Poster No. SAT-202

TERN-501, A HIGHLY SELECTIVE THYROID HORMONE RECEPTOR β AGONIST, SIGNIFICANTLY IMPROVED MRI-PDFF, cT1, AND LIVER VOLUME IN CLINICALLY RELEVANT PATIENT POPULATIONS WITH PRESUMED MASH: SUBGROUP ANALYSES FROM A 12 WEEK PHASE 2a TRIAL

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DUET

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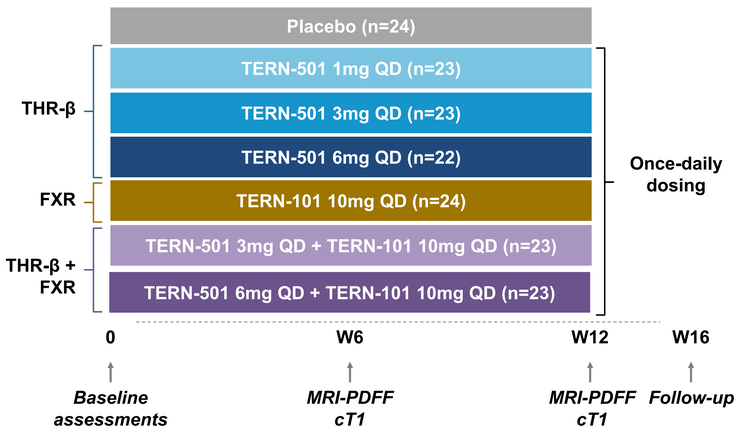
KEY TAKEHOME MESSAGE

In a Phase 2a study (DUET), TERN-501 significantly improved liver fat content, cT1 (a marker of fibroinflammation), and liver volume following 12 weeks of treatment in patients with presumed MASH including those with at-risk MASH, metabolic comorbid conditions, or risk factors associated with MASH.

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 MASH study, (DUET, Figure 1), TERN-501 was evaluated as monotherapy and in combination with TERN-101, a liver directed nonsteroidal FXR agonist, and demonstrated:[3,4]
  - Rapid, significant, and dose-dependent reductions in both MRI-PDFF and corrected T1 (cT1), meeting all primary and secondary efficacy endpoints.
  - Robust hepatic target engagement with significant, dose-dependent increases in sex hormone binding globulin (SHBG) and decreases in atherogenic lipids including ApoB.
  - A highly THR-β selective safety profile with no apparent safety signals.

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/m^2
- MRI-PDFF ≥10%
- MRI-cT1 ≥800 msec
- HbA1c ≤ 9.5%
- LDL <150 mg/dL; TG ≤ 500 mg/dL

- High risk MASH patients:
  - Having "at-risk" MASH (MASH with ≥F2) or metabolic comorbid conditions such as obesity, hypertension, dyslipidemia, type 2 diabetes has been linked to histological progression and adverse clinical outcomes.[5]
  - Hispanics have been shown to have the greatest risk/burden for MASH among different ethnicities.[6]
- Improvement in MRI-PDFF, cT1, or liver volume (LV) in patients with MASH has been associated with histologic improvement.[7,8,9]
- We evaluated efficacy of TERN-501 6mg, the highest dose tested in DUET, using the clinically relevant MR based assessments (PDFF, cT1, and LV) in key patient subgroups relevant to MASH.

2 METHODS

- This study was a 12-week, randomized, double-blind, placebo-controlled study in patients with clinically diagnosed or previous biopsy confirmed MASH.
- Changes in liver fat content measured by PDFF, fibro-inflammation measured by cT1, and LV were evaluated at 12 weeks using MRI in the following patient subgroups:
  - cT1 >875 msec at baseline ("at-risk" MASH)
  - Obesity (BMI ≥30 kg/m^2)
  - Hypertension
  - Dyslipidemia
  - Type 2 diabetes
  - Hispanic ethnicity

3 RESULTS

Table 1: Baseline MRI-PDFF, cT1, and Liver Volume in Key Subgroups (Efficacy Analysis Set)

	MRI-PDFF		MRI-cT1		MRI-LV	
	TERN-501 6mg N=22	Placebo N=24	TERN-501 6mg N=22	Placebo N=24	TERN-501 6mg N=21	Placebo N=23
Mean (SD)	17.3 (5.75)%	17.0 (5.17)%	920.0 (79.09) msec	937.3 (102.38) msec	2070.4 (346.0) m^3	2180.0 (549.81) m^3
Subgroups n (%) Mean (SD)						
Baseline cT1 >875msec	16 (72.7) 17.7 (6.38)%	17 (70.8) 17.5 (4.78)%	16 (72.7) 950.6 (69.76) msec	17 (70.8) 975.1 (98.36) msec	15 (71.4) 2069.5 (391.44) m^3	16 (69.6) 2215.2 (447.97) m^3
Obesity (BMI ≥30 kg/m^2)	20 (90.9) 17.7 (5.82)%	20 (83.3) 17.2 (5.10)%	20 (90.9) 922.9 (82.56) msec	20 (83.3) 948.0 (99.51) msec	19 (90.5) 2109.3 (320.51) m^3	19 (82.6) 2279.2 (551.08) m^3
Hypertension	13 (59.1) 15.8 (4.92)%	15 (62.5) 16.5 (5.63)%	13 (59.1) 919.1 (51.39) msec	15 (62.5) 911.93 (62.20) msec	13 (61.9) 2039.7 (394.62) m^3	14 (60.9) 2153.8 (580.66) m^3
Dyslipidemia	13 (59.1) 16.5 (5.05)%	14 (58.3) 17.2 (5.46)%	13 (59.1) 908.8 (65.42) msec	14 (58.3) 921.4 (61.73) msec	12 (57.1) 2021.2 (355.94) m^3	13 (56.5) 2284.92 (585.67) m^3
Type 2 diabetes	6 (27.3) 16.4 (4.64)%	11 (45.8) 17.5 (5.28)%	6 (27.3) 953.5 (56.55) msec	11 (45.8) 963.9 (125.09) msec	6 (28.6) 2063.1 (418.56) m^3	10 (43.5) 2219.7 (407.28) m^3
Hispanic or Latino	15 (68.2) 16.9 (6.47)%	19 (79.2) 16.7 (4.70)%	15 (68.2) 923.3 (89.06) msec	19 (79.2) 939.4 (108.44) msec	14 (66.7) 2112.6 (350.81) m^3	18 (78.3) 2015.4 (352.33) m^3

