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UNITED THERAPEUTICS

In 1990, Jenesis Rothblatt, age 6, was diagnosed with pulmonary arterial hypertension (often referred to as PAH). Without careful monitoring and treatment, she could quickly develop heart failure and die within several years.

When Jenesis's father, serial entrepreneur Dr. Martin Rothblatt, and his wife, Bina, found out the name of the disease that was turning Jenesis's lips blue and make her gasp for breath, they also learned just how rare PAH is. The rarity of the disease meant that funding was all but nonexistent and drug development was slow. Jenesis's future precariously hung on the severity of her disease, and the family knew they needed more treatment options beyond what was available on the market at that time.

Serial Entrepreneur Martine Rothblatt

Martin Rothblatt graduated summa cum laude from UCLA with a degree in communication studies and a thesis on international direct broadcast satellites. Rothblatt went on to complete a joint degree program at UCLA, graduating with a J.D./M.B.A in 1981. His Applied Management Research project, which would served as a master's thesis at the UCLA Anderson School of Management, involved preparing a business plan for the Hughes Space and Communications Group on the applicability of satellite spot beam technology as a communication service in Latin America.

After finishing at UCLA, Rothblatt took a job in Washington DC with the capital's biggest law firm, Covington and Burling, but found himself working mostly for corporate clients who sought to slow down the development of satellite communications. Rothblatt soon linked up with a satellite entrepreneur, Rene Anselmo, who launched PanAmSat, a company based on the business plan that Rothblatt had written at UCLA. Although Hughes had originally rejected Rothblatt's plan, in 1995 the company (now Hughes Electronics, a part of General Motors) acquired PanAmSat for $3 billion.

After helping Anselmo found PanAmSat, Rothblatt went on to pioneer a series of innovative satellite communications companies. These included Geostar, the first nationwide vehicle location system, Worldspace, the first global satellite radio system, and Sirius Satellite Radio, the first satellite-to-car broadcasting system.

The ability to see ahead of the curve when it comes to technology was a defining aspect of Rothblatt's success in satellite communications. As Rothblatt put it years later,

> The real entrepreneurial skillset is to find technology that's just around the corner. You don't want it to be down the block or in another city because [it's] going to be already

> occupied or twenty years before that technology is available. You want it to be just around the corner so you could be the first person to bring that technology forward. And I think that's probably been my greatest contribution is being able to watch technology trends and see the ones that are kind of just around the corner and then jump on those technology trends.[1]

Rothblatt was also a pioneer in other ways, In 1994, Rothblatt came out as transgender, changing her name from Martin to Martine. In subsequent years she would become a vocal advocate of transgenderism and the first transgendered CEO of a major company. She also promoted causes of human rights and founded a movement, Terasem, based on the idea that it would soon be possible to collect detailed digital data on humans ("mindfiles") that could support simulation of the human brain via software and computer technology.

When Jenesis was diagnosed with PAH, Rothblatt sold some holdings of telecom stock and used the $3 million to start the PPH Cure Foundation, which would research potential treatments. Unfortunately, nearly 3 years passed without any progress. Rothblatt soon learned from one of her daughter's doctors that Glaxo Wellcome (known today as GlaxoSmithKline) owned treprostinil, a drug that could prove to be the best treatment on the market for PAH. However, the company had shelved it in favor of developing another drug, epoprostenol. Armed with new information and the belief that she could transform the biotechnology industry the same way as she had rattled the satellite communications industry, Rothblatt was able to recruit the aid of angel investors. She then located and recruited Dr. John Vane and Salvador Moncada, the two researchers who had developed treprostinil and licensed the drug from Glaxo. To gain credence in the medical and biotechnology fields that she would need to navigate to further this entrepreneurial endeavor, Rothblatt began to study for a Ph.D. at the Barts and The London School of Medicine and Dentistry. (In 2001, she defended her dissertation on the possibility of resolving the bioethical issues between private and public interests in xenotransplantation, the transplantation of animal organs into humans.) In 1996, she founded United Therapeutics with the goal of developing better treatments, and ultimately, a cure for pulmonary arterial hypertension.

