COWEN
AND COMPANY

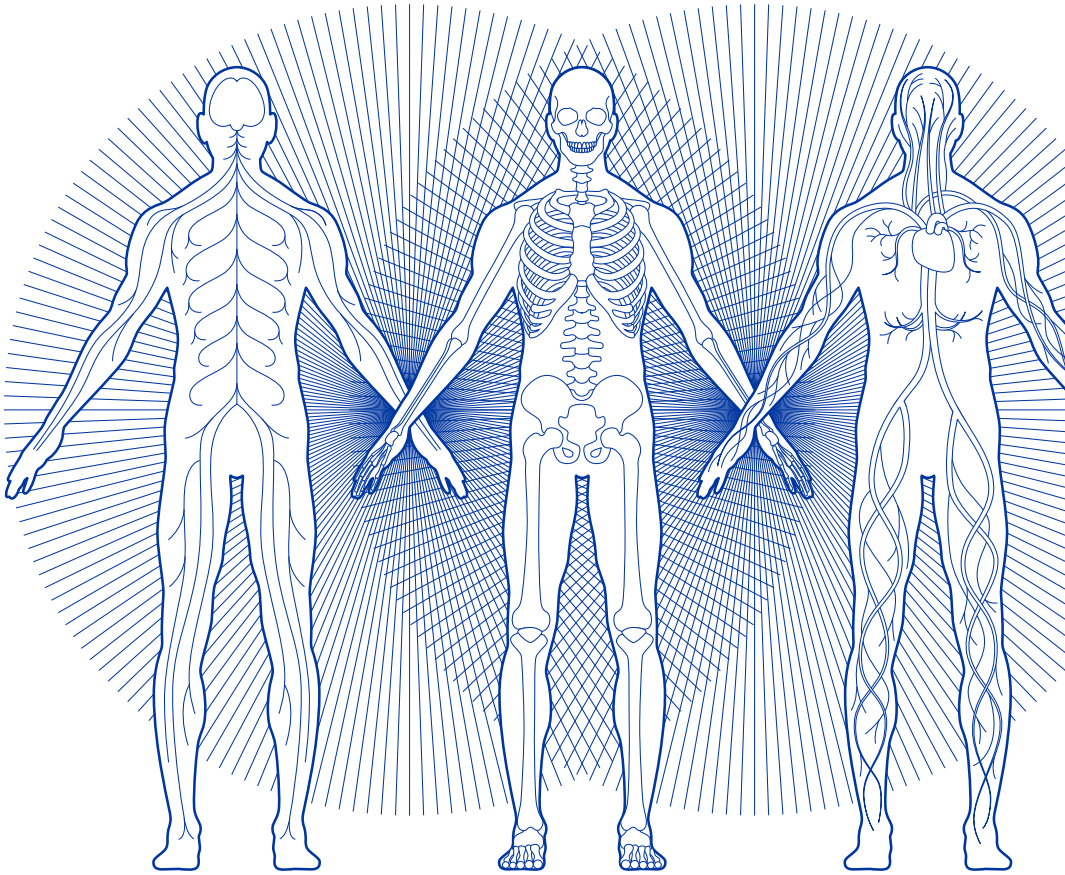
Equity Research
Health Care

Therapeutic Categories Outlook

Comprehensive Study

February 2017

Alzheimer's Disease
Bone Diseases
Cardiovascular
Central Nervous System
Dermatology
Diabetes/Obesity
Epilepsy
Gastrointestinal/Ulcer
Hepatitis
Infectious Diseases
Liver Disease
Multiple Sclerosis
Non-Malignant Hematology
Oncology/Hematology
Ophthalmology
Orphan Diseases
Pain Management
Respiratory
Rheumatology
Women's Health



much worse than it used to be. As community physicians have grown more comfortable treating mild patients with oral therapies, patients are increasingly being referred to expert centers only after their disease has become more severe.

Chronic thromboembolic pulmonary hypertension (CTEPH) is pulmonary hypertension that occurs secondary to a blood clot. Our consultants note that there are not great incidence or prevalence figures for CTEPH. However, in their experience there are about five times more PAH patients in their practices than there are CTEPH patients, suggesting that there may be about 5,000 treatable CTEPH patients in the U.S.

