Abstract No: OS123

Multiple Doses of Thyroid Hormone Receptor-Beta Agonist TERN-501 were Well-Tolerated and Resulted in Significant Dose-Dependent Changes in Serum Lipids and Sex Hormone Binding Globulin in a First-in-Human Clinical Study

Cara H Nelson[1], Christopher T Jones[1], Lois Lee[1], Tonya Marmon[1], Diana Chung [1], Kevin Klucher[1], Yizhao Li[1], Erin Quirk[1], and Daria B Crittenden[1]

[1]Terns Pharmaceuticals, Foster City, California, USA

June 25, 2022 • 18:15-18:30

Conflict of Interest

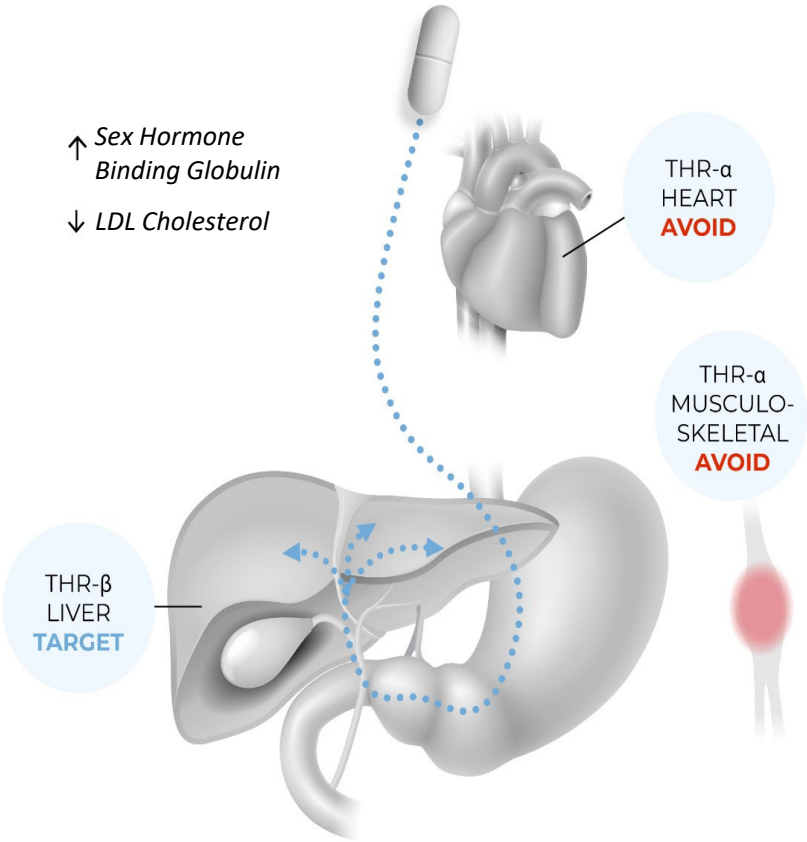
This study was funded by Terns Pharmaceuticals.

All authors are employees, consultants, and/or shareholders of Terns Pharmaceuticals.

Introduction

- THR-β is major form of thyroid hormone receptor (THR) in liver[1]
- THR-β agonism reduces LDL-c, Apo B, and TG[2]
- SHBG = key marker of hepatic THR-β target engagement
- High SHBG response (≥ 75%) associated with liver fat reduction and liver histological improvement[2]
- TERN-501 is a novel, metabolically stable, highly selective THR-β agonist
- In an FIH study, single doses of TERN-501 were well-tolerated with significant improvements in LDL-c, Apo B, and SHBG[3]
- Here we describe the results from the multiple ascending dose cohorts of the TERN-501 FIH study

THR-β regulates key aspects of energy metabolism (e.g., fatty acid & lipid synthesis, liver fat removal through fatty acid oxidation)[1]



Apo B, apolipoprotein B; FIH, first-in-human; LDL-c, low-density lipoprotein cholesterol; SHBG, sex hormone binding globulin; TG, triglycerides; THR-β, thyroid hormone receptor-beta; THR, thyroid hormone receptor.

1. Sinha R, et al. *Nat Rev Endocrinol*. 2018;14:259-269. **2.** Harrison SA, et. al. *Lancet*. 2019;394 (10213):2012-2024. **3.** Jones C, et al. Poster presented at AASLD The Liver Meeting. Nov 12-15, 2021. Poster 1889.

