Multiple ascending doses of TERN-201, a novel selective semicarbazide-sensitive amine oxidase (SSAO) inhibitor, fully suppresses plasma SSAO activity in a Phase 1 study

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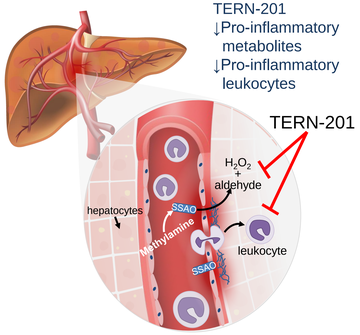
1 · INTRODUCTION



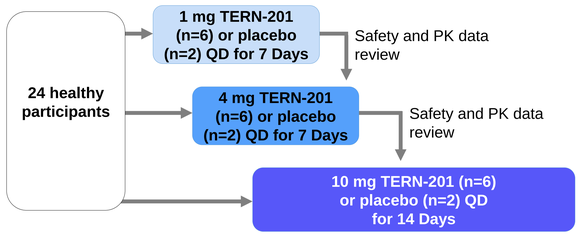
SSAO is a cellular adhesion protein and ectoenzyme with amine oxidase activity. In the liver, SSAO is expressed in the hepatic endothelium where it plays a dominant role in lymphocyte adhesion and transmigration[1]. In nonalcoholic steatohepatitis (NASH), SSAO expression is elevated and correlates with 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 with an in vitro selectivity index of >7,000-fold for SSAO over off-target monoamine oxidases (MAO). In a rat model of NASH, TERN-201 reduced liver inflammation and the expression of fibrotic markers and genes associated with hepatic stellate cell activation[3]. Here we report SSAO inhibition, pharmacokinetics (PK), and safety data for TERN-201 following multiple ascending doses for up to 14 days in healthy participants.

2 · METHODS

- 24 healthy participants were randomized to 3 cohorts of 8 unique subjects (2 placebo, 6 TERN-201); safety was assessed prior to dose escalation
- Safety was assessed during study drug administration and for 7-14 days following the last dose. Plasma samples for PK analysis were obtained at multiple timepoints following the first and last dose of study drug.
- Pharmacodynamic biomarker assessment of target engagement included:
  - Plasma total and SSAO-specific amine oxidase activity
  - Plasma methylamine accumulation
- Plasma PK parameters were determined by non-compartmental analysis
- Total amine oxidase activity was measured using a fluorometric assay to detect hydrogen peroxide (H_2O_2) generation after addition of benzylamine to plasma samples. Percent change was determined relative to Day 1 pre-dose (baseline).
- Plasma SSAO-specific amine oxidase activity was determined using a kinetic-based fluorometric assay[4]. Endogenous monoamine oxidases A and B were inhibited by adding pargyline to all samples prior to measuring H_2O_2 generation. Percent changes were calculated relative to baseline samples additionally treated with a high dose of TERN-201, which served as a background control.
- Plasma methylamine was quantified using a LC/MS/MS method with an LLOQ=8 ng/mL.

Figure 1: TERN201-US A101 Study Design



3 · RESULTS

Safety

Table 1: TERN-201 Safety and Tolerability

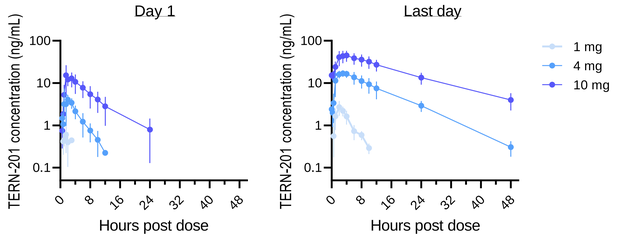
Treatment Emergent Adverse Event (TEAE)	Placebo (n=6)	1 mg TERN-201 (n=6)	4 mg TERN-201 (n=6)	10 mg TERN-201 (n=6)	Overall TERN-201 (n=18)
Subject incidence of any TEAE, n (%)	3 (50)	2 (33.3)	2 (33.3)	6 (100)	10 (55.6)
Subject TEAEs considered possibly treatment-related[1], n (%)	1 (16.7)	1 (16.7)	0	0	1 (5.6)
TEAE diagnosis and frequency					
Back pain	1 (16.7)	0	0	0	0
Catheter site inflammation	1 (16.7)	0	0	0	0
Contusion	1 (16.7)	0	0	0	0
Dermatitis contact	0	1 (16.7)	2 (33.3)	0	3 (16.7)
Diarrhea	1 (16.7)	0	0	0	0
Dizziness	0	1 (16.7)	0	0	1 (5.6)
Headache	0	1 (12.5)	0	0	1 (5.6)
Medical device site reaction[2]	2 (33.3)	0	0	6 (100)	6 (33.3)
Rhinitis	0	0	0	1 (16.7)	1 (5.6)

[1] One subject who received 1 mg TERN-201 for 7 days had an event (headache) considered possibly related to TERN-201. [2]All 8 subjects (6 TERN-201, 2 placebo) in the 10 mg cohort had mild events of contact dermatitis at the site of ECG leads ("Medical device site reaction"); ECGs were at least daily, per protocol.