Despite the relatively small number of patients afflicted, the market for pulmonary hypertension therapies is actually quite large in dollar terms. Infused and inhaled prostanoids can demand $100,000+ per patient per year for treatment. With approximately 110,000 patients worldwide, and perhaps 50,000+ patients in the U.S. itself, worldwide sales for major PAH drugs surpassed $5B in 2016.

Major PAH Drugs – Worldwide Sales And Consensus Estimates

Brand	Drug	Mechanism of Action	Company	Reported sales ($MM)							Consensus estimate ($MM)			
				2010A	2011A	2012A	2013A	2014A	2015A	2016A↓	2017E	2018E	2019E	2020E
Letairis/Volibris	*ambrisentan (oral)*	ET-A antagonist (Endothelin pathway)	GILD/GSK	$311	$449	$611	$750	$855	$932	$1,036	$1,142	$956	$793	$629
Tracleer	*bosentan (oral)*	ET-A, ET-B antagonist (Endothelin pathway)	ATLN	$1,573	$1,722	$1,600	$1,653	$1,620	$1,260	$1,020	$582	$332	$226	$165
Opsumit	*macitentan (oral)*	ET-A, ET-B antagonist (Endothelin pathway)	ATLN	$0	$0	$0	$5	$197	$537	$831	$1,005	$1,303	$1,567	$1,827
Remodulin	*treprostinil (i.v., s.c.)*	Prostacyclin agonist	UTHR	$404	$430	$458	$491	$554	$573	$602	$605	$543	$471	$395
Tyvaso	*treprostinil (inhaled)*	Prostacyclin analogues	UTHR	$152	$240	$326	$439	$463	$470	$405	$441	$460	$412	$369
Adcirca	*tadalafil (oral)*	PDE 5 inhibitor (NO pathway)	UTHR	$36	$71	$123	$177	$222	$279	$372	$355	$200	$132	$43
Revatio	*sildenafil (oral)*	PDE 5 inhibitor (NO pathway)	PFE	$481	$535	$534	$307	$276	$260	$285	$203	$181	$174	$161
Adempas	*riociguat (oral)*	Guanylate cyclase stimulator (NO pathway)	BAYN	$0	$0	$0	$4	$118	$201	$263	$375	$502	$575	$624
Uptravi	*selexipag (oral)*	IP prostanoid receptor agonist	ATLN	$0	$0	$0	$0	$0	$0	$245	$882	$1,312	$1,818	$2,322
Orenitram	*treprostinil (oral)*	Prostacyclin analogues	UTHR	$0	$0	$0	$0	$41	$118	$157	$214	$277	$336	$388
Veletri	*epoprostenol (i.v.)*	Prostacyclin analogues	ATLN	$3	$17	$26	$40	$70	$86	$97	$246	$268	$289	$311
Ventavis	*iloprost (inhaled)*	Prostacyclin analogues	ATLN	$114	$120	$117	$119	$123	$109	$73	$53	$45	$38	$34
Flolan	*epoprostenol (i.v.)*	Prostacyclin analogues	GSK	$302	$287	$214	$230	$119	$89	$70	$115	$136	$158	$179
			Total	$3,376	$3,872	$4,009	$4,215	$4,657	$4,915	$5,456	$6,217	$6,515	$6,990	$7,449
			Prostacyclin pathway	$974	$1,095	$1,140	$1,319	$1,369	$1,445	$1,649	$2,556	$3,041	$3,522	$4,000
			Endothelin pathway	$1,884	$2,171	$2,212	$2,408	$2,672	$2,729	$2,887	$2,729	$2,590	$2,587	$2,622
			Nitric Oxide pathway	$517	$606	$657	$488	$616	$740	$920	$933	$883	$881	$828

