EXECUTIVE INFORMATIONAL OVERVIEW

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Cardiology Focused Biopharmaceutical Opportunity

Snapshot

July 31, 2006

CoTherix, Inc. ("CoTherix" or "the Company") is a biopharmaceutical company focused on licensing, developing, and commercializing therapeutic products for the treatment of **cardiovascular**† disease. The Company's strategy is to in-license products or product candidates that are in mid- to late-stage clinical development. CoTherix currently markets Ventavis® (iloprost) Inhalation Solution, approved by the U.S. Food and Drug Administration (FDA) in December 2004 and launched in March 2005 for the treatment of **pulmonary arterial hypertension (PAH)** in patients with **New York Heart Association (NYHA) Functional Class III** or **IV symptoms** (World Health Organization [WHO] Group I). PAH is a highly debilitating disease characterized by severe constriction of the pulmonary blood vessels, making it difficult for the heart to pump blood through the lungs to be oxygenated. Patients suffer from shortness of breath, fatigue, and have a marked limitation in their physical activities. Ventavis, a synthetic compound, is structurally similar to **prostacyclins**—naturally-occurring molecules that cause the blood vessels to dilate. PAH affects approximately 50,000 patients in the U.S., with only about 30% diagnosed and receiving treatment. To expand its product portfolio, CoTherix in-licensed fasudil on June 23, 2006 from Japan-based Asahi Kasei Pharma to develop the oral and inhaled forms as a treatment for PAH and **chronic stable angina** in North America and Europe. The intravenous form of fasudil is currently approved in Japan for the prevention of **cerebral vasospasm** in patients with **subarachnoid hemorrhage**. Fasudil is the only **rho-kinase** inhibitor that has been tested in clinical trials. With a unique mechanism of action, fasudil has shown promise as a therapy for the management of cardiovascular and pulmonary vascular diseases. CoTherix expects to conduct clinical trials to evaluate fasudil's therapeutic potential.

Recent Financial Data

Ticker (Exchange)	CTRX (NASDAQ)
Recent Price (07/28/06)	$8.28
52-Week Range	$6.70-15.50
Shares Outstanding	28.6 million
Market Capitalization	$236.8 million
Avg. 3-month volume	223,523
Insider Owners +5%	31%
Institutional Owners	60%
EPS (year ended 12/31/05)	($1.01)
Employees (as of 3/31/06)	98

Key Points

- Ventavis (iloprost) Inhalation Solution is the first inhaled prostacyclin therapy for PAH approved and marketed in the U.S. The solution is delivered via a battery-powered inhalation device that weighs less than eight ounces and allows for precise administration. The device is non-invasive and eliminates the need for in-dwelling catheters—factors that CoTherix believes provide an advantage over other traditionally used **subcutaneously**- and **intravenously**-delivered prostacyclin therapies for PAH.
- CoTherix licensed the exclusive U.S. rights to Ventavis for the treatment of PAH from the German pharmaceutical company Schering AG (now Bayer-Schering AG), which currently markets Ventavis in 12 European Union countries, Australia, Argentina, the Republic of Korea, and Norway. CoTherix has **orphan drug** exclusivity for Ventavis in the U.S. for use in treating PAH through December 2011.
- Ventavis sales for the first quarter of 2006 were $14.5 million and $23.9 million for its first 10 months on the market through December 2005 (March 2005 launch). CoTherix issued 2006 sales guidance of between $65-$70 million.
- On June 23, 2006, CoTherix in-licensed the rights to develop and commercialize fasudil in North America and Europe for use in patients with both PAH and chronic stable angina. CoTherix also has an option for the rights to other indications (excluding stroke and eye diseases). Research in the past decade has shown that excess rho-kinase is involved in the **pathophysiology** of numerous vascular diseases, including PAH, atherosclerosis, and hypertension.
- The Company's cash, cash equivalents, and securities available for sale stands at $98 million as of March 31, 2006.

†**BOLD** WORDS ARE REFERENCED IN GLOSSARY ON PAGES 60-63.

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Executive Overview

CoTherix, Inc. ("CoTherix" or "the Company") is a biopharmaceutical company focused on licensing, developing, and commercializing therapeutic products for the treatment of cardiovascular disease. The Company's strategy is to in-license products or product candidates that are in mid- to late-stage clinical development. CoTherix currently markets Ventavis (iloprost) Inhalation Solution in the U.S. to treat pulmonary arterial hypertension (PAH) and has recently in-licensed oral and inhaled forms of a clinical stage product, fasudil, from the Japanese firm Asahi Kasei Pharma (Asahi Kasei) as a treatment for PAH (in both forms) and chronic stable angina (in oral form). The Company also has an option for the rights to other indications (excluding stroke and eye diseases). These products are briefly described below and in greater detail within the Core Story section (pages 12-29) of this Executive Informational Overview® (EIO®).

Ventavis (iloprost) Inhalation Solution

CoTherix markets Ventavis (iloprost) Inhalation Solution, an inhaled product to treat pulmonary arterial hypertension (PAH), WHO Group I, a highly debilitating disease characterized by severe constriction of the blood vessels of the lungs and high pulmonary arterial pressure, often resulting in early death. Approved in December 2004 and launched in March 2005, Ventavis specifically targets patients with New York Heart Association (NYHA) Functional Class III or IV symptoms (as defined in Table 1), where there is a marked limitation of physical activity and/or the inability to carry out any physical activity.

Table 1

NYHA FUNCTIONAL CLASS

Class	Patient Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

Source: Heart Failure Society of America.

Ventavis, a synthetic compound, is structurally similar to prostacyclins, naturally occurring molecules that cause blood vessels to dilate. It is the only product in the prostacyclin family approved for inhalation. Ventavis solution is delivered to patients using either the I-neb™ AAD® System, a battery-powered inhalation device, or the Prodose® AAD® System. As an inhaled drug, Ventavis avoids many of the shortcomings associated with other prostacyclin treatments, such as needles, catheters, and pumps. Additionally, by targeting the pulmonary vessels directly through inhalation into the lungs, many of the potential side effects associated with subcutaneous or intravenous delivery can be reduced or eliminated, as described on page 14.

In the pivotal study for Ventavis conducted by Schering AG (now Bayer-Schering AG), patients demonstrated increased exercise capacity and ability to carry out their daily activities (improvement in NYHA Class), representing a material improvement in quality of life.

CoTherix estimates that PAH afflicts approximately 50,000 people in the U.S., with only approximately 16,000 people (or approximately 30%) currently diagnosed and being treated. CoTherix believes that the number of patients under treatment could grow to approximately 23,000 by the end of 2010 due to increased awareness of PAH among healthcare professionals, earlier diagnosis, and the introduction of new patient-friendly treatment options.

CoTherix licensed the exclusive rights to develop and commercialize Ventavis for the treatment of PAH in the U.S. from Schering AG (now Bayer-Schering AG) of Germany, which currently markets the drug in 12 European Union countries, Australia, Argentina, the Republic of Korea, and Norway. CoTherix maintains orphan drug exclusivity in the U.S. for the drug's use in treating PAH through December 2011. Orphan drug exclusivity is a designation given to a rare disease that affects fewer than 200,000 people in the U.S.

Ventavis sales for the first quarter of 2006 were $14.5 million and $23.9 million for its first 10 months on the market (noting that the product was launched in March 2005). CoTherix issued 2006 sales guidance in its most recent quarter for between $65-70 million.

Fasudil

On June 23, 2006, CoTherix licensed a second drug, fasudil, a rho-kinase inhibitor as a potential therapy for patients with both PAH and chronic stable angina (also known as stable angina). CoTherix licensed the right to develop both oral and inhaled dosages of fasudil for PAH and oral dosages for stable angina in North America and Europe from the Japanese firm Asahi Kasei (http://www.asahi-kasei.co.jp/) and has an option to expand into other potential indications (excluding stroke and eye diseases).

CoTherix intends to develop fasudil in its territory as a treatment for both PAH and stable angina. PAH is defined as abnormally high blood pressure in the arteries between the heart and lungs. Over time, PAH causes the pulmonary arteries to stiffen and narrow, making the heart work harder and thus eventually leading to **right heart failure** and ultimately death.

Chronic stable angina is a condition resulting from an imbalance of oxygen supply and demand to the heart muscle, marked by recurrent episodes of discomfort in the chest, jaw, shoulder, back, or arm. Stable angina is usually the result of **coronary artery disease (CAD)**, caused by a narrowing of coronary arteries due to **atherosclerosis**, although it may also occur in patients with disease of the heart valves, **hypertrophic cardiomyopathy**, and uncontrolled hypertension. CAD is a leading cause of death in the developed world.

According to the American Heart Association's (AHA) report on Heart Disease and Stroke Statistics, updated in 2006, the **incidence** of stable angina in the U.S. is approximately 400,000 and the **prevalence** is 6.5 million. Incidence and prevalence patient populations are anticipated to grow at a rate of 1% per year through 2015. CoTherix believes that the market size for fasudil could be approximately 900,000 patients based on a target population comprised of:

(1) patients who are not well controlled with current treatment, and

(2) patients who have undergone **revascularization** procedures, but who still require anti-anginal therapy and are not well controlled with their current treatment.

As a rho-kinase inhibitor, fasudil could become the first in a new class of agents approved to treat pulmonary hypertension and stable angina that offers a unique mode of action. Fasudil is currently the only rho-kinase inhibitor that has been tested in clinical trials. The intravenous formulation is approved in Japan for the prevention of **vasospasm** in patients with subarachnoid hemorrhage.

History, Headquarters, and Employees

CoTherix was incorporated in February 2000 as Exhale Therapeutics, Inc. and changed its name in October 2003 to CoTherix, Inc. CoTherix held its initial public offering (IPO) in October 2004, raising approximately $25.2 million. In February 2005, the Company closed a follow-on offering of 4,250,000 shares of its Common Stock at a price to the public of $8.90 per share. In October 2005, CoTherix closed another secondary offering, selling 4,337,500 shares at $13.00, raising approximately $52 million. The Company is headquartered in South San Francisco, California and as of March 31, 2006, employed 98 individuals, including 24 people as professional sales representatives.

Growth Strategy

CoTherix seeks to become a leading provider of therapeutic products for cardiovascular diseases. The Company expects to implement the following key elements as part of its growth strategy:

- Broaden its portfolio by in-licensing or acquiring complementary mid- to late-stage clinical products that target highly concentrated markets in the area of cardiovascular diseases. A key element of this strategy has been accomplished by the in-licensing of fasudil from Asahi Kasei, which was announced on June 23, 2006;

- Complete clinical development of fasudil and/or establish strategic collaborations to exploit the Company's pipeline potential;

- Market and commercialize directly, or co-promote as appropriate for stable angina; and

- For PAH, market and commercialize directly with internal sales force.

Intellectual Property

The Company's composition of matter patent covering iloprost expired in September 2004 and the U.S. process patents covering the manufacture of Ventavis will expire in 2007 and 2010. Ventavis has orphan drug exclusivity for the treatment of PAH through December 2011, which could help protect its competitive position in the market. Therefore, the Company may no longer depend on this composition of matter patent and in the future is not likely to be able to rely on these process patents to exclude competitors from developing iloprost for the treatment of PAH.

The composition of matter patent covering fasudil will expire in 2016 and the extended-release oral fasudil patent will expire in 2019. There is a pending application with respect to the sustained-release method of manufacturing.

Management and Board of Directors

Management

Members of CoTherix's management team and Board of Directors have experience in the life sciences industry, specifically in the cardiovascular and pulmonary arenas. Several of these individuals came from Scios Inc. (now a member of the Johnson & Johnson [JNJ-NYSE] family of companies), where they built the sales and marketing function and guided the successful launch of Natrecor®, a novel product used to treat acute heart failure. Table 2 summarizes CoTherix's management team, followed by detailed biographies.

Table 2
CoTherix, Inc.
MANAGEMENT

Donald Santel	Chief Executive Officer and Co-Founder
Thomas Feldman	President and Chief Business Officer
Christine Gray-Smith	Executive Vice President and Chief Financial Officer
Dr. James Pennington	Executive Vice President and Chief Medical Officer
Dr. Abhay Joshi	Executive Vice President and Chief Technical Officer
Benson Fong	Senior Vice President, Corporate Development
George Mahaffey	Senior Vice President, Sales and Marketing
Robert Michitarian	Vice President and General Counsel

Source: CoTherix, Inc.

Donald Santel, Chief Executive Officer and Co-Founder

Mr. Donald Santel joined CoTherix in February 2000 as president and a member of the Board of Directors, and in 2004, was promoted to chief executive officer (CEO). Prior to CoTherix, Mr. Santel played a key role in the development of two San Francisco Bay area-based medical device start-ups, serving as president and chief operating officer (COO) of Reflow, Inc. and as general manager of CardioVasc, Inc. From 1992 to 1997, he held various positions at Cardiac Pathways Corporation, including vice president of marketing and international sales and vice president of clinical engineering. From 1982 to 1991, he was with Medtronic, Inc. (MDT-NYSE). Mr. Santel earned an M.S. in electrical engineering from the University of Minnesota and a B.S.E. in biomedical engineering from Purdue University.

Thomas Feldman, President and Chief Business Officer

Mr. Thomas Feldman joined CoTherix in December 2003 as executive vice president and chief commercial officer and was promoted to president and chief business officer in August 2004. A 30-year veteran of the life sciences industry, Mr. Feldman most recently served in a consulting capacity as acting vice president of sales and marketing at Genesoft Pharmaceuticals, Inc., and earlier as vice president of sales and marketing at Scios, where he helped build Scios' cardiovascular sales and marketing organization for the launch of Natrecor® (nesiritide). Prior to joining Scios, Mr. Feldman spent 22 years with companies in the Johnson & Johnson family, concluding as national sales manager for Ortho Pharmaceutical Corporation. Mr. Feldman received his B.S. in business and speech from North Dakota State University.

Christine Gray-Smith, Executive Vice President and Chief Financial Officer

Ms. Christine Gray-Smith joined CoTherix in April 2004 as executive vice president and chief financial officer (CFO). From June 2001 to April 2004, Ms. Gray-Smith served as CFO of Triad Therapeutics Inc., a biopharmaceutical company, and was promoted to senior vice president in 2003. From November 1997 to May 2001, Ms. Gray-Smith served as vice president of finance and CFO at Calydon, Inc., a biotechnology company. From August 1994 to November 1997, Ms. Gray-Smith served as the senior financial officer at

SUGEN, Inc., a biopharmaceutical company now part of Pfizer, Inc. (PFE-NYSE), with her most recent title being vice president of finance. From 1988 to 1994, Ms. Gray-Smith held senior management positions with companies in the software industry. Ms. Gray-Smith also spent nine years with the international accounting firm of Arthur Young & Company (predecessor to Ernst & Young LLP). Ms. Gray-Smith holds a B.A. in sociology from the University of California, Berkeley and an M.B.A. from the Haas School of Business at the University of California, Berkeley.

Dr. James Pennington, Executive Vice President and Chief Medical Officer

Dr. James Pennington joined CoTherix in February 2004 as an executive vice president and the chief medical officer. Dr. Pennington is an 18 year veteran of the pharmaceutical industry and also has an academic background in medicine, having spent 12 years as a member of the Harvard Medical School faculty. Dr. Pennington most recently served as executive vice president of medical and scientific affairs at InterMune, Inc. (ITMN-NASDAQ), where he was responsible for conducting over 30 Phase II and Phase III clinical trials. Prior to joining InterMune, Dr. Pennington was senior vice president of research, development, and clinical affairs at Alpha Therapeutic Corporation. Prior to this, he spent 11 years with Bayer Corporation's (BAY-NYSE) Pharmaceutical Division as vice president of Biological Clinical Research. Dr. Pennington received his B.A. and M.D. from the University of Oregon.

Dr. Abhay Joshi, Executive Vice President and Chief Technical Officer

Dr. Abhay Joshi joined CoTherix in April 2006 as executive vice president and chief technical officer. Dr. Joshi most recently served as the vice president of global technical operations, specialty pharmaceuticals at Allergan, Inc. (AGN-NYSE). At Allergan, he managed the Company's global biologics manufacturing operations for BOTOX® and also managed Allergan's Latin America and Asia Pacific pharmaceutical operations. Dr. Joshi received his BTech in chemical engineering from the Indian Institute of Technology, New Delhi. He also earned an MSE and a Ph.D. in chemical engineering from the University of Michigan, Ann Arbor, and received an M.B.A. from the University of California, Irvine. Dr. Joshi holds an adjunct faculty appointment at the University of Southern California School of Pharmaceutical Sciences and is a member of the Industrial Society of Pharmaceutical Engineers.

Benson Fong, Senior Vice President, Corporate Development

Mr. Benson Fong joined CoTherix in March 2002 as CFO and became vice president, corporate development in April 2004. He has been responsible for business development and licensing since joining the Company. Prior to joining CoTherix, he was a principal at The Ravix Group Inc., a financial consulting firm. From 1998 to 2000, Mr. Fong was a first vice president at Imperial Bank's Emerging Growth Division, where he structured debt financing for life science and high technology clients. From 1992 to 1997, he was CFO of Cibus Pharmaceuticals, Inc., a drug delivery company. Mr. Fong earned a B.S. in biology from the University of Oregon.

George Mahaffey, Senior Vice President, Sales and Marketing

Mr. Mahaffey joined CoTherix in March 2004 as vice president of marketing and was promoted to senior vice president of sales and marketing in September 2005. Most recently, Mr. Mahaffey was senior director, marketing and business development at Scios, where from 2000 to 2004, he built the marketing function and guided the highly successful commercialization and launch strategy for Natrecor. From 1997 to 2000, he was employed in sales and marketing roles at Neurex, Inc. Mr. Mahaffey previously worked at DuPont Co. (DD-NYSE) for 18 years in various engineering and pharmaceutical sales positions. He holds a B.S. in chemical engineering from the University of Delaware and an M.B.A. from the University of South Florida.

Robert Michitarian, Vice President and General Counsel

Mr. Robert Michitarian joined CoTherix in February 2005 as vice president and general counsel. From December 2001 to February 2005, Mr. Michitarian served as associate general counsel of Affymetrix, Inc. (AFFX-NASDAQ), where he helped to launch Affymetrix's diagnostics business. Prior to joining Affymetrix, Mr. Michitarian was vice president, general counsel, and secretary of Blaze Software, Inc. and its successor Brokat Technologies Inc., managing Blaze's initial public offering (IPO) and its acquisition

by Brokat. From 1998 to 2000, Mr. Michitarian was corporate counsel at Genentech, Inc. (DNA-NYSE), where he handled Genentech's acquisition by Roche and its subsequent IPO. From 1994 to 1998, Mr. Michitarian was associated with the law firm of Latham & Watkins. Mr. Michitarian holds a B.A. in political science from Stanford University and a J.D. from the University of Virginia, where he was a member of the Virginia Law Review and its Managing Board.

Board of Directors

CoTherix's Board of Directors oversees the conduct of and supervises the Company management. Table 3 provides a summary of board members, followed by detailed biographies.

Table 3
CoTherix, Inc.
BOARD OF DIRECTORS

Bradford S. Goodwin	Chairman
Robert B. Chess	Director
David W. Gryska	Director
Dr. James I. Healy, M.D., Ph.D.	Director
Daniel S. Janney	Director
Howard B. Rosen	Director
Donald J. Santel	Director
Nicholas J. Simon, III	Director

Source: CoTherix, Inc.

Bradford S. Goodwin, Chairman

Mr. Bradford S. Goodwin joined CoTherix's Board of Directors in January 2004 and was appointed chairman in September 2004. Since December 2001, Mr. Goodwin has served as CEO and a director of Novacea, Inc. (NOVC-NASDAQ), an oncology drug development and commercialization company. From April 2000 to July 2001, Mr. Goodwin was president, chief operating officer, and founder of Collabra Pharma Inc., a pharmaceutical development company. From 1987 to 2000, Mr. Goodwin held various senior executive positions with Genentech, Inc., most recently vice president of finance. Mr. Goodwin holds a B.S. in business administration from the University of California, Berkeley. Mr. Goodwin also serves on the boards of PDL Biopharma, Inc. (PDLI-NASDAQ), formerly called Protein Design Labs.

Robert B. Chess, Director

Mr. Robert B. Chess joined CoTherix's Board of Directors in April 2004. Mr. Chess has been the chairman of the Board of Directors at Nektar Therapeutics (NKTR-NASDAQ), formerly Inhale Therapeutic Systems, a drug delivery company, since 1999 and served as Nektar's co-CEO from 1999 to 2001, as CEO from 1992 to 1999, and as president from 1991 to 1992. From 1987 to 1989, Mr. Chess was the co-founder and president of Penederm, Inc., a dermatological pharmaceutical company. Prior to co-founding Penederm, Mr. Chess held various management positions at Intel Corporation (INTC-NASDAQ) and Metaphor Computer Systems (now part of IBM Corp. [IBM-NYSE]), and was a White House Fellow during the George H.W. Bush administration, serving as associate director, office of policy development. Mr. Chess serves on the Board of Directors of the Biotechnology Industry Organization (BIO) and is co-chairman of BIO's Intellectual Property Committee. Mr. Chess is a member of the Board of Directors of Pharsight Corporation (PHST.OB-OTC.BB) as well as a trustee of the Committee for Economic Development. He is also on the faculty of the Graduate School of Business at Stanford. Mr. Chess holds a B.S. degree in engineering from the California Institute of Technology and an M.B.A. from Harvard Business School.

David W. Gryska, Director

Mr. David W. Gryska joined CoTherix's Board of Directors in December 2004, and also serves as chairman of the Audit Committee. Most recently, Mr. Gryska served for six years as senior vice president and CFO at Scios, where he led the transaction effort for the successful sale of the company to Johnson & Johnson for $2.5 billion in February 2003. From 1993 to 1998, he served as vice president and CFO at Cardiac Pathways, a company later acquired by Boston Scientific Corporation (BSX-NYSE). Prior to Cardiac Pathways, Mr. Gryska served as a partner at Ernst & Young. During his eleven years there, he focused on technology industries, with an emphasis on biotechnology and healthcare companies. Mr. Gryska holds a B.A. in accounting and finance from Loyola University and an M.B.A. from Golden Gate University.

James I. Healy, M.D., Ph.D., Director

Dr. James I. Healy joined CoTherix's Board of Directors in April 2001. Since June 2000, Dr. Healy has served as managing director of Sofinnova Ventures, a venture capital firm focusing on life sciences investments. From January 1998 to March 2000, Dr. Healy was employed at Sanderling Ventures, a venture capital firm. During 1997, Dr. Healy was a Novartis Foundation Bursary Award recipient and performed research at Brigham and Women's Hospital. From August 1990 to July 1997, Dr. Healy was employed by the Howard Hughes Medical Institute and Stanford University. Dr. Healy serves on the Boards of Directors of InterMune, Inc. (ITMN-NASDAQ) and several private companies. Dr. Healy holds B.A. degrees in molecular biology and Scandinavian studies from the University of California, Berkeley, and an M.D. and Ph.D. in immunology from the Stanford School of Medicine.

