Study on Disease Landscape, Current Therapies for Pulmonary Arterial Hypertension in Major Markets of World

By

Abhishek Laddha

Dissertation submitted for the partial fulfillment of the

MBA Pharmaceutical Management

Academic year, 2016-2018

The IIHMR University, Jaipur

1, Prabhu Dayal Marg, Sanganer, Airport
Jaipur 302029, Rajasthan
Ph: 0141 3924700, Fax: 3924738
Website: **www.iihmr.edu.in**

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1, Prabhu Dayal Marg, Sanganer, Airport
Jaipur 302029, Rajasthan
Ph: 0141 3924700, Fax: 3924738
Website: **www.iihmr.edu.in**

INSTITUTE OF HEALTH MANAGEMENT RESEARCH
(WHO Collaborating Centre for District Health System Based on Primary Health Care)

IIHMR UNIVERSITY

TO WHOMSOEVER MAY CONCERN

This is to certify that Mr. Abhishek Laddha student of Pharmaceutical from The IIHMR University, Jaipur has undergone internship training at Woodrock Healthcare Private Limited from 26th February 2018 to 19th May 2018.

The Candidate has successfully carried out the study designated to him during internship training and his approach to the study has been sincere, scientific and analytical.

The Internship is in fulfilment of the course requirements.

I wish him all success in all his future endeavours.

Dr. Ashok Kaushik
Dean, Academics and Student Affairs
The IIHMR University, Jaipur

Dr. Ashok Peepliwal
Associate Professor
The IIHMR University, Jaipur

1, Prabhu Dayal Marg, Near Sanganer Airport, Jaipur- 302029, Rajasthan, India.
Ph.: 0141- 3924700, 2791431- 32, Fax: 0141 3924738, E-mail: iihmr@iihmr.edu.in, Web.: www.iihmr.edu.in

TULIP DIVISION

WOODROCK HEALTHCARE PRIVATE LIMITED

Marketing Office : F-1, 2nd floor, 55, B.R.B. Basu Road, Kolkata- 700 001

Phone : (033) 22342763, 2235 6553

E-mail : care@woodrockcare.com

Visit us at : www.woodrockcare.com

TO WHOM IT MAY CONCERN

This is to certify that Mr. Abhishek Laddha has undergone Dissertation at Woodrock Healthcare Private Limited (Market Research Department) From 26th February 2018 to 19th May 2018. His Dissertation work involves "A Study on Disease Landscape, Current Therapies for Pulmonary Arterial Hypertension; In Major Markets of the World"

The candidate has successfully carried out the study assigned to him while working as an "Intern" for the period of twelve weeks. His approach to the study has been sincere, analytical and scientific.

This letter is being provided at the express request of the intern for his Dissertation.

We wish him all the success in all his future endeavours.

Yours faithfully,

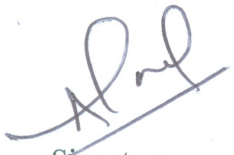
For Woodrock Healthcare Private Ltd.

Director

THE IIHMR UNIVERSITY, JAIPUR

CERTIFICATE BY SCHOLAR

This is to certify that the dissertation titled "A Study on Disease Landscape, Current Therapies for Pulmonary Arterial Hypertension; in Major Markets of World" and submitted by Abhishek Laddha Enrolment No: IIHMR-U/02/2016-18/0058 under the supervision of Dr. Ashok Kumar Peepliwal for award of MBA in Pharmaceutical Management of the University carried out during the period from 26th February 2018 to 19th May 2018 embodies my original work and has not formed the basis for the award of any degree, diploma associate ship, fellowship, titles in this or any other institute or other similar institution of higher learning.



Signature

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Abhishek Laddha

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Glossary

Acronym /Initialism	Definition
6MWD	Six-minute walking distance
ACCF	American College of Cardiology Foundation
AITD	Autoimmune thyroid disease
ALK1	Activin-like receptor kinase-1
APA	Antiphospholipid antibodies
APAH	Associated pulmonary arterial hypertension
ASK-1	Apoptosis signal-regulating kinase 1
ATP	Adenosine triphosphate
ATU	Temporary authorization for use
BMPR-2	Bone morphogenetic protein receptor type II
BNP	B-type natriuretic peptide
cAMP	Cyclic adenosine monophosphate
CEC	Clinical Event Committee
CHD	Congenital heart disease
CI	Cardiac index
CMPD	Chronic myeloproliferative disorder
CNIC	Centro Nacional de Investigaciones Cardiovasculares Carlos III
CO	Cardiac output
Cpc-PH	Combined post- and precapillary PH
CPFE	Combined pulmonary fibrosis and emphysema
CTD	Connective tissue disease
DMC	Data monitoring committee
DPLD	Diffuse parenchymal lung diseases
DPG	Diastolic pressure gradient
DVT	Deep vein thrombosis
ED	Erectile dysfunction
ERA	Endothelin receptor antagonist
ERS	European Respiratory Society
ESC	European Society of Cardiology
ESRD	End stage renal disease
FAK	Focal adhesion kinase
FGF	Fibroblast growth factor
GC	Guanylate cyclase
GI	Gastrointestinal
GSDIa	Type 1a glycogen storage disease
HF	Heart failure
HFpEF	HF with preserved ejection fraction
HFrEF	HF with reduced ejection fraction

Introduction

Pulmonary hypertension is a rare disease which involves an increase in blood pressure in pulmonary vasculature (arteries, veins, and capillaries). It is marked by decreased tolerance to physical activity, and ultimately leads to right heart failure, which is a major cause of mortality.

Until 1998, PH was crudely classified as primary pulmonary hypertension or secondary pulmonary hypertension (occurring due to identified causes or risk factors). In the second World Symposium on pulmonary hypertension held in Evian, France in 1998, PH was classified (WHO classification of PH) into the following five groups, which share similar pathological features, hemodynamic characteristics, and management (Simonneau G, 2013):

Group 1: Pulmonary arterial hypertension (PAH)

Group 2: Pulmonary hypertension due to left heart disease (PH-LHD)

Group 3: Pulmonary hypertension due to lung diseases

Group 4: Chronic thromboembolic pulmonary hypertension (CTEPH)

Group 5: Pulmonary hypertension with unclear multifactorial mechanisms.

During the successive World Symposia (which were held in 2003 [Venice, Italy], 2008 [Dana Point, US], and 2013 [Nice, France]), PH classification evolved as the understanding of the disease increased. However, the general architecture of five WHO subgroups of PH has remained the same (Simonneau G, 2013).

Pulmonary Arterial Hypertension (PAH)

Overview

PAH is one of the least common forms of PH; however, it is the most frequently studied. It is characterized by the presence of precapillary PH (arterial hypertension with pulmonary capillary wedge pressure ≤ 15 mm Hg) and elevated pulmonary vascular resistance (PVR) > 3 Wood units (Galiè N, 2017).

PAH can be classified by the clinical severity according to a system originally developed for heart failure by the New York Heart Association (NYHA) and later modified by the World Health Organization (WHO) for patients with PAH.

The NYHA/WHO functional classification grades PAH severity ranging from functional class I, where patients' PAH does not affect physical activity, to functional class IV, where patients are unable to carry out any physical activity without symptoms, and symptoms can be present even at rest.

PAH can also be described by the underlying contributing factors to disease onset. The WHO classification adopted during the Fifth World Symposium on PH held in 2013 in Nice, France, lists the following clinical subtypes of PAH (Simonneau G, 2013):

- Idiopathic PAH (IPAH)
- Heritable PAH (HPAH)
- Drug- and toxin-induced PAH
- PAH associated with (APAH) connective tissue diseases (CTD), HIV infection, portal hypertension, congenital heart diseases (CHDs), or schistosomiasis.
- NYHA/WHO Functional Classification of PAH

Functional Class Description of Symptoms

- No limitation of physical activity: Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope
- Slight limitation of physical activity: Ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope
- Marked limitation of physical activity: Less than ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope
- Inability to carry out any physical activity without symptoms: Patient manifests signs of right heart failure, Dyspnea and/or fatigue may be present at rest, Discomfort increased by any physical activity

Etiology

Secondary PAH, or APAH, which arises due to various pulmonary, cardiac, or extrathoracic conditions, is the most common form (51.1% of cases) of PAH. Primary PAH of unknown etiology, or IPAH, is the second-most common form (46.2% of cases). A minority of PAH patients have HPAH (2.7% of cases) (Fessel JP, 2011).

Genetic factors: Mutations in the gene for bone morphogenetic protein receptor type II (BMPR2) most commonly predisposes patients to PAH (75% of cases) (Austin ED, 2017; Evans JDW, 2016). BMPR2 belongs to the tumor growth factor (TGF)-β super family of cytokines, which are responsible for various cellular functions. Mutations in other genes from the family are a far less-common cause of PAH (1-3% of cases) and include activin-like receptor kinase-1 (ALK1), endoglin (ENG), and mothers against decapentaplegic 9 (Smad 9) (Austin ED, 2017; Simonneau G, 2013). Researchers identified mutations in two genes, caveolin-1 (CAV1) and KCNK3 (gene encoding potassium channel super family K member-3), which increase the risk of PAH, but do not belong to the TGF-β super family (Simonneau G, 2013).

Drugs and toxins:

The updated Nice 2013 classification of PH lists various drugs and toxins as definite, likely, possible, or unlikely risk factors for PAH (Simonneau G, 2013). Of these, the following drugs are notably associated with increased risk of PAH:

Fenfluramine and its derivatives, aminorex, dexfenfluramine, isomeride, and benfluorex were used as anorectic agents. The drugs were withdrawn from the market because they were reported to cause heart valve damage and increase the risk of PAH (FDA, press release, September 15, 1997; Frachon I, 2011).

Dasatinib, a TKI (tyrosine kinase inhibitor) used in the treatment of chronic myeloproliferative leukemia (CML), is a likely risk factor for PAH. The French PH registry reported 13 PAH cases among 2,900 patients treated with dasatinib for CML, and 100 cases of dasatinib-related PH were submitted to the EU pharmacovigilance system (Simonneau G, 2013).

Interferon (IFN)-α or -β, which are used for the treatment of hepatitis C and MS, are possible risk factors for PAH. A retrospective analysis of the French PH registry observed PAH in 53 patients treated with the drugs. Further, 16 hepatitis C patients with previously documented PAH, showed a significant increase in PVR after treatment with IFN-α. IFN-α or -β may cause PAH by inducing the release of endothelin-1 by pulmonary vascular cells (Simonneau G, 2013).

CTD: Scleroderma is the only CTD in which prevalence of PAH is well-established (Simonneau G, 2013). Two prospective studies found PAH to be prevalent in 8 to 14% of scleroderma patients (Mathai SC, 2012). PAH associated with scleroderma has a poorer disease progression, and worse survival than that in other PAH subgroups. The one-year mortality rate in scleroderma patients with PAH was 30% versus 15% in IPAH patients (Simonneau G, 2013).

HIV: The occurrence of PAH in HIV patients has remained the same (0.46%) as that in the early 1990s (Sitbon O, 2008). The use of highly active antiretroviral therapy (HAART) and PAH-specific drugs has led to significant improvement in the prognosis and survival among HIV-PAH patients (Simonneau G, 2013).

