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THYROID HORMONE BETA RECEPTOR AGONIST TERN-501 DEMONSTRATES DOSE- AND EXPOSURE-DEPENDENT INCREASES IN SEX HORMONE BINDING GLOBULIN WITH ASSOCIATED DECREASES IN ATHEROGENIC LIPIDS IN HEALTHY SUBJECTS

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TERNS PHARMACEUTICALS

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KEY TAKEHOME MESSAGE

TERN-501 demonstrated potent dose- and exposure-dependent THR-β target engagement with decreases in LDL-c, total cholesterol, and triglycerides. Data support TERN-501 for evaluation in the Phase 2 dose-ranging DUET Study in patients with presumed NASH.

1 INTRODUCTION

- THR-β is the major form of thyroid hormone receptor (THR) expressed in liver[1]
- THR-β agonism reduces LDL-c, Apo B, and TG[2]
- SHBG is a key marker of hepatic THR-β target engagement
- In NASH patients receiving a THR-β agonist, high SHBG response (≥ 75% increase from baseline) has been associated with liver fat reduction and liver histological improvement[2]
- TERN-501 is a novel, metabolically stable, highly selective THR-β agonist
- In a first-in-human study, TERN-501 was well-tolerated and resulted in significant SHBG increases as well as atherogenic lipid decreases[3,4]
- Here we describe the PK/PD and PD/PD relationships observed with 14-day TERN-501 administration in the first-in-human study

