Summer Street RESEARCH PARTNERS

101 Arch Street
Suite 2010
Boston, MA 02110
617-532-6400

MCRI Updates

Celladon's (CLDN) Mydicar for Congestive Heart Failure

November 10, 2014

Bart Classen, MD bartc@ssrp.com 617-532-6410

MCRI Updates is a recurring publication containing commentary from our internal and external physician consultant network on the products of companies for which we may not assign a rating. MCRI Updates also communicates new ideas and examines general trends in healthcare by providing background information, data points, and/or a range of opinions from thought leaders in their respective fields of expertise.

Summary

We recently hosted a conference call on Celladon's (CLDN) Mydicar for congestive heart failure. The product is a gene therapy virus that contain the gene for the enzyme sarcoplasmic reticulum Ca2+ ATPase 2a (SERCA2a). Mydicar is in phase II testing (CUPID 2). Data from a previous phase II trial (CUPID 1) showed that the gene product was expressed in cardiac cells and that there was a favorable trend in cardiac events in the high-dose group. We believe the current phase II trial (CUPID 2) will likely provide clear information on the utility of Mydicar. If there is any benefit, there should be a convincing trend regardless of statistical significance. Our view is based on the size of the trial and the previous data showing the gene is expressed in the target cells. However, we are not yet convinced, based on the phase II data, that increasing SERCA2a levels will have a therapeutic benefit. Random variation could explain the previous phase II data.

Stocks Impacted

- **Celladon (CLDN-$11.50-NR)**

Background

- ***Mydicar is in a phase II trial.*** Results are expected in 1H15. The endpoint is event driven, so the date is speculative.

Reasons for Research

- ***Investors are waiting to learn the results of the phase II trial.***

The Impact

- ***Data from the phase I/II CUPID study shows the gene therapy transcript is expressed in cardiac tissue (presumably muscle cells).*** One of the problems with gene therapy is getting the gene selectively expressed in the target tissue. CLDN's approach of intracardiac infusion solves the problem of getting high concentration of the viral vector selectively to the target tissue. CLDN also uses a specific gene promoter to have the vector selectively expressed in the target cells.
- ***Phase II data shows interesting trends, but we are not convinced the data is truly statistically significant.*** The data shows 66% of patients in the high-dose group had stable disease versus 21% in the placebo group. Because there are multiple analyses there must be statistical adjustments for these. When statistical adjustments are made for multiple analyses, the results don't seem statistically significant to us.
- ***The phase II trial (CUPID 2) is impressively large and likely to shed light on the issue.*** Genetic engineering has been most frequently applied to orphan indications with small trials. A large, 250-patient gene therapy trial in patients with a common condition, heart failure, is very uncommon. The trial has the potential to validate the concept of gene therapy.

MCRI Insights

- ***We believe the current phase II trial (CUPID 2) will likely provide clear information on the utility of Mydicar.*** If there is any benefit, there should be a convincing trend regardless of statistical significance. Our view is based on the size of the trial and the previous data that the gene is expressed in the target cells. However, we are not yet convinced, based on the phase II data, that increasing SERCA2a levels will have a therapeutic benefit. Random variation could explain the previous phase II data.

Tech Assessment: Celladon's (CLDN) Mydicar for Congestive Heart Failure

I. Mydicar
- Genetically targeted enzyme replacement therapy
- Intracoronary Infusion
- Adenovirus vector
- Gene for sarcoplasmic reticulum Ca2+ ATPase 2a (SERCA2a) enzyme

II. Mechanism of Mydicar
- Increases levels of SERCA2a enzyme
- Acts to optimize calcium flux
- Acts to optimize contraction
- Adenovirus vector with gene to SERCA2a enzyme
- Infusions to heart muscle cells by cardiac catheterization
- Gene promoter sequence to direct which cells express the gene

III. Pathophysiology of Heart Failure
- Underlying failure could be ischemic heart disease, heart valve failure, cardiomyopathy
- Patients' disease worsens because of salt intake, discontinuation of medicine, progression of disease
- Patients' heart failure worsens and patients develop symptoms as they retain fluids in periphery or lungs
- Low blood perfusion to organs is an ominous event

IV. Current Treatment of Heart Failure
- In-hospital treatment for substantial exacerbation
- Fluid buildup in lungs leads to decreased oxygen
- Short-acting venous dilator (nitroglycerin) to quickly decrease fluid return to the heart
- Diuretic to remove fluids
- Avoid products that have prolonged lowering of blood pressure
- Decreasing vascular resistance helpful to increasing circulation
- Decreasing angiotensin activity helpful for reducing salt retention
- Ionotropic agents
- Surgery to optimize heart valves or other anatomic defects
- Transplants, LVAD

V. Market for Acute Exacerbation of Heart Failure
- 1.78% of Americans have congestive heart failure
- 4.8 million Americans have congestive heart failure
- 400,000 new cases of congestive heart failure a year
- One million hospitalizations for congestive heart failure in 2010
- Novartis (NVS-NR): Serelaxin being developed in phase III testing
- Trevena (TRVN-NR): TRV027
- Amgen (AMGN-NR): Ivabradine, omecamtiv mecarbil