Study Objectives

Primary Objective

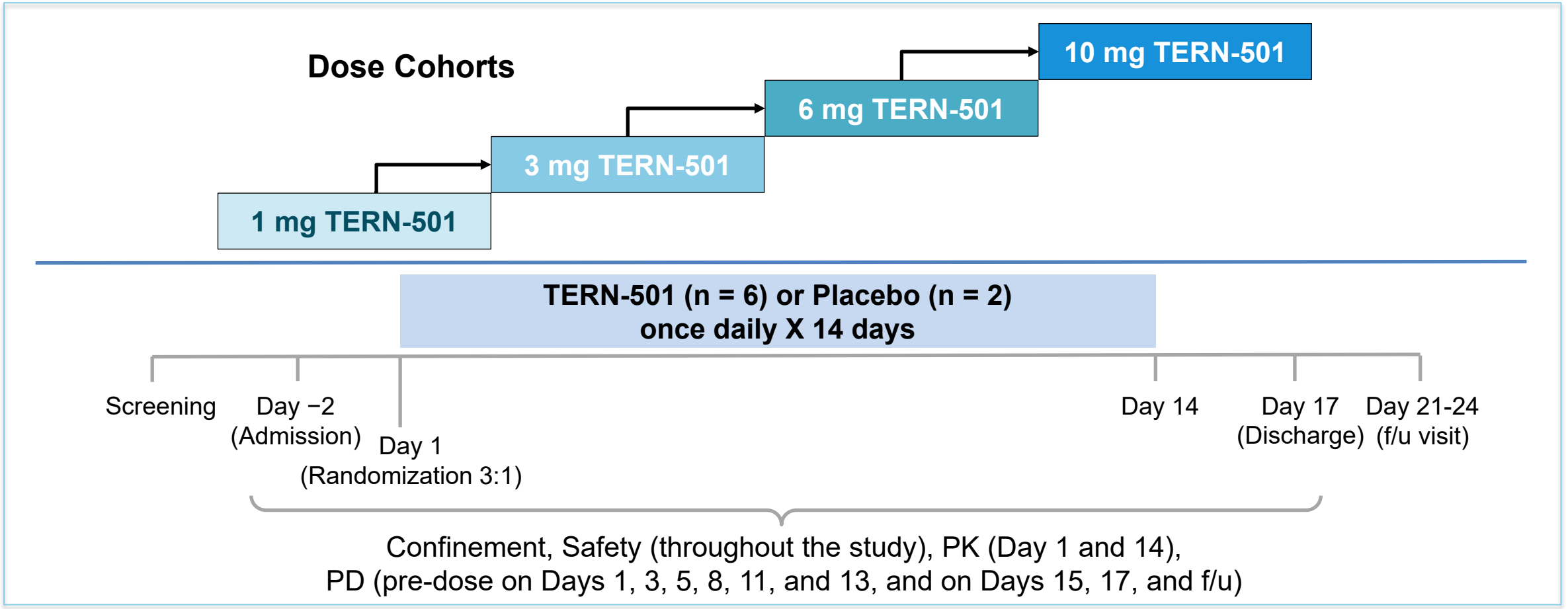
- Assess the overall safety and tolerability of multiple ascending doses of TERN-501 in healthy subjects with elevated LDL-c

Secondary Objectives

- Evaluate the PK and PD of TERN-501 in healthy subjects with elevated LDL-c following multiple ascending doses of TERN-501

Study Design

The study population included healthy adults (18–65 years of age) with BMI of 18–35 kg/m^2 and fasting LDL-c level ≥ 100 mg/dL



BMI, body mass index; f/u, follow-up; LDL-c, low-density lipoprotein cholesterol; MAD, multiple ascending dose; PD, pharmacodynamics; PK, pharmacokinetics; QD, once daily.

Demographics and Baseline Characteristics

Characteristics	Placebo (n = 8)	TERN-501 1 mg (n = 6)	TERN-501 3 mg (n = 6)	TERN-501 6 mg (n = 6)	TERN-501 10 mg (n = 6)
Age, mean (SD) [years]	45.9 (12.3)	44.7 (16.4)	43.3 (12.9)	44.5 (14.9)	39.5 (9.1)
Male, n (%)	7 (87.5%)	5 (83.3%)	5 (83.3%)	5 (83.3%)	5 (83.3%)
Race, n (%)					
White	5 (62.5%)	6 (100%)	3 (50.0%)	6 (100%)	2 (33.3%)
Black or African American	2 (25.0%)	0	3 (50.0%)	0	2 (33.3%)
American Indian or Alaskan Native	0	0	0	0	2 (33.3%)
Asian	1 (12.5%)	0	0	0	0
Ethnicity, n (%)					
Hispanic or Latino	4 (50.0%)	1 (16.7%)	0	1 (16.7%)	0
Not Hispanic or Latino	4 (50.0%)	5 (83.3%)	6 (100%)	5 (83.3%)	6 (100%)
BMI, mean (SD) [kg/m^2]	28.6 (3.5)	28.1 (3.8)	27.1 (2.5)	26.3 (4.2)	27.0 (4.0)
LDL-c, mean (SD) [mg/dL]	**149.1 (32.2)**	**121.5 (31.3)**	**131.8 (13.5)**	**120.0 (49.8)**	**126.7 (15.9)**
TSH, mean (SD) [mIU/L]	2.0 (1.0)	1.8 (0.7)	1.9 (0.8)	2.0 (0.9)	1.2 (0.7)
SHBG, mean (SD) [nmol/L]	28.0 (6.8)	39.8 (17.9)	42.2 (11.0)	38.8 (15.1)	33.3 (19.1)

BMI, body mass index; LDL-c, low-density lipoprotein cholesterol; SHBG, sex hormone binding globulin; SD, standard deviation; TSH, thyroid stimulating hormone.