THR-β regulates key aspects of energy metabolism (e.g., fatty acid & lipid synthesis, liver fat removal through fatty acid oxidation)[1]
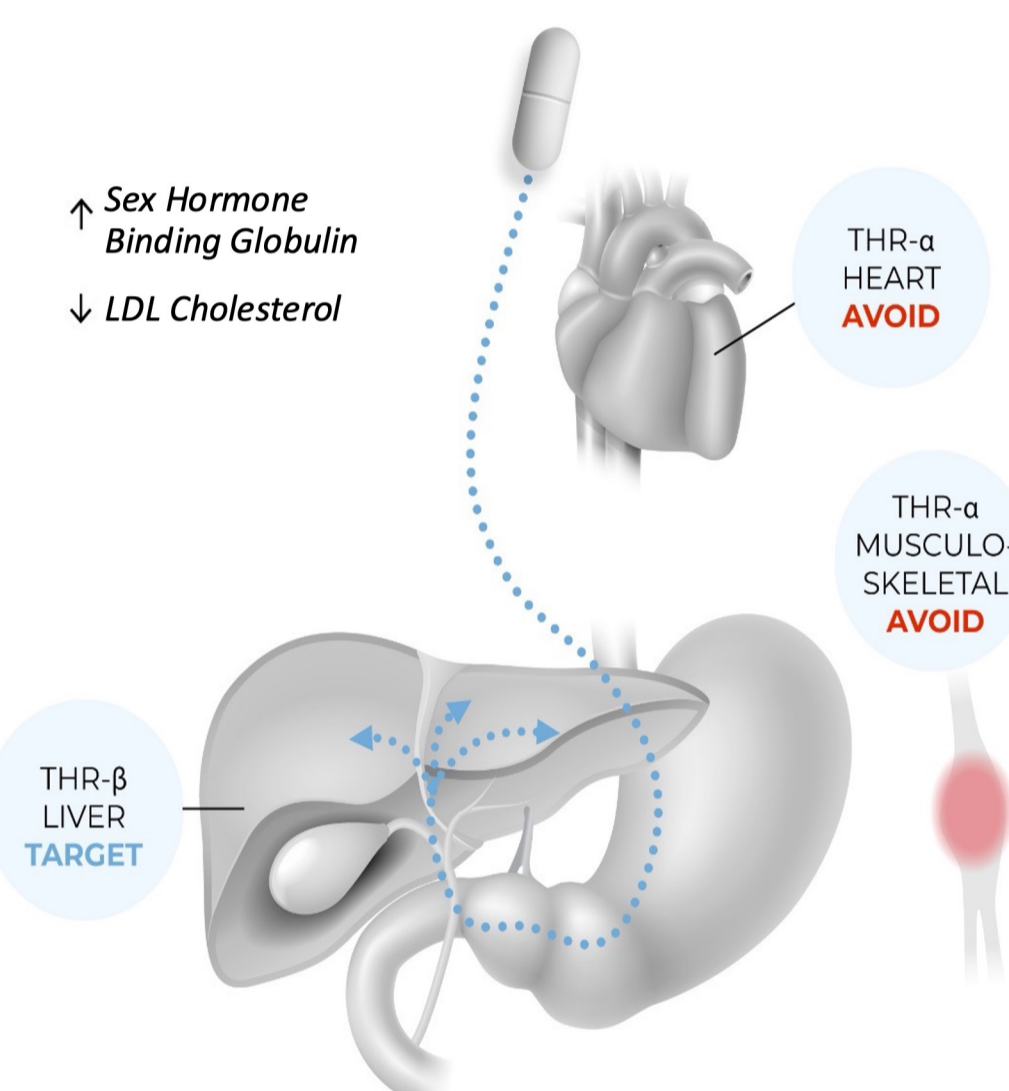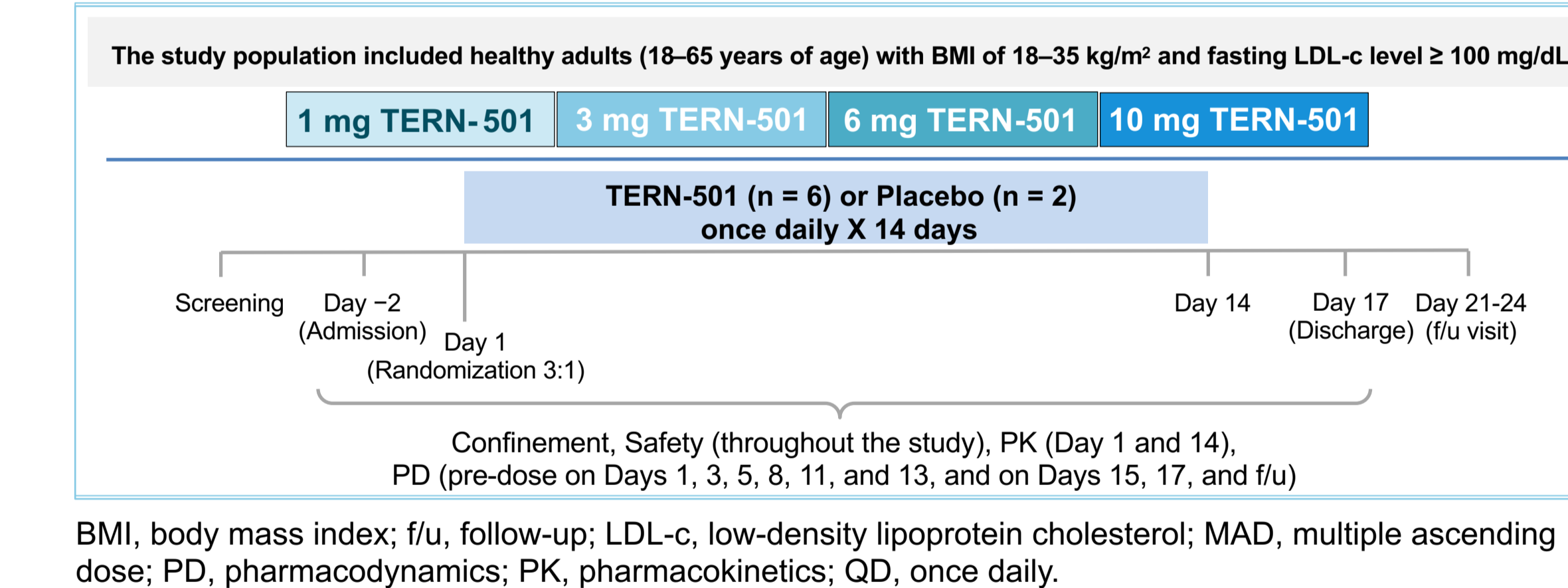
↑ Sex Hormone Binding Globulin
↓ LDL Cholesterol