Daniel S. Janney, Director

Mr. Daniel S. Janney joined CoTherix's Board of Directors in April 2001. Since 1996, Mr. Janney has been a managing director of Alta Partners, a venture capital firm focused on life sciences investments. Prior to joining Alta, he was a senior investment banker at Montgomery Securities, where his responsibilities included public offerings, strategic advisory assignments and advice on mergers, acquisitions, and divestitures for life sciences companies. Mr. Janney is currently on the Board of Directors of a number of private and public companies, including Corgentech Inc. (CGTK-NASDAQ) and Dynavax Technologies, Inc. (DVAX-NASDAQ), where he is a founder and chairman of the board. In addition, he led Alta's investments in Endonetics, Ilex Oncology, InterMune, and LJL Biosystems. Mr. Janney is also a member of the advisory board for the Rebecca and John Moores Cancer Center at University of California, San Diego. He holds a B.A. in history from Georgetown University and an M.B.A. from the Anderson School at the University of California, Los Angeles.

Howard B. Rosen, Director

Mr. Howard B. Rosen joined CoTherix's Board of Directors in September 2005. Mr. Rosen is currently vice president, commercial strategy for Gilead Sciences, Inc. (GILD-NASDAQ), where he is responsible for global brand strategy, new product planning, and project management for late stage drug development programs. Prior to joining Gilead, Mr. Rosen spent 10 years at ALZA Corporation (a member of the Johnson & Johnson family of companies), where he most recently served as its president. Previously, Mr. Rosen led the west coast strategy practice of Integral, Inc. (now Analysis Group, Inc.), was director, corporate development at GenPharm International, Inc., now a part of Medarex, Inc. (MEDX-NASDAQ), and was a consultant in the San Francisco office of McKinsey & Co. Mr. Rosen serves as a director on the board of Pharsight Corporation (PHST.OB-OTC.BB), a provider of software and strategic services designed to optimize clinical drug development. He is also a member of the National Academy of Engineering and the Stanford University Advisory Council on Interdisciplinary Biosciences and the School of Engineering. Mr. Rosen holds an M.B.A. from the Stanford Graduate School of Business, where he graduated first in his class as the Henry Ford II Scholar. He also holds an M.S. in chemical engineering from the Massachusetts Institute of Technology (MIT). Mr. Rosen graduated with distinction from Stanford University with a B.S. in chemical engineering. He is co-inventor on seven U.S. patents.

Donald J. Santel, Director

Biography on page 7.

Nicholas J. Simon, III, Director

Mr. Nicholas J. Simon, III joined CoTherix's Board of Directors in October 2003. Mr. Simon has been a managing director of Clarus Ventures LLC, a company he co-founded in 2005. Since October 2001, Mr. Simon has also been a general partner in MPM BioVentures III. From 2000 to July 2001, Mr. Simon was CEO, founder, and a director of Collabra Pharma Inc., a pharmaceutical licensing and development company. From 1989 to March 2000, Mr. Simon served in various management positions with Genentech, including vice president of business and corporate development. Mr. Simon served on the Board of Directors of InterMune Inc., Genitope, Inc., Sangstat, Inc., and Rigel Pharmaceuticals Inc. (RIGL-NASDAQ), and is currently on the Board of Directors of Barrier Therapeutics, Inc. (BTRX-NASDAQ), as well as several private companies. Mr. Simon holds a B.S. in microbiology from the University of Maryland and an M.B.A. from Loyola College.

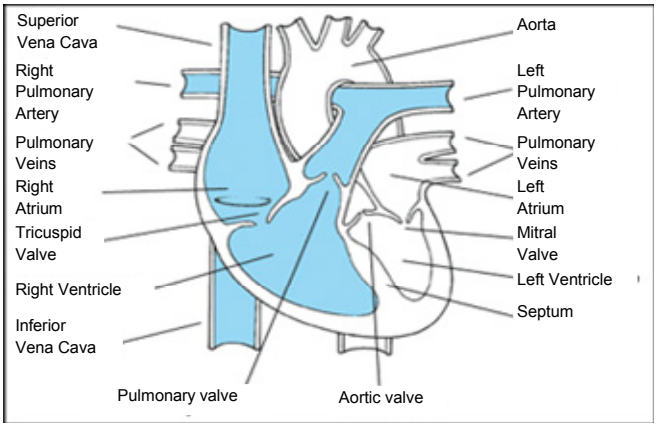
Core Story

CoTherix, Inc. ("CoTherix" or "the Company") is a biopharmaceutical company focused on licensing, developing, and commercializing therapeutic products for the treatment of cardiovascular disease. The Company's strategy is to in-license products that are in mid- to late-stage clinical development. CoTherix currently markets Ventavis® (iloprost) Inhalation Solution to treat pulmonary arterial hypertension (PAH) and has recently in-licensed fasudil from the Japanese firm Asahi Kasei Pharma (Asahi Kasei) to develop oral and inhaled forms as a treatment for PAH and oral forms as a treatment for chronic stable angina. These products are described within the accompanying section. An introduction to PAH is provided as a foundation for a discussion of Ventavis and fasudil (a rho-kinase inhibitor). An introduction to chronic stable angina is also provided followed by a detailed discussion of fasudil and the role of the rho-kinase pathway in the physiology and pathophysiology of cardiovascular and pulmonary vascular disease.

PULMONARY ARTERIAL HYPERTENSION (PAH)

Pulmonary arterial hypertension (PAH) is a disorder where there is continuously high blood pressure in the pulmonary arteries. The average blood pressure in a normal pulmonary artery is approximately 14 mmHg when a person is at rest; in PAH, however, the average blood pressure is usually greater than 25 mmHg. Patients with PAH are known to have higher levels of **endothelin**, a **vasoconstrictor**, and lower levels of prostacyclin, a **vasodilator**. As a result, those affected are often tired and have difficulties carrying out daily activities since breathing often becomes challenging.

Figure 1
CIRCULATION OF THE BLOOD



Source: Pulmonary Hypertension Association (UK).

The pulmonary arteries are the blood vessels that carry oxygen-poor blood from the right ventricle—one of the pumping chambers of the heart—to the lungs. Once the blood is oxygenated in the lungs, it is carried back to the left side of the heart by the pulmonary veins. The oxygenated blood is then pumped to the rest of the body by the left ventricle through the aorta (the largest vessel in the blood). The blood is subsequently carried to the body by the systemic arteries, where the muscles and organs extract the oxygen. Once the oxygen has been extracted, the blood is carried back to the right side of the heart by the systemic veins (the inferior and superior vena cava). The cycle is continuously repeated. The parts of the heart involved in the blood's circulation cycle are illustrated in Figure 1.

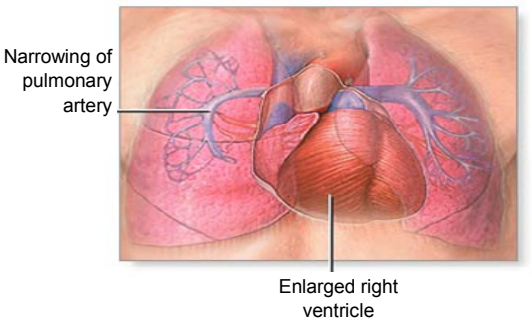
As with any other muscle in the body, the harder the right ventricle is worked, the larger it becomes. However, if the heart has to work harder than usual over a long period of time (months and often years) without a rest, it begins to work much less effectively. When the right ventricle contracts, it applies pressure to the blood within its chamber, forcing the blood through the pulmonary arteries and increasing the pressure within them. Following the contraction of the right ventricle, it relaxes, causing the pressure in the pulmonary arteries to decrease. Thus, the pressure in the pulmonary arteries goes up when it contracts and down when it relaxes.

Throughout periods of exercise, including walking, running, etc., the muscles require greater amounts of oxygen. Consequently, the body adapts to this higher demand for oxygen by increasing the cardiac output, or the amount of blood that the heart pumps, which in turn increases the amount of blood flowing through the lungs. To enable this process, the pulmonary arteries have to be able to dilate and the vessels have to be flexible.

In patients with PAH, the following changes may occur in the pulmonary arteries:

- The muscles within the walls of the arteries may constrict and narrow the **lumen,** and
- The walls of the pulmonary arteries may thicken as the amount of muscle increases, and scar tissue may form (**remodeling**). As the walls thicken and scarring occurs, the arteries become increasingly narrow and noncompliant, as illustrated in Figure 2.

Figure 2
EXAMPLE OF PRIMARY PULMONARY HYPERTENSION



Source: Medline and A.D.A.M. Medical Illustration Team.

Due to these changes, the arteries may stiffen, and over time, may become substantially narrowed. The narrowing of the pulmonary arteries causes the right side of heart to work harder to pump blood through the lungs. Over time, the heart muscle weakens and loses its ability to pump enough blood for the body's needs. This is called right heart failure and is the most common cause of death in people with PAH.

Types of PAH

There are three types of PAH:

(1) **Idiopathic pulmonary arterial hypertension (IPAH)**, which occurs for no known reason;

(2) **Familial pulmonary arterial hypertension (FPAH)**, which is an inherited disorder; and

(3) Pulmonary arterial hypertension associated with other conditions (APAH), which is either caused by or occurs because of another condition, such as connective tissue disease.

Conditions or behaviors with which PAH is often associated are listed in Table 4.

Table 4
COMMON CAUSES OF PAH

- Connective tissue diseases, such as **scleroderma** or **lupus erythematosus**
- Liver disease
- HIV infection
- Chronic use of cocaine or amphetamines
- Use of appetite suppressants, especially fenfluramine and dexfenfluramine

Source: CoTherix, Inc.

Current Treatment Options (Three Classes of Drugs Approved)

There are several treatment options for patients affected with PAH, though there is no known cure. Over the past few years, there has been an increasing awareness of PAH within the healthcare community. Both the medical profession and pharmaceutical companies have focused attention on the disease, resulting in the development of promising new therapies. Three classes of **vasoactive** drugs are currently approved to treat PAH: (1) prostacyclins, (2) **endothelin receptor antagonists (ETRAs)**, and (3) **PDE-5 inhibitors**. Additionally, other classes of drugs are used off-label to treat this condition, such as **calcium channel blockers (CCBs)**. Each of these therapies is described in the accompanying section.

- *Synthetic Prostacyclin.* Synthetic Prostacyclins are chemicals that mimic a substance called **prostaglandin**, which is naturally produced within the body to dilate blood vessels. Individuals with PAH do not produce enough prostaglandin. Therefore, giving patients prostacyclin makes up for this underproduction and helps the body dilate the blood vessels in the lungs. By increasing blood flow through the lungs, these medications increase the amount of oxygen that is carried to the heart and body, making breathing easier.

  Most patients with PAH respond well to prostacyclin treatment. Flolan®, the first approved prostacyclin, is considered the "gold standard" for those with end-stage PAH, since it is the only compound that has mortality data. In fact, studies have shown that between 70% and 80% of patients have lower pulmonary pressure and higher cardiac output after using prostacyclins. There are three approved medications in the prostacyclin group. Each medication is administered in a different way and requires different care.

  (1) Flolan (epoprostenol), marketed by Myogen, Inc. (MYOG-NASDAQ), is continuously pumped into the body through a catheter inserted into a vein in the chest. A surgical procedure is required for insertion of this catheter, called a central line. Flolan is sold as a dry powder that must be mixed with sterile diluent (liquid) every day. Once Flolan is mixed, it must be kept cool and away from light.

  (2) Ventavis (iloprost), distributed by CoTherix, is a form of prostacylin that is inhaled several times a day using either the newly launched I-neb AAD System (described on page 16), which is a compact, lightweight, battery-powered system, or the Prodose AAD System (also described on page 16), a plug-in system. Both are specially designed for use with Ventavis.

  (3) Remodulin® (Treprostinil sodium), marketed by United Therapeutics Corporation (UTHR-NASDAQ), is also a form of prostacyclin available as a continuous subcutaneous or intravenous infusion. The subcutaneous method of infusion reduces the risk of **sepsis** and hospitalization, but the incidence of site pain is extremely high (85% as reported in the product insert). United Therapeutics is also developing oral and inhaled formulations of Remodulin. The inhaled formulation of Remodulin is currently being studied in a Phase II/III study; the oral formulation is going into Phase II trials.

  Since the effects of prostacyclins and prostacyclin analogues are relatively short, Flolan and IV Remodulin are continuously infused by a pump through a permanent catheter. Administration of Flolan, in particular, is complex and requires patients to learn the techniques of sterile preparation. Additionally, both products involve care of a central line. With subcutaneous Remodulin, patients are required to change the site of the external catheter every few days. In some cases, intravenous infusion may create serious complications, including sepsis.

- *Endothelin Receptor Antagonists (ETRAs).* Endothelin is a chemical messenger released by cells that line the inside of the blood vessels. There are many types of endothelin, but all of them are hormones that cause blood vessels to tighten and constrict. Tracleer® (bosentan) was approved by the FDA in December 2001 for PAH. Tracleer was the first oral therapy approved for PAH and is typically used as a first-line treatment. However, because of rare but serious liver toxicity issues, patient liver enzyme levels must be monitored monthly. According to the FDA, the use of Tracleer for persons with PAH may present two significant risks: liver toxicity and potential damage to a fetus.

- *Phosophodiesterase Type 5 Inhibitors (PDE-5 inhibitors).* PDE-5 is a member of the phosphodiesterase family of enzymes that play an important role in cell signaling by hydrolyzing the secondary messengers, cAMP and cGMP. PDE-5 is found in high concentrations in the lungs. Sildenafil inhibits PDE-5 and thus reduces the degradation of cGMP, promoting relaxation of vascular smooth muscle and increasing blood flow. Sildenafil has been widely used for the treatment of **erectile dysfunction (ED)**. It has been re-branded by its manufacturer, Pfizer, and in 2005 was approved for the treatment of PAH under the brand name Revatio™.

- *Calcium Channel Blockers (CCBs).* Calcium channel blockers, also called calcium antagonists, are drugs that relax blood vessels and are used to treat primary PAH. CCB's are designed to prevent the entry of calcium ions into the muscle cells of the heart and blood vessels, causing these vessels to

widen and relax. As a result, blood pressure is lowered and circulation is improved. The resulting effects are an increase in blood and oxygen supply to the heart, coupled with a reduction in myocardial workload. CCBs have been the most widely tested vasodilators, and have been used off-label for PAH. They are also a treatment for stable angina (described on page 21).

In addition to the aforementioned treatment options for PAH, inhaled nitric oxide has been used in PAH patients to relax the blood vessels in the lungs while minimizing effects on systemic blood vessels. Nitric oxide is a short acting agent that has been shown to specifically affect pulmonary circulation. It is used primarily in hospitals in the peri-operative setting.

Treatments in Development

There are also a number of potential PAH treatments in development. These include additional oral ETRAs such as Encysive Pharmaceuticals' (ENCY-NASDAQ) Thelin® (sitaxsentan) and Myogen's ambrisentan. Encysive recently submitted a complete response to the FDA after Thelin received an "approvable" letter from the FDA, indicating that additional information is required before full approval is granted. Myogen is currently preparing its **New Drug Application (NDA)** submission for ambrisentan. Eli Lilly & Company (LLY-NYSE) and ICOS (ICOS-NASDAQ) are conducting a trial for Cialis® (tadalafil), a long-acting PDE-5 inhibitor. Antiproliftive agents, such as Novartis' (NVS-NYSE) Gleevec® (imatinib mesylate), a tyrosine kinase inhibitor, are also being investigated.

Market Size

The current size of the PAH population in the U.S is approximately 50,000 patients (with approximately 16,000 patients currently receiving treatment). The value of the PAH market is fairly large since effective therapies command high prices due to the seriousness of the disease. Current treatment regimens can cost between $10,000 and $250,000 per year. Ventavis, CoTherix's product, as well as four other PAH therapies, are currently approved in the U.S.—two of these being the prostacyclin/prostacyclin analogues that require needles, catheters, and pumps (described on page 14). It is estimated that approximately 500 to 600 physicians account for approximately 80% of the PAH prescriptions written—with most of these clinicians located at tertiary care medical centers.

Ventavis (iloprost) Inhalation Solution

Ventavis is an inhaled form of prostacyclin used to treat PAH patients, WHO Group I, with NYHA III or IV symptoms, described in Table 1, page 3. Its active ingredient is iloprost. Inhalation of Ventavis allows for the direct delivery of drug to the pulmonary vessels. Approved by the FDA on December 29, 2004, Ventavis is the only inhaled prostacyclin on the market. In controlled trials, Ventavis' efficacy was measured using a composite endpoint consisting of exercise **tolerance**, functional improvement according to NYHA Functional Class, and lack of deterioration.

Existing therapies have made a significant impact in treating PAH. Unfortunately, these therapies are only **palliative** for the vast majority of patients. While the preponderance of treatment and outcome data from trials utilized a single therapy, combining different classes of vasoactive drugs has been shown to be physiologically supported and is often used in clinical practice. CoTherix conducted the STEP Trial, which assessed the combination therapy approach of adding Ventavis to Tracleer therapy. The combination was well tolerated by and provided a clinical benefit to the patients (see STEP Trial discussion, page 17).

Efficacy

The accepted method of determining whether a drug provides a clinical benefit to PAH patients is to measure the change in six minute walk distances post-treatment over baseline. The pivotal study for Ventavis (performed by Schering AG) was a randomized, double-blind, placebo-controlled Phase III clinical trial in 203 adult patients with stable PAH. Iloprost or placebo was added to patients' current therapy, which could include a combination of **anti-coagulants**, traditional vasodilators, **diuretics**, oxygen, and **digitalis**, but *no* prostacyclin or any of its analogues.

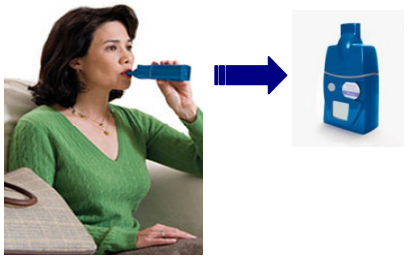
Results showed that patients who took Ventavis were able to increase the distance they could walk in six minutes by an average of 36 meters after just 12 weeks of treatment. According to the study's results, approximately 24% of patients in the Ventavis group, compared with approximately 13% of patients in the placebo group, demonstrated at least a one class improvement in NYHA classification—a result that was statistically significant. A one-step progression from a higher to a lower class represents a significant improvement in a patient's quality of life. Furthermore, use of Ventavis has been shown to reduce pulmonary artery pressure and pulmonary vascular resistance.

Delivery Devices

Figure 3
CoTherix, Inc.
PRODOSE AAD SYSTEM

Source: CoTherix, Inc.

Figure 4
CoTherix, Inc.
THE I-NEB SYSTEM



Source: CoTherix, Inc.

Ventavis (iloprost) Inhalation Solution is delivered to patients using either the Prodose AAD System by Profile Drug Delivery, Ltd., a wholly owned subsidiary of Respironics, Inc., or the I-neb AAD System by Respironics Inc. Respironics granted CoTherix an exclusive U.S. license to distribute the Prodose and I-neb devices with Ventavis and any other formulation of iloprost for the treatment of PAH. Each of these delivery devices is described below.

Prodose

The Prodose AAD System (Prodose), illustrated in Figure 3, is a delivery system based on Adaptive Aerosol Delivery (AAD) technology. The System utilizes a disc, which is pre-programmed to deliver a specific dose. Aerosol is delivered in pulses during the patient's inspiration. AAD offers advantages over other devices since it adapts to the patient's own breathing pattern, resulting in optimized delivery for each patient. The device automatically stops delivering medication when dosing is complete.

I-Neb

The I-neb AAD System, illustrated in Figure 4, was launched in December 2005 and is intended to replace the Prodose AAD System. The I-neb has the same AAD technology as the Prodose, however, since it is battery-operated, weighs less than eight ounces, and can be carried discreetly in purse, pocket, or briefcase, it offers more portability than the Prodose.

Benefits

Although Ventavis has benefits that are similar to those of other prostacyclin therapies, the product's method of delivery is unique in some important ways, highlighted in Table 5.

Table 5
CoTherix, Inc.
BENEFITS OF VENTAVIS

- the first inhaled prostacyclin therapy approved by the FDA
- delivered into the lungs without needles, catheters, or pumps
- no mixing or refrigeration
- no catheters and thus no need to worry about the infections that can sometimes occur with central lines
- no pain caused by needles
- no reports of rebound, that is, a precipitous and potentially deadly rise in pulmonary blood pressure that can occur when the delivery of a continuous parental prostacyclin is interrupted due to catheter blockage or pump failure
- usually taken during waking hours only, when patients are more active and symptoms are at their worst

Source: CoTherix, Inc.

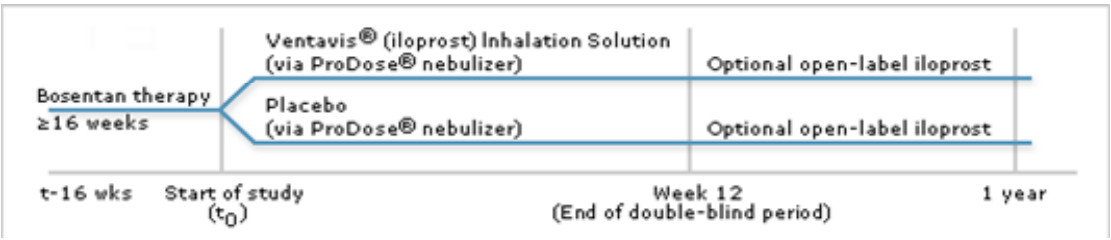
Because Ventavis is delivered non-invasively, via inhalation, it is unique compared to other marketed prostacyclin therapies. Other prostacyclin treatments require continuous delivery through subcutaneous or intravenous routes, and may cause complications associated with chronic indwelling catheters. Ventavis targets the pulmonary vessels directly through inhalation into the lungs, potentially reducing many of the side effects associated with subcutaneous or intravenous delivery. Through the AAD technology, a patient is assured of receiving the correct amount of medication, since the device continues to deliver drug until the patient receives the proper dose. A buzzer sounds to signal that the treatment is complete.

