TERN-101, a liver selective FXR agonist, is well-tolerated, and produces potent 7α-C4 reductions and FGF19 increases with no pruritis in healthy participants

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1 · INTRODUCTION

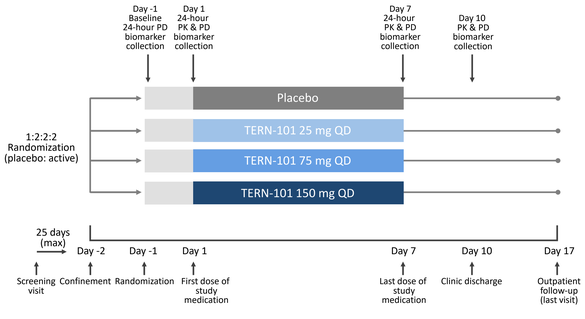
FXR is a nuclear receptor that is highly expressed in the liver and small intestine. FXR agonism has demonstrated improvement over placebo in regression of histological liver fibrosis without progression of NASH in a late-stage study, demonstrating the potential for FXR agonists to be a new treatment modality for nonalcoholic steatohepatitis (NASH).

TERN-101 is a potent, non-steroidal FXR agonist, with enhanced liver distribution being developed for the treatment of NASH. TERN-101 induced significant reductions in steatosis, inflammation, and fibrosis in a NASH rodent model and induced robust FXR agonism in the liver[1,2]. TERN-101 has been granted FastTrack Designation by the U.S. Food and Drug Administration (FDA) for the treatment of NASH.

Here we present the pharmacokinetic (PK) and pharmacodynamic (PD) responses of TERN-101 capsules administered for 7 days to healthy human participants.

2 · METHODS

Figure 1: TERN101-US A101 Study Design



- 36 healthy participants randomized to 1:1:1:1 to receive either once daily oral placebo or active TERN-101 capsules at doses of 25, 75, or 150 mg for 7 days
- Pharmacodynamic biomarker assessment of target engagement included:
  - Serum FGF19
  - Serum 7α-hydroxy-4-cholesten-3-one (7α-C4)
- Plasma PK parameters were determined by non-compartmental analysis
- For PK/PD analysis, a population PK model was built from observed TERN-101 plasma concentrations and used to calculate predicted TERN-101 AUC (AUC_{pred})
- Safety was assessed during dosing and for 10 (±1) days after dosing.

3 · RESULTS

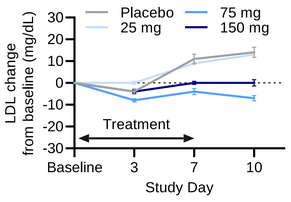
Safety

Table 1: Adverse events

Adverse events (AE) reported (all grades)	Placebo (n=5)	TERN-101 25 mg capsule (n=11)	TERN-101 75 mg capsule (n=10)	TERN-101 150 mg capsule (n=10)
Overall subject AE incidence, n (%)	0 (0)	2 (18.2)	2 (20)	2 (20)
AE diagnosis and frequency, n (%)				
Back pain	0 (0)	0	0	1 (10)
Cough	0 (0)	0	1 (10)	1 (10)
Rhinorrhea	0 (0)	1 (9.1)	1 (10)	0
Sneezing	0 (0)	1 (9.1)	0	0
Vaginal discharge	0 (0)	0 (0)	1 (10)	0

All AEs reported were mild. No subject prematurely discontinued study medication.

Figure 2: LDL cholesterol change from baseline

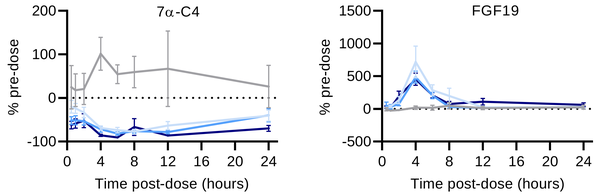


Change from baseline (Day -1) in LDL. Data are presented as mean (± SEM)

- TERN-101 was safe and well-tolerated with no reports of pruritus
- All reported AEs were mild in severity, and no subject discontinued
- Laboratory, vital signs, ECG, and other safety assessments did not show any trends across individual subjects or cohorts
- Mean serum LDL changes from baseline with TERN-101 were comparable to those seen in with placebo

Pharmacodynamics

Figure 4: TERN-101 induces sustain suppression of 7α-C4 and transient increases of FGF19