Portal hypertension: PAH occurring in patients with portal hypertension with or without a liver disease is called portopulmonary hypertension (POPH). A French registry found that POPH is the fourth-most common form of PAH after IPAH, PAH associated with CTD, and PAH associated with CHD. Further, POPH worsens the progression of liver disease, and a higher mean pulmonary artery pressure ≥ 35 mm Hg may render a patient ineligible for liver transplant (Saleemi S, 2010).

CHD: PAH affects 10% of adult CHD patients who have incomplete separation between the systemic and pulmonary blood circulation (atrial and ventricular shunts). PAH in CHD adversely impacts the QOL and outcome. The most severe form of PAH associated with CHD is Eisenmenger syndrome (involves both left-to-right and right-to-left shunts). Further, patients with large ventricular and atrial shunts are at a higher risk of PAH than those with only atrial shunts. (Simonneau G, 2013).

Schistosomiasis: Schistosomiasis is caused by infection with parasitic flat worms (schistosomes), and affects over 200 million people (mostly in tropical and subtropical countries). Hepatosplenic schistosomiasis (infection in liver and spleen), and associated portal hypertension (due to inflammation), is the major complication of the disease and develops in 10% of the patients. Of schistosomiasis patients, exclusively those with hepatosplenic schistosomiasis are likely to develop PAH at a prevalence of approximately 5% (Lapa M, 2009).

Pathophysiology

PAH involves progressive hardening and narrowing of pulmonary arteries, which increases the PVR. This condition is attributed to the following pathological processes:

Vascular remodeling: It occurs predominantly in the distal small to mid-sized pulmonary arterioles (diameter < 500 μm) and involves fibrosis and thickening of the inner most layer (intima) and muscularization of the middle layer (media) of the blood vessels. This results in the formation of vascular lesions, which are further complicated by infiltration of inflammatory cells and de novo formation of lymphoid tissue (Guignabert C, 2013).

Endothelial dysfunction: Dysfunctional proliferation of endothelial cells results in formation of fibrous bodies containing complicated capillary-like channels known as plexiform lesions, which are characteristic in PAH. Endothelial dysfunction also involves decreased production of vasodilators (e.g., NO and prostacyclin) and increased levels of vasoconstrictors (e.g., endothelin-1 and thromboxane). This causes increased vasoconstriction of the blood vessels, as well as increased growth of smooth-muscle cells and the outermost layer of the blood vessels (Budhiraja R, 2004).

Current Treatment Overview

Introduction

PH is classified into five WHO groups, each with its own disease pathways and treatment algorithms. A range of PAH therapies and one therapy indicated for CTEPH are available. Key PAH therapies encompass ERAs, PDE-5 inhibitors, prostacyclin analogues, and a soluble guanylate cyclase stimulator. Some off-label prescribing of PAH therapies in WHO groups 2-5 also occurs.

There is increasing use of upfront combination therapy for PAH patients, as well as a general increase in combination therapy use earlier in the PAH treatment algorithm, particularly following the positive results from the AMBITION trial. Indeed, a number of large PAH trials are now incorporating background therapy in their trial design and interviewed physicians believe this type of therapy is leading to a significant shift in the treatment algorithm for PAH.

The successful launches of Opsumit, Adempas, and Orenitram (currently in the United States only) have been welcomed by interviewed experts. Uptake of these therapies is expected to continue driven by positive clinical trial results and prescriber enthusiasm. Following its launch, Adempas became the first therapy indicated for more than one WHO group, and the first therapy specifically indicated for CTEPH patients.

The growing number of treatment options available for PAH is increasing the complexity of the treatment algorithm for WHO group 1 patients. Country-specific variations occur, particularly when different treatment guidelines are followed and where strict reimbursement procedures are in place in the major pharmaceutical markets.

Some PAH therapies are currently being evaluated in clinical trials for other PH groups. Off-label prescribing of PAH therapies is relatively common in WHO groups 2-5. In fact, some PAH therapies are currently being evaluated in clinical trials for other PH groups. However, for WHO groups 2, 3 and 5, treatment topically focuses on the underlying disease.

Treatment Overview

PH is classified into five WHO groups or subtypes: WHO group 1 (PAH), WHO group 2 (PH due to left heart diseases), WHO group 3 (PH due to lung diseases, and/or hypoxemia), WHO group 4 (CTEPH), and

WHO group 5 (PH with unclear multifactorial etiologies). Drugs in four therapeutic classes are available for the management of PH. In general, the type of treatment chosen is influenced by the disease severity. Patients with less-severe PAH (NYHA/WHO functional class II/ III) typically receive oral agents, and patients with more-severe PAH (NYHA/ WHO IV) are commonly treated with parenteral agents. Almost all current therapies are indicated only for PAH, so our discussion will be focused largely on this group.

PAH is a rare and debilitating disease characterized by vascular remodeling and vasoconstriction of the pulmonary arteries, which cause resistance to build in the pulmonary circuit and force the heart's right ventricle to work harder to maintain deoxygenated blood flow to the lung tissue. PAH can be described by disease severity (NYHA/WHO functional classes) and by underlying factors contributing to disease onset, which can be idiopathic (or sporadic), where no cause is apparent; familial; or associated with other conditions, such as HIV or connective tissue disease. Although primary PAH (known as idiopathic PAH) has a largely unknown etiology, a minority of diagnosed PAH patients have a family history of the disorder and are characterized as suffering from familial PAH. Secondary PAH may arise as a complication from many pulmonary, cardiac, or extrathoracic conditions.

Treatment Goals

The overall goals of PH treatment are to improve the symptoms of the disease, to improve exercise capacity and the patients' QOL, and to prolong TTCW and ultimately death. Pharmacological management of PAH aims to reduce or stabilize fibrosis caused by a buildup of smooth muscle cells in the linings of the arteries. Drugs used in the treatment of PAH work primarily as vasodilators, reducing the pressure in the arteries. However, interviewed experts largely believe that common PAH therapies, such as ERAs, PDE-5s, and prostacyclin analogues, have less-significant antiproliferative and antithrombotic effects as well. Treatment goals for PAH focus not just on short-term functional improvements but also long-term outcomes and include improvements in NYHA/WHO classification and 6MWD, decreasing or normalizing BNP, and normalization of right ventricular size and function (McLaughlin V, 2013).

Key Current Therapies

Overview

Few therapies are approved for PH, and almost all are indicated only for PAH, with the exception of Adempas, which is also indicated for CTEPH patients. Currently, there are no approved drugs for WHO groups 2, 3, and 5, though off-label prescribing of PAH therapies is relatively common. Further, the available drug treatments only bring symptomatic relief and do not reverse or stop the underlying disease progression. There are just four different drug classes currently available for the treatment of PAH; these are the ERAs, PDE-5 inhibitors, prostacyclin analogues, and a sGC stimulator. Interviewed experts stress that PAH patients should not be considered a homogenous

population, and they expect that, in the future, patients with different etiologies and underlying genetic causes will be treated differently.

Current Treatments Used for Pulmonary Hypertension

Therapy	Company/Brand	Availability
Bosentan	Actelion's Tracleer	US, F, G, I, S, UK, J
Ambrisentan	Gilead's Letairis/ GlaxoSmithKline's Volibris	US, F, G, I, S, UK, J
Macitentan	Actelion's Opsumit	US, F, G, I, S, UK, J
Sildenafil	Pfizer's Revatio, generics	US, F, G, I, S, UK, J
Tadalafil	United Therapeutics/Eli Lilly/Nippon Shinyaku's Adcirca	US, F, G, I, S, UK, J
Oral treprostinil	United Therapeutics' Orenitram	US
Parenteral treprostinil	United Therapeutics' Remodulin	US, F, G, I, J
Inhaled treprostinil	United Therapeutics' Tyvaso	US
Epoprostenol	GlaxoSmithKline's Flolan,generics	US, F, G, I, S, UK, J
RTS Epoprostenol	Actelion's Veletri	US, F, G, I, S, UK, J
Inhaled iloprost	Actelion/BayerHealthCare's Ventavis	US, F, G, I, S, UK
Beraprost	Toray/Astellas's Dorner,Kaken's Procyclin, generics	J
Beraprost MR	Toray/Astellas's CareloadLA, Kaken's Berasus	J
Selexipag	Actelion/Nippon Shinyaku's Uptravi	US, G
Riociguat	Bayer HealthCare's Adempas	US, F, G, I, S, UK, J

Impact of Current Therapy Events on the Pulmonary Hypertension Market

Event	Market Impact
Launch of Uptravi	Uptravi is the first-in-class oral nonprostanoid prostacyclin receptor (also called the IP receptor) agonist. Itoffers the advantage of oral administration over the other agents targeting the prostacyclin pathway, theinhaled and parenteral prostacyclin analogues. Further, the drug can be used in combination with anERA/PDE-5 inhibitor, which allows physicians to prescribe an aggressive combination of drugs, (targeting thethree major pathophysiological pathways in PAH) to delay disease progression. Uptravi launched in theUnited States and Germany in 2016, and we expect it to launch across the major markets under study overthe next few years.
Approval of the combination of Letairis/Volibris and Adcirca	Patent protection for Letairis/Volibris is due to expire in 2018 and generics for Adcirca are expected to launchin 2017. The approval of the combination of these two agents has increased the prescribing of Letairis/Volibris and Adcirca as a combination therapy, in addition to the greater use of upfront combinationtherapy and in later lines, significantly impacting prescribing patterns.
Launch of Orenitram	The extended-release tablet form of the drug launched in the United States in 2014, making it the firstoral prostacyclin analogue to gain approval for use in the treatment of PAH. The therapy is associatedwith high rates of GI side effects, which have limited the maximum tolerated dose and, accordingly, thedrug's efficacy. Further, it can only be prescribed by specialists or experienced practitioners, a factorthat is likely to limit market uptake of this agent. Following successful completion of the FREEDOM-EV trial, we expect Orenitram to launch across Europe.
Adempas approval for CTEPH patients	The approval of Adempas for CTEPH patients was the first drug approval specifically for WHO group 4patients. Substantial market share is anticipated for this particular group of patients given that it is theonly drug indicated for this subgroup of PH. Adempas, as a sGC stimulator, is the first drug in its class,and comes with a broad labeling in the United States (indicated both for patients after surgical treatmentor for patients with inoperable CTEPH). Interviewed physicians prescribe it for both operable andinoperable CTEPH patients.

Adempas approval for PAH patients	The concurrent approval of Adempas for PAH adds an additional treatment option for WHO group 1patients. As the first drug in its class, the sGC stimulator impacts a different pathway compared withother available pharmacological agents indicated for PAH. However, in addition to the relatively highprice for an oral therapy, contraindication with PDE-5 inhibitorsimpacts market share because PDE-5inhibitors are commonly used as a first-line therapy, particularly with the introduction of generic sildenafiland the expected emergence of generic tadalafil in the market.
Tracleer patent expiry	Following bosentan patent expiry, generics are in the process of launching and are expected tonegatively impact sales of other drugs in the same class; as an ERA, bosentan is often used as a first-or second-line therapy, according to the physicians interviewed. Additionally, market share is decreasingwith the addition of Opsumit to the list of available ERAs. Bosentan is also deemed inferior toLetairis/Volibris and Opsumit due to the requirement for monthly LFTs. Patients are widely expected tobe transitioned onto Opsumit prior to bosentan patent expiry.
Parenteral treprostinil patent expiry	Patent protection for infused treprostinil is due to expire in the United States, and a generic parenteralform of treprostinil is expected to launch shortly after in mid 2017. However, recent price increases havealready excluded parenteral treprostinil from certain markets, even though it is perceived as a veryeffective drug. Importantly, an implantable pump for parenteral treprostinil is in development byMedtronic and is expected to reduce the patient burden associated with the use of parenteralprostacyclin analogues.

