Preliminary results of a Phase I study of SZN-043, a Novel R-Spondin mimic, in Healthy Volunteers and Subjects with Liver Cirrhosis

Edward J. Gane*, Michael Lauw², Jay Tibbitts³, Josh Koons³, Janyang Hu³, Geertru vanhove³, Mark Yen³, Chris Stevens², Christian Schwabe⁵, Craig Parker²

¹Faculty of Medicine, University of Auckland, Auckland, New Zealand, ²Surrozen Inc., South San Francisco, United States, ³Longitude Capital, Menlo Park, United States, ⁴Prometheus BioSciences, Los Angeles, United States, ⁵New Zealand Clinical Research Limited, Auckland, New Zealand.

Introduction

- Severe alcoholic-associated hepatitis (SAH) is a medical area of high unmet need, with the mainstay of medical management, corticosteroids, have not been associated with improved long-term survival benefit. Retrospective research has found to be improved 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 impaired survival, suggesting that therapies which can enhance hepatocyte proliferation can benefit patients. In preclinical (RSPRO) are known enhancers of Wnt signaling. SZN-043 is a bispecific fusion protein and hepatocyte-specific RSPRO conjugate, shown to induce hepatocyte-targeted Wnt signaling and hepatocyte proliferation in preclinical studies (Figure 1).
- SZN-043 was evaluated for safety, pharmacokinetics, and pharmacodynamics in a single-center, first-in-human, Phase 1, randomized, double-blind, placebo-controlled study in healthy volunteers (HV) and patients with a history of liver cirrhosis (PHLC) (Figure 1).

Figure 1. Structure and mechanism of action of SZN-043

Methods

- Subjects enrolled in Part 1 and 3 were between the ages of 18-50 years of age found to be in good health.
- Subjects enrolled in Part 3 were patients with a history of cirrhosis (PHLC) with a Child-Pugh score between 5 and 7, inclusive; a fibroscan of ≥ 6; and a MELD score ≥ 12.
- SZN-043 was administered as an IV infusion on Day 0 (Part 1) or Days 0, 4; Days 0, 4, 28 (Part 2).
- Subjects were followed for 4 weeks after their last dose.
- Safety and tolerability were assessed throughout the following: vital signs, physical examination, clinical laboratory tests (chemistry, coagulation, serum chemistry and metabolic profiles), clinical investigational product (IP) blood samples (SZN-043 serum samples and IP whole blood), immunohistochemistry, and ELISA. HCV, and retest of ALT and AST for 15 and 30 days should they arise.
- Pharmacokinetic evaluation was conducted based on serum measurements following dosing.
- Pharmacodynamic evaluation included occupancy of ASGPR by an ASGPR binding peptide, murine ascites hepatoma (murine hepatic fat cell) and Portal Hepatic Fibrosis rate (lipid trap).

Results

Safety Summary

- SZN-043 was well tolerated at all dose levels and dosing regimens. No clinically significant vital sign changes, ECG nor physical exam findings were reported during the study. No participants experienced an infusion reaction. The majority of adverse events assessed to be probably related to SZN-043 and confirmed to have been related to the drug were elevations in alanine aminotransferase (ALT) and alanine transaminase (AST).
- The only adverse events of interest were an unplanned rise in serum transaminases that were small and no increases in maximum transaminase level were reported during the study.

Safety findings (Table 1, Figures 3, 4)

- Transaminase elevations (Table 1, Figures 3, 4)
  - Transaminase elevations were observed in a subset of SZN-043 treated subjects which were transient with incidence that was dose related, with interpatient variability.
  - Transaminase elevations were not associated with other changes in clinical pathology (e.g. GGT).
  - Transaminase elevations were confirmed as hepatocyte-related as evidenced by consistent increases in severe levels of ALT and AST.

Pharmacokinetics of SZN-043

- The pharmacokinetics of SZN-043 were consistent with an IgG-based therapeutic protein. SZN-043 was well tolerated across all populations and dosing regimens. No dose-related increase in liver function tests was observed.

- No clinically significant increases in ALT or AST were observed in PHLCs. The events assessed to be probably related to SZN-043 (and confirmed to have been related to the drug) were elevations in alanine aminotransferase (ALT) and alanine transaminase (AST).

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Antidrug Antibodies (ADA)

- Of 13 (8% of SZN-043 treated subjects showed treatment-emergent anti-drug antibodies against SZN-043. Of these, only one subject exhibited a transiently positive ADA response against SZN-043.
- There was no doserelated effect on ADA on SZN-043 exposure; nor was there any pharmacologic evidence of neutralization of endogenous RSPO2.

Pharmacodynamic biomarkers

- Strategies to identify biomarkers of SZN-043 treatment using targeted or unbiased approaches.

- The pharmacokinetics and PK-PD of SZN-043 were consistent with an IgG-based therapeutic protein. SZN-043 was well tolerated across all populations and dosing regimens. No dose-related increase in liver function tests was observed.

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Summary

- With modulation of Wnt signaling in hepatocytes is a promising new mechanism for supporting regeneration in injured livers.
- SZN-043 is a novel biologic shown to potentiate Wnt signaling and induce proliferation in hepatocytes in vivo.
- In a Phase Ia study in HVs and PHLCs, single and multiple doses of SZN-043 were safe and well tolerated.
- No evidence of transaminase elevations were noted in any treated subjects.
- SZN-043 exposure was consistent with an IgG-based protein.
- SZN-043 as a therapeutic sensor.
- SZN-043 treated subjects scheduled treatment-emergent anti-drug antibodies against SZN-043. Of these, only one subject exhibited a transiently positive ADA response against SZN-043.
- There was no doserelated effect on ADA on SZN-043 exposure; nor was there any pharmacologic evidence of neutralization of endogenous RSPO2.

- The pharmacokinetics and PK-PD of SZN-043 were consistent with an IgG-based therapeutic protein. SZN-043 was well tolerated across all populations and dosing regimens. No dose-related increase in liver function tests was observed.

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