Poster No. SAT107

FAVORABLE LIPID AND PRURITUS PROFILE OF LIVER-DISTRIBUTED FARNESOID X RECEPTOR (FXR) AGONIST TERN-101 AT CLINICALLY EFFICACIOUS DOSES IN NONALCOHOLIC STEATOHEPATITIS (NASH) PHASE 2A LIFT STUDY

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SCAN ME!

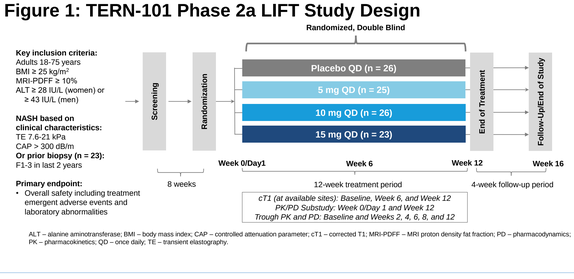
KEY TAKEHOME MESSAGE

- TERN-101 has a differentiated and favorable safety and tolerability profile overall at potentially efficacious dose levels for treatment of NASH.

1 • INTRODUCTION

- FXR agonists have previously demonstrated dose-related pruritus and unfavorable lipid effects in NASH patients.
- TERN-101 is a potent, non-steroidal FXR agonist with enhanced liver distribution, being developed for the treatment of NASH.
- In the Phase 2a LIFT study, TERN-101 5 mg, 10 mg, and 15 mg vs placebo administered for 12 weeks to NASH patients was overall safe and well-tolerated with significant reductions in corrected T1 (cT1) and decreases in alanine aminotransferase (ALT) and magnetic resonance imaging proton density fat fraction (MRI-PDFF).[1]

Figure 1: TERN-101 Phase 2a LIFT Study Design



ALT – alanine aminotransferase; BMI – body mass index; CAP – controlled attenuation parameter; cT1 – corrected T1; MRI-PDFF – MRI proton density fat fraction; PD – pharmacodynamics; PK – pharmacokinetics; QD – once daily; TE – transient elastography.

2 • OBJECTIVE

- To report details on lipids and pruritus from the LIFT study.

3 • METHODS

- LIFT was a randomized, double-blind, placebo-controlled Phase 2a study (NCT04328077) evaluating 5 mg, 10 mg, and 15 mg TERN-101 administered for 12 weeks in 100 adults with NASH (Figure 1).
- LDL and HDL were assessed at baseline and every 4 weeks.
  - Percent change from baseline in LDL and HDL over time was analyzed using an analysis of covariance (ANCOVA) model with percent change from baseline as the dependent variable including treatment group as a fixed effect and baseline as a covariate. Post-hoc analyses of degree of cholesterol change from baseline included:
    - LDL increase by threshold of ≥ 25 mg/dL at Week 12
    - HDL decrease by threshold of ≥ 10 mg/dL at Week 12
- Pruritus was graded per common terminology criteria for adverse events (CTCAE):
  - ***Grade 1:*** Mild or localized; topical intervention indicated.
  - ***Grade 2:*** Widespread and intermittent; skin changes from scratching (e.g., edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental activities of daily living (ADL).
  - ***Grade 3:*** Widespread and constant; limiting self-care, ADL, or sleep; systemic corticosteroid or immunosuppressive therapy indicated.