Clinical Development

STEP Trial

CoTherix completed a Phase II trial, called the STEP trial (acronym for iloprost inhalation solution **S**afety and pilot efficacy **T**rial in combination with bosentan for **E**valuation in **P**ulmonary arterial hypertension), assessing the safety and clinical benefit of adding Ventavis to Tracleer (bosentan). The primary endpoint was safety of add-on therapy with Ventavis. However, the potential to provide patients with additional symptomatic relief and increased exercise capacity was also evaluated. A depiction of the STEP trial design is provided in Figure 5.

Figure 5
CoTherix, Inc.
STEP TRIAL DESIGN



Source: CoTherix, Inc.

The study was a randomized double-blind, parallel-group, placebo-controlled multi-center investigation in 65 subjects with PAH at 15 study sites. Subjects being treated with Tracleer who had NYHA Class III or IV symptoms were randomized to one of two treatments: iloprost inhalation solution (2.5 µg or 5 µg per inhalation) or matching placebo for 12 weeks.

The Prodose nebulizer was used to administer the study drug. Subjects were treated with iloprost or placebo in addition to their background therapy for PAH (including bosentan). The proposed dosing regimen was six to nine times daily upon awakening, at bedtime, and four to seven times in between, at intervals of approximately two to three hours. The primary endpoint was safety, with pilot efficacy also evaluated.

The data from this study, which was announced on October 2005, showed that the combination of Ventavis added to bosentan therapy was well tolerated and provided clinical benefit in patients with PAH. It is noteworthy that Ventavis is increasingly becoming the first prostacyclin therapy used for patients sub-optimally managed by oral therapies.

CoTherix believes that Ventavis could become a preferred choice of prostacyclin for these patients. In August 2005, based on the 12-week double-blind phase of the STEP trial, the FDA approved the expansion of the Ventavis label to include information regarding the tolerability and dosing of Ventavis in combination with bosentan.

ACTIVE Trial

CoTherix initiated a Phase II clinical trial, known as the ACTIVE trial, in June 2005 to evaluate the effectiveness of Ventavis in treating patients with pulmonary hypertension associated with **idiopathic pulmonary fibrosis (IPF)**. IPF is a progressive and potentially fatal disease that results in **fibrosis**, or scarring of the lungs. It is estimated that pulmonary hypertension associated with IPF may effect roughly 10,000 individuals in the U.S. (a 20% subset of the estimated 50,000 PAH population).

CoTherix believes that Ventavis could be an effective therapy for this indication in some of these patients. The Company reported that enrollment in this trial is now complete and results are expected to be available in the second half of 2006. The trial, initiated in mid-2005, is a placebo-controlled, 12-week study in 50 patients with moderate disease randomized to receive Ventavis at its labeled dose or placebo. The primary endpoint of the study is to be safety, with a 6-minute walk evaluated at baseline, 4, 8, and 12 weeks.

VISION Trial

In March 2006, CoTherix began a Phase III clinical trial called the VISION (**V**entavis **I**nhalation with **S**ildenafil to **I**mprove and **O**ptimize Pulmonary Arterial Hypertensio**N**) trial to evaluate the safety and efficacy of adding Ventavis as a treatment for PAH patients already receiving sildenafil (Revatio or Viagra®). The study is expected to enroll 180 patients and have three arms: (1) sildenafil alone, (2) sildenafil plus Ventavis taken six times a day, and (3) sildenafil plus Ventavis taken four times a day. The primary endpoint is an increase in six-minute walk distance assessed at 16 weeks. Other endpoints are improvement in NYHA functional class (as defined in Table 1, page 3), delay in time to clinical deterioration, **hemodynamics** (measurements of pulmonary artery pressure and resistance), and safety. Data from this trial is expected in late 2007.

A 30-patient study published in April 2002 showed that sildenafil may have synergistic effects with Ventavis, producing longer lasting pulmonary vasodilatation. In the study, Ventavis alone provided a pulmonary artery vasodilatory response for 60-90 minutes and sildenafil alone reached its maximum effect within 15-45 minutes, but was still effective after 120 minutes. The overall vasodilatory response to the drugs combined, however, lasted past the 180-minute observation period of the study. The VISION trial is important since it could expand the perceived utility of Ventavis as well as strengthen the product's competitive position.

REVEAL Registry™

On March 29, 2006, CoTherix announced enrollment of the first patient in its REVEAL Registry (**R**egistry to **EV**aluate **E**arly **A**nd **L**ong-term PAH disease management). The REVEAL Registry is a longitudinal, open-label, national disease registry. It is designed to prospectively and retrospectively collect observational data to track and study the natural history and medical management of U.S. patients with PAH (WHO Group I). The REVEAL Registry is expected to be the largest PAH registry, with a goal of tracking approximately 3,000 patients, and is intended to be active for five years.

Development Activities Summary

CoTherix's current development activities, which are intended to expand the commercial potential of Ventavis, are summarized in Table 6 (page 19).

Table 6

CoTherix, Inc.

SUMMARY OF DEVELOPMENT ACTIVITIES TO EXPAND THE COMMERCIAL POTENTIAL OF VENTAVIS

STEP Trial	CoTherix has completed the Phase II trial called the STEP Trial. This trial assessed the combination therapy of Ventavis with bosentan, an approved oral treatment for PAH.
ACTIVE Trial	CoTherix completed enrollment in a Phase II clinical trial to evaluate the safety and potential effectiveness of inhaled Ventavis in the treatment of patients with pulmonary hypertension associated with idiopathic pulmonary fibrosis (IPF).
VISION Trial	CoTherix has initiated a Phase III clinical trial to evaluate the safety and efficacy of adding Ventavis as a treatment for PAH patients already receiving sildenafil, an approved oral treatment for PAH.
REVEAL Registry	CoTherix began enrollment in March 2006 in its clinical disease registry, a longitudinal, open-label, national disease registry that will retrospectively and prospectively collect observational data to track and study the natural history and medical management of U.S. patients with PAH (WHO Group I).

Source: CoTherix, Inc.

Next-Generation Formulations and Shorter Inhalation Times

CoTherix is performing ongoing development work on a dry powder formulation of iloprost with the goal of developing a single breath inhalation dose. The Company is also evaluating the potential for delivering Ventavis more rapidly into the lungs using a reprogrammed I-neb device. If successful, the Company believes the delivery time of Ventavis could be reduced from the current 8 to 10 minutes per dose to approximately 4 to 5 minutes per dose.

Marketing Strategy

CoTherix's sales force targets approximately 1,500 pulmonary and cardiology specialists involved in treating PAH patients. Management estimates that 500 to 600 of these physicians treat approximately 80% of PAH patients. CoTherix's medical science liaisons are trained to build awareness of Ventavis with PAH opinion leaders, physicians, and nurses to further expand the number of patients diagnosed and treated with PAH as well as to increase the use of Ventavis.

Sales

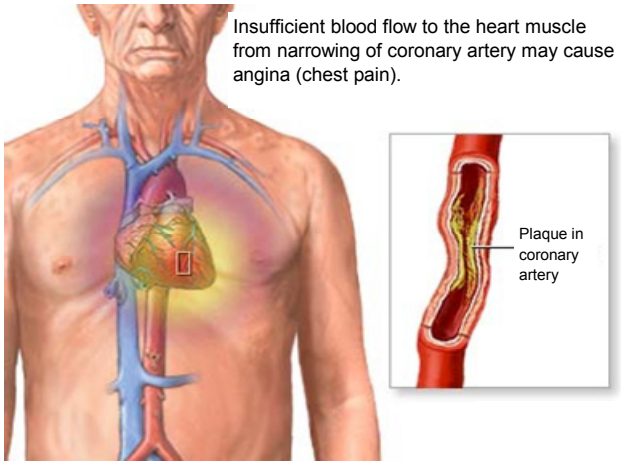
Ventavis' sales for the first quarter of 2006 were $14.5 million and $23.9 million for 2005, its first 10 months on the market (launched in March 2005). CoTherix issued 2006 sales guidance in its most recent quarter for between $65-70 million.

Competition

Various products are marketed for the treatment of PAH. Products currently marketed are summarized under Current Treatment Options (pages 13-15), and include Myogen's Flolan, United Therapeutics' Remodulin, Actelion's Tracleer, and Pfizer's Revatio. Three classes of vasoactive drugs are currently approved to treat PAH: (1) prostacyclins, (2) endothelin receptor antagonists (ETRAs), and (3) PDE-5 inhibitors. Additionally, other classes of drugs are used off-label to treat this condition, such as calcium channel blockers (CCBs).

CHRONIC STABLE ANGINA

Figure 6
STABLE ANGINA



Source: ADAM, Inc.

Chronic stable angina (also called stable angina) is defined as recurrent pain or discomfort in the chest, jaw, shoulder, back, or arm caused by insufficient blood flow to the heart muscle. The condition typically manifests as a pressure or squeezing sensation. Stable angina is most commonly a symptom of coronary artery disease (CAD), which causes the coronary arteries to narrow, but can also stem from other cardiac conditions such as **valvular heart disease**, hypertrophic cardiomyopathy, and uncontrolled hypertension.

Angina pain typically occurs in response to exercise or other stresses. An episode of angina is not a heart attack, but having angina generally indicates that CAD is present and that there is an increased risk of having a heart attack in the future. An illustration of the insufficient blood flow to the heart muscle due to a narrowing of the artery, which may cause angina is provided in Figure 6.

Angina is caused by **myocardial ischemia**, which is due to an imbalance between myocardial oxygen requirement and myocardial oxygen supply. The mechanism for cardiac pain is not well understood, although current insight into the disease suggests angina results from ischemic episodes that excite or activate **chemosensitive** and **mechanoreceptive** receptors in the heart.

Stable Versus Unstable Angina

It is important to distinguish between the two types of angina: stable angina and unstable angina. Both types result from problems within the coronary arteries; however, unstable angina can progress to **myocardial infarction (MI)** and carries a worse short-term prognosis.

Table 7
RISK FACTORS FOR DEVELOPING STABLE ANGINA

- Male gender
- Cigarette smoking
- High cholesterol levels
  (in particular, high LDL and low HDL cholesterol)
- High blood pressure
- Diabetes
- Family history of coronary heart disease before age 55
- Sedentary lifestyle
- Obesity

Source: ADAM, Inc.

- *Stable angina.* Stable angina occurs when myocardial oxygen demand exceeds oxygen supply during stress. Rest and/or medication will restore the balance of oxygen supply and demand and resolve the angina episode. Angina that has been unchanged in nature, severity, and frequency for 60 days is stable angina. Risk factors for developing stable angina are outlined in Table 7.

- *Unstable angina.* Unstable angina is usually due to the rupture or erosion of an atherosclerotic plaque with thrombus formation that occludes the coronary artery, the same pathology that results in myocardial infarction. Symptoms may occur at rest or during sleep. Unstable angina is classified as part of the Acute Coronary Syndrome. The treatment for unstable angina is different than that of chronic stable angina, and is not currently an indication addressed by CoTherix.

Current Treatment Options For Chronic Stable Angina

The goals of stable angina therapy are to improve the quality of life by reducing the frequency and severity of angina symptoms and to improve the prognosis (or quality of life) by delaying the progression of the disease and preventing subsequent heart attacks (myocardial infarction), unstable angina, or ischemic sudden death (ISD). Lifestyle modifications and medications to reduce or control hypertension, **hyperlipidemia**, diabetes, cigarette smoking, and obesity, as well as antiplatelet agents such as aspirin and clopidogrel, are used in patients with chronic stable angina to reduce the progression of the underlying coronary artery disease, and to prevent myocardial infarction or sudden death.

Symptomatic treatment of stable angina involves both acute treatment and prevention of symptomatic episodes. Treatment of an acute episode of angina involves rest and the use of **nitrates**, primarily nitroglycerine administered **sublingually**. Drugs that prevent the symptoms of chronic stable angina include long-acting nitrates, beta adrenergic blockers (**beta-blockers**), and calcium channel blockers (CCBs), and the recently approved ranolazine. In addition, patients with coronary artery disease may have revascularization by angioplasty, stent, or **coronary artery bypass grafting (CABG)**, in order to either ameliorate the symptoms or reduce the risk of myocardial infarction and death. Each of these treatments is described below.

- *Beta-Blockers.* Beta-blockers reduce heart rate and blood pressure, and therefore myocardial oxygen demand by blocking the binding of adrenaline to beta receptors. In addition to having anti-ischemic effects, beta-blockers are also effective **anti-hypertensives** and anti-arrhythmics. They are administered daily and are used to reduce the frequency of anginal attacks. Approximately 15-20% of angina patients cannot tolerate beta-blockers, and adverse effects can include severe cardiac effects, bronchoconstriction, fatigue, depression, gastrointestinal upset, and sexual dysfunction. Beta-blockers are used as an initial pharmacotherapy to manage angina.

- *Nitrates.* Nitroglycerine is intended to relieve angina symptoms by relaxing vascular smooth muscles, producing vasodilatation and increasing blood flow through the coronary arteries (increasing oxygen supply), as well as reducing blood pressure (reducing oxygen demand). Nitrates are available in different forms, including the sublingual to treat acute anginal episodes as well as the oral and transdermal for the prevention of episodes.

  Although effective in treating angina, nitrates have significant limitations. Use of nitrates, regardless of dosage form, can lead to nitrate tolerance, where use is no longer effective in treating symptoms. Nitrate withdrawal, a condition in which discontinuation of nitro-glycerine therapy can precipitate an anginal episode, is also common. Nitrates can also have significant side effects, including intense headaches, light-headedness, hypotension, flushing, and **tachycardia**. Importantly, nitrates are contraindicated with sildenafil (Viagra) because the combination causes life-threatening side effects. Finally, nitrates require storage in dark containers since they lose potency when exposed to light.

- *Calcium Channel Blockers (CCB).* As described on pages 14-15, calcium channel blockers are vasodilators that are effective in reducing cardiac demand as well as in reducing coronary artery **vasoconstriction**.

- *Ranolazine*. In January 2006, the U.S. FDA approved a new class of drug called ranolazine (Ranexa™) from CV Therapeutics (CVTX-NASDAQ) for the treatment of chronic angina. The drug is targeted for patients who do not respond to traditional angina treatment and is for use in combination with other treatments.

- *Revascularization*. In patients with angina that is refractory to medical management or that is due to certain lesions, **percutaneous transluminal coronary angioplasty (PTCA)** with/without placement of a stent, and CABG surgery may be used to relieve anginal symptoms and/or reduce the risk of subsequent myocardial infarction and death**.**

Market Size

The current prevalence of stable angina among the U.S. population is approximately 6.5 million people, with the incidence believed to be approximately 400,000, according to the American Heart Association (AHA). The incidence and prevalence patient populations are anticipated to grow at a rate of approximately 1% per year through 2015. CoTherix believes that the market size for fasudil could be approximately 900,000 patients based on a target population comprised of the following:

(1) patients who are not well controlled with current treatment, and

(2) patients who have undergone revascularization procedures but who still require anti-anginal therapy and are not well controlled with their current treatment.

CoTherix expects to initially target cardiologists who write a significant number of prescriptions for angina.

Development Efforts

The significant unmet need in the field of treatment for stable angina revolves around developing effective medical therapies with improved side effect profiles, especially as surgery-based therapeutic options are less appropriate in an aging worldwide population. In addition, therapies are needed that will target not only the symptoms of angina, but also the progression of the atherosclerotic disease in the coronary arteries.

Fasudil

CoTherix in-licensed fasudil on June 23, 2006 from Japan-based Asahi Kasei. Fasudil is one of the first products in a new class of agents called rho-kinase inhibitors. CoTherix expects to conduct clinical trials to develop fasudil as a treatment for stable angina patients who are inadequately treated with current therapies. The initial cardiovascular indication for fasudil is as an addition to beta-blockers, long-acting nitrates, and/or CCB's in patients who are not adequately managed on current therapies.

It is important to point out that despite the drug's unique mode of action, it is not likely to replace either nitrates, beta-blockers, or CCB's (which are described on pages 14-15 and 21), but rather could be utilized in combination with these agents to benefit from their different effects on cardiac function. For example, fasudil's mechanism of action could be complementary to beta-blockers in the treatment of angina. Beta-blockers are used to treat angina because they decrease cardiac workload and oxygen demand. Fasudil increases vasodilation and blood flow through the coronary arteries (increasing oxygen supply).

There is evidence from animal models of atherosclerosis that fasudil reduces vascular **inflammation** and slows the development of atherosclerosis. A compound that both reduced the symptoms of angina and slows the progression of the underlying disease would represent a new and potentially highly useful therapeutic option for patients with chronic stable angina. Once the effect of fasudil in relieving the symptoms of chronic stable angina is established, further studies may be done to investigate the effects on the progression of the underlying coronary artery disease.

A Direct Rho-kinase Inhibitor

Fasudil is an orally bioavailable rho-kinase inhibitor discovered by Asahi Kasei. It is a small molecule and is currently the only rho-kinase inhibitor in clinical trial use. Fasudil was first developed by Asahi Kasei for the prevention of cerebral vasospasm in patients with subarachnoid hemorrhage. Asahi Kasei received Japanese approval for the intravenous formulation in 1995.

Fasudil directly inhibits rho-kinase and has shown promise as a treatment for stable angina and PAH. Pre-clinical research over the past decade has identified rho-kinase as an important therapeutic target in several cardiovascular and pulmonary disease models including atherosclerosis, hypertension, restenosis, and asthma.

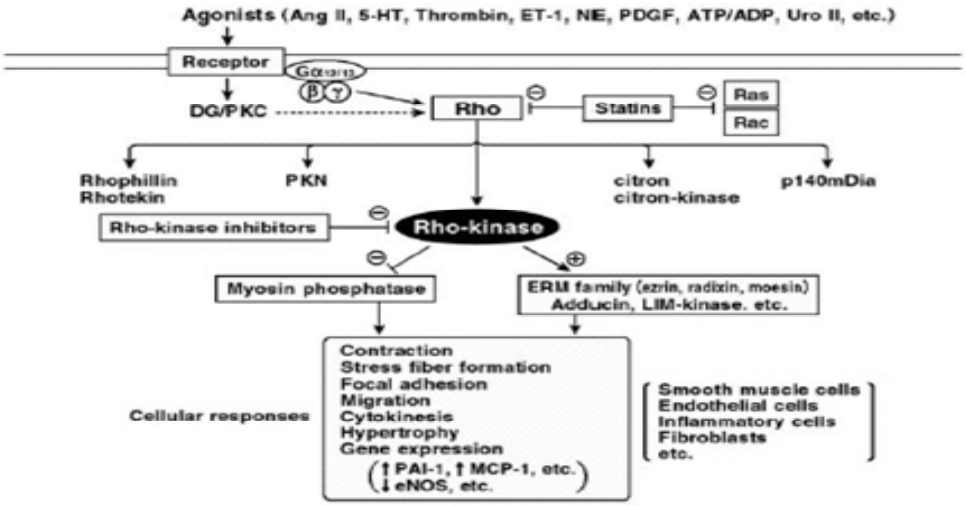
Rho GTPase is a low molecular weight G protein that acts as an intracellular switch between an inactive GDP-bound state and an active GTP-bound state to regulate cellular functions. **Rho** is the term generally used to describe the rho subfamily consisting of 3 human homologs: rhoA, rhoB, and rhoC. Several proteins are activated by rho but the best characterized is rho-kinase (consisting of two isoforms also known as ROCKα and ROCKβ), also called ROCK. Rho and rho-kinase proteins are involved in a variety of biochemical signaling pathways in cells and have important functions in vascular physiology and pathophysiology.

Rho/Rho-kinase in Cardiovascular Disease

Pre-clinical studies and emerging clinical evidence have demonstrated that the rho/rho-kinase pathway (Rho/ROCK) plays an important role in regulating and balancing several aspects of cellular function that are involved in the **pathogenesis** of cardiovascular and pulmonary vascular diseases (as illustrated in Figure 7). For example, Rho/ROCK is highly activated under conditions of inflammation and injury. Various types of inflammatory stimuli can activate Rho/ROCK signaling causing the pathway to (1) upregulate cytokines and inflammatory cells that further increase inflammation and (2) downregulate endothelial nitric oxide synthase (eNOS).

Figure 7

ROLE OF RHO/RHO-KINASE PATHWAY IN THE PATHOGENESIS OF CARDIOVASCULAR DISEASES



Source: Shimokawa, Journal of Cardiovascular Pharmacology: Vol. 39, no.3, 2002.

ROCK has a major effect on the control of tone in vascular smooth muscle (VSM). Excess activation of ROCK leads to sustained hypercontraction of VSM (sustained abnormal vasoconstriction). Pre-clinical studies in models of atherosclerosis have shown that increased Rho/ROCK activity also promotes vascular inflammation. Atherosclerotic plaque in the coronary arteries, which causes narrowing of the lumen, is a common underlying cause of stable angina.

In addition to upregulating pro-inflammatory cells and cytokines, ROCK activates a number of pathways that induce thrombosis and cell proliferation and/or hypertrophy. Models of pulmonary vascular and cardiovascular diseases have shown that inhibition of ROCK attenuates or reverses perivascular inflammation and vascular smooth muscle cell remodeling (thickening of the vessel wall). The beneficial effects of ROCK inhibition have also been demonstrated in the myocardium by the reduction of hypertrophy in heart failure models.

Inflammation, Vasoconstriction, and Remodeling in Vascular Smooth Muscle

Some of the known mediators of inflammation that initiate signal transduction of the Rho/ROCK pathway include endothelin-1, angiotensin II, serotonin, thrombin, thromboxane, and platelet derived growth factor (PDGF). These agonists are activated in pulmonary hypertension and several other cardiovascular disease states, and are associated with functional and structural vascular changes.

The primary mechanism of VSM cell contraction is regulated by increases in intracellular calcium (Ca2+). Increased intracellular Ca2+ activates **myosin light chain** kinase, which initiates muscle contraction by stimulating **phosphorylation** of myosin light chains (MLC). Another important mechanism that contributes to VSM cell contraction can occur independently of increases in cytosolic Ca2+ and is known as Ca2+ sensitization.

Ca2+ sensitization has been linked to the inhibition of myosin light chain phosphatase by ROCK. The inhibition of myosin light chain phosphatase is a key step that leads to an accumulation of phosphorylated MLC, which results in an increase in vascular tone (vasoconstriction). VSM cell hypertrophy and/or proliferation are responses to long-term vasoconstriction.

The endothelium maintains vascular homeostasis and integrity, and nitric oxide (NO) is a key signaling molecule that mediates many of these protective functions. NO improves vasorelaxation and decreases inflammatory cell accumulation at the vessel wall. Endothelial NO synthase (eNOS) is responsible for producing NO in the endothelium. Reduced eNOS has been implicated in the pathophysiology of pulmonary hypertension and other cardiovascular diseases. Pre-clinical models of pulmonary hypertension and atherosclerosis have shown that the Rho/ROCK pathway downregulates eNOS expression, which can be counteracted by inhibition of ROCK.

