A novel farnesoid X receptor agonist, TERN-101, reduces liver steatosis, inflammation, ballooning and fibrosis in a murine model of non-alcoholic steatohepatitis

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INTRODUCTION

The Farnesoid X Receptor (FXR) is a nuclear hormone receptor that controls the conversion of cholesteryl into bile acids and maintains homeostasis of multiple metabolic pathways including lipid metabolism and glucose homeostasis. Activation of the FXR pathway using synthetic FXR agonists may help control metabolic disorders such as non-alcoholic steatohepatitis (NASH). Intercept Pharmaceuticals reported top line Phase clinical results of obeticholic acid (OCA) with OCA showing superiority in the proportion of F2F3 participants with at least 1 stage of fibrosis improvement without worsening of NASH.

TERN-101, a novel non-steroidal agonist of FXR, has entered early stage clinical trials.

AIM

To evaluate the efficacy and mechanism of action of TERN-101 in a mouse model of NASH

METHOD

• EC₅₀ values for FXR agonists were determined by a fluorescence-based FXR coactivator assay. Half-log serial dilutions of TERN-101 or OCA (10µM-3M) were incubated with human FXR ligand binding domain produced in E. coli insect cells, labeled coactivator SRC-1 peptide and buffer for 1h at 29°C. TLR4 activity was measured as a cell-based cAMP assay. Half-log serial dilutions of TERN-101 or OCA (10µM-3M) were added to Chinese Hamster Ovary cells expressing recombinant human TLR4. After 30min at RT, cAMP was measured using an HTTR readout.

• EC₅₀ values for FXR-activated gene expression were determined using a cell-based RNA assay. Half-log serial dilutions of TERN-101 or OCA (3µM-3M) were added to human Hepa7 hepatoma cells. After 1hr at 37°C, RNA was isolated and analyzed by RT-qPCR using primers to small heterodimer partner (SHP), bile salt export pump (BSEP) and fibroblast growth factor 19 (FGF-19).

• Male C57BL/6J mice were fed a high fat diet (D12492, Research Diet, fat/protein/carbohydrate 60/20/20 Kcal%, 10% to induce obesity (>35g mice) prior to daily oral TERN-101 and biasely intra-peritoneal carbon tetrachloride (CCL₄) treatment for 4 weeks.

RESULTS

Table 1. TERN-101 is a potent and selective FXR agonist

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<thead>
<tr>
<th>TERN-101 (nM)</th>
<th>OCA (nM)</th>
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<tbody>
<tr>
<td>0.1</td>
<td>770</td>
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<tr>
<td>1</td>
<td>71</td>
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<tr>
<td>10</td>
<td>50</td>
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<td>100</td>
<td>200</td>
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Figure 1. TERN-101 reduces NAFLD Activity Score (NAS) and 7α-Hydroxy-4-cholesterol levels in HFD/CCL₄ NASH mice

Figure 2. TERN-101 reduces serum biomarkers of liver damage, triglycerides and cholesterol and liver inflammation and ballooning in HFD/CCL₄ NASH mice

Figure 3. TERN-101 reduces liver steatosis and triglycerides in HFD/CCL₄ NASH mice

Figure 4. TERN-101 reduces liver fibrosis in HFD/CCL₄ NASH mice

Figure 5. TERN-101 regulates liver gene expression in HFD/CCL₄ NASH mice including FXR-target, inflammatory and fibrosis genes

DISCUSSIONS/CONTACT

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