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\(^a\), Christopher T. Jones\(^b\), Kevin Klucher\(^c\), Feng Jin\(^d\), Tonya Marmont\(^e\), Diana Chung\(^f\), Erin Quirk\(^g\), and Darla B. Crittenden\(^h\)

\(^{a,b,c,d,e,f,g,h}\) Terns Pharmaceuticals, Foster City, California, USA; \(^{a}\) Polaris Consulting, Inc, San Mateo, California, USA

*Contact Information: cnelson@ternspharma.com; equirk@ternspharma.com

KEY TAKEHOME MESSAGE

-TERN-101 over 12 weeks demonstrated dose- and exposure-dependent target engagement (increases in FXR and decreases in\(\Delta cT1\)) 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).  

- TERN-101 is a potent, non-steroidal FXR agonist with enhanced liver distribution.

- Intestinal FXR agonist leads to increases in circulating fibroblast growth factor 19 (FGF19); further, FGF19 and FXR agonism lead to decreases in 7-alpha-hydroxy-4-cholesten-3-one (\(\text{cT1}\)), an intermediate in bile acid synthesis, as such, both FGF19 and \(\text{cT1}\) are pharmacodynamic (PD) markers of TERN-101 activity.

- Correlated \(\text{cT1}\) (at \(\text{T1}\)) relaxation time mapping using magnetic resonance imaging is a composite biomarker of fibroinflammatory disease and correlates with NAFLD activity score and fibrosis on liver histology.\(^3\)

- 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 \(\text{cT1}\) and decreases in alanine aminotransferase (ALT), and magnetic resonance imaging proton density fat fraction (MR-DPFF).

- 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 (\(\text{cT1}\)) and intestinal (FGF19) FXR activation.

- To evaluate the relationship between TERN-101 exposure and change in \(\text{cT1}\).

3 METHODS

- TERN-101 plasma concentrations were determined using a validated LC-MS/MS biochemical assay.

- PK parameters for TERN-101 were estimated using a nonlinear mixed effects model.

- \(\text{cT1}\) and FGF19 plasma concentrations were determined using a validated LC-MS/MS biochemical assay and FGF19 plasma concentrations were determined by ELISA.

- PD endpoints were 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 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 study (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 and all subjects.

- All dose levels of TERN-101 were overall safe and well-tolerated, with no discontinuations due to adverse events.

- 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-1 against TERN-501.

5 CONCLUSIONS

- TERN-101 treatment resulted in dose- and exposure-dependent target engagement increases in FGF19 and more persistent reductions in \(\text{cT1}\) compared to placebo during absorption followed by sustained hepatic FXR target engagement.

- TERN-101 doses ranging from 5 mg to 15 mg produced plasma concentrations below \(\text{EC}_{90}\) at trough, indicating limited potential for systemic FXR activation, consistent with the overall favorable safety profile of TERN-101 doses of 515 mg administered for 12 weeks.

- TERN-101 exhibited approximately dose proportional PK with some overlap in exposures to the 10 and 15 mg groups.

- Higher TERN-101 exposures were associated with greater decreases in \(\text{cT1}\), an imaging biomarker of fibronodulation.

- 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 doses at 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-1 against TERN-501.

6 REFERENCES


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