elimination.
N021665	Amphadase (hyaluronidase)	Amphadase (hyaluronidase)	Amphastar Pharms	1	P	26-Oct-04	Amphadase is indicated as an adjuvant to increase the absorption and dispersion of other injected drugs; for hypodermoclysis; and as an adjunct in subcutaneous urography for improving resorption of radiopaque agents.
N021743	Tarceva (erlotinib)	Tarceva (erlotinib)	OSI Pharms	1	P	18-Nov-04	Tarceva is indicated for the treatment of locally advanced or metastatic Non Small-Cell Lung Cancer (NSCLC) after failure of at least one prior chemotherapy regimen.
N021786	Kelacal	Pentetate Calcium Trisodium	CIS-US	5	P	01-Dec-04*	Kelacal is indicated for the treatment of internal contamination with plutonium, americium, or curium.
N021787	Kelazin	Pentetate Zinc Trisodium	CIS-US	5	P	01-Dec-04*	Kelazin is indicated for the treatment of internal contamination with plutonium, americium, or curium.
N021670	Vision Blue	Trypan Blue	DORC	1	P	16-Dec-04	Vision Blue is indicated as an aid in ophthalmic surgery by staining the anterior capsule of the lens.
N021756	Macugen	Pegaptanib sodium	Eyetech	1	P	17-Dec-04	Macugen is indicated for the treatment of neovascular (wet) age-related macular degeneration.
N021785	Invirase	Saquinavir Mesylate	Hoffman-La Roche	3	P	17-Dec-04	Invirase is indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults.
N021060	Prialt	Ziconotide	Elan Pharms	1	P	28-Dec-04	Prialt is indicated for the management of severe chronic pain in patients for whom intrathecal (IT) therapy is warranted and who are intolerant of or refractory to other treatment, such as systemic analgesics, adjunctive therapies, or IT morphine.
N021673	Clolar	Clofarabine	Genzyme	1	P, O	28-Dec-04	Clolar is indicated for the treatment of pediatric patients 1 to 21 years old with relapsed or refractory acute lymphoblastic leukemia after at least two prior regimens.
N021779	Ventavis	Iloprost	CoTherix	1	P, O	29-Dec-04	Ventavis is indicated for the treatment of pulmonary arterial hypertension.
N021446	**Lyrica**	**Pregabalin**	**Pfizer**	**1**	**P**	**30-Dec-04**	**Lyrica is indicated for the management of neuropathic pain associated with diabetic peripheral neuropathy.**

Priority Biologic License Application (BLA) Approvals:

BLA Number	ProprietaryName	Proper Name	Applicant	Review Classification	Approval Date	Indication
BL125084	Erbitux	Cetuximab	ImClone Systems	P	12-Feb-04	Erbitux is indicated for the treatment of EGFR-expressing, metastatic colorectal carcinoma in patients who are refractory to irinotecan-based chemotherapy (in combination with irinotecan); Treatment of EGFR-expressing, metastatic colorectal carcinoma in patients who are intolerant to irinotecan-based chemotherapy (administered as a single agent).
BL125085	Avastin	Bevacizumab	Genentech	P	26-Feb-04	Avastin is indicated for the first-line treatment of patients with metastatic carcinoma of the colon and rectum (in combination with intravenous 5-fluorouracil-based chemotherapy).
BL125104	Tysabri	Natalizumab	Biogen Idec	P	23-Nov-04	Tysabri is indicated in the treatment of patients with relapsing forms of multiple sclerosis (MS) to reduce the frequency of clinical exacerbations.
BL125103	Kepivance	Palifermin	Amgen	P	15-Dec-04	Kepivance is indicated to decrease the incidence and duration of severe oral mucositis in patients with hematologic malignancies receiving myelotoxic therapy requiring hematopoietic stem cell support.

NDA Chemical Type:
1 - New molecular entity
2 - New ester, new salt, or other noncovalent derivative
3 - New formulation
4 - New combination
5 - New manufacturer
7 - Drug already marketed, but without an approved NDA

Review Classification:
P - **Priority Review** - Significant improvement compared to marketed products, in the treatment, diagnosis, or prevention of a disease.
O - **Orphan Designation** - Pursuant to Section 526 of the Orphan Drug Act (Public Law 97-414 as amended).

* NDA 21683, Manoplex was tentatively approved on October 14, 2004.
* NDA 21786, Kelacal was tentatively approved on December 1, 2004.
* NDA 21787, Kelazin was tentatively approved on December 1, 2004.

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Journal of Internal Medicine 2005; **258**: 199–215

EXHIBIT 4

REVIEW

Current treatment strategies for pulmonary arterial hypertension

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Abstract. Lee SH, Rubin LJ (University of California, San Diego, La Jolla, CA, USA). Current treatment strategies for pulmonary arterial hypertension (Review). *J Intern Med* 2005; **258**: 199–215.
Pulmonary arterial hypertension (PAH) is a disease characterized by an elevation in pulmonary artery pressure that can lead to right ventricular failure and death. Although there is no cure for PAH, newer medical therapies have been shown to improve a variety of clinically relevant end-points including survival, exercise tolerance, functional class, haemodynamics, echocardiographic parameters and quality of life measures. Since the introduction of continuous intravenous prostacyclin, the treatment armamentarium of approved drugs for PAH has expanded to include prostacyclin analogues with differing routes of administration, a dual endothelin receptor antagonist, and a phosphodiesterase-5 inhibitor. Selective endothelin-A receptor antagonists have shown promise in clinical trials and are likely to be added to the list of options. As the number of medications available for PAH continues to increase, treatment decisions regarding first-line therapy, combination treatments, and add-on strategies are becoming more complex. This article reviews the current treatments strategies for PAH and provides guidelines for its management.

Keywords: drug therapy, hypertension, pulmonary.

Introduction

Until the introduction of intravenous (i.v.) epoprostenol in 1995, the prognosis of pulmonary arterial hypertension (PAH) was dismal as treatment was limited only to supportive measures. The median survival was 2.8 years with an estimated 5-year survival of 34% [1]. Epoprostenol was a therapeutic breakthrough that brought new hope to those with PAH. However, treatment decisions for PAH were relatively uncomplicated as they were limited to this one medication. The situation today is quite different: the last decade has witnessed considerable growth in clinical interest in PAH that has been paralleled by scientific advances in our understanding of the pathobiology of this disease (Fig. 1). Reflecting this expansion, the first expert consensus statement on primary pulmonary hypertension (PPH) published by the American College of Chest Physicians in 1993 was a 14-page document [2]. It has now evolved into a 92-page updated, evidence-based monograph [3].

There are now three classes of medications that have shown efficacy in the treatment of PAH: prostanoids, endothelin receptor antagonists (ERAs), and phosphodiesterase-5 (PDE-5) inhibitors (Fig. 2). These medications differ in terms of their pathway targets and mechanisms of action, indications for use, routes of delivery, and side-effect profiles. The challenge lies in integrating the available information

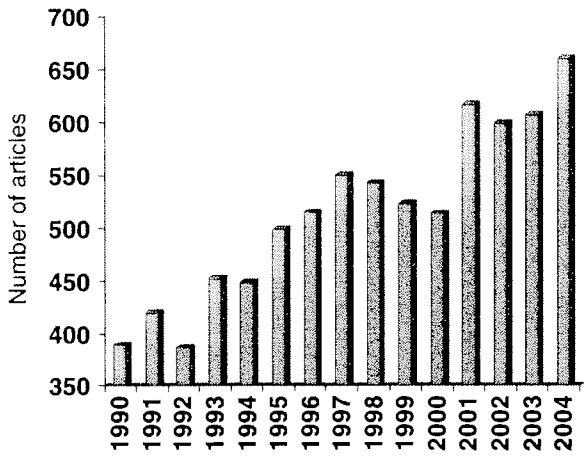

Fig. 1 Number of published articles per year listed in PubMed under the MeSH heading 'hypertension, pulmonary'. http://www.pubmed.gov (accessed 4/5/05).

into a sound treatment and management plan that provides optimal care for patients with PAH.

Establishing the diagnosis

The classification scheme for pulmonary hypertension was recently revised in 2003 at the Third World Symposium on Pulmonary Hypertension held in Venice and is shown in Table 1. Group 1 pulmonary hypertension encompasses PAH, the focus of this review, whilst a variety of secondary causes of pulmonary hypertension are grouped into groups 2–5. Effective treatment of PAH is dependent upon establishing a definitive diagnosis. Pulmonary hypertension resulting from secondary causes should be excluded as many of these conditions are treated with alternative approaches. Recommendations for systematic work-up have been recently reviewed [4, 5]. Published expert guidelines suggest that all patients with suspected PAH undergo formal right heart catheterization (RHC) prior to initiation of treatment. RHC provides important diagnostic and prognostic information based on a thorough characterization of the cardiopulmonary system.

Many secondary causes of pulmonary hypertension can be most thoroughly investigated by RHC. An elevated pulmonary artery occlusion pressure suggests the presence of left-sided heart disease caused by systolic or diastolic dysfunction, or valvular heart disease. Findings of large v-waves suggest significant mitral regurgitation. A significant systolic pressure gradient across the pulmonic

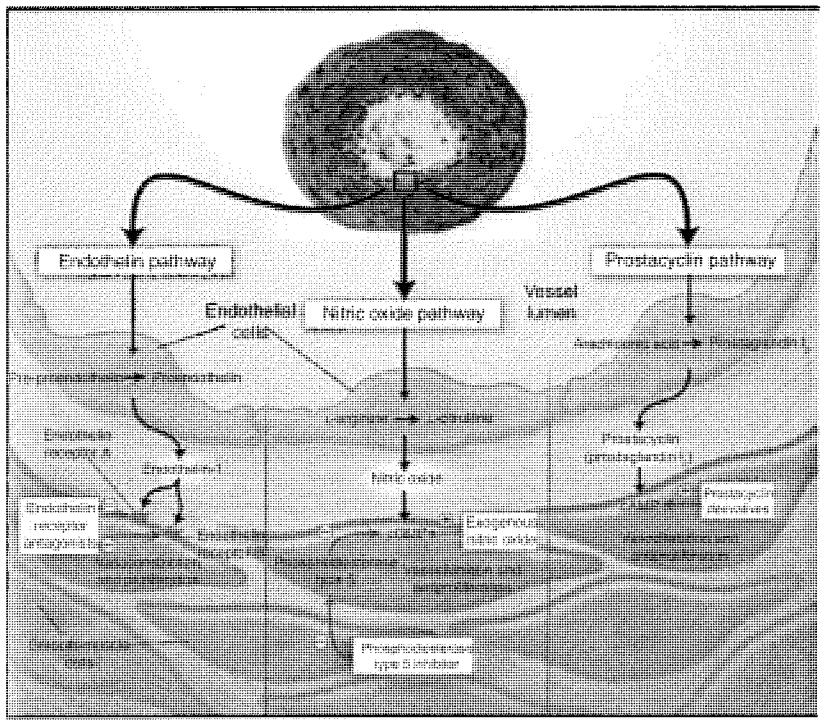

Fig. 2 Targets for current or emerging therapies in pulmonary arterial hypertension. Three major pathways involved in abnormal proliferation and contraction of the smooth muscle cells of the pulmonary artery in patients with pulmonary arterial hypertension are shown. These pathways correspond to important therapeutic targets for the medications used to treat this condition: endothelin receptor antagonists, phosphodiesterase-5 inhibitors, and prostanoids. Plus signs denote an increase in the intracellular concentration; minus signs blockage of a receptor, inhibition of an enzyme, or a decrease in the intracellular concentration (Reproduced with permission from Humbert *et al.* [100]; Copyright 2005 Massachusetts Medical Society. All rights reserved).

