Zacks Small-Cap Research

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Cardiome Pharma Corp (CRME - NASDAQ)

Construction in Progress: Building a Bridge to Europe

Based on our DCF model and a 15% discount rate, Cardiome is valued at approximately $4.00 per share. Our model applies a 70% probability of EMA approval and European commercialization for Trevyent.

Current Price (1/26/2018)	$1.53
Valuation	**$4.00**

INITIATION

Cardiome has a portfolio of six hospital-based medicines in cardiology and infectious disease. In November 2013, Cardiome acquired Aggrastat and Correvio in a transformation acquisition that provided the infrastructure for recent and future acquisition growth.

The company's strategy is to acquire drugs in existing and adjacent spaces of hospital care to leverage their commercialization platform. Currently, there are five revenue-generating products.

The groundwork undertaken for Xydalba in 2017 combined with new sales from Zevtera should accelerate growth for 2018. Sales from Esmocard Lyo and potentially other additions may also augment the growth trajectory.

In 2015, Cardiome signed a license agreement for commercialization of Trevyent in the EU, Canada and Middle East. An MAA and NDS are expected to be filed for approval in the EU and Canada respectively in 2018 and sales are expected in 2019. Additional upside exists as Trevyent is approved and commercialized.

SUMMARY DATA

52-Week High	**4.84**
52-Week Low	**1.29**
One-Year Return (%)	**-46.9**
Beta	**0.83**
Average Daily Volume (sh)	**113,895**
Shares Outstanding (mil)	**33.9**
Market Capitalization ($mil)	**51.9**
Short Interest Ratio (days)	**0.61**
Institutional Ownership (%)	**N/A**
Insider Ownership (%)	**N/A**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.00**
5-Yr. Historical Growth Rates	
Sales (%)	**N/A**
Earnings Per Share (%)	**N/A**
Dividend (%)	**N/A**
P/E using TTM EPS	**N/A**
P/E using 2017 Estimate	**N/A**
P/E using 2018 Estimate	**N/A**
Zacks Rank	**N/A**

Risk Level	**Above Average**
Type of Stock	**Small-Growth**
Industry	**Med-Biomed/Gene**

ZACKS ESTIMATES

Revenue

(In millions of USD)

	Q1 (Mar)	Q2 (Jun)	Q3 (Sep)	Q4 (Dec)	Year (Dec)
2016	$7.1 A	$5.9 A	$5.2 A	$7.0 A	$25.3 A
2017	$5.2 A	$5.8 A	$6.0 A	$7.8 E	$24.7 E
2018					$30.5 E
2019					$34.2 E

Earnings per Share

	Q1	Q2	Q3	Q4	Year
2016	-$0.06 A	-$0.37 A	-$0.19 A	-$0.18 A	-$0.77 A
2017	-$0.20 A	-$0.26 A	-$0.20 A	-$0.16 E	-$0.81 E
2018					-$0.66 E
2019					-$0.59 E

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INITIATING COVERAGE

We are initiating coverage of Cardiome Pharma Corp. (NASDAQ: CRME) with a $4.00[1] price target based on our estimates for current product growth and a 2020 launch of Trevyent in the EU and Canada. The specialty pharmaceutical company is focused on developing current and future products in the EU, Canada, Middle East and other ex-US markets. Cardiome's current stable of products targets cardiovascular and infectious disease medicines for in-hospital acute care. However, the company may pursue products in adjacent call points including pain, anti-spastics, antibiotics and others.

Through its acquisition of Correvio in late 2013, Cardiome procured a salesforce, EU licenses and worldwide sales rights (ex-US) for Aggrastat. This action provided immediate sales and infrastructure to commercialize the internally developed Brinavess as well as the structure necessary to layer on additional products. Following this initial transaction, Cardiome has obtained the rights to four other products, including two complementary anti-infectives.

On September 30, 2017, Cardiome held approximately $27 million in cash on its balance sheet. Debt and equity issuances have provided capital over the last several years to support operational expenses; an approach we expect will continue in the future. We expect the company will consume from $1.5 to $2.0 million per month as it continues to penetrate hospital formularies and grow existing assets. At forecasted burn rates, the company holds sufficient cash to support operations until 4Q:18, but is seeking an acquisition that will provide sufficient sales to generate positive earnings in the near term. With little additional infrastructure cost required for a new product, we see this as a compelling strategy.

Based on our forecasts which include revenues for currently licensed drugs and a probability-weighted contribution from Trevyent, we expect breakeven on an operational basis in 2020. This forecast assumes growth in all products, with a greater contribution from Xydalba and Zevtera in 2018 and initial contribution from Trevyent in 2020.

Cardiome is in a strong position to be a valuable partner for single-product companies that seek global distribution outside the United States. With sales force, medical affairs and customer service assets in place, the company is an attractive and experienced partner with few direct competitors. Recently launched products are going through the process of formulary addition and should begin to grow as they penetrate the highest volume hospitals. There is also a pipeline of new products that fall into existing call points, predominantly in the pain area that could be added to the portfolio. We initiate on the shares of Cardiome with a target price of $4.00.

INVESTMENT THESIS

Cardiome has developed a platform of salespeople, licenses and other infrastructure that can support both current and additional products in the European acute care hospital space. Since the 2013 acquisition of Correvio which brought Aggrastat into the portfolio and provided the infrastructure to sell Brinavess, Cardiome has been on the hunt to layer on additional products, demonstrating initial success with Xydalba, Zevtera/Mabelio and Esmocard so far with sales in 2017. They have also signed an agreement for commercialization of Trevyent, which is expected to begin the approval process with the European Medicine Agency in 2019 and see first sales in 2020. Management believes that they have capacity for four or five additional products, with only minor incremental cost. They have identified several call points that expand out from their current focus on cardiovascular and anti-infective spaces which expands the field of potential additions.

The company's strategy is to seek pharmaceutical partners with a drug commercialization plan for the US market, but that require a distributor for areas outside of the US. Attractive candidates are single-product companies that have just completed the FDA approval process but lack the knowledge, desire or capacity to commercialize a new drug in the EU, Canada and other smaller markets. While Cardiome does not assume clinical risk, it does bear regulatory risk and will steer a drug with registrational data through the marketing authorization application (MAA) or new drug submission (NDS) process. They will also take pricing and marketing risk given their knowledge of the negotiation process for these two critical parts of the equation.

[1] Despite a Canadian domicile, both price targets and financial statement are denominated in US Dollars

Key reasons to own Cardiome's shares:

- **Developed sales infrastructure for global commercialization outside the United States**
  - **Sales force in place in EU and Canada**
  - **Expanding sales force in other key regions**
  - **11-distributor sales network in place**
- **Cardiology and infectious disease call points firmly established**
- **Competitive advantage in European medicines approval, price negotiation and sales**
- **Provides comprehensive ex-US commercialization capability with direct sales and distributor network**
- **Few competitors vying for acute care hospital drugs in EU and other non-US markets**
- **Able to add acquired asset for EU and Canadian distribution with only minimal incremental cost**

In the following sections we discuss each of Cardiome's products and the conditions or diseases they treat. We also describe the commercialization process in the EU and Canada required to navigate a product though regulatory approval, pricing negotiations and sales to hospitals. A separate section reviews Cardiome's differentiated commercialization and profitability strategy that will benefit from the infrastructure and relationships that they have in place in the EU, Canada and rest of the world. The competitive environment, risks and relationships will also be examined in support of our assumptions for financial estimates. We conclude our report with the devleopment of our valuation work, which in conjunciton with our thesis provides support for the target price.

Drug Portfolio

Summary of Products

Aggrastat

Aggrastat (tirofiban hydrochloride) is a non-peptide antagonist of the platelet glycoprotein (GP) IIb/IIIa receptor, which inhibits platelet aggregation. One of its many uses is to reduce the rate of thrombotic cardiovascular events in patients with non-ST elevation acute coronary syndrome (NSTE-ACS).



Cardiome acquired Aggrastat and its distributor Correvio LLC in November of 2013 to gain access to Correvio's European sales force, import, export and wholesaler licenses as well as the registered corporate entity that is necessary for a material presence in Europe. As a result of Merck terminating its license agreement for Brinavess in 2012, Cardiome began to seek sales infrastructure and was able to both acquire a new product and obtain the necessary resources to take over Brinavess sales operations from Merck through this acquisition.

Cardiome was attracted to Correvio for its sales infrastructure and to Aggrastat, which had existing revenues. Aggrastat was initially approved in the EU in June 1999, approximately eleven months after it was submitted under the mutual recognition process to the German authority. The product is currently registered and approved in over 60 countries around the world including Canada. Just in December, Cardiome announced an additional licensing agreement with ZAO Firma Euroservice that will work towards Aggrastat approval and sales in Russia. In January 2018, an expansion of indication was granted by the Chinese Center for Drug Evaluation to include patients with ST-segment elevation myocardial infarction intended for primary percutaneous coronary intervention. With worldwide rights, excluding the United States, there is potential for partner development of other regions beyond where sales already take place.

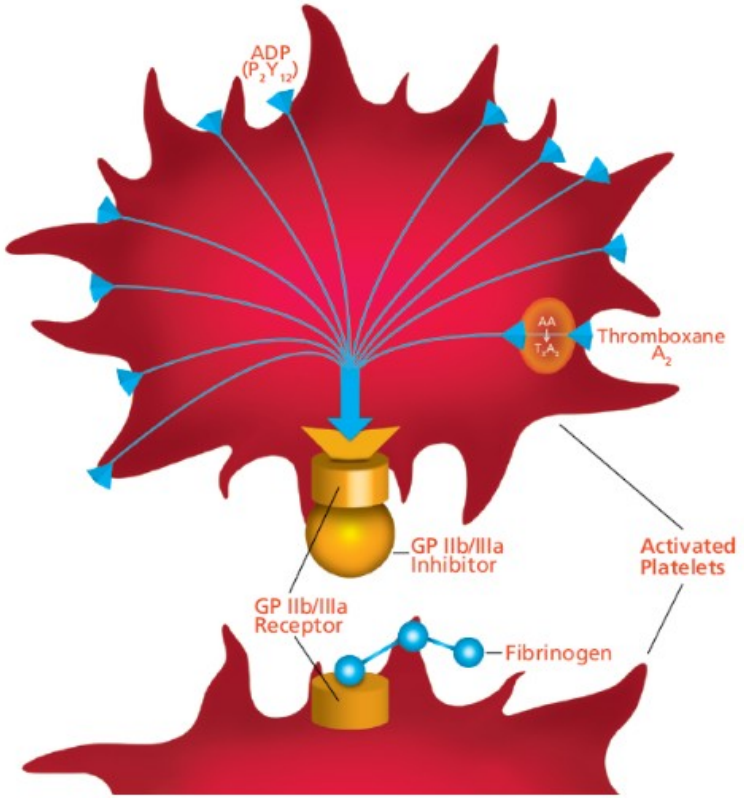
In 2016, Aggrastat made up over 90% of company revenues, but dipped below that level in 2Q:17 due to launch of new products. The drug is commercialized in over 60 countries through Cardiome's direct sales network and partner distributors. EU countries and Canada make up the majority of the revenues generated.

