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Healthcare | U.S. Biotechnology

24 February 2014

Celladon Corp.

A New Way to the Heart

Initiate coverage with Overweight rating and $15 price target. Celladon is taking a new approach to treating heart failure. Mydicar is a gene therapy that corrects deficiencies in sarco/endoplasmic reticulum CA2+-ATPase (SERCA) enzymes to treat calcium dysregulation, which is associated with a number of conditions including heart failure. While there are considerable risks associated with the development of any gene therapy, we also see significant market opportunities if the product is successfully developed given the size of the heart failure market. We believe Celladon offers investors an attractive risk/reward profile, and thus initiate coverage at Overweight.

We see lower risks with Mydicar than with other gene therapies: Despite being in development since the 1980s, gene therapy remains a new and relatively un-validated approach to treatment as safety concerns have kept gene therapies off the market. The first and only gene therapy was approved by the European Medicines Agency (EMA) in late 2012, while the FDA has yet to approve one to date. We expect the FDA approval threshold for Mydicar to be high, which has led us to assign a low probability of success (20%) for Mydicar. However, we do believe Mydicar has a lower level of risk than other gene therapies given the EMA and FDA's familiarity and recognition of AAV1 vectors as a potentially safe delivery mechanism.

Significant room for upside: Mydicar is currently being evaluated in a phase 2b trial (CUPID-2) for systolic heart failure. If results, which are expected in April 2015, show significant benefits with Mydicar, management believes it could be accepted as a pivotal trial, and an FDA approval could be granted in 2018. The EMA has also indicated to Celladon that it would accept CUPID-2 as a pivotal trial if the primary endpoint is met. Celladon estimates the initial US target market at ~350,000 patients, while we use more conservative assumptions and estimate ~100,000 patients. We also assume a low penetration level in our model. Nevertheless, we see significant upside potential to our estimates if CUPID-2 results demonstrate a significant improvement in heart failure symptoms and reduction in time to clinical events and hospitalizations.

CLDN: Quarterly and Annual EPS (USD)

	2012	2013			2014			Change y/y	
FY Dec	Actual	Old	New	Cons	Old	New	Cons	2013	2014
Q1	N/A	N/A	N/A	N/A	N/A	-0.36E	N/A	N/A	N/A
Q2	N/A	N/A	N/A	N/A	N/A	-0.36E	N/A	N/A	N/A
Q3	N/A	N/A	N/A	N/A	N/A	-0.36E	N/A	N/A	N/A
Q4	N/A	N/A	N/A	N/A	N/A	-0.36E	N/A	N/A	N/A
Year	N/A	N/A	-5.32E	N/A	N/A	-1.43E	N/A	N/A	73%
P/E	N/A		N/A			N/A			

Source: Barclays Research.
Consensus numbers are from Thomson Reuters

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PLEASE SEE ANALYST CERTIFICATION(S) AND IMPORTANT DISCLOSURES BEGINNING ON PAGE 26.

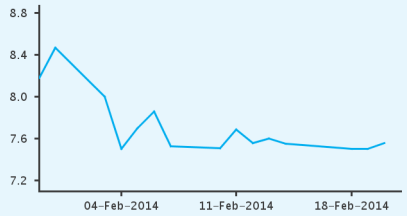
Stock Rating	OVERWEIGHT from N/A
Industry View	NEUTRAL Unchanged
Price Target	USD 15.00 from N/A

Price (21-Feb-2014)	USD 7.57
Potential Upside/Downside	+98%
Tickers	CLDN

Market Cap (USD mn)	134
Shares Outstanding (mn)	17.68
Free Float (%)	57.96
52 Wk Avg Daily Volume (mn)	0.2
Dividend Yield (%)	N/A
Return on Equity TTM (%)	N/A
Current BVPS (USD)	-2.59

Source: Thomson Reuters

Price Performance — Exchange-Nasdaq
52 Week range — USD 10.15-7.45



Link to Barclays Live for interactive charting

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U.S. Biotechnology **Industry View: NEUTRAL**

Celladon Corp. (CLDN)

Stock Rating: OVERWEIGHT

Income statement ($k)	2012A	2013E	2014E	2015E	CAGR
Revenue	N/A	0	0	0	N/A
EBITDA (adj)	-15,881	-20,138	-25,006	-18,519	N/A
EBIT (adj)	N/A	-20,187	-25,048	-20,536	N/A
Pre-tax income (adj)	N/A	-49,994	-24,816	-20,140	N/A
Net income (adj)	N/A	-63,971	-24,816	-20,140	N/A
EPS (adj) ($)	N/A	-5.32	-1.43	-0.95	N/A
Diluted shares (k)	N/A	12,035.4	17,304.3	21,161.7	N/A
DPS	N/A	N/A	N/A	N/A	N/A

Margin and return data					Average
EBITDA (adj) margin (%)	N/A	N/A	N/A	N/A	N/A
EBIT (adj) margin (%)	N/A	N/A	N/A	N/A	N/A
Pre-tax (adj) margin (%)	N/A	N/A	N/A	N/A	N/A
Net (adj) margin (%)	N/A	N/A	N/A	N/A	N/A
ROIC (%)	-55.3	-300.5	-63.3	-22.1	-110.3
ROA (%)	-44.4	-82.1	-54.1	-21.1	-50.4
ROE (%)	-55.3	-300.5	-63.3	-22.1	-110.3

Balance sheet and cash flow ($k)					CAGR
Tangible fixed assets	122	85	5,043	11,026	348.8%
Intangible fixed assets	N/A	N/A	N/A	N/A	N/A
Cash and equivalents	32,649	23,213	39,636	84,570	37.3%
Total assets	35,929	24,588	46,286	97,113	39.3%
Short and long-term debt	0	0	0	0	N/A
Other long-term liabilities	N/A	N/A	N/A	N/A	N/A
Total liabilities	4,842	40	40	40	-79.8%
Net debt/(funds)	-13,841	-9,955	-26,378	-71,312	N/A
Shareholders' equity	29,309	21,287	39,232	91,323	46.1%
Change in working capital	45,994	-11,024	12,988	46,108	0.1%
Cash flow from operations	-14,637	-11,377	-20,153	-17,992	N/A
Capital expenditure	-48	-12	-5,000	-8,000	N/A
Free cash flow	12,114	5,235	-20,153	-17,992	N/A

Valuation and leverage metrics					Average
P/E (adj) (x)	N/A	N/A	N/A	N/A	N/A
EV/EBITDA (adj) (x)	-4.9	-4.0	-2.6	-1.1	-3.1
Equity FCF yield (%)	N/A	N/A	N/A	N/A	N/A
EV/sales (x)	N/A	N/A	N/A	N/A	N/A
P/BV (x)	N/A	N/A	N/A	N/A	N/A
Dividend yield (%)	N/A	N/A	N/A	N/A	N/A
Total debt/capital (%)	-89.5	-87.8	-205.2	-356.4	-184.7

Selected operating metrics					Average
SG&A/sales (%)	N/A	N/A	N/A	N/A	N/A
R&D/sales (%)	N/A	N/A	N/A	N/A	N/A
R&D growth (%)	N/A	25.5	20.0	-25.0	6.8
SG&A growth (%)	N/A	32.3	43.7	10.0	28.6

Source: Company data, Barclays Research
Note: FY End Dec

Price (21-Feb-2014)	USD 7.57
Price Target	USD 15.00

Why Overweight? We view Celladon as having a favorable risk/reward profile for investors. The company is developing a gene therapy, Mydicar, to treat chronic heart failure. While there are considerable risks associated gene therapy, we also view the market opportunity as significant if the company is successfully develop the product.

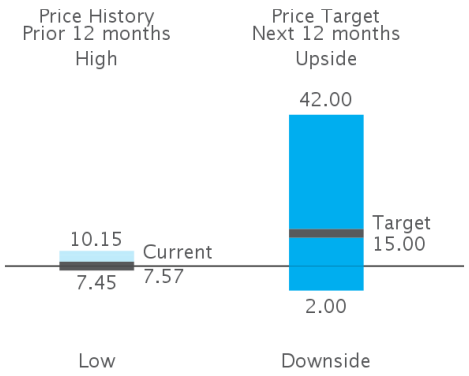
Upside case **USD 42.00**

We see significant upside potential for Celladon. If phase 2b results are positive, we see valuation increasing to $42/share.

Downside case **USD 2.00**

We see downside risks at approximately $2/share if Mydicar gene therapy does not receive approval. This assumes some value attributed to the early stage small molecule platform and some cash.

Upside/Downside scenarios



Executive Summary

Celladon is focused on the development of therapies that treat calcium dysregulation

Celladon is focused on the development of therapies that treat calcium dysregulation, which has been associated with a number of conditions. The company is currently evaluating a portfolio of therapies that correct deficiencies in sarco/endoplasmic reticulum CA2+-ATPase (SERCA) enzymes, which are essential to the regulation of intra-cellular calcium. The foremost product in the pipeline is Mydicar, a gene enzyme replacement therapy that corrects calcium dysregulation in the heart through the direct administration of SERCA2a enzymes. Celladon plans to evaluate Mydicar for the treatment of systolic heart failure, diastolic heart failure, advanced heart failure with left ventricular assist device, pulmonary arterial hypertension, and AV-Fistulae maturation failure. The company is also developing a small molecule, which is in very early development efforts for the treatment of diabetes and neurodegenerative diseases.

Celladon is currently evaluating Mydicar in a phase 2b (CUPID-2) trial for the treatment of systolic heart failure

Celladon is currently evaluating Mydicar in a phase 2b (CUPID-2) trial for the treatment of systolic heart failure. In earlier phase 1/2a trials, Mydicar demonstrated a signal in stabilizing and improving heart failure symptoms and reducing time to hospitalizations and terminal events such as heart transplantation, left ventricular assist device implantation, or death. In the phase 2a trial, patients who received a high dose of Mydicar saw an 88% risk reduction in recurrent clinical events at one year (p=0.003) and an 82% reduction out to three years (p=0.048). Mydicar was also well tolerated by patients with a reasonably clean safety profile. We believe the development and regulatory risks associated with Mydicar are lower than other gene therapies given the clinical results we have seen so far and the FDA and EMA's familiarity and recognition of AAV1 vectors as a potentially safe delivery mechanism.

We are initiating coverage of Celladon with an Overweight rating and price target of $15.

