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MCRI Updates

Trevena's (TRVN) TRV027 for Acute Exacerbation of Heart Failure

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Summary

We recently hosted a conference call to discuss Trevena's (TRVN) TRV027, a short-acting intravenous angiotensin receptor blocker being developed to treat acute exacerbations of heart failure. The product is in phase II development. The phase I and phase II data indicates the product has some beneficial hemodynamic effects, especially in those with elevated renin-angiotensin activity. We believe the current phase IIb trial will show favorable trends in at least one or more of the five primary outcomes. We are unsure if the trial will reach statistical significance based on the size of the trial and the composite endpoint. We believe the market for TRV027 is large and physicians will welcome the product if it is approved.

Stocks Impacted

- **Trevena (TRVN-$5.32-NR)**

Background

- ***TRV027 is in a phase II trial.*** Results are expected in 2H15.

Reasons for Research

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

The Impact

- ***Phase I and IIa trials showed biological activity.*** The phase I trial in healthy volunteers and the phase IIa trial in patients with stable heart disease showed that TRV027 had favorable hemodynamic effects, especially in those with elevated renin-angiotensin activity.
- ***Phase IIb trial is likely to show a favorable trend but may not be powered to show a statistical benefit.*** The primary endpoint is a composite of five different outcomes. Each outcome is not expected to be equally sensitive to treatment with TRV027 and this will dilute the statistical power to detect a benefit. The study should help in determining the ideal primary endpoint for future phase III trials.
- ***Market for TRV027 is large.*** The medical community has overwhelmingly accepted angiotensin receptor blockers as a treatment for heart failure. It should be relatively easy to convince physicians to give TRV027 in the acute setting if the data is favorable.

MCRI Insights

- ***We believe the current phase IIb trial will show favorable trends in at least one of the five primary outcomes.*** We are unsure if the trial will reach statistical significance based on the size of the trial and the composite endpoint. We believe the market for TRV027 is large and physicians will welcome the product if it is approved.

Tech Assessment: Trevena's (TRVN) TRV027 for Acute Exacerbation of Heart Failure

I. TRV027
- Intravenous
- Infusion for several days while in a hospital
- Small molecule
- Short half-life
- Angiotensin II receptor blocker

II. Mechanism of TRV027
- Angiotensin II type 1 receptor (AT1R) blocker
- Decreases smooth muscle contraction in blood vessels
- Decreases sodium retention through the aldosterone system
- Lowers blood pressure and fluid retention
- Stimulates β-arrestin affinity to AT1R
- Increases β-arrestin activity; increases contractility and decreases apoptosis (presumably)

III. Pathophysiology of Acute Exacerbation of Heart Failure
- Patients generally with history 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 Acute Exacerbation 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

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
- Serelaxin being developed by Novartis (NVS-NR); in phase III testing

VI. Supporting Data
- Multiple papers support use of angiotensin receptor blockers (ARBS) in congestive heart failure
- Use of angiotensin-converting enzymes inhibitors or ARBS is recommended in many guidelines
- Treatment of acute exacerbation of congestive heart failure with other agents can be beneficial
- Lack of data that a short course (3-7 days) of an ARB will improve survival or have outcome benefit
- Serelaxin: Short-term use had marginal symptomatic benefit, rejected approval in US and EU

VII. Ongoing Phase II Clinical Trial in Acute Exacerbation of Heart Failure
- Randomize
- n=500 adults with pre-existing congestive heart failure, mainly left heart
- Randomized to standard of care with or without TRV027
- Groups: Placebo, high, medium, low dose of TRV027
- TRV027 administered intravenously
- Treatment while in-patient (approximately several days to less than one week)
- Patients followed for 30 days from initiation of dosing
- Primary endpoint: Composite z score
    (1) Time from randomization to death through day 30
    (2) Time from randomization to heart failure re-hospitalization through day 30
    (3) Time from randomization to worsening heart failure through day 5
    (4) Change in dyspnea VAS score (calculated area under the curve) from baseline through day 5
    (5) Length of initial hospital stay (in days) from randomization.
- Data release: Second half of 2015

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