THR-α HEART AVOID
THR-α MUSCULO-SKELETAL AVOID
THR-β LIVER TARGET

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

Figure 1: Study Design

The study population included healthy adults (18–65 years of age) with BMI of 18–35 kg/m² and fasting LDL-c level ≥ 100 mg/dL

1 mg TERN-501 | 3 mg TERN-501 | 6 mg TERN-501 | 10 mg TERN-501

TERN-501 (n = 6) or Placebo (n = 2) once daily X 14 days

Screening
Day −2 (Admission) (Randomization 3:1)
Day 1
Day 14
Day 17 (Discharge)
Day 21-24 (f/u visit)

Confinement, Safety (throughout the study), PK (Day 1 and 14), PD (pre-dose on Days 1, 3, 5, 8, 11, and 13, and on Days 15, 17, and f/u)

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.

2 OBJECTIVES

- To evaluate the relationship between TERN-501 pharmacokinetics and pharmacodynamic response
- To evaluate the relationship between SHBG response and changes in other pharmacodynamic markers of TERN-501

3 METHODS

- PK parameters estimated by noncompartmental analysis (WinNonlin)
- PK/PD analyses performed in Graphpad Prism using linear and nonlinear regression
- SHBG responder was defined as ≥75% increase in SHBG from baseline

REFERENCES
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.
4) Nelson C, et al. Oral presentation at EASL International Liver Congress. Jun 22-26, 2022. Abstract OS123.

4 RESULTS

Table 1: 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/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
BMI, mean (SD) [kg/m²]	28.6 (3.5)	28.1 (3.8)	27.1 (2.5)	26.3 (4.2)	27.0 (4.0)
Apo B, mean (SD) [mg/dL]	118.8 (26.7)	95.8 (20.2)	107.8 (12.8)	100.3 (39.8)	104.8 (12.3)
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)
TC, mean (SD) [mg/dL]	222.5 (41.4)	187.3 (41.4)	209.7 (13.1)	188.0 (62.0)	197.2 (15.5)
TG, mean (SD) [mg/dL]	125.8 (63.7)	112.0 (36.4)	107.7 (50.6)	123.8 (77.4)	116.3 (63.7)
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; Apo B, apolipoprotein B; TG, triglycerides; TC, total cholesterol; SD, standard deviation

- Subjects were predominantly male, white, non-Hispanic, and overweight with mildly elevated LDL cholesterol, consistent with inclusion criteria
- Once daily dosing of TERN-501 at 1, 3, 6 and 10 mg for 14 days was overall safe and well tolerated with no clinically meaningful trends in laboratory assessments or AEs

Table 2: LSM Percent Change from Baseline on Day 15

	Placebo (N = 8)	1 mg (N = 6)	3 mg (N = 6)	6 mg (N = 6)	10 mg (N = 6)
Apo B	-4.81 (3.867)	-14.41 (4.059)	-17.85 (3.971)*	-22.77 (4.001)*	-27.02 (3.973)*
LDL-c	-3.93 (5.006)	-16.44 (5.182)	-16.68 (5.131)	-18.75 (5.200)	-20.23 (5.141)*
TC	-5.45 (3.658)	-14.27 (3.846)	-16.21 (3.801)*	-14.90 (3.841)	-19.68 (3.793)*
TG	-13.04 (7.129)	-18.26 (7.667)	-21.35 (7.685)	-20.22 (7.663)	-35.85 (7.657)*

LSM, least squares mean; Apo B, apolipoprotein B; LDL-c, low density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides; *p < 0.05 vs. placebo

