Multiple Doses of Thyroid Hormone Receptor-Beta Agonist TERN-501 were Well-Tolerated and Resulted in Significant Dose-Dependent Changes in Serum Lipids and Sex Hormone Binding Globulin in a First-in-Human Clinical Study

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Conflict of Interest

This study was funded by Terns Pharmaceuticals.

All authors are employees, consultants, and/or shareholders of Terns Pharmaceuticals.
Introduction

- THR-β is major form of thyroid hormone receptor (THR) in liver\(^1\)
- THR-β agonism reduces LDL-c, Apo B, and TG\(^2\)
- SHBG = key marker of hepatic THR-β target engagement
- High SHBG response (≥ 75%) associated with liver fat reduction and liver histological improvement\(^2\)
- TERN-501 is a novel, metabolically stable, highly selective THR-β agonist
- In an FIH study, single doses of TERN-501 were well-tolerated with significant improvements in LDL-c, Apo B, and SHBG\(^3\)
- Here we describe the results from the multiple ascending dose cohorts of the TERN-501 FIH study

**THR-β regulates key aspects of energy metabolism (e.g., fatty acid & lipid synthesis, liver fat removal through fatty acid oxidation)**\(^1\)

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**Sex Hormone Binding Globulin**

\[ \uparrow \text{LDL Cholesterol} \]

**THR-α**

\[ \text{HEART} \]

\[ \text{AVOID} \]

**THR-β**

\[ \text{LIVER} \]

\[ \text{TARGET} \]

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Primary Objective

• Assess the overall safety and tolerability of multiple ascending doses of TERN-501 in healthy subjects with elevated LDL-c

Secondary Objectives

• Evaluate the PK and PD of TERN-501 in healthy subjects with elevated LDL-c following multiple ascending doses of TERN-501
The study population included healthy adults (18–65 years of age) with BMI of 18–35 kg/m² and fasting LDL-c level ≥ 100 mg/dL. Participants (n = 8 per cohort) were randomized 3:1 to receive TERN-501 (1, 3, 6, or 10 mg) or placebo QD for 14 days in 4 cohorts in a fasted state.

**Dose Cohorts**

- 1 mg TERN-501
- 3 mg TERN-501
- 6 mg TERN-501
- 10 mg TERN-501

**Study Design**

- **Day 1** (Randomization 3:1)
- **Day 2** (Admission)
- **Day 17** (Discharge)
- **Day 21-24** (f/u visit)
- **Day 14**

TERN-501 (n = 6) or Placebo (n = 2) once daily X 14 days

Confinement, Safety (throughout the study), PK (Day 1 and 14), PD (pre-dose on Days 1, 3, 5, 8, 11, and 13, and on Days 15, 17, and f/u)

BMI, body mass index; f/u, follow-up; LDL-c, low-density lipoprotein cholesterol; MAD, multiple ascending dose; PD, pharmacodynamics; PK, pharmacokinetics; QD, once daily.
All 24 subjects completed the study without study drug discontinuations. All adverse events (AEs) were mild in severity (Grade 1).

### Demographics and Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Placebo (n = 8)</th>
<th>1 mg (n = 6)</th>
<th>3 mg (n = 6)</th>
<th>6 mg (n = 6)</th>
<th>10 mg (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD) [years]</td>
<td>45.9 (12.3)</td>
<td>44.7 (16.4)</td>
<td>43.3 (12.9)</td>
<td>44.5 (14.9)</td>
<td>39.5 (9.1)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>7 (87.5%)</td>
<td>5 (83.3%)</td>
<td>5 (83.3%)</td>
<td>5 (83.3%)</td>
<td>5 (83.3%)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>5 (62.5%)</td>
<td>6 (100%)</td>
<td>3 (50.0%)</td>
<td>6 (100%)</td>
<td>2 (33.3%)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>2 (25.0%)</td>
<td>0</td>
<td>3 (50.0%)</td>
<td>0</td>
<td>2 (33.3%)</td>
</tr>
<tr>
<td>American Indian or Alaskan Native</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (33.3%)</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (12.5%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>4 (50.0%)</td>
<td>1 (16.7%)</td>
<td>0</td>
<td>1 (16.7%)</td>
<td>0</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>4 (50.0%)</td>
<td>5 (83.3%)</td>
<td>6 (100%)</td>
<td>5 (83.3%)</td>
<td>6 (100%)</td>
</tr>
<tr>
<td>BMI, mean (SD) [kg/m²]</td>
<td>28.6 (3.5)</td>
<td>28.1 (3.8)</td>
<td>27.1 (2.5)</td>
<td>26.3 (4.2)</td>
<td>27.0 (4.0)</td>
</tr>
<tr>
<td>LDL-c, mean (SD) [mg/dL]</td>
<td>149.1 (32.2)</td>
<td>121.5 (31.3)</td>
<td>131.8 (13.5)</td>
<td>120.0 (49.8)</td>
<td>126.7 (15.9)</td>
</tr>
<tr>
<td>TSH, mean (SD) [mlU/L]</td>
<td>2.0 (1.0)</td>
<td>1.8 (0.7)</td>
<td>1.9 (0.8)</td>
<td>2.0 (0.9)</td>
<td>1.2 (0.7)</td>
</tr>
<tr>
<td>SHBG, mean (SD) [nmol/L]</td>
<td>28.0 (6.8)</td>
<td>39.8 (17.9)</td>
<td>42.2 (11.0)</td>
<td>38.8 (15.1)</td>
<td>33.3 (19.1)</td>
</tr>
</tbody>
</table>