The CUPID-2 trial is expected to read-out in April 2015. If results demonstrate a significant improvement in heart failure symptoms and reduction in time to heart failure related hospitalizations and clinical events, management believes the FDA will accept CUPID-2 as a registrational trial, which would lead to potential FDA approval in 2018. If the trial meets the primary endpoint with a p-value of close to 0.05, we would expect the FDA to request an additional phase 3 trial, which would push back a potential approval to late 2019. The European Medicines Agency (EMA) has indicated to Celladon that it would accept CUPID-2 as the pivotal trial if the trial meets the primary endpoint.

While the development of a gene therapy is risky, there is also significant market opportunity if the product is successfully developed and approved.

Valuation

We are initiating coverage of Celladon with an Overweight rating and price target of $15. We arrive at our price target using a probability-adjusted NPV based on the systolic heart failure indication at ~$12/share and cash of ~$3/share. We estimate peak revenues of ~$393 million in the U.S. and peak royalties of $36 million in Europe. We view our sales estimates as conservative as we have assumed a narrower patient population as well as a relatively low penetration rate. We have also heavily discounted the probability of success for Celladon's Mydicar product (20%) given the development and regulatory risks associated with gene therapy. We believe Celladon offers investors a favourable risk/reward profile. While the development of any gene therapy is risky, there is also significant market opportunity if the product is successfully developed and approved.

Upcoming Catalysts

- End of February 2014 – Complete enrolment of CUPID-2
- 1H14 – Start enrolment of Mydicar trial evaluating use in advanced heart failure patients with LVAD
- 2014 – Start enrolment in viral shedding and AAV1 Nab positive safety trial
- April 2015 – Trial results for CUPID-2

Heart Failure Market Overview

Heart failure is a chronic and progressive condition in which the heart muscle is unable to contract or pump an adequate amount of blood to support the body's function. The heart then compensates for this by enlarging and developing excess muscle mass to help the heart pump faster. The body also balances by narrowing the blood vessels to keep the blood pressure up and redirecting the blood flow to the most vital organs. However, this process only serves as a temporary solution, while the heart continues to worsen and the patient develops symptoms such as shortness of breath, fatigue, and other symptoms.

Systolic failure occurs when the left ventricle loses its ability to contract and it is unable to pump blood with enough force throughout the body.

Heart failure can occur on both the left and right sides of the heart. The left side of the heart is the major source of the heart's pumping power and is essential for normal function of the heart. Oxygen-filled blood flows from the lungs to the left atrium (upper chamber) and then to the left ventricle (lower chamber) to be pumped through the rest of the body. There are two types of left-ventricular (LV) heart failure.

- Systolic failure occurs when the left ventricle loses its ability to contract and it is unable to pump blood with enough force throughout the body.
- Diastolic failure occurs when the left ventricle is unable to relax after contraction and as a result does not fill with the appropriate amount of blood.

Right-sided heart failure usually occurs as a result of left-sided heart failure. Blood that returns to the heart is transferred through the right atrium and ventricle and is pumped out to the lungs to be replenished with oxygen. When the right side fails, blood flows back into the veins, which cause swelling usually in the legs.

Patients with heart failure suffer from dyspnea (shortness of breath), wheezing, edema (build-up of excess fluid in body tissues), fatigue, nausea, impaired thinking and increased heart rate.

Clinical Presentation

Patients with heart failure suffer from dyspnea (shortness of breath), wheezing, edema (build-up of excess fluid in body tissues), fatigue, nausea, impaired thinking and increased heart rate. The heart's inability to provide adequate blood flow through the body can also cause damage to other organs. The more an individual's heart failure has progressed, the more severe the symptoms and more restrictions in physical activity.

The New York Heart Association has categorized heart failure into four classes based on symptoms and severity.

- Class I (mild): Patient experiences no or mild symptoms during ordinary physical activity
- Class II (mild): Patient experiences mild dyspnea, fatigue and palpitation during moderate physical activity
- Class III (moderate): Patient experiences dyspnea, fatigue and palpitation during light physical activity
- Class IV (severe): Patient is unable to carry out any physical activities without discomfort

Treatment Paradigm

Heart failure is a progressive lifelong condition and treatment options are based on the severity of symptoms and the condition of the patient's heart. Patients with heart failure are treated with lifestyle changes and/or medications, medical devices, or ultimately a heart transplant. Mild heart failure patients are first treated with lifestyle changes including dieting and exercising but as patients' progress, medications are added to manage the symptoms. Medications used to treat chronic heart failure include angiotensin-converting enzymes (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta blockers, diuretics, digoxin, calcium channel blocker, vasodilators, anticoagulants, and inotropes. As patients progress further, medications alone are not enough to treat the symptoms and medical

devices such as implantable cardiac defibrillators and cardiac resynchronization therapies are usually added to the treatment regimen to help the heart contract, to prevent certain arrhythmias and sudden cardiac arrest, and to potentially slow or reverse the progression of heart failure.

As a progressive disease, many patients do progress to end-stage heart failure and would require a heart transplant. However, the number of available hearts each year is limited (~2,000-2,500) and patients can be on the waiting list for years (many patients die while waiting). Patients can also be implanted with a left ventricular assist device (LVAD) either while waiting for a heart to become available (bridge-to-transplant) or for patients who are not candidates for a heart transplant (destination therapy). LVAD is an implanted mechanical pump that assists the left ventricle with pumping blood through the body to prevent damage to other organs and to increase the patient's overall strength.

Despite several therapeutic and device treatment options for patients, heart failure morbidity and mortality rates remains high with patients progressing meaningfully from year to year.

Despite several therapeutic and device treatment options for patients, heart failure morbidity and mortality rates remains high with patients progressing meaningfully from year to year. According to the American Heart Association, less than 50% of patients with heart failure are living five years after diagnosis.

Cost and Burden of Heart Failure

The American Heart Association estimates there are approximately 5.1 million people in the United States with heart failure and that approximately 400,000-700,000 new patients are diagnosed each year. The number of individuals diagnosed with heart failure is rising given the aging population and an increase in the rate of obesity. Approximately 250,000-500,000 of these heart failure patients have severe symptoms and often require hospitalization – there are approximately one million heart-failure related hospitalizations in the U.S. each year. A patient's prognosis also usually worsens with each hospitalization.

Heart failure is one of the most costly chronic diseases. The total direct cost for heart failure is approximately $21 billion annually (2012) and it is expected to increase to $70 billion by 2030. Roughly half of these expenses are related to hospitalizations as readmission rates are high after the after the initial hospitalization - ~25% at one month and ~50% at 6 months. As part of the Affordable Care Act, CMS is increasing its focus on reducing payments to hospitals with high heart failure readmission rates. Therapies that are able to demonstrate a reduction in hospitalization rates will be viewed positively by both the FDA and CMS, in our view.

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Celladon's SERCA Enzyme Platform

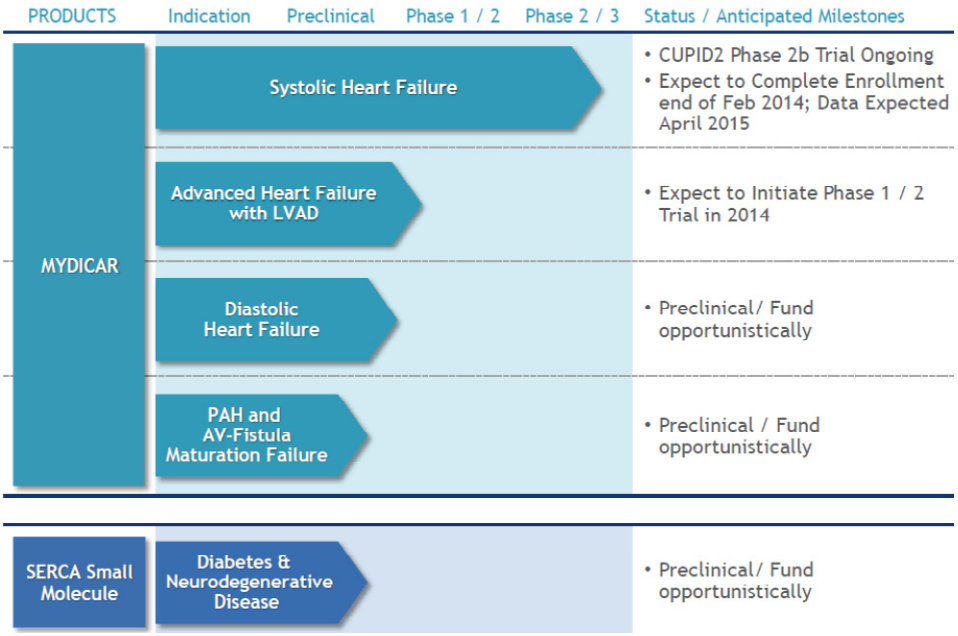
Celladon is developing both gene therapies and small molecule compounds for conditions associated calcium dysregulation

Celladon is developing both gene therapies and small molecule compounds for conditions associated calcium dysregulation or a calcium imbalance within cells. The company is currently evaluating a portfolio of therapies that correct deficiencies of sarco/endoplasmic reticulum CA2+-ATPase (SERCA) enzymes, which are critical in the regulation of calcium levels within cells. The company is targeting two SERCA2 deficiency states in its product pipeline – SERCA2a enzymes in the sarcoplasmic reticulum (SR) in muscle cells and SERCA2b enzymes in the endoplasmic reticulum (ER) of all cells.

Mydicar is a gene enzyme replacement therapy that targets calcium dysregulation in the heart through the direct administration of SERCA2a enzymes.

Celladon has five development programs underway, of which four are for its lead Mydicar product. Mydicar is a gene enzyme replacement therapy that targets calcium dysregulation in the heart through the direct administration of SERCA2a enzymes. The company is evaluating Mydicar for the treatment of systolic heart failure, diastolic heart failure, advanced heart failure with left-ventricular assist device (LVAD), and pulmonary arterial hypertension (PAH) and AV-fistula maturation failure. The company is also developing a small molecule, which is being evaluated for the treatment of diabetes and neurodegenerative diseases.

