ashhill
pharmaceutical investments

Investor Update

Summer 2012

One Year. Many Successes.

AshHill is about to celebrate its first anniversary, and we are excited to update you on the successes we have had over the last 12 months and give you a glimpse of activities we are pursuing.

Our big announcement is that we are changing our name — AshHill Pharmaceutical Investments, LLC will become AshHill Investments, LLC. While our focus remains emerging biotech companies, our name change reflects the inclusion of medical device companies into our portfolio and better identifies our investment perspective.

Three significant investments have been made since the fund's inception. All three companies are privately held, and we hold at least one board of directors seat in each of the companies. From the outset, our goal was to invest in companies where we can take an active role in managing development and direction. We have outlined below the status of their organization, AshHill's degree of ownership and a description of AshHill's role and vision for the future of the company. Consistent with our company philosophy, we have diversified investments to include one advanced-stage company (Sinusys), one early-stage company (Heart Metabolics), and one seed-stage company (Armetheon). Thus far, success in leveraging our positions through syndication with other co-investors in financing rounds of investment has been achieved in all three companies. We are continuing to raise funds in an effort to take advantage of future opportunities in these companies, and we are looking for new opportunities.

Please do not hesitate to contact us if you have questions or comments about our successes to date. Financial inquiries are best directed to Eric Ott, David Buffenbarger or Steven Smith. Any questions regarding the condition being treated or the mechanism of action of a given company's product is probably best answered by Dr. Peter Milner or Dr. Mark Midei.

Self expanding device for sinus opening dilation

SinuSys is an advanced-stage company that makes a maxillary sinus dilator for the treatment of chronic sinusitis. AshHill owns 5% of the company, and Dr. Milner will serve as one of four members of the Board of Directors as the company moves forward. Other updates:

- Additional devices to treat other sinus conditions are being developed.
- Sales of the product in Europe are slated for the fourth quarter of 2012.
- A distribution team in Europe has already been established
- Clinical trials are underway in North America for eventual sales in the US.

Development stage:

SinuSys is an established company with broad patent protection for the self-expanding maxillary sinus dilator. Proof of concept has been accomplished in vitro and in vivo. A first-in-man clinical trial began in Canada in March 2012. CE Mark approval is expected in the fourth quarter of 2012, and sales and marketing of the device in Europe are anticipated at that time.

Financing:

The company completed series B financing in September 2011. A large number of venture capital firms and high net worth individuals contributed to this round in which AshHill was a passive contributor.

Background Information

Chronic sinusitis affects more than 37 million Americans. It is characterized by frontal headaches and fever and can result in significant impairment to quality of life.

Antibiotics are often prescribed to treat sinus infections, but studies have shown that they are ineffective and often lead to the development of resistant bacteria. This in turn, may make subsequent treatment more challenging. Because the disorder is usually caused by clogging of the passageway leading from the sinus to the nasal passage, antibiotics do not provide a definitive solution to the problem and may ultimately cause more harm than good.

Otolaryngologists have long recognized the effectiveness of improving ventilation and drainage of the sinuses in treating chronic sinusitis. Because surgery is invasive, painful and costly, it is usually reserved for only the most advanced cases. Recently, enlargement of the sinus drainage pathway has been made possible using a balloon dilating system. While less invasive than surgery, it remains sufficiently uncomfortable to require performance in a surgical center and some form of sedation or anesthesia is necessary. The rapid nature of the dilation (usually over a few seconds) is responsible for the discomfort and for a tendency of the dilation to recoil after the procedure.

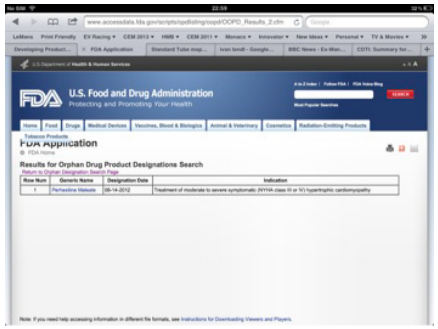
For more information check out http://SinuSys.com

HEART METABOLICS

Drug to treat Hypertrophic Cardiomyopathy

Heart Metabolics is an early-stage company with broad worldwide data exclusivity protection for the use of perhexiline in a variety of conditions. Because of the age of the drug, patents are largely expired in many parts of the world. AshHill Investments entered into an exclusive investment agreement with Heart Metabolics and owns at least 5% of the company.

