Pharmacokinetics and Tissue Distribution of TERN-201, A Novel Investigational SSAO/VAP-1 Inhibitor, in Preclinical Species

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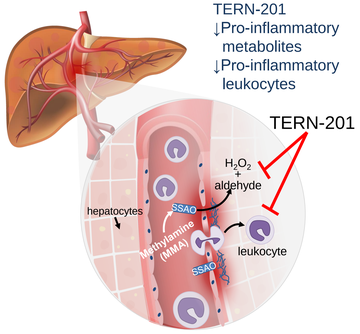
1 • INTRODUCTION •



- Semicarbazide-Sensitive Amine Oxidase (SSAO), also known as Vascular Adhesion Protein-1 (VAP-1), is a cellular adhesion molecule with amine oxidase ectoenzyme activity[1]. In the liver, SSAO is expressed in the hepatic endothelium where it plays a dominant role in lymphocyte adhesion and transmigration[1]. In chronic inflammatory diseases, such as non-alcoholic steatohepatitis (NASH), SSAO expression is elevated and correlates with disease severity and fibrosis stage[2].

SSAO inhibition is anticipated to have therapeutic benefit in NASH by reducing oxidative stress and recruitment of inflammatory cells into the liver.

TERN-201 is a potent and highly specific SSAO inhibitor >7,000-fold in vitro selectivity for SSAO over off-target monoamine oxidases (MAO). TERN-201 has been granted Fast Track Designation by the U.S. FDA for the treatment of NASH

2 • AIM •

In this study we assess the metabolic stability, pharmacokinetics (PK), tissue distribution, and route of elimination of TERN-201, an SSAO inhibitor being developed for the treatment of NASH

3 • METHODS •

- Hepatic stability of TERN-201 (2 μM) was assessed in cryopreserved rat, dog, monkey, and human hepatocytes (1.0x10^6 cells/mL) at 37°C for up to 4 hours. In vitro half-life ($t_{1/2}$) was calculated from %remaining time curves and predicted hepatic clearance values were calculated using the well-stirred liver model with no correction for plasma protein binding[5].
- Pharmacokinetics (PK) of TERN-201 in Sprague Dawley (SD) rats and Beagle dogs (n=3 animals/route) were determined following an IV bolus dose. Cynomolgus monkey PK was determined following a 30-minute intravenous (IV) infusion and oral route (n=3 animals/route). Serial blood samples (0-24h) were collected for plasma PK.
- [14-C]TERN-201 PK was determined following oral administrations (10 mg/kg, 100 μCi/kg of [14-C]TERN-201) in SD rats (n= 3 animals/time point). Blood, feces, and urine samples were collected up to 168h postdose and concentrations were determined by Liquid Scintillation Counting (LSC)
- [14-C]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 [14-C]TERN-201). Tissue samples were collected up to 168h 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.

4 • RESULTS •

In Vitro DMPK

Table 1: TERN-201 In Vitro Metabolic Stability in Hepatocytes

Species*	%Remaining (after 240 min)	$t_{½}$ (min)	In vitro metabolism (CL_{pred}, L/h/kg)†	Hepatic Extraction (%)
SD rat	4.4	54.8 ± 1.5	1.73 ± 0.10	52%
Beagle dog	68.6	454 ± 58.8	0.31 ± 0.05	17%
Cynomolgus monkey	60.6	324 ± 17.6	0.28 ± 0.06	11%
Human	101.3	> 480	< 0.10	< 8%

*Data from cryopreserved, pooled rat, dog, monkey, and human hepatocytes; 4-hour incubation with 2 μM TERN-201. †Hepatic clearance (CL_{pred}) was not corrected for plasma protein binding.

- TERN-201 was stable in human hepatocytes, showed low clearance in dog and monkey, and had moderate clearance in rat hepatocytes.

