Cirius Therapeutics Reports Positive Data for MSDC-0602K in Interim Analysis of Phase 2b Clinical Trial in NASH Patients with Fibrosis

- Interim analysis showed statistically significant reductions in liver enzymes, including ALT and AST, measured from baseline at six months

- In two highest dose groups, at least 50% of patients with high baseline ALT or AST improved to normal range at six months

- Statistically significant reductions in HbA1c and other measures of glycemic control and insulin resistance were observed

- Overall adverse event rate was similar across placebo and all doses of MSDC-0602K

- Largest Phase2b clinical trial including paired biopsies conducted in NASH; biopsy data after 12 months of treatment expected to be reported in the second half of 2019

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Cirius Therapeutics
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SAN DIEGO and KALAMAZOO, Mich., Oct. 25, 2018 /PRNewswire/ -- Cirius Therapeutics today announced positive results from an interim analysis of exploratory endpoints from its ongoing, fully enrolled Phase 2b clinical trial (the EMMINENCE trial) evaluating MSDC-0602K in 402 patients diagnosed with non-alcoholic steatohepatitis (NASH) with fibrosis. The interim analysis, which was conducted in the first 328 patients to reach their six-month follow-up visit, showed that patients treated with MSDC-0602K had significant improvements from baseline in measures of liver function and insulin resistance at six months. MSDC-0602K, a second-generation insulin sensitizer, is designed to selectively modulate the mitochondrial pyruvate carrier (MPC), which at the cellular level mediates the effects of overnutrition, a major cause of NASH and other metabolic disorders.

The subjects included in this interim analysis had significant liver disease, as established by liver biopsy, with an average non-alcoholic fatty liver disease (NAFLD) activity score at baseline of 5.3. Almost sixty percent of these subjects had a baseline fibrosis score of 2 or 3 and approximately

fifty percent also had a diagnosis of Type 2 diabetes at baseline. Overall, baseline characteristics were well-balanced across treatment groups.

Key findings from the interim analysis include improvements in liver enzymes, with placebo-corrected reductions at 6 months of 14.3 U/L ($p<0.001$) and 7.9 U/L ($p=0.012$) in ALT and AST, respectively, in the 125mg cohort, and 10.6 U/L ($p=0.004$) and 4.0 (NS) in ALT and AST, respectively, in the 250mg cohort. Placebo-corrected reductions, relative to baseline, were 25% and 18% in ALT and AST, respectively, in the 125mg cohort, and 19% and 9% in ALT and AST, respectively, in the 250mg cohort. Importantly, normalization of hepatic enzymes was observed across all three dose levels of MSDC-0602K.

Percentage of patients with high baseline values who returned to normal range				
	Placebo	62.5mg	125mg	250mg
ALT	15%	29%	60%	56%
AST	20%	36%	50%	52%

*ALT normal range defined as 6-34 U/L and 6-43 U/L for women and men, respectively; AST normal range defined as 9-34 U/L and 11-36 U/L for women and men, respectively)

"We believe these interim results around improved measures of liver function and glycemic control, together with the preliminary adverse event profile, support MSDC-0602K's potential to be used in the treatment of NASH with fibrosis, including for those patients with Type 2 diabetes, a group which represents approximately 50% of patients with NASH," said Cirius' chief medical officer Howard Dittrich, M.D. "These results support the view that therapies directed toward the MPC have the potential to achieve insulin sensitizing pharmacology with an improved profile over first generation insulin sensitizers. We look forward to presenting full data to the scientific community."

In addition to the improvement in ALT and AST, observations included significant improvement at six months in fasting glucose, HbA1c, insulin levels and HOMA-IR at the 125mg and 250mg dose levels. Significant improvement in HbA1c was also observed in subjects with a diagnosis of Type 2 diabetes in the 125mg and 250mg cohorts.

In this interim analysis, the overall rate of treatment emergent adverse events was similar across placebo and all MSDC-0602K cohorts. There was a higher rate of treatment emergent adverse events reported in the 250mg dose compared to placebo in the musculoskeletal and connective tissue disorders category. Within this category, arthralgia and back pain were the most frequently reported individual adverse events across the pooled 328 subjects. A modest dose-dependent increase in body weight was seen in MSDC-0602K treated subjects, a finding seen with insulin and with other therapies that seek to improve insulin resistance. The rate of peripheral edema observed at six months was similar to that observed at baseline and was comparable across placebo and all MSDC-0602K cohorts.

"The interim results from the EMMINENCE trial, the largest Phase 2b clinical trial to include paired biopsies ever conducted in NASH, are compelling," said Stephen Harrison, M.D., the principal investigator in the EMMINENCE trial. "The improvements in hepatic enzymes observed to date are impressive, especially when combined with the meaningful improvements in glycemic control."

About the EMMINENCE Trial

The EMMINENCE trial is a 12-month, randomized, double-blind, placebo-controlled trial evaluating three oral dose levels of MSDC-0602K. Endpoints of the clinical trial include hepatic histological changes measured by biopsy after 12 months of treatment, changes in liver and metabolic function measured by the liver enzymes ALT and AST, markers of liver fibrosis, glycemic control and safety and tolerability. Not all of these endpoints were examined in this interim analysis; rather, in addition to the safety variables of incidence of treatment-emergent adverse events and peripheral edema grades, changes from baseline relative to placebo for a number of endpoints, including liver functions tests such as ALT and AST, among others, biomarkers and indirect measures of apoptosis and fibrosis, circulating inflammatory markers and markers of bone metabolism, serum triglycerides and fasting cholesterol, markers of insulin sensitivity, and blood pressure, were examined in an exploratory manner.

About Cirius Therapeutics

Cirius is a clinical-stage pharmaceutical company focused on the development and commercialization of innovative therapies for the treatment of liver and metabolic diseases. Our lead product candidate, MSDC- 0602K, is a novel small molecule being developed as a once-daily oral therapy to treat NASH with fibrosis. MSDC-0602K is designed to selectively modulate the MPC, which mediates at the cellular level the effects of overnutrition, a major cause of NASH and

other metabolic disorders. We are conducting a Phase 2b clinical trial of MSDC-0602K, which we have fully enrolled with 402 patients diagnosed with NASH with fibrosis. We expect to report final data from this clinical trial in the second half of 2019.

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