Single doses of the THR-β agonist TERN-501 are well tolerated and result in dose-dependent changes in LDL cholesterol and sex hormone binding globulin in a first-in-human clinical trial

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TERNS PHARMACEUTICALS

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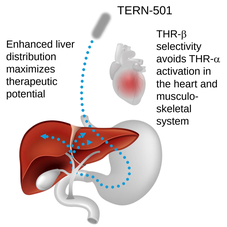
1 • INTRODUCTION •

THR-β Agonism for Treatment of NASH

- Thyroid hormone receptor-beta (THR-β) is the major form of THR expressed in the liver and plays a key role in energy balance and metabolism of fatty acids and lipids,[1] whereas THR-α predominates in the heart and musculoskeletal system and is responsible for most cardiovascular and musculoskeletal effects of thyroid hormone stimulation.[2,3]
- THR-β agonism is a promising mechanism for the treatment of nonalcoholic steatohepatitis (NASH) because of its potential to reduce hepatic steatosis and improve metabolic function and dyslipidemia in NASH patients.[4]
- Sex hormone binding globulin (SHBG) is a protein produced in the liver following activation of THR in hepatocytes and is a marker of THR-β target engagement.

TERN-501 Background

- TERN-501 is a potent and selective THR-β agonist with enhanced liver distribution in development for the treatment of NASH.
- TERN-501 lowered cholesterol in hypercholesterolemic rats and significantly reduced liver steatosis, inflammation, and fibrosis in a diet-induced mouse model of NASH at exposures of approximately 3,320 hr.ng/mL.[5]
- Key attributes of TERN-501:
  - Highly selective for THR-β to minimize effects of THR-α agonism
  - Metabolically stable to minimize potential drug-drug interactions
  - Low pharmacokinetic variability to avoid the need for individual patient dose adjustments and/or therapeutic drug monitoring
  - Slow clearance to support a low, once-daily oral dose, making it amenable to coformulation with other NASH treatments



Receptor	TERN-501 EC_{50} (SD), μM
THR-β	0.1 ± 0.05
THR-α	2.5 ± 1.5
THR-β selectivity[#] (THR-β/THR-α)	23 ± 5.8

[#]ratio is T3-normalized

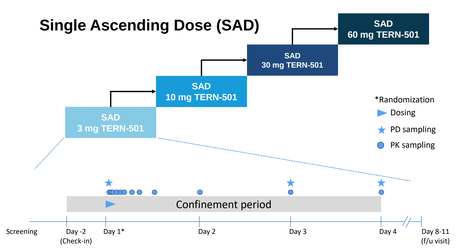
- **Here we present results from TERN501-1009, a Phase 1 first-in-human (FIH) study in healthy subjects receiving single oral doses of TERN-501.**

2 • OBJECTIVES •

Primary Objective:
- Assess the overall safety and tolerability of single ascending doses of TERN-501 in healthy subjects

Secondary Objectives:
- Evaluate the pharmacokinetics (PK) and pharmacodynamics (PD) of TERN-501 in healthy subjects following single ascending doses of TERN-501

3 • METHODS •



For each cohort, 8 subjects were randomized to receive TERN-501 or placebo in a 3:1 ratio (n=6 active and n=2 placebo), with administration as a single, oral dose during the fasted state. Preliminary data was reviewed prior to each dose escalation.

Healthy male and non-pregnant, non-lactating female subjects were eligible to participate
- Age: 18-65 years (inclusive)
- BMI: 18-35 kg/m^2 (inclusive)
- Fasting LDL cholesterol: 80 to <190 mg/dL
- Absence of NAFLD or chronic liver disease

Safety was assessed throughout the study
- Safety monitoring was consistent with typical first-in-human study designs, with additional assessments based on the mechanism of action of THR agonists[6,7]
- Adverse event (AE) monitoring, clinical laboratory testing (including thyroid axis testing [free and total T3, free and total T4, TSH], cardiac biomarkers [CK-MB, troponin I], and liver biochemistry), intensive vital signs, cardiac telemetry, and electrocardiograms were performed