Endothelin Receptor Antagonists

ERAs block the endothelin-A (ETA) receptor or both the ETA and the endothelin-B (ETB) receptors on the smooth muscle cells of the pulmonary arteries. This action inhibits endothelin (ET-1), a potent vasoconstrictor found in increased levels in the lungs of PAH patients. In addition to influencing vasoconstriction, the ETB receptor is known to exert a separate vasodilatory effect. This finding led to theories that an ETA-specific ERA may have a stronger clinical effect in PAH patients, but there is no evidence that ETA-specific ERAs, such as Letairis/Volibris and the previously available sitaxentan (Pfizer's Thelin), are more effective than dual-acting ERAs such as Tracleer.

Tracleer

Tracleer (Actelion's bosentan) was the first oral PAH-specific therapy approved for the disease in the United States and Europe and received marketing approval based on the pivotal Phase III

BREATHE-1 study. First approved in the United States in 2001, the dual ERA is dosed orally twice a day. Initially approved for functional class III and IV PAH patients, Tracleer's label was expanded to include functional class II patients in Europe and the United States in 2008 and 2009, respectively, following publication of trial data demonstrating its efficacy in this population. As the first oral PAH specific therapy available in the majority of the markets under study, Tracleer is typically used as a first- or second-line therapy for PAH. Physicians generally express satisfaction with it, and now that the agent has been available for over ten years in most markets, are comfortable prescribing it. However, the FDA's 2011 removal of the requirement for monthly LFTs for patients treated with the second-in-class ERA, Letairis/Volibiris, has reduced Tracleer's uptake in the United States. Interviewed experts say that the risk of liver injury is the drug's biggest weakness and that PAH specialists are increasingly using the second-in-class ERA, Letairis/Volibiris, a drug with a markedly lower risk of liver injury, in place of Tracleer. Following the launch of Opsumit in 2013, the trend to use alternative ERAs to Tracleer has been increasing. Other side effects more frequent in Tracleer-treated patients are typical of PAH drugs and include headache, flushing, and dizziness. Generic versions of Tracleer are expected to launch at the start of 2017 in the United States and later in 2017 across most of the EU5; these generic launches are expected to have a significant impact on sales of the branded drug Tracleer. A combination therapy of Tracleer and sildenafil was investigated in the COMPASS-2 Phase IV clinical trial, comparing the combination of the two drugs with the use of sildenafil monotherapy alone (clinicaltrials.gov, NCT00303459, accessed October 2016). The results of the study were revealed in 2014, and though the study did not reach its primary end point with a statistically significant risk reduction, an improvement in the 6MWD at week 16 was observed (Actelion, press release, March 2014). The results had relatively little impact on prescribing patterns.

Letairis/Volibris

Gilead's Letairis/GlaxoSmithKline's Volibris (ambrisentan), a once-daily oral agent, was the second-in-class ERA to launch in all markets under study. The ET-A antagonist is more than 4,000 times more selective for ET-A than for ET-B. In contrast to Tracleer, patients in the United States treated with Letairis/Volibris do not need to undergo monthly liver function tests. Furthermore, Letairis/Volibiris is dosed once a day while Tracleer must be administered twice a day. Although U.S. experts express greater familiarity with Tracleer as a result of its longer presence on the market, and despite Actelion's strength in the PAH market and the availability of more-extensive published data from clinical trials of Tracleer, interviewed thought leaders tell us that U.S. prescribing of Letairis/Volibris is increasing following the FDA's elimination of the requirement for monthly liver tests and the positive results of the AMBITION trial evaluating upfront combination therapy. In Europe and Japan, where liver function tests are still required for patients receiving Letairis/Volibris, the agent does not compete as strongly with Tracleer, largely as a result of physician familiarity with Tracleer. Approval of Letairis/Volibris in the United States and Europe was based on two pivotal Phase III studies, ARIES-1 and ARIES-2. As with the Tracleer trials, the most common adverse events observed in the ARIES-1 and ARIES-2 studies were peripheral edema, nasal congestion, and headache (Galie N, 2008). No patients in the ARIES-1, ARIES-2, or Japanese four-week Phase III study who were treated with Letairis/Volibris developed aminotransferases greater than three times the upper limit of normal (> 3ULN), a side effect that was observed with Tracleer. Letairis/Volibris' use in combination with Adcirca in PAH patients was approved by the FDA and EMA in 2015 (Gilead, press release, October 2, 2015; GSK, press release, November 24, 2015) based on the positive results from the AMBITION trial. Following Letairis/Volibris' label expansion, physicians report a substantial shift in the treatment algorithm toward starting treatment-naive PAH patients on dual combination therapy and toward using

additional combination therapies much earlier in the treatment paradigm, in addition to an increase in prescribing of Letairis/Volibris.

In June 2013, Letairis/Volibris was granted orphan drug designation in Japan for CTEPH. GSK completed a Phase III double-blind study, AMBER I (clinicaltrials.gov, NCT01884675, accessed August 2016), and its open-label extension study, AMBER II (clinicaltrials.gov, NCT01894022, accessed August 2016) in March 2015 and November 2015, respectively. The two studies evaluated the safety and efficacy of Letairis/Volibris versus placebo among CTEPH patients. The AMBER I study found that Letairis/Volibris improved 6MWD after 16 weeks (GSK, Clinical Trial Register, accessed August 2016). However, while the AMBER II study found that Letairis/Volibris increased mean 6MWD, it also led to two events of cardiac failure (including 1 fatal event) (GSK, Clinical Trial Register, accessed August 2016). Further development is not expected at this time for this patient population.

Opsumit

Actelion's Opsumit (macitentan) is a second-generation novel tissue-targeting ERA. This agent was studied in Phase III clinical trials incorporating morbidity/mortality end points, which were considered to be pivotal. Actelion has developed Opsumit worldwide except in Japan, where Nippon Shinyaku has the rights. Opsumit was approved in October 2013 in the United States and December 2013 in Europe. It is an oral therapy, with a qd dosing pattern, indicated for the treatment of adult PAH patients with WHO functional class II-III. Common side effects associated with Opsumit include headache, nasopharyngitis, and anemia (Pulido T, 2013). Results from the Phase III SERAPHIN trial (clinicaltrials.gov, NCT00660179), demonstrated that Opsumit had met the primary end point, a reduction in the composite of morbidity and mortality events. This event-driven trial compared 3 and 10 mg Opsumit with placebo in 742 NYHA/WHO class II-IV PAH patients; patients received drug treatment for up to 3.5 years. The trial was the largest placebo-controlled trial with a morbidity/mortality end point ever conducted in PAH patients at the time. Safety data results demonstrated that patients in both treatment arms experienced a lower incidence of liver enzymes > 3ULN compared with placebo (3.6% of patients treated with 3 mg Opsumit and 3.4% of patients treated with 10 mg Opsumit compared with 4.5% of patients in the placebo arm). Furthermore, edema rates were comparable between the treated and placebo groups. Due to the large trial incorporating a morbidity/mortality end point, the results differentiated the drug from other available pharmacological agents, thus improving the product positioning within the treatment algorithm. However, female patients must enroll in a REMS program due to concerns about the impact the agent may have on the development of a fetus, and it should not be used in pregnant or lactating women. Given the severity of the disease, though, this issue is not substantially impacting the market-share potential of this drug.

In May 2016, Actelion initiated the Phase III TRITON trial comparing triple upfront combination therapy of Opsumit, Adcirca, and Uptravi with dual upfront oral combination therapy (clinicaltrials.gov, NCT02558231, accessed October 2016). This trial is expected to enroll 144 PAH patients, and is estimated to complete in December 2018. Interviewed experts expect that if the results are positive, this trial will contribute to increased use of this combination, in addition to increasing the use of triple oral combination therapy for the treatment of PAH. A pediatric trial is under way and Actelion plans to file for pediatric market exclusivity in both the United States and Europe upon successful completion (Actelion, press release, July 6, 2016).

PDE-5 Inhibitors

PDE-5 is widely expressed in the smooth muscle of the pulmonary arteries and indirectly inhibits the vasodilatory effect exerted by NO (levels of which are depressed in PAH patients) in the lungs. PDE-5 inhibitors help overcome this effect by increasing vasodilation. The PDE-5 inhibitors sildenafil (Pfizer's Revatio, generics) and Adcirca (United Therapeutics/Eli Lilly/Nippon Shinyaku's tadalafil) were originally approved to treat ED (marketed as Pfizer's Viagra and Eli Lilly's Cialis, respectively). Approved to treat PAH in 2005 and 2009, respectively, sildenafil and Adcirca are commonly used as early-line therapies either as monotherapy or in combination with other PAH agents. A factor driving their uptake in PH is that, despite having efficacy only comparable to that of the ERAs, the PDE-5 inhibitors are priced at a considerable discount to the ERAs because Pfizer and Eli Lilly originally priced the drugs for the ED market rather than the premium PAH market. Interviewed experts rarely differentiate between sildenafil and Adcirca in terms of efficacy and safety and cite differences in dosing as the major differentiating factor. Experts acknowledge that Adcirca's once-daily dosing offers advantages over sildenafil's tid dosing, including improved compliance in a patient population that typically has a high pill burden.

Sildenafil

Sildenafil (Pfizer's Revatio/Viagra, generics) is a PDE-5 inhibitor that is often used in first-line treatment of PAH, primarily due to the low price resulting from the widespread availability of generic alternatives. Sildenafil was approved for PAH in Europe and the United States in 2005 and in Japan in 2008, and has also been approved for ED since 1998. Sildenafil is branded as Revatio for PAH treatment and as Viagra for the ED market. There are differences in the dosing, tablet strength, and tablet color between the two branded versions of the drug. An IV formulation was approved in the United States in November 2009 for PAH patients taking oral sildenafil who are temporarily unable to take oral medication. Oral suspensions of sildenafil are also available. Following Phase III trials, treatment with sildenafil led to improvements in exercise capacity (as determined by 6MWD) and improvements were also observed in change in NYHA/WHO functional class, hemodynamics, and Borg dyspnea score (Satoh T, 2011). In Europe, sildenafil is approved to treat NYHA/WHO II/III adult and pediatric PAH patients. In the United States, it is approved for all PAH patients to improve exercise capacity, and in Japan it is approved for all adult PAH patients. U.S. and European approval was based primarily on the results of the SUPER-1 study. Revatio lost patent protection in 2012 in the United States and in 2013 in the EU. The lower cost of sildenafil compared with other therapies is a predominant factor in the frequent use of this drug for the treatment of PAH. Off-label use in PH groups outside of group 1 (PAH) is common, largely driven by the low cost of the drug and physician familiarity.