The History of United Therapeutics

Background on Pulmonary Arterial Hypertension

Pulmonary arterial hypertension, or PAH, falls under an umbrella of diseases in the "pulmonary hypertension" group. Pulmonary hypertension describes high blood pressure within, but not limited to the small arteries of the lungs, while PAH is the diagnosis for patients with high blood pressure found only within the small arteries of the lungs. Symptoms and everyday level of function determine the severity of the disease, for which health professionals use "functional classes" (akin to stages). Because symptoms are often non-specific in nature, PAH is often diagnosed only when the disease has reached an advanced stage in individuals.

Less than 10% of patients with PAH have a gene that causes the disease to be hereditary. Other causes include sporadic cases, certain drugs/toxins or parasites, connective tissue diseases

like lupus, HIV, and congenital heart defects.[2] Overall, the number of individuals with PAH is about 15-50 cases per million.[3]

Treatment Options: 1990-2002

In 1990, few drugs were developed specifically for PAH patients. Most were placed on some combination of pills and treatment programs that involved oxygen tanks, restricted physical activity, and drugs that could adversely affect the electrical conductions in the heart. Many of the drugs were appropriated from other diseases to stand in as treatment for PAH, and some led to regrettable consequences (sildenafil, better known as Viagra, was briefly universally prescribed for PAH before it was found to increase the mortality rate in children with the disease).[4] In 1990, PAH patients with mild symptoms of the disease started out on pills and were placed on intravenous (IV) epoprostenol (Glaxo's Flolan) if the illness progressed. In this IV form, children and adults with PAH must wear an IV pump that delivered the medication at a constant rate directly into the bloodstream. Furthermore, the epoprostenol inside the IV pump had to be kept between 35.6 and 46.4 degrees Fahrenheit (2-8°C) in order to remain effective.[5] As a result, patients would be expected to wear a pouch that would carry the pump along with ice packs that would need to be changed periodically to keep temperatures within that range. As expected, wearing heavy ice packs along with a bulky pump that had tubing connected it directly to a major vein greatly affected what patients were able to do on a daily basis.

The Company

Under Rothblatt's guidance, United Therapeutics began in 1996 as a private start-up headquartered in Silver Spring, Maryland. The company's focus was to bring treprostinil, branded as Remodulin, to market.

Researchers tackled two major issues. First, there was the immediate need to run the appropriate animal and clinical trials on treprostinil, the compound Rothblatt had licensed from Glaxo. After these clinical trials, the company could then apply for approval from the Food & Drug Administration to market and sell the drug as a treatment for PAH. Second, United Therapeutics needed to begin researching additional potential compounds that could be used to treat PAH. Rothblatt believed that the next advancement in PAH treatment would be an inhalable version that would be highly competitive against the medications delivered by IV pumps at the time. Moreover, from her work with satellite radio companies, Rothblatt knew that investors liked to see real revenues arise in increments over time. In United Therapeutics' case, such incremental revenues were best delivered by producing iterations of treatments over a period of time.[6]

In 1999, United Therapeutics went public in order to raise more money to drive the momentum of its drug development. Over the next ten years, company shares increased by 800% due to its superior products in comparison to existing treatment options on the market. In January 2015, United Therapeutics had a market cap of $6.7 billion.

By 2000, treprostinil had completed its clinical trials and was submitted for FDA approval. Unfortunately, the experiments on animals on humans failed to show this drug was a

significantly better alternative than the treatment that was currently on market, Flolan. (Flolan was the brand name for epoprostenol, the drug Glaxo had originally chosen to market over treprostinil.) While both drugs had to be provided intravenously, a game-changing difference between the two drugs was that treprostinil did not need to be kept at a low temperature within its IV pump, unlike Flolan. Undaunted by the initial FDA denial, United Therapeutics ran additional trials on treprostinil over the following year and eventually obtained FDA approval in 2002. Treprostinil was branded as Remodulin and entered the market priced at $90,000 per year. In its first year, annual sales for Remodulin were $50 million.[7]

