Single Doses of TERN-201, a Novel Selective Semicarbazide-sensitive Amine Oxidase (SSAO) Inhibitor, are Safe, Well-tolerated, and Result in Reduced Plasma SSAO Activity in Healthy Participants

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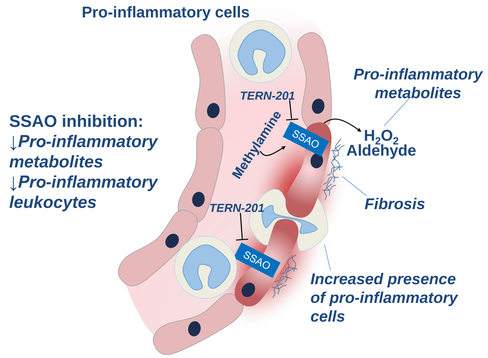
INTRODUCTION



Semicarbazide-sensitive amine oxidase (SSAO, also known as VAP-1: vascular adhesion protein-1) is a dual function cell adhesion molecule with amine oxidase ectoenzyme activity. SSAO contributes to non-alcoholic steatohepatitis (NASH) by increasing oxidative stress via breakdown of primary amines to aldehyde, ammonium, and hydrogen peroxide (H_2O_2) and by recruitment of inflammatory cells to the liver, exacerbating hepatic inflammation and injury.

Soluble SSAO, generated by metalloproteolytic cleavage of membrane-bound SSAO, is elevated in many inflammatory diseases including NASH and is independently associated liver fibrosis stage (Weston et al.). Pharmacological inhibition of SSAO is anticipated to have therapeutic benefit in the treatment of NASH by reducing oxidative stress and recruitment of inflammatory cells to the liver.

TERN-201 is a novel, potent, selective, and irreversible inhibitor of human semicarbazide-sensitive amine oxidase. Here we present first-in-human data for TERN-201-US-A101, a Phase 1 study of healthy subjects receiving a single oral dose of TERN-201.

	Biochemical activity (IC_{50}, μM)		
SSAO inhibitor	**SSAO**	**MAO-A**	**MAO-B**
TERN-201	**0.0065**	**>50**	**>50**
BI 1467335* (PXS-4728A)	0.005	>100	2.7

RESULTS

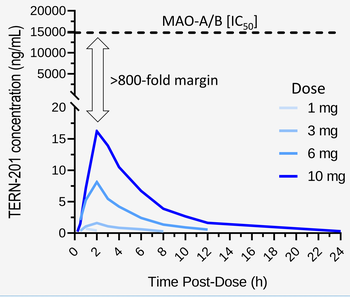
TERN-201 SAFETY AND TOLERABILITY

	Incidence, number (%) TERN-201 Cohorts, 3:1 treatment to placebo (pooled, blinded, preliminary data)				
Treatment **E**mergent **A**dverse **E**vent	**1** 1 mg TERN-201 or placebo (n=8)	**2** 3 mg TERN-201 or placebo (n=8)	**3** 6 mg TERN-201 or placebo (n=8)	**4** 10 mg TERN-201 or placebo (n=8)	**All** (n=32)
Any TEAE	0	0	3 (37.5)	5 (62.5)	8 (25)
Treatment-related TEAE	0	0	0	2 (25)	2 (6.3)
TEAE diagnosis					
constipation	0	0	0	1 (12.5)	1 (3.1)
contact dermatitis	0	0	2 (25)	0	2 (6.3)
dysgeusia	0	0	0	1 (12.5)	1 (3.1)
headache	0	0	0	1 (12.5)	1 (3.1)
oral herpes	0	0	0	1 (12.5)	1 (3.1)
sore throat	0	0	1 (12.5)	0	1 (3.1)
upper respiratory tract infection	0	0	0	1 (12.5)	1 (3.1)

- Single ascending doses of placebo and TERN-201 at 1, 3, 6, and 10 mg were safe and well tolerated
- All but 2 TEAEs were considered unrelated or unlikely related to treatment
- Possible treatment-related TEAEs (constipation [n=1] and headache [n=1]) were observed in 2 subjects in Cohort 4 (10 mg or placebo) and were mild in severity

TERN-201 PHARMACOKINETICS

PK profile of TERN-201



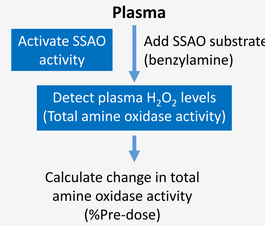
PK parameters (mean ± standard deviation)

Dose cohort	**3 mg**	**6 mg**	**10 mg**
C_{max} (ng/mL)	1.7 ± 0.9	8.6 ± 3	17 ± 5.35
T_{max} (h)	2	2	2
AUC_{0-t} (h*ng/mL)	5.1 ± 3.6	34 ± 13	83.5 ± 24.9
$t_{1/2}$ (h)	1.1 ± 0.085	2.6 ± 0.47	2.8 ± 0.8

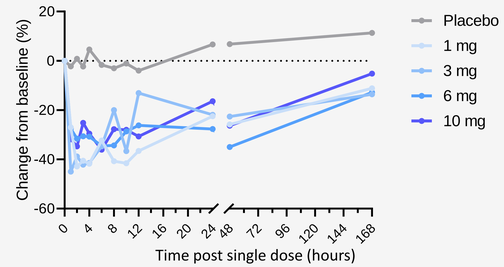
C_{max}: maximum plasma concentration; T_{max}: median time to C_{max}; AUC_{0-t}: area under the plasma concentration curve from time zero to time of the last quantifiable concentration; $t_{1/2}$: terminal elimination half-life. PK parameters for the 1 mg TERN-201 dose cohort could not be calculated.