VI. Phase I Study (CUPID 1)
- Open label, dose escalation
- n=12 patients with heart failure
- Doses: Up to 1 x 10^13 DNase-resistant particles
- Single dose administered
- Administered by coronary catheterization
- Results: Safety established
- Expression of adenovirus gene demonstrated
- Reported some patients had clinical improvement at six months

VII. Phase II Data (CUPID 1)
- Randomized
- n=39 patients with stable advanced heart failure
- Treatment arms: Placebo (14), low (8), medium (8), high dose: 1 x 10^13 DNase-resistant particles (9)
- Single intracoronary infusion
- 12-month active observation and 24-month additional follow up
- Primary endpoint: Recurrent cardiac events or death
- Myocardial infarction, worsening heart failure, heart failure-related hospitalization, ventricular assist device placement, cardiac transplantation, and death
- Results:
- Low dose (8): 1 stable, 3 deaths, 1 transplant, 2 LVAD, 1 withdrew
- Medium dose (8): 2 stable, 3 deaths, 2 transplants, 1 LVAD
- High dose (9): 6 stable (66.6%), 1 death, 2 transplant
- Placebo (14): 3 stable (21.4%), 6 deaths, 3 transplants, 2 worsen
- SERCA2a transgene: Expression seen 22 months and later in three patients who have received high-dose treatment
- When adjusted for multiple endpoints: Not statistically significant

VIII. Ongoing Phase II Clinical Trial (CUPID 2)
- Randomized, double blind
- n=250 patients with congestive heart failure
- Two treatment groups: Placebo, high dose group (1 x 10^13 DNase-resistant particles Mydicar)
- 12-month follow up
- Primary endpoint: Time to recurrent events (HF-related hospitalizations, ambulatory worsening HF)
- Secondary endpoint: Time to terminal event (all-cause death, heart transplant, LVAD implantation)

Important Disclosures and Disclaimers — Fourth Quarter 2014

Analyst Certification: *Each research analyst who authored the attached research report certifies the following: 1) All of the views expressed in this research report reflect my personal opinions about the subject company or any company mentioned in this research report; 2) I have not and will not receive compensation in exchange for the recommendation or views in this research report; and 3) Neither I nor the firm that employs me believes or have reason to believe that I have any material conflicts of interest with regard to the subject company or any company mentioned in this research report at the time of its publication.*

Analyst/Firm Financial Interest/Control: *Neither the analyst nor any members of his/her household has a financial interest in the covered company, or companies mentioned in this research report, including the ownership of shares, warrants, or options on the subject company's securities. In addition, neither the analyst nor any member of his/her family is an officer, director or advisory board member of the subject company. At the end of the month immediately preceding the publication of this research report, the firm and/or its affiliates did not beneficially own 1% or more of any class of common equity securities of the subject company, nor any company mentioned in this research report. Summer Street Research Partners ("SSRP" or "the Company") does not make markets in any securities, including those of the subject companies in this research report. The research analysts' compensation is not directly related to the specific recommendations or views expressed in this research report. Research Analyst(s) compensation is however based upon various factors including SSRP's total revenues, a portion of which may in the future be generated by investment-banking related activities.*

Investment Banking and Other Services*: SSRP has not provided investment-banking, advisory or other similar services to the subject companies described in this research report, nor are they clients of the SSRP. Further, the firm and its affiliates have not managed or co-managed a public/private offering of securities for the subject companies in this research report, and have not received compensation for investment-banking services from the subject companies in this research report. We expect to receive or intend to seek compensation from the subject companies for investment-banking related services in three months from the date of this research report. The firm has not received investment-banking revenues or participated in a public/private offering of securities as a manager or co-manager of the subject company's securities in the past 12 month from the date of this research report. Nor has the firm or its research analysts received compensation from the subject company or any company mentioned in this research report for products and services in the past 12 months. No research analyst, employee, or affiliate of SSRP with the ability to influence the substance of this research report has received any compensation for products and service provided to the subject company in the past 12 months.*

Definition of SSRP's Stock Rating System as used in this Research Report: *BUY – We believe the stock's total return will significantly outperform its peer group; NEUTRAL – We believe the stock's total return will not be significantly different than its peer group; SELL – We believe the stock's total return will significantly under perform its peer group.*

General Disclaimers: *The information contained herein is intended for distribution to institutional investors and is for informational purposes only. SSRP's research reports should be considered as only a single factor in making an investment decision. The information herein was obtained from various sources; we do not guarantee its accuracy or completeness and it should not be relied upon as such. Additional information is available by contacting SSRP. Neither the information nor any opinion expressed constitutes an offer, or an invitation to make an offer to buy or sell any securities. The data contained herein is intended for the sole and exclusive use of clients of SSRP. No reproduction, transmission or replication of any of the information or data contained within this document may be done without the expressed written consent of SSRP. Medical Consulting Research Inc. (MCRI) is a division of SSRP.*

Investment Rating Distribution for the Period 7/1/14 through 9/30/14:

Rating	Count	Percentage	Investment Banking Services (12 months)
BUY	25	89%	16%
NEUTRAL	3	11%	0%
SELL	0	0%	0%
Companies under coverage at 9/30/14	**28**	**100%**	**14%**