Ashhill authored and filed an application for Orphan Drug Designation with the US FDA in late November 2011. This designation was made official in June 2012 (See copy of FDA results below). This designation will reduce regulatory costs and extend patent protection. The next developmental step will be the design and implementation of a series of two clinical trials to prove safety and effectiveness of the drug.



FDA Orphan Designation application results

In addition, a series of agreements and licenses have been made with the drug's manufacturers, as well as with entities that might have some future claim of partial intellectual property ownership. Other updates:

- AshHill is leading a round of financing and is being followed by the Trans Tasman fund.
- Heart Metabolics is actively raising additional money to fund a series of clinical trials to advance the drug through the regulatory process.

Development Stage

We are pleased to announce that we have negotiated a worldwide manufacturing deal with Sigma Pharmaceuticals, the current sole supplier of the drug. Finally, a series of releases and licensing agreements have been achieved with Cardiff University (September 2005), the British Heart Foundation (April 2012), Birmingham University (May 2012), the University of Adelaide (July 2012), and the University of Aberdeen (July 2012).

Financing:

Ashhill is leading the Series A financing. Heart Metobolics is currently valued at $10 million, and Ashhill was offered 5% of the company at a significant discount. We are syndicating our investment with a major investment fund in Australia who is prepared to invest a significant sum initially, with additional investment upon achievement of milestones.

AshHill's Role:

AshHill members have been actively involved in both the scientific advancements and business activities of HMB. To this end:

- Dr. Milner has assumed the role of CEO of HMB.
- Dr. Midei and Dr. Milner authored an application to the US FDA, which led to the successful Orphan Drug Designation.
- Milner and Midei will continue to have a very active role in advancing perhexiline through the US and European regulatory systems.
- AshHill has participated in negotiations for license agreements and supply agreements.
- AshHill also negotiated the Series A Terms with HMB and with other Series A investors.

Background:

Hypertrophic cardiomyopathy (HCM) is the most common inherited form of heart disease, affecting 1 in 500 people worldwide. It is becoming increasingly recognized as the leading cause of premature death in young athletes, and efforts to increase awareness of and screening for the condition are underway on many fronts.

The abnormality that causes HCM is a defective contractile element in heart muscle cells. Although these elements are able to contract, they do so inefficiently, requiring abnormally large amounts of energy to produce a functioning heartbeat relative to the amount needed by the contractile elements in normal patients.

The genetic predisposition for the condition has significant variability in the expression of the disease — some patients present with debilitating disease early in life, and others may live normal-to-advanced age without symptoms. In addition:

- About 20% of patients develop significant symptoms at sometime during life and require treatment.
- Medications are notoriously limited in their benefit.
- There are no drugs approved by the FDA specifically for this condition.
- Surgery is usually recommended only for the most advanced stages.

The heart muscle is different from most tissues in the body in that it uses fatty acids preferentially over glucose as its primary fuel source for energy production. This is an inherently inefficient process in terms of the amount of oxygen that is required. It causes the heart muscle cell to switch from fatty acids to glucose as its preferred source of fuel for energy production. This makes the heart muscle more efficient in its energy production, reducing the signs and symptoms of HCM.

Perhexiline is an old drug, having been developed by Merrill Laboratories in the 1970s. It was very effective in treating patients with coronary artery disease who had chest pain because it improved energy production without the need for increased amounts of blood flow. Its use fell into disfavor, however, when a small percentage of patients developed nerve and liver toxicities.

Continued study of the drug led to an understanding of the mechanism of these toxicities. Some patients have a defective enzyme in their liver that is responsible for metabolizing and eliminating the drug from the body. In a relatively small number of patients, this defect leads to an excessive accumulation of the drug in the body.