Table 1 Classification of pulmonary hypertension (Venice 2003; revised from Evian 1998)

Group 1. Pulmonary artery hypertension (PAH)
1.1 Idiopathic (IPAH)
1.2 Familial (FPAH)
1.3 Associated with (APAH)
1.3.1 Collagen vascular disease
1.3.2 Congenital systemic-to-pulmonary shunts
1.3.3 Portal hypertension
1.3.4 HIV infection
1.3.5 Drugs and toxins
1.3.6 Other (thyroid disorders, glycogen storage disease, Gaucher disease, splenectomy, hereditary haemorrhagic telangiectasia, haemoglobinopathy)
1.4 Associated with significant venous or capillary involvement
1.4.1 Pulmonary veno-occlusive disease
1.4.2 Pulmonary capillary haemangiomatosis
1.5 Persistent pulmonary hypertension of the newborn
Group 2. Pulmonary hypertension with left heart disease
Group 3. Pulmonary hypertension associated with lung disease and/or hypoxaemia
Group 4. Pulmonary hypertension due to chronic thrombotic and/or embolic disease
Group 5. Miscellaneous (sarcoidosis, histiocytosis X, lymphangiomyomatosis, compression of pulmonary vessels)

valve is indicative of pulmonic valve stenosis. Sampling of blood to measure oxygen saturation from the vena cavae and right heart chambers could lead to the diagnosis of an intracardiac left-to-right shunt by demonstrating the presence and location of a 'step-up'.

Echocardiograms alone should not be used to diagnose or monitor the course of PAH. The diagnosis of PAH requires documentation of a mean pulmonary artery pressure >25 mmHg at rest or >30 mmHg with exercise with a normal pulmonary artery occlusion pressure. The echocardiogram directly measures neither, and only provides an estimate of the right ventricular systolic pressure based on the tricuspid regurgitant velocity. This can underestimate or overestimate the true pulmonary artery systolic pressure, depending on a number of factors, including the quality of the echo window obtained and presence or absence of pulmonary outflow obstruction. Underestimation can lead to delays in treatment, whilst overestimation may expose patients to incorrect diagnoses and unnecessary treatment. Finally, the haemodynamic responses to acute vasodilator testing cannot be reliably assessed with echocardiography.

General measures

Physical activity

Although we recommend an active lifestyle that promotes general cardiovascular health, PAH patients should be counselled against activities that abruptly increase the work of the heart during exertion [6]. Patients with mild PAH may have only minimal symptoms with exertion, whilst those with more advanced disease may experience dyspnoea at rest, exertional lightheadedness, syncope or chest pain, which are indicative of impaired right ventricular performance. Grading of functional capacity in PAH is usually based upon the World Health Organization classification scheme, which is a modification of the well-known New York Heart Association heart failure functional classification system (Table 2). Functional class is an important prognostic marker and has been used as an endpoint in PAH clinical trials.

Diuretics

Loop diuretics and potassium-sparing aldosterone inhibitors can be used to control signs and symptoms

Table 2 World Health Organization classification of functional status of patients with pulmonary hypertension

	Description
I	Patients with pulmonary hypertension in whom there is no limitation of usual physical activity. Ordinary physical activity does not cause increased dyspnoea, fatigue, chest pain, or syncope.
II	Patients with pulmonary hypertension who have mild limitation of usual physical activity. There is no discomfort at rest, but normal physical activity causes increased dyspnoea, fatigue, chest pain, or presyncope.
III	Patients with pulmonary hypertension who have a marked limitation of physical activity. There is no discomfort at rest, but less than ordinary activity causes increased dyspnoea, fatigue, chest pain, or presyncope.
IV	Patients with pulmonary hypertension who are unable to perform any physical activity at rest and who may have signs of right ventricular failure. Dyspnoea and/or fatigue may be present at rest and symptoms are increased by almost any physical activity.

Adapted from Rich *et al.* [101]. Primary pulmonary hypertension: Executive Summary. Evian, France: World Health Organization, 1998.

of volume overload from right ventricular failure, such as hepatic congestion, ascites and lower extremity oedema. Diuretics should be used cautiously to avoid precipitous reductions in preload.

Supplemental oxygen

Hypoxia is a potent pulmonary vasoconstrictor, leading to increased pulmonary arterial pressure both acutely and chronically [7]. In patients with PAH complicated or caused by chronic hypoxaemia, supplemental oxygen can improve haemodynamics by decreasing the mean pulmonary artery pressure and increasing the cardiac index, thus decreasing the calculated pulmonary vascular resistance [8]. A relatively high incidence of sleep-disordered breathing, in a pattern similar to the Cheyne–Stokes respiration pattern seen in congestive heart failure, has also been observed in idiopathic pulmonary arterial hypertension (IPAH) [9]. This nocturnal periodic breathing pattern can produce or aggravate hypoxaemia and can be markedly improved with supplemental oxygen. The use of supplemental oxygen to maintain arterial oxygen saturation above 90% both at rest and with exercise is recommended.

Cardiac glycosides

The role of cardiac glycosides (e.g. digoxin) in PAH is unclear. When administered intravenously to patients with IPAH and right ventricular failure, there is a modest, but significant, acute increase in cardiac output (3.49–3.81 L min^{-1}) [10]. However, long-term benefits of chronic cardiac glycoside administration in PAH have not been reported. Well-designed clinical trials are needed in order to further assess the role of cardiac glycosides in the management of PAH.

Anticoagulation

Although there have been no prospective, randomized, placebo-controlled trials (RCT), evidence from several studies suggests that the use of chronic anticoagulation in patients with PAH improves survival [11–13]. Patients with PAH are likely at higher risk for thromboembolic complications because of their decreased activity level, slower blood blow, dilated right-sided heart chambers, and for some, the presence of an implanted central catheter for administering PAH medications. The fragile haemodynamic state and limited cardiopulmonary reserve of patients with PAH place them at risk for death even from a small thromboembolism. Anticoagulation may also reduce the propensity for *in situ* microvascular thrombosis in the distal pulmonary arterial circulation that is commonly observed pathologically in PAH.

In the absence of contraindications, chronic anticoagulation should be a standard component of the treatment regimen in patients with PAH. Expert guidelines recommend a goal international normalized ratio of 1.5 to 2.5 times control [14].

Specific treatment of PAH

Calcium channel blockers

Treatment of PAH with calcium channel blockers (CCBs) is reserved for patients who demonstrate evidence of acute vasoreactivity, currently defined as a reduction in mean pulmonary artery pressure $\geq$10 mmHg to a level that is $\leq$ 40 mmHg, with a normal cardiac output during testing with an acute, short-acting vasodilator such as inhaled nitric oxide or iloprost or i.v. epoprostenol or adenosine [4, 15]. Although the definition of vasoreactivity has changed somewhat over the years, the underlying principle remains the same: only those with significant haemodynamic reversal of pulmonary hypertension during acute vasodilator testing should be considered candidates for chronic CCB treatment. The rationale for this stems from the thought that the primary driving force for PAH in these patients is significant reversible vasoconstriction, rather than a structural pathological vasculopathy due to chronic remodelling changes.

About 13% of IPAH patients exhibit acute vasoreactivity, and of this group, only half experience sustained benefit from chronic CCB treatment [16]. The same can roughly be said about patients with anorexigen-associated PAH. Therefore, although those with acute vasoreactivity may benefit from chronic CCB therapy, a significant number of these patients do not. Acute vasoreactivity is unlikely to be found in patients with other forms of PAH, and amongst these, the likelihood of sustained benefit from CCB treatment is exceedingly rare [17] (Fig. 3). Accordingly, CCB therapy has

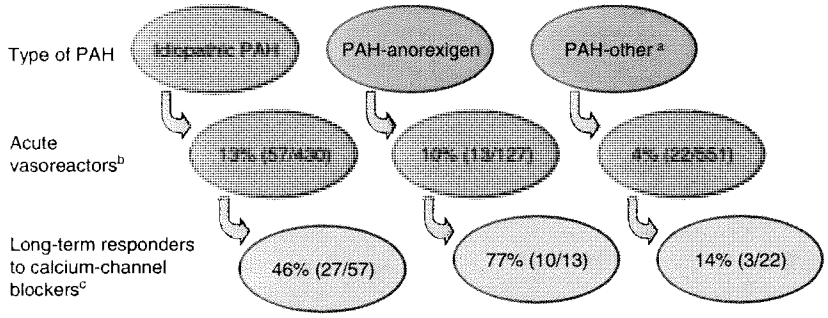

Fig. 3 Breakdown of long-term responders to calcium channel blocker (CCB) monotherapy amongst those who are acutely vasoreactive, by type of PAH (data adopted from Sitbon *et al.* [17]).
[a]Other includes PAH associated with connective tissue disease, veno-occlusive disease, pulmonary capillary haemangiomatosis, human immunodeficiency virus, portopulmonary hypertension, familial and congenital heart defects.
[b]Acute vasoreactors were defined by a fall in both mean pulmonary artery pressure and pulmonary vascular resistance >20%.
[c]Long-term responders were defined as those being in functional class I or II after at least 1 year on CCB monotherapy.

been relegated for use only in a handful of patients with PAH.

All patients treated with a CCB should be closely followed for evidence of benefit as those who do not respond have a survival rate that approximates that of untreated PAH [12]. This is particularly important as newer and more widely effective therapies that specifically target the pathogenic processes of PAH are now available. Their initiation should not be delayed when treatment with CCBs is not proving effective.

Prostanoids

Epoprostenol

In 1995, epoprostenol, or prostacyclin (Flolan), became the first drug approved by the United States Food and Drug Administration (FDA) for the treatment of pulmonary artery hypertension. Epoprostenol is a potent, short-acting vasodilator and antiproliferative agent whose efficacy and safety have been well documented in numerous short and long-term clinical trials and observational studies [18–22]. It is the only medication for PAH that has shown a survival benefit in a randomized clinical trial [19].

Epoprostenol is widely considered to be the most potent and efficacious treatment for PAH. Although it has been most extensively studied in IPAH and PAH associated with the scleroderma spectrum of disease, epoprostenol is also useful in PAH associated with systemic lupus erythematosis [23], HIV infection [24], portopulmonary hypertension [25], and Eisenmenger's syndrome [26]. Epoprostenol is indicated for use in functional classes III and IV PAH.

The beneficial acute effects of epoprostenol stem from its potent vasodilatory and, probably, inotropic actions, whilst the long-term effects are likely attributable to its antithrombotic properties and effects on vascular remodelling [27–29]. With chronic administration, epoprostenol lowers pulmonary vascular resistance to a level beyond that achieved during acute vasodilator testing [30]. Reports of successful withdrawal of chronic epoprostenol therapy suggest that reversal of the vasculopathic process may be achievable in some patients [31].

