Preliminary results of a phase I study of SZN-043, a novel R-Spondin mimetic, in healthy volunteers and subjects with liver cirrhosis

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Background and Aims: Severe alcohol-associated hepatitis (SAH) is a huge unmet medical need, associated with high mortality. Corticosteroids have not been associated with improved long-term survival benefit and there has been no improvement in survival in SAH with medical management during the last 60 years. SAH is associated with impaired hepatocyte proliferation. Elevated Wnt signaling and increased hepatocyte proliferation have been linked to greater survival, suggesting that therapies that can enhance hepatocyte proliferation can benefit patients. R-spondins (RSPOs) are known enhancers of Wnt signaling. SZN-043 is a bispecific fusion protein and hepatocyte-specific RSPO mimetic shown to induce hepatocyte-targeted Wnt signaling and hepatocyte proliferation in preclinical studies. SZN-043 was evaluated for safety, pharmacokinetics, and pharmacodynamics in a single center, first-in-human, Phase 1, randomized, double-blind, placebo-controlled, single ascending dose (SAD) and multiple ascending dose (MAD) study in healthy volunteers (HV) and subjects with liver cirrhosis (LC).

Method: Thirty-five (35) subjects were recruited across SAD and MAD cohorts. In Part 1, 12 HVs (6 active/2 placebo per cohort) received a single IV dose of SZN-043 at 1 or 3 mg/kg. In Part 2, 8 LCs (3 active/1 placebo per cohort) received a single IV dose at 0.5 or 1 mg/kg. In Part 3, 18 HVs (6 active/2 placebo per cohort) received 0.5, 1, or 1.5 mg/kg of SZN-043 on Days 0 and 4.

Results: SZN-043 was well tolerated across all populations and dosing regimens. No serious adverse reactions nor infusion reactions were observed. Asymptomatic serum transaminase elevations were observed in 4 HVs in Part 1 and 2 HVs in Part 3. No transaminitis was observed in any LC subject. Severity appeared to be dose dependent, with 5 subjects experiencing no more than a mild (Grade 1) transaminase elevation and a Grade 2 alanine aminotransaminase elevation observed in 1 subject at 3mg/kg. All resolved without intervention. No clinical sequelae or other related significant indicators of liver dysfunction were observed. In all other subjects, only mild to moderate adverse events judged to be at least possibly related were observed in 4 (other) subjects. Serum SZN-043 exposure was consistent with an IgG-based fusion protein. Pharmacologic activity in the liver was observed, as measured by increased metabolism of methacetin by cytochrome P450 1A2, a Wnt-target gene.

Conclusion: Administration of SZN-043 to HVs and LCs was well tolerated at doses where evidence of pharmacology was observed. Combined with the promise of the underlying biological mechanisms, the results from this study warrant further clinical investigation of SZN-043. A Phase Ib study in subjects with severe alcohol-associated hepatitis is under way.