Treatment-emergent Adverse Events were Mild and Mostly Unrelated with No Significant Changes in Vital Signs

Subject incidence AEs by category, n (%)	Placebo (n = 8)	TERN-501 1 mg (n = 6)	TERN-501 3 mg (n = 6)	TERN-501 6 mg (n = 6)	TERN-501 10 mg (n = 6)
Any AE, all CTCAE grades	1 (12.5%)	3 (50.0%)	1 (16.7%)	1 (16.7%)	2 (33.3%)
CTCAE Grade 1	1 (12.5%)	3 (50.0%)	1 (16.7%)	1 (16.7%)	2 (33.3%)
CTCAE Grade 2 or higher	0	0	0	0	0
Serious AEs	0	0	0	0	0
AEs by relationship to drug					
Not related	1 (12.5%)	2 (33.3%)	1 (16.7%)	0	2 (33.3%)
Unlikely related	0	1 (16.7%)	0	0	0
Possibly related	0	0	0	1 (16.7%)[a]	0
Related	0	0	0	0	0

- Heart rate and blood pressure across the treatment groups remained overall stable and no clinically significant changes were observed
- No significant changes were seen in ECG parameters

[a] Dizziness was reported in one subject.
AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; ECG, electrocardiogram.

No Safety Signals from Laboratory Assessments

Liver biochemistry

- ALT, AST, ALP and total bilirubin values were overall similar across TERN-501 and placebo groups
- No subject receiving TERN-501 had ALT increase to ≥ 2x ULN
- No evidence of DILI

Thyroid hormone

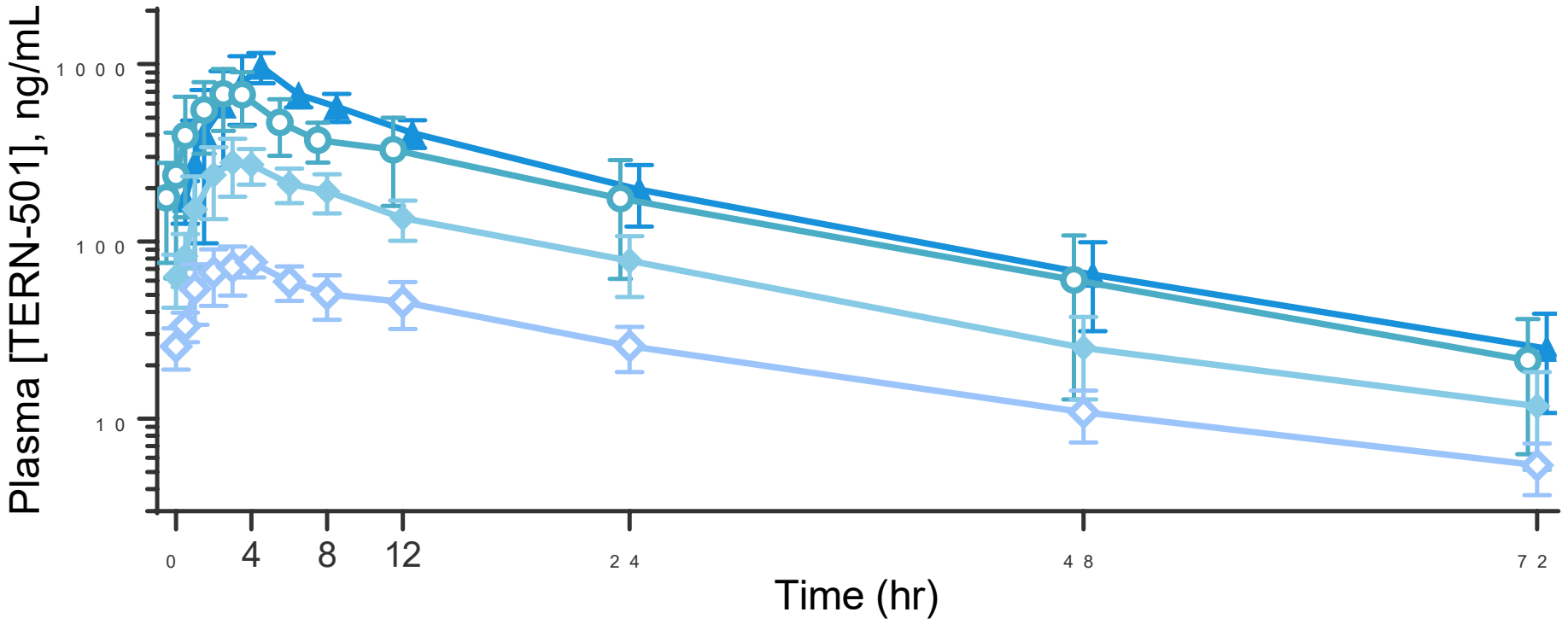
- No symptoms of hyper / hypothyroidism
- Mean TSH and free T3 values were highly variable but generally similar across TERN-501 and placebo groups
- Dose-dependent declines of free T4 were observed among TERN-501 groups consistent with peripheral thyroid hormone modulation observed with other THR-β agonists

Other laboratory assessments (e.g., clinical chemistry, hematology) showed no apparent trends

ALP, alkaline phosphatase activity; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; GGT, gamma glutamyl transpeptidase; TSH, thyroid stimulating hormone; ULN, upper limit of normal.