FIGURE 1
Celladon Product Pipeline



Source: Company Reports

Gene therapy – A Risky but Potentially Rewarding Approach

Celladon is taking a new approach to treat systolic heart failure with Mydicar – through gene therapy. While still in a relatively experimental stage, gene therapy is thought to be a potential alternate treatment form from drugs and devices. There are several approaches to gene therapy, including replacing mutated genes with a healthy copy, inactivating a mutating gene, or introducing a new gene into the body. Most commonly, a functional gene is delivered and integrated into a person's cells through a vector. These vector delivery systems are typically naturally occurring viruses, which have the ability to introduce genes into cells, but have been modified to be non-replicating.

Gene therapies have been in development since the 1980s although the FDA has not approved a gene therapy to date and the EMA only approved the first therapy in late 2012.

Gene therapies have been in development since the 1980s although the FDA has not approved a gene therapy to date, and the EMA only approved the first therapy in late 2012. In concept, gene therapy could revolutionize treatment of many genetic diseases, however in practice there have been many roadblocks and setbacks due to long-term efficacy and safety concerns. Most notably in 1999, a patient died just days after receiving a gene therapy to treat a mild form of liver disease due to mutations in a gene. The viral vector used to deliver a normal gene caused a significant immune response that resulted in brain death and multiple organ failures. In 2012, several patients treated in Europe for severe combined immunodeficiency developed leukemia-like disease, which was thought to be a result of the retroviral vector used to insert the gene. As a result, the FDA suspended 30 US trials using the same retrovirus. Finding the appropriate delivery vector and the specific cell types to target and to limit the treatment to only diseased cells/tissues/organs are the key challenges of developing a successful gene therapy.

Despite these setbacks, gene therapy remains a major field. According to clinicaltrials.gov, close to 2,000 trials for gene therapies were started over the past five years and several products are now in late-stage development. If successful, Mydicar may be one of the first gene therapies to be approved in the U.S. market.

MYDICAR – Straight to the Heart

Calcium is essential for a healthy heart as it directly activates the myofilaments in muscle fibers that cause contraction.

Calcium is essential for a healthy heart as it directly activates the myofilaments in muscle fibers that cause contraction. The sarcoplasmic reticulum (SR) is an internal membrane system in muscle cells that is responsible for the regulation of the release and storage of calcium ions during contraction and relaxation. An inadequate release of calcium by the SR can cause systolic dysfunction (decreased muscle contraction) and an inadequate removal of calcium can lead to diastolic (relaxation) dysfunction. In patients with heart failure, the gene to code for SERCA2a does not adequately translate into the enzyme causing a deficiency in SERCA2a enzymes. A deficiency of SERCA2a enzymes in heart muscle cells is thought to be a main cause of calcium dysregulation, which leads to heart failure and deficiencies in the blood vessels can also cause disorders such as AV-fistula maturation failure and pulmonary arterial hypertension (PAH).

In patients with heart failure, the gene to code for SERCA2a does not adequately translate into the enzyme causing a deficiency in SERCA2a enzymes, which is thought to be the main cause of calcium dysregulation and leads to heart failure.

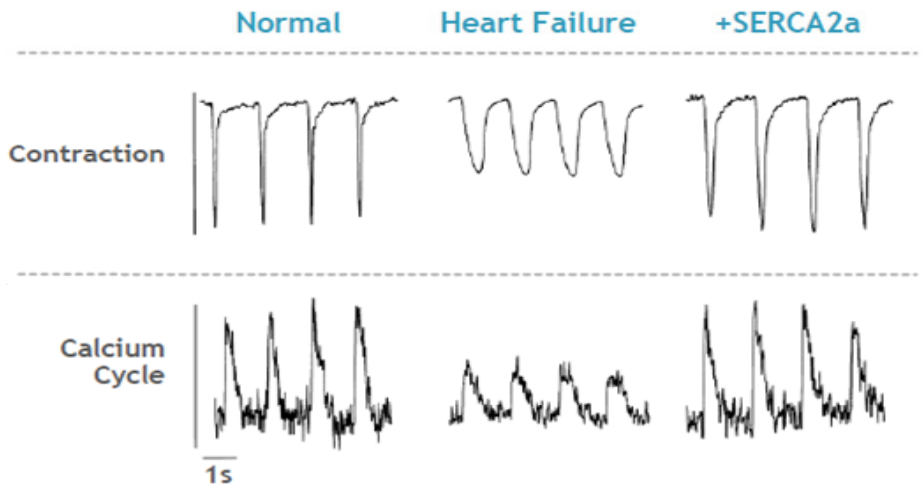
What is Mydicar?

Celladon is initially developing Mydicar (AAV1/SERCA2a) for the treatment of systolic heart failure. Systolic heart failure is characterized by the heart's inability to contract and affects approximately 50% of patients with heart failure (the other half being diastolic heart failure). With weakened contractions, a lower amount of blood pumped out of the heart and into the rest of the body, which can cause fatigue and stress and damage to other organs. Ejection fraction is used to measure the amount of blood pumped out of the heart with each contraction and is used in diagnosing patients with heart failure. Patients with a healthy heart typically have an ejection fraction in the 55%-70% range and an ejection fraction of less than 40% is considered to be a sign of heart failure.

Celladon believes a direct injection of MYDICAR (SERCA2 enzymes) to the heart will help regulate calcium levels in heart muscle cells and thereby restore normal contraction and relaxation.

Celladon believes a direct injection of MYDICAR (SERCA2 enzymes) to the heart will help regulate calcium levels in heart muscle cells and thereby restore normal contraction and relaxation. When used in human end-stage heart failure cells, the injection of SERCA2a enzymes was able to restore normal contractions. SERCA enzyme was first validated as a molecular target for heart failure in the 1990s. Several pharmaceutical companies have attempted but failed to develop therapies targeting SERCA enzymes. Celladon believes its gene therapy approach will be able to overcome the difficulties with a more direct and targeted approach.

FIGURE 2
In Vitro Study of Mydicar



Source: Celladon

Mydicar consists of a capsid (outer protein shell) and an inner DNA genome that contains the SERCA2a gene. The capsid delivers the genome to the cell nucleus where it then directs expression of normal SERCA2a protein. Different serotypes of adeno-associated viruses (AAV) have different capsids that target specific cell types. The adeno-associated viral vector 1 (AAV1) serotype has been shown to be efficient in delivering genes to muscle cells.

Patients treated with Mydicar receive one administration of Mydicar through an outpatient procedure in the cardiac catheterization lab.

Patients treated with Mydicar receive one administration of Mydicar through an outpatient procedure in the cardiac catheterization lab. Mydicar is administered directly to the coronary artery through a catheter inserted either through the groin or arm and the procedure typically takes approximately 10 minutes.

Delivery mechanism – Recombinant AAV vectors are accepted by the FDA and EMEA. With gene therapy, the delivery mechanism used to deliver the gene is an important aspect of the product. As noted above, the delivery mechanism can cause potential safety concerns as seen with past gene therapy failures. Celladon is using AAV vectors as the company believes AAVs are less immunogenic (lowers risk of inflammation) and safer than other viral vectors such as retroviruses and lentiviruses that have been studied or evaluated for use in gene therapy. Approximately 90% of individuals are exposed to wild type AAV (serotype 2) during their childhood with no presenting symptoms. Recombinant AAV does not integrate into the patient's own DNA and presents a lower risk of insertional mutagenesis, which occurs with the insertion of foreign DNA and may lead to cancers such as leukemia. In addition, very small quantities of Mydicar need to be given to be effective, which lowers the overall risk of therapy.

We believe the use of the AAV1 vector reduces Celladon's development and regulatory risks.

We believe the use of the AAV1 vector reduces Celladon's development and regulatory risks. Both the FDA and the EMEA are familiar with AAV1. The AAV1 vector is used by UniQure's Glybera gene therapy, which received EMA approval in late 2012. As stated by the FDA in the Guidance for Gene Therapy, recombinant AAV vectors are viewed as non-integrating and non-reactivating and present a low risk of delayed adverse events.

Companion diagnostic. A patient's acceptance and response to AAV1 is crucial for Mydicar to be effective. Patients who have AAV1 neutralizing antibodies will not benefit from treatment. Celladon has developed a companion diagnostic to identify individuals who are eligible for treatment and estimates that approximately 40% of individuals in the US are AAV1 Nab negative.

IP Protection. Mydicar currently has patent protection through 2030 in the US and until 2028 in Europe. However, as a gene therapy, we would not expect a "generic" substitution to be launched on the market even after patent expiration.

Available Clinical Evidence

CUPID 1 (Phase 1 and Phase 2a)

Phase 1 shows acceptable safety and signals of efficacy. The phase 1 trial was an open-label dose escalation trial that enrolled 12 patients with NYHA Class III or IV heart failure, an implantable cardiac defibrillator, a left ventricular ejection fraction of $\leq$30%, and stable on optimal outpatient therapy for at least 30 days prior to treatment. In the trial, 9 patients received Mydicar (3 patients in each of the 3 doses being evaluated) and 3 were on placebo. Patients in the treatment groups received a single intracoronary injection of Mydicar in addition to optimized heart failure therapy. Patients were evaluated on a composite endpoint of symptomatic parameters (NYHA class and Minnesota Living with Heart Failure Questionnaire (MLWHFQ)), functional parameters (6-minute walk test (6MWT) and peak maximal oxygen consumption (VO_2 max)), biomarker (NT-proBNP to evaluate heart failure progression) and LV functional/remodelling parameters (left ventricular ejection fraction (LVEF) and left ventricular end-systolic volume (LVESV)). Echocardiograms were also performed on the patients.

A number of the patients saw clinically meaningful improvements in several parameters from baseline to 6 months although a few patients also saw a worsening of symptoms.

A number of the patients saw clinically meaningful improvements in several parameters from baseline to 6 months although a few patients also saw a worsening of symptoms. Of the 9 treated patients, 5 patients saw improved MLWHFQ scores, 4 patients improved from NYHA Class III to Class II, 4 patients improved in VO_2 Max, 3 patients saw a clinically meaningful increase in 6MWT, 3 patients improved in end systolic volume, 2 patients saw a decrease in the biomarker for heart failure progression, and 1 patient saw a 6% improvement in ejection fraction. Three patients saw a worsening in one parameter each of the-VO_2 max, biomarker, and left ventricular end systolic volume endpoints.

No treatment related toxicities were observed.