Adcirca

Adcirca (United Therapeutics/Eli Lilly/Nippon Shinyaku's tadalafil) is the second PDE-5 inhibitor approved for PAH in the United States, Europe, and Japan. Like sildenafil, Adcirca was originally approved in all seven markets for ED (as Eli Lilly's Cialis). In the ED market, tadalafil differentiated itself from sildenafil based on its different pharmacokinetic profiles. In this population, sildenafil has a shorter onset of action compared with Adcirca (30-60 minutes compared with 1-2 hours), but its duration of clinical efficacy is substantially shorter (4-5 hours compared with 36 hours). These differences allow Adcirca to be dosed qd (as two pills) compared with sildenafil, which must be dosed tid for the treatment of PAH. Interviewed experts rarely differentiate between sildenafil and Adcirca based on the drugs' efficacy and safety profiles. Nevertheless, Adcirca's dosing advantage has allowed it to capture patient share from the first-in-

class sildenafil, particularly in the United States. Patients with PAH typically have a considerable pill burden associated with both their PAH and other associated and/or unassociated comorbidities. Thus, the use of a qd agent as opposed to tid has important drug compliance ramifications and can be an important driving factor in physicians' prescribing decisions. Adcirca was approved to treat PAH in the United States, Europe, and Japan in 2009. Submissions to regulatory authorities in all three regions were based on a single, 16-week, randomized, multicenter Phase III study. Generic tadalafil is due to launch from 2017 onward and is expected to impact branded sales significantly.

Following positive results from the AMBITION trial (clinicaltrials.gov, NCT01178073, accessed August 2016), the use of the combination of Adcirca and Letairis/Volibris for PAH patients was approved in the United States and Europe in late 2015. Interviewed thought leaders expressed enthusiasm toward the positive results of this trial, and it has been predicted that the positive results could lead to a change in the guidelines for PAH treatment, as well as significantly impacting prescribing patterns and treatment algorithms, with increased combination therapy earlier in the treatment paradigm. Furthermore, a Phase II pharmacokinetic study for pediatric patients with PAH being treated with Adcirca is also being conducted and currently recruiting participants; similar to sildenafil, this trial will likely lead to a pediatric patent extension period for the brand (clinicaltrials.gov, NCT01484431, accessed August 2016).

Prostacyclin Analogues

Prostacyclin analogues act upon the prostacyclin receptors to stimulate production of cAMP, which mediates vasodilatory pathways and inhibits cell proliferation and platelet aggregation. PAH patients experience suppressed levels of prostacyclin compared with healthy individuals. Epoprostenol (GlaxoSmithKline's Flolan, Actelion's Veletri, generics), an intravenously administered prostacyclin analogue, was the first PAH-specific therapy approved in the United States and Europe and is still considered by many experts the gold-standard treatment for severe PAH (NYHA/WHO functional class IV). Nevertheless, disadvantages associated with epoprostenol—e.g., a requirement for constitution before use, short half-life, poor room temperature stability, and the need for continuous IV infusion— fueled the development of other prostacyclin analogues. Parenteral treprostinil, developed by United Therapeutics, has a significantly longer half-life (four hours compared with epoprostenol's six minutes), significantly reducing the risks associated with any interruption in treatment. Furthermore, it is stable at room temperature and, unlike epoprostenol, does not require constitution before use. In addition to an IV infusion, a subcutaneously infused formulation of parenteral treprostinil is available, eliminating the need for a central line. Inhaled formulations of prostacyclin analogues have also become available, but because of arduous dosing requirements and limited efficacy, inhaled prostacyclin analogues are largely used as niche drugs in combination with oral therapies in PAH patients who are not sufficiently afflicted to justify use of parenteral agents and in PAH patients who refuse treatment requiring continuous infusion. The launch of United Therapeutics' Orenitram in 2014 represented the first oral prostacyclin analogue, currently only available in the United States; launches in Europe are anticipated in the next few years following completion of additional clinical trials.

Parenteral Epoprostenol

Epoprostenol (GlaxoSmithKline/Gilead's Flolan, generics; both are continuously infused) is a prostacyclin therapy. Epoprostenol was the first PAH-specific therapy approved in the United States in 1995. Its approval was based on the results of a pivotal Phase III clinical study, which included 81 patients with NYHA/WHO functional class III or IV PAH. Open-label short- and long-

term studies of epoprostenol-treated PAH associated with scleroderma demonstrated similar beneficial effects on exercise capacity and survival. Despite the absence of published clinical data on the effect of epoprostenol on other forms of PAH, the FDA approved it for all types of PAH (Frumkin LR, 2012). Despite recognizing epoprostenol as a very effective drug, particularly as a rescue therapy in NYHA/WHO IV patients, interviewed experts acknowledge the limitations in its administration. In addition to being an IV-infused agent (due to a short half-life), it must be reconstituted with sterile diluent daily and stored under refrigerated conditions because of poor stability at room temperature. All forms of epoprostenol are associated with several adverse events. In addition to flushing, headache, and hypotension, which are often associated with PAH therapies, epoprostenol commonly increases the risk of GI side effects, including vomiting and/or nausea, and it increases the risk of pain at a variety of body sites. Furthermore, patients who cease treatment with epoprostenol may experience rapid worsening of their PAH. Indeed, epoprostenol's label advises against even brief interruptions in treatment with the drug given the risk of severe adverse events including death. The risks associated with cessation, the risk of severe adverse events, and the need for IV administration of epoprostenol ensure that all formulations are typically limited to later-line therapy of PAH patients already treated with oral and sometimes inhaled PAH therapies. Although epoprostenol is available generically, there is also some physician reluctance to use generic epoprostenol, particularly in the United States following supply issues, which can be a major problem for patients with PAH.

Veletri

Veletri is a second-generation epoprostenol product that has the added benefit of advanced preparation of the active pharmaceutical ingredient, and which is RTS. The difficulties associated with reconstitution and storage of the original form of epoprostenol led to the development of Veletri (Actelion's RTS epoprostenol), which contains arginine and mannitol as excipients (Flolan and its generics contain glycine and mannitol as excipients). RTS epoprostenol can be stored at room temperature for up to 48 hours after dilution and can be stored for up to 7 days under refrigerated conditions (compared with 8 hours and 1 day for the original formulation, respectively). In June 2012, Actelion announced that the FDA approved a second-generation formulation of Veletri (which contains undisclosed excipients) for PAH offering better storage compared with existing formulations (Actelion, press release, June 29, 2012). Both forms of Veletri were approved on the basis of equivalence to branded epoprostenol (GlaxoSmithKline/Gilead's Flolan), and there is no evidence of any variation in pharmacodynamics, efficacy, or safety profiles between the different epoprostenol formulations (Nicolas LB, 2012). Research exploring the use of the two different forms of parenteral epoprostenol for the treatment of PAH in a Phase IV open-label study demonstrated that Veletri, with its novel RTS formulation, was well tolerated (Chin K, 2014). Veletri has proved to be popular among interviewed thought leaders thanks to its ease of use, room-temperature stability, and greater flexibility, as well as easier storage, preparation, and usage requirements. The risks associated with cessation, the risk of severe adverse events, and the need for IV administration of epoprostenol ensure that all formulations are typically limited to later-line therapy of PAH patients already treated with oral and sometimes inhaled PAH therapies.

Remodulin

The FDA approved Remodulin (United Therapeutics' parenteral treprostinil) in 2002, and this drug can be administered as either a continuous SC or an IV infusion. Its approval was based on the submission of results from a placebo-controlled, double-blind, multicenter Phase III clinical trial involving 470 PAH patients. Approval followed in France, Germany, and Italy in August 2005 for the SC formulation. However, United Therapeutics elected to withdraw its application for SC

treprostinil in the United Kingdom and Spain following a request for additional information by the regulatory agencies of these countries. Nevertheless, United Therapeutics sells (but does not market) parenteral treprostinil in the United Kingdom and Spain under the named-patient system, which allows hospitals in the EU to import drugs not approved for sale in Europe for the treatment of specifically identified patients. Infused treprostinil is sold in Japan under the name Treprost by Mochida Pharmaceutical for injection for the treatment of PAH by IV and SC administration (United Therapeutics, press release, March 26, 2014). IV treprostinil was approved in December 2011 by the French regulatory agency in its role as the European reference country for the drug's review. This approval permitted the marketing of IV treprostinil in France, Germany, Italy, and 19 other European member nations where SC treprostinil was already available. The high frequency of side effects observed with parenteral prostacyclin and parenteral prostacyclin analogues, combined with the need for continuous infusion, relegates them to later lines of therapy and to patients diagnosed with severe symptoms (i.e., NYHA/WHO class III and IV). Patients treated with Remodulin commonly receive it in combination with oral agents such as ERAs and/or PDE-5 inhibitors and may previously have been treated with inhaled prostacyclin analogues, such as Actelion/Bayer HealthCare's Ventavis (iloprost) or Tyvaso (United Therapeutics' inhaled treprostinil). Although a study has demonstrated that it is generally safe to transition patients from epoprostenol to treprostinil, physicians are generally unlikely to do so with stable PAH patients and will switch only patients who cannot tolerate or do not respond to drug therapy. In collaboration with Medtronic, United Therapeutics is developing an implantable drug system to deliver infused treprostinil. United Therapeutics plans to seek FDA approval in parallel to gain permission for the use of infused treprostinil with the implantable system.

Tyvaso

In July 2009, Tyvaso (United Therapeutics' inhaled treprostinil) became the second formulation of treprostinil in the United States, where it is indicated for increasing exercise capacity in PAH patients with NYHA/WHO class III symptoms. Tyvaso is predominantly used in patients whose PAH is uncontrolled despite treatment with combination oral therapy and whose symptoms are not yet severe enough that parenteral therapy with a prostacyclin agent is deemed appropriate, and in patients who do not wish to initiate parenteral therapy with these agents, as is Ventavis. FDA approval of Tyvaso was based on the results of the Phase III study, TRIUMPH-1. Tyvaso is administered by nebulization with the OPTINEB ultrasonic pulsed delivery device (Nebu-Tec, Elsenfield, Germany). Patients administer four separate treatments of Tyvaso each day, approximately four hours apart during waking hours. The recommended initial dose is three inhalations during each session (reduced to one or two, if three cannot be tolerated), and the dose is increased by three breaths if tolerated at one- to two-week intervals until a target maintenance dose of nine inhalations per session is reached. These requirements, although seemingly arduous, compare favorably with the only other inhaled agent approved for PAH—i.e., Ventavis, which requires inhalation six to nine times a day. Furthermore, a single day's supply of Tyvaso comes in a single ampule, which necessitates cleaning of the nebulizer just once a day; Ventavis nebulizers usually require more-frequent cleaning (Frumkin LR, 2012). As part of Tyvaso's approval process, the FDA required that United Therapeutics conduct a series of postmarketing studies. The ASPIRE study enrolled 1,333 patients and was completed in December 2014 (clinicaltrials.gov, NCT01266265). Results from the study revealed that the observed respiratory AEs with Tyvaso were consistent with the drug's profile (Zamanian RT, 2014). Further, to encourage the transition of patients from Ventavis to Tyvaso, United Therapeutics conducted a two-year, open-label trial investigating the efficacy and safety of Tyvaso in patients transitioning from a stable dose of Ventavis. Results showed significantly improved QOL scores for patients treated with Tyvaso and a reduction in total time spent administering treatment (66%) compared with Ventavis. Significant

improvements in exercise capacity (as measured by 6MWD) from baseline at 12 weeks (38 m [P = 0.002]) and a significant reduction in NT-proBNP levels from baseline at 12 weeks (61 mg/mL [P < 0.01]) were also observed (Channick RN, 2012).