Diseased vessels in pulmonary hypertension and coronary artery disease show visible changes in their structural features. Endothelial dysfunction has a central role in the initiation and progression of disease. Changes in the endothelium, including increased permeability and expression of adhesion molecules, initiate an inflammatory response that promotes cell migration, proliferation, and hypertrophy. Pre-clinical studies have provided evidence that the inhibition of Rho/ROCK attenuates accumulation of inflammatory cells and VSM cell migration, hypertrophy and proliferation induced by angiotensin II, thrombin, and PDGF.

Fasudil: A Promising Mechanism of Action in Cardiovascular Disease

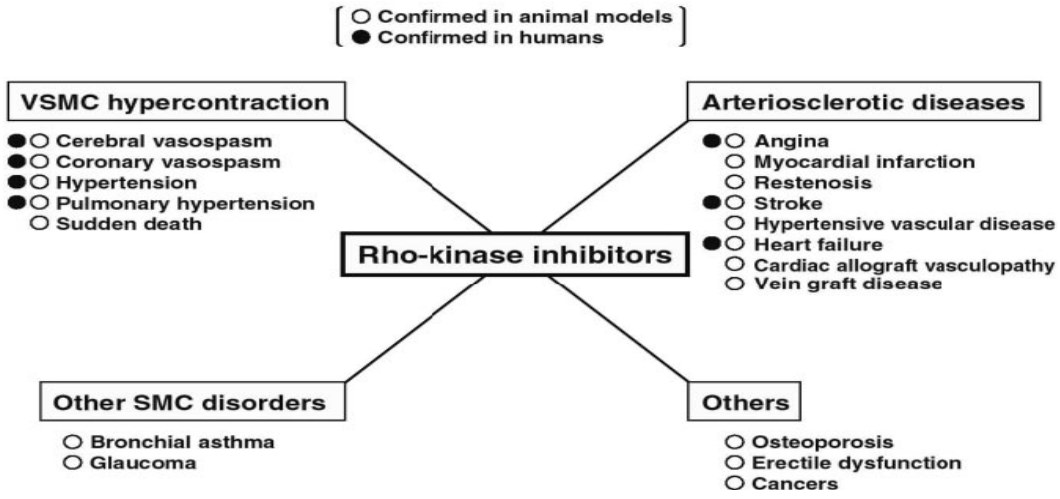
Fasudil directly inhibits ROCK, which is a well-characterized target implicated in vascular disease. Fasudil has vasodilating properties and attenuates inflammation, cell migration, and proliferation in disease models. CoTherix plans to conduct trials to explore the clinical implications of treatment with fasudil. In particular, CoTherix intends to develop an extended-release oral formulation of fasudil with a goal of enabling twice-daily dosing and providing a smoother pharmacokinetic profile. The Company also intends to explore the development of inhaled fasudil for pulmonary arterial hypertension.

In addition to treating patients with stable angina and pulmonary arterial hypertension (PAH), fasudil has the potential to treat a number of diseases and conditions, including the following: (see also Figure 8, page 25):

- *Atherosclerosis.* Rho/ROCK activation has been identified as a contributing factor in experimental models of vascular inflammation. Inhibition of ROCK has been associated with a reduction of early atherosclerotic lesion formation in pre-clinical studies. Angiotensin II, in addition to increasing blood pressure, promotes vascular inflammation and appears to have a central role in the pathophysiology of atherosclerosis. Fasudil was shown in an experimental model of apolipoprotein E-deficient mice (apoE-KO) to attenuate Ang II-induced abdominal aortic aneurysm formation by inhibiting apoptosis and proteolysis. Inhibiting ROCK activation in atherosclerosis may provide a clinical benefit.

- *Hypertension and hypertensive cardiac hypertrophy.* ROCK activity has also been investigated in the pathogenesis of hypertensive vascular disease. Some of the cellular processes that influence vascular resistance include abnormal vasoconstriction, VSM cell proliferation and hypertrophy, and inflammatory cell adhesion. ROCK is a known mediator of the pathways that regulate these processes, as well as a regulator of smooth muscle contraction. Short-term administration of a ROCK inhibitor decreased blood pressure in several animal models of systemic hypertension. In another experimental model, long-term administration of fasudil inhibited angiotensin II-induced cardiac hypertrophy. Also, non-hypotensive doses of fasudil have been shown to suppress coronary vascular lesion formation in spontaneously hypertensive rats.

Figure 8
THERAPEUTIC TARGETS OF RHO-KINASE INHIBITORS



Source: Shimokawa, Journal of Cardiovascular Pharmacology: Vol. 39, no.3, 2002.

Japanese investigators conducted two trials of an immediate release oral formulation for the treatment of stable angina in Japan. In August 2001, Schering AG in-licensed the oral formulation of fasudil from Asahi Kasei with rights to develop and market the product in the U.S. and Europe for stable angina. In August 2002, Schering AG in-licensed the intravenous formulation of the drug with marketing rights in the U.S. and Europe. Schering AG subsequently made a corporate decision that cardiovascular disease would no longer represent a core business area, divested its cardiovascular assets, and returned the rights to develop fasudil to Asahi Kasei in late 2005.

Fasudil: Clinical Proof-of-Concept in Pulmonary Hypertension

Pre-clinical studies have reported that Rho/ROCK signaling is involved in increased vasoconstriction and remodeling in models of pulmonary hypertension. Furthermore, it has been shown that inhibition of ROCK attenuated or reversed these effects. This preliminary work led two separate physician investigator groups in Japan to examine the acute effects of intravenous fasudil on the hemodynamics of patients with PAH. These trials have provided early proof-of-concept that single intravenous infusions of fasudil could provide a beneficial acute hemodynamic response in pulmonary hypertension.

- *Intravenous fasudil study conducted by Fukumoto, et. al. in Japan (Investigator-sponsored trial at Kyushu University Hospital).* In a single center, nine patients with PAH (six female and three male) were treated acutely with intravenous fasudil.
    - Patients were allowed to continue all medications, including oral or intravenous prostacyclin. A Swan-Ganz catheter was inserted to measure pulmonary hemodynamics.
    - Patients received 30mg of fasudil over 30 minutes. Hemodynamic measurements were reported over a 60-minute period.

After treatment, the patients had a slightly decreased mean pulmonary arterial pressure (PAP) and a small increase in cardiac index (CI) compared to baseline. Furthermore, the treatment caused a significant reduction of 17% in pulmonary vascular resistance (PVR). The investigators reported no side effects.

- *Intravenous fasudil study conducted by Ishikura, et. al. in Japan (Investigator-sponsored trial at Mie University Hospital).* In a single center, eight patients with PAH (all female) were treated acutely with intravenous fasudil. Five patients had idiopathic PAH (IPAH) and three had PAH associated with collagen vascular disease (CPAH). Four patients were diagnosed with PAH within two months prior to trial enrollment and were not on any treatment. Results from the trial were published in 2006.

  - No vasodilator was given for at least 12 hours before administration of fasudil. A Swan-Ganz catheter was inserted to measure pulmonary hemodynamics.

  - Patients received 1mg/min of fasudil for 30 minutes. Hemodynamic monitoring was performed continuously and recorded for up to 60 minutes after administration.

  After treatment with fasudil, patients in this trial had a significant decrease in total pulmonary resistance (TPR) of -23.9% of baseline ($p< 0.005$), a significant decrease in PAP of -9.9±10.7% of baseline ($p< 0.05$), and a significant increase in CI of 19.4±15.5% of baseline ($p< 0.02$). There was no significant change in oxygen saturation, which can occur with systemic vasodilators. No major side effects were reported.

Fasudil: Clinical Proof-of-Concept in Chronic Stable Angina

ROCK plays a major role in Ca2+ sensitization of VSM and appears to be involved in the pathogenesis of coronary vasospasm and anginia. Inhibition of ROCK with fasudil causes vasodilation of the vessels.

Shimokawa has published several dose escalation trials of fasudil in stable angina, which provide the first proof-of-concept in humans. Details of these trials are provided below.

- *Oral study conducted by Shimokawa, et. al. in Japan (Phase IIa).* In a Phase IIa multi-center (23 center) study, 67 patients with stable exercise-induced angina pectoris were treated with two different ascending dose regimens of fasudil. A two week placebo run-in period preceded treatment in both parts of the study.

  In the first part of the study, 45 patients were treated with increasing doses of fasudil at 15, 30, and 60 mg/day, t.i.d., administered sequentially for two-week periods until anginal attacks resolved. In this part of the study, it was shown that fasudil significantly decreased the number of anginal attacks per week ($p<0.001$) and significantly prolonged the maximum exercise time ($p<0.01$), as well as the time to the onset of 1-mm ST segment depression.

  In the second part of the study, 22 patients were treated with fasudil at 60 mg/day for two weeks, then 120 mg/day, t.i.d., for two weeks. In this part of the study, the number of angina attacks was significantly reduced ($p<0.001$), the use of sublingual nitroglycerine significantly decreased ($p<0.05$), and the maximum exercise time was significantly prolonged ($p<0.05$).

- *Oral study conducted by Shimokawa et. al. in Japan (Phase IIb).* In a Phase IIb multi-center (46 center) study, 125 patients with stable exercise-induced angina pectoris were randomized to receive fasudil 15, 30, 60, or 120 mg/day, t.i.d., for four weeks.

  Although all exercise parameters (1) total exercise duration, (2) time to onset of 1-mm ST segment depression, and (3) ST segment depression at the same time, were prolonged during fasudil treatment, there was no apparent dose-response relationship in terms of the effects of fasudil on the individual parameters. However, when the three indices were combined as an exercise tolerance index, a highly significant dose-response relationship was observed ($p=0.006$), which best fit a linear relationship. No dose-response relationship was observed with respect to any of the other investigated parameters. However, the number of angina attacks significantly decreased in all groups,

although there was no significant dose-dependent decrease in the number of anginal attacks across the four groups.

- *Oral study conducted by Berlex (Schering AG) (Phase II).* In a Phase II randomized double-blind, placebo-controlled study conducted by Schering AG, 84 patients with **stable angina pectoris** received oral fasudil or placebo (41 fasudil, 43 placebo). Doses of fasudil were increased every two weeks for eight weeks to the highest dose of 240 mg/day administered in three divided doses. Patients were allowed to take one anti-anginal medication, short-acting nitrates as needed, as well as their usual cardiovascular medications, including aspirin and statins.

  Results showed that exercise duration at eight weeks was increased by 1.43 minutes in the placebo group and by 1.97 minutes in the fasudil group.

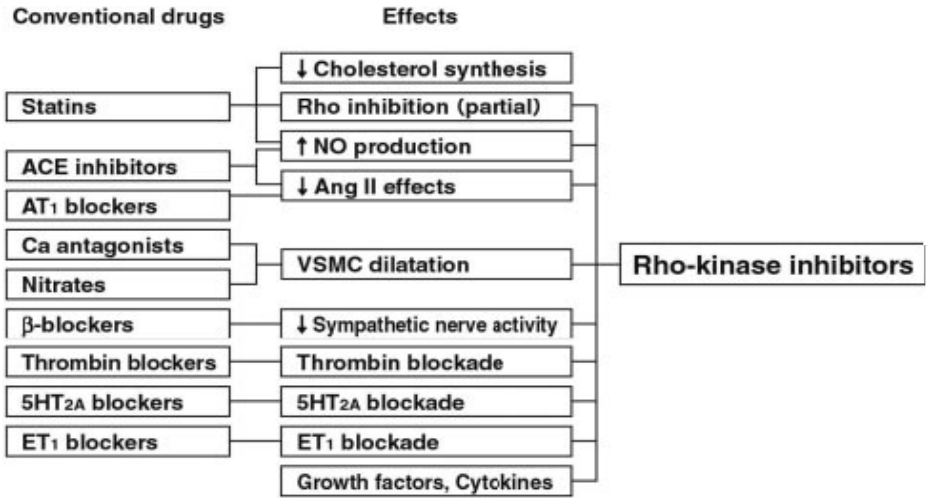
  Time to 1-mm ST segment depression (onset of myocardial ischemia) was increased by 2.83 minutes in the fasudil group compared to placebo at eight weeks (p=0.012). Fasudil was well tolerated in patients with stable exercise-induced angina pectoris.

CoTherix Development Activities Summary

CoTherix intends to develop fasudil for the treatment of PAH and stable angina. Fasudil is the only ROCK inhibitor that has been tested in the clinic and, if approved, would be a first-in-class drug. Rho/ROCK proteins have important functions in vascular physiology and pathophysiology. Pre-clinical studies have shown repeatedly that the inhibition of ROCK has potential as a treatment for both pulmonary vascular and cardiovascular diseases. The inhibition of ROCK has broad pharmacological implications and has the possibility of complementing the therapeutic activities of a number of different drugs, depicted in Figure 9.

Figure 9

BROAD PHARMACOLOGICAL PROPERTIES OF RHO-KINASE INHIBITORS



Source: H Shimokawa, Arteriosclerosis Thombosis Vascular Biology: Sept 2005.

The addition of fasudil to CoTherix's pipeline enables the Company to expand its footprint in PAH and the cardiovascular market. Given encouraging Phase II data from Japan, U.S., and Europe for oral fasudil in stable angina, the potential for use in other diseases, and its stage of development, CoTherix believes that it is likely to benefit from this new product opportunity.

Potential Product Benefits

The potential benefits that CoTherix believes fasudil could provide are summarized in Table 8.

Table 8
CoTherix, Inc.
POTENTIAL BENEFITS OF FASUDIL

▪ First in a new class of agents	Fasudil would be the first in a new class of agents, Rho/ROCK, for the treatment of stable angina. Fasudil may potentially possess activity that could impact not only the symptoms of chronic stable angina, but also the underlying atherosclerotic changes.
▪ If effective in treating pulmonary hypertension, could significantly increase its value to CoTherix	If fasudil were shown to be effective in the treatment of pulmonary hypertension, this would provide the Company with a novel second product for PH, in addition to being one that could be used in conjunction with Ventavis.
▪ Could create efficiencies	A second PH product would offer CoTherix efficiencies in terms of sales force deployment and activity.

Source: CoTherix, Inc.

Competition for Stable Angina

CoTherix faces potential competition in this area from established pharmaceutical and biotechnology companies, as well as from academic institutions, government agencies, and private and public research institutions, among others. Some of the potential competitors are described below.

- *CV Therapeutics, Inc.* CV Therapeutics, Inc.'s Ranexa™, a partial fatty acid oxidation (pFOX) inhibitor, was launched in late Q1 2006. The approval of Ranexa marked the first new pharmaceutical approach to treating stable angina in the U.S. in more than 20 years. CV Therapeutics has a sales force of 250 sales representatives to promote the drug, which is approved for the treatment of chronic stable angina. According to the approved labeling, because Ranexa prolongs the QTc interval, it should be reserved for patients who have not achieved an adequate response with other antianginal drugs. In addition, since Ranexa is metabolized by cytochrome p 450 isoenzyme 3A4, administration of Ranexa can lead to drug interactions with diltiazem and verapamil. Ranexa should be used in combination with amlodipine, beta-blockers, or nitrates.

  CV Therapeutics recently completed patient enrollment in its MERLIN-TIMI 36 trial. If treatment with Ranexa in this study is not associated with an adverse trend in death or arrhythmia compared to placebo, the study's safety database could support potential approval of Ranexa as first-line chronic stable angina therapy, even if the primary endpoint is not met. In addition, if the primary endpoint is met, Ranexa could also be approved for treatment of acute coronary syndromes (ACS) and secondary prevention. This drug currently has a **black box warning** because it can prolong the QTc interval.

- *Servier.* French-based Servier's Procoralan®, a benzocyclobutane-derivative potassium channel blocker (If inhibitor), was recently approved in the European Union (EU) for the symptomatic treatment of chronic stable angina pectoris in patients with normal sinus rhythm who have a contraindication or intolerance to beta-blockers. Procoralan inhibits the Na+/K+ cardiac current (If). By selectively slowing the heart rate and reducing myocardial oxygen demand, Procoralan may provide a novel mechanism for preventing angina. Clinical trials suggest that Procoralan has improved efficacy over beta-blockers, while having fewer side effects.

- *Mitsubishi-Pharma Corporation.* Welfide (now Mitsubishi-Pharma), in collaboration with researchers at Kyoto University, has been investigating the pyridine derivative Y-27632, an inhibitor of ROCK, for the potential treatment of several forms of hypertension, including spontaneous, renal, and sodium-induced hypertension. Other potential indications for the agent included cerebrovascular spasm, bronchial asthma, and inhibition of cancer metastasis. CoTherix believes it is no longer in development but has been made available to researchers.

- *Nippon Shinyaku.* HMN 1152 is a vascular relaxant that was undergoing pre-clinical development with Nippon Shinyaku in Japan. HMN 1152 binds to rho and inhibits rho-kinase. It may be useful in the treatment of delayed vasospasm after subarachnoid hemorrhage. However, no recent development has been reported.

- *Surface Logix.* SLx-2119 has been designed as an orally active ROCK 2 inhibitor for cancer. An **Investigational New Drug (IND)** application is currently being prepared for submission to the FDA. SLx-2119 is a selective, potent rho-kinase inhibitor that is being developed for oncology and fibrosis. Most notable is the lack of cardiovascular effects associated with this ROCK-II selective inhibitor.

- *BioAxone Thérapeutique Inc.* BioAxone Thérapeutique Inc., a privately-owned company located in Montreal, Canada, is developing small molecule ROCK inhibitors for the treatment of cancer metastasis. Rho signaling is important for regulating cellular processes involved in cell motility and malignant transformation, and ROCK mediates the induction of migratory activity. Inhibition of this enzyme prevents the cellular cascade involved in the dissemination of tumor cells and may have the potential to prevent angiogenesis and tumor cell escape. The drug is currently in the pre-clinical stage of development.

- *Ube Industries and Santen Pharmaceutical*. The two companies have jointly announced that they will collaborate to develop the ROCK inhibitor, DE-104, as an ophthalmic solution for treating glaucoma and ocular hypertension. The drug is currently pre-clinical stage of development.

Partnerships, Alliances, In-Licensing Agreements, and Academic Collaborations

CoTherix has a series of relationships in place to assist and facilitate the Company's development, manufacturing, licensing, supply, and distribution efforts. These agreements are described below.

- *Schering AG License and Manufacturing Agreement.* CoTherix has a development and license agreement with Schering AG (now Bayer-Schering AG) that grants CoTherix the exclusive right to develop and commercialize Ventavis for inhaled use in treating pulmonary hypertension in the U.S. CoTherix is obligated to use its best efforts to commercialize Ventavis in the U.S.

- *Respironics Supply and Exclusivity Agreement.* CoTherix entered into an agreement with Respironics, which grants CoTherix the exclusive right to Respironics' devices with AAD technology for use with prostacyclines for the treatment of PAH in the U.S.

- *Accredo Health Inc. Distribution Agreement.* CoTherix has an agreement with Accredo Health Incorporated (a wholly owned subsidiary of Medco Health Solutions, Inc. [MHS-NYSE]), appointing Accredo as one of its specialty pharmacy distributors of Ventavis and its approved devices. Under the agreement, Accredo is obligated to provide services to patients and physicians, such as reimbursement assistance, patient education, and counseling to ensure patient understanding of and compliance with the Ventavis dosing regimen. The agreement designates Accredo as the exclusive provider of call center support services for Ventavis.

- *Curascript Inc. Distribution Agreement.* CoTherix has an agreement with Curascript, Inc., which appoints Curascript as one of its specialty pharmacy distributors for Ventavis and its approved devices. Under the agreement, Curascript is also obligated to provide services to patients and physicians, such as reimbursement assistance, patient education, and counseling to ensure patient understanding of and compliance with the Ventavis dosing regimen.

- *Cardinal Health Inc. Distribution Agreement.* CoTherix entered into an agreement with Cardinal Health, Inc. (CAH-NYSE) that designates Cardinal Health as the exclusive distribution agent to its specialty pharmacy distributors for the sale of Ventavis within the U.S.

- *Asahi Kasei Pharma.* Asahi Kasei Pharma is the core operating company for all operations of the Asahi Kasei Group, which serves the healthcare industries. On June 23, 2006, CoTherix licensed oral and inhaled forms of fasudil from Asahi Kasei for the treatment of PAH and oral forms for the treatment of stable angina. Fasudil is currently the only ROCK inhibitor available for clinical use and is approved in Japan for the prevention of vasospasm in patients with subarachnoid hemorrhage.

Recent Milestones

- In March 2005, CoTherix successfully launched Ventavis, the first inhaled prostacyclin therapy for PAH. Ventavis achieved approximately $38 million in revenue during its first 12 months on the market.

- In August 2005, the FDA approved a supplemental New Drug Application (sNDA) expanding Ventavis' label to include data resulting from CoTherix's safety study. The study evaluated the combination of Ventavis (versus placebo) in patients already receiving bosentan.

- In August 2005, the FDA also approved a sNDA that allows the use of Ventavis with the I-neb AAD-inhalation device from Respironics. The I-neb device is a battery-operated, portable device that continually monitors and adapts to patients' breathing patterns to ensure they receive a precise dose during each treatment.

    - In December 2005, CoTherix amended its agreement with Respironics to obtain exclusivity in the pulmonary hypertension market for the I-neb and future devices using Respironics' AAD and vibrating mesh technologies for prostacyclin delivery.

- During the first quarter 2006, CoTherix initiated the VISION trial to evaluate the safety and efficacy of Ventavis in combination with sildenafil, a therapy for PAH.

- In April 2006, CoTherix announced the launch of the REVEAL Registry™. The registry is designed to answer some of the most fundamental questions associated with the treatment of PAH. On March 29, 2006, the first patient was enrolled in this Registry.

- As of May 2006, CoTherix completed enrollment in its ACTIVE trial, a Phase II trial of Ventavis for pulmonary hypertension associated with idiopathic pulmonary fibrosis (IPF).

- On June 23, 2006, CoTherix licensed oral and inhaled forms of fasudil from Asahi Kasei for the treatment of PAH and oral forms for the treatment of stable angina. Fasudil is currently the only ROCK inhibitor available for clinical use and the intravenous form is approved in Japan for the prevention of vasospasm in patients with subarachnoid hemorrhage.

Potential Upcoming Milestones

- By year end 2006, CoTherix could report top-line results from the Phase II trial of Ventavis for PAH associated with IPF.
- In the second half of 2006, CoTherix plans to initiate a clinical trial to evaluate the potential of delivering Ventavis more rapidly into the lungs using a reprogrammed I-neb device. If successful, the delivery time of Ventavis could be reduced from the current eight to ten minutes per dose to four to five minutes per dose.
- Following the June 23, 2006 in-licensing of fasudil, CoTherix is expected to continue to focus on in-licensing opportunities.

