Topline Results from a 12-Week Phase 2a Trial (DUET) Evaluating TERN-501, a Highly Selective Thyroid Hormone Receptor (THR) β Agonist, Either as Monotherapy or in Combination with TERN-101, a Nonsteroidal Farnesoid X Receptor (FXR) Agonist, Demonstrated Significant Reductions in MR-Based Liver Fat Content and Fibroinflammation in Patients with Presumed MASH

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- Scientific advisor or consultant for: 89bio, Altimmune, Boehringer Ingelheim, Cytodyn, EchoSens, GSK, Madrigal, Merck, NovoNordisk, Perspectum, Roche diagnostic, Siemens, Takeda, Terns

- Share options: ChronWell, CIMA, Rivus Pharma

- Grant/Research support: Akero, Allergan, Bristol Myers Squibb, Conatus, Corcept, Enanta, Galectin, Genfit, Gilead, GSK, Madrigal, Novartis, NovoNordisk, Shire, Takeda, Terns, Viking, Zydus
We would like to acknowledge and thank the patients and their families / caregivers, the investigators and their support staff who participated in this work
THR-β regulates key aspects of energy metabolism (e.g., fatty acid & lipid synthesis, liver fat removal through fatty acid oxidation)

- THR-β is the major form of thyroid hormone receptor in liver\(^1\)
  - THR-β agonism can lead to MASH resolution and fibrosis regression as demonstrated in a biopsy-based Phase 3 non-cirrhotic MASH study\(^2\)
- TERN-501 is a potent, highly selective THR-β agonist
  - In a Phase 1 study, once-daily dosing of TERN-501 was safe, well-tolerated, and showed robust target engagement\(^3,4\)
- We conducted the DUET Study, a 12-week clinical trial in presumed MASH, to evaluate TERN-501 as a monotherapy or in combination with TERN-101, a liver directed nonsteroidal FXR agonist

**Fig. 1.** Schematic diagram of TERN-501’s effect on liver metabolism.

DUET: 12-week Phase 2a Trial in Presumed MASH Patients

**Key Entry Criteria**
- Non-cirrhotic; presumed MASH
- BMI ≥25 kg/m²
- MRI-PDFF ≥10%
- MRI-cT1 ≥800 msec
- HbA1c ≤ 9.5%
- LDL <150 mg/dL; TG ≤ 500 mg/dL

**Randomized, double-blind, placebo-controlled trial (N=162)**

- Placebo (n=24)
- TERN-501 1mg QD (n=23)
- TERN-501 3mg QD (n=23)
- TERN-501 6mg QD (n=22)
- TERN-101 10mg QD (n=24)
- TERN-501 3mg QD + TERN-101 10mg QD (n=23)
- TERN-501 6mg QD + TERN-101 10mg QD (n=23)

**Baseline assessments**
- MRI-PDFF

**Follow-up**
- W6
- W12
- W16

**Once-daily dosing**

BMI, body mass index; cT1, corrected T1; HbA1c, hemoglobin A1c; MRI-PDFF, magnetic resonance imaging proton density fat fraction; QD, once-daily; TG, triglycerides; W, week
### DUET: 12-week Phase 2a Trial in Presumed MASH Patients

**Primary Endpoint**
- Relative change in MRI-PDFF of TERN-501 vs placebo

**Secondary Endpoints**
- Relative change in MRI-PDFF of '501+'101 vs placebo
- Changes in cT1 of TERN-501 vs placebo and of '501+'101 vs placebo
- Safety and tolerability

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### Endpoints At Week 12

**Primary Endpoint**
- Relative change in MRI-PDFF of TERN-501 vs placebo

**Secondary Endpoints**
- Relative change in MRI-PDFF of '501+'101 vs placebo
- Changes in cT1 of TERN-501 vs placebo and of '501+'101 vs placebo
- Safety and tolerability

---

**Randomized, double-blind, placebo-controlled trial (N=162)**

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<td><strong>FXR</strong></td>
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<tr>
<td><strong>THR-β + FXR</strong></td>
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</tbody>
</table>

**Endpoints At Week 12**
- Baseline assessments
- MRI-PDFF
cT1

**Follow-up**
- MRI-PDFF
cT1
- 0, 6, 12, 16 weeks
>90% Rate of Trial Completion With Similar Frequency of Study Withdrawal Among All Arms

Randomized and Dosed
N=162

Placebo n=24

TERN-501 1mg n=23

TERN-501 3mg n=23

TERN-501 6mg n=22

TERN-101 10mg n=24

TERN-501 3mg + TERN-101 10mg n=21

TERN-501 6mg + TERN-101 10mg n=23

Lost to follow-up (n=1)
Physician decision (n=1)
Withdrawal of consent (n=1)

