Semicarbazide-sensitive amine oxidase (SSAO), also known as VAP-1: vascular adhesion protein-1, is a dual function cell adhesion molecule with amine oxidase exoenzyme activity. SSAO contributes to non-alcoholic steatohepatitis (NASH) by increasing oxidative stress via breakdown of primary amines to aldehyde, ammonia, and hydrogen peroxide (H₂O₂) 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.

**RESULTS**

**TERN-201 PHARMACOKINETICS**

**PK profile of TERN-201**

<table>
<thead>
<tr>
<th>Dose cohort</th>
<th>3 mg</th>
<th>6 mg</th>
<th>10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAO-A/B [%IC₅₀]</td>
<td>1.5 ± 0.3</td>
<td>2.0 ± 0.4</td>
<td>2.5 ± 0.6</td>
</tr>
<tr>
<td>MAO-A [%IC₅₀]</td>
<td>1.2 ± 0.2</td>
<td>1.6 ± 0.3</td>
<td>2.1 ± 0.5</td>
</tr>
<tr>
<td>MAO-B [%IC₅₀]</td>
<td>2.0 ± 0.4</td>
<td>2.5 ± 0.6</td>
<td>3.0 ± 0.8</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>1.1 ± 0.08</td>
<td>2.6 ± 0.47</td>
<td>2.8 ± 0.8</td>
</tr>
</tbody>
</table>

**PB data review**

- 32 healthy subjects randomized to four cohorts; 2 placebo and 2 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 (H₂O₂ generation)
  - Total plasma SSAO-specific amine oxidase activity (H₂O₂ generation)

**PK parameters (mean ± standard deviation)**

- Plasma samples for TERN-201 concentration and SSAO activity determination were collected at 0, 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.
- Plasma SSAO activity was assessed by measuring hydrogen peroxide (H₂O₂) 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 (Shibli et al.). Semicarbazide-sensitive amine oxidase and H₂O₂ were inhibited by adding paraglucuronic to plasma samples prior to measuring H₂O₂ generation levels in placebo and active TERN-201 recipients. Maximum inhibition was defined as pre-dose (baseline) samples treated with a high dose of TERN-201 and percent changes in SSAO-specific activity were calculated relative to baseline samples.

**REFERENCES**

**CONCLUSIONS**

- TERN-201 is potent and selective SSAO inhibitor (IC₅₀ 0.0065 μM; MAO-A/B IC₅₀ >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 55 mg.
- TERN-201 plasma concentrations (IC₅₀) were more than 860 times lower than the IC₅₀ concentrations for MAO-A and MAO-B at all dose levels.
- Inhibition of plasma SSAO activity was observed for up to 7 days 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.