After Remodulin, United Therapeutics was able to produce a few improved and new medications. In 2004, United Therapeutics announced a subcutaneous method of delivering Remodulin, which is less painful than the IV method that PAH treatments had previously relied upon. A few years later, Remodulin was offered as a tablet that could be taken orally and this form was marketed under the name Orenitram or O. (Orenitram is the first nine letters of Martine Rothblatt spelled backwards.) Eventually, by mid-2009, Rothblatt's initial vision of an inhaled PAH treatment received FDA approval. Research at United Therapeutics had found a way to make treprostinil inhalable, and it entered the market under the brand name Tyvaso.

Today, Remodulin continues to see improvements in its delivery. At the close of 2014, United Therapeutics announced that it would be working with DEKA Research & Development Corp. to design a small pump that could be filled with Remodulin and implanted within the patient, for those with PAH unable to use the oral or inhalable forms of the drug.[8]

In 2014, the United Therapeutics patent for Remodulin expired, leaving one of the company's most prized products open to marketing and sales as a generic drug by other pharmaceutical companies. In addition to the threat of generics, United Therapeutics now works in direct competition with several other large biotechnology companies that also offer drugs for PAH.

The Competition

United Therapeutics faces several large pharmaceutical companies with products that are sometimes interchangeable with Remodulin and United Therapeutics' other PAH treatments. One of its most well known competitors is GlaxoSmithKline (market cap $105.66 billion) and its product, Flolan, which was the major treatment for PAH treatments market prior to the arrival of United Therapeutics' Remodulin.

Actelion Pharmaceuticals US, Inc. (market cap $14.15 billion) is another major competitor against United Therapeutics. Actelion's lead PAH product is Tracleer (bosentan), which was the first oral treatment approved for PAH. The company also produces Veletri (intravenous) and Opsumit (another oral treatment). In 2014, Actelion's phase III trials on selexipag (branded Uptravi) demonstrated overwhelming success as a new oral treatment for PAH. Actelion has begun filing for FDA approval on selexipag, and such an approval would all but guarantee the company a dominant position in the drug market for PAH.[9,10]

Pfizer (market cap $206.66 billion) manufactures Revatio (sildenafil), an oral treatment for PAH. The company also produces an intravenous form of Revatio for patients incapable of taking the oral form.

Gilead Sciences, Inc. (market cap $151.94 billion) is the maker of Letairis (ambrisentan), an oral medication for PAH. The FDA first approved the treatment in 2007 and Gilead's Letairis patent is scheduled to expire in 2017.

In October 2013, Bayer (market cap $102.29 billion) secured FDA approval for Adempas (riociguat) as a treatment option for PAH in the U.S.[11] In Australia and New Zealand, Bayer also holds marketing authorization for Ilomedin, or intravenous iloprost for PAH.

Finally, there exists a few privately held companies, such as Pulmokine, that plan to compete in the PAH drug market.

Diversification

Today, United Therapeutics describes itself as "a biotechnology company focused on the development and commercialization of unique products to address the unmet medical needs of patients with chronic and life-threatening conditions." Since its inception, the company has expanded its repertoire of medications to address rare diseases beyond PAH. Neuroblastoma, dengue fever, prophylactic agents against viral infection, and lung transplantation technologies form the major products coming down the United Therapeutics pipeline.

Diversification of a pharmaceutical company's pipeline has risks and benefits analogous to diversification of an investment portfolio. In most cases, diversification beyond a specific disease or drug class can reduce the risks associated with the research and development and probability of successful products within a company. Moreover, having several different products in the pipeline in various stages of clinical trials increases the likelihood of consistent streams of revenue every few years. Brand building and expansion are also issues that pharmaceutical and biotechnology companies consider when expanding their portfolio of products.