In addition to NSTE-ACS, Aggrastat is used as a blood thinner for several procedures and indications. Some of the procedures include balloon angioplasty, balloon stent placement, percutaneous coronary intervention and coronary artery bypass graft (CABG). The drug is also administered with other medications, such as beta blockers, nitrates, aspirin or heparin, to stop or prevent a heart attack.

Aggrastat is administered intravenously at a rate of 0.4 µg/kg/m for 30 minutes to address NSTE-ACS. After the initial infusion, the drug is continued at a rate of 0.1 µg/kg/m with unfractionated heparin and antiplatelet therapy. In patients that are receiving percutaneous coronary intervention (PCI), the rate of infusion is substantially increased. Coagulation parameters turn to normal 4 to 8 hours after the drug is withdrawn. Aggrastat is removed by hemodialysis.

Results from Aggrastat's registrational PRISM-PLUS trial found that there was a 32% risk reduction in the primary endpoint of refractory ischemia, myocardial infarction, and death within 7 days after starting tirofiban hydrochloride. This represented 50 events per 1,000 treated. The primary adverse event related to the use of the drug is bleeding, which was noted as mild in intensity in the PRISM-PLUS clinical study and takes place at the site of entry for catheterization. Decreases in platelet counts, hypersensitivity and thrombocytopenia were also observed.

Exhibit I – Aggrastat Mechanism of Action[2]



Brinavess

Brinavess (vernakalant IV) is an amino-cyclohexyl ether drug, which has a unique ion channel-blocking profile compared to other cardioversion drugs. It exerts a frequency- and voltage-dependent active sodium channel block, including inhibition of the latent sodium current, which is probably the most important of its electrophysiological effects with regard to termination of atrial fibrillation (AF). The effect on intra-atrial conduction at fast rates is due to blockade of this current. However, it also inhibits the early activating potassium channels specific to the atrium. This inhibition causes prolongation of atrial rather than ventricular refraction and is thought to contribute to the efficacy of the drug. The European Medicines Agency (EMA) approved the drug in 2010 for rapid onset or recent onset AF and it is available in 50 countries.



Brinavess was incubated at the University of British Columbia and was Cardiome's original program when it began operations in 1986. Phase III studies for the drug were completed and reported results in 2004, 2005 and 2007. Co-development partner Astellas Pharma (TYO: 4503) submitted a new drug application (NDA) to the FDA in 1Q:06

[2] http://aggrastathdb.com/mechanism-of-action/

for acute conversion of AF, but the drug was issued a refusal to file letter. The NDA was resubmitted in 4Q:06 and received an approvable letter from the FDA, however, an additional Phase III confirmatory study was required. The confirmatory trial was begun in 2009 under a Special Protocol Assessment (SPA) and continued into 2010, at which time a patient death in South America led to the suspension of the trial. The Data Safety Monitoring Board (DSMB) cleared the drug from being at fault for the death; however, the trial was put on hold indefinitely. In 2011, Astellas transferred its US Brinavess rights to Merck (NYSE: MRK), thereby giving them the global license for the product.

While still working with Astellas, Cardiome entered into a collaboration agreement with Merck in the second quarter of 2009 to commercialize Brinavess outside the US. Merck subsequently filed a MAA with the EMA and received marketing approval in September 2010. In early 2012, the product was approved in 37 countries.

On September 25, 2012, Merck gave notice that it would be exiting the collaboration and license agreements that it had with Cardiome due to the indefinite hold at the FDA and weak sales elsewhere. This action returned global rights to Brinavess back to Cardiome forcing them to develop their own salesforce in several European markets. In April 2013, Cardiome took responsibilities for worldwide sales of Brinavess and royalty payments from Merck ceased. Shortly thereafter, Cardiome assumed responsibility for commercialization in the European Union and completion of the post-marketing study for Brinavess. By the end of 2013, Cardiome acquired Correvio and its European-based salesforce providing the infrastructure required to commercialize Brinavess using the existing Aggrastat salesforce.

After regaining the U.S. rights to Brinavess from Merck, Cardiome began the process of forging a pathway towards FDA approval. In 2017, Cardiome submitted a request to the FDA, seeking guidance regarding a submission of post-marketing data that had been generated in Europe subsequent to the clinical hold that was imposed in 2010. Six years of safety data and results from over 1,100 patients from the SPECTRUM study were not sufficient to convince the FDA to recommend a resubmission. Cardiome will continue interacting with the agency to determine the best path forward. We believe the lack of FDA approval has held back further penetration into the EU and other regions where Brinavess is approved.

Health Canada provided a notice of compliance for the drug in the first quarter of 2017 and the company began commercializing the drug in the second quarter, recognizing first sales in June. Based on research cited by the company, there are approximately 350 thousand individuals with AF in Canada.

Cardiome entered into a development and commercialization agreement with Eddingpharm in 2014 for Brinavess, and received $1 million as an upfront payment. In 2015 a Phase I study was announced and completed which was supportive of a Phase III study. The Phase III study is now prepared to enroll, but on hold pending the response from Chinese regulatory authorities regarding a request for approval based on the EMA filing.

Atrial Fibrillation is an irregular heart rhythm brought about by improper electrical signal propagation in the heart. The heart's rhythm is regulated by the sinoatrial node, which acts as pacemaker. However, in some cases, disorganized electrical impulses, usually originating in the pulmonary veins, can lead to irregular conduction and misaligned contraction of the cardiac muscle. For proper function to take place, the contraction of the four chambers of the heart must be synchronized, and not be affected by extraneous electrical impulses. The occurrence of AF is common in patients after cardiac surgery and a third of patients may experience AF following heart surgery.

First line therapy to treat arrhythmia is prescription and administration of antiarrhythmic drugs (AADs). Sodium channel blockers, calcium channel blockers and beta blockers are commonly used to restore the proper rhythm of the heart. However, these medications do not always work and can in some cases make the arrhythmia worse. Some of the common medications used to treat irregular heartbeat include amarodarone, sotalol, flecainide and propafenone among others. Electrical cardioversion may also be used. Brinavess shows faster action and greater efficiency[3] than many alternatives and also maintains a favorable safety profile with dysgeusia (taste disturbances) and sneezing as the most common side effects.

[3] https://academic.oup.com/europace/article/18/1/51/2398746

Xydalba

Xydalba (dalbavancin) is an antibiotic used to treat skin infection. It is a bactericidal lipoglycopeptide and is used to treat acute bacterial skin and skin structure infections (ABSSSI). The agent works in Gram-positive bacteria by interrupting cell-wall synthesis. This action is disrupted by the drug binding to the D-alanyl-D-alanine terminal of the stem peptide in nascent cell wall peptidoglycan, thereby preventing cross-linking of disaccharide subunits and causing cell death. Dalbavancin has shown effectiveness against *Staphylococcus aureus* (MRSA)*, Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus dysgalactiae, and the Streptococcus anginosus group which includes S. anginosus, S. intermedius, and S. constellatus* where standard antibiotics do not work.



Xydalba is shipped as a powder in 500 mg vials, then mixed with sterile water and glucose in the hospital for administration as an infusion. There are two dose regimens used. A single 1500 mg single infusion or a 1000 mg infusion followed one week later by a 500 mg infusion.

The EMA considered five Phase III and many other earlier stage trials in its approval process.[4] Almost 3,000 patients enrolled in the various Phase III trials that compared dalbavancin with vancomycin, linezolid, and cefazolin. Most of the Phase 3 trials were randomized, double-blind, double-dummy studies with a one to two week duration in the treatment of acute bacterial skin and skin structure infections. Adverse reactions to Xydalba include headache, nausea and diarrhea. Less common reactions include urinary tract infections, insomnia, constipation and itching.

The FDA approved dalbavancin in May 2014, which was subsequently marketed by Allergan in the United States. The European Commission granted marketing authorization for the drug in February 2015. In May 2016, Cardiome signed an agreement with Allergan for commercialization of Xydalba in all major EU nations, the Middle East and Canada. First sales of Xydalba were in 2Q:17 as the company presented it to key opinion leaders (KOLs) and infectious disease physicians to gain support. Cardiome is currently in the process of negotiating formulary inclusion with between 300 and 400 hospitals and we expect the process to continue in 2018.

The drug is used for acute bacterial skin and skin structure infections (ABSSSIs), which are common in hospital and community environments. The bacterial infections result in significant morbidity and mortality and are especially harmful in elderly patients that may suffer from weakened immune systems and co-morbidities. ABSSSIs are characterized by redness, edema, induration (thickening) of the dermis, and accompanied by enlarged lymph nodes and fever.

Competing medicines include vancomycin (also a glycopeptide), linezolid, teicoplanin and clindamycin. While the clinical trial for Xydalba compared the drug to vancomycin testing for non-inferiority, it does have several characteristics that are superior to other alternatives. Higher compliance is an important factor, as Xydalba is most often given as a single infusion, eliminating the need for the patient to follow an extended dosing schedule. In a review of the literature, we observed generally low compliance rates for antibiotics, with the level dropping inversely with the number of pills required per day. These rates varied from 20% to 80+%. When considering compliance in comparison with antibiotic success rates from 60% to 80+%, it stands to reason that some of the lack of success

[4] http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002840/WC500183871.pdf

can be attributable to poor compliance. The single infusion is also beneficial in that it allows for a patient to be discharged from the hospital if the only reason why he or she was an inpatient was for antibiotic administration. The leading antibiotic treatment, vancomycin IV, is given for two or more weeks, and requires a hospital stay to perform. If a hospital stay is not required, then a course of treatment using vancomycin IV can be very expensive, making Xydalba a very attractive alternative for hospitals.

IV-based antibiotics are more potent than oral options and must be used for severe bacterial infections. They have an increased level of bioavailability since they do not pass through the digestive system. They also have a much higher rate of compliance compared to oral therapy as they are administered in a hospital. IV based antibiotics do not directly enter the gastrointestinal tract which can reduce the impact of the antibiotics on gut microflora.

Zevtera/Mabelio

Zevtera/Mabelio (ceftobiprole medocaril) is a broad-spectrum antibiotic indicated for treatment requiring a broad-spectrum antibiotic with activity against a wide range of Gram-positive bacteria. It works by attaching to certain types of proteins on the surface of the bacteria cells. Its action prevents the bacteria from building the walls that surround the cells, thereby inhibiting growth, cell division and the formation of the cellular structure. The drug works similarly to other β-lactam antibiotics and mimics the protein that binds to PBP[5] binding sites, inhibiting PBP crosslinking of peptidoglycan. The peptidoglycan layer is important for the structural integrity of the cell wall, particularly in Gram-positive organisms. The drug belongs to the class of β-lactam antibiotics originally derived from the fungus cephalosporin.