Source: Cowen and Company, Consensus estimate from Thomson

There are currently 13 drugs indicated for the treatment of PAH in the U.S., and these can be broadly categorized based on their route of administration. Oral therapies include Adempas (riociguat) from Bayer, Revatio (sildenafil) from Pfizer, Adcirca (tadalafil) and Orenitram (treprostinil) from United Therapeutics, Tracleer (bosentan), Opsumit (macitentan), and Uptravi (selexipag) from Actelion, and Letairis (ambrisentan) from Gilead. These therapies tend to be used in newly presenting, less severe patients. There are three branded infused (intravenous and subQ) prostacyclins on the U.S. market including Remodulin (treprostinil) from United Therapeutics, Flolan (epoprostenol) from GlaxoSmithKline, and Veletri (epoprostenol) from Actelion. In addition, in 2008 Teva launched a generic version of Flolan. These therapies are considered the most potent, and are used in the most severe patients (WHO FC-III and IV). There are currently two inhaled options, Actelion's Ventavis (iloprost), and United Therapeutics' Tyvaso (treprostinil), and these therapies are typically positioned for use in patients who require treatment benefit beyond oral therapies, but whose condition is not considered severe enough to warrant infused prostanoids.

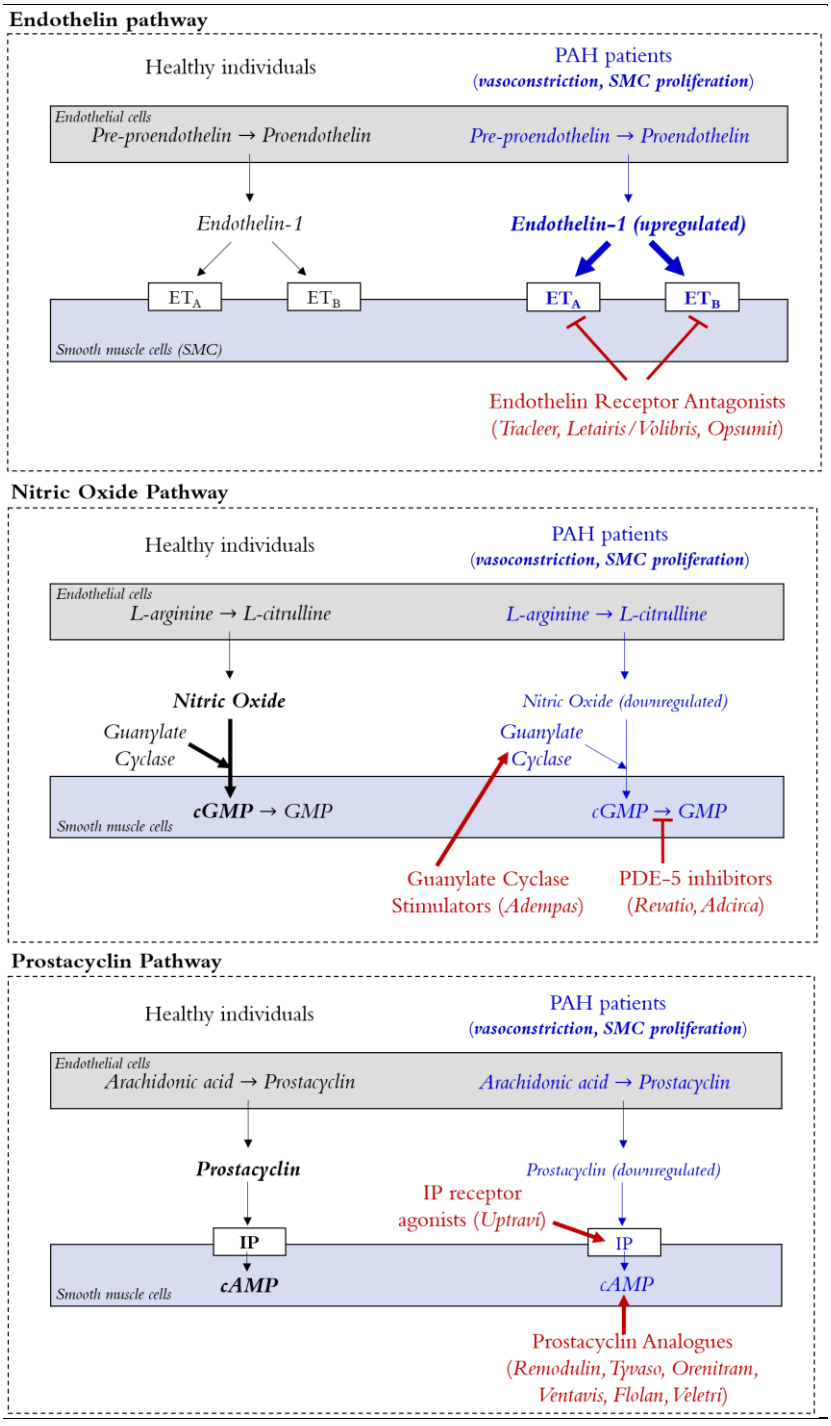
Pathways And Molecular Targets Associated With PAH

