Poster No. SAT-208

SEX HORMONE BINDING GLOBULIN AS AN EFFECTIVE PREDICTOR OF TREATMENT RESPONSE TO TERN-501, A POTENT, HIGHLY SELECTIVE THYROID HORMONE RECEPTOR-B AGONIST: POST-HOC ANALYSES FROM A 12-WEEK PHASE 2a TRIAL

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DUET

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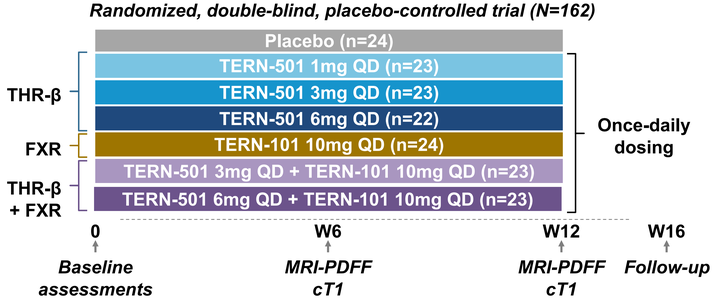
KEY TAKEHOME MESSAGE

- Response to TERN-501 for the treatment of MASH may be effectively monitored using sex hormone binding globulin (SHBG), a simple blood-based, target engagement marker for THR-β agonism
- Patients who achieve a high SHBG increase with TERN-501 treatment may not require MR-based imaging to demonstrate liver fat reduction

1 INTRODUCTION

- THR-β, the major form of thyroid hormone receptor in the liver, regulates key aspects of energy and lipid metabolism including liver fat removal via fatty acid oxidation.[1]
- TERN-501 is a potent, highly selective THR-β agonist.[2]
- In a 12-week, Phase 2a study, (DUET, Figure 1), in patients with clinically diagnosed or previous biopsy confirmed MASH, TERN-501 demonstrated significant, dose-dependent decreases in MRI-PDFF with high responder rates of achieving ≥30% reduction from baseline (Figure 2).[3,4]
  - MRI-PDFF reduction ≥30% has been linked to histologic improvement in MASH.[5]
- In DUET, SHBG, a protein produced in the liver in response to THR-β agonism, also significantly increased in a rapid, dose-dependent manner, demonstrating robust target engagement (Figure 2).[3,4]
  - Both TERN-501 3 mg and 6 mg treatment groups have demonstrated statistically significant MRI-PDFF reduction and SHBG increase from baseline vs. placebo.
- SHBG increase ≥120% has been associated with histologic improvement and MRI-PDFF reduction in Phase 3 THR-β agonist trials.[5,6]
- In this post-hoc analysis, we evaluated the potential clinical utility of SHBG, a simple blood-based marker, in monitoring TERN-501 efficacy as assessed by MRI-PDFF.

Figure 1: DUET Study Design (NCT05415722)



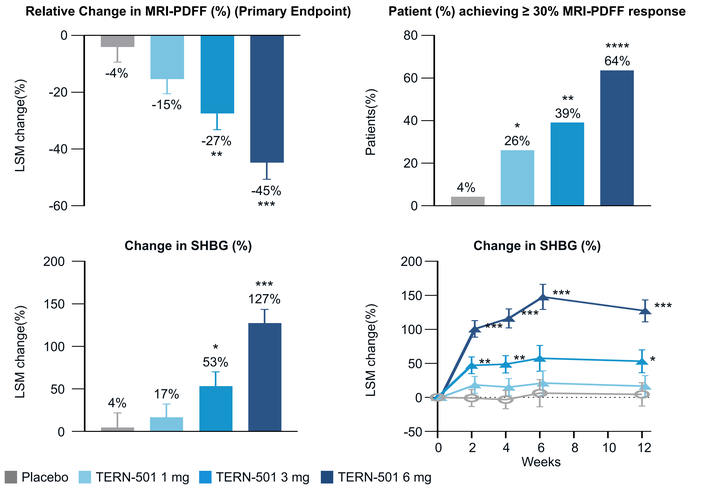
Endpoints At Week 12

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

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

Figure 2: Dose-Dependent, Significant Liver Fat Reduction and SHBG Increases Were Observed After 12-weeks of TERN-501 Treatment



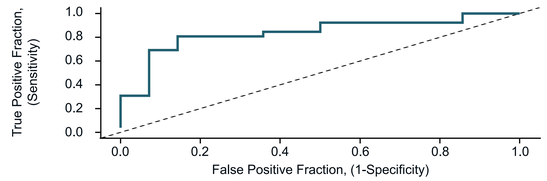
*p-value <0.05; **p-value <0.01; ***p-value <0.001 for TERN-501 vs placebo
Error bars represent standard error; ANCOVA, Analysis of covariance; LS Mean, least squares mean from ANCOVA model