BMI, body mass index; LDL-c, low-density lipoprotein cholesterol; SHBG, sex hormone binding globulin; SD, standard deviation; TSH, thyroid stimulating hormone.
Treatment-emergent Adverse Events were Mild and Mostly Unrelated with No Significant Changes in Vital Signs

<table>
<thead>
<tr>
<th>Subject incidence AEs by category, n (%)</th>
<th>Placebo (n = 8)</th>
<th>1 mg (n = 6)</th>
<th>3 mg (n = 6)</th>
<th>6 mg (n = 6)</th>
<th>10 mg (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE, all CTCAE grades</td>
<td>1 (12.5%)</td>
<td>3 (50.0%)</td>
<td>1 (16.7%)</td>
<td>1 (16.7%)</td>
<td>2 (33.3%)</td>
</tr>
<tr>
<td>CTCAE Grade 1</td>
<td>1 (12.5%)</td>
<td>3 (50.0%)</td>
<td>1 (16.7%)</td>
<td>1 (16.7%)</td>
<td>2 (33.3%)</td>
</tr>
<tr>
<td>CTCAE Grade 2 or higher</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>AEs by relationship to drug</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not related</td>
<td>1 (12.5%)</td>
<td>2 (33.3%)</td>
<td>1 (16.7%)</td>
<td>0</td>
<td>2 (33.3%)</td>
</tr>
<tr>
<td>Unlikely related</td>
<td>0</td>
<td>1 (16.7%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Possibly related</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (16.7%)</td>
<td>0</td>
</tr>
<tr>
<td>Related</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

- Heart rate and blood pressure across the treatment groups remained overall stable and no clinically significant changes were observed
- No significant changes were seen in ECG parameters

* Dizziness was reported in one subject.

AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; ECG, electrocardiogram.
Liver biochemistry
• ALT, AST, ALP and total bilirubin values were overall similar across TERN-501 and placebo groups
• No subject receiving TERN-501 had ALT increase to ≥ 2x ULN
• No evidence of DILI

Thyroid hormone
• No symptoms of hyper / hypothyroidism
• Mean TSH and free T3 values were highly variable but generally similar across TERN-501 and placebo groups
• Dose-dependent declines of free T4 were observed among TERN-501 groups consistent with peripheral thyroid hormone modulation observed with other THR-β agonists

Other laboratory assessments (e.g., clinical chemistry, hematology) showed no apparent trends

ALP, alkaline phosphatase activity; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; GGT, gamma glutamyl transpeptidase; TSH, thyroid stimulating hormone; ULN, upper limit of normal.
TERN-501 Exhibited Dose-Proportional PK

TERN-501 Plasma Concentration-Time Profile, Day 14

- TERN-501 half-life (median 15 to 21 hours) supports once daily dosing

Figure: Data presented as mean (SD)
AUC$_{\text{tau}}$, area under the concentration-time curve from time 0 to end of the dosing period; hr, hour; PK, pharmacokinetics
Low Variability in TERN-501 PK

- Variability in PK was generally low (\%CV 16 to 44\% for AUC_{tau} and C_{max})

TERN-501 Plasma Exposure (AUC_{tau}), Day 14

- Efficacious exposure in NASH mouse model

Figure: Boxes represent interquartile range with median and whiskers represent min to max; dashed line represents efficacious exposure in mouse model of NASH

AUC_{tau}, area under the concentration-time curve from time 0 to end of the dosing period; hr, hour; PK, pharmacokinetics
Sex Hormone Binding Globulin (SHBG) Significantly Increased in a TERN-501 Dose-Dependent Manner

Mean percent change refer to LSM from ANCOVA model and SE; shaded area represents dosing period

ANOVA, analysis of covariance; f/u, follow-up; LSM, least squares mean; SE, standard error; SHBG, sex hormone binding globulin

p-value vs placebo: *<0.05; **<0.01
TERN-501 Significantly Decreased Low-density Lipoprotein Cholesterol (LDL-c) Over Time

LDL-c (Percent Change from Baseline)