TERN-501 Exhibited Dose-Proportional PK

TERN-501 Plasma Concentration-Time Profile, Day 14

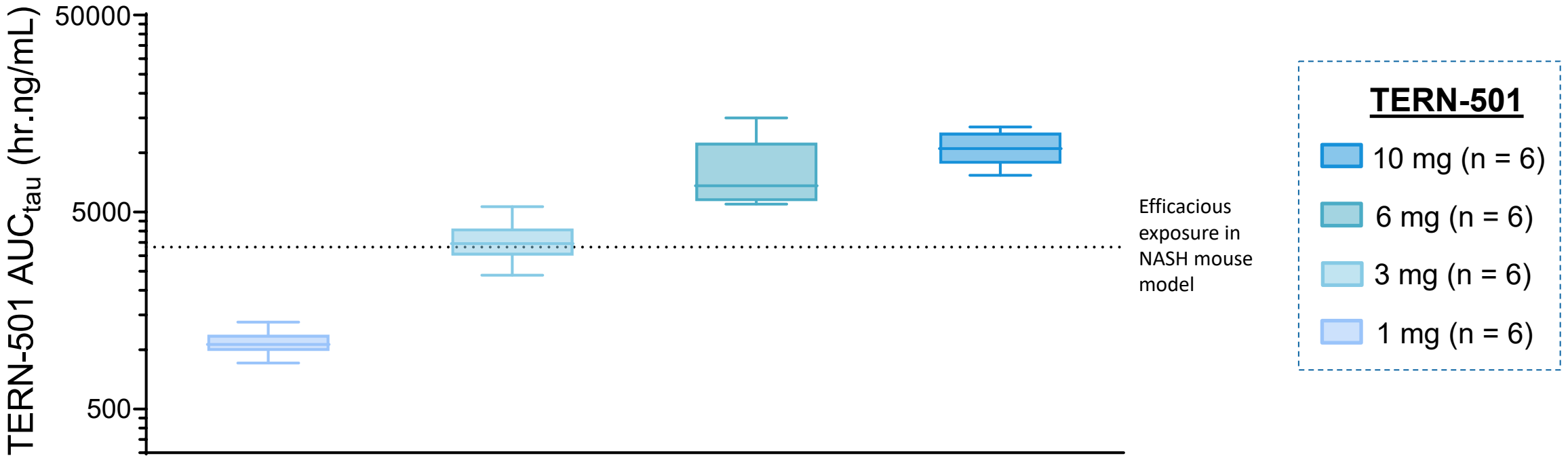


- TERN-501 half-life (median 15 to 21 hours) supports once daily dosing

Figure: Data presented as mean (SD)
AUC_{tau}, area under the concentration-time curve from time 0 to end of the dosing period; hr, hour; PK, pharmacokinetics