Placebo n=21

TERN-501 1mg n=23

TERN-501 3mg n=23

TERN-501 6mg n=20

TERN-101 10mg n=22

TERN-501 3mg + TERN-101 10mg n=23

TERN-501 6mg + TERN-101 10mg n=21

Lost to follow-up (n=1)
Withdrawal of consent (n=1)

Physician decision (n=1)
Sponsor discretion (n=1)
Protocol deviation (n=1)
Withdrawal of consent (n=1)

Patients Completing Trial
N=149
## Baseline Characteristics: Balanced Across Arms

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=24)</th>
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<th>10mg (N=24)</th>
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</tr>
</thead>
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<tr>
<td><strong>Age, mean (SD) [years]</strong></td>
<td>52 (11)</td>
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<td>52 (12)</td>
<td>54 (12)</td>
<td>56 (13)</td>
<td>55 (8)</td>
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<tr>
<td><strong>Female</strong></td>
<td>63%</td>
<td>48%</td>
<td>57%</td>
<td>73%</td>
<td>50%</td>
<td>48%</td>
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</tr>
<tr>
<td><strong>Hispanic</strong></td>
<td>79%</td>
<td>74%</td>
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<td>68%</td>
<td>42%</td>
<td>48%</td>
<td>61%</td>
</tr>
<tr>
<td><strong>BMI, mean (SD) [kg/m(^2)]</strong></td>
<td>37 (7)</td>
<td>38 (8)</td>
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<tr>
<td><strong>Type 2 diabetes</strong></td>
<td>46%</td>
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</tr>
<tr>
<td><strong>GLP-1 agonists</strong></td>
<td>8%</td>
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<td>13%</td>
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<tr>
<td><strong>ALT, mean (SD) [IU/L]</strong></td>
<td>44 (19)</td>
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<td><strong>LDL cholesterol, mean (SD) [mg/dL]</strong></td>
<td>87 (29)</td>
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<td><strong>MRI-PDFF, mean (SD) [%]</strong></td>
<td>17 (5)</td>
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<tr>
<td><strong>cT1, mean (SD) [msec]</strong></td>
<td>937 (102)</td>
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ALT: alanine aminotransferase; AST: aspartate aminotransferase; GLP-1: glucagon-like peptide-1; SD: standard deviation
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Primary Endpoint: TERN-501 Showed Rapid, Dose Dependent, and Significant Reductions in MRI-PDFF

**Relative Change (%) in MRI-PDFF at Week 12 (Primary Endpoint)**

- Placebo: -4%
- TERN-501 1mg: -15%
- TERN-501 3mg: -27%
- TERN-501 6mg: -45%

**Relative Change in MRI-PDFF Over Time**

- Placebo
- TERN-501 1mg
- TERN-501 3mg
- TERN-501 6mg

-60 -40 -20 0 20 LS Mean change (%)

**p-value <0.01; ***p-value <0.001 for TERN-501 monotherapy vs. placebo**

Error bars represent standard error.

ANCOVA, analysis of covariance; LS Mean, least squares mean from ANCOVA model.
TERN-501 Demonstrated Robust Liver Fat Reduction with High Responder Rates by MRI-PDFF

- 64% of patients with ≥30% liver fat reduction and 23% patients normalized liver fat at Week 12 in the TERN-501 6mg group

Proportion (%) of Responders Achieving MRI-PDFF Response Criteria at Week 12

**p-value <0.05; ***p-value <0.001**

- **≥30% Reduction in MRI-PDFF**
- **≥50% Reduction in MRI-PDFF**
- **Normalization (<5%) of Liver Fat**

*Placebo 501 1 mg 501 3 mg 501 6 mg

Normalization of liver fat = MRI-PDFF <5%

n=number of responders; N=number of patients in analysis set
Secondary Endpoint: TERN-501 6 mg Led to Significant and Rapid Improvement in cT1, a Marker of Liver Fibro-Inflammation

- Significant reduction in cT1 suggests potential antifibrotic effect of TERN-501 and of THR-β class as shown in a Phase 3 trial

![Graph showing the change in cT1 over time for Placebo and different TERN-501 doses.](image-url)

**Change (msec) in cT1 Over Time**

- **Placebo**
- **TERN-501 1 mg**
- **TERN-501 3 mg**
- **TERN-501 6 mg**

**LS Mean change (msec)**

- **Baseline**
- **6 Weeks**
- **12 Weeks**

- **Error bars represent standard error**
- **Harrison S, et.al. Abstract GS-001. J Hep. 2023; 78 (Suppl. 1).**

***p-value <0.001 for TERN-501 monotherapy vs. placebo
TERN-501 Showed Robust, Dose Dependent Increases in SHBG

- SHBG is an important marker of THR-β agonism in the liver
- SHBG increase ≥120% has been associated with histological MASH improvement and liver fat reduction in Phase 3 THR-β agonist trials