In the UK, Germany, Switzerland, and Austria the drug is branded Zevtera and in France and Italy it is branded Mabelio. Ceftobiprole is active against several types of bacteria, including methicillin-resistant *Staphylococcus aureus* (MSSA, MRSA) and susceptible *Pseudomonas* species. The drug comes in powder form and is added to solution for infusion. The recommended dose is 500 mg of ceftobiprole every eight hours administered over a two hour period. Lower doses are recommended for patients with kidney problems.

Zevtera was initially refused by the EMA in June 2010 in contrast to a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) in November 2008. The refusal materialized after the Committee found that an FDA inspection into study sites for the clinical trial work in the United States was not performed in compliance with good clinical practice. Therefore the CHMP felt it could not rely on the results from the trial and rejected the marketing authorization. Basilea then decided to pursue the decentralized procedure and gained approval in 13 European countries including Italy, France, Germany, the U.K., Austria and Switzerland by the fourth quarter of 2013.

Two Phase III studies were conducted and both were double blind, randomized, multicenter, controlled non-inferiority studies. Together they enrolled over 1,400 patients, comparing ceftobiprole with vancomycin and vancomycin plus ceftazidime. Endpoints for the trial demonstrated non-inferiority with the comparator in subjects

[5] PBPs (Penicillin binding proteins) are a group of proteins that are characterized by their affinity for and binding of penicillin and are a normal constituent of many bacteria.

with community acquired pneumonia and nosocomial pneumonia. The most common treatment related adverse events were nausea, dysgeusia, diarrhea, infusion site reactions, vomiting, hepatic enzyme elevations and hyponatremia.[6]

Additional Phase 3 trials are currently being conducted in an effort to expand the label to include the treatment of bloodstream infections caused by *Staphylococcus aureus* and acute bacterial skin and skin structure infections.

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a Gram-positive bacterium that has evolved from other strains of *Staphylococcus aureus* and is very difficult to treat. Up to 24% of patients in intensive care units are colonized with MRSA and 20% of nosocomial bloodstream infections are attributable to MRSA. This pathogen has developed a drug resistance to many of the common β-lactam antibiotics and arises in public treatment areas such as hospitals where open wounds or invasive devices are used. MRSA can cause many complications including skin infections, sepsis, pneumonia and bloodstream infections and is acquired from contact with an infected wound or from items such as razors or catheters. Good hygiene is recommended to avoid MRSA infection; however, if it is contracted, medical attention is necessary. Treatment for MRSA requires the administration of a combination of topical, infused and oral antibiotics. For MRSA contracted in the hospital, vancomycin, linezolid and daptomycin are frequently used, but some strains of MRSA fail to respond. This requires the use of alternate antibiotics such as ceftobiprole, for which MRSA has largely not developed a tolerance.

First sales of Zeftera/Mabelio recognized on Cardiome's income statement were in 3Q:17. During the last two quarters of 2017, Cardiome was party to a transition agreement with Basilea where Basilea will sell and manage the marketing process and Cardiome will recognize revenues and costs on their financial statements. Beginning in 2018, Cardiome will bring this in-house and will also add several infectious disease focused sales representatives largely based in Italy.

Esmocard

Esmocard (esmolol HCl)[7] is intended for short-term treatment of supraventricular tachycardia (except for pre-excitation syndromes) and for the rapid control of the ventricular rate in patients with AF or atrial flutter in perioperative, postoperative, or other circumstances where short-term control of the ventricular rate with a short-acting agent is desirable. Treatable indications include paroxysmal supraventricular tachycardia[8] and the short-term treatment of tachycardia and hypertension that occur during induction and tracheal intubation, during surgery, on emergence from anesthesia and during the postoperative period. The drug is a beta-1 adrenergic blocker. It addresses accelerated heart rate by decreasing the force and rate of heart contractions by blocking beta-adrenergic receptors of the sympathetic nervous system. Esmocard prevents the action of epinephrine and norepinephrine by blocking neurotransmitters and competing for receptor binding sites. Esmolol is used when a short acting agent is required, and is frequently employed in conjunction with surgery.



[6] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4547641/
[7] https://www.rxlist.com/brevibloc-drug.htm
[8] EMA cites data giving incidence of paroxysmal supraventricular tachycardia at 35 per 100,000 person years and the estimated prevalence is 2.25 per 1000. In the European Union, the prevalence of atrial fibrillation in adults >55 years of age was estimated to be 8.8 million in 2010 and was projected to rise to 17.9 million by 2060.2 https://www.prnewswire.com/news-releases/cardiome-and-aop-orphan-pharma-enter-esmocard-commercialization-agreement-503412481.html

In May 2015 Cardiome entered into an agreement with AOP Orphan Pharma to commercialize Esmocard and Esmocard Lyo in several European countries. AOP is conducting additional clinical research to expand Esmocard's indications to include the management of septic patients that remain tachycardic after 24 hours. The drug provides its benefit by decreasing the heart rate and providing other positive hemodynamic responses.

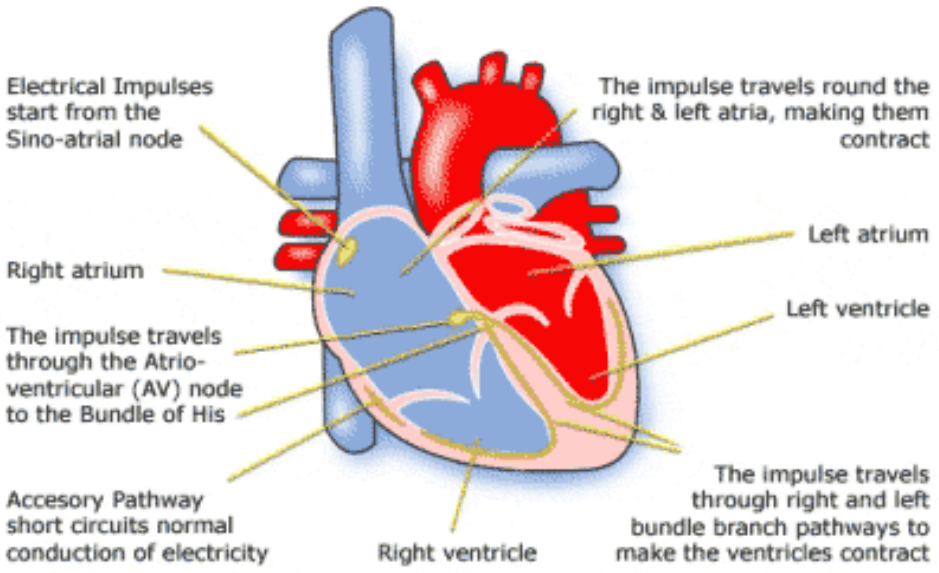
Esmocard was approved in Europe in two presentations, a 10 mg/ml solution for injection (Esmocard) and a 2500 mg powder (Esmocard Lyo) for solution and infusion. The lyophilized[9] version is preferred over the pre-mixed version as the concentration can be adjusted to patient needs. We expect that the lyophilized form will comprise the majority of sales going forward.

Supraventricular tachycardia (SVT) is the manifestation of a high heart rate for a reason other than exercise, high fever or stress. There are a few classifications of the disease, but all are related to an error in the heart's electrical system which doesn't allow it to work correctly. SVT can cause the heart to race from 100 to 300 beats per minute. Other symptoms of SVT include pounding heart, shortness of breath, chest pain, rapid breathing, dizziness and loss of consciousness in serious cases. Faulty electrical connections in the heart or some medicines may cause the condition which has symptoms of palpitations, a pounding pulse and a lightheaded or dizzy sensation. Sometimes unconsciousness may occur. The condition is usually diagnosed with an electrocardiogram or a Holter monitor if longer term assessment is required. Cardioversion is usually first line therapy and there are various medications that are used to address CVT. If medicines fail, then catheter ablation is usually performed.

There are a number of known causes for SVT and it may also be idiopathic. Some of these associated reasons may include heart failure, thyroid disease, heart disease, smoking, excessive use of stimulants or depressants, surgery and pregnancy among others. Diagnosis of the condition requires the use of diagnostic testing such as an electrocardiogram (ECG), Holter monitor, echocardiogram, stress test or other approach which can measure the electrical signals in the heart. There are a number of treatments available that include invasive, non-invasive and pharmaceutical approaches. Cardioversion, which can be either be administered through electrical shock or as a medicine may also be able to restore normal rhythm.

Some of the medicines used to address SVT include adenosine, calcium channel blockers, digoxin, or beta blockers. Esmocard belongs in the category of beta blockers and acts as an adrenergic beta 1 receptor antagonist that acts against the cardiac muscle. It has a short duration of action with an elimination half-life of 9 minutes after intravenous infusion. Esmocard contrasts with other medicines used for SVT in its short duration of action which is applicable in perioperative, postoperative or other emergent circumstances where rapid clearance is required. After stable clinical status is achieved, transition to an alternative antiarrhythmic drug is sought.

Exhibit II – Supraventricular Tachycardia[10]



[9] Lyophilization is the removal of ice or other frozen solvents from a material through the process of sublimation and the removal of bound water molecules through the process of desorption.
[10] Children's Heart Specialists. http://www.mykentuckyheart.com/medical-information/arrhythmias/supraventricular-tachycardia.html

Treyvent

Trevyent (treprostinil sodium) is a combination drug and device which employs SteadyMed's PatchPump infusion system with treprostinil. Treprostinil is a vasodilator in development to be used for pulmonary arterial hypertension (PAH). The drug dilates the pulmonary arteries, prevents blood clotting and lowers the pressure in the pulmonary artery, thereby improving the disease symptoms. It is able to achieve this result by increasing the amount of cyclic adenosine monophosphate, which then stabilizes the excess calcium released in the cytosol. When the calcium levels are balanced, enzyme induced dephosphorylation results, allowing for muscle relaxation and vasodilation.

Currently treprostinil is being marketed as branded Remodulin for pulmonary arterial hypertension in the EU. Remodulin is a complex infusion pump system that requires a miniature pump, catheter, and drug for subcutaneous infusion. It can also be administered as an intravenous infusion if the subcutaneous route is not tolerated due to discomfort. This discomfort has been associated with the use of the preservative meta-cresol, which has been shown to cause local injection side effects including nausea, diarrhea and vomiting in conjunction with insulin use.[11]

The complexity of the administration, side effects from the use of preservative and high cost spurred SteadyMed's development of Trevyent. It is a drug device combination that delivers a measured dose of treprostinil via a patch on the skin and does not use a preservative. The system is comprised of an E-cell disposable battery, a processor and microcomputer to deliver a controlled dose as needed. The product is inconspicuous and can stay in position during bathing and other physical activity. After 48 hours of use, Trevyent can be disposed without special treatment and be replaced with a new patch pump.