In a long-term follow-up study of patients with IPAH treated with epoprostenol, McLaughlin *et al.* observed survival rates of 88%, 76% and 63% at 1, 2 and 3 years respectively [21]. In a similar study, Sitbon *et al.* reported survival rates of 85%, 70% and 63% [20]. Survival rates in both studies were significantly better than those predicted by the National Institutes of Health Primary Pulmonary Hypertension (NIH-PPH) Registry equation [1].

Of the therapies available for PAH, epoprostenol is the most complex to administer. It requires a portable infusion pump for continuous i.v. administration through a central catheter because of its short half-life (<5 min) and high pH of the diluent. Ice packs must be used to keep the infusate cold as the drug is unstable at room temperature. The most common side-effects are jaw pain, flushing, headache,

diarrhoea and arthralgias. Many of these side-effects are dose dependent and respond to conservative measures or decreases in dose. Patients are also at increased risk for catheter-related complications such as infection and thrombosis.

Prostacylin analogues

The complexity of continuous i.v. epoprostenol therapy and its attendant risks has led to the development of stable prostacyclin analogues that can be administrated by simpler routes. In contrast to epoprostenol, the prostacyclin analogues are stable at room temperature and can be diluted in physiological saline without inactivation [32]. These characteristics allow them to be delivered by the inhaled or subcutaneous (s.c.) routes.

Treprostinil

Treprostinil is a stable prostacyclin analogue with a half-life of 55–117 min [32]. It can be administered subcutaneously using a minipump, similar to that used to deliver insulin. The infusion site is typically rotated every few days to minimize local skin reactions.

The therapeutic efficacy of s.c. treprostinil was investigated in a large, 12-week RCT involving patients with functional classes II–IV IPAH or PAH associated with connective tissue disease or congenital systemic-to-pulmonary shunt [33]. The treprostinil group had a small, but significant increase in the 6-minute walk test (6MWT) compared with placebo (+16 m). The magnitude of effect appeared to be dose related. Although effective, the improvement in 6MWT seen with treprostinil appeared to be relatively modest when compared with studies that used epoprostenol [19, 20]. Improvements were also seen in haemodynamic parameters and the Borg dyspnoea score. However, deaths and study discontinuations because of clinical worsening were not significantly different between the two treatment groups.

Notably, 85% of patients reported pain at the infusion site and 83% had an infusion site reaction, leading to discontinuation of the study by 8%. Other commonly reported side-effects included headache, diarrhoea, nausea and rash. Five patients (2%) who were receiving treprostinil were transitioned to epoprostenol for worsening clinical status. Long-term data from an open-label extension study has shown continued efficacy of s.c. treprostinil after 24 months of therapy [34].

Treprostinil can also be delivered as a continuous i.v. infusion. It is dosed similarly to s.c. treprostinil as they are bioequivalent at steady state [35]. Twelve-month data from a prospective transition study of i.v. epoprostenol to i.v. treprostinil has shown it to be effective in this form [36]. This was accomplished without evidence of deterioration, suggesting that epoprostenol's benefits were being maintained by treprostinil. It is important to note that no RCT using i.v. treprostinil as initial treatment has been performed. Its efficacy in this situation is extrapolated from the bioequivalence data to s.c. treprostinil and the fact that s.c. treprostinil has been found to be effective as an initial treatment regimen. In general, experience with i.v. treprostinil is relatively limited.

One advantage of treprostinil over epoprostenol is that it does not require constant cooling as it is stable at room temperature. The longer half-life may also theoretically allow unintentional dose interruptions to be better tolerated than epoprostenol, which has a very short half-life. The s.c. route also offers the advantage of a less complex delivery system compared with the i.v. route as it does not require an implanted i.v. catheter; however, it suffers from a high incidence of skin infusion site complications that may limit its usefulness. Treprostinil is also being investigated as an inhalation treatment.

Iloprost

Iloprost has been marketed as both an i.v. and inhaled medication. It is stable at room temperature and ambient light and has a plasma half-life of almost 30 min [37]. Most of the attention has focused on iloprost as an inhalation drug. This route allows it to selectively promote vasodilation in the pulmonary artery circulation whilst minimizing the systemic effects commonly associated with i.v. prostanoids [38, 39]. The inhaled route also promotes drug deposition and selective action to those areas that are well ventilated, thereby minimizing ventilation–perfusion mismatch. This may be especially important in patients with PAH who have underlying parenchymal lung disease. In contrast, i.v. prostacyclin increases the shunt fraction in this setting [38].

The safety and efficacy of inhaled iloprost was studied in a pivotal 12-week RCT involving 203 patients with functional classes III–IV IPAH or PAH associated with appetite suppressants, scleroderma, or inoperable chronic thromboembolic pulmonary hypertension (Aerosolized Iloprost Randomized, AIR) [40]. Those receiving inhaled iloprost showed significant improvement in the combined primary end-point of 6MWT, functional class, and absence of clinical deterioration, in addition to the dyspnoea and quality of life scores. Notably, this study produced positive results for inhaled iloprost despite including a significant proportion of class IV patients. The greatest benefit on the 6MWT occurred in those with IPAH compared with non-IPAH and the magnitude of change was similar to that seen in studies using i.v. epoprostenol [19]. A subgroup analysis of AIR showed no benefit of inhaled iloprost in those with chronic thromboembolic pulmonary hypertension.

The inhaled route theoretically provides the advantage of minimizing systemic side-effects associated with infused prostanoid therapy. However, the incidence of reported adverse events from the pivotal s.c. treprostinil RCT [33] and the inhaled iloprost RCT [40] shows mixed results, respectively: headache (27% vs. 30%), diarrhoea (25% vs. 9%), nausea (22% vs. 13%), jaw pain (13% vs. 12%), vasodilation/flushing (11% vs. 27%), dizziness/vertigo (9% vs. 7%), and oedema (9% vs. 13%). As expected, increased cough was a commonly reported side-effect in the inhaled iloprost study.

Iloprost requires administration six to nine times a day, with each inhalation taking 5–10 min through a special nebulizer device.

Beraprost

Beraprost is an orally active prostacyclin analogue that has been used in Japan since 1995 for the treatment of PAH [41]. It was not until 2002, however, that the first RCT of beraprost was published which showed short-term efficacy in improving exercise capacity and symptoms [42]. A similar, but longer RCT of 12 months duration was subsequently performed in the US [43]. This study confirmed the short-term benefits of beraprost seen in the previous trial; however, these improvements were no longer evident at either 9 or 12 months. Therefore, as monotherapy, beraprost has found little use in the management of PAH.

This trial highlighted the importance of performing longer-term pivotal PAH drug trials to investigate the durability of short-term gains. A primary end-point measured at 12 weeks, which is not uncommon in the published PAH literature, may not accurately reflect what happens to that end-point in the long-term. In the case of beraprost, although it may not be useful as monotherapy in the chronic management of PAH, the prospect of having an orally active prostanoid in the treatment armamentarium is appealing. Further studies may be warranted to determine whether an oral prostanoid could be effective as part of a combination treatment regimen. Beraprost is currently approved for use only in Japan.

Endothelin receptor antagonists

Since the characterization of endothelin (ET-1) in 1988 as a potent vasoconstrictor [44], numerous lines of scientific evidence have pointed to a prominent role of ET in the regulation of pulmonary vasomotor tone and possible role in vascular remodelling, processes which are important in the pathogenesis of PAH. Antagonism of ET receptors is now firmly established as a therapeutic target for patients with PAH.

The endothelins represent a family of 21-amino acid proteins derived from vascular endothelial cells with three known isoforms in humans, ET-1, ET-2 and ET-3 [45]. All three isoforms are characterized by two intramolecular disulphide bonds between cysteine amino acids at residues 1–15 and 3–11. ET-1, the endothelin that is thought to play the most prominent role in PAH, exerts its actions via two receptor subtypes: ET_A, which is located on vascular smooth muscles cells, and ET_B, which is found on both vascular smooth muscle cells and vascular endothelium [46]. Activation of ET_A by ET-1 leads to potent vasoconstriction due to an increase in cytosolic calcium levels via influx of extracellular calcium [47, 48] and release of intracellular calcium stores [49].

The actions of ET_B are more complicated. Like ET_A, activation of ET_B on vascular smooth muscles cells leads to vasoconstriction [50]. Furthermore, some studies suggest that blockade of both ET_A and ET_B is necessary to achieve maximal vasodilation

in the pulmonary hypertensive state [51–53]. Conversely, other studies suggest a protective role of ET_B in pulmonary hypertension by producing nitric oxide and prostacyclin and clearing circulating ET-1 [54–58]. Therefore, the overall net effect of ET_B in regulating pulmonary vasomotor tone is unclear. There may be theoretical benefit in selectively blocking ET_A whilst leaving ET_B unopposed.

Dual endothelin receptor antagonism

Bosentan is an oral, nonselective ERA that has proved its efficacy for the treatment of PAH in two pivotal RCTs [59, 60]. The second and larger trial, Bosentan Randomized trial of Endothelin Antagonist Therapy (BREATHE-1), confirmed the benefits of bosentan given at a dose of 125 mg twice daily in improving the 6MWT, Borg dyspnoea index, and functional class, whilst increasing the time to clinical worsening [59]. The higher dose of 250 mg twice daily was associated with a higher incidence of aminotransferase abnormalities without a significant increase in efficacy. Consistent with a prior study showing a poorer prognosis in scleroderma-associated PAH patients [61], a subgroup analysis of BREATHE-1 showed that bosentan increased the 6MWT in those with IPAH, whereas it prevented deterioration in those with scleroderma (compared with each group's respective placebo arms).

It is important to keep in mind that lack of absolute improvement in clinical parameters does not necessarily equate to treatment failure. The main treatment effect may be one of disease stabilization or decreasing the rate of deterioration rather than overt improvement. Whilst this may not be an optimal response, bosentan is still clearly exerting a beneficial effect by delaying the time to clinical worsening. For this reason, we do not recommend withdrawing bosentan therapy once it has been started unless clinical deterioration is thought to be directly attributable to bosentan or there are intolerable side-effects.

Long-term extension study data with bosentan show Kaplan–Meier survival estimates of 96%, 89% and 86% at 1, 2 and 3 years respectively [62]. These are significantly higher than those predicted by the NIH-PPH Registry equation [1]. At 2 years, 70% of patients remained on bosentan monotherapy. Clearly, the majority of patients experience long-term benefits from bosentan alone; however, there is certainly a subset of patients who will require other agents as add-on therapy as the disease continues to progress.

Data regarding use of bosentan in other forms of PAH are limited. BREATHE-4, a small, prospective, noncomparative cohort study of human immunodeficiency virus (HIV)-associated PAH patients showed significant improvements in a variety of clinical end-points including the 6MWT and Borg dyspnoea index, indicating less dyspnoea despite increased walk distance [63]. Bosentan had no impact on control of the HIV infection. Additionally, despite the fact that several of the patients were co-infected with either hepatitis B or hepatitis C virus and the majority were receiving potentially hepatotoxic antiretroviral therapy, elevated liver function tests were seen only in a minority (12.5%).

Studies investigating the use of bosentan in PAH associated with Eisenmenger's syndrome (BREATHE-5 trial) and functional class II patients with PAH (EARLY trial) are ongoing and should shed further light into the role of bosentan in these conditions.