4 • RESULTS

Table 1: Patient Demographics and Baseline Characteristics

Patient Demographics and Baseline Characteristics	Placebo (n = 26)	TERN-101 5 mg (n = 25)	TERN-101 10 mg (n = 26)	TERN-101 15 mg (n = 23)
Age, mean (SD) [years]	50.4 (11.0)	48.0 (12.3)	52.5 (13.6)	51.6 (9.5)
Sex, n (%)				
Female	16 (61.5%)	15 (60.0%)	17 (65.4%)	17 (73.9%)
Race, n (%)				
White	21 (80.8%)	23 (92.0%)	21 (80.8%)	21 (91.3%)
Black or African American	2 (7.7%)	1 (4.0%)	2 (7.7%)	0
Asian	1 (3.8%)	1 (4.0%)	1 (3.8%)	0
Other	2 (7.7%)	0	2 (7.7%)	2 (8.7%)
Ethnicity, n (%)				
Hispanic or Latino	20 (76.9%)	17 (68.0%)	16 (61.5%)	17 (73.9%)
ALT, mean (SD) [IU/L]	55.5 (23.64)	56.2 (16.27)	60.8 (29.08)	55.8 (26.45)
AST, mean (SD) [IU/L]	39.5 (18.29)	41.5 (16.23)	45.8 (22.97)	39.3 (17.58)
GGT, mean (SD) [IU/L]	44.4 (21.09)	65.5 (43.91)	60.6 (36.16)	54.8 (57.85)
BMI, mean (SD) [kg/m²]	36.5 (5.43)	37.2 (6.44)	36.3 (6.63)	36.2 (4.74)
MRI-PDFF, mean (SD) [%]	21.43 (7.572)	21.08 (8.194)	20.05 (7.083)	22.78 (8.443)
cT1[a], mean (SD) [msec]	908.9 (90.85)	925.4 (75.16)	942.0 (143.51)	974.7 (175.26)
LDL, mean (SD) [mg/dL]	103.4 (30.4)	105.4 (25.2)	99.2 (33.7)	105.8 (26.6)
HDL, mean (SD) [mg/dL]	48.1 (8.6)	45.8 (10.2)	47.0 (9.7)	45.6 (9.8)
Any lipid lowering agent at baseline[b], n (%)	8 (30.8%)	9 (36.0%)	13 (50.0%)	10 (43.5%)
Statin use, n (%)	7 (26.9%)	8 (32.0%)	10 (38.5%)	7 (30.4%)

[a]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.
[b]Patients were required to be on a stable dose of lipid-lowering agents for at least 3 months prior to randomization; dose adjustment and lipid-lowering treatment initiation was allowed while study treatment was ongoing.
ALT – alanine aminotransferase; AST – aspartate aminotransferase; BMI – body mass index; cT1 – corrected T1; GGT – gamma-glutamyl transferase; HDL – high-density lipoprotein; LDL – low-density lipoprotein; MRI-PDFF – MRI proton density fat fraction; SD – standard deviation.

OVERALL SAFETY

- Overall AE incidences were generally similar across all treatment groups.
- There were no treatment discontinuations due to any AE, including pruritus, in any treatment group or treatment related serious AEs.
- Common treatment emergent AEs (TEAEs) other than pruritus were balanced across TERN-101 groups and placebo.

LIPID PROFILE

- No difference in LDL and HDL percent change from baseline was observed for 5 mg and 10 mg TERN-101 vs placebo at any timepoint.
- In the TERN-101 15 mg group, LDL (Figure 2A) and HDL changes (Figure 2B) were significantly different from placebo.
- Lipid-lowering therapy was not initiated or changed for any patients during the treatment period.
- LDL increases of ≥ 25 mg/dL as Week 12 were similar across TERN-101 treatment groups and placebo (Figure 2C).
- Less than 10% patients in TERN-101 5 mg or placebo had decreases from baseline in HDL of ≥ 10 mg/dL (Figure 2C).

PRURITUS

- Pruritus AEs were balanced across TERN-101 groups.
  - 14.9% overall across all dose groups (Table 3)
- Pruritus onset ranged from Day 2 to Day 73 and resolved with ongoing TERN-101 treatment for 8 of 11 patients.
- There were no Grade 3 pruritus events or study drug discontinuation due to pruritus in any treatment group.
- Grade 2 pruritus occurred in only three patients:
  - Two patients in the TERN-101 10 mg group (generalized pruritus)
  - One patient in the TERN-101 15 mg group (pruritus localized to bilateral forearms)