There are several types of pulmonary hypertension, which are brought about by a variety of causes.[12] PAH is a subtype where mean blood pressure in the pulmonary circulation is above 25 mm Hg. It usually arises as a result of congenital heart defects due to septal imperfections and results in excessive blood pressure in the pulmonary arterioles, while pressure in capillaries and pulmonary veins are normal. Obesity, infections such as HIV, thyroid disorders and family history can also contribute to PAH. The disorder is twice as common in females as in males. As a result of the excessive pressure, pulmonary edema and right ventricle hypertrophy can occur resulting in fatigue, shortness of breath, lightheadedness, fainting and a dry cough.

Treatment for PAH include administration of prostaglandins, PDE-5 inhibitors, endothelin receptor antagonists and prostacyclins. Treprostinil falls into the last category. Other drugs that have been approved for PAH include iloprost, bosentan, epoprostenol sodium and riociguat. Failure of medication may result in the need for a lung transplant.

PAH is considered a rare disease in the EU. Based on data provided by the EMA, PAH affects approximately 64,000 people in the Union or about 1.4 per 10,000, within the 5 per 10,000 threshold for orphan diseases. PAH occurs as a result of an imbalance of endothelin, prostacyclin and nitric oxide, which if present in the incorrect amounts can cause vessel contraction and the disease. Low levels of prostacyclin result in constricted vessels. Treprostinil as an analogue of prostacyclin is able to increase low levels and reverse the vessel constriction.

[11] Raipar, SF, et al; Severe adverse cutaneous reaction to insulin due to cresol sensitivity. Contact Dermatitis. 2006 Aug;55(2):119-20.
[12] The WHO classified pulmonary hypertension into five groups. PAH is classified in Group 1.

Exhibit III – Comparison of Healthy and Affected Vessel[13]



Symptoms of the disease usually begin with shortness of breath, and exertion becomes more difficult over time. PAH may also cause chest pain, fatigue, unconsciousness and swelling of the lower extremities. Diagnosis of the disease requires diagnostic testing such as an echocardiogram, CT scan, ventilation-perfusion scan or chest X-ray. A stress test may also be administered to make a diagnosis. To verify the initial assessment, the physician may perform a heart catheterization which will measure the internal pressures of the chambers of the heart and the stiffness of the pulmonary arteries.

Commercializing in Europe[14]

After the United States, the EU is the second largest market in the world. With 28 nations, an estimated population of 510 million, broad health care coverage and high living standards, the European Union is the second most important pharmaceutical market in the world. Germany is the largest country in the alliance with 82 million people, followed by France, the UK and Italy, which together comprise over half the entire bloc's population and the majority of pharmaceutical sales.

Exhibit IV – Map of Europe (with EU Highlighted)[15]



[13] United Therapeutics' patient primer on PAH and Remodulin, "Remodulin Information for Patients with PAH" http://www.phaeurope.org/wp-content/uploads/Remodulin-Information-for-patients-with-PAH1.pdf
[14] https://www.rand.org/content/dam/rand/pubs/research_reports/RR200/RR240/RAND_RR240.pdf
[15] University of Kentucky Libraries: http://libguides.uky.edu/EUBusiness

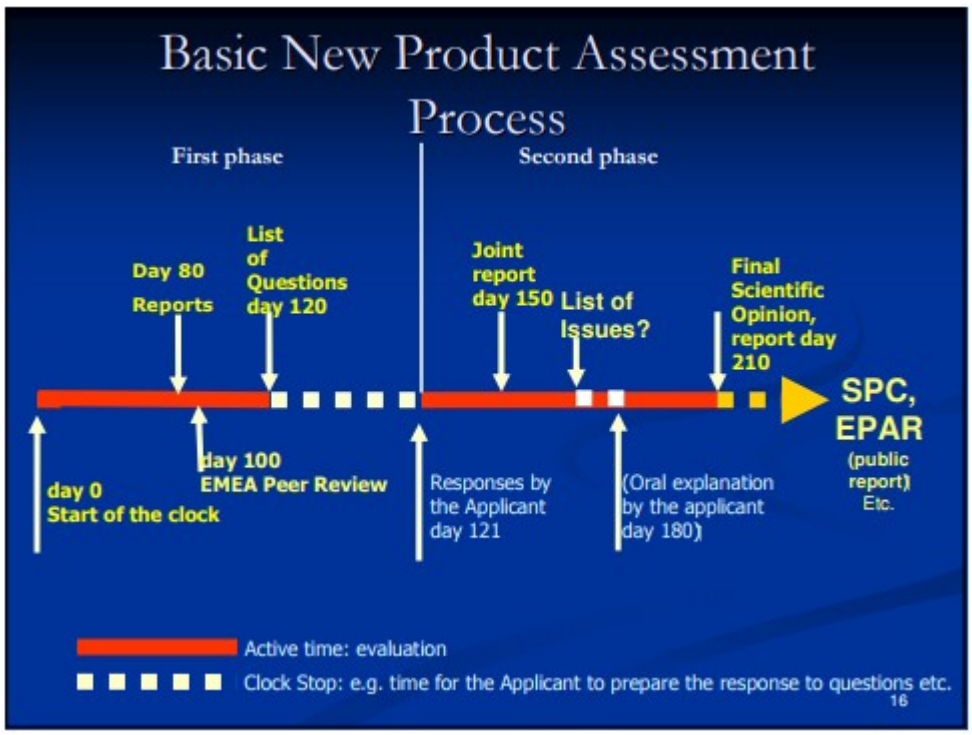
Europe has four routes by which a drug can be approved:

1) Centralised Procedure (CP)
2) Decentralised Procedure (DP)
3) Mutual Recognition Procedure (MRP)
4) National Procedure (NP)

The CP allows for the authorization of a drug in all EU member states and is required for orphan medicines, medicines intended for HIV, cancer, diabetes, neurodegenerative/autoimmune diseases, and other immune dysfunctions, and drugs derived from genetic engineering processes. Not all products will qualify for the CP, but most new innovative medicines will pass through this process. The CP is controlled through the EMA and provides a single license that covers all member states. The most common approach to obtain approval for a new drug is to use the DP where manufacturers apply for simultaneous approval in multiple EU states. This approach is used for products that do not fall under the EU's essential drugs list and for drugs that have not yet been authorized in any EU country. The MRP allows for a drug approved in one country to be approved in all of them. The NP is conducted on a country by country basis and is rarely used.

A Marketing Authorisation Application (MAA) is a process to request approval for a drug to be approved using the CP. The filing of an MAA is usually a year-long process with a break in the middle that provides an opportunity for questions and answers. As shown in the following exhibit, for the first 120 days, the EMA reviews the application and prepares questions. On day 120, the EMA submits its questions to the sponsor. The time required to respond to the questions depends entirely on the sponsor, and when the answers are prepared and provided to the reviewers, the clock restarts. Over the next 90 days, the reviewers develop their opinion and provide a response.

Exhibit V – Timeline for EMA Approval[16]



The next step following the approval of the drug candidate is to begin negotiating with the individual countries' pricing authorities. These negotiations vary by country, but there is usually an assessment of price for value, and a quantification of the benefit on the quality of life for patients using the drugs. In some cases, the national authority will not reimburse for the drug, but allow it to be available for private pay.

[16] EMA Centralized Procedure Presentation, February 1 & 2 2010, Presented by George Wade

Germany

In Germany, new pharmaceuticals are evaluated for their therapeutic benefit and then their prices are negotiated with sponsors. If the negotiations fail, then the decision falls to an arbitration board. Prices are generally based on a drug's superiority over a comparator. The process is governed by the Arzneimittelmarktneuordnungsgesetz[17] (AMNOG or Act to Reorganize Pharmaceuticals Market in the Statutory Health Insurance System) and was launched in 2011. It allows a pharmaceutical company to immediately provide marketing, sale and reimbursement of a drug in its first year while the prices are being negotiated between the sponsor and the pricing organization.

United Kingdom

The UK uses a value-based pricing mechanism which seeks to find a balance between affordable prices and a reasonable return for pharmaceutical developers. A government agency called National Institute for Health and Care Excellence (NICE) assesses new drugs using a metric known as "quality adjusted life-years" (QALY). The value of a year of life in perfect health is set at £30,000 per year and drug costs above this threshold are usually not approved. If NICE and the drug company cannot come up with an agreed price, then there are options for other arrangements called Patient Access Schemes.[18] Drug inflation is limited, and once the price is set there are two years of steady prices after which only low single digit increases are allowed.

France

Following a Marketing Authorisation (MA), a drug sponsor will submit an application for inclusion on the list of reimbursable medicines. The French system appraises the drug's reimbursement level based on its benefit in comparison with alternatives and identifies the population for which the candidate is eligible.[19] The Transparency Committee (TC) evaluates medicines and assesses the medical benefit of the candidate drug. After completing its work, the TC passes the responsibility to the National Union of Health Insurance Funds to determine the reimbursement rate. Drug prices are determined based on their therapeutic value which is compared to existing therapies and is assessed by the TC. The process is expected to take less than 90 days following the start of pricing negotiations. There are five gradations of added therapeutic value in the scale which ranges from major improvement to no improvement and this factor is re-assessed every five years to account for new products entering the market. In some cases a drug will be made available for emergency interventions prior to reimbursement being determined. Following the quantification of added therapeutic value, the Health Product Pricing Committee negotiates a contractual agreement that may include future pricing levels, minimum volumes and pricing renegotiations. Stable pricing is required for five years following the agreement.

Italy

In Italy, the Italian Medicine Agency (AIFA - Agenzia Italiana del Farmaco) manages pricing and reimbursement approvals. An authorized product will be referred to a technical and scientific committee, which conducts an economic assessment of the candidate drug to determine if there is additional therapeutic benefit over existing drugs. The drug sponsor must show how the new product adds value to patients and to the health care system as a whole. Negotiations use prices in other markets, therapeutic value, pharmaco-vigilance data, innovation and projected patient usage and other data to determine pricing and reimbursement. Italy also has regional authorities that can determine whether or not access to a certain drug is granted. Risk sharing agreements are encouraged and reference pricing is used to determine the maximum price. If no agreement regarding pricing and reimbursement is reached through negotiations, drugs are classified as non-reimbursable.

Following the pricing negotiation with the regulatory authorities, the sponsor will present the hospital medicines to formulary committees to make the case for formulary inclusion. Cardiome management estimates that the top 100 hospitals in each of the major markets comprise the majority of sales making it relatively easy to identify the most impactful contributors. Cardiome sales representatives will visit with each hospital and request meetings with the formulary committees which individually convene on different cycles. The meetings can be quarterly, semi-annually or some other periodicity that is conducive to the hospital's schedule. Due to pricing pressures and local budgets, many times hospitals will delay the addition of new products until they have appeared elsewhere or they will approve them near the end of the year. This can suspend first sales of a new product months behind its initial launch date as the sales force adjusts to meeting schedules.