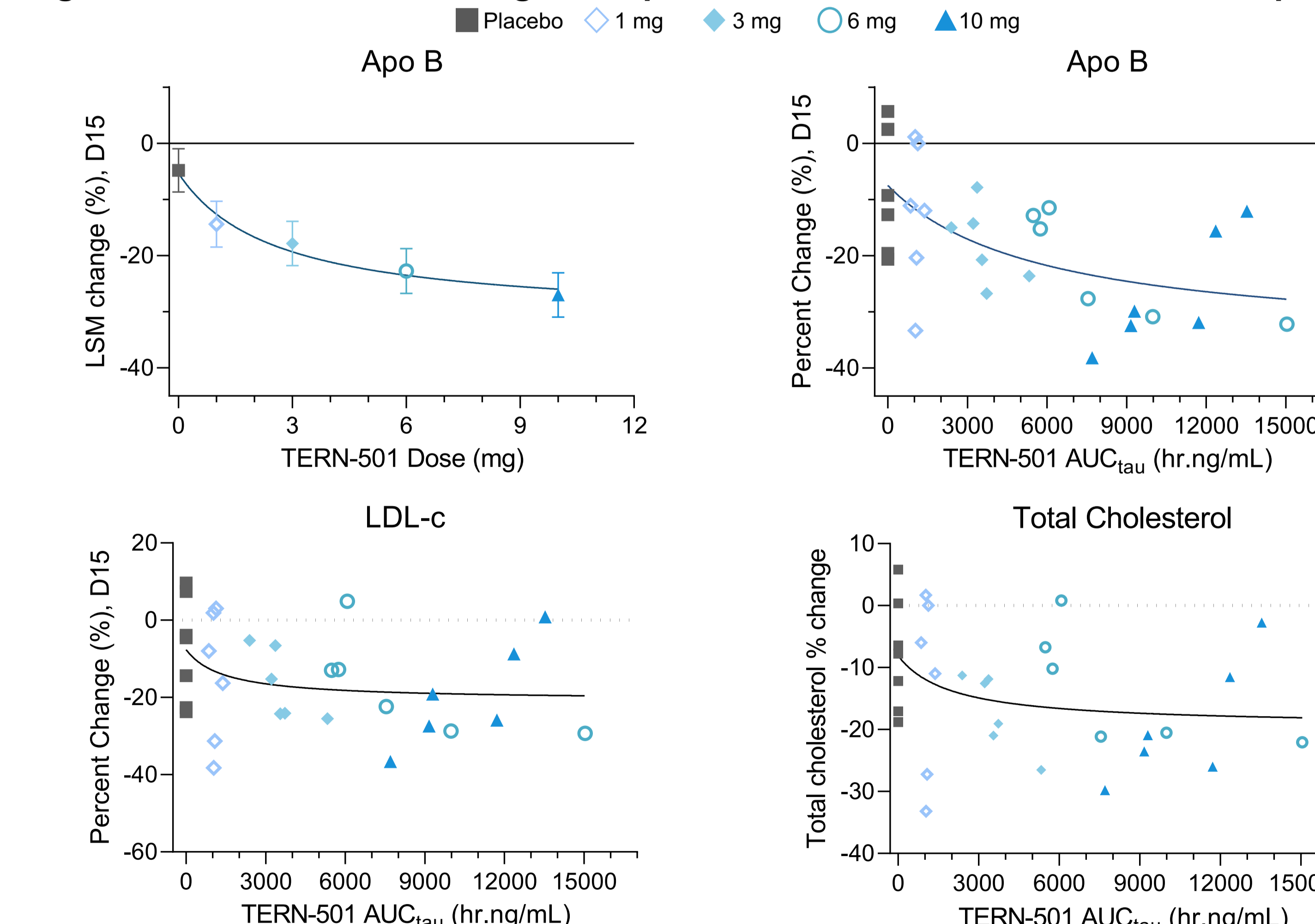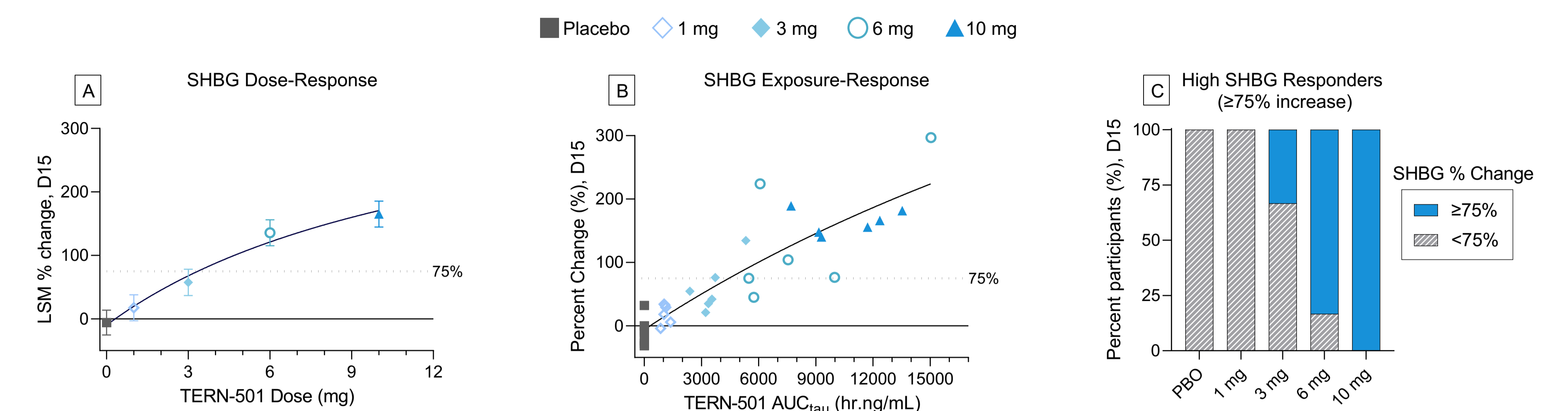### Figure 2: Decreases in Atherogenic Lipids across TERN-501 Treatment Groups