In a 10-Q filing in April 2012, United Therapeutics announced that it would no longer pursue approval of Tyvaso in Europe. United Therapeutics previously withdrew a marketing application for Tyvaso in Europe in November 2009 following a CHMP ruling that the application was nonapprovable based on agency inspections at two different trial sites of the Phase III TRIUMPH study that were not compliant with GCP. Although the company indicated that it intended to perform new clinical trials and submit a new marketing authorization, the April 2012 announcement stated that such an action would not be commercially beneficial. Instead, United Therapeutics made Tyvaso available in Europe under the named patient scheme.

The Phase III BEAT trial is currently evaluating the use of Tyvaso in combination with a modified release formulation of beraprost, referred to as Esuberaprost (clinicaltrials.gov, NCT01908699, accessed October 2016). With an estimated 240 PAH participants, this trial is due to complete in early 2018, and if successful could lead to an increase in prescribing of Tyvaso in the United States. Importantly, the complicated nature of the nebulizer is likely to deter any generic manufacturer.

Ventavis

Ventavis (Actelion/Bayer HealthCare's inhaled iloprost) was the first inhaled and the third PAH-specific drug approved for PAH in Europe (2003) and the United States (2004). In the United States, Ventavis experiences notable competition from Tyvaso. Administered by nebulization using the I-neb Adaptive Aerosol Delivery (AAD) system or the Prodose AAD system, Ventavis requires the patient to inhale six to nine times a day. Like other inhaled PAH agents, Ventavis is most commonly used as an adjunctive therapy for patients with uncontrolled PAH on existing treatment with oral combination therapy. In the United States, Ventavis is approved specifically for PAH patients to improve exercise capacity and other symptoms; in Europe, it is indicated for use in NYHA/ WHO class III idiopathic PAH patients to improve exercise capacity and symptoms. However, in practice, U.S. and European physicians (except in the United Kingdom) use Ventavis in any PAH patients if they deem it is to their advantage, even if the patient does not fall into the indicated population. U.S. and European approval of Ventavis was based on a pivotal Phase III AIR study—in which 203 patients with PAH or CTEPH were randomized to six or nine inhalations per day of iloprost or placebo. A 12-week Phase III study is investigating inhaled iloprost in 20 Japanese PAH patients (IBUKI study; clinicaltrials.gov, NCT01469169, accessed August 2016). The primary end point is change in PVR from baseline. The trial is expected to complete in March 2017, although some results have already been published (Saji T, 2016). Following successful trial outcomes, we forecast a 2018 launch in Japan. If approved in Japan, Ventavis will become the first inhaled PAH therapy to reach the market.

Orenitram

United Therapeutics' oral form of treprostinil, Orenitram/UT-15C sustained release, was launched (following a collaboration with Supernus Pharmaceuticals) in the United States in May 2014. The drug was already available in inhaled (Tyvaso) and parenteral (Remodulin) forms. The extended-release tablet form of the drug was approved in December 2013, making it the first oral prostacyclin analogue to gain approval for use in the treatment of PAH. This approval came as a surprise to many thought leaders given that the drug had been rejected twice previously by the

FDA. The drug's development has been dogged by high rates of GI side effects, which have limited the maximum tolerated dose and, accordingly, the drug's efficacy. The drug is indicated for the treatment of PAH but should be prescribed only by specialists or experienced practitioners, a factor that is limiting market uptake of this agent to a certain extent. The U.S. approval was based on the results of the three major trials: the FREEDOM-M trial (clinicaltrials.gov, NCT00325403, accessed August 2016) in patients on no background therapy, and the FREEDOM-C (clinicaltrials.gov, NCT00325442, accessed August 2016) and FREEDOM-C2 trials (clinicaltrials.gov, NCT00887978, accessed August 2016) in patients receiving treatment with an ERA and/or a PDE-5 inhibitor. The FREEDOM-M trial demonstrated that the use of Orenitram led to an improvement in the 6MWD and in the Borg dyspnea score, but not the other secondary outcome measures (Jing Z, 2013). However, results from the FREEDOM-C and FREEDOM-C2 studies demonstrated that the use of Orenitram as an adjunct to either an ERA or a PDE-5 inhibitor did not lead to a statistically significant improvement in exercise capacity as measured by the 6MWD (Tapson V, 2013). Further, all three clinical studies most commonly reported GI side effects with Orenitram (headache, nausea, and diarrhea with an incidence of more than 10%) (United Therapeutics, press release, December 20, 2013). Indeed, in clinical trials in North America and Europe, oral prostacyclin analogues have had poor efficacy and a high rate of GI side effects. Experts believe that this weak efficacy has arisen because poor patient tolerance prevents the majority of patients from receiving therapeutically relevant doses of oral prostanoids.

United Therapeutics is conducting an open-label, long-term Phase III extension study to assess the impact of Orenitram in patients with PAH (clinicaltrials.gov, NCT01560637, accessed August 2016). This study has an estimated enrollment of 610 patients and a primary completion date of May 2021. Data from the 522 patients, who completed the 12-month efficacy assessment, revealed an improvement in mean 6MWD improved by 24 meters compared with baseline (30 m in monotherapy patients and 20 m when Orenitram was used in combination with an ERA and/or a PDE-5 inhibitor) (Orenitram, prescribing information, accessed August 2016). Further, a Phase II trial evaluating the transitioning of patients from Tyvaso to Orenitram in 33 PAH patients (clinicaltrials.gov, NCT01588405, accessed August 2016) was completed in December 2014. All the patients enrolled in the trial transitioned to Orenitram, with 31 patients completing transition in five days (Orenitram, prescribing information, accessed August 2016). The results of this trial are expected to be significant in mitigating any potential loss of sales United Therapeutics may experience in the future after patent protection for Remodulin expires in 2017.

United Therapeutics is expected to apply for EMA approval following the completion of the Phase III FREEDOM-EV trial, which has an estimated study completion date of March 2017 (clinicaltrials.gov, NCT01560624, accessed August 2016). The FREEDOM-EV trial is assessing the use of combination therapy comprising Orenitram with either a PDE-5 inhibitor or an ERA, in the early stages of the PAH treatment process, in approximately 610 study participants. A launch in Europe is expected from 2018 onward; a launch in Japan is not expected at present.

Beraprost and Beraprost MR

Beraprost (Toray/Astellas's Dorner, Kaken's Procyclin, generics) was the first PAH-specific therapy approved in Japan. Its approval by the Japanese MHLW in 1994 was based on data that demonstrated idiopathic PAH patients treated open label with beraprost had improved clinical outcomes compared with historical registry data for untreated PAH patients (White RJ, 2009). An MR formulation, beraprost MR (Toray/Astellas's Careload LA/Kaken's Berasus), was subsequently developed and approved for marketing in Japan in October 2007 (Astellas, press

release, December 18, 2007). Beraprost MR is a long-acting formulation typically administered as two separate doses following the morning and evening meal, initially as one 60 µg tablet per dose and increasing to 180 µg (three tablets) per dose depending on patient response and tolerability. Beraprost and beraprost MR are typically used in early lines of therapy for PAH patients in Japan either as monotherapy or more commonly in combination with other oral agents such as ERAs or PDE-5 inhibitors. Interviewed Japanese experts report that use of both beraprost and beraprost MR is declining, and this trend will likely continue as the number of PAH treatments available in Japan increases. Despite attempts to develop beraprost and beraprost MR for the European markets, neither agent has demonstrated efficacy in clinical trials conducted in Europe. Beraprost and Beraprost MR are currently available only in Japan.

Adempas

Bayer HealthCare has developed Adempas (riociguat), a sGC stimulator, which was approved in the United States in October 2013, in Europe in March 2014, and in Japan in February 2015. Adempas is an oral treatment, and it is the first pharmacological agent to be approved for two classes of PH in adults, for both PAH and CTEPH. As the first drug to show benefit in two PH WHO groups, it is also likely to be used offlabel for the other WHO groups. The drug received approval for PAH on the basis of the Phase III PATENT-1 trial, which enrolled 445 PAH patients and had a primary outcome measure of change in 6MWD (clinicaltrials.gov, NCT00810693, accessed August 2016), and for CTEPH on the basis of the CHEST-1 trial, which enrolled 262 patients (clinicaltrials.gov, NCT00855465, accessedAugust 2016). In addition, it was approved for the treatment of adults with persistent/recurrent CTEPH after surgical treatment or inoperable CTEPH to improve exercise capacity and WHO functional class, and for the treatment of adults with PAH to improve exercise capacity, improve WHO functional class, and delay clinical worsening. Bayer HealthCare is also conducting long-term extension studies, PATENT-2 (clinicaltrials.gov, NCT00863681, accessed August 2016) and CHEST-2 (clinicaltrials.gov, NCT00910429, accessed August 2016), to evaluate the long-term safety and efficacy of Adempas for the treatment of PAH and CTEPH, respectively. Two-year data presented in 2014 from the PATENT-2 and CHEST-2 studies demonstrated that Adempas was safe with sustained efficacy over two years in patients with inoperable CTEPH or persistent or recurrent CTEPH after surgical treatment, and in patients with PAH (Bayer HealthCare, press release, September 8, 2014). Bayer is also conducting a Phase III study, RESPITE, to evaluate the use of Adempas in patients who do not benefit from taking a PDE-5 inhibitor and demonstrate an insufficient treatment response. The trial enrolled 61 study participants and is expected to complete in December 2017 (clinicaltrials.gov, NCT02007629, accessed August 2016).

As the first drug to be approved for CTEPH, Adempas is expected to be prescribed as a first-line treatment for this group of patients. Adempas is likely to be used as a first-line pharmacotherapy for both operable and inoperable CTEPH, given that some residual CTEPH usually remains after surgery. As the first and only drug indicated specifically for the treatment of CTEPH, it is likely to be widely used for this patient group. Nevertheless, one notable hurdle for Adempas will be that pulmonary endarterectomy is the treatment of choice for WHO Group 4 PH patients. For the treatment of PAH, Adempas faces an overcrowded market, but as a novel therapy and drug class, it is expected that Adempas will achieve significant market uptake for the treatment of CTEPH; however, inPAH, modest market uptake is expected. Possible side effects include reduced blood pressure, an increased risk of bleeding, and serious birth defects, with common side effects of headache, dizziness, indigestion, peripheral edema, nausea, diarrhea, and vomiting. The EXPERT EXPOSURE registry has been established to evaluate long-term safety for patients taking Adempas in a real-world clinical setting (clinicaltrials.gov , NCT02092818, accessed August 2016).