The most important adverse effect associated with bosentan is hepatocellular injury. Aminotransferase elevations at least three times above the upper limit of normal occurred in about 5–10% of patients treated with bosentan in the pivotal RCTs [59, 64]. Long-term safety data up to 2 years from a European postmarketing surveillance system (TRAX) of patients treated with bosentan showed that the cumulative incidence of abnormal transaminases was about 7% [65]. There were no fatal outcomes related to liver injury.

The likelihood of first aminotransferase elevation appears to diminish over time; however, it can develop at any time. Therefore, it is important to continue monthly monitoring of liver enzymes throughout the duration of treatment. If needed, most patients can be successfully managed with dose reduction or temporary cessation of treatment. Guidelines are available in the packaging insert. Other commonly reported side-effects include flushing and headache, with a few patients experiencing unexplained decreases in haemoglobin concentration.

Bosentan is a pregnancy category X drug. Women of childbearing potential must be monitored with pregnancy tests before and regularly

during treatment with bosentan. In addition, women using a hormonally based method of contraception must use a second form of birth control as bosentan decreases hormone levels. Bosentan should not be co-administered with glyburide or cyclosporin because of a pharmacological interaction that increases the risk of liver enzyme abnormalities.

Selective ET_A receptor antagonism

Selective antagonism of the ET_A receptor has the theoretical advantage of blocking the deleterious vasoconstrictive and vascular smooth muscle proliferative effects mediated through ET_A, whilst maintaining the vasodilatory and ET-1 clearance actions of ET_B.

The safety and efficacy of sitaxsentan, an orally active, selective ET_A receptor antagonist, was originally shown in a small, open-label pilot study [66]. This was followed by a larger RCT involving functional classes II–IV PAH patients randomized to placebo or either of two sitaxsentan dosing groups (Sitaxsentan to Relieve Impaired Exercise, STRIDE-1) [67]. Patients receiving sitaxsentan had significant improvements in 6MWT, functional class, and haemodynamic parameters. Unlike the studies with bosentan, however, there was no difference seen in the time to clinical worsening. A small 1-year follow-up study showed persistent improvement in several clinical parameters compared with baseline [68]. Although potentially useful in treating PAH, the data to date suggest that selectivity for the ET_A receptor does not confer superior effects in PAH compared with dual receptor antagonism.

The incidence of liver enzyme abnormalities with sitaxsentan does not appear to be noticeably different from that seen with bosentan, although direct comparisons are not yet available. The dose of warfarin may need to be decreased as sitaxsentan can cause an increase in the protime international normalized ratio.

Several other studies are underway with sitaxsentan. STRIDE-2 is investigating the safety and efficacy of sitaxsentan compared with placebo and open-label bosentan. STRIDE-6 is studying the use of sitaxsentan in patients who have failed therapy with bosentan because of clinical deterioration or liver enzyme abnormalities. Ambrisentan, another selective ET_A-receptor blocker, is currently in phase III trials.

Phosphodiesterase-5 inhibitors

Cyclic guanosine monophosphate (cGMP) is an intracellular second messenger that is responsible for mediating the vasodilatory activity of nitric oxide [69]. cGMP is rapidly inactivated by PDE-5, an enzyme abundantly found in lung tissue [70]. In the pulmonary circulation, PDE-5 inhibition promotes vascular relaxation by inhibiting the breakdown of cGMP. Numerous studies have suggested a beneficial effect of sildenafil, a PDE-5 inhibitor, in patients with pulmonary hypertension from a variety of causes, including interstitial lung disease, thromboembolism, and hypoxia [7, 71–73].

A cross-over RCT of patients with PAH showed significant improvements in exercise duration, cardiac index, and dyspnoea and fatigue scores with sildenafil treatment [14]. More recently, the results of a 12-week RCT involving patients with PAH predominantly in functional classes II–III (96%) were reported in a late-breaking clinical trials session at the American College of Chest Physicians' meeting in October 2004 (Sildenafil Use in Pulmonary Arterial Hypertension, SUPER-1). The pooled sildenafil dosing groups showed significant improvements in 6MWT and functional class. A more thorough evaluation and interpretation of SUPER-1 are not possible until the full results are published; however, the US FDA has already announced approval of sildenafil 20 mg three times daily for the treatment of PAH without functional class restriction. The regulatory approval process in other countries is ongoing.

Further supporting the efficacy of sildenafil in PAH, preliminary data from a 1-year open-label extension of SUPER-1 presented at the 2005 International Conference of the American Thoracic Society (SUPER-2) showed continued benefit of sildenafil on 6MWT and functional class [74], in addition to survival [75].

Sildenafil appears to be well tolerated with headache as the most commonly reported side effect. Others include dyspepsia, sinus congestion, epistaxis and back pain. No specific laboratory monitoring is recommended; however, its use is contraindicated in those taking nitrate medications because of potentiation of hypotensive effects. A summary of the

currently approved medications for PAH is presented in Table 3.

Treatment decisions

A treatment algorithm for PAH is presented in Fig. 4. All patients with PAH should be treated with anticoagulants and, if indicated, diuretics, and supplemental oxygen. For acutely vasoreactive patients with functional class I to early III IPAH or PAH associated with anorexigen use, an initial strategy using a CCB is reasonable. Still, these patients need to be closely monitored for evidence of improvement as up to 50% will not have a beneficial long-term response and thus have poorer survival. Those who do not show evidence of benefit after 3–6 months of CCB therapy should start treatment with a PDE-5 inhibitor, ERA, or prostanoid.

Although the most recently published evidence-based treatment algorithms recommend CCB therapy as first-line therapy in all patients with PAH who are acutely vasoreactive, many experts are re-considering whether such a broad management strategy is appropriate. For example, it may be reasonable to reserve use of CCBs only to those with acutely vasoreactive IPAH or PAH associated with anorexigen use, as the incidence of long-term response to CCB therapy in other forms of PAH is exceedingly low (Fig. 3). For several reasons, strong consideration should also be given to using a PDE-5 inhibitor, ERA or prostanoid instead of a CCB as first-line therapy for those in advanced functional classes, despite being acutely vasoreactive. First, these patients have little cardiopulmonary reserve and may deteriorate quickly if they turn out to be nonresponders to chronic CCB therapy. Secondly, numerous proven PAH-specific therapies for advanced functional classes are available. Thirdly, there are now less invasive and simpler methods to deliver these effective medications. Thus, in an era in which the number of definitive treatment options for PAH are expanding, the role of CCBs is diminishing.

Nevertheless, it is still currently recommended that acute vasoreactivity testing be performed in all patients with PAH. The presence and magnitude of vasoreactivity may have some prognostic implication, although this is controversial [76–78].

At present, early functional classes of PAH may potentially be treated with sildenafil or continuously administered s.c./i.v. treprostinil, although the latter

Table 3 Summary of medications approved for use in pulmonary arterial hypertension. (a) Approval may be limited to certain PAH subgroups, depending on the country; (b) approved for classes III–IV in the US and III in Europe

Drug (class)	Route	Dose range	Major class	Functional side-effects	Contraindications	Regulatory approval (a)
Epoprostenol (prostanoid)	i.v.	2 ng kg^{-1} min^{-1} and up	III–IV	Flushing, headache, nausea, diarrhoea, jaw pain, lightheadedness, arthralgias	None	US, Europe, Canada, Australia
Iloprost (prostanoid)	inh.	2.5–5 mcg 6–9 times daily during waking hours; total daily dose usually <45 mcg	III–IV (b)	Flushing, cough, headache, jaw pain, insomnia, nausea, hypotension	None	US, Europe, New Zealand, Australia
Treprostinil (prostanoid)	s.c.	1.25 ng kg^{-1} min^{-1} and up, i.v. usually <40 ng kg^{-1} min^{-1} (s.c. and i.v. routes are bioequivalent)	II–IV	Infusion site pain and reaction (i.v./s.c.), headache, diarrhoea, nausea, jaw pain, flushing	None	US, Europe, Canada
Bosentan (Dual ERA)	p.o.	62.5 mg q.d. ×4 weeks, then 125 mg b.i.d.	III–IV	Hepatocellular injury, flushing, headache, oedema, sinus congestion, haemoglobin decrease	Concurrent use of cyclosporin or glyburide; pregnancy; moderate-to-severe pre-existing liver impairment	US, Europe, Canada, Australia, Japan
Sildenafil (PDE-5 inhibitor)	p.o.	20 mg t.i.d.	I–IV	Headache, dyspepsia, epistaxis, back pain, sinus congestion	Concurrent use of organic nitrate medication	US, under review in Europe