Low Variability in TERN-501 PK

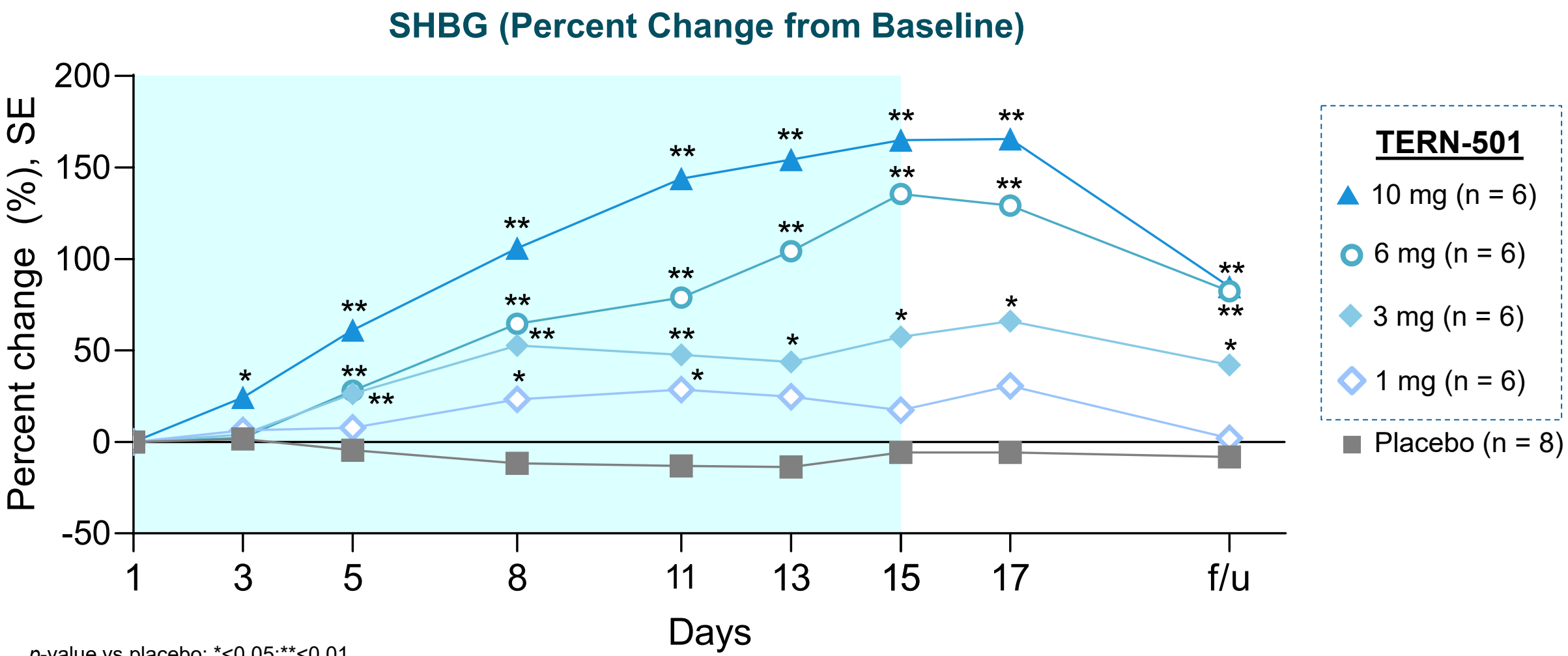
TERN-501 Plasma Exposure (AUC_{tau}), Day 14



- Variability in PK was generally low (%CV 16 to 44% for AUC_{tau} and C_{max})

Figure: Boxes represent interquartile range with median and whiskers represent min to max; dashed line represents efficacious exposure in mouse model of NASH
AUC_{tau}, area under the concentration-time curve from time 0 to end of the dosing period; hr, hour; PK, pharmacokinetics

Sex Hormone Binding Globulin (SHBG) Significantly Increased in a TERN-501 Dose-Dependent Manner