Days

Percent change (%), SE

p-value vs placebo: *<0.05; **<0.01
Mean percent change refer to LSM from ANCOVA model and SE; shaded area represents dosing period
ANCOVA, analysis of covariance; f/u, follow-up; LDL-c, low-density lipoprotein cholesterol; LSM, least squares mean; SE, standard error
End of Treatment (Day 15) SHBG Increases and LDL-c Reductions were TERN-501 Dose-Dependent

TERN-501

- Placebo (n = 8)
- 1 mg (n = 6)
- 3 mg (n = 6)
- 6 mg (n = 6)
- 10 mg (n = 6)

**SHBG**

Percent change (%), SE

- Placebo: -5.8
- 1 mg: 17.4 (p<0.05)
- 3 mg: 57.4 (p<0.01)
- 6 mg: 135.5
- 10 mg: 165.0

**LDL-c**

Percent change (%), SE

- Placebo: -3.9
- 1 mg: -16.4
- 3 mg: -16.7
- 6 mg: -18.8
- 10 mg: -20.2

*p-value vs placebo: *<0.05; **<0.01

Mean percent change refer to LSM from ANCOVA model and SE

ANCOVA, analysis of covariance; Apo B, apolipoprotein B; LDL-c, low-density lipoprotein cholesterol; LSM, least squares mean; PD, pharmacodynamics; SE, standard error; SHBG, sex hormone binding globulin; TC, total cholesterol; TG, triglycerides
TERN-501 Dose-Dependent Decreases in Other Atherogenic Lipids at End of Treatment (Day 15)

- No significant changes in HDL cholesterol were observed on Day 15

**TERN-501**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>8</td>
</tr>
<tr>
<td>1 mg</td>
<td>6</td>
</tr>
<tr>
<td>3 mg</td>
<td>6</td>
</tr>
<tr>
<td>6 mg</td>
<td>6</td>
</tr>
<tr>
<td>10 mg</td>
<td>6</td>
</tr>
</tbody>
</table>

![Graph showing percent change in TC, Apo B, and TG](image)

- Percent change (%), SE
- TC: Total Cholesterol
- Apo B: Apolipoprotein B
- TG: Triglycerides

*p*-value vs placebo: *<0.05; **<0.01

Mean percent change refer to LSM from ANCOVA model and SE

ANCOVA, analysis of covariance; Apo B, apolipoprotein B; LDL-c, low-density lipoprotein cholesterol; LSM, least squares mean; PD, pharmacodynamics; SE, standard error; SHBG, sex hormone binding globulin; TC, total cholesterol; TG, triglycerides
Conclusions

- Once daily dosing of TERN-501 at 1, 3, 6, and 10 mg for 14 days was overall safe and well-tolerated with no clinical signs or symptoms of hypo/hyperthyroidism or THR-α agonism.

- TERN-501 exhibited dose-proportional PK with low variability and a half-life suitable for once daily dosing.

- TERN-501 increased SHBG, a key marker of hepatic THR-β engagement, in a dose-dependent manner.

- TERN-501 led to significant decreases in circulating atherogenic lipid levels including LDL-c, Apo B, total cholesterol, and triglycerides.

- Taken together, PD data indicate that administration of TERN-501 led to robust THR-β target engagement in the liver.

- Significant reductions in atherogenic lipids along with increases in SHBG and favorable PK and safety observed in this study support further investigation of TERN-501 for NASH treatment alone or in combination with other agents including FXR agonist TERN-101.

Apo B, apolipoprotein B; FXR, farnesoid X receptor; LDL-c, low-density lipoprotein cholesterol; NASH, nonalcoholic steatohepatitis; PD, pharmacodynamics; PK, pharmacokinetics; SHBG, sex hormone binding globulin; THR-α, thyroid hormone receptor-alpha; THR-β, thyroid hormone receptor-beta.

Phase 2a DUET Study Underway

Randomized, Double-Blind, Placebo-Controlled, Factorial Design, Phase 2a Study (N=~140)

Noncirrhotic NASH patients with fibrosis with MRI-PDFF ≥10% and BMI ≥25 kg/m²

Screening

Randomization

Week 0 / Day1

Placebo QD (n=20)

THR-β

FXR

THR-β + FXR

Week 6

12-week treatment period

Week 12

TERN-501 1 mg QD (n=20)

TERN-501 3 mg QD (n=20)

TERN-501 6 mg QD (n=20)

TERN-101 10 mg QD (n=20)

TERN-501 3 mg QD + TERN-101 10 mg QD (n=20)

TERN-501 6 mg QD + TERN-101 10 mg QD (n=20)

4-week follow-up period

MRI-PDFF and cT1 at Baseline, Week 6, and Week 12

clinicaltrials.gov ID: NCT05415722
• TERN-501 is an investigational drug being developed by Terns Pharmaceuticals, which provided funding for the study as well as the oral presentation preparation services.

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QR link to presentation:

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