N=number of patients in the treatment or placebo arm within the analysis set; n=number of patients in each subgroup with available baseline data.

- The mean baseline MRI-PDFF, cT1, and liver volume values were generally similar between TERN-501 6mg patients and placebo patients in all key subgroups as well as the overall group (all patients in the TERN-501 6mg and placebo groups).
- Compared to other subgroups, the type 2 diabetes subgroup had the least number of patients.
  - Only 6 patients (27.3%) with type 2 diabetes were randomized in the TERN-501 6 mg group.

Figure 2: Relative Change (%) in MRI-PDFF from Baseline to Week 12 in Key Subgroups

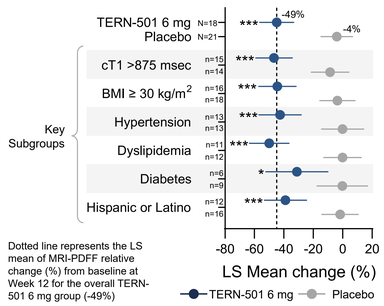


Figure 3: Change in MRI-cT1 (msec) from Baseline to Week 12 in Key Subgroups

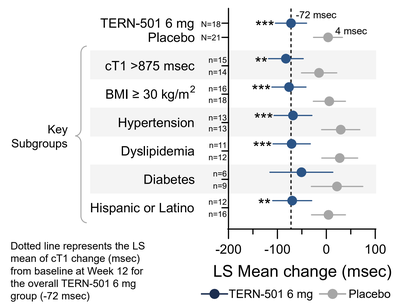
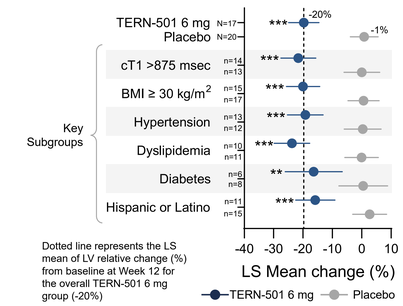


Figure 4: Relative Change (%) in MRI-Liver Volume from Baseline to Week 12 in Key Subgroups



*p-value <0.05; **p-value <0.01; ***p-value <0.001 for TERN-501 6mg vs placebo; Error bars represent standard error; LS Mean, least squares mean from ANCOVA model

- Significant reductions in liver fat content at Week 12, as assessed by relative change in MRI-PDFF from baseline, were observed in all the key patient subgroups as well as in the overall TERN-501 6 mg group vs. placebo, as previously reported (–49% vs. –4%, respectively, p<0.001).[3,4]
  - MRI-PDFF reduction ≥30% has been linked to histologic improvement in MASH.[10,11]
- As previously reported, significant reductions in MRI-cT1 at Week 12 were observed in the TERN-501 6mg vs. placebo (–72 msec vs. 4 msec, respectively, p<0.001)[3,4], suggesting improvement in fibroinflammation.
  - Significant reduction in cT1 suggests potential antifibrotic effect of TERN-501 and of THR-β class as shown in a Phase 3 trial.[11]
  - 88 msec reduction in cT1 has been associated with 2-point reduction in NAS.[8]
- The cT1 improvement was statistically significant vs. placebo in all key subgroups except in the type 2 diabetes subgroup.
  - The small sample size of diabetic patients (n=6 in TERN-501 6mg; n=9 Placebo) limited the analysis results despite the considerable reduction seen in TERN-501 6mg vs. placebo.
- Statistically significant reductions in liver volume were observed at Week 12 in the overall TERN-501 6 mg group (–20%; p<0.001) and all key subgroups vs. placebo.
  - Liver volume reduction ≥15% at Week 12 has been associated with histologic improvement at Week 36.[9]

4 CONCLUSIONS

- Overall, TERN-501 6mg, given once daily for 12 weeks consistently demonstrated significant improvement in MRI-PDFF, cT1, and liver volume compared to placebo in key patient subgroups including those with at-risk MASH, metabolic comorbid conditions, or risk factors associated with MASH.
- These results demonstrate TERN-501, a highly selective THR-β agonist, has the potential to be an effective MASH treatment across common patient subtypes associated with adverse outcomes in MASH including the presence of common metabolic comorbidities or a high degree of fibroinflammation.

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ABBREVIATIONS

ANCOVA, Analysis of covariance; 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); LS Mean, least squares mean from ANCOVA model ; LV, liver volume; MASH, metabolic dysfunction-associated steatohepatitis; MRI-PDFF, magnetic resonance imaging-proton density fat fraction; NAFLD, nonalcoholic fatty liver disease; NAS, NAFLD activity score; THR-β, thyroid hormone receptor β; QD, once-daily; TG, triglycerides; W, week

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