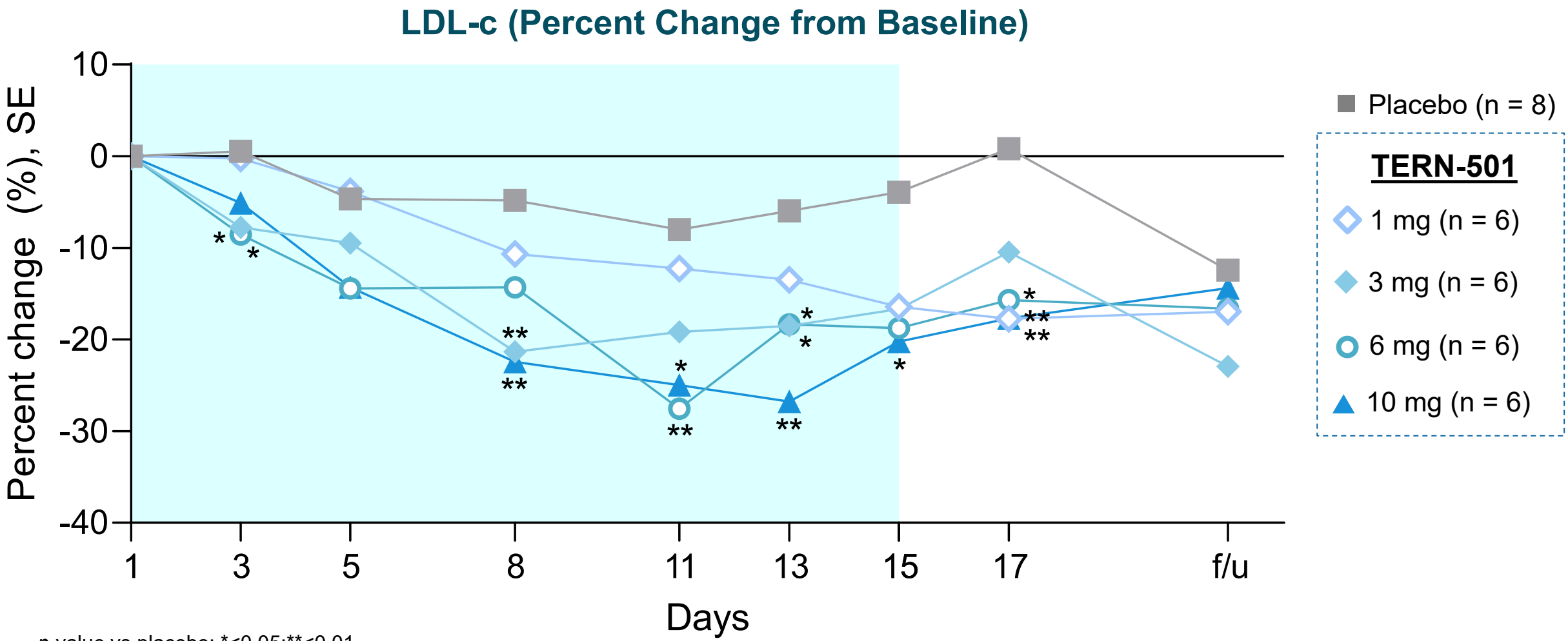


p-value vs placebo: *<0.05;**<0.01

Mean percent change refer to LSM from ANCOVA model and SE; shaded area represents dosing period

ANCOVA, analysis of covariance; f/u, follow-up; LSM, least squares mean; SE, standard error; SHBG, sex hormone binding globulin

TERN-501 Significantly Decreased Low-density Lipoprotein Cholesterol (LDL-c) Over Time

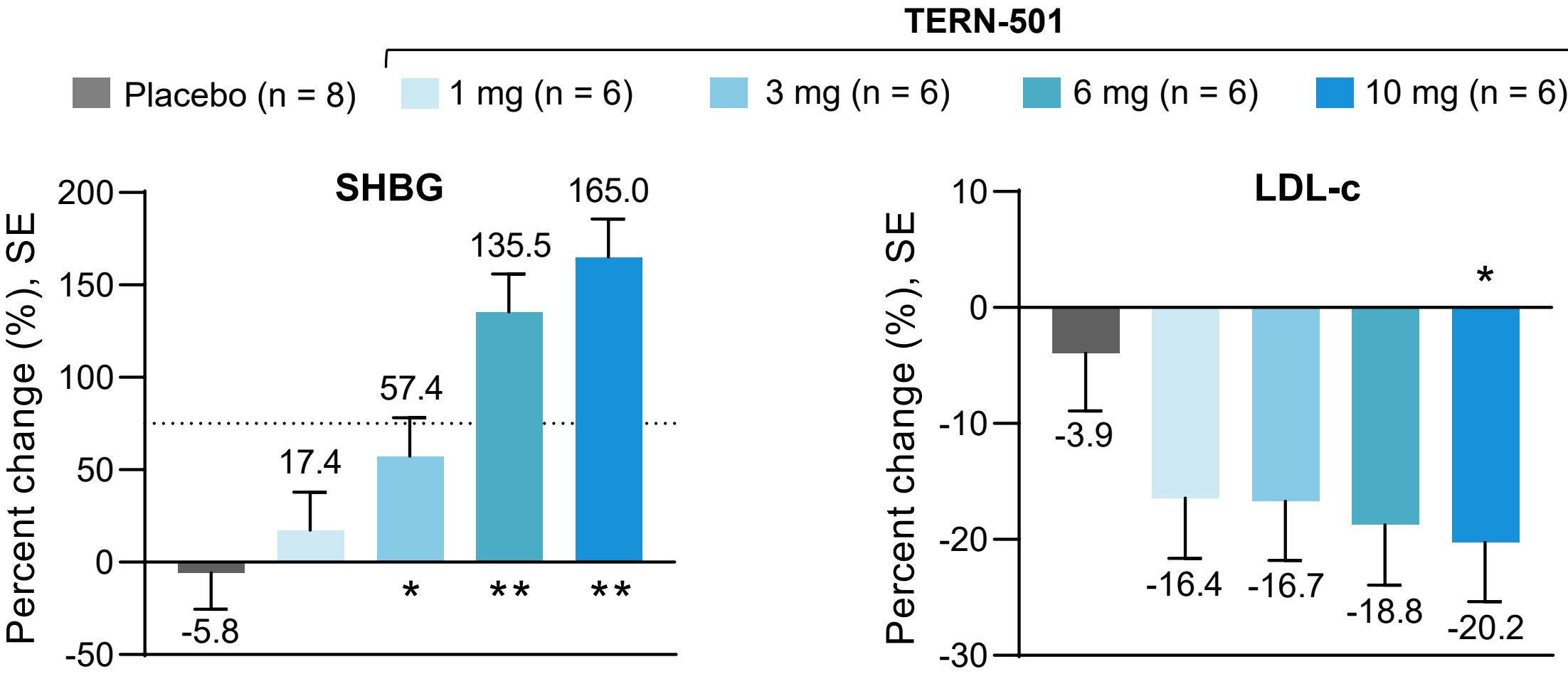


p-value vs placebo: *<0.05;**<0.01

Mean percent change refer to LSM from ANCOVA model and SE; shaded area represents dosing period

ANCOVA, analysis of covariance; f/u, follow-up; LDL-c, low-density lipoprotein cholesterol; LSM, least squares mean; SE, standard error

End of Treatment (Day 15) SHBG Increases and LDL-c Reductions were TERN-501 Dose-Dependent