There are three major biochemical pathways that have been shown to be associated with PAH: the endothelin pathway, nitric oxide pathway and prostacyclin pathway. These pathways play a critical role in the regulation of vascular tone, and their dysregulation results in vasoconstriction and pulmonary smooth muscle cell proliferation.

Endothelin (ET-1) is an endogenous peptide formed by proteolytic processing of preproendothelin-1. ET-1 signaling through the endothelin receptors ET_A and ET_B, present in the pulmonary vascular smooth muscle cells, maintains vascular tone. In PAH patients, ET-1 levels are elevated in the blood stream and the ability to clear ET-1 from the systemic circulation is reduced. Elevated signaling of the endothelin pathway in smooth muscle cells, from increased levels of ET-1 and endothelin receptors, produces pronounced vasoconstriction and smooth muscle proliferation effects. Endothelin receptor antagonists target ET_A and/or ET_B receptors to attenuate ET-1 signaling in the smooth muscle cells. There are currently three approved endothelin receptor antagonist drugs: bosentan (Tracleer from Actelion), ambrisentan (Letairis in US from Gilead and Volibris in ex-US from GSK), and macitentan (Opsumit from Actelion). Tracleer and Opsumit target both the ET_A and ET_B receptor whereas Letairis/Volibris target only the ET_A receptor. Drugs targeting the endothelin pathway (Tracleer, Letairis/Volibris, and Opsumit) had worldwide sales of ~$2.9B in 2016. The cumulative sales from these drugs are expected to marginally decline over the next four years. Tracleer and Letairis/Volibris are expected to see heavy generic erosion during this time period, whereas Opsumit, launched in 2013 (and not anticipated to be subject to generic competition during this time period) is expected to grow strongly.

Nitric oxide (NO) is a vasodilator and plays a major role in smooth muscle cell signaling. NO is normally produced continuously by the endothelial cells from the conversion of L-arginine to L-citrulline aided by the enzyme NO synthase. NO diffuses into the vascular smooth muscle cells and binds to Guanylate Cyclase to stimulate the synthesis of cGMP, a second messenger that inhibits cell proliferation and produces muscle relaxation. In PAH patients there is decreased bioavailability of NO, resulting in reduced cGMP in smooth muscle cells. In addition, cGMP levels are also affected by the phosphodiesterase 5 (PDE-5) enzyme, which inactivates cGMP in smooth muscle cells. There are two class of approved drugs that target the NO pathway in PAH patients – soluble guanylate cyclase stimulators (GCS) and PDE-5 inhibitors. GCS directly bind to guanylate cyclase and mediates the synthesis of cGMP. Riociguat (Adempas from Bayer) is the only drug approved in this category. PDE-5 inhibitors preserve cGMP levels by blocking the inactivation of cGMP by the PDE-5 enzyme. Tadalafil (Adcirca from United Therapeutics) and sildenafil (Revatio) are the two major PDE-5 inhibitors approved for PAH. Drugs targeting the nitric oxide pathway (Adcirca, Revatio, and Adempas) reported worldwide sales of ≈$920MM in 2016. Cumulative sales from these drugs are expected to marginally increase for the next four years. Revatio sales have eroded due to generic entry and Adcirca is also expected to see competition from generic entry at the end of 2017. Adempas, launched in 2013, is expected to grow strongly during this time period.