These patients can be identified in two ways: 1) genetic testing of the enzyme responsible for metabolism can be performed, or 2) blood levels of the drug can be measured, and dosing modified according to these levels. Using these methodologies, the drug has been used safely in thousands of patients in Australia and New Zealand for nearly twenty years.

Background continued on the next page

Background continued

Perhexiline's safety and effectiveness has led to its use on a limited basis in the United Kingdom. Although it has been shown to be effective for a number of conditions, there is perhaps no more clear an indication than its use in HCM, where energy production efficiency is the primary defect. Perhexiline acts specifically at correcting energy production inefficiency. In addition, the lack of effective medications specific for HCM means that there exists an unmet clinical need for perhexiline.

The genetic basis for HCM, and the relatively small percentage of patients with HCM likely to require treatment has resulted in the condition being neglected by major pharmaceutical companies, who are interested in developing blockbuster drugs for large populations of patients. The FDA has designed a drug development track — Orphan Drug Designation — to address this issue specifically. This process requires significantly lower regulatory hurdles in order to accelerate and incentivize drug development for such conditions. It also extends the life of intellectual property protection for the drug.

Heart Metabolics seeks to develop Perhexiline for use in patients with HCM whose symptoms require additional therapy.

Additional information:

The condition was responsible for the untimely death of basketball star Hank Gathers. There are several more recent public cases regarding individuals with this condition.

Hypertrophic Cardiomyopathy received a great deal of media attention recently when eighteen-year-old Ben Breedlove died from the disease shortly after producing a video. His story is very moving and can be viewed at **http://www.youtube.com/watch?v=vw5HLT-TyRs**

A Cincinnati LaSalle athlete, Reid Rizzo, died as a result of Hypertrophic Cardiomyopathy and was featured in a recent Cincinnati Enquirer article: **http://news.cincinnati.com/article/20120605/SPT0301/306040073**

Ashhill is partnering with the Hypertrophic Cardiomyopathy Foundation as we move forward to achieve FDA approval for the use of perhexiline in this condition. They are a very active advocacy group and they also have a wealth of information on their website: **http://4hcm.org/**

Developer of antibiotics against resistant bacteria and a new anticoagulant

Armetheon is a seed-stage company that is currently performing initial chemistry studies to identify promising compounds for testing of antibiotic effectiveness against multi-drug resistant organisms. It has also acquired the rights to a new anticoagulant, tecarfarin. The company is incorporated and has patents filed.

Development Stage:

Armetheon seeks to develop new antibiotic agents effective against multi-drug resistant organisms. Mainstream antibiotics sometimes lose their effectiveness due to bacterial enzymes. The company is currently performing initial chemistry studies in order to identify promising compounds for use in their innovative approach to antibiotic compounds.

In its other development line, Armetheon, which has the rights to tecarfarin from ARYC Therapeutics, is pursuing regulatory approval for the use of the drug as an anticoagulant to replace warfarin. Armetheon is slated to meet with the FDA to determine what further clinical testing will be required to achieve this approval.

They have authored a presentation on the product and are actively completing a manuscript for publication on the drug. An abstract presentation of tecarfarin's benefit over warfarin will be presented at the European Society of Cardiology meeting in Munich this September (See below).

Financing:

Armetheon raised the seed financing from AshHill and Atheneos Capital.

AshHill's Role:

We are proud to announce that AshHill Investments:

- Has financed the seed stage of the company along with Atheneos Capital.
- Has a 5% ownership in Armetheon.
- Has been awarded two of five Board seats.
- Will maintain an active role in management and direction as activities proceed.
- Has authored a white paper in support of Congressional efforts to ease the regulatory pathway for antibiotic development.
- Assisted in designing clinical trials to test new antibiotic compounds.