- TERN-201 was overall safe and well-tolerated
- All AEs were considered mild (Grade 1) except for one moderate (Grade 2) AE of diarrhea in the placebo treatment group. No subject discontinued due to an AE.
- Laboratory, vital signs, ECG, and other safety assessments with no notable findings across subjects or cohorts

Pharmacokinetics

Figure 2: TERN-201 plasma PK in healthy subjects



Dose (mg)	Day	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-t} (h*ng/mL)	$t_{1/2}$ (h)	AR (C_{max})	AR (AUC)
1	Day 1	0.568 (64)	1.53 (0.82, 2.00)	NC			
	Last Day	2.75 (36)	2.51 (1.02, 3.00)	13.3 (14)	2.27 (2.00, 2.48)	5.98 (49)	NC
4	Day 1	5.11 (64)	2.02 (1.02, 3.07)	17.1 (29)			
	Last Day	18.6 (20)	3.03 (1.03, 4.02)	198 (32)	6.71 (2.85, 8.13)	4.32 (34)	11.7 (22)
10	Day 1	17.7 (49)	1.90 (1.48, 4.00)	102 (53)			
	Last Day	47.5 (31)	3.98 (2.03, 4.02)	656 (29)	13.3 (9.97, 14.9)	3.35 (57)	8.2 (63)

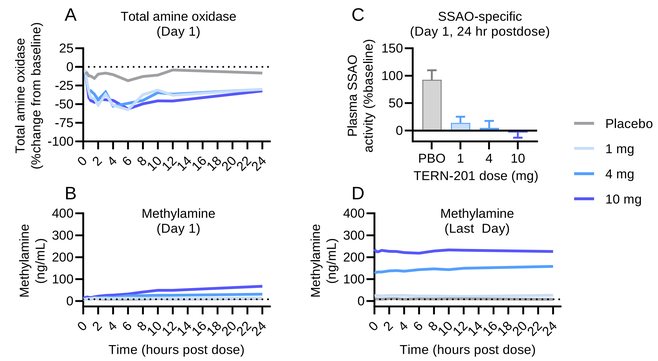
TERN-201 exposure curves represented by mean (±SD). PK parameters presented as mean (CV%), except for T_{max} and $t_{1/2}$ presented as median (min, max). AR = accumulation ratio between Day 1 and Last day. NC, not calculable

- TERN-201 was rapidly cleared from plasma on Day 1 and exposure was greater than dose proportional between doses
- TERN-201 accumulated between Day 1 and the last day of dosing; steady state was achieved after day 7 of dosing in the highest dose group
- TERN-201 half-life increased with dose, suggesting saturable target-mediated clearance

Pharmacodynamics

Figure 3: TERN-201 plasma PD markers

- TERN-201 rapidly inhibited plasma total and SSAO-specific amine oxidase activity in all subjects on Day 1 (A,C) and resulted in dose-dependent increases in plasma methylamine (B).
- After multiple doses, further increases in plasma methylamine were observed on the last day of TERN-201 administration (D).
- Inhibition of total amine oxidase was incomplete due to the presence plasma amine oxidases that are not inhibited by TERN-201 (e.g., MAO-A/B)
- Methylamine is an endogenous substrate of SSAO and predicted to increase in the plasma upon SSAO inhibition



Lines represent mean in A, B, and D. (C) Plasma SSAO-specific amine oxidase activity detected on Day 1, 24 h postdose (mean ±SD). Dotted line in (B) and (D) indicates LLOQ (8 ng/mL) for detection of plasma methylamine.

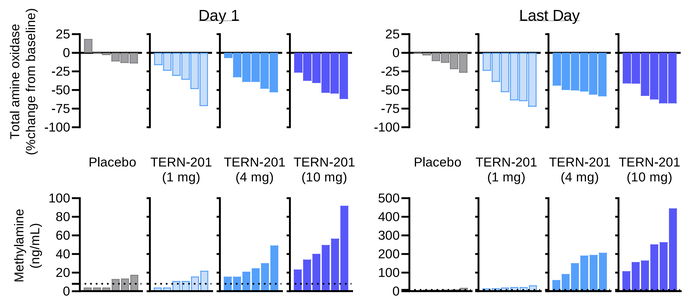


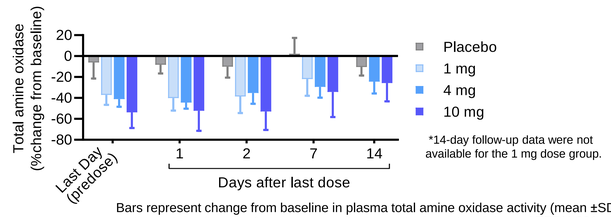
Figure 4: Individual subject PD response to TERN-201

- Individual subject response to TERN-201 on plasma total amine oxidase activity (top) and methylamine (bottom) at 12 hours postdose on Day 1 (left) and on the last day of dosing (right).

Bars represent individual subjects and are rank ordered by response in each plot. Dotted line in (B) and (D) indicates LLOQ (8 ng/mL) for detection of plasma methylamine.

Figure 5: Sustained inhibition of total amine oxidase activity

- Evidence of sustained TERN-201 activity on plasma total amine oxidase on days following the last administered dose of TERN-201



*14-day follow-up data were not available for the 1 mg dose group.

Bars represent change from baseline in plasma total amine oxidase activity (mean ±SD) on the last day (predose) and on days after the last administered dose of TERN-201.

4 · CONCLUSIONS

- TERN-201 was overall safe and well-tolerated in healthy participants administered up to 10 mg TERN-201 once daily for 14 days
- The half-life of TERN-201 at steady state and prolonged PD effect support once daily dosing or possibly less frequent administration
- Robust target engagement was supported by rapid and sustained inhibition of total plasma amine oxidase activity and accumulation of methylamine, a potentially useful biomarker of SSAO inhibition
- Additional studies are warranted to further investigate the therapeutic potential of TERN-201 for the treatment of NASH

5 · REFERENCES

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