In regards to safety, no treatment related toxicities were observed. There were no clinically meaningful changes in blood pressure, body temperature, electrolytes, heart rate, and liver and kidney function after the administration of Mydicar. Electrocardiograms also didn't show any significant changes in rhythm, intervals, or QRS morphology. Approximately 37 adverse events were reported amongst the 9 patients evaluated, of which 81% were deemed to be mild or moderate. Severe adverse events occurred in 5 patients and one event was prior to the infusion of Mydicar. Potential treatment-related adverse events included one event of orthopnea (shortness of breath when lying down) possibly from fluid overload during the catheterization process, 2 events of increased fatigue, 1 incidence of fever, and 1 incidence of muscle spasms.

Overall, we believe the phase 1 study demonstrated that Mydicar has an acceptable safety profile with few treatment related adverse events.

Overall, we believe the phase 1 study demonstrated that Mydicar has an acceptable safety profile with few treatment related adverse events. While difficult to determine with only 9 patients, we believe the phase 1 results suggest a clinical benefit from treatment with Mydicar.

Phase 2a demonstrates significant decrease in clinical events with high dose Mydicar. The phase 2a trial was a randomized, double-blind, placebo-controlled trial that enrolled 39 patients with NYHA Class III or IV systolic heart failure, an implantable cardiac defibrillator (ICD), left ventricular ejection fraction of $\leq$35%, and stable on optimal medical therapy for at least 30 days prior to treatment. These patients were randomized to receive either a low, mid, or high dose of Mydicar (total of 25 patients) or placebo (14 patients) on top of optimized heart failure therapy. Given the severity of heart failure with the patients enrolled in the trial, the estimated 1-year mortality rate was approximately 25%.

Similar to the phase 1 trial, the study evaluated seven efficacy parameters in 4 groups – symptoms (NYHA class and MLWHFQ), functional status (6MWT and VO_2 max), biomarker (NT-proBNP), and left ventricular function/remodelling (LVEF and LVESV) as well as clinical outcome measures (cardiovascular hospitalizations and time to terminal events). Success in the primary endpoint was defined as achieving efficacy at 6 months in any of the three levels – group (consistent improvements in the 7 efficacy parameters and no clinical worsening in any parameter – improvement if at least 2 of the 4 groups at $p<0.2$), individual (total score for predefined clinically meaningful changes in the seven parameters at $p<0.2$), or outcomes (time to terminal event versus placebo $p<0.2$ or if $p>0.2$ then mean duration of cardiovascular hospitalization $p<0.2$). Efficacy in one level had to be associated with a positive trend in the other two levels. The success of meeting these requirements on chance alone is 2.7%. Patients who received a LVAD implant, heart transplant, or died were excluded from the primary endpoint analysis but were included in the long-term safety analysis. The primary endpoint was prospectively evaluated at 6 months and another pre-specified analysis was conducted at 12 months. Long-term follow-up out to 3 years is also available for these patients.

Celladon conducted a number of sensitivity studies to evaluate these imbalances and it was determined that the outcomes of the trial could not be explained by these imbalances alone.

There were some differences at baseline between the placebo and high dose Mydicar group. Of note, the high dose Mydicar group had a lower percentage of patients on beta blockers (although primarily due to comorbidities and intolerance), lower level of BT-proBNP biomarker (increases with worsening heart failure), higher baseline VO_2max (decreases with worsening heart failure), and higher percentage of left ventricular ejection fraction (decreases with worsening heart failure). Celladon conducted a number of sensitivity studies to evaluate these imbalances and it was determined that the outcomes of the trial could not be explained by these imbalances alone.

FIGURE 3

Baseline Characteristics - CUPID-1 Phase 2a Trial

Characteristic	Placebo (n=14)	AAV1/SERCA2a Low Dose (n=8)	AAV1/SERCA2a Mid Dose (n=8)	AAV1/SERCA2a High Dose (n=9)	All AAV1/SERCA2a (n=25)	All Patients (n=39)
Age, mean (SD), y	61.0 (11.9)	60.3 (10.3)	63.9 (8.9)	56.6 (14.0)	60.1 (11.3)	60.5 (11.4)
Sex, n (%)						
Female	1 (7.1)	1 (12.5)	0	3 (33.3)	4 (16.0)	5 (12.8)
Male	13 (92.9)	7 (87.5)	8 (100.0)	6 (66.7)	21 (84.0)	34 (87.2)
Heart failure treatment regimen, n (%)						
Angiotensin-converting enzyme inhibitor	8 (57.1)	6 (75.0)	6 (75.0)	7 (66.7)	19 (76.0)	27 (69.2)
Angiotensin II receptor blocker	4 (28.6)	1 (12.5)	2 (25.0)	2 (22.2)	5 (20.0)	9 (23.1)
Aldosterone antagonist	8 (57.1)	4 (50.0)	3 (37.5)	4 (44.4)	11 (44.0)	19 (48.7)
ß-Blocker	14 (100.0)	8 (100.0)	7 (87.5)	6 (66.7)	21 (84.0)	35 (89.7)
Diuretic	12 (85.7)	8 (100.0)	8 (100.0)	8 (88.9)	24 (96.0)	37 (94.9)
Symptomatic, laboratory, functional, and echocardiographic measures						
NYHA class III, n (%)	14 (100)	8 (100)	8 (100)	9 (100)	25 (100)	39 (100)
MLWHFQ total score, mean±SD	48.7±16.4	57.6±16.4	35±29.0	41.4±26.5	44.6±25.4	46.0±22.0
Creatinine, mean±SD, mg/dL	1.6±0.6	1.0±0.2	1.5±0.6	1.1±0.3	1.2±0.4	1.3±0.5
NT-proBNP, mean±SD, pg/mL	4072±3906	1353±386	3310±3112	2141±1997	2268±2209	2932±3028
6-Minute walk test, mean±SD, m	336±138	359±134	334±117	347±120	346±119	343±124
$\dot{V}O_2$max, mean±SD, mL/kg per minute	12.4±4.2	14.8±4.2	14.4±3.7	15.1±3.2	14.8±3.6	13.9±3.9
LVEF, mean±SD, %	22.6±6.7	25.4±7.4	26.6±8.8	27.9±5.3	26.7±7.0	25.0±2.0
LV end-systolic volume, mean±SD, mL	201±64	206±97	236±150	169±48	202±104	202±91

Source: Celladon, Circulation

Patients who received low and mid doses of Mydicar were able to show a favourable trend in efficacy but only the high dose group was able to meet the primary endpoint

Patients who received low and mid doses of Mydicar were able to show a favourable trend in efficacy but only the high dose group was able to meet the primary endpoint (demonstrated efficacy in functional and LV function/remodelling parameters). Patients in the placebo group deteriorated at 6 months and had a meaningfully higher rate of hospitalizations and other terminal events while patients in the high dose group either stabilized or improved with minimal terminal events. Improvements in the high dose Mydicar group over placebo were confirmed through 12 months.

- Symptomatic: Patients in the high dose Mydicar group saw a meaningful improvement from baseline to 6 months versus placebo though not superior (did not meet endpoint).
    - NYHA Class – Mean decrease of 0.6 in the high dose versus a decrease of 0.2 in the placebo group.
    - MLWHFQ score – Score in the high dose group decreased (improved) 10.3 points versus an increase (deteriorated) of 3.4 points in the placebo group.
- Functional: The high dose Mydicar group demonstrated a superior improvement over placebo in the 6 minute walk test (met endpoint).
    - 6MWT – The placebo group declined 87 meters in the 6MWT while the high dose Mydicar group was relatively stable with an increase of 1 meter (p=0.18)

- Peak VO_2 – All three doses of Mydicar showed an improvement over placebo in peak VO_2 but were not clinically meaningful.

- Biomarker – Patients in the placebo group saw a significant increase in NT-proBNP (up 5540 pg/mL) versus a decrease of 14% in the high-dose Mydicar group though the difference was not clinically meaningful.

- LV function/remodelling: The high dose Mydicar group was able to demonstrate a significant improvement over placebo in left ventricular end systolic volume and ejection fraction.

  - Ejection fraction – All three doses of Mydicar and the placebo group saw a decrease in ejection fraction, though the high dose decreased to a lesser extent versus placebo (met prespecified criteria at p=0.17).

  - End systolic volume – The change in end systolic volume in the high dose Mydicar group was significant versus placebo (p=0.057).

- Individual analysis – Scores of 1, 0, and -1 were given to patients for who clinically improved, did not clinically change, or clinically worsened, respectively from baseline to 6 months. Mean individual efficacy score for patients in the placebo group deteriorated 1.2 points versus an improvement of 1.1 points for patients in the high dose group (p=0.052).

FIGURE 4

Primary Endpoint Analysis 6 months (Mydicar vs. Placebo)

Efficacy Endpoints	Placebo (n=14) Mean (SD)	AAV1/SERCA2a Low (n=8) Mean (SD)	P vs Placebo	AAV1/SERCA2a Mid (n=8) Mean (SD)	P vs Placebo	AAV1/SERCA2a High (n=9) Mean (SD)	P vs Placebo	Domain Success Criteria Met?
Symptomatic								Yes (low)
NYHA class, Δ †= 1	-0.2 (0.70)	-0.8 (0.71)‡	0.101‡	-0.8 (0.89)‡	0.132‡	-0.6 (0.73)	0.273	
MLWHFQ, Δ = 10	3.4 (36.00)	-7.6 (20.99)	0.709	7.9 (27.28)	0.798	-10.3 (12.21)	0.208	
Functional								Yes (low, high)
6-Minute walk, m, Δ=50	-86.6 (164.30)§	13.0 (61.40)‡	0.137‡	-59.5 (213.64)§	0.749	1.0 (99.69)‡	0.181‡	
Peak VO_2, mL/kg per min, Δ=15	-2.10 (4.462)§	-0.73 (4.88)	0.530	-1.07 (5.076)	0.633	-0.43 (0.802)	0.342	
Biomarker								No
NT-proBNP, pg/mL, Δ=max (300, 35%)								
Absolute	5540.0 (11 873.46)	694.1 (1444.94)§	0.628	2073.1 (4224.22)§	0.509	-13.5 (928.48)	0.372	
Percentage	198.5 (455.11)§	52.4 (112.15)§	0.300	119.2 (313.78)§	0.619	12.4 (47.83)	0.220	
LV function/remodeling								Yes (high)
End-systolic volume, ml, Δ=max (20mL, 10%)								
Absolute	18.2 (39.45)§	0.4 (26.16)	0.286	10.5 (45.91)	0.964	-9.6 (27.55)‡	0.057‡	
Percentage	10.7 (20.01)§	2.1 (11.34)	0.285	10.7 (20.05)§	0.749	-4.0 (13.76)‡	0.029‡	
Ejection fraction, %, Δ = 3	-2.1 (6.90)	0.0 (1.87)	0.248	-1.5 (6.35)	0.446	-0.7 (3.76)‡	0.174‡	

‡ improvement of p<0.2 (superior)
§ clinically significant worsening

Source: Celladon, Circulation, American Heart Association

- Outcome measures: Reduction in duration of hospitalizations was superior for the high dose Mydicar group versus placebo (met endpoint). Time to event was also higher in the high dose Mydicar group versus placebo but was not significant.