2 METHODS

- Receiver operating characteristic (ROC) curve was built to identify an optimal TERN-501 induced SHBG increase threshold associated with ≥30% MRI-PDFF reduction at Week 12.
  - Pooled data at Week 12 from the TERN-501 3 mg and 6 mg groups were used since both 3 mg and 6 mg groups demonstrated statistically significant MRI-PDFF reduction and SHBG increase from baseline vs. placebo.
- "High" category was defined as the subgroup who achieved the SHBG increase threshold; "Low" category was defined as those who did not achieve the SHBG increase threshold.
- The percentage of responders with ≥30% MRI-PDFF reduction at Week 12 in "High" and "Low" subgroups was assessed using the following SHBG increase thresholds at Week 12:
  - The optimal SHBG increase threshold identified from the ROC curve.
  - A previously reported SHBG increase threshold of ≥120%.[5,6]
- Since rapid SHBG increases were observed from DUET (as early as Week 6; Figure 2), the percentage of responders with ≥30% MRI-PDFF reduction at Week 12 was also evaluated using the same SHBG increase thresholds at Week 6.

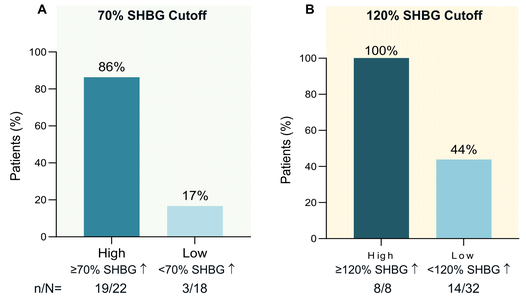
3 RESULTS

Figure 3: Receiver operating characteristic (ROC) curve



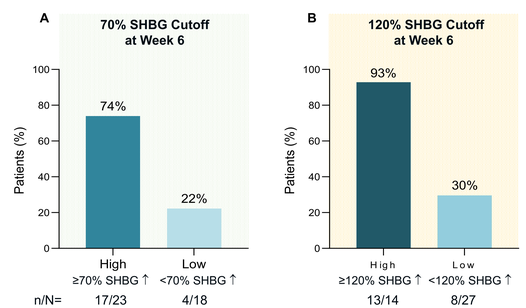
- SHBG increase of ≥70% was identified as an optimal threshold associated with ≥30% MRI-PDFF reduction at Week 12 (sensitivity=80.7%; specificity=85.7%; AUROC=0.84) (Figure 3).

Figure 4: Patients (%) Achieving ≥30% Relative Reduction in MRI-PDFF at Week 12 by SHBG Cutoff at Week 12



- Majority (86%) of the patients with ≥70% SHBG increase ("High") at Week 12 achieved ≥30% MRI-PDFF reduction at Week 12 compared to only 17% of patients with <70% SHBG increase ("Low") (Figure 4A).
- At a higher SHBG increase threshold of ≥120%, while all patients (100%) with ≥120% SHBG increase at Week 12 achieved ≥30% MRI-PDFF reduction at Week 12, 44% of patients with <120% SHBG increase still achieved ≥30% MRI-PDFF reduction at Week 12 (Figure 4B).

Figure 5: Patients (%) Achieving ≥30% Relative Reduction in MRI-PDFF at Week 12 by SHBG Cutoff at Week 6



- Of the patients with ≥70% SHBG increase at Week 6, 74% achieved ≥30% MRI-PDFF reduction at Week 12 (Figure 5A).
- A total of 93% of the patients with ≥120% SHBG increase at Week 6 achieved ≥30% MRI-PDFF reduction at Week 12 compared to 30% of patients with <120% SHBG increase at Week 6 (Figure 5B).

Results based on pooled data from the TERN-501 3 mg and 6 mg groups only
High is defined as ≥70% or ≥120% increase from baseline at Week 12 in SHBG; Low is defined as <70% or <120% increase from baseline at Week 12 in SHBG; n represents the number of patients who achieved ≥30% relative reduction in MRI-PDFF at Week 12; N represents the number of number of patients who achieved the defined SHBG response criteria ("High"/"Low")

4 CONCLUSIONS

- TERN-501 led to significant, dose-dependent increases in SHBG indicating potent liver THR-β target engagement and potential histologic improvement with TERN-501.
- Treatment response to TERN-501 in patients with MASH may be effectively monitored, potentially as early as Week 6 with SHBG, a simple blood-based marker that measures TERN-501 target engagement.
- Patients who achieve a high SHBG increase (e.g., ≥120% from baseline at Week 12) with TERN-501 may not require MR-based imaging to monitor response to TERN-501 treatment.

**Terns Pharmaceuticals would like to acknowledge the late Dr. Stephen Harrison, a pioneer in the development of therapeutics to treat patients with MASH, for his guidance and contribution to this work.*

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ABBREVIATIONS

ApoB, apolipoprotein B; BMI, body mass index; cT1, corrected T1; FXR, farnesoid X receptor; HbA1c, hemoglobin A1c; LDL, low density lipoprotein; LDL-c, low density lipoprotein cholesterol; Lp(a) lipoprotein (a); MASH, metabolic dysfunction-associated steatohepatitis; MRI-PDFF, magnetic resonance imaging-proton density fat fraction; QD, once-daily; SHBG, sex hormone binding globulin; TG triglycerides; W, week

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