Single doses of TERN-201, a novel selective semicarbazide-sensitive amine oxidase (SSAO) inhibitor, are safe, well-tolerated, and result in sustained reduction of SSAO activity in healthy participants

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INTRODUCTION

Semicarbazide-sensitive amine oxidase (SSAO, also known as vascular adhesion protein-1 [VAP-1]) is expressed in vascular endothelium and functions as both a leukocyte adhesion molecule and a primary amine oxidase. SSAO contributes to hepatic inflammation and injury in non-alcoholic steatohepatitis (NASH) through recruitment of inflammatory cells to the liver and increasing oxidative stress via breakdown of primary amines (e.g., methylamine) to aldehyde, ammonium, and hydrogen peroxide (H_2O_2). 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, and irreversible covalent inhibitor of human SSAO. TERN-201 is selective for SSAO over other monoamine oxidases (e.g., MAO-A/B), reducing potential off-target safety concerns. Here we present interim, single-ascending dose results from TERN201-US-A101, a Phase 1 first-in-human study in healthy subjects receiving a single oral dose of TERN-201. The study remains ongoing and blinded.

Biochemical activity (IC_{50}, μM)

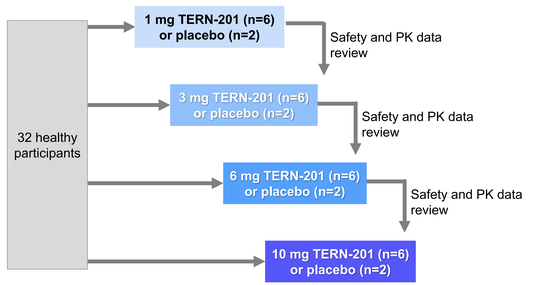
SSAO inhibitor	SSAO	MAO-A	MAO-B
TERN-201	**0.0065**	**>50**	**>50**
BI 1467335* (PXS-4728A)	0.005	>100	2.7

*Schilter et al.

METHODS

TERN201-US-A101 DESIGN

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



- 32 healthy subjects randomized to four cohorts: 2 placebo:6 active TERN-201
- Assessment of safety and intensive PK prior to initiation of each subsequent cohort
- 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 assessed by measuring plasma hydrogen peroxide (H_2O_2) generation levels from placebo and active TERN-201 recipients. Percent change was determined relative to the corresponding pre-dose (baseline) samples.
- SSAO-specific amine oxidase levels were determined using a kinetic-based assay (Schilter et al). Endogenous monoamine oxidases A and B were inhibited by adding pargyline to all plasma samples prior to measuring H_2O_2 generation levels. Percent changes were calculated relative to baseline samples additionally treated with a high dose of TERN-201.
- Methylamine concentration in plasma was determined using an internally validated LC/MS/MS method developed by Frontage Laboratories with an LLOQ = 8 ng/mL.

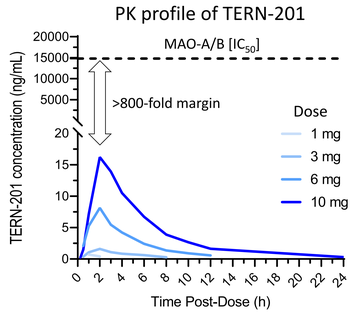
RESULTS

TERN-201 SAFETY AND TOLERABILITY

Treatment Emergent Adverse Event (TEAE)	Subject incidence or TEAE frequency, number (%) TERN-201 Cohorts, 3:1 treatment to placebo (pooled, blinded, preliminary data)				
	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)
Subject incidence of any TEAE	0	0	2 (25)	3 (37.5)	5 (15.6)
Subject incidence of TEAEs considered possibly treatment-related	0	0	0	1 (12.5)	1 (3.1)
TEAE diagnosis and frequency					
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 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
- One subject in Cohort 4 (placebo or 10 mg TERN-201) reported 2 mild TEAEs (constipation and dysgeusia) that were considered possibly related to study medication

TERN-201 PHARMACOKINETICS



- TERN-201 was rapidly cleared from plasma
- 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 single dose levels