Bundled pricing is allowed in the EU which may allow volume growth for companies like Cardiome that have several product offerings.

[17] https://www.akdae.de/en/index.html
[18] https://www.nice.org.uk/about/what-we-do/patient-access-schemes-liaison-unit?unlid=43992995201761492623
[19] http://apps.who.int/medicinedocs/documents/s20974en/s20974en.pdf

Commercializing in Canada

In Canada the Patented Medicine Prices Review Board (PMPRB) determines pricing for drugs in the country. The PMPRB has a Human Drug Advisory Panel (HDAP) which determines if it is a new molecule or an extension of a previously approved drug. If a new molecule, the panel evaluates its therapeutic value and uses comparator prices and costs in other countries to determine a maximum average potential price (MAPP) allowed for the drug. If the drug is being offered at a rate lower than the MAPP, then no action is required. If the price set by the sponsor is above the MAPP, then the PMPRB will negotiate and go through a process to align the two parties. Drug price inflation is limited to the rise of the CPI.

Approval in other countries, such as in the Middle East will be granted following approval by the FDA or EMA and a relatively basic application. Pricing varies widely from very favorable in Middle Eastern countries, to competitive in other areas such as South America. Cardiome in many cases works with distributors (which we discuss in further detail later in the report) who purchase drug directly from Cardiome at a transfer price and assumes all responsibility for approval, pricing and distribution in these regions.

Company Strategy

Cardiome is a revenue-producing specialty pharmaceutical company but does not yet have sufficient scale to generate a profit. In 2017, three new products were added to the company's portfolio, however, due to the dynamics in Europe with country by country price negotiations and long lead times for formulary inclusion, sales growth is an extended process. We anticipate that with the current product set, breakeven will be several years in the future. Under this scenario, Cardiome will require additional financing to either support operations until breakeven or it will make an acquisition of additional assets which will leverage the current infrastructure to provide profitable operations. Our sense is that management would like to do a deal for an established product that will provide sufficient revenue to cross the threshold to breakeven prior to undertaking additional growth products.

When Cardiome acquired Correvio in 2013, they were able to buy the company using a combination of 20% of shares outstanding combined with $12 million in deferred cash payments, worth $21.9 million[20]. The company may follow this strategy again in a subsequent acquisition, which will avoid the need for additional debt. This approach is more likely for a product that is already established and non-strategic for the selling company. The other side of the acquisition program is to bring on new products. For new products, Cardiome can offer the originating company its experience in navigating new chemical entities through the EMA regulatory process and negotiating pricing with each of the member states. As we describe above, this is a detailed and specific process for each country and Cardiome's experience can speed a product to market and efficiently commercialize it compared to a go-it-alone approach in the region.

Cardiome is in a strong position to grow its product offerings now that the infrastructure for European and Canadian commercialization is in place and there are sales from multiple products. The company's business strategy has been refined in recent years as elucidated below.

- Pursue business development opportunities in both Europe and Canada
- Secure assets that can provide:
    - Immediate revenues
    - An acceleration in achieving corporate profitability
    - Improved strategic position with existing call points
- Obtain medicines in a pain, antibiotic or other acute care category seeking an EU commercial channel
- Pursue in-hospital products to address areas of high unmet medical need in advanced state of development
    - Late Phase 3 trials
    - Launch ready

With the 2013 acquisition of Correvio and the associated licenses and sales assets, Cardiome created a valuable structure that allows for the layering of additional products for distribution in Europe. Areas that are complementary to the current portfolio include cardiovascular, infectious disease, pain, anti-spasticity agents, and adjacent classes related to these hospital call points.

[20] Closing price of $4.01 as of November 18, 2013

Many drug development companies throughout the market capitalization range lack European and Canadian infrastructure required to efficiently access hospital markets. In the absence of sufficient sales to justify a $40 or $50 million sales force, many companies seek a partner to commercialize high-quality products in key areas outside of the US. Cardiome is able to fill this need and provide the commercialization activities to obtain approval, pricing and sales with the key customers in the region. With available sales capacity and infrastructure in-place, the incremental cost of hospital sales in these targeted markets is very low, making Cardiome a very attractive partner.

Chemistry, Manufacturing and Control (CMC)

Cardiome maintains a robust program to ensure that current good manufacturing processes (cGMP) are in place and that no 483s or warning letters have been filed at partner operations. The company has a quality assurance (QA) and global quality management system (QMS) that reviews and inspects manufacturers, packaging company, labelers and others. Cardiome's QA and QMS teams target on-site visits to partners and their frequency of inspections and audits depends on volume of product generated by the partner, whether or not there have been problems at the partner and the importantce of the function the partner provides. The QA and QMS teams ensure that senior management is kept apprised of partner status.

Cardiome is also proactive if there is a planned periodic inspection or inspection for cause. Frequently, Cardiome's QA and QMS teams will perform a pre-inspection in preparation for a regulatory review and will accompany partner management as the inspection teams perform their work.

Strong lines of communication and protocols have been developed between Cardiome and its partners allowing for regular communication that ensures the techincal, quality and business compliance of external providers. Quality control efforts have been strongly defined and frequent inspections ensure that partners comply with regulatory agency standards. Zacks continuously highlights the importance of good practices at partners who perform manufacturing, testing, packaging, labeling and other services.

Distributor Partners

Cardiome is able to offer global distribution outside of the US through its own salesforce and in conjunction with partners who cover the vast majority of other geographies. In addition to its own distribution in Canada and Europe, relationships with partners expand the reach into Mexico, Central America, South America, Africa, the Middle East, Asia, Eastern Europe, Australia and now into Russia with the addition of ZAO Firma Euroservice.

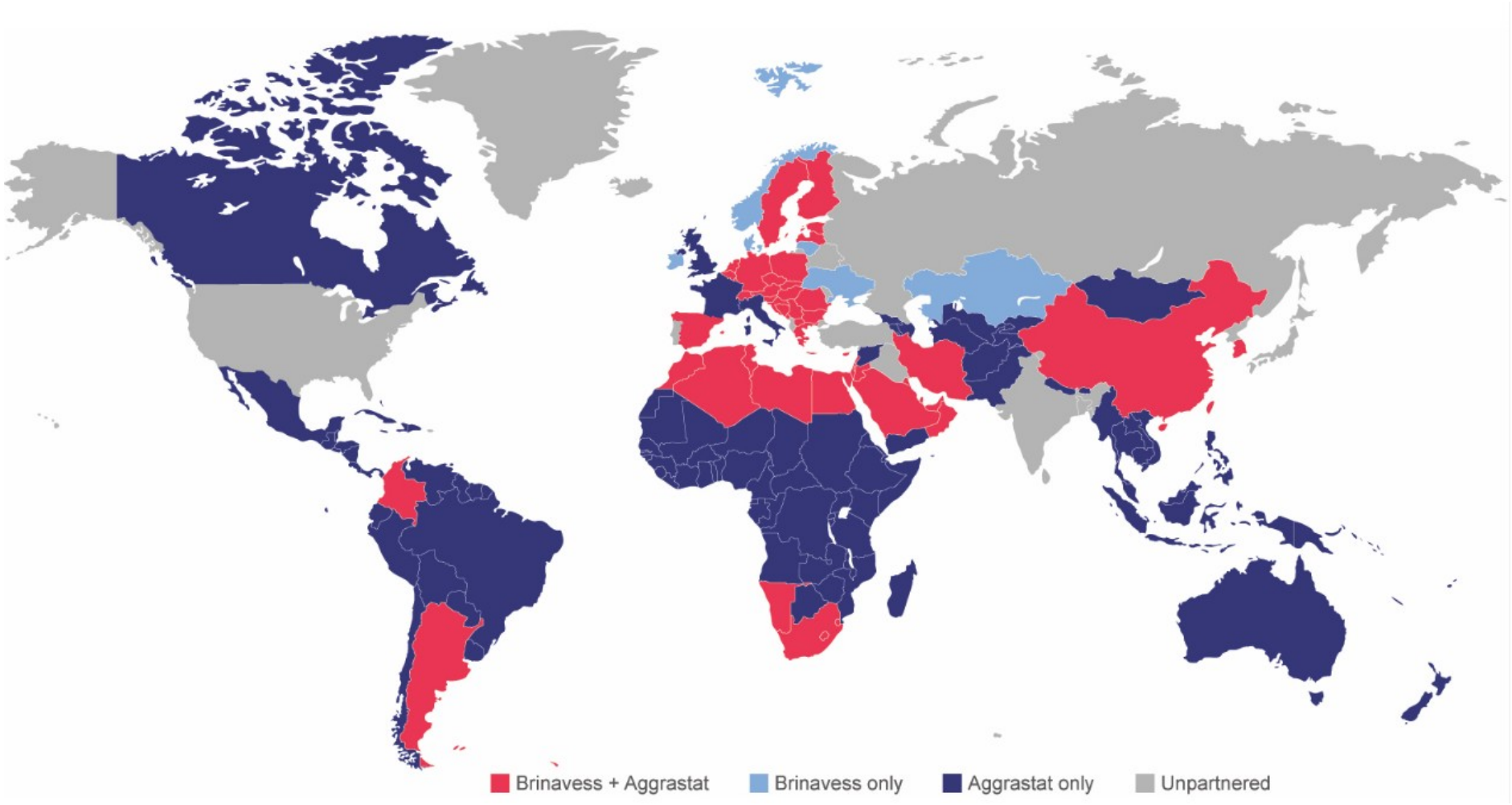
Cardiome currently has eleven relationships that expand its reach globally, many of which were initiated by Correvio. Below we summarize the selected details of these distributor relationships.

Exhibit VI – Distribution Partners

Distributor Network	Drug	Regions	Headquarters
Aspen	Brinavess	S. America/S. Africa/S. Korea/Taiwan	Durban, S. Africa
Algorithm S.A.L.	Brinavess	Middle East, North Africa	Beirut, Lebanon
Eddingpharm	Brinavess, Aggrastat	China	Hong Kong, China
DrugSales Ltd	Aggrastat	Malta, Italy	Lija, Malta
AOP Orphan Pharma	Aggrastat	Several EU Countries	Vienna, Austria
Atco Laboratories Limited	Brinavess	Pakistan	Karachi, Pakistan
Lifepharma Ltd	Brinavess	Cyprus	Nicosia, Cypress
NoraMeda	Aggrastat	Lithuania, Latvia, Estonia	Vilnius, Lithuania
Tzamal	Xydalba	Israel	Petach Tikva, Israel
Vianex	Brinavess, Aggrastat	Greece	Athens, Greece
ZAO Firma Euroservice	Aggrastat	Russia	Moscow, Russia

Cardiome generally passes through product at a transfer price to its partner which is responsible for obtaining approval, pricing negotiations, and commercializing the drug. License holders that are seeking a global distributor outside of the United States can either license to Cardiome only in areas where they have a company sales force or Cardiome can be a one-stop partner for all ex-US sales for convenience. In the latter case, Cardiome can employ the relationships represented above to reach the vast majority of the world's population.