Unfortunately, diversification requires that companies allot resources, time, and money towards the research and development of various products. As in the case of United Therapeutics, spreading resources out amongst different products for extremely different diseases can potentially detract from the company's overall competitiveness in the drug market for PAH. For United Therapeutics and other biotechnology companies, there remains a question of whether they should remain specialized or strive to encompass treatments for a wide variety of illnesses.

Thinking in the Next: From Treatment to Cure

In recent years, United Therapeutics has begun to explore the possibility of creating and commercializing artificial organs. Due to the nature of PAH, lung transplants are the definitive cure for the disease. However, transplants rely on human-to-human organ donations, and for specific tissues, cadaver-to-human transplants. Unfortunately, the world is critically short on

organ donors. For those who choose to donate lungs, their lung tissue may be diseased or otherwise unqualified for transplantation. As a result, researchers and physicians have looked elsewhere, notably at the possibility of animal-to-human transplantation, or xenotransplantation. Xenotransplants bring serious challenges and alarming potential for harm, such as organ rejection, an increased risk of cross-species infections (such as swine flu), the ability of the animal lungs to function in a human body given anatomical differences, and the bioethical concerns surrounding the treatment of these transplant animals and the genetic manipulation of these animals to design organs that meet transplant criteria.[12]

At United Therapeutics, Rothblatt believed that the solution to the organ shortage lay with pig lungs. Advancements in medicine and technology hinted tantalizingly that pig lungs could be genetically modified to become suitable for transplant into humans. To that end, United Therapeutics established a subsidiary, Lung Biotechnology, Inc. (originally Lung LLC), which would function with the core focus of improving lung transplants. To drive revenue for this effort, United Therapeutics bought Eli Lilly's license for Adcirca (tadalafil), an oral medication for PAH, and markets the drug via Lung Biotechnology. In addition, a phase III clinical trial on beraprost is also underway at the subsidiary as a potentially new oral treatment for PAH.[13] Staying true to Rothblatt's belief in providing sequential products and sources of revenue to investors, the company is also exploring technologies in collaboration with two lung perfusion companies that will preserve the quality of lungs that have been removed from the human body so that the organs are more likely to reach someone in need.

At Lung Biotechnology, however, the end goal has been to genetically re-engineer the pig genome with the goal to successfully transplant a set of pig lungs into a human by the end of the decade.[14] To do so, Lung Biotechnology labs are addressing two major concerns with xenotransplants. First, they have been able to produce pigs with blood type O, which means the blood will be compatible with any human recipient. Second, the company has been identifying the tissue markers and genes in pig lung cells that must be eliminated in order to prevent the rejection response that normally develops with pig-to-human transplants. To aid these ventures, United Therapeutics entered a license agreement with Pluristem and purchased all outstanding stock of Revivicor. Pluristem is attractive to United Therapeutics and Lung Biotechnology for its cell-based technology that holds applications in PAH treatment, while Revivicor owns genetic biotechnology platforms that could play key roles in shaping humanized pig lungs.

Conclusion

Jenesis has been doing well for the past 25 years and treatment regimens have prevented PAH from progressing beyond its mild form in her case. However, there exist other PAH patients every day who develop more serious symptoms and complications. The treatments themselves also come with risks and side effects, and some patients can fail to respond to these medications or eventually develop a resistance to their therapeutic effects. Ultimately, the only true cure for PAH is lung transplantation. Rothblatt and United Therapeutics have long understood this fact, and the company now stands at a crossroads.

For United Therapeutics, the vast majority of their revenue comes from Remodulin sales, and improvements upon their current repertoire of drugs for PAH and the methods of delivery

appears crucial to the continued success of the company. However, competitors continue to crop up and encroach upon the drug market for PAH, driving Rothblatt to wonder if United Therapeutics is better off further diversifying their pipeline to explore treatments for other rare diseases. Finally, Rothblatt has been able to set up partnerships and subsidiaries to begin exploring the possibility of humanized pig lung transplants. Though the final product may be well over a decade away, United Therapeutics holds the opportunity to be the first company at that finish line. Should Rothblatt continue to advance in this arena or will the resources and time dedicated to pursuing lung transplants drain United Therapeutics of the competitive advantage that they currently hold in the PAH drug market?

