Poster No. SAT108

LIVER-DISTRIBUTED FARNESOID X RECEPTOR (FXR) AGONIST TERN-101 DEMONSTRATES POTENT TARGET ENGAGEMENT WITH A FAVORABLE EXPOSURE-RESPONSE PROFILE IN NONALCOHOLIC STEATOHEPATITIS PATIENTS

Cara H. Nelson[1a], Christopher T. Jones[1], Kevin Klucher[1], Feng Jin[2], Tonya Marmon[1], Diana Chung[1], Erin Quirk[1a], and Daria B. Crittenden[1]

[1]Terns Pharmaceuticals, Foster City, California, USA; [2]Polaris Consulting, Inc, San Mateo, California, USA

[a]Contact Information: cnelson@ternspharma.com; equirk@ternspharma.com

1065 E. Hillsdale Blvd, Suite 100
Foster City, California 94404

SCAN ME!

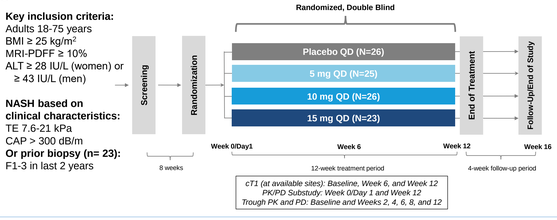
KEY TAKEHOME MESSAGE

TERN-101 over 12 weeks demonstrated dose- and exposure-dependent target engagement (increases in FGF19 and decreases in 7αC4) and efficacy (decreases in cT1) in NASH patients with no obvious exposure-safety relationship.

1 • INTRODUCTION •

- Activation of farnesoid X receptor (FXR), a nuclear hormone receptor that is highly expressed in the liver and small intestine, improved histological liver fibrosis in a late-stage study, demonstrating the potential for FXR agonists in the treatment of nonalcoholic steatohepatitis (NASH)[1]
- TERN-101 is a potent, non-steroidal FXR agonist with enhanced liver distribution
- Intestinal FXR agonism leads to increases in circulating fibroblast growth factor 19 (FGF19); further, FGF19 and hepatic FXR agonism leads to decreases in 7-alpha-hydroxy-4-cholestene-3-one (7αC4), an intermediate in bile acid synthesis; as such, both FGF19 and 7αC4 are pharmacodynamic (PD) markers of TERN-101 activity
- Corrected T1 (cT1) relaxation time mapping using magnetic resonance is a composite biomarker of fibroinflammatory disease and correlates with NAFLD activity score and fibrosis on liver histology [2,3]
- The Phase 2a LIFT Study assessed multiple doses of TERN-101 vs placebo for 12 weeks in non-cirrhotic patients with NASH (Figure 1)
- The LIFT study showed TERN-101 was overall safe and well-tolerated with significant reductions in cT1 and decreases in alanine aminotransferase (ALT) and magnetic resonance imaging proton density fat fraction (MRI-PDFF)[4].
- Here we present separate analyses of pharmacokinetics (PK), PD, and TERN-101 exposure-response relationships from the LIFT study

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



2 • OBJECTIVES •

- To evaluate the PK of TERN-101
- To evaluate FXR target engagement of TERN-101 using pharmacodynamic markers of liver (7αC4) and intestinal (FGF19) FXR activation
- To evaluate the relationship between TERN-101 exposure and change in cT1

3 • METHODS •

- TERN-101 plasma concentrations were determined using a validated LC-MS/MS bioanalytical assay
- PK parameters for TERN-101 were estimated using a nonlinear mixed effects model (NONMEM)
- 7αC4 plasma concentrations were determined using a validated LC-MS/MS bioanalytical assay and FGF19 plasma concentrations were determined by ELISA
- PD endpoints were analyzed using an analysis of covariance (ANCOVA) model with percent change or change from baseline as the dependent variable including treatment group as a fixed effect and baseline as a covariate to compare placebo and each active TERN-101 treatment group

4 • RESULTS •

- 100 patients were randomized and received at least one dose of study drug
- 26 patients participated in the PK/PD substudy (N = 7, 6, 7, and 6 for the placebo, 5 mg, 10 mg, and 15 mg groups, respectively) with all but one subject completing both the Week 0 and Week 12 visits (one subject in 10 mg group did not complete Week 12 visit)
- In general, demographics and baseline characteristics were similar between the PK/PD substudy and all patients
- All dose levels of TERN-101 were overall safe and well-tolerated, with no discontinuations due to adverse events

