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

TERN-201 (®-inflammatory metabolites ¦®-inflammatory mediators), a novel SSAO inhibitor, is a potential drug candidate for the treatment of non-alcoholic steatohepatitis (NASH). 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. In non-alcoholic steatohepatitis (NASH), SSAO expression is elevated and correlates with disease severity and fibrosis stage. 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 for SSAO over target monoamine oxidases (MAO). In a rat model of NASH, TERN-201 reduced liver fibrosis and the expression of fibrotic markers and genes associated with hepatic stellate cell activation. 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. The study was conducted at Terns Pharmaceuticals, Inc. in San Bruno, California, USA. Safety and PK data were not available for the 14 mg dose.

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 (H2O2) generation after addition of benzylamine to plasma samples. Percent change was determined relative to Day 1 predose (baseline). Plasma SSAO-specific amine oxidase activity was determined using a kinetic-based fluorometric assay. Endogenous monoamine oxidases A and B were inhibited by adding pyridine to all samples prior to measuring H2O2 generation. Percent changes were calculated relative to baseline samples additionally treated with a high dose of TERN-201, which served as a background control.

3. RESULTS

Safety

Table 1: TERN-201 Safety and Tolerability

<table>
<thead>
<tr>
<th>Treatment Emergent Adverse Event (TEAE)</th>
<th>Placebo</th>
<th>TERN-201 (1 mg)</th>
<th>TERN-201 (4 mg)</th>
<th>TERN-201 (10 mg)</th>
<th>Overall (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject incidence of any TEAE, n (%)</td>
<td>3 (50)</td>
<td>2 (33.3)</td>
<td>2 (33.3)</td>
<td>0 (0)</td>
<td>10 (55.5)</td>
</tr>
<tr>
<td>Subject TEAEs considered related to treatment-related, n (%)</td>
<td>1 (16.7)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (5.6)</td>
</tr>
</tbody>
</table>

TEAE: treatment-emergent adverse event

Pharmacodynamics

Figure 2: TERN-201 plasma PK in healthy subjects

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).

Illicitation of total amine oxidase was incomplete due to the presence of plasma amine oxidase activities 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.

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).

4. CONCLUSIONS

TERN-201 was overall safe and well-tolerated

• All AEs were considered mild (Day 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.

Figure 5: Sustained inhibition of total amine oxidase activity

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

5. REFERENCES

6. CONTACTS

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