These strategic and financial decisions will be deeply influential on where United Therapeutics stands in the pharmaceutical and biotechnology industries in years to come. Rothblatt must make the decision that best provides for her company, its shareholders, and the hundreds of thousands of individuals with PAH.

APPENDIX

Exhibit A: Financial Statements

UNITED THERAPEUTICS CORPORATION
CONSOLIDATED STATEMENTS OF OPERATIONS
(In thousands, except per share data)

	Three Months Ended December 31,		Year Ended December 31,	
	2013	2012	2013	2012
Revenues:				
Net product sales	$ 286,297	$ 240,431	$ 1,106,944	$ 906,123
Other	2,720	3,386	10,040	9,953
Total revenue	289,017	243,817	1,116,984	916,076
Operating expenses:				
Research and development	121,552	37,476	299,348	173,387
Selling, general and administrative	157,178	40,073	394,010	201,746
Cost of product sales	38,778	37,665	131,127	119,297
Total operating expenses	317,508	115,214	824,485	494,430
Operating (loss) income	(28,491)	128,603	292,499	421,646
Other (expense) income:				
Interest income	1,111	716	3,827	3,941
Interest expense	(4,562)	(4,490)	(18,058)	(16,639)
Other, net	312	123	635	31,723
Total other (expense) income, net	(3,139)	(3,651)	(13,596)	19,025
(Losses) earnings before income taxes	(31,630)	124,952	278,903	440,671
Income tax benefit (expense)	1,316	(41,697)	(104,343)	(136,229)
Net (loss) income	$ (30,314)	$ 83,255	$ 174,560	$ 304,442
Net (loss) income per common share:				
Basic	$ (0.60)	$ 1.65	$ 3.49	$ 5.84
Diluted	$ (0.60)	$ 1.60	$ 3.28	$ 5.71
Weighted average number of common shares outstanding:				
Basic	50,281	50,503	50,076	52,093
Diluted	50,281	52,133	53,231	53,280

SELECTED CONSOLIDATED BALANCE SHEET DATA
(In millions)

	December 31,	
	2013	2012
Cash, cash equivalents and marketable securities (excluding restricted amounts of $5.4 million as of December 31, 2013 and 2012)	$ 1,136.7	$ 784.9
Total assets	2,087.6	1,626.6
Total liabilities and temporary equity	828.3	542.6
Total stockholders' equity	1,259.3	1,084.0

	Year Ended December 31,				Three Months Ended December 31,	
	2013	2012	2011	2010	2013	2012
Net income (loss), as reported	$ 174,560	$ 304,442	$ 217,868	$ 105,916	$ (30,314)	$ 83,255
Add (subtract) non-cash charges (benefits):						
Interest expense	18,058	16,639	21,372	19,714	4,562	4,490
Non-cash license fees	—	—	37,049	—	—	—
Depreciation and amortization	31,259	27,145	20,535	17,919	7,753	7,290
Impairment charges	—	4,839	—	7,688	—	—
Share-based compensation expense (benefit)	320,786	30,115	(15,715)	113,942	178,202	(10,453)
Non-GAAP earnings	$ 544,663	$ 383,180	$ 281,109	$ 265,179	$ 160,203	$ 84,582
Non-GAAP earnings per share:						
Basic	$ 10.88	$ 7.36	$ 4.92	$ 4.72	$ 3.19	$ 1.67
Diluted	$ 10.23	$ 7.19	$ 4.73	$ 4.46	$ 2.88	$ 1.62
Weighted average number of common shares outstanding:						
Basic	50,076	52,093	57,163	56,142	50,281	50,503
Diluted	53,231	53,280	59,395	59,516	55,648	52,133