TERN-501 plasma and urine concentrations were determined using validated liquid chromatography-tandem mass spectrometry assay
- PK parameters estimated via noncompartmental methods using Phoenix® WinNonlin® (Certara, LP, Princeton, NJ)

Concentrations of serum pharmacodynamic (PD) biomarkers apolipoprotein B (Apo B) and sex hormone binding globulin (SHBG) were measured using an immunoassay and serum lipids were determined by spectrophotometry. All samples were run at local laboratories (Quest Diagnostics).
- Percent change from baseline for PD markers were calculated using an ANCOVA model with percent change from baseline as dependent variable, treatment group as fixed effect, and baseline as covariate. Analyses used observed data only without imputation for missing data.

4 • RESULTS •

SAFETY

- All adverse events were mild or moderate in severity and most were unrelated to the study drug as determined by the Investigator except for AEs in one subject were considered possibly related
- No cardiac-related AEs (e.g., tachycardia, arrythmias), clinically significant changes in ECG parameters or notable changes in heart rate or other vital signs occurred
- No subject discontinued due to adverse event or other reason

Treatment-Emergent Adverse Events

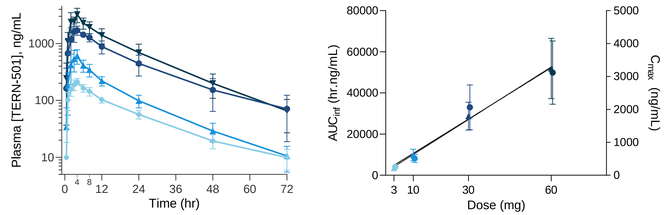
Subject incidence of AEs by category n (%)	Placebo (N=8)	TERN-501 3 mg (N=6)	TERN-501 10 mg (N=6)	TERN-501 30 mg (N=6)	TERN-501 60 mg (N=6)
Any AE, all CTCAE grades	1 (12.5%)	2 (33.3%)	0	2 (33.3%)	0
CTCAE Grade 1	1 (12.5%)	2 (33.3%)	0	1 (16.7%)	0
CTCAE Grade 2	0	0	0	1 (16.7%)	0
CTCAE Grade 3 or higher	0	0	0	0	0
Serious AEs	0	0	0	0	0
Subject incidence of AEs by preferred term					
Contact dermatitis[1]	1 (12.5%)	0	0	0	0
Dermatitis[2]	0	0	0	1 (16.7%)	0
Headache	0	0	0	1 (16.7%)*	0
Pleuritic pain	0	0	0	1 (16.7%)*	0
Procedural complication[3]	0	1 (16.7%)	0	0	0
Rash[4]	0	0	0	1 (16.7%)	0
Vessel puncture site rash[5]	0	1 (16.7%)	0	0	0

CTCAE = common terminology criteria for adverse events, version 5.0
*AEs considered possibly related to study drug; one subject reported headache on Day 1 and Day 3, which resolved spontaneously, and pleuritic pain (left axilla) on Day 2, which lasted a few hours and resolved after one dose (1000 mg) of acetaminophen.
[1]Contact dermatitis, antecubital on left arm due to tape; [2]Unspecified dermatitis left wrist due to clothes; [3]Syncope secondary to blood draw; [4]Nonspecific skin eruption due to clothes right medial wrist; [5]Rash, due to blood draws left forearm.

Safety Laboratory Assessments

- TSH, free T3, and free T4 levels remained within normal range
- No remarkable changes in liver enzymes or bilirubin were observed
- Cardiac biomarkers remained within normal range with no notable changes observed
- No remarkable changes in other clinical safety labs

PHARMACOKINETICS



TERN-501 mean (SD) plasma concentration-time profiles following a single dose of 3 mg (●), 10 mg (▲), 30 mg (●) or 60 mg (▼)
TERN-501 (left). TERN-501 PK parameters (●AUC$_{inf}$ and ▲C$_{max}$) versus dose (right).