Adempas has a novel mechanism of action as a sGC stimulator that it acts on the NO/sGC/cGMP pathway to increase vasodilation and reduce platelet aggregation. This mechanism is the same pathway targeted by the PDE- 5 inhibitors, except that Adempas acts at an earlier step in the pathway, prompting some experts to hypothesize it may have greater clinical efficacy. Adempas requires dose titration to avoid tolerability issues. For this reason, it is unlikely to displace ERAs and PDE- 5 inhibitors as a first-line treatment for PAH and is expected to be used as a later-line therapy for patients with PAH. Adempas should not be used in combination with PDE-5 inhibitors because they both induce systemic vasodilatory effects. Given that PDE-5 inhibitors are often used as first-line therapy for PAH patients, impact on market uptake of Adempas is expected within this patient group. Because it also has a higher cost than sildenafil and Adcirca, Adempas is expected to be used as a later-line therapy for PAH patients. Furthermore, the use of Adempas requires enrollment in a REMS program for all female patients, due to embryo-fetal toxicity. Owing to the risk of birth defects, the use of Adempas is contraindicated in pregnant women or those planning to become pregnant (Adempas company website).

In May 2016, Bayer HealthCare terminated the RISE-IIP Phase II clinical trial, which was assessing the use of Adempas in patients with symptomatic PH associated with idiopathic interstitial pneumonias, part of the WHO group 3 class of patients, and a group of patients for whom no approved PH-specific treatment is currently available (clinicaltrials.gov, NCT02138825, accessed August 2016). The trial was terminated following a recommendation by an independent DMC, which found a possible increased risk for death and other serious adverse events with Adempas as compared to placebo (Bayer HealthCare, press release, May 12, 2016). However, interviewed experts donot expect the outcome to have a significant impact on uptake in CTEPH or PAH.

Market Outlook

Market Overview

Overall, the PAH market is expected to expand from $5.84 billion to $6.71 billion during the forecast period of 2015 to 2025. This will be driven by a number of key factors, including the launches of novel therapies and increasing combination therapy, but will also be constrained by a number of patent expiries and the anticipated generic erosion of a number of key PAH therapies. There is increasing use of combination therapy in the treatment of PAH, particularly earlier in the treatment algorithm. This represents a significant shift in the PAH treatment algorithm in recent times, and is expected to continue during the forecast period. There is also a shift toward more-aggressive use of combination therapy throughout the PAH treatment algorithm. The Phase III AMBITION, GRIPHON, and SERAPHIN trials, all evaluating combination therapy, in addition to the ongoing TRITON and FREEDOM-EV trials, are driving increased use of combination therapy, and thus overall sales for the PAH market. The TRITON trial evaluating upfront triple combination therapy with Uptravi, Opsumit, and Adcirca, may lead to further shifts in the treatment algorithm. The launches of a number of key therapies in recent years, and the ongoing uptake of Opsumit, Adempas, and Orenitram, and ongoing launches of Uptravi following the pivotal Phase III GRIPHON trial, are expected to drive growth of the PAH market during the forecast period. The launch of Esuberaprost in the United States will also drive growth in this market, although uptake will be constrained due to an anticipated launch in the United States only. The FREEDOM-EV trial evaluating Orenitram, on top of background therapy of an ERA and/or a PDE-5 inhibitor, is expected to contribute to a European regulatory submission and approval, leading to a commercial launch across the EU5, and will also contribute to the range of therapies available for the treatment

of PAH, and the growth of the PAH market across the EU5 and the United States. The inclusion of 'harder' end points such as morbidity/mortality and TTCW, and less of a focus on end points such as the 6MWD, is helping to drive the uptake of novel therapies. Nevertheless, the 6MWD still has a key role to play, particularly for physicians wishing to compare new therapies with more-established therapies indicated for the treatment of PAH.

The launches of the first oral prostacyclin therapies are contributing to some decline in the use of inhaled therapies, with inhaled prostacyclin therapies often being regarded as bridging therapies between oral and parenteral therapies for PAH patients. The launch of the sGC stimulator Adempas, representing the first therapy for two PH groups, and also representing a novel drug class, is a key factor that will also help to drive the overall PAH market. Nevertheless, this therapy's contraindication with PDE-5 inhibitors is hampering uptake in the PAH patient population. A number of patent expiries of key PAH therapies are expected during the forecast period; these are expected to lead to generic erosion of the respective branded therapies, notably Tracleer, Letairis/Volibris, Adcirca, and Remodulin, with some switching of therapies in the same drug class expected. Generic erosion will contribute to a decline in the PAH market in 2020, before the market expands again due to the continuing uptake and launches of novel therapies. The availability of generic formulations of key oral therapies is also expected to contribute to increasing combination therapy.

Market Drivers

- Increasing combination therapy for the treatment of PAH, particularly in earlier lines of therapy, is driving growth in the PAH market. The pivotal AMBITION trial evaluating upfront dual combination therapy, and the evaluation of triple upfront combination therapy in the TRITON trial, in addition to the design of GRIPHON and SERAPHIN trials, are driving the increasing use of upfront combination therapy, and more-aggressive therapy across the PAH treatment algorithm in general.

- The launch and uptake of Uptravi following the successful completion of the Phase III GRIPHON trial, demonstrating a reduction in the incorporating of a morbidity/mortality rate, will contribute to the growth of the PAH market across the major markets. Interviewed experts in the United States report that Uptravi is currently being prescribed either as a monotherapy, or most frequently in combination with an ERA and/or a PDE-5 inhibitor for the treatment of PAH.

- The launch and uptake of Orenitram, representing the first oral prostacyclin in the United States, is alsocontributing to PAH market growth. The anticipated regulatory approval and commercial launch across Europe, following the successful completion of the FREEDOM-EV trial, will also contribute to the range of therapies available in these markets and further growth of the PAH market.

- The launch and uptake of the implantable Remodulin pump in the United States will offer an alternativetreatment approach for this therapy for PAH patients. The availability of this delivery system is expected to increase the use of parenteral treprostinil, and branded Remodulin in general, with notable improvements in convenience of use and with QOL benefits for patients. Although some interviewed experts express concern regarding the accuracy of the implantable pump at present, these issues are expected to be resolved prior to regulatory approval. This delivery system will also help protect branded Remodulin sales in the face of generic erosion beginning in 2018.

- The anticipated regulatory approval, commercial launch, and uptake of Esuberaprost in the United Stateswill offer an additional treatment approach for PAH patients in this market. Following the successful completion of the Phase III BEAT trial, the modified formulation of beraprost, prescribed in combination with Tyvaso, will also modestly contribute to the expansion of the PAH market.

Market Constraints

- The patent expiry and launch of generic formulations of bosentan, the first oral therapy and ERA approved for PAH, will constrain the PAH market to a certain extent. There is expected to be some switching in more cost-conscious markets, although the availability and continuing uptake of Letairis/Volibris and Opsumit, in addition to concerns about edema and the requirement for LFTs associated with Tracleer, will limit the impact of the patent expiry of Tracleer. Generic erosion of bosentan began in Spain in 2015, and is anticipated in the United States and across other markets under study from 2017 onward.

- The patent expiry and launch of generic formulations of Letairis/Volibris will constrain the PAH market. As a key ERA, and a prominent feature of earlier lines of treatment in the PAH treatment algorithm, particularly following the successful outcome of the AMBITION trial, the generic erosion of ambrisentan is expected to have a notable impact on the size of the overall PAH market. There has been increasing uptake and prescribing of ambrisentan following the AMBITION trial, but sales of branded formulations of ambrisentan are expected to decline with increasing uptake of generic alternatives from 2018 in the United States, and from 2020 across other key markets.

- The patent expiry and launch of generic formulations of tadalafil will negatively impact the growth of the PAH market. With its once-daily dosing and inclusion in the pivotal trial evaluating the upfront combination of ambrisentan and tadalafil, uptake and prescribing of this PDE-5 inhibitor will be impacted by generic erosion, with a negative impact on branded Adcirca. This is expected from 2018 onward in the United States and across the other markets under study. The increasing use of tadalafil is also contributing to a decline in the use of sildenafil, and will increase further, following the entry of generic tadalafil.

- The patent expiry and anticipated launch of generic formulations of parenteral treprostinil will constrain the PAH market to a certain extent from 2018 onward in the United States. As a key parenteral prostacyclin analogue, and with increasing use of parenteral prostacyclin therapies due to a continuing focus on more-aggressive treatment of PAH, the anticipated launch of generic formulations of parenteral treprostinil will constrain the PAH market. Nevertheless, the impact of this event is expected to be minimized by the launch of the implantable Remodulin pump in the United States in 2017.

- Access and reimbursement issues are expected to become a more-prominent issue with PAH therapies during the forecast period. Interviewed experts anticipate increasing reimbursement hurdles, with requirements to use generic therapies, and possibly step therapy and prior authorization, in addition to cost-sensitivity among payers during the forecast period. There is concern among interviewed experts that the increasing prescribing of combination therapy earlier in the treatment algorithm will lead to increasing reimbursement hurdles and challenges to prescribers.

Review of Literature

Pulmonary arterial hypertension (PAH) is a haemodynamic disorder defined as a mean pulmonary arterial pressure (mPAP) >25 mm Hg at rest during right heart catheterisation (RHC). This increase in mPAP causes increased pulmonary vascular resistance (PVR) and cardiac remodelling, which eventually gives rise to right heart failure.[1] PAH is most often idiopathic (IPAH) but it can also arise from a number of underlying medical conditions, including connective tissue disease, chronic thromboembolic pulmonary disease and congenital heart disease, among others[2] (box). PAH due to congenital heart disease (PAH-CHD) refers to PAH that is associated with small cardiac defects (ventricular septal defects (VSDs)<1 cm or atrial septal defects (ASDs)<2 cm), systemic-to-pulmonary shunts, Eisenmenger syndrome (ES) or corrective cardiac surgery.

A number of potential future therapies are in clinical development for the treatment of PAH. These include:

- the first representatives of two new drug classes intended for oral use:

▪a soluble guanylate cyclase (sGC) stimulator (riociguat)
▪an highly selective prostacyclin receptor agonist (selexipag)

- a new PAH indication for two existing drugs:

▪a PDE-5 inhibitor (vardenafil)
▪an oral tyrosine kinase inhibitor (imatinib)

- inhaled and oral formulations of treprostinil.

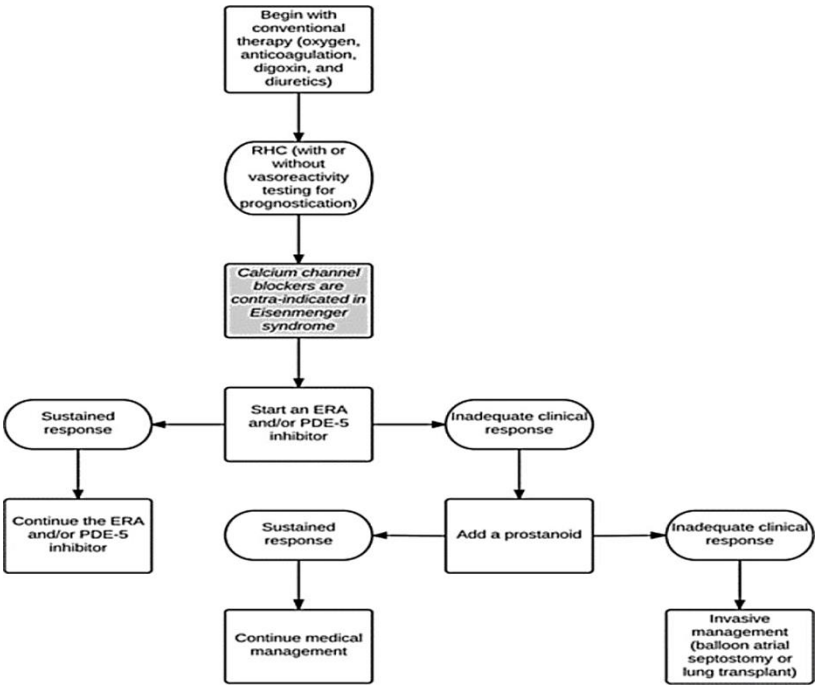
Limitations of this review

Most of the limitations of this review are related to the limitations common among the included studies. Small population size was common among many of the studies, especially those studies which included patients with a variety of causes of PAH; when the PAH-CHD subgroup was looked at in those studies, the sample size was usually very small, often <20 patients. Also, many of the studies included in this review were of varying durations, which makes making direct comparisons between the results of each study difficult. Additionally, studies which lasted for longer durations may have suffered from bias due to loss to follow-up.