Exhibit B: United Therapeutics Products

Product	Delivery Method	Market	Current Status
Remodulin	Continuous subcutaneous, continuous intravenous	Pulmonary arterial hypertension	Commercially available
Tyvaso	Inhaled	Pulmonary arterial hypertension	Commercially available
Adcirca	Oral	Pulmonary arterial hypertension	Commercially available
Orenitram	Oral	Pulmonary arterial hypertension	Commercially available
Orenitram combination therapy	Oral	Pulmonary arterial hypertension	Phase III
Remodulin	Continuous IV with implantable pump	Pulmonary arterial hypertension	Phase III
Beraprost 314d	Oral	Pulmonary arterial hypertension	Phase III
PLX cells	Intravenous	Pulmonary arterial hypertension	Phase I
TransCon treprostinil	Self-injected	Pulmonary arterial hypertension	Pre-Clinical
TransCon beraprost	Self-injected	Pulmonary arterial hypertension	Pre-Clinical
Lung transplantation	Various	End-stage lung disease	Pre-Clinical
Ch14.18 MAb	Intravenous	Neuroblastoma	Commercially available
UV-4B	Oral	Dengue	Phase I
Glycobiology antiviral agents	Oral	Broad-spectrum agents against viral infectious diseases	Pre-Clinical

Exhibit C: In-depth Overview of Pulmonary Hypertension (adapted from the National Heart, Lung, and Blood Institute)

Pulmonary hypertension, or PH, is increased pressure in the pulmonary arteries. These arteries carry blood from the heart to the lungs to pick up oxygen. PH causes symptoms such as shortness of breath during routine activity (for example, climbing two flights of stairs), tiredness, chest pain, and a racing heartbeat. As the condition worsens, its symptoms may limit all physical activity.

Overview

To understand PH, it helps to understand how the heart and lungs work. The heart has two sides, separated by an inner wall called the septum. Each side of the heart has an upper and lower chamber. The lower right chamber of the heart, the right ventricle, pumps blood to the pulmonary arteries. The blood then travels to the lungs, where it picks up oxygen. The upper left chamber of the heart, the left atrium, receives the oxygen-rich blood from the lungs. The blood is then pumped into the lower left chamber of the heart, the left ventricle. From the left ventricle, the blood is pumped to the rest of the body through an artery called the aorta.

PH begins with inflammation and changes in the cells that line the pulmonary arteries. Other factors also can affect the pulmonary arteries and cause PH. For example, the condition may develop if:

- The walls of the arteries tighten.
- The walls of the arteries are stiff at birth or become stiff from an overgrowth of cells.
- Blood clots form in the arteries.

These changes make it hard for the heart to push blood through the pulmonary arteries and into the lungs. As a result, the pressure in the arteries rises. Also, because the heart is working harder than normal, the right ventricle becomes strained and weak. The heart may become so weak that it can't pump enough blood to the lungs. This causes heart failure. Heart failure is the most common cause of death in people who have PH.

PH is divided into five groups based on its causes. In all groups, the average pressure in the pulmonary arteries is higher than 25 mmHg at rest or 30 mmHg during physical activity. The pressure in normal pulmonary arteries is 8–20 mmHg at rest. (The mmHg is millimeters of mercury—the units used to measure blood pressure.)
Other diseases or conditions, such as heart and lung diseases or blood clots, usually cause PH. Some people inherit the condition (that is, their parents pass the genes for PH on to them). In some cases, the cause isn't known.

Outlook

PH has no cure. However, research for new treatments is ongoing. The earlier PH is treated, the easier it is to control. Treatments include medicines, procedures, and other therapies. These treatments can relieve PH symptoms and slow the progress of the disease. Lifestyle changes also can help control symptoms.

Types of Pulmonary Hypertension

The World Health Organization divides pulmonary hypertension (PH) into five groups. These groups are organized based on the cause of the condition. In all groups, the average pressure in the pulmonary arteries is higher than 25 mmHg at rest or 30 mmHg during physical activity. The pressure in normal pulmonary arteries is 8–20 mmHg at rest. (Note that group 1 is called pulmonary arterial hypertension (PAH) and groups 2 through 5 are called pulmonary hypertension. However, together all groups are called pulmonary hypertension.)