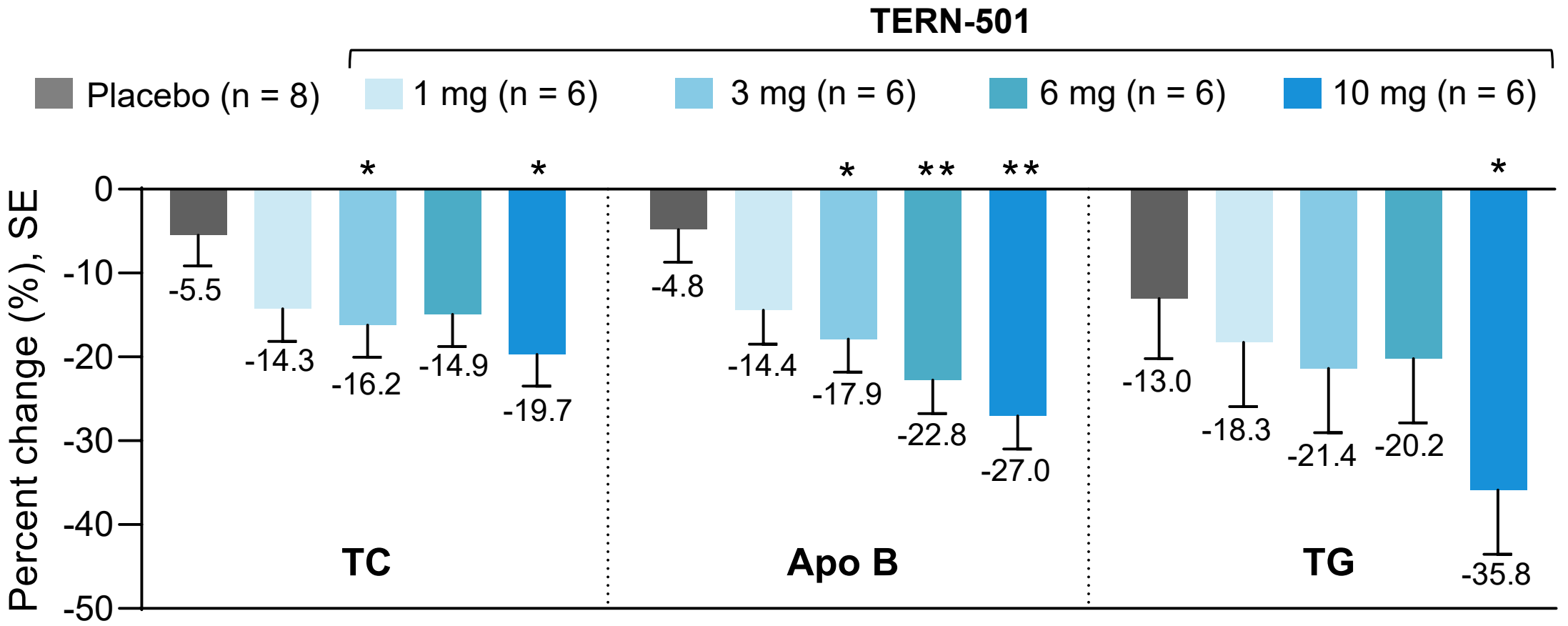


p-value vs placebo: *<0.05;**<0.01

Mean percent change refer to LSM from ANCOVA model and SE

ANCOVA, analysis of covariance; Apo B, apolipoprotein B; LDL-c, low-density lipoprotein cholesterol; LSM, least squares mean; PD, pharmacodynamics; SE, standard error; SHBG, sex hormone binding globulin; TC, total cholesterol; TG, triglycerides

TERN-501 Dose-Dependent Decreases in Other Atherogenic Lipids at End of Treatment (Day 15)



- No significant changes in HDL cholesterol were observed on Day 15

p-value vs placebo: *<0.05;**<0.01
Mean percent change refer to LSM from ANCOVA model and SE
ANCOVA, analysis of covariance; Apo B, apolipoprotein B; LDL-c, low-density lipoprotein cholesterol; LSM, least squares mean; PD, pharmacodynamics; SE, standard error; SHBG, sex hormone binding globulin; TC, total cholesterol; TG, triglycerides

Conclusions

- Once daily dosing of TERN-501 at 1, 3, 6, and 10 mg for 14 days was overall safe and well-tolerated with no clinical signs or symptoms of hypo/hyperthyroidism or THR-α agonism
- TERN-501 exhibited dose-proportional PK with low variability and a half-life suitable for once daily dosing
- TERN-501 increased SHBG, a key marker of hepatic THR-β engagement, in a dose-dependent manner
- TERN-501 led to significant decreases in circulating atherogenic lipid levels including LDL-c, Apo B, total cholesterol, and triglycerides
- Taken together, PD data indicate that administration of TERN-501 led to robust THR-β target engagement in the liver
- Significant reductions in atherogenic lipids along with increases in SHBG and favorable PK and safety observed in this study support further investigation of TERN-501 for NASH treatment alone or in combination with other agents including FXR agonist TERN-101