Key Points to Consider

- CoTherix's commercial product, Ventavis, is an inhaled form of prostacyclin, a class of drug with an established clinical record as an efficacious therapy for pulmonary arterial hypertension (PAH). Ventavis is the only inhaled version of any drug that is approved as a therapy for PAH, a condition where blood pressure is extremely high in the blood vessels between the heart and the lungs. The condition is relatively uncommon (prevalence of approximately 50,000 in the U.S.), but serious and often fatal.

- Synthetic Prostacyclins are chemicals that mimic a substance called prostaglandin, which dilates blood vessels and is naturally produced within the body. Individuals with PAH do not produce enough prostaglandin. Therefore, giving patients prostacyclin makes up for this underproduction and helps the body dilate the blood vessels in the lungs. By increasing blood flow through the lungs, these medications increase the amount of oxygen carried to the heart and body, making breathing easier.

- Ventavis is penetrating the market with approximately $38 million in sales reported in its first 12 months on the market. The availability of an inhaled form of prostacyclin has allowed physicians to prescribe a prostacyclin earlier in the disease process. Additionally, the portability of the new I-neb device has enhanced patient acceptance.

- During the first quarter of 2006, the Company initiated a 180-patient Phase III trial (VISION) to evaluate the safety and efficacy of Ventavis in combination with sildenafil for the treatment of PAH. The study will also assess the feasibility of reducing Ventavis dosing from six to four times per day. The Company has completed enrollment in its Phase II ACTIVE trial, investigating the use of Ventavis for pulmonary hypertension associated with idiopathic pulmonary fibrosis (IPF). Data is expected to be released by year-end 2006.

Fasudil

- On June 23, 2006, CoTherix licensed oral and inhaled forms of fasudil, a ROCK inhibitor, as a potential treatment for patients with PAH and oral forms of fasudil for the treatment of stable angina. CoTherix licensed the right to develop oral and inhaled dosages of fasudil in North America and Europe from Asahi Kasei and has an option to expand into other potential indications (excluding stroke and eye diseases). Combination therapy—utilizing agents that affect multiple pathways—is being increasingly used to treat PAH.

- If approved, fasudil would be a new class of drug for the treatment of PAH. Fasudil is intended as an addition to beta-blockers, long-acting nitrates, and/or calcium channel blockers (CCB's) for the treatment of chronic stable angina.

- Fasudil is currently the only ROCK inhibitor in clinical development. The drug is approved for use in Japan for prevention of cerebral vasospasm in patients with subarachnoid hemorrhage. Given encouraging Phase II data from Japan and the U.S. for oral fasudil in stable angina, the potential for use in other diseases, and its stage of development, CoTherix believes that it can benefit from this new product opportunity.

    - The Rho/ROCK pathway is involved in a variety of biochemical signal transductions in cells and has important functions in vascular physiology and pathophysiology. Fasudil has vasodilating properties and attenuates inflammation, cell migration, and proliferation.

    - The addition of fasudil to CoTherix's pipeline enables the Company to enhance its position in the cardiovascular arena with a promising drug candidate that has the potential to treat several cardiovascular diseases.

- The CoTherix management team was responsible for the successful NDA filing for Ventavis and the subsequent product launch in 2005. The management team brings years of drug development, manufacturing, and commercialization experience to the Company. The senior members of the commercial team also have experience building the necessary infrastructure and market awareness to launch a new cardiovascular product

- The Company's current cash, cash equivalents, and securities available-for-sale position stands at $98 million as of March 31, 2006.

Historical Financial Results

Tables 9, 10, and 11 provide a summary of CoTherix's key historical financial statements, including its Statements of Operations, Balance Sheets, and Statements of Cash Flows.

Table 9
CoTherix, Inc.
STATEMENTS OF OPERATIONS
(In thousands, except share and per share data)

	Years Ended December 31, 2005	2004
Revenues:		
Product sales, net	$ 23,874	—
Grant revenue	—	—
Total revenue	23,874	—
Operating expenses:		
Cost of goods sold	8,704	—
Research and development	11,632	15,577
Selling, general and administrative	26,184	7,840
Acquired product rights	—	7,150
Amortization of employee stock-based compensation related to:		
Research and development	1,574	1,748
Selling, general and administrative	2,475	5,940
Total operating expenses	50,569	38,255
Loss from operations	(26,695)	(38,255)
Interest and other income, net	2,336	463
Interest expense	(217)	(4)
Net loss	(24,576)	(37,796)
Accretion to redemption value of redeemable convertible preferred stock	—	(60)
Deemed dividend upon issuance of Series C redeemable convertible preferred stock and issuance of common stock upon exchange of convertible preferred warrants	—	(24,987)
Net loss attributable to common stockholders	$ (24,576)	$ (62,843)
Basic and diluted net loss per share attributable to common stockholders	$ (1.01)	$ (13.39)
Weighted average shares used to compute basic and diluted net loss per share attributable to common stockholders	24,385,414	4,692,097

Source: CoTherix, Inc.

Table 10
CoTherix, Inc.
BALANCE SHEETS
(In thousands, except share and per share data)

	December 31, 2005	December 31, 2004
ASSETS		
Current assets:		
Cash and cash equivalents	$ 25,865	$ 43,251
Securities available-for-sale	76,965	—
Interest receivable	965	—
Accounts receivable, net of allowance for doubtful accounts of $36 and none at December 31, 2005 and 2004, respectively	2,390	—
Inventory, net	510	—
Prepaid expenses and other current assets, including restricted cash of $49 and none at December 31, 2005 and 2004, respectively	2,216	876
Total current assets	108,911	44,127
Restricted cash	95	144
Property and equipment, net	1,572	1,139
Acquired product rights, net	8,100	9,000
Total assets	$ 118,678	$ 54,410
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 1,192	$ 376
Accrued compensation	3,845	1,333
Accrued clinical development liabilities	113	596
Accrued acquired product rights	—	9,000
Other accrued liabilities	5,008	1,657
Liability for early exercise of stock options	20	245
Total current liabilities	10,178	13,207
Liability for early exercise of stock options-non-current portion	5	38
Deferred rent-non-current portion	192	261
Commitments:		
Stockholders' equity:		
Preferred stock, $0.001 par value; 10,000,000 shares authorized; no shares issued and outstanding	—	—
Common stock, $0.001 par value; 100,000,000 shares authorized; 28,356,792 shares and 19,426,688 shares issued and outstanding at December 31, 2005 and 2004, respectively	28	19
Additional paid-in capital	198,764	111,698
Deferred stock compensation	(6,703)	(11,729)
Accumulated other comprehensive loss	(126)	—
Accumulated deficit	(83,660)	(59,084)
Total stockholders' equity	108,303	40,904
Total liabilities and stockholders' equity	$ 118,678	$ 54,410

Source: CoTherix, Inc.

Table 11
CoTherix, Inc.
STATEMENTS OF CASH FLOWS
(In thousands, except share and per share data)

	Years Ended December 31, 2005	2004
Cash flows from operating activities:		
Net loss	$ (24,576)	$ (37,796)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation and amortization	442	263
Amortization of acquired product rights	900	—
Amortization of deferred stock compensation	4,049	7,688
Fair value of stock options issued for services	223	205
Loss on disposal of fixed assets	7	19
Amortization of premium on securities available-for-sale	650	—
Non-cash interest expense	—	—
Changes in assets and liabilities:		
Accounts receivable, net	(2,390)	—
Interest receivable	(965)	—
Inventory, net	(510)	—
Prepaid and other current assets	(1,340)	(246)
Restricted cash	49	(91)
Other long-term assets	—	—
Acquired product rights	—	(9,000)
Accounts payable	816	(17)
Accrued compensation	2,512	982
Accrued clinical development liabilities	(483)	596
Accrued acquired product rights	(9,000)	9,000
Other accrued liabilities	3,280	1,278
Net cash used in operating activities	(26,336)	(27,119)
Cash flows from investing activities:		
Purchases of property and equipment	(882)	(1,027)
Proceeds from securities available-for-sale	39,157	—
Purchases of securities available-for-sale	(116,898)	—
Net cash used in investing activities	(78,623)	(1,027)
Cash flows from financing activities:		
Proceeds from issuance of common stock, net of repurchased shares and excluding early exercised options	87,560	25,651
Proceeds from issuance of redeemable convertible preferred stock warrants	—	—
Proceeds from early exercise of options	13	210
Proceeds from issuance of convertible debt	—	—
Proceeds from issuance of redeemable convertible preferred stock, net of issuance costs	—	24,987
Net cash provided by financing activities	87,573	50,848
Net increase (decrease) in cash and cash equivalents	(17,386)	22,702
Cash and cash equivalents at the beginning of period	43,251	20,549
Cash and cash equivalents at the end of period	$ 25,865	$ 43,251

Source: CoTherix, Inc.

Risks

Some of the information in this report relates to future events, business strategy, and financial performance. Such statements can only be predictions and actual events or results may differ from those discussed herein due to the risks described in CoTherix's Annual Report on Form 10-K, Quarterly Reports on Form 10-Q, and other filings made with the Securities and Exchange Commission from time to time. Any of these risks could harm CoTherix's business. Investors should carefully consider the risks and the information about CoTherix's business described below. Investors should not interpret the order in which these considerations are presented as an indication of their relative importance. The risks and uncertainties described below are not the only risks that CoTherix faces. Additional risks and uncertainties not presently known to CoTherix or that CoTherix currently believes to be immaterial may also adversely affect its business. If any of the following risks and uncertainties develops into actual events, CoTherix's business, financial condition, and results of operations could be materially and adversely affected, and the trading price of its shares could decline.

RISKS RELATED TO COTHERIX'S BUSINESS

Ventavis® is the Company's only commercial product, and if CoTherix does not successfully market and sell Ventavis, it may not generate sufficient sales to expand or continue its business operations.

CoTherix's ability to successfully market and sell Ventavis, its only commercial product, depends on a number of factors, including its ability to:

- achieve sufficient market demand for Ventavis through patient acceptance, continued use of Ventavis, and patient compliance with the Ventavis dosing regimen;
- educate patients, physician prescribers, others in the medical community, and third-party payors about Ventavis and PAH;
- sell Ventavis at acceptable prices;
- expand the commercial potential of Ventavis through successful completion of CoTherix's ongoing and planned development activities;
- obtain and maintain adequate third-party payor reimbursement of Ventavis and the inhalation devices used to administer Ventavis;
- ensure that Ventavis and the inhalation devices used to administer Ventavis are manufactured in accordance with and continue to meet regulatory requirements;
- obtain sufficient quantities of Ventavis to meet market demand;
- ensure adequate supply of the inhalation devices used to administer Ventavis; and
- maintain the Company's agreements with the specialty pharmacy and third-party logistic companies that distribute Ventavis, and ensure that those companies perform their obligations under those agreements.

If CoTherix does not successfully market and sell Ventavis, the Company may not generate sufficient sales to expand or continue its business, including its efforts to develop and commercialize its new product candidate, fasudil, a rho-kinase inhibitor, for the treatment of PAH and stable angina.

CoTherix has a history of net losses and may never achieve or maintain profitability.

CoTherix is a biopharmaceutical company incorporated in February 2000 with a limited operating history. Through March 31, 2006, CoTherix had generated only $38.3 million of net product sales. The Company has funded its operations primarily from sales of its equity securities. CoTherix has incurred losses in each year since its inception, and through March 31, 2006, had an accumulated deficit totaling $87.6 million. The Company's net losses for the years ended December 31, 2005, 2004, and 2003 were $24.6 million, $37.8 million, and $12.6 million, respectively, and its net loss for the quarter ended March 31, 2006 was $3.9 million. These losses, among other things, have had and will continue to have an adverse effect on CoTherix's cash flow, stockholders' equity, and working capital. The Company may not generate sufficient sales of Ventavis, which is its only commercial product, for it to achieve or maintain profitability.

CoTherix expects its research and development expenses to increase significantly in connection with pre-clinical and clinical studies and other development activities to expand the use of Ventavis and related to the development of fasudil. In the first half of 2006, the Company paid $8.75 million in connection with the fasudil agreement and will be required to pay additional development milestones. In addition, the Company expects to incur increased selling, general, and administrative expenses in future years versus comparable periods in the past principally due to higher sales and marketing expenses related to the commercialization of Ventavis and expenses related to its clinical registry. As a result, CoTherix expects to continue to incur significant operating losses. In addition, the Company may continue to acquire or license the rights to additional products or product candidates, which it anticipates would further increase and continue its losses. Because of the numerous risks and uncertainties associated with developing and commercializing therapeutic drugs, CoTherix may experience larger than expected future losses and may not become profitable.

The Company's product sales depend on two distributors to whom it sells Ventavis, and a limited number of physicians who prescribe Ventavis. Product sales may fluctuate from quarter to quarter based on the buying patterns of these distributors, the prescribing patterns of these physicians, and the seasonal work and travel schedules of physicians and patients, as well as any events that affect the geographic areas in which these physicians are concentrated.

CoTherix sells Ventavis to only two specialty pharmacy distributors, Accredo Health Care Group, Inc., or Accredo, a Medco company, and Curascript Inc., a wholly-owned subsidiary of Express Scripts, Inc. (formerly Priority Healthcare Corporation), or Curascript, and accordingly they are the Company's only customers. For the three months ended March 31, 2006, Accredo and Curascript represented 81% and 19% of CoTherix's sales, respectively. Any failure by Accredo or Curascript to pay the Company on a timely basis or at all could have a material adverse effect on CoTherix's financial position, results of operations, and cash flows. In addition, a limited number of physicians are responsible for the majority of Ventavis prescriptions.

The Company's sales could fluctuate from quarter to quarter based on the buying patterns of Accredo and Curascript, and the prescribing patterns of these physicians, including fluctuations due to the seasonal work and travel schedules of both physicians and patients. For example, during the summer and the winter holiday season, patients may be less likely to seek medical consultation and physicians are more likely to be on vacation, resulting in fewer prescriptions for and lower sales of Ventavis. Furthermore, there can be no guarantee that physicians currently prescribing Ventavis will continue to do so. Most of these physicians are geographically concentrated in metropolitan areas that have academic medical centers, and natural disaster, terrorism, work stoppages, or other such events in any of these areas could have a material adverse effect on CoTherix's sales.

Any failure to manage and maintain its distribution network could compromise Ventavis sales and harm the Company's business.

CoTherix relies on third parties to distribute Ventavis to patients. The Company has contracted with Cardinal Health PTS, LLC, or Cardinal Health, a third-party logistics company, to warehouse Ventavis and distribute it to CoTherix's two specialty pharmacies, Accredo and Curascript, which in turn distribute Ventavis to patients and provide reimbursement and other support services. This distribution network requires significant coordination with the Company's sales and marketing and finance organizations. Cardinal Health is CoTherix's exclusive supplier of distribution logistics services; therefore the Company

is wholly dependent on Cardinal Health to perform satisfactorily its obligations under its agreement with CoTherix. Accredo is the exclusive provider of the Company's call center. Accredo and Curascript administer reimbursement support programs that provide patients with benefit information and assist with reimbursement of Ventavis by private payors and state (Medicaid) and federal (Medicare) programs for uninsured and disabled patients, respectively. Accordingly, CoTherix is wholly dependent on Accredo and Curascript for these services, upon which the Company relies to help maintain and expand the market for Ventavis.

Failure by CoTherix to maintain its contracts with its logistics company and specialty pharmacies, or the inability or failure of any of them to adequately perform as agreed under their respective contracts with CoTherix, could harm the Company's business. The Company does not have its own warehouse or distribution capabilities, and it lacks the resources and experience to establish any of these functions and does not intend to do so in the foreseeable future. CoTherix would be unable to replace Cardinal Health, Accredo, or Curascript in a timely manner in the event of a natural disaster, failure to meet FDA and other regulatory requirements, business failure, strike, or any other distribution failure. Since CoTherix is dependent upon Cardinal Health, Accredo, and Curascript for information regarding Ventavis sales, shipments, and inventory, failure in their financial systems could negatively impact the Company's ability to accurately report and forecast product sales and fulfill its regulatory obligations. Any failure to effectively manage and maintain its distribution network could damage CoTherix's results of operations and market position, have a material adverse effect on sales of Ventavis, and harm its business.

The Company's ability to generate sales of Ventavis depends in significant part on achieving and maintaining adequate insurance coverage and reimbursement and government pricing policies.

CoTherix's ability to achieve and maintain acceptable levels of insurance coverage and reimbursement for Ventavis and the inhalation devices used to administer Ventavis by third-party payors such as governmental authorities, private health insurers, and other organizations has a significant effect on the Company's sales. It is time-consuming and costly to seek appropriate coverage and reimbursement treatment from third-party payors.

Medicare has determined a reimbursement amount and reimbursement code for Ventavis. Medicare has also determined a reimbursement code and a maximum amount of reimbursement for the inhalation devices used to administer Ventavis, which reimbursement amount became effective in April 2006. Medicaid plans in all fifty states are mandated to cover Ventavis. Notwithstanding this coverage requirement, Utah Medicaid has rescinded its Ventavis coverage; CoTherix is currently working to resolve this change.

Decisions regarding the extent of coverage and amount of reimbursement for Ventavis are made on a state-by-state basis. The Company's specialty pharmacy distributors negotiate with each state for Medicaid coverage and reimbursement for Ventavis and the inhalation devices. CoTherix's sales and its financial condition could be negatively impacted if the reimbursement by Utah Medicaid for Ventavis continues to be refused or if reimbursement otherwise currently provided by Medicare or Medicaid in different states is unavailable or inadequate.

The Company does not manufacture, market, or sell the Adaptive Aerosol Delivery (AAD) inhalation devices used to deliver Ventavis, and the availability and amount of coverage and reimbursement for the inhalation devices is beyond its control. CoTherix believes that government reimbursement policies have not historically recognized the increased cost inherent in devices that have very complex designs capable of providing the dose precision of the AAD inhalation devices. The maximum reimbursement amount set by Medicare for the AAD inhalation devices may be seen as inadequate. In such case, the Company's specialty pharmacy customers may stop distributing AAD inhalation devices, which would significantly harm sales of Ventavis as they are the only inhalation devices approved for use with Ventavis, or may seek to renegotiate their contracts with CoTherix, which could increase the Company's costs and have a material adverse effect on its business, financial condition, and profitability.

An ongoing trend has been for government payors to apply downward pressure on the reimbursement of pharmaceutical products and devices. CoTherix expects this trend to continue. There are currently, and the Company expects that there will continue to be, a number of federal and state proposals to implement controls on reimbursement and pricing, directly and indirectly. While CoTherix cannot predict whether

such legislative or regulatory proposals will be adopted, the adoption of such proposals could have a material adverse effect on the Company.

In addition, any coverage or reimbursement by third-party payors, including governmental authorities, private health insurers, and other organizations, may be decreased or eliminated in the future due to, among other things, any failure by CoTherix or its specialty pharmacy distributors to comply with regulatory requirements. Coverage and reimbursement may not be available or adequate to allow the Company to sell Ventavis on a competitive and profitable basis. Many payors are increasingly challenging the prices charged for pharmaceutical products, medical products, and services. CoTherix's business and financial condition would be affected negatively if reimbursement is inadequate or not available for Ventavis or the inhalation device used to administer Ventavis.

If the Company's competitors have or introduce products that are preferred over Ventavis, its commercial opportunity will be significantly reduced or eliminated.

CoTherix faces intense competition from established pharmaceutical and biotechnology companies, as well as from academic institutions, government agencies, and private and public research institutions, among others. The Company's commercial opportunity may be reduced significantly if its competitors develop and commercialize products that are safer, more effective, more convenient, have fewer side effects, or are less expensive than Ventavis. There currently is no cure for PAH other than lung transplantation. If a cure for PAH is developed, Ventavis may become obsolete.

Various products currently are marketed for the treatment of PAH, including prostacyclins such as epoprostenol, marketed as Flolan® by Myogen, and subcutaneous and intravenous versions of treprostinil, marketed as Remodulin® by United Therapeutics. There are also approved oral therapies for the treatment of PAH. These include an endothelin receptor antagonist, or ETRA, bosentan, marketed as Tracleer® by Actelion, and a phosphodiesterase inhibitor, or PDE-5 inhibitor, sildenafil, which is marketed as Revatio™ by Pfizer. The availability of these competitive products may harm sales of Ventavis.

In addition, a number of new PAH treatments are being developed. United Therapeutics is currently enrolling patients in a Phase II/III study of an inhaled formulation of treprostinil. According to United Therapeutics, the inhaled formulation of trepostinil requires a shorter period of inhalation compared to Ventavis, as well as fewer doses per day. Other products being developed include additional oral ETRAs such as Encysive Pharmaceuticals' Thelin™ (sitaxsentan), which received an approvable letter from the FDA in March 2006 indicating that further information or clinical trials will be required by the FDA before final approval is granted (and with respect to which Encysive has since said it has responded), and Myogen's ambrisentan, which is currently in Phase III clinical trials, as well as other classes of agents, including long-acting PDE-5 inhibitors such as Lilly ICOS' Cialis® (tadalafil), and antiproliferative agents such as Novartis AG's Gleevec® (imatinib mesylate).

If any other drugs or an inhaled formulation of trepostinil are approved by the FDA and prove to be safer, more effective, or more convenient than Ventavis, then prescriptions of Ventavis by physicians and patient use of Ventavis would likely be significantly reduced. Many of CoTherix's competitors currently have significantly greater financial resources than the Company does that could be applied to identifying new products, researching, and developing new and existing products, conducting clinical trials, obtaining regulatory approvals, managing manufacturing, and marketing, selling, and distributing approved products. Pricing by its competitors may require CoTherix to sell Ventavis at a price that adversely affects its operating results.

The Company's ability to compete effectively depends upon, among other things:

- effectively utilizing its sales and marketing organization;
- ensuring availability of Ventavis and availability and market acceptance of the I-neb device;
- expanding the commercial potential of Ventavis through successful completion of its ongoing and planned clinical development activities;

- reprogramming the I-neb device to decrease duration of dosing; and
- investigating alternative formulations of iloprost, the active ingredient in Ventavis, to reduce dosing frequency and/or treatment time to improve patient convenience.

If Ventavis does not retain and continue to gain significant market acceptance in the U.S. among patients and health care professionals, CoTherix's business will be harmed.

