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MCRI Updates

Expecting Favorable Biomarkers in Upcoming Phase II Results for CNAT's Emricasan for Liver Diseases

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Summary

We recently hosted a conference call to discuss Conatus Pharmaceuticals' (CNAT) emricasan, which is in phase II testing for acute-on-chronic liver disease and non-alcoholic fatty liver disease. Previous phase II data showed that when emricasan was given to patients with hepatitis C who had elevated liver enzymes in the blood, the liver enzymes substantially declined by 50%. After discontinuing the drug, the liver enzymes returned to their previous levels. While the blood liver enzymes never reached "normal" levels, indicating liver disease persisted, the decline in liver enzymes suggests destruction of liver cells was decreasing. We believe the upcoming results from the phase II trials will show improved biomarkers, including reduction in liver enzymes. However, this does not guarantee an improvement in outcomes in later phase III trials.

Stocks Impacted

- **Conatus Pharmaceuticals (CNAT-$5.90-NR)**

Background

- ***CNAT's emricasan is in phase II clinical trials for acute-on-chronic liver disease and non-alcoholic fatty liver disease.*** Results are expected in 2H14.

Reasons for Research

- ***Investors are now waiting to learn if the trial is successful.***

The Impact

- ***Emricasan is an antagonist of caspase, an enzyme that is activated during cell injury that induces cell death (apoptosis).*** Emricasan's mode of action is unique and offers a chance to slow cell damage in diseases where there is no cure.
- ***Phase II data shows emricasan decreases blood liver enzymes (ALT and AST) in patients with hepatitis C.*** In a phase II clinical trial, ALT decreased from about 120 to 70 (p=0.0001); the upper limit of normal was 45. Levels returned to the pretreatment level after the drug was discontinued. A similar response was also seen with AST. A second phase II study of 105 patients with an assortment of liver diseases also showed similar results.
- ***Emricasan appears to be well tolerated.*** Phase II trials have shown no problematic adverse events, to our knowledge. There have been reports of abdominal pain, fatigue, dizziness, and headaches that did not cause discontinuation of treatment.

MCRI Insights

- ***We believe the upcoming results from the phase II trials will show improved biomarkers, including reduction in liver enzymes in the blood.*** However, this does not guarantee an improvement in outcomes in later phase III trials. We remain supportive of the development of emricasan.

Tech Assessment: Conatus Pharmaceuticals' (CNAT) Emricasan for Assorted Liver Diseases

I. Emricasan
- Oral
- Small molecule
- Pan caspase protease inhibitor

II. Mechanism of Emricasan
- Antagonist of caspase (cysteine-aspartic proteases)
- A series of different caspases exist, involved in apoptosis (programmed cell death), inflammation
- Caspases are produced in an inactive form but are activated by certain stimuli

III. Acute-on-Chronic Liver Disease

Pathophysiology of Acute-on-Chronic Liver Disease
- Controversial if condition even exists
- Unclear pathophysiology
- Acute deterioration in someone with stable, well compensated cirrhosis
- Often associated with a precipitating event (infections, drugs)
- Patients with chronic disease are hospitalized
- Mortality of 50% or more

Market for Acute-on-Chronic Liver Disease
- Market very difficult to estimate based on lack of an agreement of definition
- Cirrhosis prevalence was estimated at 0.15%, or 400,000, in the US
- Cirrhosis estimated to account for more than 25,000 deaths annually in the US
- In 2006: 26,300 patients admitted in US for liver failure
- Unclear how many admissions were acute-on-chronic because of lack of a good definition
- Duration of admission: 14 days

Current Diagnosis and Treatments for Acute-on-Chronic Liver Disease
- Diagnosis of liver disease by blood tests
- No specific treatment for acute-on-chronic liver disease
- Treatments of chronic liver disease are symptomatic
- Encephalopathy: Antibiotics
- No specific drug to restore liver function or decrease decline in liver function

IV. Existing Data on Emricasan

Phase I Studies in Healthy Volunteers
- Total of six phase I trials
- 191 healthy volunteers
- Single dose or multiple doses, oral and IV
- Administered once or twice daily
- Dose: 1 to 500 mg per day orally or 0.1 to 10 mg/kg per day intravenously for up to 14 days
- Generally well tolerated

Phase II Studies in Patients with Liver Disease
- Four phase II studies
- 306 subjects with elevated ALT levels and 53 liver transplant subjects
- Biomarkers of liver damage and inflammation, such as ALT and AST
- Mechanistic biomarkers, such as cCK18, caspase activity

Phase IIb Dose Response Study in HCV Patients (Study A8491003, Trial 003)
- Randomized, multicenter, placebo-controlled, double-blind, dose-response trial
- 204 HCV (hepatitis C) patients
- Randomized to emricasan twice daily, 5 mg, 25 mg, 50 mg, or placebo
- 12 weeks
- Primary endpoint: Changes from baseline in ALT and AST levels
- Secondary endpoints: cCK18 levels and caspase 3 and 7 activity
- Results: Declines in ALT from about 120 to 70 (ULN is 45) (p=0.0001)
- ALT returned to about 120 after drug stopped at end of the trial
- CK18 appear to decline to normal levels while on drug
- Caspase 3, 7 had statistically significant declines of about 50-66%

Phase II Dose Study in Patients with Hepatic Impairment (Study A8491004, Trial 004)
- Randomized, multicenter, placebo-controlled, double-blind, ascending dose trial
- 105 patients with mild to moderate hepatic impairment
- Predominant hep C, but heb B, NASH, primary biliary cirrhosis/primary sclerosing cholangitis
- Emricasan was administered orally for up to three times daily for 14 days
- Dosing included 5 mg, 25 mg, 100 mg, 200 mg each day
- Primary endpoint: Safety
- Secondary endpoint: Effects on ALT and AST
- Results: Subset of heb C, placebo (n=25) versus 5 mg, 25 mg, 100 mg, 200 mg (n=6 or n=7)
- Roughly 40% decline in ALT seen in once-daily doses of 25 mg, 100 mg, 200 mg (p from 0.0041 to <0.0001)
- ALTs returned to pretreatment levels after medicine was discontinued
- In similar design and patient number, twice-daily dosing, even better, up to 50% decline in ALT
- Adverse events: Upper abdominal pain, dyspepsia, fatigue, dizziness, and headache
- No subject was discontinued due to an adverse event

V. Ongoing Phase II Trial of Emricasan in Acute-on-Chronic Liver Disease
- UK and US trial
- Double-blind, randomized, placebo-controlled trial
- Patients with acute-on-chronic liver disease
- N=60
- Receive 5 mg, 25 mg, 50 mg, or placebo
- Twice daily
- Duration: 28 days
- Primary outcome: Pharmacokinetics at day 28
- Secondary endpoints: Biomarkers, clinical outcomes (transplantation, progression to organ failure, death)
- Results expected in 2H14

VI. Trial in Non-Alcoholic Fatty Liver Disease
- Double-blind, randomized, placebo-controlled trial
- Patients with NAFLD with elevated liver enzymes
- N=40 patients
- Dose: 25 mg twice a day or placebo
- Treatment for 28 days
- Primary outcome: Changes in ALT levels from baseline
- Secondary outcome: AST, cCK18, flCK18, and caspase 3 and 7
- Results expected in 2H14

VII. Our Prediction
- Safety: No serious adverse event signals yet
- Efficacy: Biomarker data likely positive based on previous studies, studies too short and too small to demonstrate outcome improvement

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