A couple of studies have reported that the effects of medications on PAH may be related to the severity of disease, suggesting that the studies which included more patients with advanced disease (eg, patients who were WHO FC III and IV) were more likely to show greater improvement in 6MWD than studies that included more patients with less advanced disease (eg, patients who were WHO FC I and II). Also, many of the studies focused on patients with PAH-CHD due to a specific cause; PATENT-1 and PATENT-2 looked exclusively at patients with PAH-CHD post-corrective cardiac surgery, and many of the other studies assessed patients with PAH-CHD due to ES. Some studies have shown that patients with ES are more responsive to treatment than patients without ES; Duffels *et al* showed that patients with ES were more likely to exhibit long-term improvement in 6MWD while on bosentan, while patients without ES exhibited a gradual return to baseline by 2 years of treatment. Studies on patients with Down syndrome have shown variable responses to treatment, most likely due to the questionable validity of the 6 min walking test in this population. Zeng *et al* addressed the issue that the type and location of the congenital heart defect (eg, ASD, VSD, PDA) may also play a role in patients' response to PAH-specific medical therapies, and they found that the location of the defect did not significantly influence patients' response to treatment. More research is necessary to provide additional insight into how the severity and aetiology of patients' congenital heart disease affects their response to treatment.

Another major limitation is that some of the studies in this review evaluated medications used as monotherapy for PAH-CHD, while others evaluated the study drug after patients had received prior treatment with other PAH-specific medications. If patients had already received prior treatment, then their response to the study drug may be blunted by any improvements previously attained in response to those earlier treatments,a finding which may hold particularly true for the currently available studies on macitentan, where many patients had previously been treated with bosentan for an extended period. Additionally, pharmacokinetic interactions between drugs may also occur; some studies have suggested that bosentan may significantly decrease plasma concentrations of sildenafil when co-administered to patients with PAH, and it is possible that similar interactions may occur between other PAH medications as well.

Finally, PATENT-1, PATENT-2 BREATHE-5 and ALPHABET were placebo-controlled trials. However, many of the studies were not placebo-controlled, making it difficult to assess whether or not a placebo effect was impacting the results reported in those studies.



Objectives

- To assess the Pulmonary Arterial Hypertension disease landscape in major markets of World.
- To find out sales of key current therapies and forecast throughout forecast period (2017 to 2023).
- To find out the emerging therapies in pulmonary arterial hypertension market.

Methodology

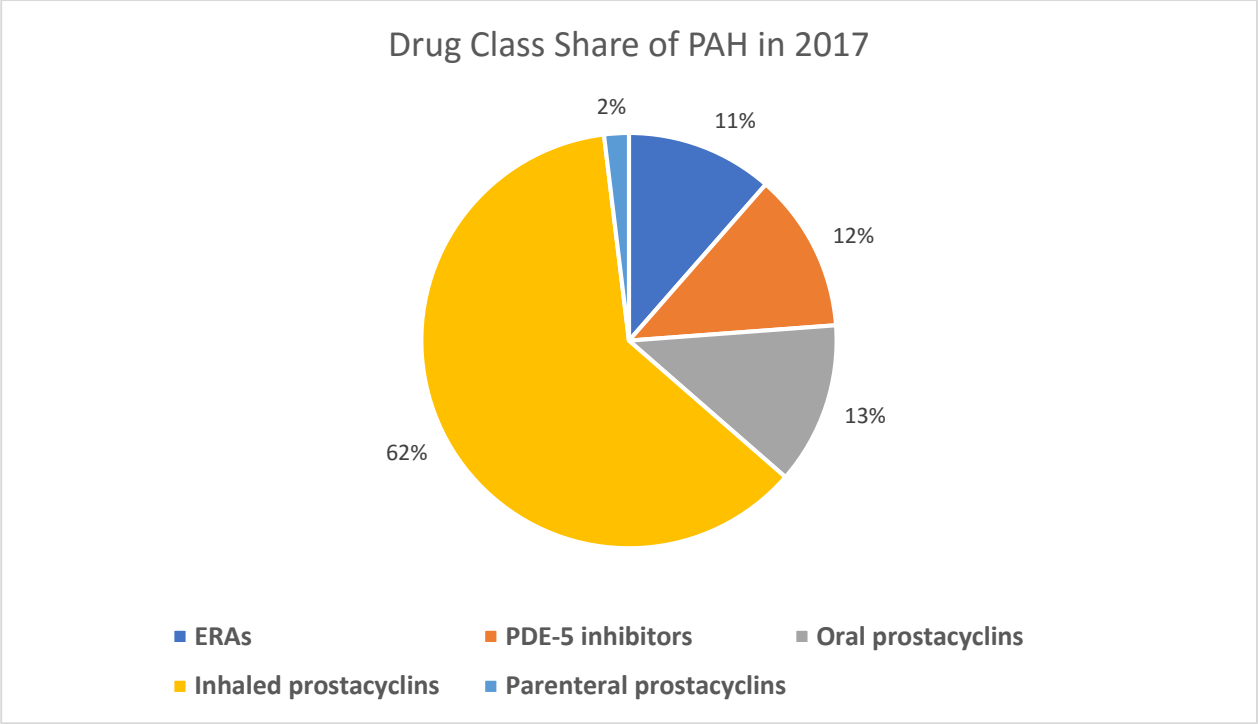
Research Design: Descriptive research

Data source and sampling: This is a secondary study includes data from various published articles, pharmaceutical company annual reports, different clinical trial studies, epidemiological studies.

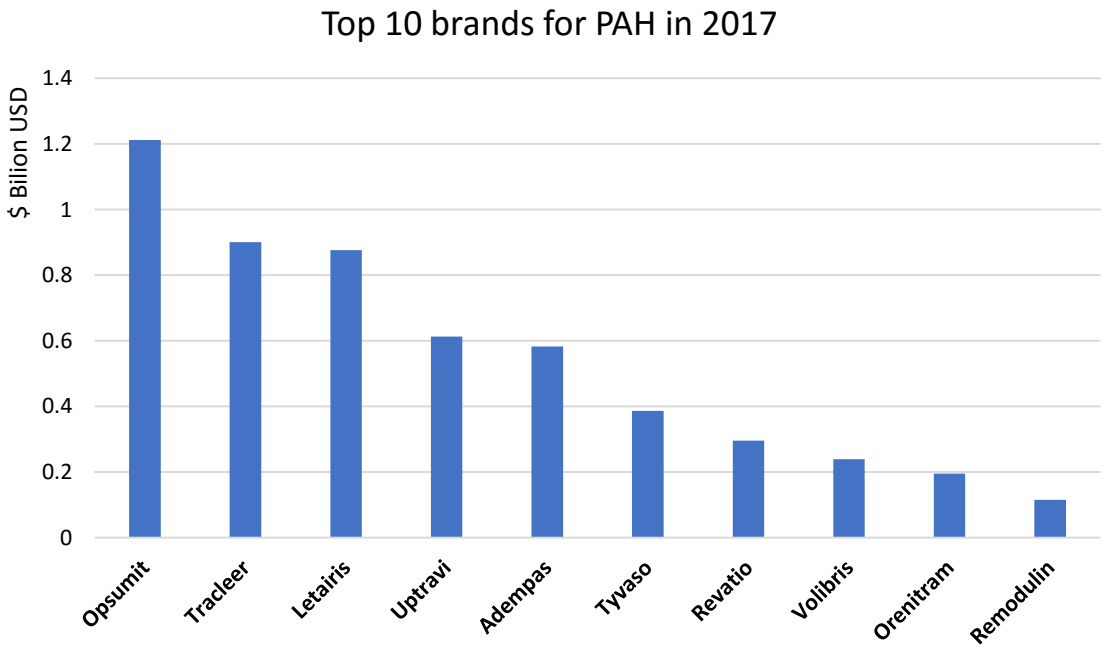
Key findings

1. SWOT analysis of Pulmonary Arterial Hypertension Market:

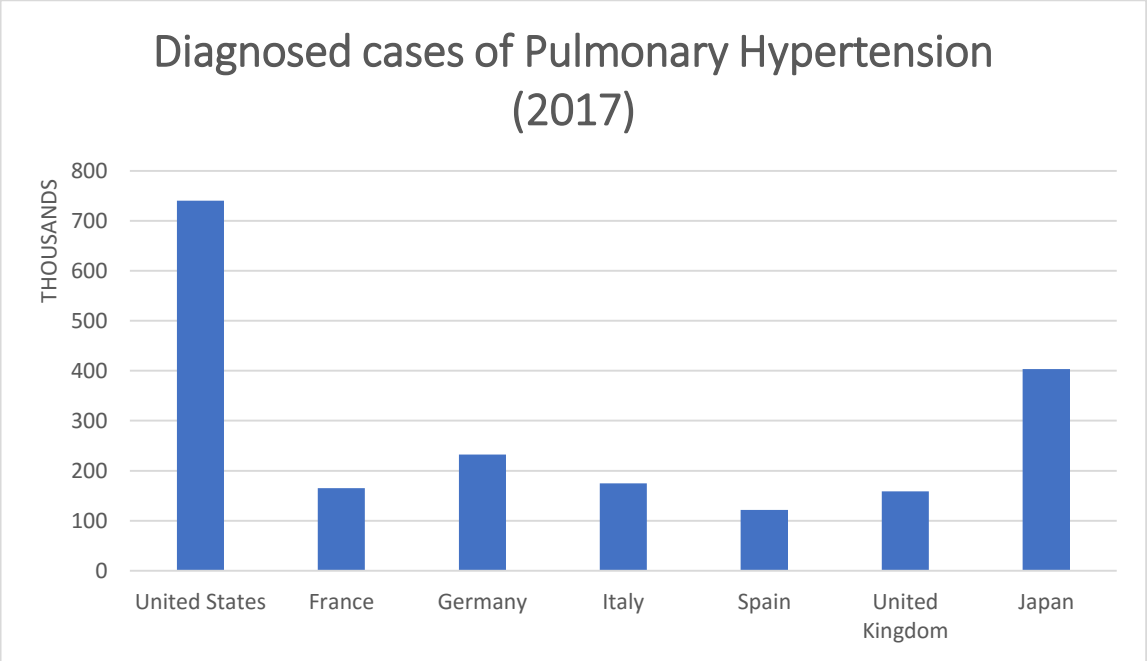
2. Market share of Pulmonary Arterial Hypertension Drug classes

