Liver-distributed FXR Agonist TERN-101 Demonstrates Favorable Safety and Efficacy Profile in NASH Phase 2a LIFT Study

Presented by Rohit Loomba, MD
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Rohit Loomba, MD

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Background

• FXR is a nuclear hormone receptor that is highly expressed in the liver and small intestine

• TERN-101 is a potent, non-steroidal FXR agonist with enhanced liver distribution, being developed for the treatment of NASH

• TERN-101 induced significant reductions in steatosis, inflammation, and fibrosis in a NASH rodent model and induced robust FXR agonism in the liver\(^1,2\)

• We aimed to assess safety and efficacy of several dose levels of TERN-101 versus placebo in patients with NASH

TERN-101 LIFT Study: Phase 2a Study in NASH Patients

Key inclusion criteria:
Adults 18-75 years
BMI ≥ 25 kg/m²
MRI-PDFF ≥ 10%
ALT ≥ 28 IU/L (women) or ≥ 43 IU/L (men)

NASH based on clinical characteristics:
TE 7.6-21 kPa
CAP > 300 dB/m
Or prior biopsy (n= 23):
F1-3 in last 2 years

Alanine aminotransferase (ALT), body mass index (BMI), corrected T1 (cT1), magnetic resonance imaging (MRI), once daily (QD), proton density fat fraction (PDFF), transient elastography (TE); NCT04328077

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Endpoints

Primary:
• Overall safety including treatment-emergent adverse events and laboratory abnormalities

Secondary:
• Percent change from baseline in ALT at Week 12

Exploratory:
• Changes in other liver enzymes
• MRI-PDFF and cT1 change
• Proportion of patients achieving $\geq 30\%$ relative decline in MRI-PDFF
• Proportion of patients achieving $\geq 80$ msec decline in cT1
Disposition

Patients Randomized and Treated
N=100

Placebo
N=26
n=26
Completed study treatment

5 mg
N=25
n=24
Completed study treatment
n=1
Lost to follow-up

10 mg
N=26
n=25
Completed study treatment
n=1
Withdrawal by patient

15 mg
N=23
n=21
Completed study treatment
n=2
Withdrawal by patient

• Overall, 96% of patients completed the treatment period
• No patient discontinued due to an adverse event
# Patient Demographics

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=26)</th>
<th>5 mg (N=25)</th>
<th>10 mg (N=26)</th>
<th>15 mg (N=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD) [years]</td>
<td>50.4 (11.0)</td>
<td>48.0 (12.3)</td>
<td>52.5 (13.6)</td>
<td>51.6 (9.5)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>16 (61.5%)</td>
<td>15 (60.0%)</td>
<td>17 (65.4%)</td>
<td>17 (73.9%)</td>
</tr>
<tr>
<td>Race and Ethnicity, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>21 (80.8%)</td>
<td>23 (92.0%)</td>
<td>21 (80.8%)</td>
<td>21 (91.3%)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>2 (7.7%)</td>
<td>1 (4.0%)</td>
<td>2 (7.7%)</td>
<td>0</td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>20 (76.9%)</td>
<td>17 (68.0%)</td>
<td>16 (61.5%)</td>
<td>17 (73.9%)</td>
</tr>
<tr>
<td>BMI, mean (SD) [kg/m²]</td>
<td>36.5 (5.43)</td>
<td>37.2 (6.44)</td>
<td>36.3 (6.63)</td>
<td>36.2 (4.74)</td>
</tr>
<tr>
<td>Baseline statin use*, n (%)</td>
<td>7 (26.9%)</td>
<td>8 (32.0%)</td>
<td>10 (38.5%)</td>
<td>7 (30.4%)</td>
</tr>
<tr>
<td>History of diabetes, n (%)</td>
<td>11 (42.3%)</td>
<td>11 (44.0%)</td>
<td>16 (61.5%)</td>
<td>8 (34.8%)</td>
</tr>
</tbody>
</table>