Figure 2: Apo B least squares mean (LSM) percent change from baseline (Day -1) and standard error on Day 15 were plotted by treatment group; dose-response relationship was fitted using an Emax equation. Percent change from baseline (Day -1) on Day 15 for each lipid parameter was plotted against individual subject steady-state exposure (AUCtau) determined after last dose on Day 14. Exposure-response relationships for Apo B, LDL-c, and total cholesterol were fitted using an Emax equation.

- Decreases in Apo B were strongly correlated with TERN-501 dose (R^2 = 0.97) and moderately correlated with TERN-501 exposures (R^2 = 0.36) with EC_{50} exposure corresponding to an approximately 5 mg dose
- LDL-c, TC, and triglycerides (not shown) decreased in all TERN-501 dose groups and were weakly associated with TERN-501 exposures (R^2 = 0.11-0.21)

Figure 3: TERN-501 Showed Dose-dependent Increases in SHBG Levels and Response Rate

Figure 3A: SHBG least squares mean (LSM) percent change from baseline (Day -1) and standard error on Day 15 were plotted by treatment group. Dose-response relationship was fitted using an Emax equation.
Figure 3B: SHBG percent change from baseline (Day -1) on Day 15 were plotted against individual steady-state exposures (AUCtau) of TERN-501 as determined after last dose (Day 14). Exposure-response relationship was fitted using an Emax equation.
Figure 3C: The proportion of subjects within each treatment group achieving a high SHBG response (≥75% increase from baseline) on Day 15 of the study.