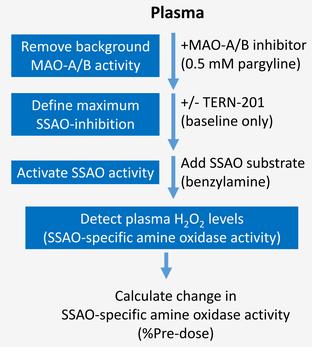
- TERN-201 was rapidly cleared from plasma
- PK parameters for the 1 mg group could not be calculated because TERN-201 was detectable in only 3/6 subjects in the 1 mg cohort (at 1-2 hours post-dose)
- TERN-201 plasma PK exposure was greater than dose-proportional between the 3 and 10 mg dose levels

TERN-201 PHARMACODYNAMICS

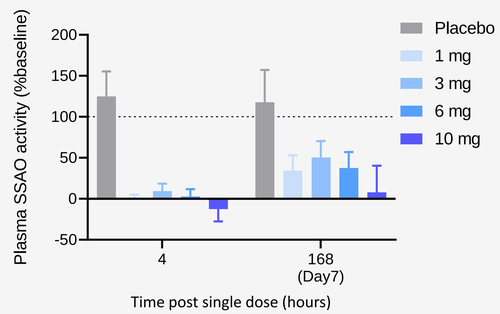


Inhibition of total plasma amine oxidase activity





Inhibition of SSAO-specific plasma amine oxidase activity

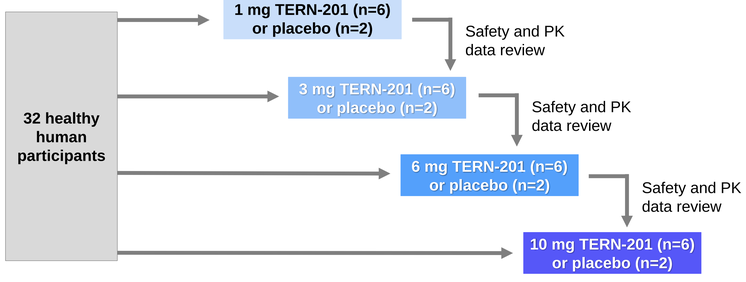


- Single doses of TERN-201 rapidly and potently decreased plasma amine oxidase activity in all subjects
  - No significant change from baseline was observed in placebo recipients
- Inhibition of total plasma amine oxidase levels were comparable across all dose groups
- Near complete inhibition of SSAO-specific activity was observed at 4 hours post-dose
  - SSAO inhibition was detectable for up to 7 days following a single dose of TERN-201
- TERN-201 exhibited potent target engagement supporting once daily dosing despite a short plasma half-life

METHODS

TERN-201-US-A101 DESIGN

Single-ascending dose study of TERN-201 in normal healthy volunteers



- 32 healthy subjects randomized to four cohorts: 2 placebo:6 active TERN-201 per cohort
- Assessment of safety and intensive PK prior to initiation of each subsequent cohort
- Pharmacodynamic biomarker assessment of target engagement included:
  - Total plasma amine oxidase activity (H_2O_2 generation)
  - Total plasma SSAO-specific amine oxidase activity (H_2O_2 generation)

- Plasma samples for TERN-201 concentration and SSAO activity determination were collected at 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 48 (SSAO activity only), and 168 (SSAO activity only) hours after administration of a single dose of study medication (placebo or TERN-201)
- Plasma PK parameters were determined by non-compartmental analysis
- SSAO activity was assessed by measuring hydrogen peroxide (H_2O_2) generation levels in plasma samples from placebo and active TERN-201 recipients. Percent change in total amine oxidase activity was determined relative to the corresponding pre-dose (baseline) samples.
- SSAO-specific amine oxidase levels in plasma were determined using a kinetic-based assay essentially as described previously (Schilter et al). Endogenous monoamine oxidases A and B were inhibited by adding pargyline to plasma samples prior to measuring H_2O_2 generation levels in placebo and active TERN-201 recipients. Maximum inhibition was defined by pre-dose (baseline) samples additionally treated with a high dose of TERN-201 and percent changes in SSAO-specific activity were calculated relative to baseline samples.

CONCLUSIONS

- TERN-201 is a potent and selective SSAO inhibitor (SSAO IC_{50} = 0.0065 μM; MAO-A/B IC_{50} >50 μM) being developed for the treatment of NASH due to its anti-inflammatory mechanism of action
- TERN-201 is safe and well tolerated in healthy subjects administered a single oral dose ranging from 1 mg to 10 mg and exhibited greater than dose proportional plasma PK between 3 and 10 mg
- TERN-201 plasma concentrations (C_{max}) were more than 800 times lower than the IC_{50} concentrations for MAO-A and MAO–B at all dose levels.
- Inhibition of plasma SSAO activity was observed for up to one week after single oral doses of TERN-201 despite a short plasma half-life, indicating potent plasma SSAO target engagement across the dose range
- Additional studies are warranted to further investigate TERN-201 for the treatment of NASH

DISCLOSURES

Authors are employees/stockholders in Terns Pharmaceuticals

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- *Schilter et al. Effects of an anti-inflammatory VAP-1/SSAO inhibitor, PXS-4728A, on pulmonary neutrophil migration. Resp Res. (2015) 16:42