Ventavis is the Company's only commercial product. Ventavis may not retain and continue to gain market acceptance among patients and health care professionals in the U.S. The degree of market acceptance of Ventavis depends on a number of factors. Market acceptance of Ventavis may be limited because the available method of delivery, and the prescribed dosing duration and frequency, are inconvenient compared to some other drugs. The inhalation device previously provided with Ventavis, the Prodose AAD device, is not compact and must be plugged into an electrical outlet. The newer AAD inhalation device, the I-neb, is hand-held and battery operated. The I-neb has only recently become commercially available and the Company cannot guarantee that it will gain general or lasting market acceptance. Any problems encountered with inhalation devices may cause patients to use other drugs, which may negatively impact CoTherix's sales and harm its business.

Market acceptance of Ventavis may also be impaired by any problems that affect the performance of the inhalation devices used to deliver Ventavis. Inadequate quality assurance, quality control, or failure to adhere to manufacturing standards by Respironics could discourage patients or physicians from adopting Ventavis as a therapy. The performance capabilities of the I-neb device and the reliability of Respironics' quality assurance and controls in its manufacturing process over the long term are uncertain. Failure to increase acceptance of prostacyclin therapy delivered through inhalation as opposed to continuous infusion by subcutaneous delivery or by infusion pump could limit the Company's market opportunity. CoTherix believes some patients may prefer to use, and some physicians may prefer to prescribe, other prostacyclin treatments rather than Ventavis. Patients who have severe PAH may require other prostacyclin therapies because of the need for continual dosing.

Side effects also could negatively affect market acceptance of Ventavis. Side effects of Ventavis observed during clinical trials included fainting, shortness of breath, fatigue, chest pain, nausea, coughing, and headaches. In addition, although the FDA label for Ventavis specifies six to nine doses per day, the Company cannot be certain that patients will comply with this dosing regimen, which may reduce efficacy of the treatment and, in turn, have a material adverse effect on its sales of Ventavis. CoTherix believes patients on average take six doses of Ventavis per day, and this average may be reduced in the future. Any or all of these factors could limit market acceptance of Ventavis and significantly harm the Company's business.

Any interruption in the supply or problems that adversely affect the AAD inhalation devices could seriously harm CoTherix's business or result in its inability to sell Ventavis.

Respironics is the sole supplier of AAD inhalation devices, which are the only inhalation devices approved for use with Ventavis. If for any reason Respironics fails to supply specialty pharmacy companies with an adequate number of inhalation devices to meet patient demand, the Company's business would be significantly harmed. If inhalation devices approved for use with Ventavis became unavailable, its specialty pharmacy customers could not secure inhalation devices from a third party on a timely basis, and therefore CoTherix's sales will be significantly harmed.

The I-neb device became commercially available in December 2005, and is the first commercial device utilizing Respironics' novel vibrating mesh technology together with its AAD technology. The design of the device may not provide the advantages expected, and the I-neb device may not perform in the marketplace as expected or gain general or lasting acceptance by patients and physicians. The Company believes the adoption of the I-neb device will expand its market opportunity and increase its sales. However, if the I-neb device is not perceived by patients and physicians as improving convenience, CoTherix's reputation, market opportunity, and future sales could be harmed.

Inhalation devices are inherently mechanical, and, as a result, any individual device may not operate as intended and can fail from time to time and may fail to provide the intended advantages based on improper usage by patients. In particular, newly introduced devices or devices using new technology, such as the I-neb device, may experience unexpected difficulties that are not discovered until they are in use by patients for a significant period of time. In addition, patients may find unfamiliar devices to be difficult to use and may require additional training.

If devices fail to operate properly or efficiently or failures were to occur on a widespread basis, or if the devices are harder to use or require additional patient training, the Company cannot be certain that such issues could be resolved in a timely and cost-effective manner. If it is determined that a device could potentially harm patients, distribution of the device could be suspended or recalled, which could have a material adverse effect on CoTherix's business.

If the Company decides to seek an alternate supplier of inhalation devices, it will need to identify and contract with that new supplier to demonstrate comparability with this new device and to obtain FDA approval for the use of the new device with Ventavis. The FDA process requires the clearance of a 510(k) application for the device and the approval of a supplemental New Drug Application, or sNDA for the use of the device with Ventavis. Seeking FDA clearance and approval of any device is costly and time-consuming, with no assurance that the FDA will grant clearance or approval.

Respironics manufactures the I-neb devices outside of the U.S., utilizing a third-party manufacturer, and is subject to the quality system regulation requirements of the FDA and other manufacturing standards and regulatory requirements imposed by the FDA and foreign authorities. CoTherix has no control over Respironics' manufacturing process. Failure by Respironics to maintain required manufacturing standards or to implement proper quality assurance and quality control could result in serious patient injury, product recalls or withdrawals, delays or failures in product testing or delivery, product malfunctions or inefficiencies, cost overruns, or other problems that could seriously harm the Company's business. Respironics could also encounter difficulties involving production yields as well as shortages of qualified personnel. In addition, Respironics is subject to ongoing inspections and regulation by the FDA and corresponding foreign and state agencies and may fail to meet these agencies' acceptable standards of compliance.

CoTherix has no manufacturing capabilities and relies on third parties for the clinical and commercial production of its product and product candidates, which puts at risk its ability to obtain Ventavis for distribution and continued development and fasudil for development.

The Company does not operate manufacturing facilities. It has little experience in drug formulation and no experience in drug manufacturing, and it lacks the resources and the capabilities to manufacture Ventavis or fasudil on a clinical or commercial scale. The Company does not intend to develop manufacturing facilities in the foreseeable future.

CoTherix relies on Schering AG (now Bayer-Schering AG) as its sole supplier for the clinical and commercial production of Ventavis. Schering AG may not perform as agreed, may not continue producing Ventavis, or its performance may be disrupted by internal corporate reasons, including its recent acquisition by Bayer AG. Moreover, although Bayer AG is obligated to perform under the Company's contracts with Schering AG, Bayer AG may have other corporate priorities. CoTherix relies on Asahi Kasei as its initial supplier of fasudil for a limited amount of early clinical supplies and will need to identify a future third-party manufacturer in the future. Any failure to do so on a timely or cost-effective basis would delay CoTherix's fasudil development program and have a material adverse affect on its business and financial position. In addition, in the event of a natural disaster, failure to continue to meet FDA or other regulatory requirements, business failure, strike, or other difficulty, the production and supply of Ventavis would be interrupted, resulting in delays and additional costs.

CoTherix's supply of Ventavis and fasudil are subject to additional risks of interruption because they are manufactured outside of the U.S. Schering AG manufactures the iloprost drug substance for Ventavis in Germany and then transports it to Spain where the final drug product is finished and packaged. The Company must maintain clearance from the appropriate foreign health authorities to export Ventavis into the U.S. CoTherix may face difficulties in importing Ventavis and fasudil into the U.S. as a result of, among other things, FDA import inspections, incomplete or inaccurate import documentation, or defective

packaging. In addition, the Company's manufacturers are subject to ongoing inspections and regulation by the FDA and corresponding foreign and state agencies and may fail to meet these agencies' acceptable standards of compliance.

The Company's manufacturers may also fail to maintain required FDA manufacturing standards, including the FDA's current Good Manufacturing Practices, or cGMP. Any failure by to maintain such standards could result in patient injury or death, product recalls or withdrawals, delays or failures in product testing or delivery, cost overruns, or other problems that could seriously harm the Company's business. The Company's manufacturers also could encounter difficulties involving production yields, quality control, and quality assurance, as well as shortages of qualified personnel.

Upon the occurrence of any of the aforementioned events, CoTherix's ability to switch manufacturers would be very difficult and prolonged for a number of reasons, including:

- the number of potential manufacturers is limited and the Company may not be able to negotiate agreements with alternative manufacturers on commercially reasonable terms or at all;
- the proprietary manufacturing process is lengthy and complex; and
- the FDA must approve any replacement facility prior to manufacturing product for commercial use, which requires new testing and compliance inspections.

The Company has agreed to purchase its Ventavis requirements exclusively from Schering AG. The process of manufacturing Ventavis is an extremely complex and lengthy process. If Schering AG ceases to manufacture Ventavis or is unable to provide CoTherix with supplies of Ventavis for any reason, it may experience significant interruption or failure of its supply of Ventavis or in further clinical development of the product as the Company develops internal manufacturing capabilities or seeks a third-party manufacturer.

CoTherix must commit to minimum purchase requirements of Ventavis from Schering AG and if it fails to accurately forecast its need for Ventavis its business will be harmed.

Under the Company's agreement with Schering AG, it has currently committed to purchasing minimum amounts of Ventavis through the third quarter of 2008. If CoTherix underestimates its purchase requirements, it will not be able to meet the needs of patients and patients may turn to alternate treatments. The Company evaluates the need to provide reserves for contractually committed future purchases of inventory that may exceed forecasted future demand. In making these assessments, CoTherix is required to make judgments as to the future demand for current or committed inventory levels. The Company is also required to make judgments as to the expiration dates of its product, since product can no longer be used after its expiration date. As part of its excess inventory assessment CoTherix also considers the expiration date of product to be manufactured in the future under minimum purchase obligations.

Significant differences between the Company's current estimates and judgments, and future estimated demand for product and the useful life of inventory, may result in significant charges for excess inventory or purchase commitments in the future. These differences, whether CoTherix overestimates or underestimates its purchase requirements, could have a material adverse effect on its financial condition and results of operations.

CoTherix's product sales may depend on the health and personal preferences of patients.

PAH is a fatal disease and the discontinuance rate of use of Ventavis is affected by the seriousness of the illness. As the health of a PAH patient declines, he or she may not be able to administer drugs using an inhalation device, such as the AAD inhalation devices, or may require 24-hour continuous treatment. Under these or other circumstances, or because of personal preference, the patient may opt for competitors' prostacyclin products administered intravenously or subcutaneously. In addition, doctors may prescribe, or patients who use Ventavis may choose to take, fewer than the recommended number of doses of Ventavis, or may believe using Ventavis is inconvenient and opt for other treatments. The Company believes patients take on average six doses of Ventavis per day, and that this number may

decrease as more is learned about the use of Ventavis in combination with other drugs. All of the above factors may have the effect of weakening CoTherix's sales and harming its business.

The Company's sales could be harmed by imports from countries where Ventavis may be available at a lower price.

Rights to market Ventavis in Canada are held by Berlex Laboratories, a subsidiary of Schering AG. Berlex Laboratories filed for marketing approval with Health Canada, which is reviewing the application and which could grant approval as early as this year. In the U.S., prices for pharmaceuticals are generally higher than in other countries, including the bordering nations of Mexico and Canada, which may maintain government price controls. The ability of patients and other customers to obtain lower priced imports has grown significantly as a result of regulatory harmonization, common market or other trade initiatives, and the Internet. The volume of illegal imports into the U.S. continues to rise as foreign pharmacies target American purchasers and American purchasers become more aware of less expensive illegal imports. In addition, political forces may result in U.S. legislative or executive action that would legalize lower priced imports. CoTherix's sales of Ventavis in the U.S. may be reduced if products are imported into the U.S. from lower price markets whether legally or illegally. Any decrease in the Company's sales could have a material adverse impact on its business.

The loss of CoTherix's rights to market and sell Ventavis would eliminate its only current source of product sales and the Company may not be able to continue its business.

The Company has licensed from Schering AG the exclusive U.S. rights to develop and commercialize Ventavis for the treatment of pulmonary hypertension. Schering AG has the right to terminate CoTherix's license if the Company materially breaches its obligations under the agreement and fails to cure any such breach within a specified period of time, including if CoTherix fails to use its best efforts to commercialize Ventavis in the U.S. or make payments required under the agreement, or if the Company becomes insolvent. CoTherix's ability to meet these obligations is dependent upon numerous factors, including some factors that are outside of the Company's control. If CoTherix's agreement with Schering AG were terminated, it would have no further rights to develop and commercialize Ventavis for any indication. Ventavis is the Company's only commercial product, and its only current source of product sales. The termination of the Schering AG agreement would eliminate CoTherix's product sales and it may not be able to continue its business.

The Company is subject to extensive government regulation. This increases its costs and may impair sales of Ventavis.

Government regulation includes inspection of and controls over testing, manufacturing, safety and environmental controls, efficacy, labeling, advertising, marketing, promotion, record keeping, reporting, sale and distribution, import, export and the distribution of samples of pharmaceuticals, and electronic records and signatures. The FDA and foreign regulatory authorities impose significant restrictions on the indicated uses and marketing of approved pharmaceutical products, including Ventavis; subject a marketed product, its manufacturer, and the manufacturer's facilities to continual review and periodic inspections; require ongoing adverse event and other reporting; and may impose ongoing requirements for post-approval studies. CoTherix must also obtain additional approvals for product manufacturing and labeling changes.

The FDA closely regulates the labeling, marketing, and promotion of approved drugs. FDA rules for pharmaceutical promotion require that the Company only promotes Ventavis for uses that have been approved by the FDA, and that all of its promotional materials be adequately substantiated and that information presented contain a fair and balanced description of the risks and benefits of Ventavis, the safety of Ventavis, and the limitations on its use. For example, while CoTherix's label includes information regarding the tolerability and dosing of Ventavis in combination with bosentan, it is not permitted to promote Ventavis as a combination therapy with bosentan or any other drug unless and until it has developed what the FDA calls substantial evidence or clinical experience to support such uses. Government regulators recently have increased their scrutiny of the promotion and marketing of drugs.

In addition to FDA requirements, regulatory and law enforcement agencies such as the Department of Health and Human Services' Office of Inspector General, the U.S. Department of Justice, and state Attorneys General monitor and investigate pharmaceutical sales, marketing, and other practices. For example, sales, marketing, and scientific/educational grant programs must comply with the Medicare-Medicaid Anti-Fraud and Abuse Act, as amended, the False Claims Act, as amended, Medicaid rebate requirements, and similar state laws.

In recent years, actions by companies' sales forces and marketing departments have been scrutinized intensely to ensure, among other things, that actions by such groups do not qualify as "kickbacks" to healthcare professionals. A "kickback" refers to the provision of any item of value to a healthcare professional or other person in exchange for purchasing, recommending, or referring an individual for an item or service reimbursable by a federal healthcare program. These kickbacks increase the expenses of the federal healthcare program and may result in civil penalties, criminal prosecutions, and exclusion from participation in government programs, any of which would adversely affect the Company's financial condition and business operations. In addition, even if CoTherix is not determined to have violated these laws, government investigations into these issues typically require the expenditure of significant resources and generate negative publicity, which would also harm the Company's business and financial condition.

CoTherix is also subject to government regulation with respect to the prices it charges and the rebates it offers or pays to customers, including rebates paid to certain governmental entities, such as the Medicaid rebate requirements of the Omnibus Budget Reconciliation Act of 1990. Products made available to authorized users of the Federal Supply Schedule of the General Services Administration are subject to additional laws and requirements. All of the Company's activities are potentially subject to federal and state consumer protection and unfair competition laws. These legal and regulatory requirements are enforced by the FDA, the Centers for Medicare and Medicaid Services, other divisions of the U.S. Department of Health and Human Services, the U.S. Department of Justice, state and local governments, and their respective foreign equivalents. Government regulation substantially increases the cost of developing, manufacturing, distributing, marketing, and selling pharmaceutical products.

CoTherix has developed and instituted a corporate compliance program based on what it believes are current best practices, and it continues to update the program in response to newly implemented or changing regulatory requirements. The Company has significantly fewer employees than many other companies in its industry, and it relies heavily on third parties to conduct many important functions, but cannot control the compliance activities of these third parties. Furthermore, CoTherix cannot ensure that it is or will be in compliance with all potentially applicable regulations, or that this program will protect it from future lawsuits or investigations.

Depending on the circumstances, failure to meet applicable legal and regulatory requirements can result in costly and burdensome investigations, adverse publicity, warning letters, criminal prosecution, fines, or other penalties, injunctions, recall or seizure of products, total or partial suspension of production, suspension or revocation of its regulatory approval of Ventavis, denial or withdrawal of other pre-marketing product approvals, suspension or termination of ongoing clinical trials, refusal to approve pending applications or supplements to approved applications filed by the Company or accept filings for new applications or supplements, private "qui tam" actions brought by individual whistleblowers in the name of the government, or refusal to allow CoTherix to enter into supply contracts, including government contracts.

If fasudil fails in clinical studies, the Company will not be able to obtain FDA, EMEA, and other international approvals and will not be able to sell fasudil.

Fasudil has not been approved for sale in the U.S. or any foreign market for treatment of PAH or stable angina. In order to commercialize fasudil, CoTherix must receive regulatory approvals. To obtain those approvals, it must conduct clinical studies demonstrating that fasudil is safe and effective. If the Company cannot obtain approval from the FDA, EMEA, and other international drug regulators for fasudil, it could not be commercialized and CoTherix would not be able to recoup the significant expenses it will incur for fasudil's development.

CoTherix currently plans to initiate Phase II clinical trials of fasudil for treatment of PAH and stable angina in 2007. If the Company identifies any safety issues associated with fasudil during these trials, it may be delayed or prevented from initiating a pivotal Phase III trial for fasudil. Despite the time and money expended, regulatory approvals are never guaranteed. CoTherix's planned clinical studies might be delayed or halted for various reasons, including:

- fasudil is not effective, or physicians think that the drug is not effective;
- patients do not enroll in the clinical trials at the rate the Company expects;
- patients experience unacceptable side effects during treatment;
- other investigational or approved therapies are viewed as more effective or convenient by physicians or patients; or
- drug supplies are not available or suitable for use in the clinical trials.

In addition, the FDA, EMEA, and other international regulatory authorities have substantial discretion in the approval process. The FDA, EMEA, and other international regulatory authorities may not agree that CoTherix has demonstrated that fasudil is safe and effective in indications it is pursuing.

The Company's clinical trials for fasudil may be extended, suspended, delayed, or terminated at any time. Even short delays in the commencement and progress of CoTherix's trials may lead to substantial delays in the regulatory approval process for fasudil, which will impair the Company's ability to generate revenues from it.

CoTherix may extend, suspend, delay, or terminate clinical trials for fasudil at any time for various reasons, including regulatory actions by the FDA, EMEA, or other international regulatory agencies, actions by institutional review boards, failure to comply with good clinical practice requirements, concerns regarding health risks to test subjects, or inadequate supply of the product candidate. In addition, the Company's ability to conduct clinical trials for fasudil may be limited by the number of suitable patient candidates. Consequently, CoTherix may experience delays in obtaining regulatory approval for fasudil. Extension, suspension, delay, or termination of its clinical trials for fasudil may:

- adversely affect its ability to develop or commercialize fasudil;
- impose significant additional costs on the Company;
- potentially diminish any competitive advantages that it may attain;
- adversely affect its ability to enter into other collaborations;
- cause the termination of its license agreement with Asahi Kasei, which termination may impose significant penalties on CoTherix;
- cause the Company to abandon the development of fasudil; or
- limit its ability to obtain additional financing on acceptable terms, if at all.

State pharmaceutical marketing compliance and reporting requirements may expose CoTherix to regulatory and legal action by state governments or other government authorities.

In recent years, several states, including California, Vermont, Maine, Minnesota, New Mexico, and West Virginia, as well as the District of Columbia, have enacted legislation requiring pharmaceutical companies to establish marketing compliance programs and file periodic reports with the state on sales, marketing, pricing, and other activities. For example, California has enacted a statute requiring pharmaceutical companies to adopt a comprehensive compliance program that is in accordance with the Office of Inspector General of the Department of Health and Human Services *Compliance Program Guidance for Pharmaceutical Manufacturers*. This compliance program must include policies for compliance with the

Pharmaceutical Research and Manufacturers of America *Code on Interactions with Healthcare Professionals,* as well as a specific annual dollar limit on gifts or other items given to individual healthcare professionals in California. The policies must be posted on the Company's public website along with an annual declaration of compliance.

Vermont, Maine, Minnesota, New Mexico, Texas, the District of Columbia, and West Virginia have also enacted statutes of varying scope that impose reporting and disclosure requirements upon pharmaceutical companies pertaining to drug pricing and payments and costs associated with pharmaceutical marketing, advertising, and promotional activities, as well as restrictions upon the types of gifts that may be provided to healthcare practitioners. Similar legislation is being considered in other states. In addition, a number of states have adopted or are considering adoption of what are known as "drug pedigree laws," which require tracking drug distribution to prevent counterfeit drugs from being introduced into the supply chain, and loss reporting requirements, which require drug manufacturers to report any drug products that are unaccounted for. Many of these state requirements are new and uncertain, and available guidance is limited. The Company is in the process of identifying the universe of state laws applicable to pharmaceutical companies and is taking steps to ensure that it comes into compliance with all such laws. Unless and until CoTherix is in full compliance with these laws, it could face enforcement action and fines and other penalties, and could receive adverse publicity, any of which could harm its business.

Sales of Ventavis could be harmed and the Company's clinical trials in PAH can be disrupted or delayed due to a large number of clinical trials competing for available PAH patients.

There are a number of current and planned clinical trials by companies that compete with CoTherix and that currently have drugs available to treat PAH, as well as companies with investigational drugs to treat PAH. These trials compete for patients who might otherwise be available to participate in the Company's clinical trials or be appropriate for Ventavis therapy. Through 2007, the Company expects up to 1,500 PAH patients to enroll in clinical trials conducted by it and other companies. The competition among clinical trials for patients could harm the Company's ability to enroll patients in its PAH clinical trials for Ventavis, and fasudil, delaying its development plans.

Patients who enroll in clinical trials generally receive free drug during the trial, and are therefore taken out of the potential market for Ventavis. In addition, patients who participate in clinical trials also may be offered free drug for up to one year after a trial has concluded. If other clinical trials successfully recruit patients who would otherwise be Ventavis patients, CoTherix's sales or sales growth would be harmed and its clinical trials could be disrupted or delayed, which could harm future market opportunities for Ventavis.

The Company relies on third parties to conduct its clinical trials. If these third parties do not successfully carry out their contractual duties or meet expected deadlines, CoTherix may not be able to obtain additional regulatory approval for Ventavis, or obtain regulatory approval to commercialize fasudil.

The Company relies on third parties, such as contract research organizations (CROs), medical institutions, clinical investigators, and contract laboratories, to conduct its clinical trials, including its ongoing Phase II ACTIVE Trial and Phase III VISION Trial, as well as other planned trials for Ventavis. CoTherix may not be able to control the amount and timing of resources that third parties devote to its clinical trials. Identifying and enrolling patients in clinical trials from the limited available patient population is a time-consuming and sometimes difficult process, and the Company depends on these third parties to achieve full and timely enrollment. Establishing and maintaining good relationships with individual principal investigators and clinical trial sites is critical to CoTherix.