Group 1 Pulmonary Arterial Hypertension
Group 1 PAH includes:

- PAH that has no known cause.
- PAH that's inherited (passed from parents to children through genes).
- PAH that's caused by drugs or toxins, such as street drugs and certain diet medicines.
- PAH that's caused by conditions such as:
- Connective tissue diseases. (Connective tissue helps support all parts of the body, including the skin, eyes, and heart.)
- HIV infection.
- Liver disease.
- Congenital heart disease
- Sickle cell disease
- Schistosomiasis, an infection caused by a parasite. Schistosomiasis is one of the most common causes of PAH in many parts of the world.
- PAH that's caused by conditions that affect the veins and small blood vessels of the lungs.

Group 2 Pulmonary Hypertension
Group 2 includes PH with left heart disease. Conditions that affect the left side of the heart, such as mitral valve disease or long-term high blood pressure, can cause left heart disease and PH. Left heart disease is likely the most common cause of PH.

Group 3 Pulmonary Hypertension
Group 3 includes PH associated with lung diseases, such as COPD (chronic obstructive pulmonary disease) and interstitial lung diseases. Interstitial lung diseases cause scarring of the lung tissue. Group 3 also includes PH associated with sleep-related breathing disorders, such as sleep apnea.

Group 4 Pulmonary Hypertension
Group 4 includes PH caused by blood clots in the lungs or blood clotting disorders.

Group 5 Pulmonary Hypertension
Group 5 includes PH caused by various other diseases or conditions. Examples include:

- Blood disorders, such as polycythemia vera and essential thrombocytopenia.
- Systemic disorders, such as sarcoidosis and vasculitis.
- Systemic disorders involve many of the body's organs.
- Metabolic disorders, such as thyroid disease and glycogen storage disease.
- Other conditions, such as tumors that press on the pulmonary arteries and kidney disease.

Causes
Pulmonary hypertension (PH) begins with inflammation and changes in the cells that line the pulmonary arteries. Other factors also can affect the pulmonary arteries and cause PH. For example, the condition may develop if:

- The walls of the arteries tighten.
- The walls of the arteries are stiff at birth or become stiff from an overgrowth of cells.
- Blood clots form in the arteries.

These changes make it hard for the heart to push blood through the pulmonary arteries and into the lungs. Thus, the pressure in the arteries rises, causing PH.

Many factors can contribute to the process that leads to the different types of PH. Group 1 pulmonary arterial hypertension (PAH) may have no known cause, or the condition may be inherited. Some diseases and conditions also can cause group 1 PAH. Examples include HIV infection, congenital heart disease, and sickle cell disease. Also, the use of street drugs (such as cocaine) and certain diet medicines can lead to PAH.

Many diseases and conditions can cause groups 2 through 5 PH (often called secondary PH), including:

- Mitral valve disease
- Lung diseases, such as COPD (chronic obstructive pulmonary disease)
- Sleep apnea
- Sarcoidosis

Signs & Symptoms
Signs and symptoms of pulmonary hypertension (PH) may include:

- Shortness of breath during routine activity, such as climbing two flights of stairs
- Tiredness
- Chest pain
- A racing heartbeat
- Pain on the upper right side of the abdomen
- Decreased appetite

As PH worsens, you may find it hard to do any physical activities. At this point, other signs and symptoms may include:

- Feeling light-headed, especially during physical activity
- Fainting at times
- Swelling in the legs and ankles
- A bluish color on the lips and skin

Treatments
Pulmonary hypertension (PH) has no cure. However, treatment may help relieve symptoms and slow the progress of the disease. PH is treated with medicines, procedures, and other therapies. Treatment will depend on what type of PH you have and its severity.

Group 1 Pulmonary Arterial Hypertension
Group 1 pulmonary arterial hypertension (PAH) includes PH that's inherited, that has no known cause, or that's caused by certain drugs or conditions. Treatments for group 1 PAH include medicines and medical procedures.