Exhibit VII – Cardiome Distribution[21]



[21] Source: Cardiome website: http://cardiome.com/partners/#outlicensing.

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Licensing Partners

Cardiome's infrastructure throughout Europe and Canada makes them an attractive partner for licensors with a hospital-based product requiring distribution. Building on their original product set of Brinavess and Aggrastat, Cardiome added three more products in 2017 and signed an agreement to seek approval and commercialize one other. The company's most exciting new licensed product is Allergan's (NYSE: AGN) Xydalba, which is being marketed in the United States as Dalvance. Efforts are being made in the UK, Germany and France to obtain formulary placement in hospitals. Primary rights to Esmocard and Esmocard LYO are held by AOP Orphan Pharma (private) and Cardiome obtained a license to distribute Esmocard in selected European countries in May 2015. Pricing negotiations for Esmocard have been completed and first sales were in October 2017. In September of 2017 Cardiome and Basilea (SWX: BSLN) announced a distribution agreement for Zevtera and Mabelio in Europe (excluding the Nordics) and Israel. The product is already approved in 13 European countries and commercialized in about half of them. Cardiome will receive the drug at a transfer price and will be responsible for negotiating pricing in new territories. The company's largest opportunity comes from Trevyent which will soon seek EMA approval for PAH. License owner SteadyMed will have Cardiome commercialize Trevyent in the EU, Canada and the Mideast. We anticipate that SteadyMed will manufacture the product and provide it to Cardiome through a transfer price.

We expect Cardiome to pursue expansion of these products beyond the current licensed regions through either further development of their salesforce or further leveraging distribution partner relationships. Below we summarize partners and key details of the licensing agreements.

Exhibit VIII – Licensing Partners

Licensor	Headquarters	Drug	Licensed Regions	Launch	License Date
Allergan	Dublin, Ireland	Xydalba	EU, Mideast + expansion	Dec 2016	May 2016
AOP Orphan Pharma	Vienna, Austria	Esmocard (LYO)	Italy, France, Spain, Belgium	Jan 2016	May 2015
Basilea	Basel, Switzerland	Zevtera/Mabelio	34 Euro countries, Israel	Sept 2017	Sept 2017
SteadyMed	San Ramon, CA	Trevyent	EU, Canada, Mideast	est. 2019	June 2015

Intellectual Property

Cardiome is reliant on intellectual property protection for its drug portfolio. The patents, some of which are licensed, cover various aspects of their owned and licensed products including composition of matter and method of administration. Below we list the portfolio of products and the length of intellectual property protection.

Exhibit IX – Key Patent Expirations

Drug	Market	Patents
Aggrastat	Worldwide	Generic
Brinavess	Canada, EU, OUS	2024
Esmocard	EU, Canada, MidEast	2028
Trevyent	EU, Canada, Israel, Mideast	2024+
Xydalba	EU, Mideast	2023
Zevtera/Mabelio	Europe & Other	Generic

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Significant Event Timeline

Cardiome has a number of recent and upcoming milestones related to new geographic launches and interacting with regulatory authorities regarding the approval process. Over the next year we anticipate the following events to take place on or around the indicated date.

- 4Q:17 – Esmocard Lyo launch in Belgium, France & Italy
- 4Q:17 – Filing for approval of Xydalba in Canada
- 4Q:17 / 1Q:18 – Commercial rollout of Brinavess in Canada
- FY:18 – Business development efforts in targeted areas
- FY:18 – Capital raise using ATM
- 2Q:18 – Launch of Zevtera/Mabelio in Spain & Ireland
- 4Q:18 – Launch Xydalba in Belgium & Netherlands
- 1H:19 – Capital raise using available funds from the debt facility
- FY:19 – Filing for approval of Trevyent in EU
- FY:20 – Launch of Trevyent in EU and other regions

Financial Position

As of September 30, 2017 Cardiome held approximately $27.2 million in cash and cash equivalents and debt of $39.0 million on its balance sheet. Cash burn is expected to range from $4.5 to $6.0 million per quarter, indicating the company will need to raise capital in 2018 to fund growth initiatives, absent a transformative acquisition. We see additional debt or share issuance as the most likely routes for raising additional capital.

Cardiome has an agreement with FBR Capital Markets and MLV & Co. to issue shares using an at-the-market (ATM) facility. It also has access to a term loan with CRG with $10 million remaining available. Based on our forecast of $5 million of cash burn per quarter, we anticipate Cardiome will raise $10 million from each of these sources over the next year, supporting additional quarters of operational expenses.

RISKS

All investments contain an element of risk which reflects the uncertainty of the business and what it will ultimately achieve. Some investments exhibit higher predictability, with current cash flows and established sales. These enterprises will have a lower level of perceived risk while other companies that are betting on a new technology that has not yet been fully defined have a much higher level of perceived risk.

The specialty pharmaceutical and biotechnology space includes companies at both ends of the spectrum, from mega-cap pharmaceutical powerhouses that have multiple products currently generating revenues, to small operations with a handful of employees conducting pre-clinical studies and many companies in-between. Many of the risks faced by the large pharmaceutical companies and smaller biotechnology-focused firms are similar; however, there are some hazards that are particular to smaller companies that have not yet established themselves or their products.

For smaller early-stage companies with expense structures still below breakeven, investing in growth is an extended process. The timeframe for taking a new drug through the approval process, pricing negotiation and formulary addition can take multiple years. There also may be several other competitors pursuing similar indications that may dominate market share despite inferior safety or efficacy. The risks of new product launches are substantial.

Even if a company has a strong, experienced team that is launching a new product with a high likelihood of approval, evident formulary addition and a large addressable market, physicians may not use the product due to familiarity with legacy products and a hesitancy to change familiar prescribing practices.

Access to financing is another risk for companies that have not yet achieved positive cash flow. Availability of capital comes and goes in cycles. During periods of improving confidence, new funding may be easy to access; however, during a liquidity crisis or a period of heightened risk perception, even companies with bright prospects may be in trouble if they are dependent on the financial markets to fund their initiatives. If capital is needed to sustain the company and it is not readily available, it may be forced to suspend operations, sell equity at a substantial discount to previous valuations and dilute earlier shareholders. A lack of funding may leave potentially promising growth plans without a viable route to market or force a company to accept onerous terms. The presence of debt during a period of operational losses is another risk early stage companies must face. If debt terms require repayment before profitability is reached, or interest burden is too great, equity is at risk of severe dilution and potentially recapitalization.

All drugs must navigate the regulatory approval process in the US, EU and other countries before commercialization in those regions. This effort is a material uncertainty which may take years and depends upon the needs and desires of the determining authority. Substantial expense is undertaken to bring a molecule or compound through clinical trials and address all of the regulatory agencies' concerns. Isolating companies that have a long history of research success in drug development, with opinion leaders and experts in the field are important fundamentals that can help mitigate this risk. Companies that have had previous success with the FDA, EMA or other regulatory agencies also are more attractive than those who may be new to the process. Some accelerated pathways to approval have been put forth such as the ones for orphan drugs, however, changes in sentiment or perceived safety of pharmaceuticals could alter the regulatory environment to demand a more thorough process and these pathways may be extended or additional requirements may be put in place.

Cardiome is seeking approval for Trevyent through a MAA with the European Medicines Agency (EMA) which is targeted to occur in 2019. They will submit the MAA under the centralised process. The company is also interacting with Health Canada on a similar timeline. Regulatory success is not guaranteed and approval rates for MAAs based on our cursory review range from 60% to 80%.[22] While we anticipate approval, it may be delayed or not granted.

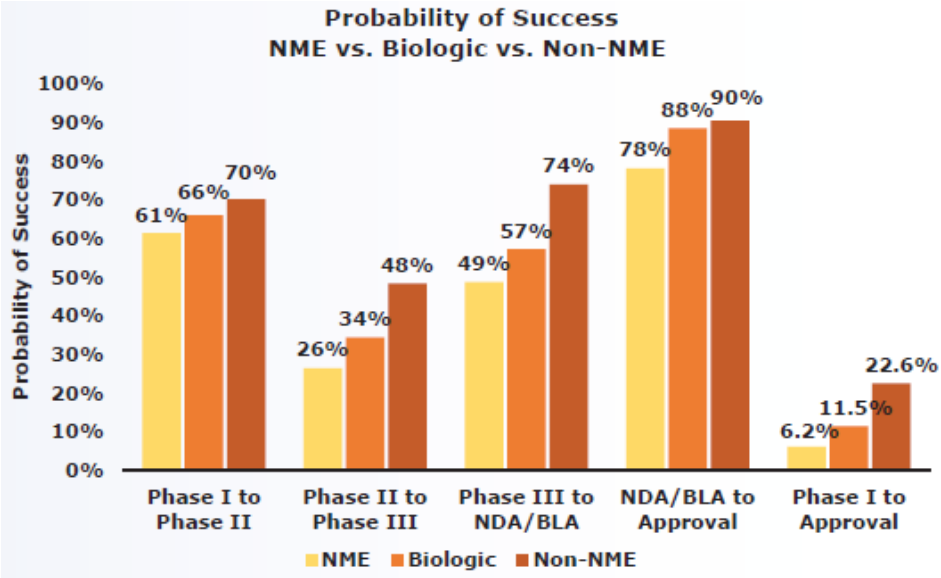
Partner SteadyMed is currently pursuing FDA approval for Trevyent in the United States. In August 2017, SteadyMed received a refuse to file (RTF) letter from the FDA and in December reached an agreement for work necessary to resubmit Trevyent's NDA. If SteadyMed is not able to obtain approval from the FDA for Trevyent, this could damage Cardiome's chances for approval for its MAA. Failure to eventually obtain approval for Trevyent in

[22]Hartman, Markus, et al. Approval probabilities and regulatory review patterns for anticancer drugs in the European Union http://www.croh-online.com/article/S1040-8428(13)00030-9/fulltext

the United States could negatively impact the success of eventual commercialization in other regions throughout the world. Even for drugs that are not new molecular entities (NMEs), there remains a risk that the medicine may not be approved by the regulatory bodies. Delays in SteadyMed preparing the necessary information for Trevyent's NDA may postpone Cardiome's submission to the EMA as final device design is required before the application can be presented to European regulatory authorities.