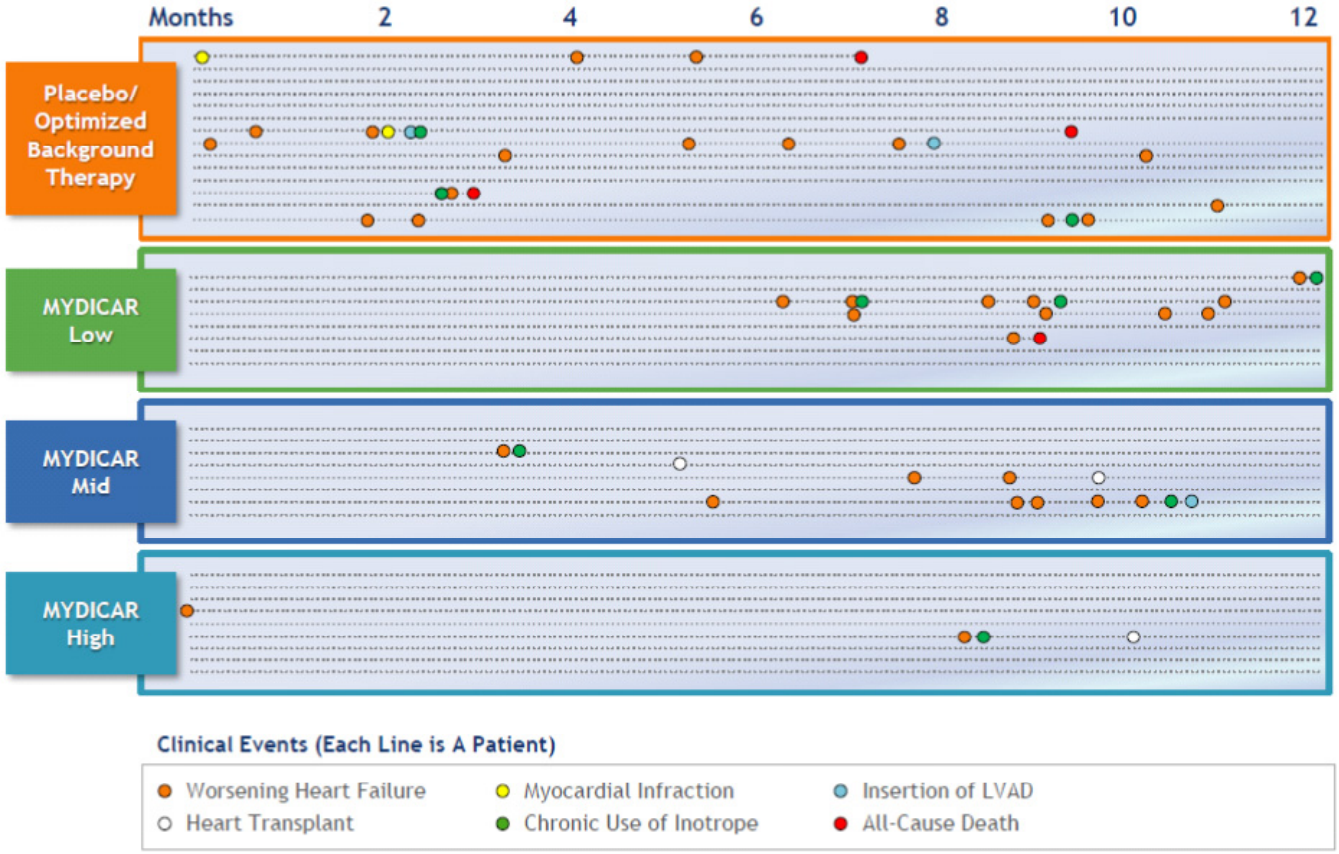
  - Time to event (death, heart transplant, ventricular assist device implant). Mydicar high dose reduced the number of heart failure clinical events (hospitalizations, myocardial infarction, LVAD implant, heart transplant, chronic inotrope use, and death) versus placebo. At 6 months, there were 2 events in the placebo group, 1 event in the mid-dose Mydicar group and no events in the low dose and high dose groups. At 12 months, this increased to 6 events in the placebo group, 1 in the low dose group, 3 in the mid dose group, and 1 event in the high dose group.

- Duration of heart failure related hospitalizations. The duration of hospitalizations was 2.1 days in the placebo group versus 0.2 days in the high dose group (p=0.08) meeting the prespecified criteria.

- Multiple clinical events over time. When looking at multiple clinical events including worsening heart failure, myocardial infarction, LVAD implant, chronic inotrope use, heart transplant, and death, the high dose Mydicar group also saw a significantly lower number of events when compared to placebo and the low and mid doses at 12 months. At 12 months, the numbers of events were 17 for the low dose, 12 for mid dose, and 4 for high dose versus 26 events in the placebo group. For the low and mid doses, the number of events increased substantially after 6 months and sustained out to three years while the high dose group had relatively few events through 3 years.

FIGURE 5

Patients and Clinical Events Through 12 Months in Phase 2a CUPID-1 Trial

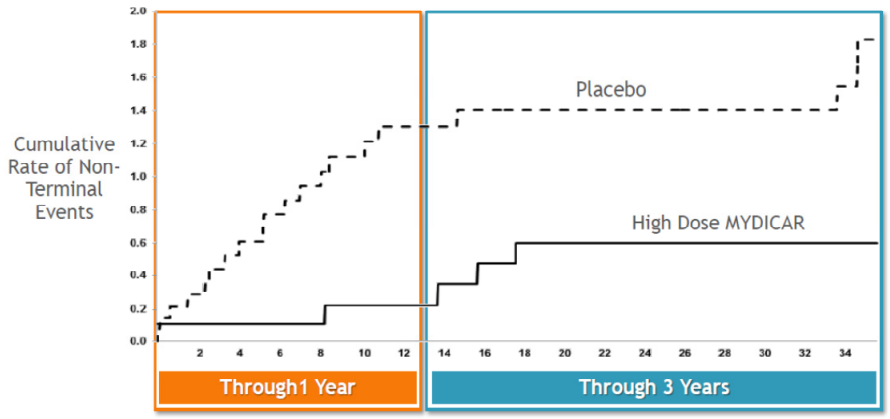


Source: Company data

- Risk reduction of recurrent clinical events: The three doses of Mydicar were able to show a 60% (p=0.11), 56% (p=0.12), and 88% (p=0.003) risk reduction in recurrent clinical events at 1 year. The reduction seen in the high dose Mydicar group was statistically significant. High dose Mydicar demonstrated an 82% reduction out to 3 years (p=0.048).

FIGURE 6

Three Year Follow-Up of Mydicar High Dose in CUPID-1 (Phase 2a)



Hazard Ratio (CI)*	0.12 (0.03, 0.49)	0.18 (0.03, 0.99)
Risk Reduction	88%	82%
p-Value	p = 0.003	p = 0.048

Source: Company data

- **Overall survival.** For the first 12 months, there were 3 deaths in the placebo group and 1 death in the low dose Mydicar group and no deaths in the mid and high dose Mydicar groups. Out to three years, there were approximately 13 deaths in the trial, of which 6 were in the placebo group, 3 in the low dose, 3 in the mid dose, and 1 patient in the high dose. At year 3, high dose Mydicar demonstrated an improvement in overall survival, though not statistically significant (p=0.11).
- **Safety.** Mydicar was shown to be well tolerated by patients. There were 8 treatment-emergent adverse events in each of the three Mydicar doses and 13 in the placebo group. There were no serious treatment-emergent adverse events related to Mydicar in all three doses. A number of patient enrolled suffered from ventricular arrhythmias and atrial fibrillation at baseline but no new arrhythmias and no increase in pre-existing arrhythmias occurred out to 12 months.

FIGURE 7

Incidence of Treatment-Emergent Adverse Events

Parameter	Placebo (N=14) n (%)	Mydicar Low (N=8) n (%)	Mydicar Mid (N=8) n (%)	Mydicar High (N=9) n (%)	All Mydicar (N=25) n (%)	All Patients (N=39) n (%)
Any AE	13 (92.9)	8 (100.0)	8 (100.0)	8 (88.9)	24 (96.0)	37 (94.9)
Treatment-emergent AEs (TEAEs)	13 (92.9)	8 (100.0)	8 (100.0)	8 (88.9)	24 (96.0)	37 (94.9)
TEAEs related to Mydicar	8 (57.1)	4 (50.0)	1 (12.5)	1 (11.1)	6 (24.0)	14 (35.9)
TEAEs related to Mydicar administration	8 (57.1)	1 (12.5)	2 (25.0)	1 (11.1)	4 (16.0)	12 (30.8)
Serious TEAEs	9 (64.3)	5 (62.5)	4 (50.0)	3 (33.3)	12 (48.0)	21 (53.8)
Serious TEAEs related to Mydicar	3 (21.4)	0	0	0	0	3 (7.7)
Serious TEAEs related to Mydicar admin.	4 (28.6)	0	0	0	0	4 (10.3)

Source: Celladon, Circulation, American Heart Association

Persistence of SERCA2a transgene. Analysis was also performed on biopsy samples of cardiac tissue in patients who either died during the trial, underwent a LVAD or heart transplant, and other cardiac procedures to study the persistent of the transferred gene. For the three patients evaluated (all in the high dose group), tissue from one patient showed

persistence of the SERCA2a transgene out to month 31, one out to month 22, and the third out to month 23.

In our view, these phase 2a results demonstrate a clear signal that Mydicar is able to improve heart failure symptoms and potentially reduce the number of clinical events and cardiac related hospitalizations with a reasonably clean safety profile.