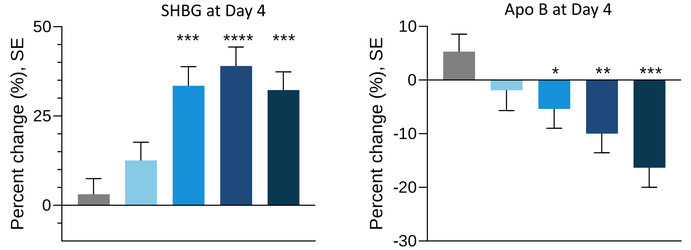
PK Parameter	TERN-501 3 mg N=6	TERN-501 10 mg N=6	TERN-501 30 mg N=6	TERN-501 60 mg N=6
AUC$_{inf}$ (hr.ng/mL)	4060 (16.6)	8110 (23.9)	33000 (33.1)	50000 (31.4)
C$_{max}$ (ng/mL)	217 (13.9)	614 (29.0)	1800 (23.7)	3330 (33.2)
T$_{max}$ (hr)	4.00 (3.00-4.00)	4.00 (3.00-4.03)	4.00 (3.00-6.00)	4.00 (4.00-4.00)
t$_{1/2}$ (hr)	17.3 (14.0-20.9)	14.4 (11.5-16.2)	16.1 (12.4-23.1)	13.8 (10.5-16.9)
f$_e$ (% dose, urine)	2.95 (62)	2.05 (74)	1.78 (35)	1.22 (24.1)

Parameters are presented to 3 significant figures as mean (%CV) except T$_{max}$ and t$_{1/2}$ which are presented as median (range)
f$_e$ is fraction of dose excreted in urine as TERN-501

- TERN-501 was generally well-absorbed with low variability (%CV ≤33%) under fasting conditions
- TERN-501 exposures (AUC$_{inf}$ and C$_{max}$) were approximately dose-proportional
- TERN-501 median half-life ranged from 13.8 to 17.3 hrs, supportive of once daily dosing
- Minimal renal excretion of unchanged parent at all dose levels
- TERN-501 exposures at or above the predicted efficacious exposure were achieved at all single dose levels evaluated in humans

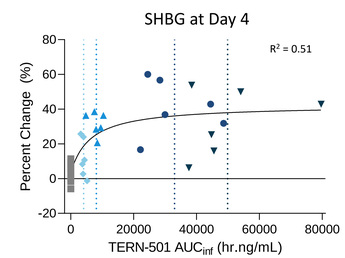
PHARMACODYNAMICS

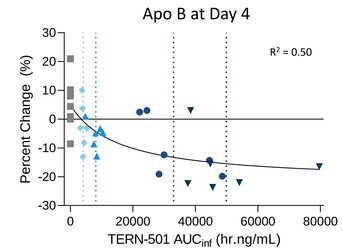
PD Markers at Baseline and Day 3		Placebo (PBO) (N= 8)	TERN-501 3 mg (N= 6)	TERN-501 10 mg (N= 6)	TERN-501 30 mg (N= 6)	TERN-501 60 mg (N= 6)
SHBG	Baseline (nmol/L)	35.0 (17.97)	46.7 (26.30)	55.0 (20.63)	26.0 (11.19)	39.3 (31.97)
	Change (nmol/L)	-0.77 (2.17)	0.20 (2.52)	15.77 (2.61)	6.00 (2.6)	5.05 (2.49)
	Percent change (%)	-3.8 (3.91)	6.3 (4.52)	31.3 (4.69)	16.5 (4.67)	13.8 (4.48)
	P-value vs. PBO		0.1082	**<0.0001**	**0.0023**	**0.0064**
LDL-c	Baseline (mg/dL)	106.1 (36.07)	137.5 (17.4)	133.7 (18.2)	123.3 (23.55)	125.2 (45.96)
	Change (mg/dL)	5.81 (3.44)	-3.98 (3.39)	0.68 (3.34)	-15.67 (3.32)	
	Percent change (%)	5.6 (2.85)	-3.1 (2.80)	0.70 (2.77)	-12.5 (2.75)	n/a
	P-value vs. PBO		**0.0482**	0.2436	**0.0002**	
HDL-c	Baseline (mg/dL)	45.4 (11.40)	51.0 (22.53)	63.7 (23.55)	49.5 (7.82)	48.2 (13.93)
	Change (mg/dL)	0.29 (0.93)	0.87 (0.91)	-1.07 (0.96)	-6.09 (0.91)	
	Percent change (%)	1.7 (1.77)	2.4 (1.73)	-1.0 (1.83)	-12.1 (1.74)	n/a
	P-value vs. PBO		0.7829	0.3027	**<0.0001**	
TC	Baseline (mg/dL)	171.8 (45.05)	216.5 (29.87)	217.7 (38.10)	196.2 (31.2)	191.2 (51.68)
	Change (mg/dL)	2.25 (4.73)	-1.85 (4.59)	-1.93 (4.61)	-24.14 (4.52)	
	Percent change (%)	1.6 (2.15)	-0.9 (2.09)	-0.8 (2.09)	-11.8 (2.06)	n/a
	P-value vs. PBO		0.4370	0.4478	**0.0002**	
Apo B	Baseline (mg/dL)	86.8 (23.18)	113.5 (20.06)	105.8 (9.26)	101.2 (15.89)	92.3 (24.9)
	Change (mg/dL)	3.84 (2.72)	-1.48 (3.14)	-5.91 (3.01)	-11.47 (2.97)	-13.92 (3.01)
	Percent change (%)	5.5 (2.63)	-2.7 (3.04)	-6.0 (2.91)	-11.1 (2.88)	-15.75 (2.91)
	P-value vs. PBO		0.0638	**0.0081**	**0.0003**	**<0.0001**