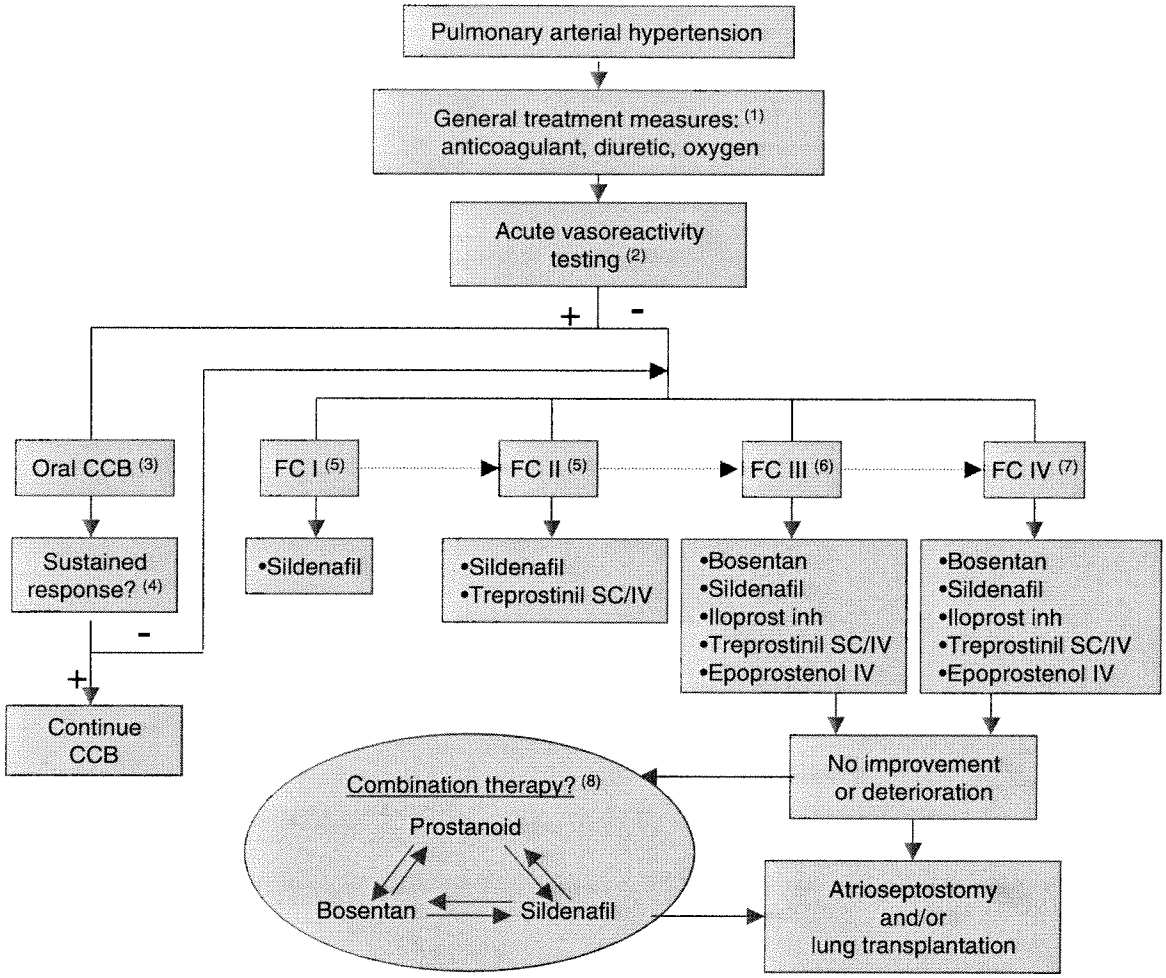

Fig. 4 Treatment algorithm for pulmonary arterial hypertension. The recommended therapies presented in this algorithm have been evaluated mainly in those with idiopathic pulmonary arterial hypertension (IPAH), or PAH associated with connective tissue disease or anorexigen use. Extrapolation to other forms of PAH should be made with caution. Medications are listed in order of increasing invasiveness. Country-specific regulatory agency approval status and functional class indications for PAH medications vary. (1) All patients should receive treatment with an anticoagulant. Diuretics and oxygen should be added as necessary. (2) A positive acute vasodilator response is defined as a fall in the mean pulmonary artery pressure from ≥10 to ≤ 40 mmHg with a normal or increased cardiac output when challenged with inhaled nitric oxide, i.v. epoprostenol or i.v. adenosine. (3) Consideration should be given to using a PAH-specific medication such as a PDE-5 inhibitor, endothelin receptor antagonist (ERA), or prostanoid as first-line treatment instead of a calcium channel blocker (CCB) in those with PAH that is not IPAH or PAH associated with anorexigen use, or in those in an advanced FC given the exceedingly low long-term response rate to CCB monotherapy in the former and poor prognosis in the latter. (4) Sustained response to CCB therapy is defined as being in FC I or II with normal or near-normal haemodynamics after several months of treatment. (5) The risks and benefits of treatment in early PAH should be considered. (6) First-line therapy for FC III includes bosentan, epoprostenol, inhaled iloprost, sildenafil, and s.c./i.v. treprostinil. (7) Most experts recommend i.v. epoprostenol as first-line treatment for unstable patients in FC IV. (8) RCTs studying add-on combination treatment regimens are underway.

is rarely used in these instances due to the potential serious risks and complications related to its administration. Given its oral availability, sildenafil is an attractive option for early PAH, especially in patients who are class II. There is actually very little information about sildenafil's efficacy in functional class I patients. In fact, only one patient in the sildenafil SUPER-1 trial was from this class. Oral bosentan is also currently being studied for use in functional class II patients in the EARLY trial.

Patients in functional classes III and IV pose a significant challenge in choosing an initial treatment

regimen. For patients in class IV, most experts recommend first-line treatment with i.v. epoprostenol given the extensive experience with its use, proven efficacy, survival benefit, and rapidity of action. This is consistent with the most current evidence-based treatment algorithms published [15, 79].

For the rest of the patients in class III or IV, treatment with inhaled iloprost, treprostinil s.c./i.v., bosentan, and sildenafil are available. Because direct, prospective comparisons between different PAH medications are not available (with the exception of one study, discussed below), the decision to use one treatment over another in the majority of cases will ultimately be influenced by the clinical scenario, availability of medication, preferred route of administration, medication side-effect profile, patient preference and provider experience. Still, there are situations in which it may be rational to use one medication over another.

Inhaled iloprost is an attractive option for PAH as it comes from the powerful prostanoid class of medication and administration is noninvasive. Compared with systemic therapies, the inhaled route may also particularly be useful in situations in which the ventilation–perfusion relationship is significantly altered, e.g. those with parenchymal lung disease complicating PAH associated with connective tissue disease, although more studies are needed to investigate this. The downside to inhaled iloprost includes the relatively short duration of action requiring repeated treatments six to nine times a day. Additionally, long-term efficacy data are not yet available.

In terms of administration, treprostinil has some advantages over epoprostenol in that it does not have to be continually cooled and, at least for the subcutaneous form, an implanted central venous catheter is not required. However, long-term efficacy data for s.c. treprostinil are not yet available. As for i.v. treprostinil, it has been shown to be effective as a transition therapy from i.v. epoprostenol; however, data are not available about its efficacy as initial treatment. This must be extrapolated from the bioequivalence data to s.c. treprostinil.

With respect to bosentan, it should be kept in mind that the beneficial effects probably take at least 8 weeks to manifest. Therefore, bosentan is not appropriate for use as monotherapy in unstable class IV patients. Additionally, haemodynamic evidence of right heart failure on initial RHC may help predict poor response to bosentan and could persuade one to use a prostanoid as first-line treatment in this situation [80]. For those in functional class III, there are data to suggest that survival estimates up to 36 months are similar between those initially treated with bosentan compared with those initially treated with epoprostenol [81]. Using an initial treatment combination of bosentan with epoprostenol may provide some additional benefit compared with using epoprostenol alone in class III/IV patients (BREATHE-2 trial) [82].

Sildenafil's place within the treatment algorithm is most firmly established for functional classes II and III as 96% of the patients in the SUPER-1 trial were from these classes; however, general clinical experience with its use in PAH is still in its infancy. Certainly, for those in whom oral therapy is being considered and/or bosentan is contraindicated, sildenafil is a viable option. A more thorough evaluation will be possible when the SUPER-1 results are published. Additionally, more complete follow-up data from SUPER-2 are needed regarding its long-term efficacy. In this respect, at least in comparison with the only other oral therapy available for PAH, bosentan may have an advantage as data regarding 3-year survival and need for add-on therapy are already available [62]. It is unknown whether the difference in dosing frequency between bosentan (twice daily) and sildenafil (three times daily) could potentially affect treatment compliance.

Keeping these factors in mind, one small, double-blind RCT has already been published investigating the efficacy of bosentan versus sildenafil over a 16-week period in patients with class III IPAH or PAH associated with connective tissue [83]. One patient in the sildenafil group died unexpectedly. When analysed by intention-to-treat, there were no significant differences between the treatment groups with respect to changes in right ventricle mass, 6MWT, echocardiographic parameters, brain natriuretic peptide, or Borg dyspnoea index.

Combination/add-on therapy

Unfortunately, not everyone responds to the initial drug treatment regimen chosen. The addition of a second PAH drug may be reasonable for patients who deteriorate or have a suboptimal response to monotherapy. Potential candidates include those

with worsening symptoms or deteriorating exercise capacity, functional class, or haemodynamics. In those initially treated with epoprostenol, persistence of an advanced functional class or lack of improvement in certain haemodynamic parameters at follow-up portend a poor prognosis [20, 62, 84]. These are also appropriate candidates for combination drug therapy.

An approach that uses a combination of drugs that targets different pathways has been successfully employed in systemic hypertension and congestive heart failure, and a similar strategy in PAH may increase efficacy whilst minimizing toxicity. Although prostanoids, ERAs and PDE-5 inhibitors work through different intracellular pathways, there may be important interactions between them. For example, the stable prostacyclin analogue cicaprost inhibits the release of ET-1 from pulmonary artery smooth muscle cells, whilst the antiproliferative effects of cicaprost are attenuated by ET-1 [32, 85]. Similarly, PDE-5 inhibitors increase the intracellular levels of cyclic adenosine monophosphate, a mediator for the cardiovascular effects of prostanoids [32].

A handful of case series and observational cohort studies preliminarily have shown promising results using various combinations of sequential add-on therapy including prostanoids + sildenafil [73, 86, 87], prostanoids + bosentan [88], and bosentan + sildenafil [89]. However, rigorous RCTs, several of which are currently ongoing, are needed to clarify definitively the proper timing and appropriate combination of drugs to use [90].

Switching therapies

Transitioning therapies has been made possible with the availability of less invasive and more convenient treatment options. The concept of transitioning therapy is one of de-evolution: going from a more invasive and complex treatment to one that is less invasive and simpler. This should be accomplished without clinical deterioration. Preliminary data suggest that transitioning patients from chronic i.v. epoprostenol to i.v. treprostinil [36] or s.c. treprostinil [91] can be carried out safely and without clinical deterioration. For patients who have made adequate improvement with epoprostenol or treprostinil, transitioning to oral therapies such as an ERA or PDE-5 inhibitor may also be possible. As there are no guidelines available for the selection of candidates for transitioning therapies, the timing, or the choice of agents, these decisions should be reserved for highly experienced physicians.

Lung or heart-lung transplantation

Lung or heart-lung transplantation for PAH remains the treatment of last resort when medical therapy has failed. Atrial septostomy can be used as a bridge to transplantation in patients with refractory right heart failure or as an alternative when transplantation is not a viable option. Septostomy is a high-risk procedure that should only be performed in centres with expertise [92].

Between January 1995 and June 2002, the Registry of the International Society for Heart and Lung Transplantation reported that 427 lung transplants were performed around the world for IPAH [93]. The majority were bilateral lung transplants (85%). Compared with other conditions for which transplantation was performed, those with IPAH had the highest risk of death within the first year of transplantation. However, for those who survived the first year, the prognosis improved considerably compared with the outcome of other recipient groups. The median survival after transplantation for IPAH was 4 years.

We recommend considering transplantation for PAH patients in class III or IV who are deteriorating on medical therapy [92]. For those being treated with epoprostenol, the presence of right-sided heart failure, persistence of NYHA functional classes III–IV, or the absence of a significant fall in total pulmonary resistance >30% relative to baseline after 3 months of therapy is associated with poor survival and may be useful in the consideration and timing of transplantation [20].

Monitoring treatment

Pulmonary arterial hypertension is a progressive disease for which no single therapy may suffice. Accordingly, ongoing and methodic monitoring of the responses to treatment is crucial in order to optimize outcomes. We reassess the clinical status every 2–3 months using noninvasive assessments such as functional class and 6MWT. Decisions regarding dose changes or add-on therapy depend on subjective and objective criteria. In general, our

goal is to improve the 6MWT to >380 m and functional class to I/II whilst on treatment, given their prognostic significance [20]. In instances when add-on therapy is being considered or the haemodynamic status is unclear, we perform repeat RHC. Echocardiography can also noninvasively provide useful measurements that have prognostic significance [94–99].

Conclusions

Until quite recently, PAH was an untreatable condition that invariably progressed to premature death. Whilst i.v. epoprostenol, the first medication introduced specifically for PAH, is still widely considered the 'gold standard' of therapy, newly studied prostacyclin analogues, ERAs and PDE-5 inhibitors provide alternative means of treatment that are less complex yet still efficacious for many patients with PAH.

Each advance, however, raises new questions about first-line treatment strategies and proper use of combination regimens. Certainly, treatment and management decisions are becoming increasingly complex. Referral of PAH patients to centres that have physicians and clinical support staff with particular expertise in managing patients with PAH may be necessary. In the meantime, as more data become available, the treatment algorithm will continue to evolve to optimize the evidence-based decision-making process.