5 • CONCLUSIONS

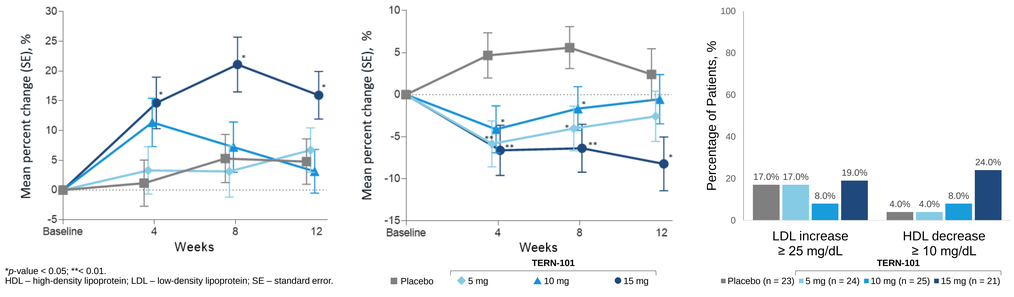
- TERN-101 was generally well-tolerated with minimal pruritus and no difference from placebo in LDL or HDL change from baseline in the 5 mg and 10 mg dose groups.
- TERN-101 doses lower than 15 mg did not result in a clinically meaningful or sustained change from baseline in LDL or HDL through 12 weeks of treatment.
  - LDL and HDL mean changes, and proportion of patients with lipid changes by specified thresholds, were similar for 5 and 10 mg TERN-101 and placebo at Week 12.
- Pruritus reported with TERN-101 was generally mild and transient.
- Pruritus AEs were not TERN-101 dose-dependent and did not lead to treatment discontinuation.
- No widespread and constant pruritus (Grade 3) occurred with TERN-101
- TERN-101 has a favorable, differentiated safety and tolerability profile at potentially efficacious dose levels.

Table 2: Most Common TEAEs by Preferred Term

Patient incidence of TEAEs by Preferred Term, n (%)	Placebo (n = 26)	TERN-101 5 mg (n = 25)	TERN-101 10 mg (n = 26)	TERN-101 15 mg (n = 23)
Pruritus	0 (0%)	3 (12.0%)[a]	3 (11.5%)	4 (17.4%)
Headache	2 (7.7%)	1 (4.0%)	3 (11.5%)	2 (8.7%)
Constipation	2 (7.7%)	1 (4.0%)	1 (3.8%)	1 (4.3%)
Dizziness	1 (3.8%)	1 (4.0%)	2 (7.7%)	0 (0%)
Decreased appetite	1 (3.8%)	0 (0%)	2 (7.7%)	1 (4.3%)

[a]Excludes one patient in the TERN-101 5 mg group who had an event of pruritic rash.
TEAE – treatment-emergent adverse event.

Figure 2: Lipid Profile



*p-value < 0.05; **< 0.01.
HDL – high-density lipoprotein; LDL – low-density lipoprotein; SE – standard error.

Table 3: Overall Summary of Pruritus

Patient incidence of any pruritus AE, n (%)	Placebo (n = 26)	TERN-101 5 mg (n = 25)	TERN-101 10 mg (n = 26)	TERN-101 15 mg (n = 23)
Pruritus, all CTCAE grades	0	3 (12.0%)[a]	3 (11.5%)	4 (17.4%)
Grade 1	0	3 (12.0%)[a]	1 (3.8%)	3 (13.0%)
Grade 2	0	0	2 (7.7%)[b]	1 (4.3%)[c]
Grade 3	0	0	0	0
Study drug discontinuation due to pruritus	0	0	0	0
Pruritus considered related or possibly related to study drug by Investigator	0	3 (12.0%)	3 (11.5%)	1 (4.3%)
Definitely related	0	0	1 (3.8%)	0
Possibly related	0	3 (12.0%)	2 (7.7%)	1 (4.3%)

[a]Excludes one patient in the TERN-101 5 mg group who had an event of pruritic rash.
[b]The Grade 2 pruritus AEs in the 10 mg group reflect generalized symptoms, deemed possibly or definitely related to study drug by the investigator; both AEs resolved despite ongoing treatment.
[c]The Grade 2 pruritus AE in the 15 mg group reflect symptoms localized to bilateral forearms, treated with oral diphenhydramine, deemed unrelated to study drug by the investigator; AE was ongoing at the time of study completion.
AE – adverse event; CTCAE - common terminology criteria for adverse events

6 • ACKNOWLEDGEMENTS

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7 • CONTACTS AND DISCLOSURES

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- TERN-101 is an investigational drug being developed by Terns Pharmaceuticals, which provided funding for the study as well as the poster preparation services.

8 • REFERENCES

1) Loomba R et al. Liver-distributed FXR Agonist TERN-101 demonstrates favorable safety and efficacy profile in NASH Phase 2a LIFT study. Abstract presented at: The Liver Meeting® of the American Association for the Study of Liver Diseases; November 12-15, 2021.
2) Adapted from IFSI SIG/EADV Task Force Pruritus assessments available at http://www.pruritussymposium.de/numericalratingscale.html.