In Vivo DMPK

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

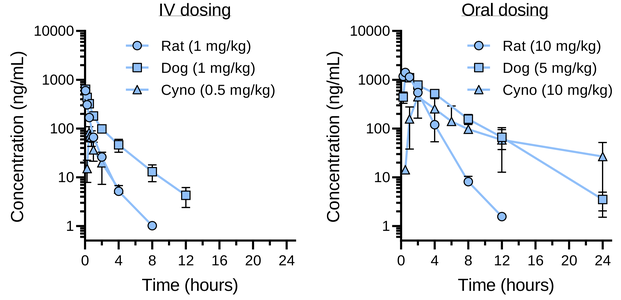


Table 2: TERN-201 PK Parameters in Preclinical Species

Species	CL (L/h/kg)	V_{dss} (L/kg)	IV Terminal $t_{1/2}$ (h)	Bioavailability (F %)*
SD rat	2.97 ±0.25	2.13 ±0.207	0.920 ±0.257	85[a]
Beagle dog	1.23 ±0.167	2.68 ±0.339	2.30 ±0.243	129[a]
Cynomolgus monkey	6.18 ±3.96	5.87 ±1.53	0.757 ±0.260	36 -131[b]

*%F was estimated using IV arm exposure data at low dose levels
[a]Suspension formulation: 1% hydroxyethylcellulose (w/v)/0.25% polysorbate 80 (v/v)/0.05% Antifoam (v/v) in water
[b]Solution formulation: 12% captisol in water orally at 1, 3, and 10 mg/kg in monkeys

- TERN-201 demonstrated moderate to high *in vivo* clearance and good oral absorption in preclinical species
- TERN-201 volume of distribution (V_{dss}) was greater than the volume of total body water (0.70 L/kg) across all preclinical species, suggesting good distribution into tissues

Tissue Distribution

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

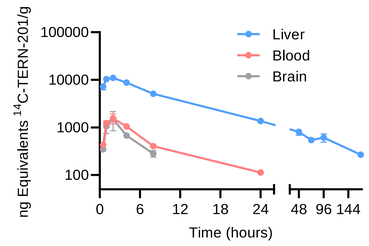
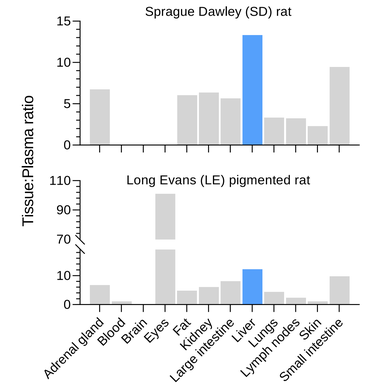
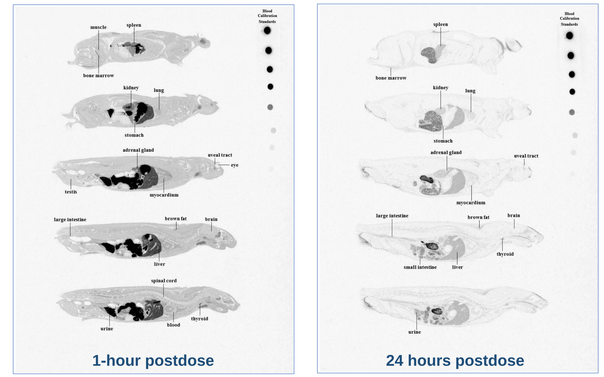


Figure 3: Tissue:plasma ratios of ^{14}C-TERN-201 in SD and LE rats (24 hrs postdose)



- TERN-201 achieves high and sustained concentrations in the liver relative to other tissues
- The exposure of TERN-201 in the brain tracks with concentrations in the blood

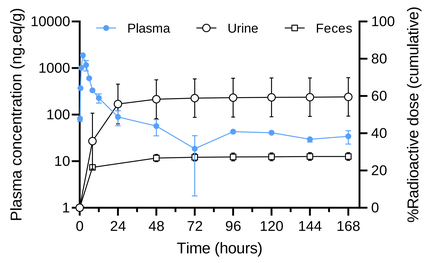
Figure 4: Quantitative whole-body autoradiograph (QWBA) of ^{14}C-TERN-201 and Metabolites In SD Rats



- Tissues with the highest radioactivity concentrations were Harderian gland, adrenal gland, liver, exorbital lacrimal gland, and kidney; the uveal tract had the highest concentration in pigmented LE rats (data not shown)

In Vivo Elimination

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



- Urinary excretion was the predominant route of elimination for TERN-201

5 • CONCLUSIONS •

- TERN-201 exhibited moderate to high metabolic stability and moderate clearance across preclinical species
- TERN-201 has a large volume of distribution (Vd_{ss}) 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

6 • REFERENCES •

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[2]Weston et al. J. Clin. Invest. 2015; 125:501−520
[3]Obach et al. J. Pharmacol. Exp. Ther. 1997; 283:46-58

7 • CONTACT INFORMATION •

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