Table 1: Disposition, Demographics, and Baseline Characteristics in All Patients

Demographics and Key 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)
Female, n (%)	16 (61.5)	15 (60.0)	17 (65.4)	17 (73.9)
BMI, mean (SD) [kg/m²]	36.5 (5.43)	37.2 (6.44)	36.3 (6.63)	36.2 (4.74)
ALT, mean (SD) [IU/L]	55.5 (23.6)	56.3 (16.3)	60.8 (29.1)	55.8 (26.5)
MRI-PDFF, mean (SD) [%]	21.43 (7.6)	21.08 (8.2)	20.05 (7.1)	22.78 (8.4)
Stiffness by TE, mean (SD) [kPa][1]	10.4 (2.6)	12.0 (3.6)	9.6 (1.7)	9.8 (2.4)
cT1, mean (SD) [msec][2]	908.9 (90.9)	925.4 (75.2)	942.0 (143.5)	974.7 (175.3)

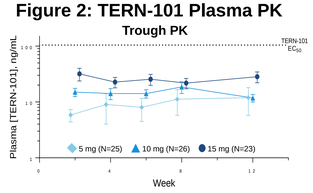
[1]Transient elastography (TE) conducted in placebo N= 20, 5 mg N=16, 10 mg N=22, 15 mg N=20; [2]cT1 conducted in placebo N=22, 5 mg N=24, 10 mg N=20, 15 mg N=18

Table 2: TERN-101 Exposures Estimated by Population PK

Dose (mg)	N	C_{max} (ng/mL)	AUC_{tau} (hr.ng/mL)	C_{tau} (ng/mL)
5	25	93.7 (18.8)	729 (68.8)	9.21 (194)
10	26	185 (8.33)	1390 (22.0)	14.1 (48.3)
15	22	293 (9.97)	2420 (28.0)	28.9 (61.8)

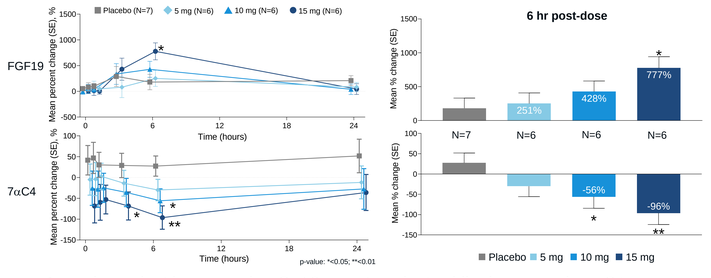
Parameters presented as Mean (CV%)

Figure 2: TERN-101 Plasma PK



- TERN-101 exposures were approximately dose-proportional
- Mean plasma concentrations of TERN-101 remained below FXR EC_{50} at trough in all dose groups

Figure 3: PK/PD FGF19 and 7αC4 at Week 12 (intensive PK/PD subgroup)



- Dose-dependent increases in FGF19 were transient, while decreases in 7αC4 were more sustained over the dosing interval
- Maximal changes in FGF19 and 7αC4 were observed at 6 hrs postdose and were generally dose-dependent

6 • REFERENCES •

1) Younossi Z.M., Lancet, 2019 Dec 14;394(10215):2184-2196
2) Banerjee R, et al., J Hepatol, 2014;61(1):69-77
3) Dennis, A., et al, Frontiers in Endocrinology, 2021, Jan 27;11:575843
4) Loomba, R, et al. Presented at the Liver Meeting 2021 (AASLD). Abstract #143. Journal of Hepatology 2021 Vol. 74 Issue 1 Supplement 97A

7 • ACKNOWLEDGEMENTS AND DISCLOSURES •

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- CHN, CJ, KK, FJ, TM, DC, EQ, and DBC are employees/consultants/shareholders of Terns Pharmaceuticals

Figure 4: Trough 7αC4 in All Patients by Visit and by TERN-101 Exposure Quartile

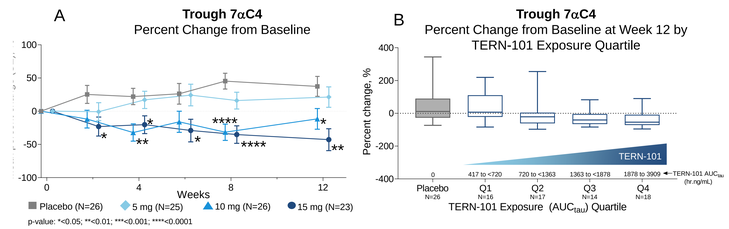


Figure 4A: Mean percent change from baseline at trough (predose); Means and standard error (SE) refer to least squares mean (LSM) from ANCOVA model; all patients
Figure 4B: TERN-101 exposures (AUC_{tau}) were pooled across TERN-101 groups and subjects were separated by quartile (Table 3), irrespective of dose group. Percent change from baseline in 7αC4 at Week 12 associated with the subjects in each quartile was then plotted above; box represents median with interquartile range and whiskers represent min to max. Not all subjects in the Pop PK analysis set had a corresponding Week 12 7αC4 value