Below we show approval rates for NMEs, biologics and non-NMEs under the FDA regulatory regime. For non-NME NDAs, the FDA has a historical approval rate of 90% based on the study we cite.

Exhibit X – Success Rates for FDA Regulatory Approval[23]



Cardiome relies on third parties for manufacturing drug substance and devices, analytical testing services, packaging and labeling. Risks of poor manufacturing processes, quality control issues and product delays may halt production of a drug if partners are out of compliance with regulatory agency requirements. Cardiome has developed long-term relationships with its partners and has implemented a thorough process of inspections and communication to ensure good practices. While the company has made substantial efforts here to ensure a productive relationship, the partner may lack the desire or skill to successfully maintain the required good practices and the partner may have other competing products under its control that receive greater attention and focus.

Drug price inflation has gained increased attention over the last several years and has contributed materially to the increase in health care costs over the last decades. As new therapies have been approved, drug prices have set new records and increased at a substantial rate in the United States. Cardiome does not currently have exposure to US markets; however, if Brinavess is approved they could generate sales here and be exposed to these dynamics. The company currently directly sells product in over 30 different countries, which limits the risks of dramatic action by any one payor. The government negotiates prices in countries where Cardiome sells its product, leading to lower and steadier prices than those found in the United States.

We highlight several risks that come from higher prices and increased spending on pharmaceuticals. New drugs may see delayed introduction in Cardiome's markets and pricing authorities may take a stronger negotiation position for products that are approved. Governments, elected officials and regulators may implement requirements that are less favorable to the pharmaceutical industry. Additionally, governments may impose additional non-price related regulation and disclosure requirements that can increase costs and burden.

While we have discussed a broad variety of risks above, we believe that our forecast parameters, discount rates, success probabilities and valuation metrics address these eventualities and our target price reflects an assumption of these risks faced by all biotechnology companies.

[23]Clinical Development Success Rates 2006-2015. David Thomas, Justin Burns, John Audette, Adam Carroll, Corey Dow-Hygelund, Michael Hay.

PEERS AND COMPETITORS

There are many specialty pharmaceutical companies that distribute in regional and global markets. While there are a variety of call points for the diversity of drug products available in the marketplace, there are no direct competitors that can commercialize in all markets outside of the US in the acute care hospital market. Despite the lack of a direct competitor, there are other firms that commercialize a portfolio of products in their specific market niche or the same call points as Cardiome.

Exhibit XI – Peers and Competitors[24]

Ticker	Company	Price	MktCap (MM)	EV (MM)	Therapeutic Area
STDY	SteadyMed Ltd	$3.30	$88	$50	Development of Trevyent
CPIX	Cumberland Pharma	$7.03	$111	$69	Commercialization of branded prescription products
UTHR	United Therapeutics	$136.97	$5,919	$4,708	Commercialization of Remodulin
GUD.TO	Knight Therapeutics	CAD 7.67	CAD 1,095	CAD 350	Commercializing products in Canadian market
MCUJF	Medicure Inc	$5.80	$92	$526	Sale/Market of Aggrastat in US
MDCO	The Medicines Company	$33.60	$2,424	$2,858	Sale/Market of hospital products in US
TLGT	Teligent Inc	$3.31	$177	$257	Sale/Market Canada/US products
MLNT	Melinta Therapeutics	$14.55	$456	$283	Anti-infectives
AKRX	Akorn, Inc.	$32.47	$4,061	$4,530	Prescription pharma & consumer health
CRME	**Cardiome Pharma**	**CAD 1.53**	**CAD 52**	**CAD 64**	**OUS Commercialization of Hospital Products**

STDY is a partner with Cardiome for Trevyent, the generic competitor to Remodulin. They are seeking FDA approval for Trevyent in the United States and have granted Cardiome commercialization rights for the drug in the EU, Canada and Middle East.

CPIX is focused on commercialization of hospital acute care and gastroenterology pharmaceutical products. It has seven commercial and six development stage medicines in its pipeline. The corporate strategy seeks to license additional products with similar call points to its current portfolio, thus leveraging its sales force.

UTHR is a US-based pharmaceutical company which developed and received FDA approval for Remodulin and other drugs for the treatment of PAH. UTHR is developing other treprostinil-based products with improved delivery methods as well as other cardiopulmonary medicines for PAH, COPD, lung cancer and other indications.

GUD.TO maintains and seeks to grow its portfolio of pharmaceutical products through in-licensing and acquiring of product rights for commercialization in Canada and other geographies. Portfolio is focused on opioid-related, pain and ophthalmology products among others. The company is also developing a prostate ablation device and a diagnostic tool.

MCUJF develops and commercializes cardiovascular therapeutics for the US market. Aggrastat sales in the US are the primary revenue generator for the company; however, the company is developing a portfolio of products for the US cardiovascular market that are expected to launch in 2018 and beyond.

MDCO commercializes cardiovascular, infectious disease and surgery/perioperative care pharmaceutical products in US and global markets. The company is also developing cholesterol drug Inclisiran under license from Alnylam Pharmaceuticals which recently began Phase 3 trials.

TLGT is a generic pharmaceutical company commercializing products in the United States and Canada. The company emphasizes injectables, topical products and topical solutions that are focused on the hospital and other markets. It has 24 products commercialized the US and 33 ANDAs on file.

MLNT targets antibiotics, developing and commercializing a portfolio of several products in this therapeutic area. In November 2017, the company agreed to acquire MDCO's infectious disease business unit which is expected to close in 1Q:18.

AKRX is a specialty pharmaceutical company that develops, manufactures and markets generic and branded products. Their broad portfolio or revenue generating products includes inhaled, injectable, nasal, ophthalmic, topical and other categories of medicines. Akorn distributes its products in the United States.

[24] Price and market capitalization data is as of January 26, 2018

MANAGEMENT PROFILES

Management Team Changes

In May 2017, Cardiome made changes to its management team and Justin Renz was appointed as CFO, Jennifer Archibald to Chief Business Operations Officer, David Dean to Chief Business Development Officer and Hugues Sachot to Chief Commercial Officer. Below we highlight the background for key members of the management team.

William Hunter, M.D., President and Chief Executive Officer

Dr. William Hunter has been a member of Cardiome's Board of Directors since 2007 and became the Company's President and CEO in July, 2012. Prior to Cardiome, Dr. Hunter co-founded Angiotech Pharmaceuticals in 1992 and assumed the position of Chief Executive Officer in 1997 when Angiotech was a venture-stage, private, pre-clinical company with fewer than 50 employees. He led Angiotech through three rounds of private equity financing, the Company's IPO and listing on the Toronto Stock Exchange and NASDAQ, over $1B in equity and debt financings, a debt restructuring and eight separate corporate acquisitions. During that time, Angiotech grew to become a profitable, diversified, healthcare company with over 1,400 employees, several thousand commercial products, 12 facilities in five countries and worldwide annual revenues exceeding $250 million. Dr. Hunter currently serves a director of Epirus Biopharmaceuticals, Inc. (NASDAQ: EPRS) and Union Medtech. Dr. Hunter served as a practicing physician in British Columbia for 5 years and has over 200 patents and patent applications to his name.

Justin A. Renz, CPA, Chief Financial Officer

Mr. Justin Renz currently serves as Cardiome's Chief Financial Officer, with responsibility for overseeing Cardiome's finances and investor relations. Mr. Renz served as Executive Vice President, Chief Financial Officer and Treasurer at Karyopharm Therapeutics from August 2014 to April 2017, where he led core business and finance functions. Prior to Karyopharm, Mr. Renz was Executive Vice President, Chief Financial Officer and Treasurer at Zalicus Inc. (formerly CombinatoRx, Inc.), which he joined in September 2006. He oversaw multiple rounds of equity and debt financing and led the company's asset monetization strategy and two reverse mergers, culminating with the sale of Zalicus to Epirus Pharmaceuticals in July 2014. Prior to Zalicus, Mr. Renz served in senior finance and accounting roles at Serono, Inc. and Coley Pharmaceutical Group, Inc.

Earlier in his career, Mr. Renz held increasingly senior finance positions at ArQule, Inc. and Millipore Corporation. Mr. Renz began his career with Arthur Andersen LLP in 1993. He received a Bachelor of Arts in Economics and Accounting from the College of the Holy Cross, a Master of Science in Taxation from Northeastern University and a Master of Business Administration from Suffolk University.

David Dean, Chief Business Development Officer

Mr. David Dean is a member of Cardiome's executive team as Chief Business Development Officer and is responsible for overseeing the company's business development activities. Mr. Dean first joined Cardiome as Vice President, Business Development and Investor Relations with over 15 years of capital markets experience as a top ranked industry analyst focused exclusively on the Canadian healthcare sector, most recently as a Director and Research Analyst at one of Canada's leading independent investment banks. Mr. Dean earned an M.Sc. from the University of Ottawa (Physiology) as well as an MBA (Finance) from Queen's University. In addition to his research analyst registrations in the United States, he was also a registered representative.

Sheila Grant, Chief Operating Officer

Ms. Sheila Grant currently serves as Cardiome's Chief Operating Officer, with responsibility for overseeing Cardiome's medical, regulatory and manufacturing operations. Ms. Grant was most recently Cardiome's VP of Product Development, with responsibility for the overall management of the vernakalant IV and oral development programs from pre-clinical studies through to commercialization. Ms. Grant's past roles at Cardiome have included VP Commercial Affairs, and Director of Business & Clinical Development. Prior to joining Cardiome, Ms. Grant acted as a business consultant to De Novo Enzyme Corporation and Coopers & Lybrand. Ms. Grant also worked in research and development, production, and quality assurance with Schering Agrochemicals U.K., Wellcome Biotechnologies U.K. and Serono Diagnostics U.K., respectively. Ms. Grant holds an MBA degree from Simon Fraser University.

Financial Results

Cardiome filed a press release announcing third quarter 2017 results on November 14, 2017. In addition to posting a 15% increase in revenues, the company added Zevtera/Mabelio to the portfolio and launched Xydalba in several new European countries. Other highlights include approval for Aggrastat's new label by Health Canada, presentation of clinical data for Brinavess at ESC and an update on SteadyMed's interaction with the FDA.

Revenues of $6.0 million were recognized in 3Q:17, which was a 15% increase over the previous year's $5.2 million. The initiation of Xydalba sales and an increase in Middle East Aggrastat sales generated the increase. Gross margin improved by 100 basis points to 75.1%[25] which represents the highest level in 7 quarters, aided by changes in customer and product mix.

Selling, General and Administrative costs rose 18% in the period as the company expanded the size of its salesforce to support the launch of Xydalba and it added a Canadian team. Amortization increased slightly to $0.9 million.

Operating loss of ($4.8) million was lower than the loss of ($4.1) million in the prior year.

Interest expense doubled to $1.8 million representing higher interest payments due to higher levels of debt. Cardiome drew a third tranche of $10 million under its CRG agreement. Income tax expense was *de minimus* in both periods.