Medicines
Physicians may prescribe medicines to relax the blood vessels in the lungs and reduce excess cell growth in the blood vessels. As the blood vessels relax, more blood can flow through them. Physicians may prescribe medicines that are taken by mouth, inhaled, or injected.
Examples of medicines for group 1 PAH include:

- Phosphodiesterase-5 inhibitors, such as sildenafil
- Prostanoids, such as epoprostenol
- Endothelin receptor antagonists, such as bosentan and ambrisentan
- Calcium channel blockers, such as diltiazem

A doctor may prescribe one or more of these medicines. To find out which of these medicines works best, patients may likely have an acute vaso-reactivity test. This test shows how the pressure in the pulmonary arteries reacts to certain medicines. The test is done during right heart catheterization.

Medical and Surgical Procedures
With group 1 PAH, the doctor may recommend one or more of the following procedures.

Atrial septostomy – For this procedure, a thin, flexible tube called a catheter is put into a blood vessel in the leg and threaded to the heart. The tube is then put through the wall that separates the right and left atria (the upper chambers of the heart). This wall is called the septum. A tiny balloon on the tip of the tube is inflated. This creates an opening between the atria. This procedure relieves the pressure in the right atria and increases blood flow. Atrial septostomy is rarely done in the United States.

Lung transplant – A lung transplant is surgery to replace a person's diseased lung with a healthy lung from a deceased donor. This procedure may be used for people who have severe lung disease that is causing PAH.

Heart–lung transplant – A heart–lung transplant is surgery in which both the heart and lung are replaced with healthy organs from a deceased donor.

Group 2 Pulmonary Hypertension
Conditions that affect the left side of the heart, such as mitral valve disease, can cause group 2 PH. Treating the underlying condition will help treat PH. Treatments may include lifestyle changes, medicines, and surgery.

Group 3 Pulmonary Hypertension
Lung diseases, such as COPD (chronic obstructive pulmonary disease) and interstitial lung disease, can cause group 3 PH. Certain sleep disorders, such as sleep apnea, also can cause group 3 PH. With this type of PH, patients may need oxygen therapy. This treatment raises the level of

oxygen in the blood. Oxygen therapy can be done at home or in a hospital. The doctor also may recommend other treatments if there is underlying lung disease.

Group 4 Pulmonary Hypertension
Blood clots in the lungs or blood clotting disorders can cause group 4 PH. With this type of PH, the doctor will likely prescribe blood-thinning medicines. These medicines prevent clots from forming or getting larger. Sometimes doctors use surgery to remove scarring in the pulmonary arteries due to old blood clots.

Group 5 Pulmonary Hypertension
Various diseases and conditions, such as thyroid disease and sarcoidosis, can cause group 5 PH. An object, such as a tumor, pressing on the pulmonary arteries also can cause group 5 PH. Group 5 PH is treated by treating its cause.

All Types of Pulmonary Hypertension
Several treatments may be used for all types of PH. These treatments include:

- Diuretics, also called water pills. These medicines help reduce fluid buildup in the body, including swelling in the ankles and feet.
- Blood-thinning medicines. These medicines help prevent blood clots from forming or getting larger.
- Digoxin. This medicine helps the heart beat stronger and pump more blood. Digoxin sometimes is used to control the heart rate if abnormal heart rhythms, such as atrial fibrillation or atrial flutter, occur.
- Oxygen therapy. This treatment raises the level of oxygen in the blood.
- Physical activity. Regular activity may help improve the ability to be active.

Exhibit D. United Therapeutics Historical Stock Price

Endnotes

[1] Martine Rothblatt, interview by Michael Hirshman, Sept 12, 2014. Quoted from "Martine Rothblatt and UCLA Anderson's Greatest AMR Project," UCLA Anderson Teaching Case, July 2014.
[2] http://www.uptodate.com/contents/overview-of-pulmonary-hypertension-in-adults?source=preview&search=pulmonary+hypertension&selectedTitle=3~150&language=en-US&anchor=H3#H4
[3] http://www.pah-info.com/How_common_is_PAH
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