Conflict of interest statement

Stephen H. Lee MD does not have a financial relationship with a commercial entity that has an interest in the subject of this article. Lewis J. Rubin MD has served as an investigator and consultant for the following commercial entities with an interest in the subject of this manuscript: Actelion, Pfizer, Schering, United Therapeutics, CoTherix, Myogen, MondoBiotech and Nitrox.

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EXHIBIT 5

Getting Started on VENTAVIS® (iloprost) Inhalation Solution

A Patient's Guide to Taking VENTAVIS

INDICATION

What is VENTAVIS?

VENTAVIS is a prescription medicine used to treat adults with certain kinds of severe pulmonary arterial hypertension (PAH), a condition in which blood pressure is too high in the blood vessels between the heart and the lungs. VENTAVIS may improve your ability to exercise and your symptoms for a short time by lowering your blood pressure and opening up the blood vessels in your lungs.

The study showing VENTAVIS is effective included mainly patients with NYHA Functional Class III-IV PAH. In these patients, PAH was caused by unidentified or hereditary factors (65%) or connective tissue diseases (23%).

VENTAVIS has not been studied in children younger than 18 years old.

Please see accompanying full Prescribing Information and Patient Information, and Important Safety Information on pages 3 and 4.

INHALED Ventavis® (iloprost) INHALATION SOLUTION

Understand Your PAH Therapy with

Your doctor has prescribed VENTAVIS to treat your pulmonary arterial hypertension (PAH)

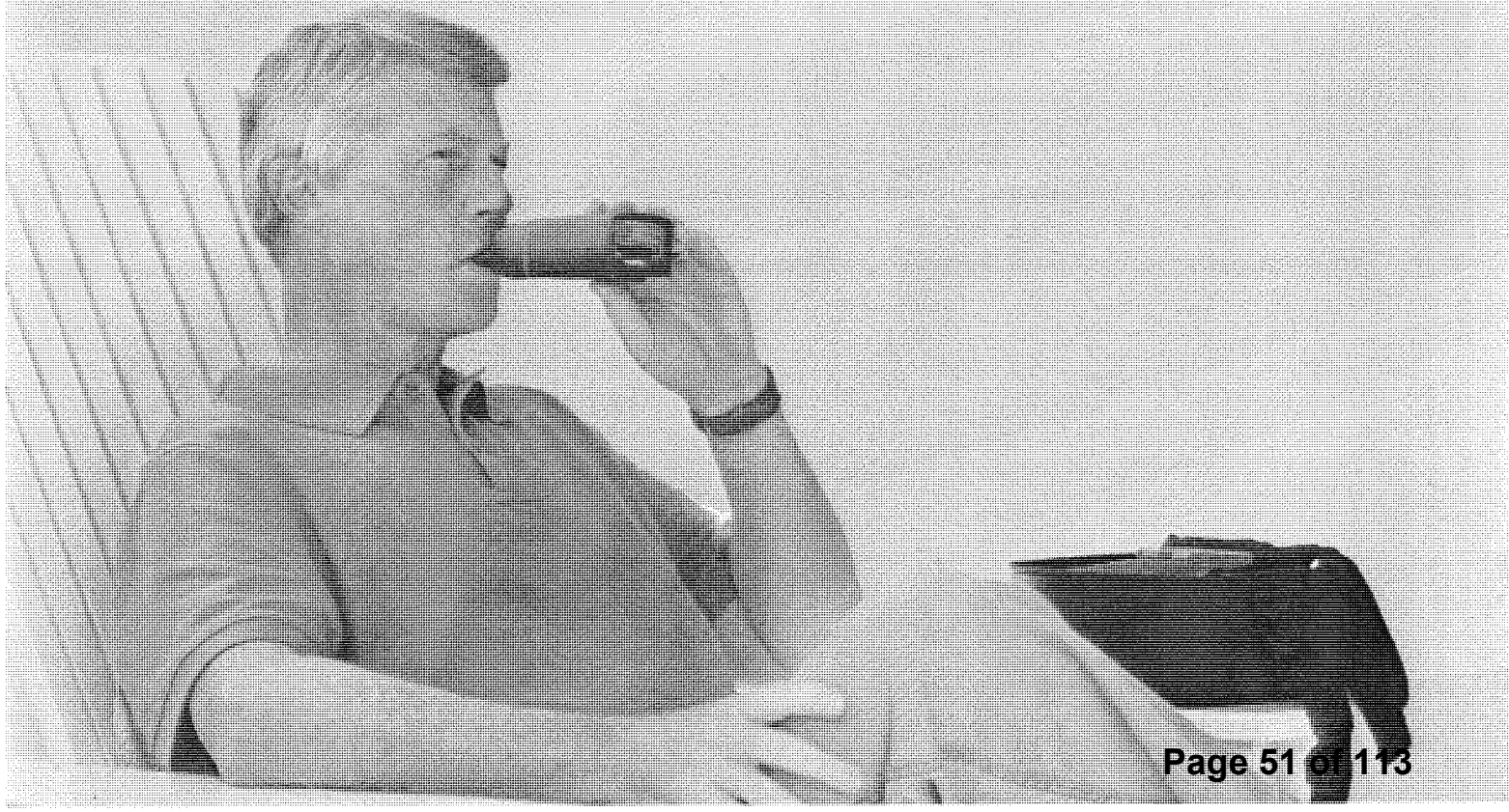
VENTAVIS is an inhaled PAH therapy that can be given to help patients improve some symptoms of PAH.

VENTAVIS has been shown to help some patients[1]:

- Improve some PAH symptoms (NYHA Functional Class III-IV)
- Walk farther in a timed test
- Slow down the progression of PAH

This brochure will help you to:

- Understand VENTAVIS
- Learn how to take VENTAVIS
- Use the I-neb® AAD® System
- Find and use resources for help and information
  - Actelion Services and Support—If you enroll, Actelion can provide you with services and support such as helping you with:
    - Answering your questions about filling your prescription
    - Coordinating with your doctor, insurance company, and specialty pharmacy to find out whether you have coverage for your medicine or if additional information is needed
    - Informing you of possible financial assistance programs based on your eligibility
  - Actelion Patient Services—trained Nurse Educators who can help answer your questions about VENTAVIS and the I-neb AAD System.



VENTAVIS® (iloprost) Inhalation Solution

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IMPORTANT SAFETY INFORMATION

What should I tell my doctor before taking VENTAVIS?

VENTAVIS may not be right for you. Before taking VENTAVIS, tell your doctor about all of your medical conditions, including if you:

- have liver or kidney problems. Your doctor may need to give you a lower dose of VENTAVIS.
- are pregnant, or plan to become pregnant. It is not known if VENTAVIS can harm your unborn baby. VENTAVIS should only be used during pregnancy if the benefit to you is worth the possible risk to your baby.
- are breast-feeding. It is not known if VENTAVIS passes into your breast milk. You and your doctor should decide if you will take VENTAVIS or breast feed.

Tell your doctor about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements.

VENTAVIS and other medicines may affect each other causing side effects. VENTAVIS may affect the way other medicines work, and other medicines may affect how VENTAVIS works.

Especially tell your doctor if you take:

- medicines used to treat high blood pressure or heart problems
- medicines that lessen blood clotting (warfarin, Coumadin, Jantoven)

Know the medicines you take. Keep a list of your medicines and show it to your doctor and pharmacist when you get a new medicine.

How should I take VENTAVIS?

- Take VENTAVIS exactly as your doctor tells you to take it. Your doctor may change your dose if needed.
- You should not take VENTAVIS more than every 2 hours. The benefits of VENTAVIS may not last 2 hours, so you may adjust the times that you use it to cover planned activities.
- Do not drink VENTAVIS.
- Do not let VENTAVIS solution come into contact with your skin or eyes. If it does, rinse your skin or eyes with water right away.

Please see accompanying full Prescribing Information and Patient Information.
Please see the Important Safety Information continued on the next page.

IMPORTANT SAFETY INFORMATION (continued)

- Do not allow other people to be exposed to VENTAVIS while you are breathing it, especially babies and pregnant women.
- If you take too much VENTAVIS, you may have a headache, red face, dizziness, nausea, vomiting and diarrhea. If this happens stop taking VENTAVIS. If your symptoms do not go away, call your doctor or get emergency help right away.

What are the possible side effects of VENTAVIS?

VENTAVIS may cause side effects, including feeling dizzy, lightheaded and faint. If you have any of these side effects, you should stand up slowly when you get out of chairs or bed. Tell your doctor if your fainting gets worse during treatment with VENTAVIS. Your doctor may need to change your dose or your treatment.

Do not drive a car or operate any tools or machines if dizziness or fainting from low blood pressure is a problem for you.

You may have trouble breathing after taking VENTAVIS because it may cause the muscles around your airway to tighten (bronchospasm). Get emergency help right away if you have trouble breathing.

Other important side effects of VENTAVIS include:

- bleeding
- red face (flushing)
- increased cough
- low blood pressure
- headaches
- nausea
- spasm of your jaw muscles that makes it hard to open your mouth

Talk to your doctor if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of VENTAVIS. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088.

More about how VENTAVIS can help

VENTAVIS is delivered right to the lungs—the site of the disease. VENTAVIS is an inhaled therapy that can be given alone to help patients walk farther and breathe easier with daily activities.

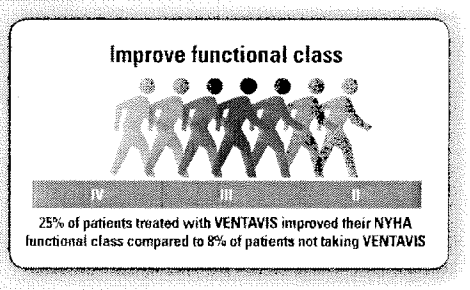
In clinical studies, VENTAVIS has been shown to lower high blood pressure and resistance in the pulmonary artery (main blood vessel) leading to the lungs to allow the heart to pump better.[1]

VENTAVIS is the only inhaled PAH therapy which has shown that patients have clinical improvement with treatment—defined as the combination of 3 different clinical measurements. The clinical study showed that PAH patients treated with VENTAVIS*:

Improved functional class[1]

- **Patients felt better doing daily activities and improved their NYHA Class.**

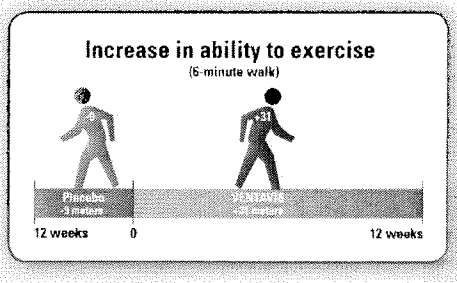
  Many patients who felt short of breath (even when sitting still) found that they were able to be more active.



Increased their ability to exercise*[1]

- **Also, patients were able to walk farther in a timed test.**

  Patients who took VENTAVIS were able to walk farther by at least 10% in a 6-minute walk test. On average, patients who took VENTAVIS could walk 40 meters farther than those who did not take VENTAVIS.