In our view, these phase 2a results demonstrate a clear signal that Mydicar is able to improve heart failure symptoms and potentially reduce the number of clinical events and cardiac related hospitalizations with a reasonably clean safety profile. In addition, longer-term results out to 3 years demonstrate this benefit is sustainable. However, whether these results can be replicated in a larger trial is yet to be seen. We look to results from the larger CUPID-2 trial to confirm these findings and will focus on results in reducing heart failure related hospitalizations and any imbalances in safety signals between the treatment and placebo arms.

What's Next? CUPID-2 Trial Enrolling Patients

Based on the CUPID 1 results, Celladon has moved forward with the evaluation of the high dose of Mydicar and is currently enrolling patients in its phase 2b (CUPID 2) trial. CUPID-2 is an international, randomized, and placebo-controlled trial and will enroll approximately 250 patients with NYHA Class II-IV systolic heart failure in approximately 60 sites in the US and Europe. Patients are required to have left ventricular ejection fraction of ≤35%, AAV Nab titer negative, and are at an increased risk of terminal events due to elevated levels of the NT-ProBNP biomarker, or had a recent heart failure-related hospitalization. Patients are randomized 1:1 to receive either high-dose Mydicar or placebo on top of optimized heart failure therapy. Patients will be followed quarterly for 12 months and until at least 186 heart failure-related hospitalizations have occurred. The trial is 83% powered to detect at least a 45% risk reduction (HR=0.55).

The primary endpoint is time to recurrent heart failure related hospitalizations with terminal events (all-cause death, heart transplant, and LVAD implantation). Secondary and other measures include time to first terminal event, change from baseline in NYHA Class, exercise capacity (6-minutes walk test), overall survival, and quality of life (Kansas City Cardiomyopathy Questionnaire).

Enrollment is expected to complete at the end of February 2014 and results from the trial are expected in April 2015.

Enrollment is expected to complete at the end of February 2014 and results from the trial are expected in April 2015. Based on results from CUPID-1, we believe the trial should be able to achieve the primary endpoint of a 45% risk reduction in time to recurrent heart failure-related hospitalization. However, given the unknowns and risks associated with gene therapies we are using a 30% probability of success in our model.

A Phase III Trial Would Delay a Potential Approval by 1-2 Years

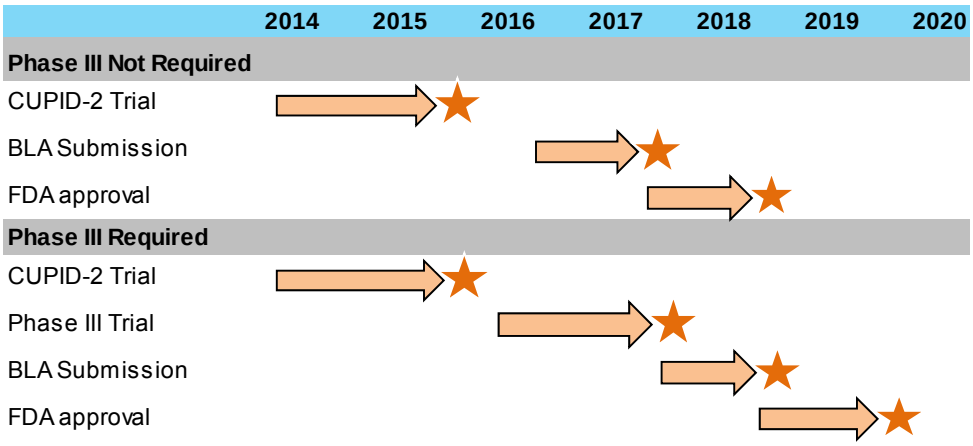
Mydicar was granted Fast Track Designation by the FDA in December 2011 and the company has requested both Breakthrough Therapy Designation and priority review with the FDA, all of which will help expedite the time to market.

A big question mark on the timing of Mydicar potentially entering the US market surrounds the necessity of a phase III trial for approval. Celladon believes the FDA will accept CUPID-2 as a registrational trial if results demonstrate a significant benefit with Mydicar treatment. Management believes the trial results will need to be more robust than just meeting the primary endpoint (p=0.05) but will not need to be as robust as what was seen in CUPID-1 (p=0.003). We believe the FDA will likely need to see a p-value=0.01-0.02 or lower to be convinced that a larger pivotal phase 3 trial is not needed for approval. However, if the p-value is closer to 0.05, Celladon believes secondary measures such as time to first terminal events and improvements in symptoms, overall survival, and quality of life will be important for the FDA to determine whether or not to approve on CUPID-2 results.

- If the CUPID-2 results demonstrate a significant benefit with Mydicar and the FDA accepts the CUPID-2 trial as a registration trial, the company expects to submit for approval in 2017 and receive FDA approval for the systolic heart failure indication sometime in 2018. For a full submission, the company will need to wait for results from the viral shedding and AAV Nab positive trials which are expected to start in 2014 and complete in the second half of 2015. The company will also need to complete testing of its manufacturing facilities.

  If approved, we would expect the label to be closely aligned with the inclusion criteria of the CUPID trials. Celladon will also continue to follow these patients to gather and maintain a long-term safety database.

FIGURE 8
Mydicar Timeline to Approval



Source: Barclays Estimates, Company data

- However, if after evaluating CUPID-2 results, the FDA does require Celladon to conduct a phase III trial, the company has already obtained a Special Protocol Assessment (SPA) that will help advance the process. The SPA was granted in 2012 and requires a total of 572 patients to be evaluated (includes CUPID-2 patients) and has time-to recurrent heart failure related hospitalizations as an acceptable primary endpoint (same endpoint as CUPID-2). The FDA has also indicated to Celladon that the proposed safety database of approximately 610 patients (50% treated 50% placebo) would be acceptable if the safety profile in CUPID-2 is similar to CUPID- Celladon will likely need to raise an additional round of capital to fund the phase III trial. 1.

  If CUPID-2 results are positive, we have assigned a 65% probability of FDA approval to adjust for the possibility of a phase III trial being required. An FDA approvalwill be delayed by ~1.5 years if a phase III trial is required.

If CUPID-2 results are favourable, Celladon could receive EU approval for Mydicar in 2018.

In Europe, the European Medicines Agency (EMA) has informed Celladon that if the CUPID-2 trial meets the primary endpoint and demonstrates significant efficacy with an acceptable safety profile, a phase 3 trial will not be required for approval. The agency also specified that a safety database of approximately 205-230 patients (which will be met with the CUPID-2 trial) may be sufficient for approval. If CUPID-2 results are favourable, Celladon could receive EU approval for Mydicar in 2018.

Market Opportunity and Launch Preparations

Celladon estimates ~350,000 patients in the US with systolic heart failure could benefit from Mydicar.

Celladon estimates there are approximately 6 million individuals in the U.S. who are currently diagnosed with heart failure and that about 350,000 patients of these systolic heart failure patients could benefit from Mydicar. This estimate assumes that approximately 50% of heart failure patients have systolic heart failure and of these patients ~30% have more severe symptoms and are considered NYHA Class III or IV. Assuming 40% of these patients are AAV1 Nab negative and can benefit from Mydicar treatment, this equates to approximately 350,000 patients that Celladon will target with this initial indication.

We are using more conservative market assumptions and estimates and estimate the initial market opportunity at ~100,000 patients.

We are using more conservative market assumptions and estimates. According to the American Heart Association, we are using an initial heart failure population of ~5.1 million in the U.S. We assume that approximately 550,000 new heart failure patients are diagnosed each year while approximately 13% of patients diagnosed die each year (both based off of estimates by the American Heart Association). Given Mydicar will be a novel therapy and will likely be priced relatively high, we have only assumed a sicker portion of the NYHA Class III/IV patients will utilize the therapy in our model (starting at 10% of Class III/IV systolic heart failure patients and increasing to 15% versus Celladon's assumption of 30%). Still assuming 50% of heart failure patients are systolic and that 40% of individuals are AAV1 Nab negative, we arrive at a more conservative initial target population of about 100,000 patients but increasing to over 120,000 patients over time. As the market becomes more familiar with Mydicar and gene therapy in general, we believe there is significant upside potential in the patient population the product could address and greater penetration into these patient populations.

FIGURE 9

Initial US Market Opportunity for Mydicar (Celladon vs. Barclays estimates)

Mydicar	Celladon Estimates	Barclays Estimates
Heart failure patients in the US	6,000,000	5,100,000
Systolic heart failure	50%	50%
NYHA Class III/IV patients	30%	10%
AAV1 Nab negative	40%	40%
Target patients	**~350,000 patients**	**~100,000 patients**

Source: Company data, Barclays Research Estimates

For international markets, we have only included estimates for Europe in our model given the price and also the novel mechanism. Based on estimates by the European Heart Journal, there are approximately 5.3 million heart failure patients in Europe and we also assume that approximately 550,000 new patients are diagnosed each year. We are assuming an even smaller portion of the NYHA Class III/IV patients will be eligible for treatment and a lower penetration rate given Europe's slower adoption of new products and sensitivity to cost and this treatment will likely be used in addition to optimal medical therapy and devices. We estimate the initial market opportunity in Europe at approximately 85,000 patients and increasing to just over 100,000 patients over time.

We estimate the initial market opportunity in Europe at approximately 85,000 patients and increasing to just over 100,000 patients over time.

Plenty of room for upside. While we are being conservative in our market assumptions and estimates, we do see plenty of room for potential upside if trial results are very favourable and particularly if the company is able to demonstrate cost-effectiveness of the treatment - that therapy is able to help reduce hospitalizations and thus reduce costs for payors and hospitals. This would expand both the eligible patient population as well as the penetration level, in our view.

Launch Preparations

Salesforce. If Mydicar is approved by the FDA, Celladon plans to hire a sales force to target selected cardiologists and heart failure specialists in the US. The company believes it will need only 50-100 sales representatives to target specific cardiologists and interventional cardiologists.

Outside the US, Celladon will likely find a partner with an existing presence in the region. We have assumed a 15% royalty rate on sales in Europe in our model.

Outside the US, Celladon will likely find a partner with an existing presence in the region. We have assumed a 15% royalty rate on sales in Europe in our model.

