**Pharmacokinetics, Tissue Distribution and Pharmacodynamics of TERN-101, A Novel Farnesoid X Receptor (FXR) Agonist, in Preclinical Species**

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**INTRODUCTION**

- The Farnesoid X Receptor (FXR) is a nuclear receptor that controls the conversion of cholesterol into bile acids and maintains homeostasis of multiple metabolic pathways.1,2
- FXR is an important clinical target for non-alcoholic steatohepatitis (NASH), validated by the positive Phase 3 results of obeticholic acid (OCA), a steroidal FXR agonist that activates FXR through binding of bile acid receptors.
- TERN-101, a non-steroidal, liver-expressed FXR agonist currently in Phase 1 clinical trials, was assessed in preclinical species for its pharmacokinetics (PK), tissue distribution, and pharmacodynamics (PD).

**METHODS**

**In vitro**

- The rate of hepatic metabolism of TERN-101 (1 µM) was assessed in cryopreserved mouse, rat, dog, monkey, and human hepatocytes (0.5x10⁶ cells/mL) at 1 µM in vitro, half-life values were determined and then scaled to predict hepatic clearance using the well-stirred liver model with no correction for protein binding.
- In vitro uptake test systems for transporters OATPs (1B1 and 1B3) used a polarized monolayer of MDCK-II cells grown on permeable support. The MDCK-II cells were treated to express the transporter of interest in a cost vector.
- TERN-101 was tested at 1 µM, 3 µM (with and without 100 µM rifampin), and 10 µM.

**In vivo**

- **TERN-101 PK in Sprague Dawley (SD) rats, beagle dogs, and cynomolgus monkeys were determined following intravenous (IV) bolus and oral administrations of TERN-101. Serial blood samples (0-24h) were collected for plasma PK.**
- **TERN-101, clofibrate, and trofisetin tissue distribution in SD rats (n=3 rats/group) was determined following a 30-minute IV infusion at 2 mg/kg for each compound. Blood, liver, kidney, and lung tissue samples were collected at 2h post dose to determine tissue/plasma ratios.**
- **11C-TERN-101 tissue distribution (PET) was determined in pigmented Long-Evans rats following an oral dose of TERN-101 at 5 mg/kg [11C]-labeled TERN-101. Tissue samples were collected at 1h and 2h.**
- **TERN-101 PK/PD profiles were determined in cynomolgus monkeys via oral administration of TERN-101 suspension at 0 (vehicle, 0.1), 1, and 5 mg/kg, and tissue samples were collected at 2h post dose to determine tissue/plasma ratios.**
- **11C-TERN-101 tissue distribution was determined in pigmented Long-Evans rats following an oral dose of TERN-101 at 5 mg/kg [11C]-labeled TERN-101. Tissue samples were collected at 1h and 2h.**
- **For mouse PK/PD experiments, C57BL/6 mice (ncoh) were given a single oral dose of vehicle, TERN-101 120 mg/kg, or OCA 50 mg/kg. Tissue RNA was collected at 2h post-dose and analyzed by RT-qPCR and RNAseq. For RT- qPCR, gene-specific primers were used to quantitate FXR-regulated gene expression in liver and ileum using the 2-ΔΔCT method. For RNAseq analysis, mRNA was extracted from total liver and sequenced using standard Illumina library preparation and sequencing protocols. Differentially expressed genes were determined using RSEM and edgeR software packages and analyzed using Adavita Bio’s PathwayGuide software.**

**RESULTS**

**In Vivo DMPK**

TERN-101 in Vivo Metabolic Stability in Hepatocytes

<table>
<thead>
<tr>
<th>Compound</th>
<th>% Metabolized</th>
<th>Hepatic Extraction (%)</th>
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<tbody>
<tr>
<td>Mouse</td>
<td>64.0 ± 0.5</td>
<td>37.0 ± 0.3</td>
</tr>
<tr>
<td>Sprague-Dawley Rat</td>
<td>131 ± 6.31</td>
<td>157 ± 0.03</td>
</tr>
<tr>
<td>Beagle Dog</td>
<td>180.5 ± 0.05</td>
<td>73.0 ± 0.06</td>
</tr>
<tr>
<td>Cynomolgus Monkey</td>
<td>63.4 ± 0.78</td>
<td>168 ± 0.01</td>
</tr>
</tbody>
</table>

- *11C-TERN-101 uptake was measured in liver and ileum using the 2-ΔΔCT method.*
- *Untreated and OCA (30 mg/kg) treated small intestine, and cecum.*
- *In vivo uptake test systems for transporters OATPs (1B1 and 1B3) used a polarized monolayer of MDCK-II cells grown on permeable support. The MDCK-II cells were treated to express the transporter of interest in a cost vector.*
- *In-vitro predicted hepatic clearance was not corrected for protein binding.*
- *TERN-101 was moderately metabolized in hepatocytes of all species tested.*

**TERN-101 Tissue Distribution**

TERN-101 Preferentially Distributions to Liver in Sprague Dawley Rats

- **A. Liver to plasma distribution of TERN-101 compared to steroidal (OCA) and non-steroidal (clofibrate and trofisetin) FXR agonists.**
- **Relative increase in liver to plasma distribution of TERN-101 in kidney, lung, and liver. TERN-101 concentration is approximately 20-fold higher in liver than in other organs.**

**TERN-101 Tissue Distribution and Metabolites in Long-Evans Rats**

- **The tissues with the highest radioactivity concentrations were the liver, small intestine, and cecum.**

**TERN-101 Liver Gene Expression and Pathway Analysis**

- **Differentially expressed genes relative to vehicle treated mice (fold-change 23.5, p-value <0.05).**
- **Average expression (CPM values) of FXR-related genes in vehicle, OCA (130 mg/kg), and TERN-101 (10 mg/kg) treated mice (n=per group).**
- **Global pathways significantly enriched in OCA and TERN-101 treatment groups ranked by statistical significance.**

**CONCLUSIONS**

- **TERN-101 preferentially distributed to the liver and exhibited high liver/plasma ratio in rodent species, approximately 5 to 20-fold higher than other investigational FXR agonists being studied for the treatment of NASH.**
- **The preferential liver distribution of TERN-101 is supported by preclinical PK/PD studies in mice; sustained suppression of 7-α-C4 observed in cynomolgus monkeys after repeat dosing suggests robust target engagement.**
- **RNAseq analysis of livers from mice treated with TERN-101 showed a robust modulation of FXR-related genes and metabolic pathways relevant to non-alcoholic fatty liver disease compared to OCA treatment.**
- **TERN-101 exhibited low in vivo metabolism, moderate volume of distribution, and oral bioavailability in the preclinical species tested. Bilirubin excretion was identified as the major elimination pathway for TERN-101.**
- **Taken together, the PK/PD profile of TERN-101 in preclinical species supports advancement into clinical trials and suggests TERN-101 has differentiated tissue distribution, and PD effects compared to other FXR agonists being studied for the treatment of NASH.**

**DISCLOSURE / CONTACT**

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**REFERENCES**

- Employees/shareholders in Terns Pharmaceuticals, Inc.

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