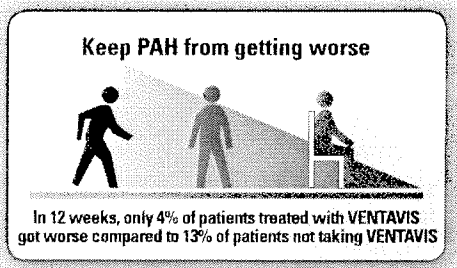


Experienced less worsening of PAH symptoms[1]

- **VENTAVIS decreased the worsening of PAH symptoms.**

  PAH is a progressive disease, which means it tends to get worse if not treated. Many patients who took VENTAVIS had less worsening of PAH.

It is important to remember that each person responds differently to therapy.



*In a study of 146 patients with NYHA Class III or IV PAH, researchers compared 2 groups of patients for 12 weeks: 1 group received VENTAVIS inhaled 6 to 9 times per day, while the other group inhaled placebo (no active medicine). About 5 times as many patients taking VENTAVIS had clinical improvement compared to those who took placebo during the study (19% vs 4%).[1]

Connect with *Actelion Pathways*™...

Getting your VENTAVIS® (iloprost) Inhalation Solution prescription

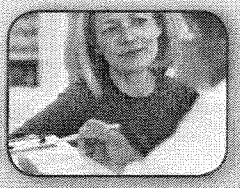
Your VENTAVIS prescription comes with helpful services brought to you by *Actelion Pathways*. *Actelion Pathways* is your one point of contact for access to VENTAVIS, answers to questions about filling your prescription, and help in coordinating with your doctor, insurance company, and specialty pharmacy to find out whether you have coverage for your medicine.

Here's how it happens...

1. Your healthcare provider will send your prescription form directly to *Actelion Pathways*. An Actelion Patient Services Counselor will coordinate with your doctor, insurance company, and specialty pharmacy to find out whether you have coverage for your medicine.

2. Then, *Actelion Pathways* will work with the specialty pharmacy to help you get your prescription filled as soon as possible.

3. Your specialty pharmacy contacts you to set up a meeting between you and a VENTAVIS-trained specialty pharmacy nurse. The specialty pharmacy will send your VENTAVIS prescription and the I-neb® AAD® System directly to you. Then the specialty pharmacy nurse meets with you at your doctor's office or your home to show you how to take VENTAVIS with the I-neb AAD System.



Please see accompanying full Prescribing Information and Patient Information.

Actelion Pathways is with you on your journey

When your VENTAVIS prescription is written, it goes to Actelion. A VENTAVIS prescription cannot be filled at your neighborhood pharmacy. It must be dispensed through a specialty pharmacy that is part of the VENTAVIS network.

Is VENTAVIS covered by insurance?

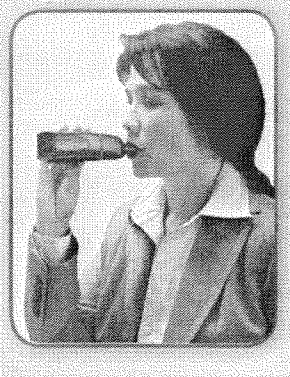
Every insurance company is different. Our Actelion Patient Services Counselors will help in coordinating with your doctor, insurance company, and specialty pharmacy to find out whether you have coverage for your medicine.

If you have any questions about the services and support offered by Actelion, call toll-free, **1-866-ACTELION** (1-866-228-3546) Monday through Friday, 12 PM-8 PM (ET)/ 9 AM-5 PM (PT).

Please see pages 3 and 4 for Important Safety Information.

Taking VENTAVIS® (iloprost) Inhalation Solution

How is VENTAVIS taken?



VENTAVIS is inhaled through a special system called the I-neb® AAD® System, which is compact, portable, and lightweight. The I-neb AAD System is small—about the size of a box of kitchen matches—and it has an internal rechargeable battery like a cell phone, so you can take your medication almost anywhere at any time. VENTAVIS should be inhaled as your doctor prescribes, usually 6-9 times a day, but not more often than every 2 hours.[1]

What does AAD stand for?

Adaptive **A**erosol **D**elivery.

- The word "Adaptive" is important because it means that this system adjusts to fit your breathing pattern each time you use it. It releases the medicine (as a mist) only when you breathe in. This device was designed to deliver the right amount of medication.[1]
- "Aerosol" means fine mist.

Why is VENTAVIS inhaled?

Inhaling VENTAVIS gets it right to the lungs—the site of the disease. There are other ways to deliver medications like VENTAVIS into the body that require pumps, needles and catheters.

Can I take VENTAVIS only with the I-neb AAD System?

VENTAVIS must be taken with the I-neb AAD System because it is the only system approved by the FDA and available for use with VENTAVIS. This special handheld system turns VENTAVIS liquid medicine into a fine mist (or "aerosol") that you breathe in. Its advanced technology provides direct-to-lung delivery of VENTAVIS.

Please see accompanying full Prescribing Information and Patient Information.

A high-tech handheld system

The I-neb AAD System has been developed with high-tech features so that it:

- Adjusts to fit your breathing pattern each time you use it (unlike other nebulizers which make you adjust when and how you breathe)
- Produces a fine mist that can reach into the tiny airways throughout the lungs
- Makes sure dosing is accurate every time you take VENTAVIS
- Records treatment information to help your doctor follow your progress

Handy carrying case

The I-neb AAD System is compact, portable, and comes with a convenient over-the-shoulder carrying case, making your treatments accessible and easy when you're on the go.

Learning how to use the I-neb AAD System

After you receive your VENTAVIS prescription and I-neb AAD System from your specialty pharmacy, they will schedule a meeting between you and a VENTAVIS-trained nurse educator. The nurse educator will meet with you (either at home or in your doctor's office) to show you how to take your VENTAVIS treatments, and how to use and clean the I-neb AAD System:

- Each treatment should take about 4-10 minutes.
- If you notice that your treatments are starting to take longer than usual, call your specialty pharmacy or your healthcare professional to ask for help.
- Or you can call Actelion's team of Registered Nurses and Respiratory Therapists, who will be glad to help answer your questions. Call **1-866-ACTELION** (1-866-228-3546) Monday through Friday, 12 PM-8 PM (ET)/ 9 AM-5 PM (PT).

To learn more about VENTAVIS and watch videos about using the I-neb AAD System, visit the I-neb AAD Learning Center at: **www.VENTAVIS.com.**

Please see pages 3 and 4 for Important Safety Information.

Understanding Your I-neb® AAD® System

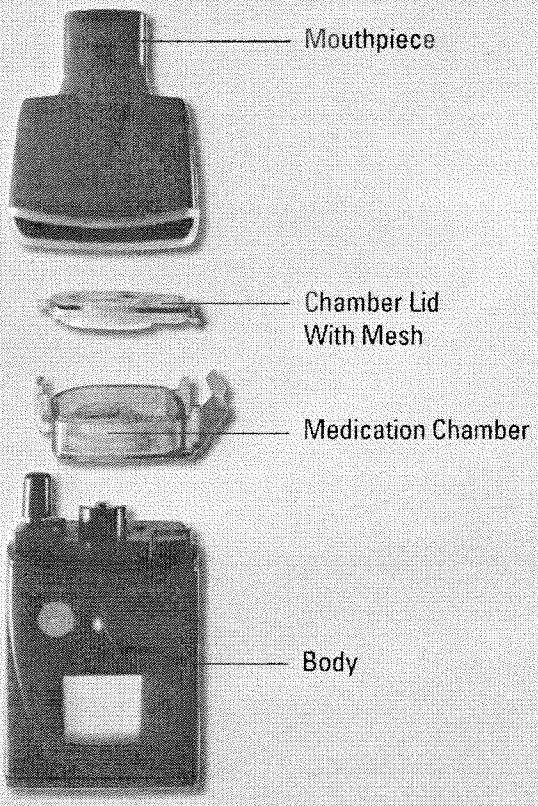
Help when you start

A VENTAVIS-trained nurse educator from your specialty pharmacy will be with you to help you get started on VENTAVIS® (iloprost) Inhalation Solution. The nurse educator will show you, step-by-step, how to use and clean your I-neb AAD System. You will also get a more detailed instruction booklet.

Your I-neb AAD System[2]

Mobility and portability. That's what you get with the I-neb AAD System. You can take the I-neb AAD System with you for treatments almost anywhere at any time.*

The I-neb AAD System comes with two convenient carrying cases for your chamber lids with mesh.



For full details on how to use the I-neb AAD System, see the user manual that accompanies your device.

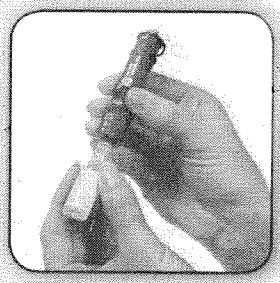
*Usually 6 to 9 times a day but no more than once every 2 hours.[1]

Please see accompanying full Prescribing Information and Patient Information.

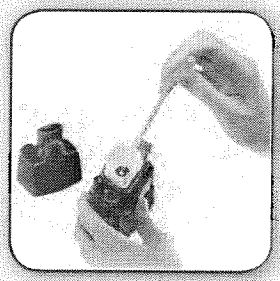
Setting up is simple and easy

- Make sure the battery is charged. The I-neb AAD System, when fully charged, will last for up to 40 treatments before recharging is needed.

- Hold the VENTAVIS ampule with the blue dot facing away from you and align with dot on ampule breaker to open the ampule.



- After removing the medication lid, put the dosing guide over the medication chamber. Use the pipette to draw VENTAVIS out of the ampule. Carefully squeeze the liquid into the medication chamber.



- Replace the lid, cover the latch, and attach the mouthpiece.

If you have any questions about VENTAVIS or the I-neb AAD System, help is just a phone call away. Contact Actelion Patient Services at **1-866-ACTELION** (1-866-228-3546) Monday through Friday, 12 PM-8 PM (ET)/ 9 AM-5 PM (PT). Or call your specialty pharmacy.

Please see pages 3 and 4 for Important Safety Information.

The ABCs of Using the I-neb® AAD® System

Learn the ABCs—**Angle, Breathing, Cleaning**—to help you manage your VENTAVIS® (iloprost) Inhalation Solution treatment. These are the three keys to taking VENTAVIS with the I-neb AAD System.

Angle:

Holding the I-neb AAD System at the right angle ensures the best drug delivery.

- Sit in a comfortable, upright position.
- Hold the I-neb AAD System at a 90-degree angle to your mouth, like you would when eating a hamburger; resting your elbows on the table while holding your I-neb AAD System makes it easy.
- The I-neb AAD System will remind you with 4 short beeps if you are not holding it at a 90-degree angle.
- Holding the I-neb AAD System at the wrong angle will increase the length of treatment time.

Practice your ABCs every day

Please see accompanying full Prescribing Information and Patient Information.

Breathing:

Proper breathing is the single most important part of your treatment.

Keep your lips closed around the I-neb AAD System mouthpiece as you breathe in and out.

- Breathe in and out through your mouth, not your nose.
- The I-neb AAD System will take the first 3 breaths in and out to adapt to your own breathing pattern. As you begin your 4th breath in, VENTAVIS will be delivered.
- The I-neb AAD System will vibrate as you begin to take a breath in to let you know VENTAVIS is being delivered.