Manufacturing. Celladon currently has a clinical contract manufacturing agreement with Lonza for Mydicar and plans to negotiate with Lonza and potentially other manufacturers for a commercial scale agreement if the product receives approval. Celladon licensed its vector and manufacturing technology from AmpliPhi Biosciences and is currently in the process of developing a scalable manufacturing process for Mydicar, which the company will likely transfer to Lonza once completed.

Pricing. Mydicar is a one-time administration treatment and therefore we would expect pricing to be more closely aligned with devices rather than medications taken over time. Currently implantable defibrillators are priced in the $20,000-$50,000 range and left ventricular assist devices (LVADs) are priced at a high $80,000-$100,000. We would expect Celladon to price Mydicar in the $30,000-$50,000 range and we are using a $40,000 price in our model. Taking our initial target market estimate of approximately 100,000 patients, this equates to a ~$4 billion market.

Potential Competition

There are a number of early stage companies developing gene therapies targeted at treating heart failure, all of which are behind Celladon in development efforts.

There are a number of early stage companies developing gene therapies targeted at treating heart failure, all of which are behind Celladon in development efforts.

Renova Therapeutics

Renova Therapeutics was formed in 2009 to advance the research of Dr. Kirk Hammond, a top cardiologist from the University of California, San Diego. Renova's gene therapy for chronic heart failure consists of increasing the heart's content of the AC6 gene, which increases the levels of the cyclic adenosine monophosphate (cAMP), causing the heart to beat stronger. Based on positive preclinical trial results, the company has initiated a phase I/II trial, which is expected to complete by December 2014.

NanoCor Therapeutics

NanoCor Therapeutics was spun off from Asklêpios BioPharmaceutical in 2005 to develop a gene therapy for the treatment of chronic heart failure. Its product, Carfostin, has demonstrated the ability to improve contractile function of failing heart muscle and also enables positive effects in the remodeling of the heart. Carfostin is delivered using Biological NanoParticle (BNPs) and self-complementary vector technologies, both derived from human adeno-associated virus vectors (rAAV). Carfostin is currently in preclinical stage.

Juventas Therapeutics

Juventas Therapeutics is focused on developing therapies for ischemic cardiovascular disease. Its lead product, JVS-100 is an injectable non-viral plasmid that encodes for stromal cell-derived factor-1 (SDF-1), which increases organ function by promoting cell survival, recruiting endogenous stem cells to the damaged region, and promoting new blood vessel growth. Following positive results in its phase I trial, Juventas has initiated two Phase II studies to test the efficacy of JVS-100 in heart failure and critical limb ischemia patients. The company has also started a phase I/II study in heart failure patients using retrograde infusion.

VentriNova

VentriNova is developing a gene therapy for the regeneration of heart tissues in patients with heart failure. Its main product, VN-100 is viral vector-based gene therapy that induces cardiomyocyte division in adult heart tissue by delivering the cyclin A2 gene, the principal gene regulating cell cycle activity. The drug has been shown to improve ejection fraction in small and large animal models along with evidence of cellular regeneration through cardiomyocyte mitotic division. The company expects to file an IND with the FDA in the coming months.

Beat BioTherapeutics

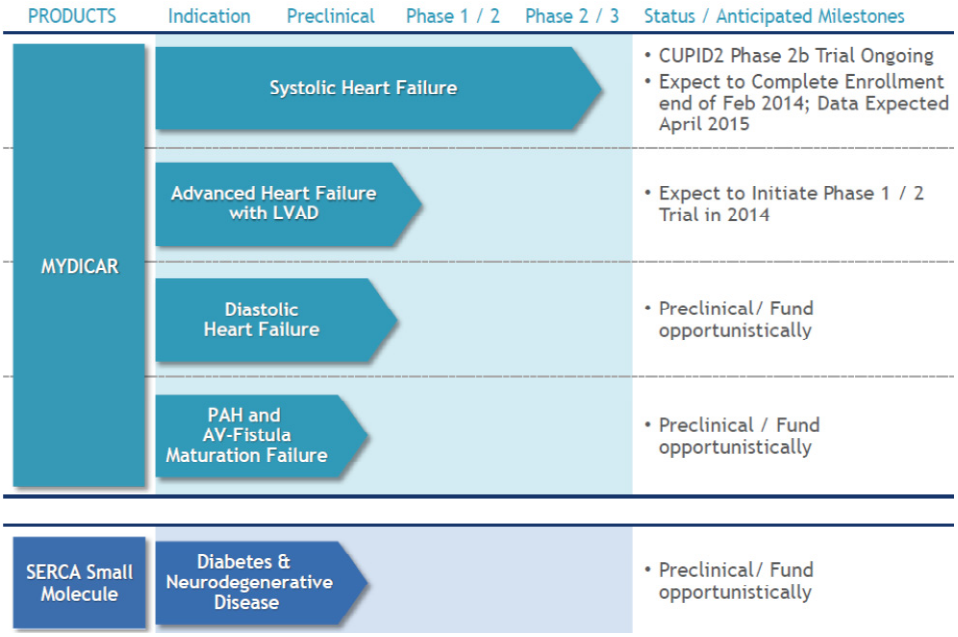
Beat BioTherapeutics is focused on developing a gene therapy, BB-R12, to improve cardiac performance and help in preventing or delaying the onset of heart failure. It increases intracellular dATP to promote myofilament cross-bridge formation resulting in improved cell contraction, tissue and organ contraction, improved muscle relaxation and over cardiac performance. The company is currently seeking funding to complete enabling studies and phase I first-in-man trials.

Pipeline

Our valuation currently only includes the systolic heart failure indication.

Our valuation currently only includes the systolic heart failure indication. We have not included any of the other indication given the lack of clinical data available and the need for additional capital raises or partnerships needed to fund most of these trials.

FIGURE 10
Celladon Pipeline Overview



Source: Company Reports

Additional Mydicar trials.

For safety reasons and per the FDA's requirement, the company is running a trial to evaluate the use of Mydicar in patients who are AAV1 Nab positive.

AAV1 Nab positive safety trial. For safety reasons and per the FDA's requirement for a BLA submission, the company is also running a trial to evaluate the use of Mydicar in patients who are AAV1 Nab positive and would not necessarily benefit from treatment. This trial will evaluate the safety of Mydicar use in approximately 70 patients who are AAV1 Nab positive given potential off-label use if Mydicar is FDA approved for use with AAV1 Nab negative patients. The trial will also compare the level of activity of Mydicar in AAV1 NAb positive versus Nab negative patients. The trial will start with a phase 1 dose escalation study and then expanded to phase 2 if no safety signals are seen. The primary endpoint is safety measured by the incidence and severity of adverse events, including heart failure-related hospitalizations and all-cause mortality. This trial will start enrolment in 2014.

For safety reasons and per the FDA's requirement for a BLA submission, the company is also running a trial to evaluate the use of Mydicar in patients who are AAV1 Nab positive and would not necessarily benefit from treatment.

Celladon is conducting a viral shedding trial to be included as part of the BLA submission in the US and Europe.

Viral shedding. Celladon is conducting a viral shedding trial to be included as part of the BLA submission in the US and Europe. The purpose of the trial will be to determine how long patients treated with Mydicar will be excreting Mydicar and could potentially spread the virus to health care workers, family, and the public. This open-label trial will enroll approximately 10-20 patients with heart failure (similar patient inclusion criteria as CUPID-2) and will be treated with high-dose Mydicar. Patients will be followed until two consecutive bodily fluid samples taken are negative for the SERCA2a gene and will continue to be followed for safety events for up to 2 years thereafter. This trial will be initiated in 2014.

Reverse remodelling. Celladon is conducting a trial, AGENT-HF, to evaluate if Mydicar leads to reverse remodelling of the heart. The trial will enrol approximately 44 heart failure patients, of which half will receive Mydicar and the other half placebo. The primary endpoint is change in left ventricular end systolic volume from baseline to 6 months. Results from this trial are not required for regulatory submission or approval of Mydicar for the systolic heart failure indication.

Other indications for Mydicar

Celladon is also evaluating Mydicar for the treatment of patients implanted with a left ventricular assist device (LVAD), diastolic heart failure, pulmonary arterial hypertension (PAH), and AV-Fistula maturation failure.

In addition to systolic heart failure, Celladon is evaluating Mydicar for the treatment of patients implanted with a left ventricular assist device (LVAD), diastolic heart failure, pulmonary arterial hypertension (PAH), and AV-Fistula maturation failure.

Advanced heart failure with LVAD. Celladon is conducting a proof-of-concept trial to evaluate the safety and feasibility of the use of Mydicar to wean patients off of an LVAD. LVADs were initially used to "bridge-to-transplant" – an interim device for a patient with end-stage heart failure as they wait for an available heart for transplant. Use is now slowly moving into "less sick" patients and for longer-term use however the durability of LVADs and the risks of infections and thrombosis remain as concerns for the device. Celladon hopes to show that the use of Mydicar will be able to improve patients enough to take them off of LVAD use and thus reduce the risks associated with the device. The trial will enrol approximately 24 patients (16 to treatment and 8 to placebo) and is expected to start in the first half of 2014.

The trial will evaluate the use of Mydicar to treat patients who have an LVAD, to determine how well Mydicar transfers the SERCA2a gene to heart muscle cells, and the impact of AAV1 neutralizing antibodies on Mydicar's ability to deliver the gene. All patients will have a heart biopsy to collect heart tissue 6 months after treatment to evaluate the presence of the SERCA2a gene. The company will also measure LV function and safety endpoints.

Diastolic heart failure – The opposite of systolic, diastolic heart failure is the heart's inability to relax between contractions. Based on the Framingham Heart Study conducted by the National Heart, Lung and Blood Institute and Boston University, the five-year mortality rate for patients with diastolic heart failure is about 45%–60%. A decrease in SERCA2a expression has also been connected to diastolic heart failure and in preclinical studies an over expression of SERCA2a has been shown to improve diastolic function.

With the company's experience in developing Mydciar for systolic heart failure, Celladon believes the FDA will likely allow the company to advance directly into a phase I/II trial with approximately 40 patients with diastolic heart failure. The study will be used to assess safety and preliminary efficacy of Mydicar compared to placebo. Similar to the systolic heart failure studies, fffficacy will be determined by improvements at 6 months in diastolic function, NYHA, QoL, 6MWT, recurrent heart failure-related hospitalizations, and biomarker.

Celladon will likely need to raise additional capital to fund these trials to evaluate the diastolic heart failure indication.