* Per protocol, initiation of statins within 3 months of randomization or dose adjustment expected during study participation is exclusionary.
## Key Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=26)</th>
<th>5 mg (N=25)</th>
<th>10 mg (N=26)</th>
<th>15 mg (N=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ALT, mean (SD) [IU/L]</strong></td>
<td>55.5 (23.6)</td>
<td>56.3 (16.3)</td>
<td>60.8 (29.1)</td>
<td>55.8 (26.5)</td>
</tr>
<tr>
<td>ALT &gt; 60 IU/L, n (%)</td>
<td>7 (26.9%)</td>
<td>8 (32.0%)</td>
<td>11 (42.3%)</td>
<td>6 (26.1%)</td>
</tr>
<tr>
<td><strong>AST, mean (SD) [IU/L]</strong></td>
<td>39.5 (18.3)</td>
<td>41.5 (16.2)</td>
<td>45.8 (23.0)</td>
<td>39.3 (17.6)</td>
</tr>
<tr>
<td><strong>LDL cholesterol, mean (SD) [mg/dL]</strong></td>
<td>103.4 (30.4)</td>
<td>105.4 (25.2)</td>
<td>99.2 (33.7)</td>
<td>105.8 (26.6)</td>
</tr>
<tr>
<td><strong>Hgb A1c, mean (SD) [%]</strong></td>
<td>6.3 (1.2)</td>
<td>6.2 (0.9)</td>
<td>6.5 (0.9)</td>
<td>6.1 (1.0)</td>
</tr>
<tr>
<td><strong>CAP by TE, mean (SD) [dB/m]</strong></td>
<td>350.1 (34.0)</td>
<td>356.8 (27.9)</td>
<td>345.1 (29.9)</td>
<td>353.3 (27.8)</td>
</tr>
<tr>
<td><strong>Stiffness by TE, mean (SD) [kPa]</strong></td>
<td>10.4 (2.6)</td>
<td>12.0 (3.6)</td>
<td>9.6 (1.7)</td>
<td>9.8 (2.4)</td>
</tr>
<tr>
<td><strong>MRI-PDFF, mean (SD) [%]</strong></td>
<td>21.43 (7.6)</td>
<td>21.08 (8.2)</td>
<td>20.05 (7.1)</td>
<td>22.78 (8.4)</td>
</tr>
<tr>
<td><strong>cT1, mean (SD) [msec]</strong></td>
<td>908.9 (90.9)</td>
<td>925.4 (75.2)</td>
<td>942.0 (143.5)</td>
<td>974.7 (175.3)</td>
</tr>
</tbody>
</table>

Transient elastography (TE) conducted in placebo N=20, 5 mg N=16, 10 mg N=22, 15 mg N=20
cT1 conducted at sites with this capability, with baseline cT1 values in placebo N=22, 5 mg N=24, 10 mg N=20, 15 mg N=18
Controlled attenuation parameter (CAP); Hemoglobin A1c (Hgb A1c), Transient Elastography (TE), Magnetic resonance imaging proton density fat fraction (MRI-PDFF), Corrected T1 (cT1)
Adverse Event (AE) Summary

- All AEs were mild or moderate except for 2 unrelated Grade 3 events (also considered SAEs)
  - 1 SAE of COVID-19 (placebo) and 1 SAE of UTI requiring hospitalization (TERN-101 15 mg)
- No deaths occurred
- No patient discontinued due to an AE

<table>
<thead>
<tr>
<th>Patient incidence AEs by category, n (%)</th>
<th>Placebo (N=26)</th>
<th>5 mg (N=25)</th>
<th>10 mg (N=26)</th>
<th>15 mg (N=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE, all CTCAE grades</td>
<td>10 (38.5%)</td>
<td>13 (52.0%)</td>
<td>14 (53.8%)</td>
<td>15 (65.2%)</td>
</tr>
<tr>
<td>CTCAE Grade 3 or higher AEs</td>
<td>1 (3.8%)</td>
<td>0</td>
<td>0</td>
<td>1 (4.3%)</td>
</tr>
<tr>
<td>Serious AE</td>
<td>1 (3.8%)</td>
<td>0</td>
<td>0</td>
<td>1 (4.3%)</td>
</tr>
<tr>
<td>AE leading to death</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>AE leading to study or drug discontinuation</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

CTCAE = Common Terminology Criteria for Adverse Events, AE = adverse event, UTI = urinary tract infection; AEs reported refer to treatment-emergent AEs, defined as any AE with a start date on or after the date of first administration of study drug through 30 days after the last administration of study drug or through the Follow-Up Period (Week 16)
## Pruritus AE Summary

- All pruritus-related AEs* were mild or moderate
- Patient incidence of pruritus was generally balanced across TERN-101 treatment groups
- No patient discontinued study drug due to pruritus
- Most pruritus AEs were mild, self-limited and resolved without treatment interruption

<table>
<thead>
<tr>
<th>Patient incidence of any pruritus AE, n (%)</th>
<th>Placebo (N=26)</th>
<th>5 mg (N=25)</th>
<th>10 mg (N=26)</th>
<th>15 mg (N=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritus, all CTCAE grades*</td>
<td>0</td>
<td>4 (16.0%)</td>
<td>3 (11.5%)</td>
<td>4 (17.4%)</td>
</tr>
<tr>
<td>Grade 1</td>
<td>0</td>
<td>4 (16.0%)</td>
<td>1 (3.8%)</td>
<td>3 (13.0%)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>0</td>
<td>0</td>
<td>2 (7.7%)</td>
<td>1 (4.3%)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Study drug-related pruritus AEs, per Investigator</td>
<td>0</td>
<td>3 (12.0%)</td>
<td>3 (11.5%)</td>
<td>1 (4.3%)</td>
</tr>
<tr>
<td>Study drug discontinuation due to pruritus</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*All preferred terms reflecting pruritis including an event of pruritic rash (5 mg group) were included which was a pre-specified analysis (MedDRA version 23.0)