Baseline, mean change, and mean percent change in PD markers at Day 3 (Table, left); change and percent change values are reported as LSM (SE) change from baseline. Mean percent change and standard error in sex hormone binding globulin (SHBG) and apolipoprotein B (Apo B) at Day 4 after a single dose of placebo (▥) or 3 mg (▥), 10 mg (■), 30 mg (■) or 60 mg (■) TERN-501 (above).
P-value vs. placebo: *<0.05;**<0.01;***<0.001; ****<0.0001. n/a, not available for analysis due to collection error at investigative site

PK/PD





TERN-501 exposure (AUC$_{inf}$) response (percent change on Day 4 from pre-dose) relationship with PD markers sex hormone binding globulin (SHBG) and apolipoprotein B (Apo B) following a single dose of placebo (▥) or 3 mg (●), 10 mg (▲), 30 mg (●) or 60 mg (▼) on Day 1. Vertical dashed lines represent the mean exposures for 3, 10, 30, and 60 mg cohorts. Data were fitted to an E$_{max}$ model.

- Significant increases in SHBG were observed following a single dose of ≥10 mg TERN-501 with dose dependent increases through 30 mg TERN-501 at Day 4
- Significant decreases in LDL-c, total cholesterol, and Apo B were observed by Day 3 following single dose administration of TERN-501 in one or more dose groups with dose-dependent reductions on Day 4
- No significant reductions in triglyceride levels were observed after a single dose of TERN-501
- Changes in SHBG and Apo B were exposure-dependent

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DISCLOSURES

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5 • CONCLUSIONS •

- Single ascending doses of TERN-501 up to 60 mg were overall safe and well-tolerated in healthy volunteers
- Single doses of TERN-501 exhibited dose-proportional plasma exposures with low variability
- TERN-501 half-life was >13 hours at all single dose levels, supportive of once daily oral dosing
- Renal excretion of unchanged TERN-501 was minimal, indicating renal elimination is a minor pathway
- Significant and dose-dependent effects on SHBG, Apo B, and LDL-c were observed following a single dose of TERN-501, indicating potent target engagement
- All TERN-501 dose levels evaluated achieved plasma exposure levels at or above the target efficacious exposure range based on studies of TERN-501 in a preclinical NASH model
- **The safety, PK, and PD results support continued development of TERN-501 and indicate that it is well-suited for co-formulation with other oral small molecule NASH agents as an oral, once-daily fixed dose combination**
  - **A clinical trial of TERN-501 co-administered with the farnesoid X receptor agonist TERN-101 (Abstract #143) is planned to initiate in the first half of 2022**
- Additional cohorts of this first-in-human study, including multiple ascending dose cohorts, remain ongoing