TERN-201 PHARMACODYNAMICS

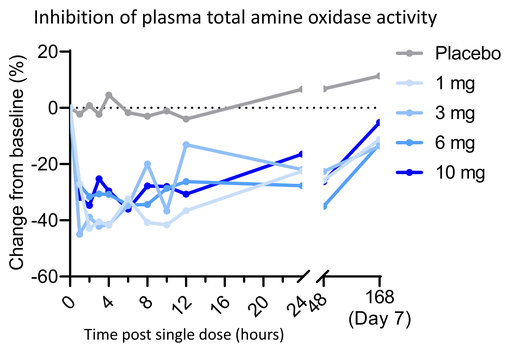
ASSAY WORKFLOWS

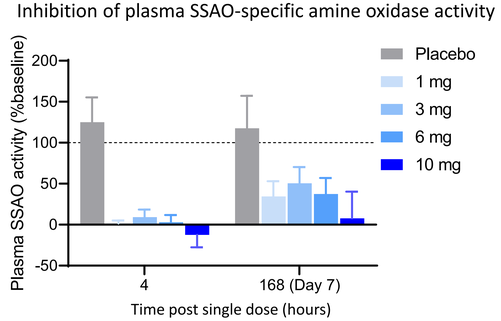
Total amine oxidase

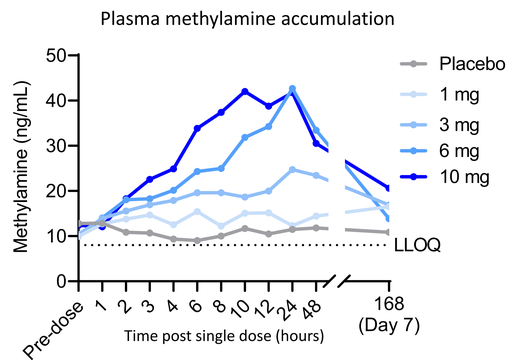
Plasma → Activate SSAO activity (+benzylamine) → Detect plasma H_2O_2 levels (Total amine oxidase activity) → Calculate change in total amine oxidase activity (%Pre-dose)

SSAO-specific amine oxidase

Plasma → Remove background MAO-A/B activity (+MAO-A/B inhibitor (0.5 mM pargyline)) → Define maximum SSAO-inhibition (+/- TERN-201 (baseline only)) → Activate SSAO activity (+benzylamine) → Detect plasma H_2O_2 levels (SSAO-specific amine oxidase activity) → Calculate change in SSAO-specific amine oxidase activity (%Pre-dose)





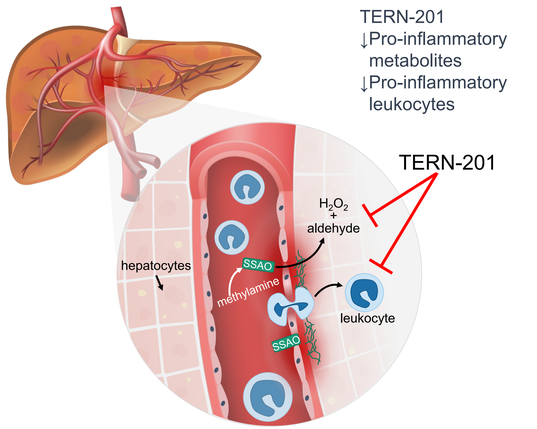


- TERN-201 rapidly and potently decreased plasma amine oxidase activity in all subjects and were comparable across all single dose groups
  - No significant change from baseline was observed in placebo recipients
- Near complete inhibition of SSAO-specific activity was observed at 4 hours post-dose
  - SSAO inhibition was detectable for up to 7 days following a single dose of TERN-201
- Dose-dependent increases in plasma methylamine levels were observed, indicative of SSAO target engagement

CONCLUSIONS

- TERN-201 was 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
- Dose-dependent increases in methylamine were observed, indicating potent plasma SSAO target engagement across the dose range
- 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
- 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.
- A Phase 2 study in NASH patients is planned to assess TERN-201 for the treatment of NASH

MODEL OF TERN-201 MOA



REFERENCES

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

CONTACT INFORMATION

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