Grade 1: Mild or localized; topical intervention indicated; Grade 2: Widespread and intermittent; skin changes from scratching; oral intervention indicated; limiting activities of daily living

CTCAE = common terminology criteria for adverse events

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Cholesterol Percent Change from Baseline

- No difference from placebo in LDL percent change in the TERN-101 5 mg and 10 mg groups
- HDL decreased initially in all TERN-101 groups versus placebo and returned to baseline in the 5 and 10 mg groups
- LDL increased and HDL decreased significantly in the TERN-101 15 mg group versus placebo at Week 12

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**Percent change from baseline in LDL Cholesterol through Week 12**

**Percent change from baseline in HDL Cholesterol through Week 12**

- p-value: *< 0.05, **< 0.01

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**ALT Percent Change from Baseline and Responder Analysis**

- Significant ALT percent decreases in the TERN-101 10 mg and 15 mg groups compared to placebo as early as Week 2
- Numerically more patients with $\geq 17$ IU/L decline from baseline in TERN-101 10 mg and 15 mg groups than placebo and TERN-101 5 mg

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- **Mean percent change (SE), %**
  - Placebo
  - 5 mg
  - 10 mg
  - 15 mg
- **Percent of patients (95% CI)**
  - Placebo: 16.0%
  - 5 mg: 16.7%
  - 10 mg: 28.0%
  - 15 mg: 38.1%

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- **Percent change from baseline in ALT through Week 12**
- **Percent of patients with a decrease in ALT of $\geq 17$ IU/L from Baseline to Week 12**

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*p-value: *$< 0.05$, **$< 0.01$*

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GGT Percent Change from Baseline

- Statistically significant GGT declines occurred in all TERN-101 groups vs placebo at all timepoints
- Magnitude of GGT decreases similar in TERN-101 10 mg and 15 mg groups

* p-value < 0.05; ** p-value < 0.01; *** p-value < 0.001; **** p-value < 0.0001
• MRI-PDFF was significantly decreased at Week 6 for TERN-101 10 mg and 15 mg vs placebo

• Percent of patients with a relative decrease of ≥ 30% in MRI-PDFF was 12.0%, 21.7%, 20.0% and 15.0% for placebo, TERN-101 5, 10, and 15 mg, respectively, at Week 12
cT1 Change from Baseline

- cT1 declined significantly as early as Week 6 in all TERN-101 groups
- Significant mean cT1 declines persisted at Week 12 in all TERN-101 groups compared to placebo

Corrected T1 (cT1) was conducted only at available sites.

Mean change (SE), msec

<table>
<thead>
<tr>
<th>Weeks</th>
<th>Placebo, n=22</th>
<th>5 mg, n=24</th>
<th>10 mg, n=20</th>
<th>15 mg, n=18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>22</td>
<td>23</td>
<td>19</td>
<td>15</td>
</tr>
<tr>
<td>6</td>
<td>21</td>
<td>22</td>
<td>19</td>
<td>16</td>
</tr>
<tr>
<td>12</td>
<td>21</td>
<td>22</td>
<td>19</td>
<td>16</td>
</tr>
</tbody>
</table>

*p-value < 0.05; **p-value < 0.01; ***p-value < 0.001; ****p-value < 0.0001
cT1 Change from Baseline to Week 12: Individual Patient Responses

- cT1 values decreased for majority of TERN-101 patients
- Significantly greater proportion of patients with decrease of ≥ 80 msec in the TERN 101 5 mg and 10 mg groups compared to placebo

*p-value < 0.05; corrected T1 (cT1)
Conclusions

- TERN-101 is a highly liver-distributed FXR agonist that was overall safe and well-tolerated at all doses studied in patients with biopsy-diagnosed or presumed NASH
  - No discontinuations due to AEs or treatment-related SAEs
  - No differences from placebo in LDL and HDL percent change from baseline to Week 12 in the TERN-101 5 mg and 10 mg groups

- TERN-101 10 mg and 15 mg showed a numerical reduction in ALT and MRI-PDFF, and a significant reduction in GGT

- Significant decreases in cT1 as early as Week 6 and through Week 12 suggest that TERN-101 decreases fibro-inflammation (additional cT1 results presented in Abstract #1875)

- Further clinical studies of TERN-101 for the treatment of NASH, either alone or in combination with other agents, are warranted
  - A clinical trial of TERN-101 co-administered with the thyroid hormone receptor beta agonist TERN-501 (Abstract #1889) is planned to initiate in the first half of 2022
Acknowledgements

Thank you to all the participants, site staff and investigators for their continued dedication to the study and contributions to NASH research efforts during the COVID-19 pandemic
Thank you!

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