For example, in the event that the Company is unable to maintain its relationships with any of its selected clinical trial sites, or elects to terminate the participation of any of these sites, it may experience the loss of follow-up information on patients enrolled in the affected clinical trial unless it is able to transfer the care of those patients to another qualified site.

In addition, principal investigators for its clinical trials may serve as scientific advisors or consultants to the Company from time to time and receive compensation in connection with such services. If these relationships and any related compensation result in perceived or actual conflicts of interest, the integrity of the data generated at the applicable clinical trial site may be jeopardized. CoTherix has no experience in conducting clinical trials in Europe, and consequently, for the VISION Trial, it is relying on a CRO to act as its European legal representative and conduct the VISION Trial, including assisting in preparation of regulatory submissions in Europe and assisting in managing the clinical sites in Europe. CoTherix also plans to rely on third parties with respect to other clinical trials for Ventavis and fasudil in Europe.

If any third parties do not successfully carry out their contractual duties or obligations or meet expected deadlines, or if the quality or accuracy of the clinical data obtained in clinical trials is compromised due to the failure to adhere to its clinical protocols or for other reasons, the Company's clinical trials may be extended, delayed, or terminated, and it may not be able to obtain regulatory approval of fasudil or expand commercial opportunities for Ventavis.

CoTherix intends to contract with third parties to conduct its clinical trials for fasudil. If these third parties do not carry out their contractual duties or obligations or meet expected deadlines, if the third parties need to be replaced, or if the quality or accuracy of the clinical data they obtain is compromised due to failure to adhere to clinical protocols or for other reasons, the Company's planned clinical trials may be extended, delayed, or terminated. Any extension, delay, or termination of its trials would delay the Company's ability to commercialize fasudil.

If CoTherix's clinical trials or clinical disease registry generate data that are less favorable than historical data or are viewed as unsuccessful, or if its clinical trials experience significant delays or adverse events, its business could be harmed significantly.

The Company conducted pre-clinical studies and clinical trials with respect to Ventavis and plans to do so with respect to fasudil, and has initiated a clinical disease registry to collect observational data on U.S. patients with PAH, WHO Group 1. Clinical development is a long, costly, and uncertain process and is subject to delays. CoTherix may encounter delays or rejections based on its inability to enroll or maintain enrollment of enough patients to complete its clinical trials or clinical disease registry due to study design, competition for patients by other clinical trials, or other reasons.

Even if the Company is able to enroll a sufficient number of patients, its current or future clinical trials may not produce positive results or adequate clinical data necessary to obtain the desired marketing approval, or may result in adverse events, which could interrupt, delay, or halt its clinical trials, and could result in unfavorable regulatory actions, including denial for Ventavis to be marketed for new indications, in combination with other therapies, or otherwise outside of its current label. CoTherix's product development costs will also increase if it experiences delays or failures in its clinical trials, and significant delays could allow its competitors to bring products to market before it does and impair its ability to commercialize its products or potential products.

Furthermore, any future product candidate, including alternative formulations of iloprost, the active ingredient in Ventavis, Ventavis used in combination therapy or for additional indications, or fasudil, may prove to be ineffective or only moderately effective in treating a targeted indication or when used in combination therapy, or may prove to have undesirable or unintended side effects, toxicities, or other characteristics that may preclude CoTherix from obtaining the desired regulatory approval, prevent or limit an intended commercial use, or raise concerns regarding the safety or efficacy of Ventavis for its current approved uses or fasudil for its intended treatment of PAH and stable angina—any of which could have a material adverse effect on the Company's business. In addition, its clinical disease registry may not produce positive data with respect to Ventavis or its use.

The FDA and other regulatory authorities may not approve any future product that CoTherix may develop, approve Ventavis for any additional indications or combination therapy, or approve fasudil for the treatment of PAH and stable angina. Any such failure may severely harm the Company's business. In addition, any approvals it may obtain may not cover all of the clinical indications for which CoTherix seeks approval, or contain significant limitations in the form of narrow indications, warnings, precautions, or contraindications with respect to conditions of use, or in the form of onerous risk management plans, restrictions on distribution, or post-approval study requirements.

Even if Ventavis, fasudil, or any future product candidate meets safety and efficacy endpoints in clinical trials, regulatory authorities may not approve the Company's request for labeling claims, or it may face post-approval problems that require withdrawal from the market.

Ventavis, any alternative formulations of iloprost (the active ingredient in Ventavis), fasudil, or any of CoTherix's future product candidates, may not receive the sought-after regulatory approval even if they achieve their endpoints in clinical trials. Regulatory agencies may approve fasudil, an alternative formulation of iloprost, or another product candidate for fewer conditions than requested or raise concerns regarding the safety or efficacy of Ventavis for its current approved use, may grant approval subject to the performance of post-marketing studies, or may not approve the labeling claims that are necessary or desirable for the successful commercialization of Ventavis, an alternative formulation of iloprost, fasudil, or any future product candidates. Even after regulatory approval, the Company's product or future product candidates may later exhibit adverse effects that limit or even prevent their widespread use or that force it to withdraw from the market. Any unforeseen problems with an approved product or any violation of regulations could result in restrictions on the product, including its withdrawal from the market.

CoTherix is, and potentially may be, subject to new federal and state requirements to submit information on its open and completed clinical trials to public registries and databases.

In 1997, a public registry of open clinical trials involving drugs intended to treat serious or life-threatening diseases or conditions was established under the Food and Drug Administration Modernization Act, or FDMA, in order to promote public awareness of and access to these clinical trials. Under FDMA, pharmaceutical manufacturers and other trial sponsors are required to post the general purpose of these trials, as well as the eligibility criteria, location, and contact information of the trials. Since the establishment of this registry, there has been significant public debate focused on broadening the types of trials included in this or other registries, as well as providing for public access to clinical trial results. A voluntary coalition of medical journal editors has adopted a resolution to publish results only from those trials that have been registered with a no-cost, publicly accessible database, such as www.clinicaltrials.gov.

The Pharmaceuticals and Research Manufacturers of America, or PhRMA, has also issued voluntary principles for its members to make results from certain clinical studies publicly available and has established a website for this purpose. Other groups have adopted or are considering similar proposals for clinical trial registration and the posting of clinical trial results. The state of Maine has enacted legislation, with penalty provisions, requiring the disclosure of results from clinical trials involving drugs marketed in the state, and similar legislation has been introduced in other states. Federal legislation has been introduced to expand www.clinicaltrials.gov and to require the inclusion of study results in this registry. In some states, such as New York, prosecutors have alleged that a lack of disclosure of clinical trial information constitutes fraud, and these allegations have resulted in settlements with pharmaceutical companies that include agreements to post clinical trial results. The Company's failure to comply with any clinical trial posting requirements could expose it to negative publicity, fines, and other penalties, all of which could materially harm its business.

If product liability lawsuits are asserted against CoTherix, it may be required to limit or halt commercialization of Ventavis, may incur substantial liabilities, and may suffer damages that exceed its insurance coverage.

The Company faces product liability exposure related to the marketing and distribution of Ventavis and the clinical testing of Ventavis, fasudil, and other product candidates. It also faces such exposure related to inhalation devices used to administer its product or product candidates, even though it does not manufacture or commercially distribute those devices. If CoTherix cannot defend itself against product liability claims, it may incur substantial liabilities. Regardless of merit or eventual outcome, liability claims may result in:

- decreased demand for its product and any future product candidates;
- injury to its reputation;
- withdrawal of clinical trial participants;
- costs of related litigation;
- diversion of its management's attention;
- substantial monetary awards to patients and others;
- loss of sales; and
- the inability to commercialize Ventavis or any future product or product candidates, including fasudil and alternative formulations of Ventavis.

CoTherix has product liability insurance that covers the sale of its commercial product and its clinical trials in amounts that it believes are adequate and appropriate for similarly situated companies in the industry. The Company monitors the levels of its coverage and adjusts them periodically. However, it may not have adequate protection against potential liabilities. In addition, insurance coverage is becoming increasingly costly. CoTherix may not be able to maintain existing insurance coverage at a reasonable cost and it may not be able to obtain additional insurance coverage that will be adequate to satisfy any potential liability that may arise.

Third parties may own or control patents or patent applications that the Company may be required to license to continue commercializing Ventavis or to develop and commercialize fasudil, or that could result in litigation that would be costly and time-consuming.

CoTherix's continued commercialization of Ventavis depends upon its ability to develop, manufacture, market, and sell Ventavis without infringing the proprietary rights of third parties. Similarly the Company's ability to develop and commercialize fasudil depends on the sufficiency of the proprietary rights it licensed from Asahi Kasei Pharma and not infringing on the proprietary rights of others. A number of pharmaceutical and biotechnology companies, universities, and research institutions have or may be granted patents that cover technologies similar to the technologies owned by or licensed to CoTherix. The Company may choose to seek, or be required to seek, licenses under third-party patents, which would likely require the payment of license fees or royalties or both. For example, CoTherix is aware of a use patent that it may seek to license that covers the combination of Ventavis and PDE-5 inhibitors.

The Company may also be unaware of existing patents that may be infringed by Ventavis or fasudil. Because patent applications can take many years to issue, there may be other currently pending applications that may later result in issued patents that are infringed by Ventavis or fasudil. Moreover, any necessary license may not be available to CoTherix on commercially reasonable terms, or at all.

There is a substantial amount of litigation involving patent and other intellectual property rights in the biotechnology and pharmaceutical industries generally. If a third party claims that the Company infringes on its technology, its business and results of operations could be harmed by a number of factors, including:

- infringement and other intellectual property claims, even if without merit, are costly and time-consuming to litigate and can divert management's attention from its core business;
- monetary damage awards for past infringement can be substantial;
- a court may prohibit the Company from selling Ventavis unless the patent holder chooses to license the patent to it;
- a court may prohibit CoTherix from developing fasudil unless the patent holder chooses to license the patent to it; and

- if a license is available from a patent holder, it may have to pay substantial royalties and other amounts.

The Company may be forced to bring an infringement action if it believes that a competitor is infringing its protected intellectual property. Any such litigation will be costly and time-consuming and will divert management's attention, and the outcome of any such litigation may not be favorable to CoTherix.

The Company's intellectual property rights may not preclude competitors from developing competing products and its business may suffer.

If CoTherix is not able to protect its proprietary technology, trade secrets, and know-how, its competitors may use its intellectual property to develop competing products. The Company's patents, including its licensed patents relating to the use and manufacture of iloprost and fasudil, may not be sufficient to prevent others from competing with CoTherix. The composition of matter patent covering iloprost expired in September 2004, and the U.S. process patents covering the manufacture of Ventavis will expire in 2007 and 2010. The U.S. patent licensed from Asahi Kasei Pharma covering fasudil hydrochloride hydrates and tablets comprising fasudil hydrochloride expires in June 2016, and the U.S. patent licensed from Asahi Kasei Pharma covering oral sustained release formulations of fasudil hydrochloride providing particular dissolution rates as well as methods of evaluating sustained release formulations of fasudil hydrochloride expires in August 2019.

Therefore, CoTherix may no longer depend on this composition of matter patent and in the future will not be able to rely on these process patents to exclude competitors from developing iloprost for the treatment of PAH or fasudil for the treatment of PAH and stable angina. Further, while Schering AG may have trade secrets relating to the manufacture of Ventavis, such trade secrets may become known or independently discovered, or competitors may develop alternative ways to manufacture the drug. All of these factors may harm the Company's competitive position. CoTherix's issued patents and those that it may issue in the future, or those licensed to it, may be challenged, invalidated, or circumvented—any of which could limit its ability to stop competitors from marketing related products or limit the term of patent protection that it otherwise may have.

CoTherix may require additional financing to fund its operations and continue to commercialize Ventavis and to develop fasudil and alternate formulations of iloprost.

The Company expects that its operating expenses will increase for the next several years, and that it will continue to spend substantial amounts to commercialize Ventavis; invest in its development to, among other things, expand Ventavis' potential for additional indications and for use in combination with other FDA-approved products; develop alternative formulations of iloprost, the active ingredient in Ventavis, and decrease its inhalation time; conduct pre-clinical and clinical studies and other development of fasudil; and license or acquire other products or product candidates. CoTherix estimates that its existing cash and cash equivalents and securities available-for-sale will be sufficient to meet its projected operating requirements at least through 2007. However, the Company's forecast of the period of time through which its cash and cash equivalents and securities available-for-sale will last, including cash from its sales of Ventavis, could vary materially if Ventavis sales do not grow as expected, if costs increase more than it anticipates, or if CoTherix licenses or acquires any additional products or product candidates such as fasudil and alternate formulations of ilprost.

In any such event, the Company would likely seek to finance future cash needs through public or private equity offerings or debt financings. To the extent that CoTherix raises additional funds by issuing equity or debt securities, its stockholders may experience dilution. Any debt financing may involve granting a security interest in all or a portion of its assets or restrictive covenants, including limitations on the Company's ability to incur additional debt, limitations on its ability to acquire or license intellectual property rights, and other operating restrictions that could adversely impact its ability to conduct its business.

Future additional funding may not be available on acceptable terms, or at all. If CoTherix is unable to raise additional capital when required or on acceptable terms, it may have to significantly delay, scale back, or discontinue the development or commercialization of Ventavis or one or more product candidates.

If the Company fails to attract and retain management and other personnel, it may be unable to successfully acquire or license additional products or product candidates, or continue its development and commercialization activities.

CoTherix's success depends on its continued ability to attract, retain, and motivate highly qualified management and other personnel, and on its ability to develop and maintain important relationships with leading academic institutions, clinicians, and scientists. The loss of services of one or more of the Company's members of senior management could jeopardize, delay, or interrupt its efforts to acquire or license additional products or product candidates, successfully complete clinical trials, or further develop and commercialize Ventavis. CoTherix does not currently carry key person insurance on the lives of members of senior management.

There is significant competition from other companies and research and academic institutions for qualified personnel in the areas of the Company's activities. CoTherix's offices are located in the San Francisco Bay Area, where competition for personnel with biopharmaceutical skills is intense. If the Company fails to identify, attract, retain, and motivate these highly skilled personnel, it may be unable to continue its development and commercialization activities.

CoTherix has significantly increased the size of its organization and will need to continue to do so, and it may experience difficulties in managing growth.

The Company is a small company that significantly increased its number of employees from 39 full-time employees at December 31, 2004, to 85 full-time employees at December 31, 2005 and to 98 full-time employees at March 31, 2006. In order to execute its business strategy, CoTherix will need to continue to increase its operations, particularly due to the Company's in-license of fasudil and if it licenses or acquires additional products or product candidates, including further expanding its employee base of managerial, sales and marketing, clinical, and operational personnel. Recent growth has imposed significant added responsibilities on members of management, as will anticipated future growth, including the need to identify, recruit, maintain, and integrate additional employees. CoTherix's future financial performance and its ability to further develop and commercialize Ventavis, its ability to develop and commercialize fasudil, its ability to license or acquire any future products or product candidates and to develop and commercialize them, and the Company's ability to compete effectively will depend, in part, on its ability to manage growth effectively. To that end, CoTherix must be able to:

- manage its clinical trials effectively;
- attract, integrate, and train new personnel and retain current personnel; and
- further develop its administrative, accounting, and management information systems and controls.

The Company is exposed to fluctuations in foreign currency exchange rates, particularly the euro, and foreign economic market conditions.

CoTherix purchases Ventavis from Schering AG under a supply contract whose price and payment terms are denominated in euros. In addition, the price of Ventavis in the Company's supply contract is subject to annual adjustment in order to keep pace with inflation or deflation in accordance with the change of the consumer price index for Germany by the German Federal Statistical Office. As a result, a relative weakening of the U.S. dollar against the euro may result in increased inventory costs and expenses. CoTherix currently does not engage in foreign currency hedging transactions. The Company may in the future choose to limit its exposure by the purchase of forward foreign exchange contracts or through similar hedging strategies. However, no such currency hedging strategy would fully protect against exchange-related losses.

The Company's orphan drug exclusivity for Ventavis may not provide it with a competitive advantage.

CoTherix's orphan drug exclusivity for Ventavis for the treatment of PAH is an important element to its competitive strategy because Schering AG's composition of matter patent for Ventavis expired in September 2004. Any company that obtains the first FDA approval for a designated orphan drug for a

rare disease generally receives marketing exclusivity for use of that drug for the designated condition for a period of seven years from approval, which for Ventavis means through December 2011. However, the FDA may permit other companies to market a form of iloprost, the active ingredient in Ventavis, to treat PAH if any such product demonstrates clinical superiority, or if the Company is unable to provide sufficient drug supply to meet medical needs. More than one product may be approved by the FDA for the same orphan indication or disease as long as the products are different drugs. Any of these FDA actions could create a more competitive market for CoTherix. The Company's orphan drug exclusivity for Ventavis does not apply to drugs to treat PAH that do not contain iloprost, or to drugs containing iloprost that seek approval for uses other than PAH. CoTherix's orphan drug exclusivity may thus not ultimately provide it a true competitive advantage, and its business could suffer as a result.

CoTherix's licensing agreement with Asahi Kasei Pharma relating to fasudil has specified restrictions on its ability to develop and market fasudil that could limit the ability to realize fasudil's full potential.

Pursuant to the licensing agreement with Asahi Kasei Pharma, the Company received exclusive rights to develop and commercialize fasudil only in North America and Europe and only for the treatment of PAH and stable angina. Further, CoTherix's development and commercialization rights are limited to oral and inhaled formulations of fasudil for the treatment of PAH and oral formulations of fasudil for the treatment of stable angina. Although the Company has an option to develop fasudil in North America and Europe for other potential indications using the licensed formulations (except stroke and eye diseases), this option will require the payment of additional licensing fees and compliance with specified milestones. The restrictions that CoTherix has accepted in its license agreement with Asahi Kasei Pharma may limit its ability to develop and fully maximize the marketability of fasudil and realize its full potential.

Identifying and licensing or acquiring other products or product candidates and obtaining FDA approval for their commercialization may put a strain on CoTherix's operations and will likely require it to seek additional financing.

One of CoTherix's key strategies is to continue to license or acquire products or product candidates and develop them for commercialization. The Company has no internal discovery capabilities and relies on its ability to license or acquire any additional products or product candidates to expand its pipeline. Other than fasudil, which CoTherix recently licensed, the Company has no present agreement to license or acquire any future material products or product candidates. The market for licensing and acquiring products and product candidates is intensely competitive and many of its competitors have greater resources than the Company. If CoTherix is successful in this strategy, the process of integrating an additional product or product candidate into its business may put a strain on the Company's operations, including diversion of personnel, financial resources, and management's attention. In addition, any such license or acquisition would increase CoTherix's operating costs and will likely require it to seek additional financing.

CoTherix may be required to conduct pre-clinical and clinical studies for any product or product candidates that it may license or acquire. Significant delays in clinical development could materially increase its product development costs or allow its competitors to bring products to market before it does, impairing its ability to successfully commercialize any such products or product candidates.

Future licenses or acquisitions could result in additional issuances of equity securities that would dilute the ownership of existing stockholders. They could also result in the incurrence of debt, contingent liabilities, or the amortization of expenses related to other intangible assets—any of which could adversely affect the Company's operating results.

Competitors could develop and gain FDA approval of inhaled iloprost for a different indication, which could adversely affect CoTherix's competitive position.

Inhaled iloprost manufactured or distributed by other parties may be approved for different indications in the U.S. in the future. For example, although the Company has an exclusive license from Schering AG to commercialize Ventavis in the U.S. to treat pulmonary hypertension, Schering AG could sell, or license to other companies the right to sell, Ventavis in the U.S. for other indications. In the event there are other inhaled iloprost products approved by the FDA to treat indications other than those covered by Ventavis,

physicians may elect to prescribe a competitor's inhaled iloprost to treat PAH. This is commonly referred to as off-label use.

While under FDA regulations a competitor is not allowed to promote off-label uses of its product, the FDA does not regulate the practice of medicine or the practice of pharmacy. As a result, the FDA cannot direct physicians as to which inhaled iloprost to prescribe to their patients, and physicians could prescribe and pharmacists could dispense another iloprost product for PAH even if it were not approved for PAH. Third-party payors could also develop formulary and other reimbursement policies intended to prompt use of another iloprost product instead of Ventavis whether or not that other product were approved by FDA for PAH. CoTherix would have limited ability to prevent off-label use of a competitor's inhaled iloprost to treat PAH.

Failure to comply with internal control attestation requirements could lead to loss of public confidence in CoTherix's financial statements and negatively impact its stock price.

As a public reporting company, CoTherix is required to comply with the Sarbanes-Oxley Act of 2002, including Section 404, and the related rules and regulations of the Securities and Exchange Commission, including expanded disclosures and accelerated reporting requirements and more complex accounting rules. Compliance with Section 404 and other requirements will continue to increase the Company's costs and require additional management resources. CoTherix may need to continue to implement additional finance and accounting systems, procedures, and controls to satisfy new reporting requirements. While the Company completed a favorable assessment as to the adequacy of its internal control over financial reporting for its fiscal year ended December 31, 2005, there is no assurance that future assessments of the adequacy of its internal control over financial reporting will be favorable. If CoTherix is unable to obtain future unqualified reports as to the effectiveness of its internal control over financial reporting, investors could lose confidence in the reliability of its internal controls over financial reporting, which could adversely affect its stock price.

Changes in financial accounting standards or practices may cause adverse unexpected financial reporting fluctuations and affect the Company's reported results of operations.

A change in accounting standards or practices can have a significant effect on CoTherix's reported results and may even affect its reporting of transactions completed before the change is effective. New accounting pronouncements and varying interpretations of accounting pronouncements have occurred and may occur in the future. Changes to existing rules or the questioning of current practices may adversely affect the Company's reported financial results or the way it conducts its business. For example, CoTherix adopted SFAS 123(R) on January 1, 2006 using the modified prospective transition method, which requires that stock-based compensation cost is recognized for all awards granted, modified, or settled after the effective date as well as for all awards granted to employees prior to the effective date that remain unvested as of the effective date. The adoption of SFAS 123(R) increased the Company's basic and diluted net loss per share for the three months ended March 31, 2006 by $0.06 per share. CoTherix expects the adoption of SFAS 123(R) to have a material adverse effect on its results of operations for subsequent periods.

Anti-takeover defenses that CoTherix has in place could prevent or frustrate attempts by stockholders to change its Board of Directors or the direction of the Company.

Provisions of the Company's certificate of incorporation and bylaws and provisions of Delaware law may make it more difficult for or prevent a third party from acquiring control of the Company without the approval of its Board of Directors. These provisions include:

- providing for a classified Board of Directors with staggered three-year terms;
- restricting the ability of stockholders to call special meetings of stockholders;
- prohibiting stockholder action by written consent;
- establishing advance notice requirements for nominations for election to the Board of Directors or for proposing matters that can be acted on by stockholders at stockholder meetings; and

- granting CoTherix's Board of Directors the ability to designate the terms of and issue new series of Preferred Stock without stockholder approval.