The white paper was authored for the California Healthcare Institute that was presented to Congress by Dr. Milner in April 2012. The GAIN Act was subsequently passed by an overwhelming majority of both Houses of Congress. This Act will streamline antibiotic development by compelling a relaxation of regulatory hurdles at the US FDA, resulting in a quicker and less costly development pathway. In addition, patent life of new chemical entities is extended by the GAIN Act. AshHill's contribution was chronicled in a Biocentury Report last month (See below).

Background Information

Antibiotics

The widespread use (some would say misuse) of antibiotics worldwide has caused bacteria to evolve resistance mechanisms that make infections increasingly difficult and, at times, impossible to treat. Antibiotics are a drug class in which the development of such obsolescence is inevitable, and development of new compounds is imperative for treatment of new infectious diseases. These drugs often become ineffective before they reach the end of their patent protection, and they are taken by limited numbers of patients for relatively short periods of time.

The development costs of these drugs, however, are similar to any other drugs, including those which are taken by large populations of patients for chronic conditions. For these reasons, large pharmaceutical manufacturers have largely abandoned antibiotic discovery and development programs, and they have channeled resources into more predictably profitable areas.

Bacteria resist antibiotics in many ways. One of the most common mechanisms involves the secretion of an enzyme that degrades a vulnerable segment of the antibiotic molecule, rendering it inactive. Armetheon's lead candidate compounds take existing antibiotics and chemically bond them together. In mainstream antibiotics, the bacterial enzyme interferes with the drug's effectiveness. In Armetheon's innovative approach, the compound is paradoxically activated by bacterial enzymes. Then, the active antibiotics in the compound are released as the chemical bond is degraded, allowing the antibiotics to combat the infection.

Anticoagulants

Patients with a variety of conditions require anti-coagulation ("blood thinning") for prevention of the harmful effects of blood clots forming and travelling throughout the body. Approximately 40 million Americans are eligible for such therapy. Examples of conditions for which anti-coagulation is indicated include: chronic heart rhythm disturbances (such as atrial fibrillation), artificial heart valves, congestive heart failure, or a history of blood clots (such as DVT). Traditionally, this has been done with warfarin (also known by its brand name "Coumadin"). Warfarin is notorious for its unpredictable and inconsistent effects in individual patients and between groups of patients. This erratic behavior is largely the result of its interaction with a large number of foods and drugs, and results in the need for monitoring of its effect in patients with regular, periodic blood testing.

Big Pharma has responded to this problem by developing alternative anticoagulants that do not require monitoring. These agents work through a different mechanism, and their behavior in patients appears to be more predictable. When they were first FDA approved, these agents were expected to largely replace warfarin as the drugs of choice for anticoagulation. This enthusiasm has been tempered, however, by some reports of bleeding complications in the real-world marketplace. As a result, they have acquired less than 10% of the US anticoagulation market.

Tecarfarin is an anticoagulation agent that acts by a mechanism identical to that of warfarin. However, it is metabolized by the body by a different mechanism. This alternative process results in far fewer interactions with other drugs, and a more predictable behavior in patients.

Additional information:

A recent NY Times article on the growing problem of antibiotic misuse in animal feed is available at: **http://www.nytimes.com/2012/01/05/health/policy/fda-restricts-use-of-antibiotics-in-livestock.html**

A recent Yahoo finance report detailing the passage of the GAIN Act and its potential benefit for drug companies developing antibiotics is available at: **http://finance.yahoo.com/news/gain-act-benefit-antibiotic-makers-160000929.html**

AshHill's authorship of a CHI White Paper on Promoting Antibiotic Discovery and Development is available at: **http://www.chi.org/uploadedfiles/CHI_Antibiotic_Discovery.pdf**

A recent Reuters article on the tempered enthusiasm of US physicians for the new anticoagulant medications is available at: **http://www.reuters.com/article/2012/06/14/us-drugs-bloodthinners-idUSBRE85D06G20120614**

A recent Biocentury article on Armetheon which includes a reference to AshHill is available at: **http://www.biocentury.com/biotech-pharma-news/emergingcompany/2012-06-11/armetheon-refocusing-anticoagulant-tecarfarin-on-underserved-population-a8**