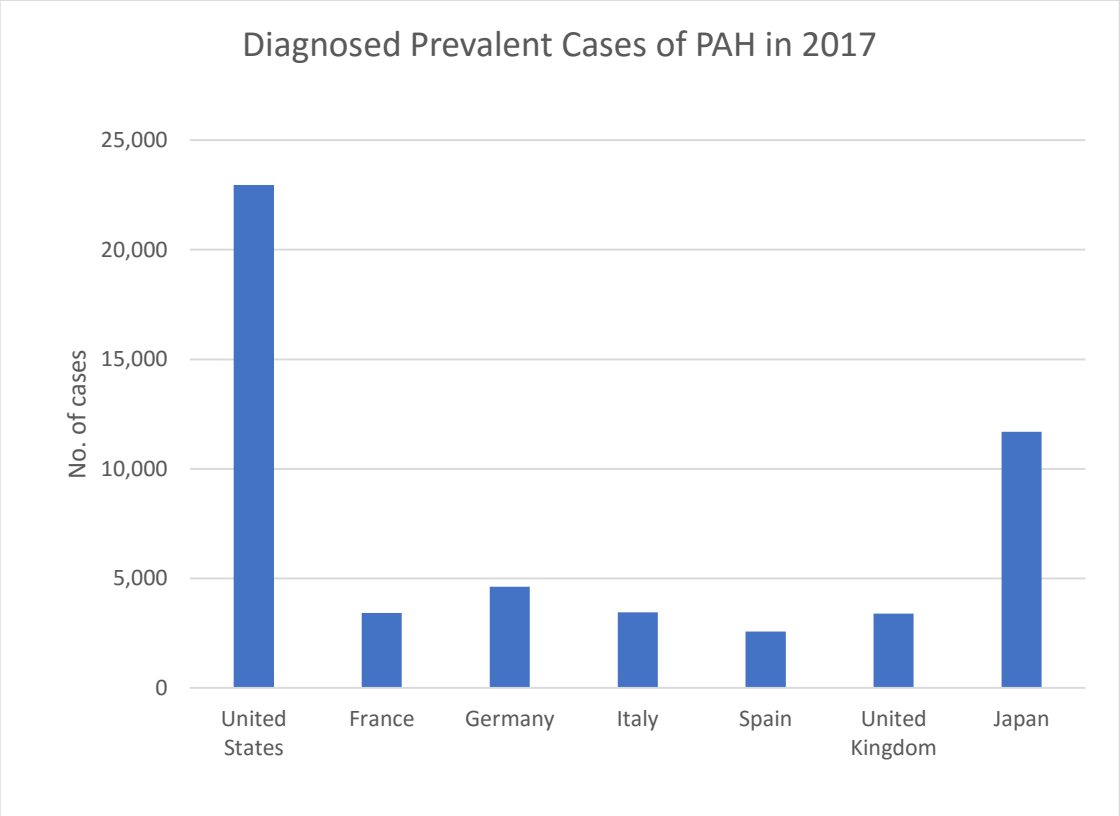


3. Sales of top drugs used for pulmonary arterial hypertension:

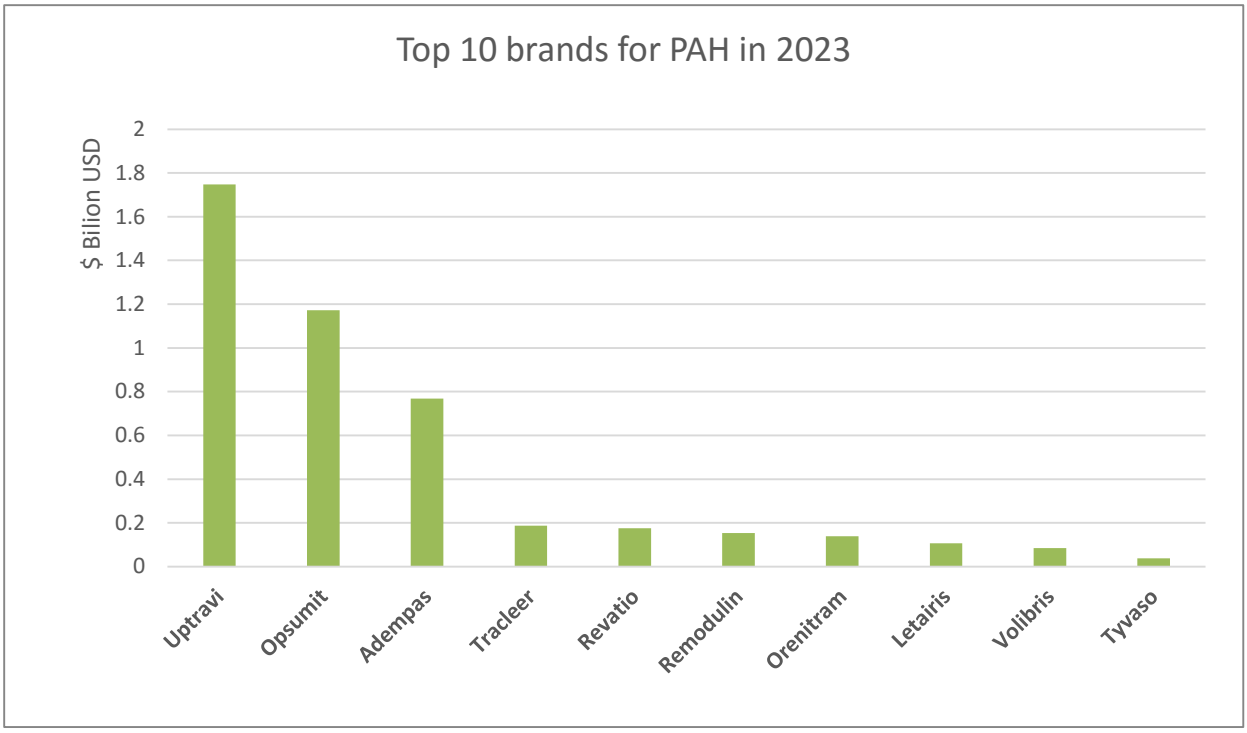


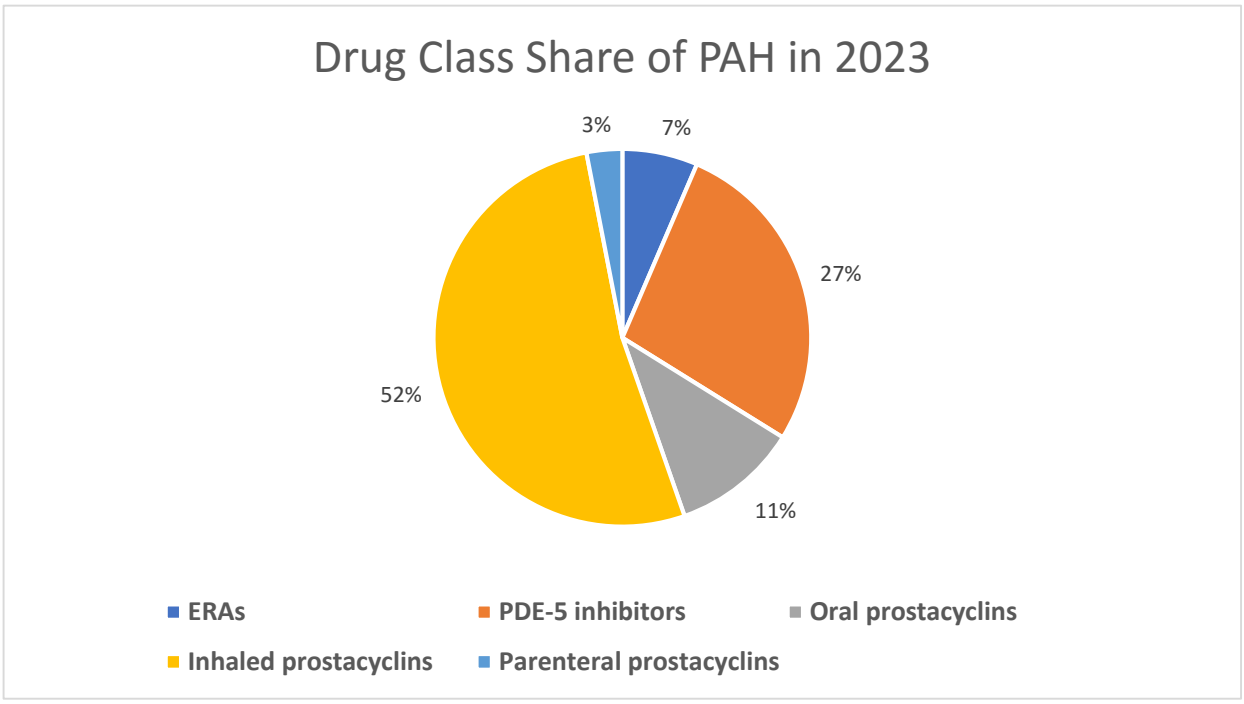
4. Epidemiological representation of Pulmonary Hypertension:





5. Forecasted sales of Top 10 drugs and drug classes





6. Emerging Therapies

Compound	Status	Marketing Company	Potential[a] ($MM)
Uptravi			
United States	Launched	Actelion	1,000+
Europe	Launched	Actelion	
Japan	Regulatory application submitted	Nippon Shinyaku	
Esuberaprost			
United States	Phase III	Lung Biotechnology LLC/United Therapeutics	50-100
Implantable Remodulin Pump			
United States	Regulatory application submitted	Medtronic/United Therapeutics	500-1,000+ overall
Bardoxolone methyl			
United States	Phase II/III	Reata Pharmaceuticals	No launch expected
Europe	Phase II/III	Reata Pharmaceuticals	
Japan	Phase II/III	Reata Pharmaceuticals	
Nitric oxide therapy			
United States	Phase III	Bellerophon Therapeutics	No launch expected
Ubenimex			
United States	Phase II	Eiger Biopharmaceuticals	No launch expected

Summary

- Overall, the PAH market is expected to expand from $5.84 billion in 2017 to $6.71 billion in 2023. This growth will be driven by the launches of several novel PAH therapies, continuing uptake of recently launched therapies such as Opsumit and Adempas, and increasing use of combination therapy.

- Patent expiries and generic erosion of a number of key PAH therapies will constrain the PAH market. During the forecast period, therapies including Tracleer, Letairis/Volibris, Adcirca, and Remodulin will experience loss of patent protection, and generic erosion of these therapies is expected.

- There are almost 2 million people diagnosed with PH in the markets under study. Cases of PH are expected to increase by 16% during the forecast period of 2017 to 2023. The largest PH WHO group is estimated to be due to left heart disease, accounting for almost 77% of all diagnosed cases of PH.

- The launches of a number of novel therapies during the forecast period, such as Uptravi, Orenitram, and Esuberaprost, will contribute to the expansion of the PAH market, in addition to providing alternative therapeutic options for the treatment of PAH. The launches of oral prostacyclins have been eagerly awaited by interviewed experts, who welcome the addition of these treatments to the PAH treatment algorithm.

- Increasing combination therapy, particularly following the Phase III AMBITION trial, in addition to the design of the Phase III GRIPHON and SERAPHIN trials in which background therapy was also taken by some trial participants, is leading to a shift in the treatment algorithm for PAH. Upfront combination therapy is becoming increasingly common, in addition to more-aggressive treatment for PAH across different lines of therapy.

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