- Statistically significant decreases in trough 7αC4 levels were observed at multiple time points in the 10 mg and 15 mg groups. There were no significant changes in the 5 mg group
- Changes in trough 7αC4 values at Week 12 in the lowest TERN-101 exposure quartile (Q1) were generally similar to placebo, while the majority of subjects in the highest three quartiles (Q2-Q4) had decreases in 7αC4 at Week 12

Figure 5: TERN-101 Exposure vs Change from Baseline cT1 at Week 12

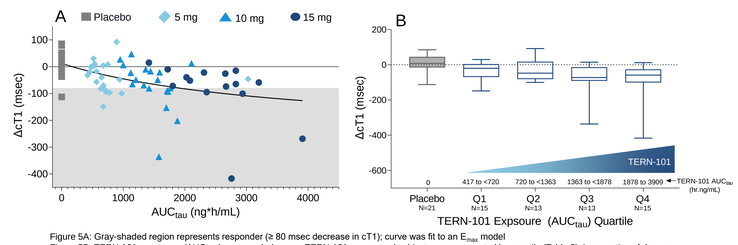
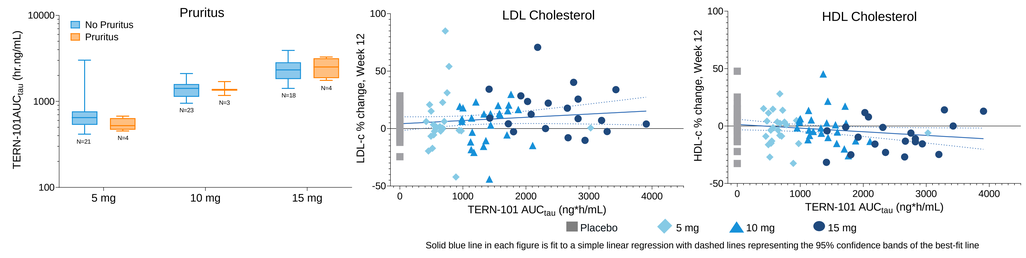


Figure 5A: Gray-shaded region represents responder (≥ 80 msec decrease in cT1); curve was fit to an E_{max} model
Figure 5B: TERN-101 exposures (AUCtau) were pooled across TERN-101 groups and subjects were separated by quartile (Table 2), irrespective of dose group. Change in cT1 at Week 12 associated with the subjects in each quartile was then plotted above; box represents median with interquartile range and whiskers represent min to max. Not all subjects in the Pop PK analysis set had a corresponding Week 12 cT1 value

- cT1 generally decreased in an exposure-dependent manner
- cT1 decreases were similar in the highest two exposure quartiles (Q3 and Q4); in the highest two quartiles (n=28), all but one subject were in the 10 or 15 mg groups

Figure 6: Exposure-safety analyses



Solid blue line in each figure is fit to a simple linear regression with dashed lines representing the 95% confidence bands of the best-fit line

- There was no difference in TERN-101 exposures between subjects that did and did not experience pruritus within each TERN-101 treatment group
- Low correlation between TERN-101 exposures and percent change from baseline in LDL or HDL cholesterol

5 • CONCLUSIONS •

- TERN-101 treatment resulted in dose- and exposure-dependent transient increases in FGF19 and more persistent reductions in 7αC4 indicating brief intestinal FXR activation during absorption followed by sustained hepatic FXR target engagement
- TERN-101 doses ranging from 5 mg to 15 mg produced plasma concentrations below EC_{50} at trough, indicating limited potential for systemic FXR activation, consistent with the overall favorable safety profile of TERN-101 doses of ≤15 mg administered for 12 weeks
- TERN-101 exhibited approximately dose-proportional PK with some overlap in exposures between the 10 and 15 mg doses
- Higher TERN-101 exposures were associated with greater decreases in cT1, an imaging biomarker of fibroinflammation
- Rates of pruritus were low and not TERN-101 exposure-dependent
- No strong association between TERN-101 exposures and change from baseline in either LDL or HDL cholesterol in NASH patients receiving TERN-101 at doses of ≤15 mg for 12 weeks
- These analyses, in conjunction with previously presented efficacy and safety results, support the continued development of TERN-101 in NASH, including the ongoing Phase 2a combination study with THR-β agonist TERN-501