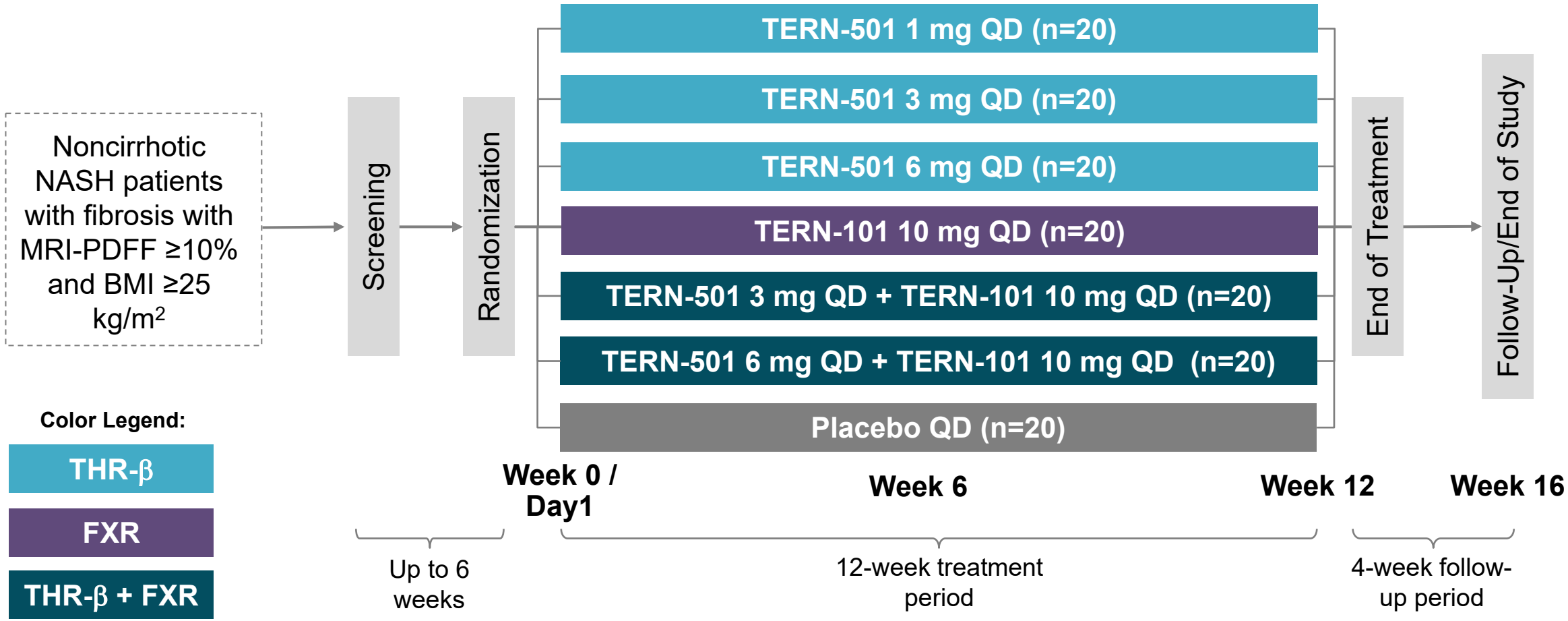
Apo B, apolipoprotein B; FXR, farnesoid X receptor; LDL-c, low-density lipoprotein cholesterol; NASH, nonalcoholic steatohepatitis; PD, pharmacodynamics; PK, pharmacokinetics; SHBG, sex hormone binding globulin; THR-α, thyroid hormone receptor-alpha; THR-β, thyroid hormone receptor-beta.

1. Sinha R, et al. *Nat Rev Endocrinol*. 2018;14:259-269. **2.** Harrison SA, et. al. *Lancet*. 2019;394 (10213):2012-2024. **3.** Jones C, et al. Poster presented at AASLD The Liver Meeting. Nov 12-15, 2021. Poster 1889.

Phase 2a DUET Study Underway

DUET

Randomized, Double-Blind, Placebo-Controlled, Factorial Design, Phase 2a Study (N=~140)



MRI-PDFF and cT1 at Baseline, Week 6, and Week 12

clinicaltrials.gov ID: NCT05415722

Acknowledgements

- TERN-501 is an investigational drug being developed by Terns Pharmaceuticals, which provided funding for the study as well as the oral presentation preparation services.
- The authors are grateful to the study volunteers, investigators, and research staff for participation and conduct of the study.
- The authors would like to thank Forward WE Go, a division of Wesley Enterprise, Inc. (Huntington Beach, CA, USA) for providing writing assistance.

QR link to presentation:

Contact Information

Cara Nelson, PhD
1065 East Hillsdale Blvd., Suite 100
Foster City, CA 94404, USA
cnelson@ternspharma.com

Erin Quirk, MD
1065 East Hillsdale Blvd., Suite 100
Foster City, CA 94404, USA
equirk@ternspharma.com