* p-value <0.05; *** p-value <0.001 for TERN-501 monotherapy vs. placebo
SHBG, sex hormone binding globulin
TERN-501 Improved Atherogenic Lipids and ALT at Week 12

*All TERN-501 monotherapy doses achieved statistically significant reductions in ApoB*

Change (%) in Lipids at Week 12

ALT Change (IU/L) at Week 12

Patients With Baseline ALT ≥30 IU/L

Lower apolipoprotein B levels associated with reduced cardiovascular risk. (Sniderman et al JAMA Cardiology 2019;4(12):1287-1295)
Secondary Endpoints: TERN-501+TERN-101 Showed Significant Reduction in MRI-PDFF and cT1

• First study of a THR-β agonist combined with another mechanism of action for the treatment of MASH

**p-value <0.001; **p-value <0.01; *p-value <0.05 for TERN-501 monotherapy or combination therapy vs. placebo**
## Favorable Safety Profile with No Drug Related AEs Grade 3 or Higher

### Treatment Related Adverse Events (AEs)

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<th>6mg + 10mg (N=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall, Any Grade</strong></td>
<td>5 (21%)</td>
<td>1 (4%)</td>
<td>4 (17%)</td>
<td>4 (18%)</td>
<td>2 (8%)</td>
<td>6 (26%)</td>
<td>4 (17%)</td>
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<tr>
<td><strong>Grade 3 or Higher</strong></td>
<td>0</td>
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<tr>
<td><strong>Serious Adverse Event</strong></td>
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<tr>
<td><strong>Leading to Treatment Discontinuation</strong></td>
<td>1 (4%)</td>
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### Treatment Related AEs Occurring in >1 Patient in Any Arm

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<tr>
<td><strong>Pruritus</strong></td>
<td>2 (8%)</td>
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<td>2 (9%)</td>
<td>1 (4%)</td>
<td>4 (17%)</td>
<td>2 (9%)</td>
</tr>
<tr>
<td><strong>Diarrhea</strong></td>
<td>1 (4%)</td>
<td>1 (4%)</td>
<td>2 (9%)</td>
<td>1 (5%)</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
<td>0</td>
</tr>
</tbody>
</table>

- Treatment related nausea was not seen in more than 1 patient in any arm
- Adverse events in the combination arms were comparable to the TERN-501 monotherapy groups and placebo
No Cardiovascular Safety Signals Observed

- No drug-related cardiovascular adverse events were reported
- There were no differences from placebo in mean heart rates, QTc intervals, and blood pressure in any TERN-501 containing arms (monotherapy and combination [not shown])
  - No clinically significant ECG abnormalities were reported

The blue shaded area indicates treatment period

ECG, electrocardiogram; QTc, QT interval corrected using Fridericia’s formula
No Evidence of Central Thyroid Axis Modulation Observed

- Mean changes in thyroid axis hormones (TSH, free T3, and free T4) at Week 12 were similar to placebo and remained within normal limits in all TERN-501 containing arms (monotherapy and combination [not shown])
  - No difference from placebo in TSH and free T3 at any time point
  - Initial transient decreases in free T4 up to Week 6 in TERN-501 3 mg and 6 mg arms, as observed with other THR-β agonists; no difference from placebo at Week 12

*p-value <0.05; **p-value <0.01 for monotherapy vs. placebo
The blue shaded area indicates treatment period
T3, triiodothyronine; T4, thyroxine; TSH, thyroid stimulating hormone
No Significant Increase in Serum Bone Turnover Markers

- No apparent mean changes were observed during the dosing period in sCTX (a marker of bone resorption) or sPINP (a marker of bone formation) in any TERN-501 containing arm (monotherapy and combination [not shown])
Conclusions

• In this Phase 2a study in MASH population, 12 weeks of TERN-501 treatment demonstrated:
  – **Rapid, significant, and dose-dependent reductions** in both liver fat content (by MRI-PDFF) and fibroinflammation (by cT1), meeting all primary and secondary efficacy endpoints
  – **Robust hepatic target engagement** with significant, dose-dependent increases in SHBG and decreases in atherogenic lipids including ApoB
  – **A highly THR-β selective safety profile** with no apparent safety signals
    • Generally mild AEs evenly distributed across arms, including placebo
    • No dose related AEs or SAEs
    • No adverse cardiovascular or gastrointestinal effects
    • No clinically significant changes in thyroid axis hormones or serum bone markers

• When TERN-501 was combined with TERN-101, efficacy was generally maintained or modestly improved without additional safety findings, demonstrating **combinability of TERN-501**

• Collectively, these data warrant further investigation of TERN-501 as a monotherapy or in combination with other mechanisms of action for MASH