Net loss was ($6.6) million or ($0.20) per share which compares to net loss of ($5.3) million and ($0.19) per share in the prior year. Average diluted shares outstanding grew from 28.4 million in 3Q:16 to 33.9 million in 3Q:17.

Cash and equivalents were $27.2 million and long term debt $39.0 million as of September 30, 2017. Cash burn, which includes cash used in operations and purchase of intangible assets was ($9.5) million in 3Q:17. $5.2 million of this amount was a payment to Basilea for the license to commercialize Zevtera/Mabelio. Absent the intangible assets, cash burn was ($4.3) million in the third quarter and ($18.4) million in the first nine months of 2017, which is equivalent to a ($1.4) and ($2.0) million monthly cash burn rate.

[25] Our gross margin calculation excludes license revenues.

VALUATION

We are initiating coverage of Cardiome Pharma Corp. with a price target of $4.00. Cardiome has a portfolio of five revenue producing products and one product seeking regulatory approval. Drug product launches in the EU are lengthy, multi-step processes that require regulatory approval, pricing negotiations on a country by country basis and requests for inclusion on hospital formularies. This process can take two years or more before material revenues are recognized and require numerous relationships to effectively commercialize a drug.

The company's foundation product is Aggrastat. It is a generic drug that has experienced competition and suffered market share losses for several years; however, Cardiome and partners are expanding the drug's reach and indications into new areas, such as in Russia with the recently signed Euroservice deal. We estimate that Aggrastat is exposed to almost 5 billion consumers based on licensed regions, although ultimate penetration is very low. Aggrastat sales are well established, but we anticipate some growth (1%) as new regions are penetrated. Our model anticipates Aggrastat sales to be approximately $21 million in 2022 with gross margins in the 70% range.

Cardiome has worldwide rights to Brinavess, and has obtained approval for the drug in most developed regions in the world, outside the United States. The drug has exposure to the Chinese and other Asian markets through a relationship with Eddingpharm. We estimate exposure to approximately 5 billion in population based on the regions where the drug is approved and / or licensed. Penetration is expected to be low, but growing at 2% as commercialization activities and anticipated approvals increase usage. An unanticipated but potentially impactful event would be approval by the FDA, which we believe would not only allow for material sales in the United States, but also lift the cloud hanging over Brinavess in other regions, potentially supporting materially higher growth. Our model anticipates Brinavess sales to be $5.3 million in 2022 with gross margin in the 80 – 85% range.

Xydalba is licensed to Cardiome in the European Union, Middle East and Canada, providing an addressable population of almost 800 million. The company is in the process of negotiating with hospitals for formulary inclusion in Europe and has submitted an application to near 350 hospitals and reported about 15% penetration as of 3Q:17. We anticipate that penetration and usage will rise substantially in coming years, providing accelerating sales growth. Cardiome is also expanding sales of Xydalba through distributors, and recently signed an agreement with Tzamal for commercialization in Israel. The combination of these multiple factors supports strong sales growth over the next several years. The argument for using Xydalba is very compelling, adding yet another supportive factor to our thesis. Due to the need for new and effective treatments for ABSSSI, as well as the "one-and-done" administration utility of the drug provides a compelling argument for what we anticipate will be the fastest growing product in the portfolio (from $1.6 million in 2017 to $34 million by 2022). Gross margins are anticipated to fall in the 80% range.

Zevtera was acquired from Basilea in September 2017. Cardiome recognized revenues and costs for this product immediately as per a transition agreement. Starting in 2018, the company will bring operations in house, including an additional 10 salespersons with anti-infectives sales experience. This product is a fitting complement for Xydalba as it addresses the same call point and addresses a different indication. Current annual sales are between $2 and $3 million and are expected to expand to approximately $18 million by 2022. In the third quarter 2018, Zevtera sales were taking place only in six countries and the licensing agreement includes 30 countries in Europe and Israel providing substantial new opportunity as new approvals materialize.

Cardiome recognized first sales of Esmocard in 3Q:17. The drug recently expanded its presentation to offer a lyophilized form that has increased utility allowing for precise concentrations of the drug to be used in solution. We expect that most esmolol hydrochloride will be sold in lyophilized form. Competitor BreviBloc generates $8 million in sales in the category and we anticipate that Esmocard can achieve approximately 20% market share by 2022, or $1.7 million in revenues.

We anticipate SteadyMed will submit Trevyent to the FDA in 2H:18 followed by Cardiome's submission to the EMA in early 2019. With an estimated one-year review period, first sales are anticipated in 2020. As all patients receiving Remodulin are listed on a registry, we model a faster ramp of Trevyent than for other products in the portfolio as the commercialization efforts will be more targeted. 2022 revenues are expected to be $42 million. We apply a 70% probability of ultimate commercialization to Trevyent and adjust model revenues accordingly.

The sum of the portfolio of products yields adjusted revenues of $30.5 million in 2018 rising to $109.4 million in 2022. Product gross margin is anticipated to be approximately 72% in 2018 and decline slightly to 70% in later years as growth in lower margin new products reduce the overall level.

With the addition of 10 new sales representatives in 2018, we forecast $38 million in SG&A this year. Apart from normal inflation, we anticipate costs to remain fairly steady over time as Cardiome's infrastructure is sufficient to support several additional products in their targeted call points. Taxes, which will be paid after the company works through its NOLs, are anticipated to be 20%, which is a mix of rates in the Switzerland, Canada and other operational jurisdictions.

While management has expressed an interest in acquiring an established product, there is not yet enough evidence to determine what form this might take or the value that might be derived from it. Therefore, costs or benefits from such a transaction do not appear in our model. Cardiome will require capital later this year to continue to fund operations and support its growth initiatives. Our forecasts include the issuance of approximately eight million additional shares over the next two years and additional draws of the credit line of $10 million.

Our target price is generated using a discounted cash flow model employing a 15% discount rate and a 2% terminal growth rate. We apply a 70% probability of commercialization success for Trevyent. Based on the assumptions above and after adjusting for shares, restricted stock and options outstanding, we generate a target price of $4.00.

CONCLUSION

Cardiome has invested in infrastructure that makes them an attractive partner for hospital drugs that require distribution in Europe, Canada and the rest of the world. The company has developed and refined its sales force over the last several years to emphasize cardiology and anti-infective call points and has the ability to expand into pain and other areas of the hospital as well. Cardiome is seeking acquisitions to leverage its current infrastructure and build a bridge for products in the US to be developed in Europe, Canada and the rest of the world. We believe the company's primary goal in the short term is to acquire an established product that can provide sufficient revenues to achieve breakeven or better. After the company has become self-sufficient, we anticipate efforts to acquire late-stage development and patent protected growth products will be next. Cardiome has the experience and skill to navigate new products through the regulatory, pricing and hospital formulary inclusion process. We see the company's platform as highly leverageable and with few competitors in the company's specialized hospital-based call point.

Key reasons to own:

- **Developed sales infrastructure for global commercialization outside the United States**
  - **Sales force in place in EU and Canada**
  - **Expanding sales force in other key regions**
  - **11-distributor sales network in place**
- **Cardiology and infectious disease call points firmly established**
- **Competitive advantage in European sales**
- **Provides comprehensive ex-US commercialization capability with direct sales and distributor network**
- **Few competitors vying for acute care hospital drugs in EU and other non-US markets**
- **Able to add acquired asset for EU and Canadian distribution with only minimal incremental cost**

In summary, we believe Cardiome represents an attractive platform for growth in the European, Canadian and global ex-US market. Based on our DCF model, the shares are undervalued relative to their potential. While we did not include any value for future acquisitions, a tenet of our thesis is that these will occur and will be highly accretive given the company's in-place infrastructre. Based on our analysis and forecasts, we initiate Cardiome Pharma Corp with a target price of $4.00.

PROJECTED FINANCIALS

Cardiome Pharma Corp. - Income Statement

Cardiome Pharma Corp (USD)	2016 A	Q1 A	Q2 A	Q3 A	Q4 E	2017 E	2018 E	2019 E
Product & royalty revenues	$25.1	$5.2	$5.7	$6.0	$7.7	$24.5	$30.3	$34.2
Licensing & other fees	$0.2	$0.0	$0.0	$0.1	$0.1	$0.2	$0.2	$0.2
Total Revenues	**$25.3**	**$5.2**	**$5.8**	**$6.0**	**$7.8**	**$24.7**	**$30.5**	**$34.4**
	20.8%	-26.7%	-2.7%	15.0%	10.4%	-2.1%	23.4%	12.8%
Cost of Product Sales	$6.3	$1.6	$1.7	$1.5	$1.9	$6.8	$8.4	$10.3
Gross Margin	74.8%	68.3%	69.8%	75.1%	75.0%	72.4%	72.4%	70.0%
SG&A	$30.5	$8.2	$9.6	$8.5	$8.5	$34.8	$37.8	$39.0
Amortization	$0.0	$0.8	$0.8	$0.9	$0.9	$3.5	$3.8	$3.6
Other	$3.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0	$0.0
Operating Income	($14.6)	($5.5)	($6.4)	($4.8)	($3.6)	($20.3)	($19.4)	($18.5)
Operating Margin	*($0.6)*	*-105.6%*	*-111.0%*	*-80.4%*	*-46.1%*	*-82.1%*	*-63.7%*	*-53.7%*
Interest Expense	$2.5	$0.8	$1.2	$1.8	$1.8	$5.6	$5.2	$6.5
Total Other Income	$2.4	$0.0	$0.9	($0.1)	$0.0	$0.9	$0.0	$0.0
Pre-Tax Income	($19.5)	($6.3)	($8.5)	($6.5)	($5.4)	($26.7)	($24.6)	($25.0)
Taxes & Other	$0.2	$0.0	$0.0	$0.1	$0.0	$0.1	$0.0	$0.0
Tax Rate	*-0.8%*	*-0.7%*	*0.1%*	*-1.1%*	*0.0%*	*-0.4%*	*0.0%*	*0.0%*
Net Income	($19.6)	($6.3)	($8.5)	($6.6)	($5.4)	($26.8)	($24.6)	($25.0)
Reported EPS	**($0.77)**	**($0.20)**	**($0.26)**	**($0.20)**	**($0.16)**	**($0.81)**	**($0.66)**	**($0.59)**
YOY Growth	*-42.4%*	*226.6%*	*-28.9%*	*5.4%*	*-10.5%*	*4.6%*	*-19.2%*	*-9.3%*
Shares Outstanding	25.3	31.9	32.4	33.9	34.2	33.1	37.6	42.0

Source: Company Filing // Zacks Investment Research, Inc. Estimates

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HISTORICAL STOCK PRICE

Cardiome Pharma Corp. – Five Year Price Chart[26]



[26] Chart provided courtesy of Google Finance.

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