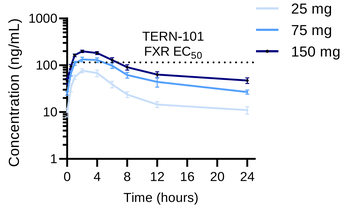


Change in 7α-C4 and FGF19 relative to baseline (Day -1) on Day 7. Data are presented as mean (± SEM)

- On Day 7, maximum suppression of serum 7α-C4 levels from predose was observed six hours after dosing, corresponding to a reduction of 74%, 82%, and 91% in the 25, 75, and 150 mg TERN-101 capsule dose groups, respectively
- Maximum increases from baseline of 718%, 486%, and 454% in serum FGF19 levels were observed at four hours after dosing on Day 7 in the TERN-101 25, 75, and 150 mg capsule dose groups, respectively
- FGF19 levels decreased rapidly 4 hours after TERN-101 administration, indicating lack of sustained intestinal FXR activation

Pharmacokinetics

Figure 3: TERN-101 (capsule) plasma PK (Day 7)



TERN-101 plasma concentration (ng/mL) over time on Day 7. Data are presented as mean (± SEM)

Table 2: TERN-101 (capsule) PK parameters

Dose (mg)	Day	C_{max} (ng/mL)	T_{max} (h)	AUC_{0-t} (h*ng/mL)	$t_{1/2}$ (h)
25	Day 1	59 (18.8)	2 (1, 4)	479 (209)	
	Day 7	83 (33)	2 (2, 4)	880 (413)	15.6 (9.5, 79.3)
75	Day 1	102 (25)	4 (2, 6)	896 (167)	
	Day 7	157 (45)	3 (1, 4)	2100 (627)	20.5 (7.5, 34)
150	Day 1	156 (47)	2 (2, 8)	1420 (339)	
	Day 7	217 (31)	2 (1, 4)	3470 (1220)	25.4 (10.1, 57.5)

PK parameters presented as mean (SD), except for T_{max} and $t_{1/2}$ presented as median (min, max).

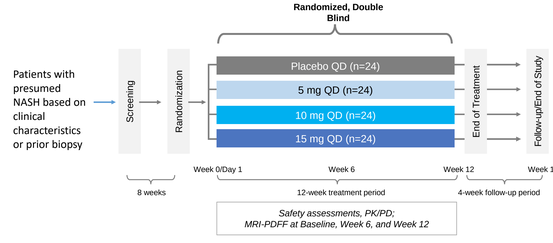
Table 3: Single dose TERN-101 tablet formulation PK

TERN-101 Tablet (mg)	AUC_{0-t} (h*ng/mL)†	C_{max} (ng/mL)†
5	459 (154)	105 (30)
10	~1000‡	~210‡
15	1500‡	~315‡
25	2770 (684)	410 (113)

†under fasted conditions; ‡Predicted values

- TERN-101 capsules exhibited less than dose proportional PK and steady state exposure was achieved by day 5 of dosing
- The half-life of TERN-101 capsule doses ranged between 16 to 26 hours on Day 7, which supports a once daily dosing schedule
- Mean TERN-101 plasma levels were below EC_{50} at all time points for the 25 mg capsule dose and at 8-hours postdose for the 75 and 150 mg doses, indicating limited systemic FXR activation potential
- A completed TERN-101 PK bridging study[3] comparing capsule with tablet formations suggests that a 5 mg tablet can achieve comparable exposure as the 25 mg capsule

Figure 5: Phase 2a LIFT Study Design for TERN-101 Tablet Formulation in Phenotypic NASH Patients (NCT04328077)



The 5 mg, 10 mg, and 15 mg TERN-101 tablet doses selected for the ongoing Phase 2a LIFT study are projected to achieve plasma exposures at which we observed 74-91% 7α-C4 reduction

4 · CONCLUSIONS

- TERN-101 potently suppressed 7α-C4 serum levels and transiently induced FGF-19 serum levels, consistent with the preferential liver distribution of TERN-101
- Target engagement was observed at all doses of TERN-101 capsule studied
- TERN-101 capsules were overall safe and well tolerated in healthy volunteers at all doses with no significant changes in LDL and no reports of pruritus
- TERN-101 plasma half-life and 7α-C4 serum reductions support once daily administration of TERN-101
- TERN-101 tablet doses selected for the ongoing Phase 2a study in phenotypic NASH patients are anticipated to result in plasma TERN-101 concentrations that are well tolerated and at which potent FXR target engagement is achieved in the liver

REFERENCES

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