Pulmonary arterial hypertension (PAH). Pulmonary arterial hypertension is due to an overgrowth of pulmonary artery smooth muscle cells (PASMC) and is thought to be a result of a significant decrease in SERCA2a expression. PAH occurs with an increase in blood pressure in the pulmonary vein/artery and can cause dyspnea (shortness of breath), dizziness, swelling, and fainting and patients with PAH are also at an increased risk of heart failure. In animal models, an intratracheal delivery of SERCA2a resulted in a decrease in pulmonary artery pressure and vascular remodelling. The company is conducting additional toxicology and formulation studies and expects to file a separate IND for the indication. The company may also consider partnering for this indication.

AV-Fistula Maturation Failure. There are over 500,000 patients in the US who require dialysis as a result of end-stage renal failure and Celladon estimates approximately 100,000 fistulae are placed each year. AV-fistula is surgically created in the patient's arm to connect an artery to a vein for use during hemodialysis. However, approximately 40% are not usable due to blockage from rapid growth of vascular smooth muscle cells (VSMC). Celladon believes an infusion of SERCA2a would help prevent growth of VSMC and help reduce the number of AV fistulae failures. Addition formulation studies may need to be completed and Celladon believes a separate IND may need to be filed with the FDA for this indication. The company may consider partnering for this indication.

SERCA small molecule

Diabetes and neurodegenerative disease. Celladon is also developing a small molecule platform that is able to modulate SERCA2b enzymes. Preclinical proof-of-concept studies have been completed in the treatment of heart failure, diabetes, and neurodegenerative diseases.

Valuation

We are initiating coverage of Celladon with an Overweight rating and price target of $15. We derive our price target from a probability-adjusted NPV model. We are estimating US peak US sales of ~$393 million and peak royalties of $36 million in Europe. We have assigned a low probability of success of 20%. This accounts for development and regulatory risks associated with gene therapy and the possibility of the FDA requesting a phase III trial. Using a 10% discount rate and terminal growth of -5%, we arrive at a price target of $15.

FIGURE 11
Celladon Valuation Summary

Drug	Peak Sales ($M)	Royalties	Stage	Estimated launch	Probability of Reaching Market	Probability Adjusted NPV ($M)	Per Share Value
US Mydicar	$393						
EU Mydicar	$241	$36	Phase IIb	2018	20%	$125	$7
Terminal value						$82	$5
Total						$207	$12
Other ($M)							
Net Cash (Cash/Equivalents - Debt)						**$56**	**$3**
					Total ($M)	**$263**	**$15**
					Shares out. (M)	**17.7**	

Discount Rate	10%
Time of Valuatior	2015

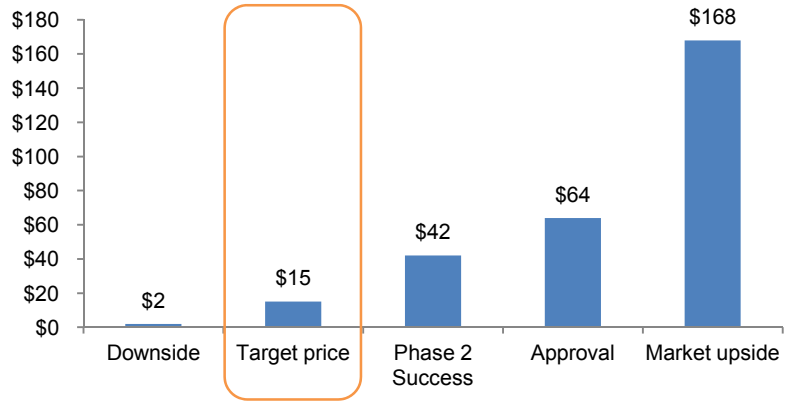
Source: Company Reports, Barclays Estimates

We have been relatively conservative in our valuation given the development and regulatory risks associated with gene therapy.

We have been relatively conservative in our valuation given the development and regulatory risks associated with gene therapy and market risks with potentially being one of the first gene therapies to reach the U.S. market. However, there are several factors that could present significant upside if the product is successfully developed and approved by the FDA/EMA. For illustrative purpose, we have calculated what the potential valuation Celladon based on FDA approval and expansions of market assumptions.

- Positive phase 2b results. If the phase 2b trial meets the primary endpoint, this increases our price target to $42.
- FDA approval– Our current model assumes only half of Class III/IV patients for the peak patient population and a low peak penetration rate of 10% in the US and even lowers assumptions in Europe. If Mydicar receives FDA approval, this increases the value per share to $64 using 100% probability of success.
- Market assumptions – If CUPID-2 trial results are very favourable and demonstrate a significant risk reduction in time to hospitalization and terminal events and improvements in symptoms, we see potential increases in both market size and penetration versus our estimates. If we expand the patient population to include all Class III/IV patients (30% of total heart failure patients) and at 100% probability of success this would result in a valuation of $168/share. There could be even more upside if we also include Class II patients (included in CUPID-2 trial criteria) given a much higher percentage of heart failure patients are considered Class II or if we increase the penetration rate.

FIGURE 12
Upside/Downside Scenarios



Source: Barclays Estimates

- Price increases – We have assumed a flat price of $40,000 in our model. If the therapy is well received by the market, we believe Celladon has some pricing power to increase the price each year.
- Geographic expansion. We have not included revenues from other international markets outside of Europe, which could represent upside if Mydicar is successfully developed. We would expect Celladon to partner for these regions.
- Additional indications – Celladon is evaluating Mydicar in additional indications such as diastolic heart failure, pulmonary arterial hypertension, and AV-Fistulae. These indications could result in considerable upside versus our model, which is based on only the systolic heart failure indication.

However, there is also significant risk to the development of gene therapy. If CUPID-2 results are unfavourable or there is an imbalance in safety signals between the treatment and placebo arms, we see Celladon's downside at ~$2/share assuming some value in the early stage small molecule pipeline and cash.

Management

Krisztina M. Zsebo, Ph.D. (President, CEO)

Krisztina Zsebo join Celladon in 2004 as President and Chief Executive Office. Dr. Zesbo has over 29 years of experience in the pharmaceutical industry. Prior to Celladon, Dr. Zesbo held executive positions at Remedyne Corporation, Connetics Corporation, ALZA Corporation, Cell Genesys and Amgen. Dr. Zsebo received a BS in Biochemistry from the University of Maryland, an MS in Biochemistry and Biophysics from Oregon State University and a Ph.D. in Comparative Biochemistry from the University of California.

Rebecque J. Laba (Vice President, Finance and Administration)

Rebecque Laba joined Celladon in 2007 as Vice President, Finance and Adminstration. She has served as an external consultant to Celladon on finance and administrative matters since 2005. Laba has also severed in several financial and operational roles in Idun Pharmaceuticals (acquired by Pfizer) and Asset Management Group.

Risks

Risks associated with gene therapy. Despite development starting in the 1980s, gene therapy is still an early, developing field with only one product approved on the market so far in Europe. There have been many setbacks, particularly with regards to safety concerns. With this, we believe the development risks associated with gene therapy is considerably higher than that of known small molecules and biologics.

Development risks. While trial data to date have been encouraging, if CUPID-2 results are unfavourable or unexpected safety concerns arise from the use of AAV vectors, Celladon may need to make significant adjustments to its Mydicar product before progressing further.

Regulatory risk. As no gene therapies have been approved to date by the FDA, we believe the threshold for approval is high and the timeline to approval may also be extended.

Capital risk. Celladon's current cash position should support the company through 2015. Celladon would need to raise additional rounds of capital to further develop its pipeline, particularly if a phase 3 triais required by the FDA for the systolic heart failure indication.

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I, Ying Huang, Ph.D., hereby certify (1) that the views expressed in this research report accurately reflect my personal views about any or all of the subject securities or issuers referred to in this research report and (2) no part of my compensation was, is or will be directly or indirectly related to the specific recommendations or views expressed in this research report.

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Primary Stocks (Ticker, Date, Price)

Celladon Corp. (CLDN, 21-Feb-2014, USD 7.57), Overweight/Neutral, A/C/D/J/K/L/M

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Celladon Corp. (CLDN)	Dendreon Corp. (DNDN)	Fibrocell Science Inc. (FCSC)
Gilead Sciences (GILD)	GlycoMimetics Inc. (GLYC)	Halozyme Therapeutics Inc. (HALO)
Idenix Pharmaceuticals (IDIX)	Incyte Corp. (INCY)	Intrexon Corp. (XON)
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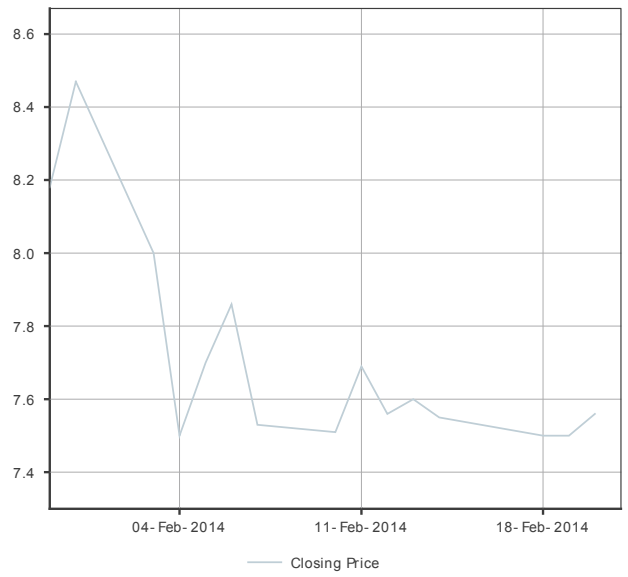
Celladon Corp. (CLDN)

	Stock Rating	Industry View
USD 7.57 (21-Feb-2014)	**OVERWEIGHT**	**NEUTRAL**

Rating and Price Target Chart - USD (as of 21-Feb-2014) **Currency=USD**

Date	Closing Price	Rating	Adjusted Price Target



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Valuation Methodology: Our price target is based on a probability-adjusted NPV analysis. We have only included the systolic heart failure indication in our model which contributes ~$12/share. Including cash of ~$3/share, we arrive at our price target of $15.

Risks which May Impede the Achievement of the Barclays Research Price Target: Downside risks include failure of CUPID-2 trial, need for phase 3 trial, and inability to receive FDA approval for Mydicar.

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