Mechanism Of PAH Drugs

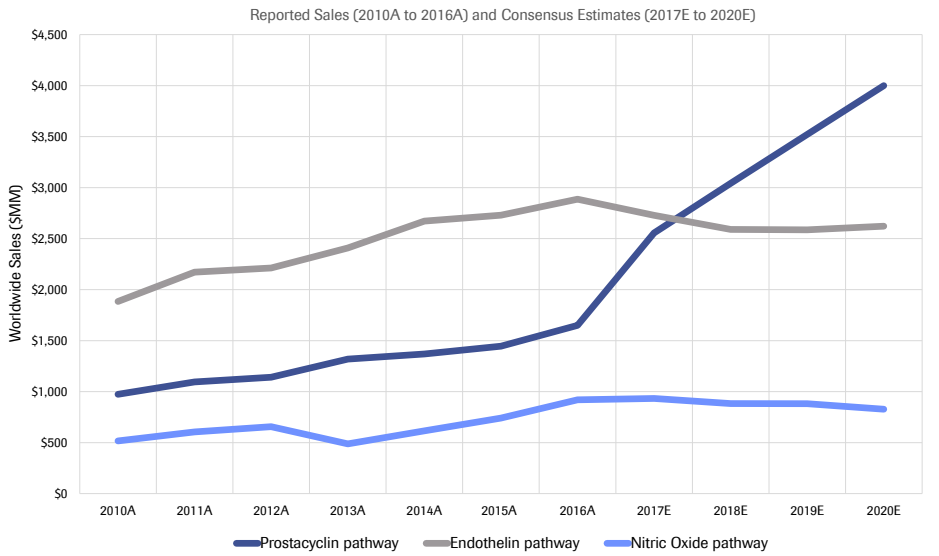


Source: Cowen and Company

Prostacyclin is the major arachidonic acid metabolite of vascular endothelial and smooth muscle cells. Prostacyclin binds to the prostaglandin IP receptor on the smooth muscle cells to promote vasodilation and inhibit smooth muscle proliferation through the activation of cAMP. Prostacyclin levels are reduced in PAH patients thereby leading to reduced dilatory and anti-proliferative effects. Prostacyclin

pathway in PAH patients. Epoprostenol (Flolan from GSK and Veletri from Actelion), iloprost (Ventavis from Actelion) and treprostinil (Remodulin, Tyvaso and Orenitram from United Therapeutics) are prostacyclin analogues approved to treat PAH. Selexipag (Uptravi from Actelion) is the only approved prostaglandin IP receptor agonist in the market. Drugs targeting the prostacyclin pathway (Remodulin, Tyvaso, Uptravi, Orenitram, Flolan, Veletri and Ventavis) reported a worldwide sales of ≈ $1.6B in 2016. Cumulative sales from these drugs are expected to grow sharply for the next four years, primarily due to the growth expected in oral prostacyclin agent (Uptravi and Orenitram).

Worldwide Sales (Reported And Consensus) From PAH Drugs Targeting Major Pathways



Source: Cowen and Company

In 2016, drugs targeting the prostacyclin, endothelin and nitric oxide pathways contributed 30%, 53%, and 17% to the worldwide PAH sales, respectively. In 2020, prostacyclin drugs are expected to contribute a majority share of 54%, whereas endothelin drugs are predicted to decline to a 35% market share. Nitric oxide pathway drugs market share are also expected to decline to 11% by 2021.

Treatment Algorithm For PAH Patients

Right-sided heart catheterization (RHC) is generally used to establish the hemodynamic criteria to arrive at a diagnosis for PAH. If PAH is confirmed at an expert center, then an acute vasoreactivity test is conducted to identify a small number of PAH patients (< 15%) that are *vasoreactive* and can be successfully treated with high-dose calcium channel blockers like nifedipine, diltiazem and amlodipine. All of these drugs are available as generics. A majority of diagnosed PAH patients, however, are non-vasoreactive and thus their treatment sequence is determined by their WHO functional classification.

Low-risk WHO FC II and intermediate-risk WHO FC III patients start treatment with either a single agent or a combination of agents. ERA, PDE-5i, GCS, IP agonists drugs are used in the monotherapy setting, and ERA+PDE-5i is commonly used in the combination setting. For WHO FC III patients, due to their higher risk profile, can also start with a prostacyclin as a monotherapy. A prostacyclin is then added to the ERA or

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