Relax and breathe in and out in a slow and steady manner

- While breathing in a slow and steady manner, try counting one one-thousand, two one-thousand, three one-thousand.
- The longer you can breathe in, the more VENTAVIS is delivered and your treatment times may decrease.
- If you need a break, take one. Rest a minute or 2, then restart your treatment. Remember, the I-neb AAD System will take 3 breaths in and out to adapt to your breathing pattern before VENTAVIS will be delivered again.

Cleaning:

Keeping your I-neb AAD System clean is important to treatment success. Thorough cleaning keeps the I-neb AAD System working well. The parts must be cleaned once a day and boiled once a week. See the "Cleaning the I-neb AAD System" section for more details on cleaning.

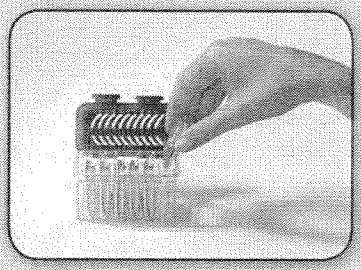
Please see pages 3 and 4 for Important Safety Information.

Once-Daily Cleaning...Easy as 1-2-3

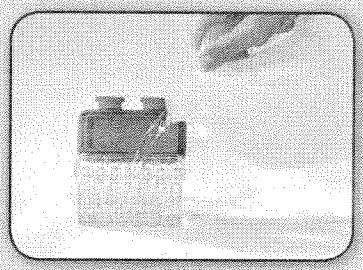
To keep your I-neb® AAD® System in the best working condition, clean it once a day and boil it weekly.

1. Starting the day

- Load the blue case with 6 clean, dry chamber lids with mesh—the blue case is always for clean chamber lids with mesh.
- Fill the orange case with distilled water and secure the lid—the orange case is now ready to store up to 6 used chamber lids with mesh.



Load blue case with clean, dry chamber lids with mesh.



Fill orange case with distilled water and secure the lid.

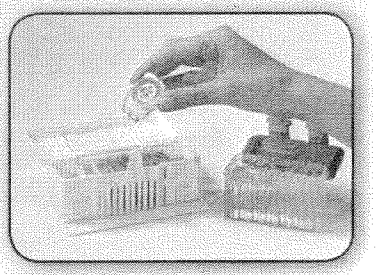
2. During the day

- Remove a chamber lid with mesh from the blue carrying case and place it on top of the I-neb AAD System medication chamber. Close the latch and attach the mouthpiece.
- Take your VENTAVIS® (iloprost) Inhalation Solution treatment.
- When finished with your treatment, remove the used chamber lid with mesh and place it in the orange carrying case.
- Repeat the steps above each time you take a VENTAVIS treatment.

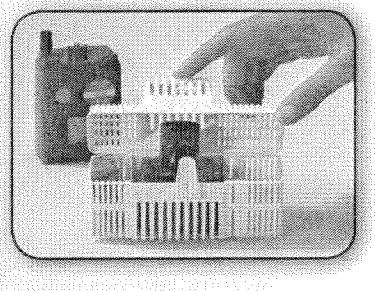
Please see accompanying full Prescribing Information and Patient Information.

3. Ending the day

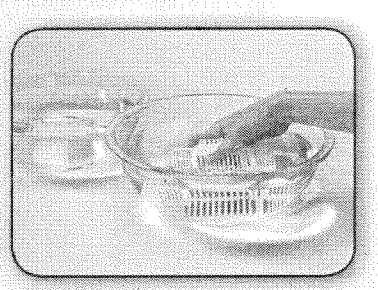
- When your orange case is filled with used chamber lids with mesh from the day's treatments, you're ready for once-daily cleaning.
- Remove the chamber lids with mesh and place them in the mesh wash basket.



- Place the mouthpiece, medication chamber, chamber lids with mesh, and drug guide in the main wash basket.
- Using only one drop of dishwashing liquid,* wash all of the pieces in distilled water.



- Rinse the pieces with more distilled water (never reuse the distilled water).
- Shake off the water and then air dry the pieces for 2 hours before using again.
- Be sure to clean the orange used chamber lid with mesh carrying case with soapy water at least once a week.



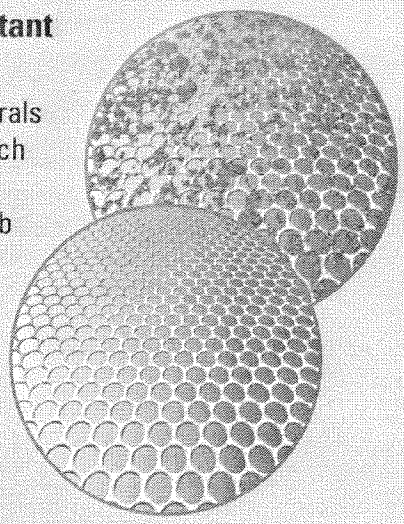
Note: If you want, you can wash each chamber lid with mesh after each treatment instead of all at once at the end of the day. Use the same cleaning method described above.

*Use any liquid detergent without bleach, fragrance, or antibacterial ingredients—examples are Original Dawn®, Ultra Dawn®, Palmolive® Original, Method® Go Naked Dish Soap, and Seventh Generation® Free & Clear Natural Dish Liquid. Only one drop is needed per cleaning.

Please see pages 3 and 4 for Important Safety Information.

Distilled Water

Why cleaning with distilled water is so important



Your I-neb® AAD® System contains chamber lids with mesh that has very tiny holes. Tap water contains minerals that can build up and collect on the mesh over time. Each chamber lid has over 5000 holes smaller than a human hair. If the chamber lids with mesh are blocked, the I-neb AAD System will not work as it should. As a result, it may take longer to do your treatments.

It is important to use ONLY distilled water for your daily cleaning and weekly boil. Do not reuse your distilled water. Keeping the mesh clear of minerals is important to maintaining the I-neb AAD System and to helping you manage your VENTAVIS® (iloprost) Inhalation Solution treatments.

Once-Weekly Cleaning

Weekly boiling

- Put all of the parts in the cleaning basket (do not boil the main body).
- Boil for 6-10 minutes—do not microwave since some of the parts are metal (also, do not wash in the dishwasher as this may damage the parts).
- Rinse with distilled water.
- Shake off the water and then allow to air dry.

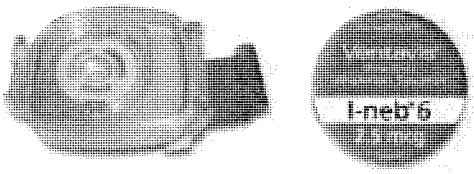
Tip: Keep all of your supplies together to make it as easy as possible.

If you have any questions about the use, care, and cleaning of your I-neb AAD System, just call Actelion Patient Services, toll-free, at **1-866-ACTELION** (1-866-228-3546). Monday through Friday, 12 PM-8 PM (ET)/9 AM-5 PM (PT). Or call your specialty pharmacy.

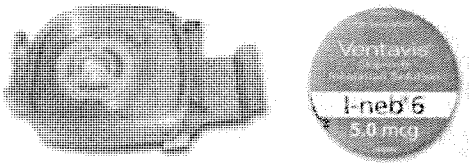
VENTAVIS Dosing Options

VENTAVIS is available in 3 dosing options

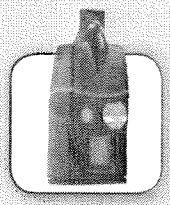
2.5 mcg with 10 mcg/mL – Red*



5.0 mcg with 10 mcg/mL – Purple*



5.0 mcg with 20 mcg/mL – Gold*



You will start with this dose, which uses the red-latched medication chamber.

If tolerated

Nearly all patients transition to this dose, which uses the purple-latched medication chamber.

If you are experiencing long treatment times, your doctor may transition you to this dosing option, which may decrease your treatment time.

Take your VENTAVIS treatments as prescribed by your doctor. FDA-recommended dosing is 6-9 times each day, at least 2 hours apart, or as prescribed by your doctor.

VENTAVIS 20 mcg/mL:

Your doctor may prescribe VENTAVIS 20 mcg/mL if you have long treatment times and are maintained at the 5 mcg dose. The higher concentration of medicine lowers the amount of solution you need to take by 50% which gives you shorter treatment time.[1]

*Different colored chambers and dosing discs are NOT interchangeable. Do not use the 20 mcg/mL ampule with the purple- or red-latched medication chambers.

Please see pages 3 and 4 for Important Safety Information.

Actelion Pathways™

Your VENTAVIS prescription comes with support from *Actelion Pathways.*

A dedicated support team

Actelion Patient Services provides a dedicated team of Registered Nurses and Respiratory Therapists who are available to answer your questions about VENTAVIS or the I-neb® AAD® System, including:

- Use of the I-neb AAD System
- Cleaning and maintenance of the I-neb AAD System

If you would like to enroll in *Actelion Pathways,* you will receive information updates from *Actelion Pathways* about changes or improvements in the I-neb AAD System or new or expanded information about treatment with VENTAVIS.

If you have any questions about VENTAVIS or the I-neb AAD System, call Actelion Patient Services at **1-866-ACTELION** (1-866-228-3546), Monday through Friday, 12 PM-8 PM (ET)/9 AM-5 PM (PT).

Please see accompanying full Prescribing Information and Patient Information.

Understanding Your Support Team

As you can see, getting your VENTAVIS involves a team of people and several organizations. Here is a brief outline of the various groups you'll interact with:

Your Healthcare Team: Diagnoses and treats PAH. They're a great resource to answer your questions about PAH, VENTAVIS, and your I-neb AAD System.

Your Specialty Pharmacy: VENTAVIS is supplied through specialty pharmacies only. The specialty pharmacy will deliver VENTAVIS and the I-neb AAD System to you, and show you how to use them. You can call the specialty pharmacy with questions about your VENTAVIS drug shipment.

Your Actelion Patient Services Team: We are dedicated to helping you make your treatment a success. Remember, our team of Registered Nurses and Respiratory Therapists is waiting to help you with answers to your questions about VENTAVIS and the I-neb AAD System.

***Actelion Pathways*:** Coordinates with your doctor, insurance company, and specialty pharmacy to find out whether you have coverage for your medication. Call **1-866-ACTELION** (1-866-228-3546) Monday through Friday, 12 PM-8 PM (ET)/9 AM-5 PM (PT).

References:
1. VENTAVIS (iloprost) full prescribing information. Actelion Pharmaceuticals US, Inc. May 2013.
2. I-neb AAD System user guide. Koninklijke Philips Electronics N.V. 2010.

Please see pages 3 and 4 for Important Safety Information.

Actelion Pathways™

If you enroll, Actelion can provide you with services and support such as helping you with:

- Answering your questions about filling your prescription
- Coordinating with your doctor, insurance company, and specialty pharmacy to find out whether you have coverage for your medicine or if additional information is needed
- Informing you of possible financial assistance programs based on your eligibility

Through Actelion's Patient Services Department, you'll also have access to a dedicated team of nurse educators—including Registered Nurses and Respiratory Therapists.

An Actelion Nurse Educator can be reached from Monday through Friday, 12 PM-8 PM (ET)/9 AM-5 PM (PT) at **1-866-ACTELION** (1-866-228-3546).

Please see accompanying full Prescribing Information and Patient Information, and Important Safety Information on pages 3 and 4.

ACTELION

Ventavis® (iloprost) INHALATION SOLUTION