INTRODUCTION

- Semicarbazide-Sensitive Amine Oxidase (SSAO), also known as Vascular Adhesion Protein 1 (VAP-1), is a cellular adhesion molecule with amine oxida
toectonase activity. SSR is expressed in the
ehapatic endothelium where it plays a dominant role in lymphocyte adhesion and transmigration. In chronic inflammatory diseases such as non-
alcoholic steatohepatitis (NASH), SSAO expression is elevated and correlates with disease severity and fibrosis stage.

- TERN-201 is a novel SSAO inhibitor being developed for the treatment of NASH.

METHODS

- Hepatic stability of TERN-201 (2 µM) was assessed in cryopreserved rat, dog, monkey, and human hepatocytes (1.0×10^6 cells/mL) at 37°C for up to 4 hours. In vitro half-life (t1/2) was calculated from enzymatic stability curves and predicted hepatic clearance values.

- Pharmacokinetics (PK) of TERN-201 in Sprague Dawley (SD) rats and Beagle dogs (n=3 animals/route) were determined following IV bolus dose. Cynomolgus monkey PK was determined following a 30-minute intravenous (IV) infusion and oral route (n=3 animals/route).

- Tissue samples (0-24 h) were collected for plasma PK.

- IV-14C-TERN-201 PK was determined following oral administrations (10 mg/kg, 100 µCi/kg of 14C-TERN-201) in SD rats (n=3 animals/time point). Blood, feces, urine samples were collected at 168 postdose and concentrations were determined using liquid scintillation counting.

- IV-14C-TERN-201 tissue distribution was determined in both SD and Long Evans (LE) rats (n=10 rats, 1 animal/time point) following a single oral dose of TERN-201 at 10 mg/kg (100 µCi/kg of 14C-TERN-201). Tissue samples were collected up to 169 postdose and cross sectional slides of whole animal autoradiography were taken at successive time points to show distribution over time.

- Plasma PK parameters were determined by non-compartmental analysis.

RESULTS

In Vitro DMPK

- Table 1: In Vitro Metabolic Stability in Hepatocytes

Tissue Distribution

- Figure 2: Tissue Distribution of 14C-TERN-201 in SD/LE Rats

- Figure 3: Tissue/plasma ratios of 14C-TERN-201 in SD and LE rats (24 h postdose)

In Vivo DMPK

- Figure 1: TERN-201 Plasma PK Profiles in Preclinical Species

Tissue Distribution

- Figure 4: Quantitative whole-body autoradiograph (QWBA) of 14C-TERN-201 and Metabolites in SD Rats

- Figure 5: Plasma concentration of 14C-TERN-201 and Cumulative Percent of Radioactive Dose in Urine and Feces in Male SD Rats

CONCLUSIONS

- TERN-201 exhibited moderate to high metabolic stability and moderate clearance across preclinical species.

- TERN-201 has a large volume of distribution (Vdss) and sustained concentration in the liver, which should allow for robust SSAO target engagement in NASH patients; renal excretion was identified as the major elimination pathway.

- The PK and tissue distribution profile of TERN-201 in preclinical species supports its continued clinical development for NASH.

REFERENCES


CONTACT INFORMATION

Presenting author: Erin Quirk, MD Terns Pharmaceuticals equirk@ternspharma.com

Corresponding author: Erin Quirk, MD Terns Pharmaceuticals R&D eq@ternspharma.com

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