These provisions may have the effect of entrenching the Company's Board of Directors and may deprive or limit strategic stockholders opportunities to sell their shares.

If a company that competes with Ventavis attempts to acquire CoTherix, Schering AG's right of first negotiation could prevent or delay a change of control.

If the Company intends to pursue a transaction where it would be acquired by or otherwise merge with a pharmaceutical company that sells a pulmonary hypertension drug that is directly competitive with Ventavis, Schering AG has a right of first negotiation to acquire the Company subject to the terms set forth in its agreement. This may discourage other companies from seeking to acquire CoTherix.

RISKS RELATED TO THE COMPANY'S STOCK

The Company's stock price has been and will likely continue to be extremely volatile, and purchasers of CoTherix's Common Stock could incur substantial losses.

The Company's stock price has been and will likely continue to be extremely volatile. The stock market in general and the market for biotechnology companies in particular have experienced extreme volatility that has often been unrelated to the operating performance of particular companies. The following factors, in addition to the other risk factors described in this report, may also have a significant impact on the market price of CoTherix's Common Stock:

- announcements concerning product development programs or results of clinical trials by CoTherix or its competitors;
- regulatory developments and related announcements, including announcements by the FDA and foreign regulatory authorities;
- conditions or trends in the pharmaceutical and biotechnology industries;
- fluctuations in stock market prices and trading volumes of similar companies or of the markets generally;
- changes in or the Company's failure to meet or exceed investors' and securities analysts' expectations;
- actual or anticipated fluctuations in CoTherix's or its competitors' quarterly or annual operating results;
- sales of large blocks of the Company's Common Stock, or sales by its executive officers, directors, or greater than 5% stockholders;
- CoTherix's entering into licenses, strategic partnerships, and similar arrangements, or the termination of such arrangements;
- acquisition of products or businesses by the Company or its competitors;
- litigation or government inquiries, whether or not meritorious; and
- economic and political factors, including natural disasters, wars, terrorism, and political unrest.

If there are significant sales of CoTherix's Common Stock, its stock price could decline, even if it's business is doing well.

If the Company's existing stockholders sell a significant number of shares of its Common Stock or the public market perceives that existing stockholders might sell shares of Common Stock, the market price of its Common Stock could decline significantly. Sales of a substantial number of these shares in the public market could also impair its ability to raise capital through the sale of additional equity securities.

The Company's stock is controlled by a small number of stockholders and the interests of these stockholders could conflict with stockholders interests.

As of March 31, 2006, CoTherix's executive officers, directors, and their affiliates beneficially owned in the aggregate 37.4% of its Common Stock. As a result, these stockholders, if they acted together, could significantly influence all matters requiring approval by its stockholders, including the election of directors and the approval of mergers or other business combination transactions. The interests of these stockholders may not always coincide with the Company's interests or the interests of other stockholders.

Exercise of stock options or any warrants that may be issued by the Company will cause dilution in net tangible book value.

CoTherix's stockholders will experience dilution in net tangible book value upon the exercise of options or warrants granted by the Company. To the extent CoTherix raises additional capital by issuing equity securities, its stockholders may experience additional substantial dilution.

Because its Common Stock has been and may continue to be subject to high volatility, the Company may be forced to expend money and resources defending securities class action litigation claims.

Securities class action litigation actions may be brought against CoTherix, particularly following a decline in the market price of its securities. This risk is especially relevant for the Company because it has experienced greater than average stock price volatility, as have other biotechnology companies in recent years. If the Company faces such litigation, it could result in substantial costs and a diversion of management's attention and resources, which could harm CoTherix's business, operating results, and financial condition.

Recent Events

06/28/2006—CoTherix, Inc. and Asahi Kasei Pharma Corporation announced that the companies have entered into an agreement granting CoTherix exclusive rights in North America and Europe to develop and commercialize oral and inhaled formulations of fasudil, a rho-kinase inhibitor, for the treatment of pulmonary arterial hypertension (PAH). Additionally, CoTherix has acquired exclusive rights to develop and commercialize oral formulations of fasudil for the treatment of stable angina in the same territories. Under the terms of the agreement, CoTherix made an upfront payment of $8.75 million to Asahi Kasei Pharma, and will pay development and revenue milestone payments and royalties on future products. CoTherix also has an option to develop fasudil in North America and Europe for other potential indications using the licensed formulations with the exception of stroke and eye diseases.

06/06/2006—Announced that it had filed a universal shelf registration statement on Form S-3 with the Securities and Exchange Commission. Upon being declared effective by the SEC, the shelf registration statement would permit the Company, from time to time, to issue various securities for proceeds in the aggregate amount of up to $80 million. The terms of any such future offerings and the type of securities to be issued would be determined at the time of any future offering.

05/03/2006—Reported results for the first quarter ended March 31, 2006. Net product sales from the Company's Ventavis® (iloprost) Inhalation Solution in the first quarter of 2006 were $14.5 million, up 32% from $11.0 million in the fourth quarter of 2005. On a GAAP basis, the Company reported a net loss of $3.9 million, or ($0.14) per share, in the first quarter of 2006 versus a net loss of $8.1, million or ($0.37) per share, for the same period in 2005. On January 1, 2006, the Company adopted SFAS123(R) and is reporting employee stock-based compensation expenses in its GAAP results. Excluding the impact of SFAS123(R), the Company reported a non-GAAP net loss of $2.2 million, or ($0.08) per share, in the first quarter of 2006. The Company believed this non-GAAP financial information was useful in providing a better understanding of the Company's operating performance.

04/11/2006—Announced the appointment of Abhay Joshi, Ph.D. as executive vice president and chief technical officer. Dr. Joshi has over seventeen years of global manufacturing operations and product and process development experience in biologics, pharmaceutical, and medical device industries in the U.S., Europe, Latin America, and Asia. Dr. Joshi would be responsible for the overall management of CoTherix's technical operations, including lifecycle development and planning.

04/04/2006—Announced enrollment of the first patient in its REVEAL Registry™, the first broadly defined registry designed to track and study the clinical course and medical management of PAH. The REVEAL Registry is designed to provide physicians with real world data about PAH disease management.

03/08/2006—Reported results for its fourth quarter and year ended December 31, 2005. Net product sales from Ventavis in the fourth quarter of 2005 were $11.0 million, up 30% from $8.4 million in the third quarter of 2005. Total 2005 net product sales for Ventavis, which was launched in March 2005, were $23.9 million.

12/13/2005—Announced, together with Respironics, Inc., the launch of a new portable, battery-operated inhalation device for the delivery of Ventavis. The new I-neb Adaptive Aerosol Delivery® (AAD) device weighs less than eight ounces and can be carried discreetly in a purse or briefcase.

11/02/2005—Announced results for its third quarter ended September 30, 2005. Net product sales from Ventavis (iloprost) Inhalation Solution were $8.4 million, more than double second quarter 2005 levels.

10/31/2005—Announced newly presented data from a Phase II randomized clinical study designed to evaluate the safety and pilot efficacy of adding Ventavis (iloprost) Inhalation Solution to stable doses of Tracleer® (bosentan) in patients with PAH. These data from the Company's STEP Trial were presented at the American College of Chest Physicians meeting (CHEST) in Montreal.

10/24/2005—Announced its plans to initiate the REVEAL Registry, a first-of-its-kind national disease registry that would retrospectively and prospectively collect observational data to track and study the natural history and medical management of PAH, World Health Organization (WHO) Group I.

09/19/2005—Announced the election of Mr. Howard B. Rosen as a member of the Company's Board of Directors. Mr. Rosen is currently vice president, commercial strategy for Gilead Sciences, Inc., where he is responsible for global brand strategy, new product planning, and project management for late stage drug development programs. Prior to joining Gilead, Mr. Rosen spent 10 years at ALZA Corporation, a member of the Johnson & Johnson family of companies, where he most recently served as its president. Previously, Mr. Rosen led the west coast strategy practice of Analysis Group, Inc., was director, corporate development at GenPharm International, Inc., now a part of Medarex, Inc., and was a consultant in the San Francisco office of McKinsey & Co.

08/30/2005—Announced that it had received approval from the U.S. FDA to modify the Ventavis label to include: (1) information from the Company's clinical study evaluating the safety of Ventavis used in combination with Actelion's Tracleer (bosentan) for PAH; and (2) the use of Respironics, Inc.'s portable, hand-held I-neb AAD device for the delivery of Ventavis pending receipt of 510(k) regulatory clearance.

08/03/2005—Reported results for its second quarter ended June 30, 2005. Net product sales for the quarter were $4.1 million, which represented the first full quarter of sales of Ventavis, which became commercially available on March 22, 2005.

06/01/2005—Announced it had initiated a Phase II trial for Ventavis, to potentially expand the indication to include pulmonary hypertension (PH) associated with idiopathic pulmonary fibrosis (IPF).

05/23/2005—Announced that researchers had presented results involving inhaled iloprost therapy for the treatment of PAH, a debilitating and potentially fatal disease characterized by high blood pressure in the pulmonary arteries. Results were presented at the American Thoracic Society (ATS) International Conference in San Diego during the Thematic Poster Session for Pulmonary Hypertension.

05/02/2005—Announced results for its first quarter ended March 31, 2005. Net product sales for the quarter were $345,000, which represented the initial sales of Ventavis.

03/22/2005—Announced the commercial availability of Ventavis (iloprost) Inhalation Solution in the U.S. for the treatment of PAH (WHO Group I) in patients with New York Heart Association (NYHA) Class III or IV symptoms.

03/09/2005—Announced results for the fourth quarter and fiscal year ended December 31, 2004. During the fourth quarter 2004, operating expenses were $6.7 million, compared to $7.8 million, for the same period in 2003. Operating expenses for the fourth quarter of 2003 reflected a $5.3 million milestone payment for the consummation of the licensing agreement with Schering AG for Ventavis. Without the effect of this milestone payment, operating expenses for the fourth quarter of 2004 were higher due to increased clinical and regulatory activities and expansion of the employee base to support overall corporate growth, as well as the impact of CoTherix becoming a publicly traded company in October 2004. Operating expenses for the year ended December 31, 2004 were $38.3 million, compared to $11.6 million in the 2003 period.

03/08/2005—Announced top-line safety and efficacy results from the STEP clinical study. The analysis of this study showed that the combination of Ventavis added to Tracleer (bosentan) therapy was well tolerated and provided clinical benefit in patients with PAH.

12/29/2004—Announced that following priority review, the U.S. FDA had approved Ventavis for the treatment of PAH (WHO Group I) in patients with NYHA Class III or IV symptoms.

11/10/2004—Reported recent highlights and financial results for the third quarter ended September 30, 2004. Recent highlights included (1) Obtaining U.S. FDA priority review of a NDA and receiving orphan drug designation for Ventavis (iloprost) Inhalation Solution; (2) Completing enrollment in the STEP clinical trial, which was designed to evaluate the safety of using Ventavis in combination with bosentan for patients with PAH; and (3) Raising net proceeds of approximately $25.4 million through an initial public offering. For the third quarter of 2004, the net loss was $13.6 million, or a pro forma loss of $1.00 per share, versus a net loss of $2.6 million, or a pro forma loss of $0.86 per share, in the same period in 2003.

10/15/2004—Announced the initial public offering of 5,000,000 shares of Common Stock at $6.00 per share.

Glossary of Lesser-Known Terms

Angina—A heart condition marked by paroxysms of chest pain due to reduced oxygen to the heart.

Anti-coagulant—A substance that prevents blood from clotting.

Anti-hypertensive—A drug used to reduce or control high blood pressure.

Atherosclerosis—A form of arteriosclerosis characterized by the deposition of atheromatous plaques containing cholesterol and lipids on the innermost layer of the walls of large and medium-sized arteries.

Beta-blocker—A drug, such as propanolol, that opposes the excitatory effects of norepinephrine released from sympathetic nerve endings at beta-receptors and is used for the treatment of angina, hypertension, arrhythmia and migraine.

Black Box Warning—A warning indicating that a drug carries a significant risk of serious or even life-threatening adverse effects. It is so named for the black border that usually surrounds the text of the warning. The U.S. Food and Drug Administration (FDA) can require a pharmaceutical company to place a black box warning in the labeling of a prescription drug or in literature describing it. It is the strongest warning that the FDA can require.

Calcium Channel Blocker (CCB)—Any of a class of drugs that prevents or slows the influx of calcium ions into smooth muscle cells, particularly those in the heart, and that is used to treat some forms of angina pectoris and cardiac arrhythmias.

Cardiovascular—Of, relating to, or involving the heart.

Cerebral vasospasm—An episodic narrowing of an artery in the brain.

Chemosensitive—Capable of perceiving changes in the chemical composition of the environment.

Chronic—Lasting for a long period of time or marked by frequent recurrence, as certain diseases.

Coronary Artery Bypass Grafting (CABG)—Open-heart surgery in which the rib cage is opened and a section of a blood vessel is grafted from the aorta to the coronary artery to bypass the blocked section of the coronary artery and improve the blood supply to the heart.

Coronary Artery Disease (CAD)—A condition (such as sclerosis or thrombosis) that reduces the blood flow through the coronary arteries to the heart muscle. Also called *coronary disease or coronary heart disease.*

Digitalis—A drug that strengthens the contraction of the heart muscle, slows the heart rate, and helps eliminate fluid from body tissues.

Diuretic—A substance or drug that tends to increase the discharge of urine.

Endothelin—A polypeptide that plays a role in regulating vasomotor activity, cell proliferation, and the production of hormones that have been implicated in the development of vascular disease.

Endothelin Receptor Antagonist (ETRA)—A drug that blocks endothelin receptors. There are two main kinds of ETRAs: selective (e.g. sitaxsentan) and dual, which affect both endothelin A and B (e.g. bosentan).

Erectile dysfunction (ED)—The inability to achieve penile erection or to maintain an erection until ejaculation.

Familial pulmonary arterial hypertension (FPAH)—Pulmonary arterial hypertension is an increase in blood pressure in the pulmonary artery or lung vasculature. Depending on the cause, it can be a severe disease with a markedly decreased exercise tolerance and right-sided heart failure. When a family history exists, the disease is termed familial pulmonary arterial hypertension (FPAH). **IPAH** (see definition below) and FPAH are now considered to be genetic disorders linked to mutations in the *BMPR2* gene, which encodes a receptor for bone morphogenic proteins, as well as the *5-HT(2B)* gene, which codes for a serotonin receptor.

Fibrosis—The formation of excessive fibrous tissue, as in a reparative or reactive process.

Hemodynamics—The study of the forces involved in the circulation of blood.

Hemorrhage—An excessive discharge of blood from the blood vessels; profuse bleeding.

Hyperlipidemia—An excess of fats or lipids in the blood.

Hypertrophic cardiomyopathy—A disorder in which the heart muscle is so strong that it does not relax enough to fill the heart with blood and so reduces its pumping ability.

Idiopathic pulmonary arterial hypertension (IPAH)—Replacing the term primary pulmonary hypertension, IPAH is a rare, progressive disorder characterized by high blood pressure (hypertension) of the main artery of the lungs (pulmonary artery). The pulmonary artery is the blood vessel that carries blood from the heart through the lungs. Symptoms of primary pulmonary hypertension include shortness of breath (dyspnea) especially during exercise, chest pain, and fainting episodes. The exact cause of primary pulmonary hypertension is unknown.

Idiopathic Pulmonary Fibrosis (IPF)—An inflammatory lung disorder of unknown origin (idiopathic) characterized by abnormal formation of fibrous tissue (fibrosis) between the tiny air sacs (alveoli) or ducts of the lungs. Coughing and rapid, shallow breathing occur with moderate exercise. The skin may appear slightly bluish (cyanotic) due to lack of circulating oxygen. Complications such as infection, emphysema, or heart problems may develop.

Incidence—Rate, range, or amount of occurrence of a disease.

Inflammation—The act of inflaming or the state of being inflamed.

Intravenously—Within or administered into a vein.

Investigational New Drug (IND)—Refers to the Food and Drug Administration's (FDA) program by which a pharmaceutical company obtains permission to ship an experimental drug across state lines (usually to clinical investigators) before a marketing application for the drug has been approved. The FDA reviews the IND for safety to assure that research subjects will not be subjected to unreasonable risk. The application has three main sub-sections: Animal Pharmacology and Toxicology Studies; Manufacturing Information; and Clinical Protocols and Investigator Information.

Lumen—The inner open space or cavity of a tubular organ, as of a blood vessel or an intestine.

Lupus erythematosus—Any of several connective tissue disorders, especially systemic lupus erythematosus, which primarily affect women of childbearing age, have a variety of clinical forms, and are characterized by red scaly skin lesions.

Mechanoreceptive—A specialized sensory end organ that responds to mechanical stimuli, such as tension, pressure, or displacement.

Myocardial infarction (MI)—Destruction of heart tissue resulting from obstruction of the blood supply to the heart muscle.

Myocardial ischemia—A disorder of cardiac function caused by insufficient blood flow to the muscle tissue of the heart. The decreased blood flow may be due to narrowing of the coronary arteries (coronary

arteriosclerosis), to obstruction by a thrombus (coronary thrombosis), or less commonly, to diffuse narrowing of arterioles and other small vessels within the heart. Severe interruption of the blood supply to the myocardial tissue may result in necrosis of cardiac muscle (myocardial infarction).

Myosin Light Chain—The light chains of the muscle protein myosin. Each molecule of myosin is composed of two heavy chains and two pairs of light chains. The light chains have a molecular weight of about 20 kD and there is one dissimilar pair of light chains associated with each heavy chain.

New Drug Application (NDA)—The vehicle through which drug sponsors formally propose that the Food and Drug Administration approve a new pharmaceutical for sale and marketing in the U.S. The data gathered during the animal studies and human clinical trials of an IND become part of the NDA.

New York Heart Association (NYHA) Class III Symptoms—Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.

New York Heart Association (NYHA) Class IV Symptoms—Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

Nitrates—A group of medications that are made from a chemical with a nitrogen base. Nitrates relax smooth muscle, dilate veins, lower blood pressure, and improve blood flow through the coronary arteries.

Orphan Drug—Any of various drugs or biologicals that may be useful in treating disease but are not considered to be commercially viable.

Palliative—Relieving or soothing the symptoms of a disease or disorder without effecting a cure.

Pathogenesis—The development of a diseased or morbid condition.

Pathophysiology—The functional changes associated with or resulting from disease or injury.

PDE-5 inhibitor—A drug used to block the degradative action of phosphodiesterase type 5 on cyclic GMP in the smooth muscle cells lining the blood vessels supplying the corpus cavernosum of the penis. These drugs are used in the treatment of erectile dysfunction and were the first effective oral treatment available for the condition.

Percutaneous Transluminal Coronary Angioplasty (PTCA)—One of the most common non-surgical treatments for opening obstructed coronary arteries using a balloon placed across an arterial using a special catheter.

Phosphorylation—The addition of a phosphate group to an organic molecule.

Prevalance—The proportion of individuals in a population having a disease.

Prostacyclins—A prostaglandin produced in the walls of blood vessels that acts as a vasodilator and inhibits platelet aggregation.

Prostaglandin—Any of a group of potent hormone-like substances that are produced in various mammalian tissues, which are derived from arachidonic acid and that mediate a wide range of physiological functions, such as control of blood pressure, contraction of smooth muscle, and modulation of inflammation.

Pulmonary Arterial Hypertension (PAH)—Continuous high blood pressure in the pulmonary artery. The average blood pressure in a normal pulmonary artery is about 14 mmHg when the person is resting. In PAH, the average is usually greater than 25 mmHg.

Remodeling—A cyclical process by which bone maintains a dynamic steady state through sequential resorption and formation of a small amount of bone at the same site; unlike the process of modeling, the size and shape of remodeled bone remain unchanged.

Revascularization—Reestablishment of blood supply to a part or organ.

Rho and Rho-Kinase—Rho is a low molecular weight G protein that acts as an intracellular switch between an inactive GDP-bound state and an active GTP-bound state to regulate cellular functions. Rho is the term generally used to describe the rho subfamily consisting of 3 human homologs: RhoA, RhoB and RhoC. **Rho-kinase**, also known as **ROCK**, (consisting of two isoforms also known as ROCKα and ROCKβ) is an effector of rho. Rho and rho-kinase proteins are involved in a variety of biochemical signal transductions in cells and have important functions in vascular physiology and pathophysiology.

Rho GTPase—A low molecular weight G protein that acts as an intracellular switch between an inactive GDP-bound state and an active GTP-bound state to regulate cellular functions.

Right heart failure—Occurs when the right side of the heart loses its ability to pump blood efficiently. It is often a complication of other conditions.

Scleroderma—A pathological thickening and hardening of the skin.

Sepsis—A systemic infection due to the presence of pathogenic organisms or their toxins in the blood or tissues that can lead to multiple organ failure and death.

Stable angina—Results from a fixed obstruction of blood flow to the heart and occurs when there is not enough blood for a fast-pumping heart. However, sufficient blood can get through when the heart slows down and the individual is at rest. This type of angina typically is caused by widespread, irregular disease throughout the coronary arteries. The blockages that result may not seriously hinder the flow of blood, and usually do not damage the heart unless a plaque suddenly ruptures.

Stable angina pectoris—Severe paroxysmal pain in the chest associated with an insufficient supply of blood to the heart.

Subarachnoid hemorrhage—Occurs when a blood vessel just outside the brain ruptures. The area of the skull surrounding the brain (the subarachnoid space) rapidly fills with blood. A patient with subarachnoid hemorrhage may have a sudden, intense headache, neck pain, and nausea or vomiting. Sometimes this is described as the worst headache of one's life. The sudden build-up of pressure outside the brain may also cause rapid loss of consciousness or death.

Subcutaneous—Located or placed just beneath the skin.

Sublingually—Situated beneath or on the underside of the tongue.

Tachycardia—A rapid heart rate, especially one above 100 beats per minute in an adult.

Tolerance—Decreased responsiveness to a stimulus, especially over a period of continued exposure.

Valvular heart disease—Heart disease caused by stenosis of the cardiac valves and obstructed blood flow or caused by degeneration and blood regurgitation.

Vasoactive—Causing constriction or dilation of blood vessels.

Vasoconstriction—Constriction of a blood vessel, as by a nerve or drug.

Vasoconstrictor—A nerve, drug, etc., that causes vasoconstriction.

Vasodilator—A nerve drug that causes vasodilation.

Vasospasm—A sudden constriction of a blood vessel, causing a reduction in blood flow.

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