- Increases in SHBG from baseline were highly correlated to both TERN-501 dose (R^2 = 0.98) and exposure (AUCtau R^2 = 0.78)
  - Overlap in exposures and SHBG response between the 6 mg and 10 mg groups
- The proportion of subjects achieving high SHBG response was dose-dependent
  - High SHBG response was observed in all subjects in the 10 mg TERN-501 group and in 5 of the 6 subjects (83%) in the 6 mg group after a short treatment duration (Day 15)
  - No subject in the placebo or 1 mg TERN-501 groups achieved a high SHBG response by end of treatment (Day 15)

Figure 4: High SHBG Response Associated with Greater Decreases in Serum Lipids
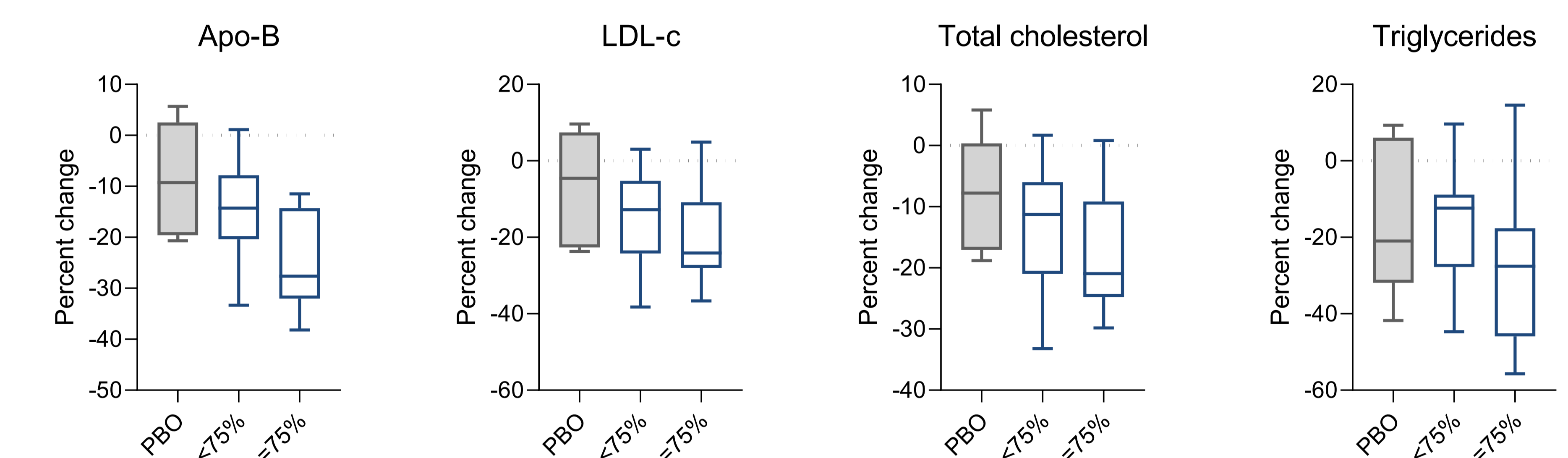

Figure 4: TERN-501 treated subjects were pooled across doses and divided by SHBG response (<75% and ≥75% change from baseline on Day 15). Placebo (PBO) subjects were pooled across cohorts; no placebo subject had ≥75% increase in SHBG from baseline. The corresponding percent change from baseline in each lipid on Day 15 was then plotted. Box represent median and interquartile range and whiskers represent min to max.

- At the end of treatment (Day 15), TERN-501 treated subjects with high SHBG response (≥75% increase from baseline; N=13) had greater median decreases in serum lipids than TERN-501 treated subjects with low SHBG response (<75% increase from baseline; N=11) or placebo subjects (N=8)

5 CONCLUSIONS

- SHBG increases were strongly correlated to TERN-501 dose and plasma exposures, with overlap in both exposure and SHBG response in subjects receiving 6 mg and 10 mg TERN-501, indicating little potential for further increase in response with TERN-501 doses >6 mg.
- High SHBG response (≥75% increase from baseline) was dose-dependent, with the greatest number of responders in the 6 mg and 10 mg groups
- In TERN-501 treated subjects, high SHBG response corresponded to greater median reductions in atherogenic lipids compared to low SHBG response
- Similar to SHBG, Apo B changes correlated with TERN-501 dose and exposure
- Decreases in LDL-c, total cholesterol, and triglycerides were seen at all TERN-501 doses without obvious exposure-dependence
- Taken together, these data indicate potent dose- and exposure-dependent THR-β target engagement by TERN-501
- These data, along with previously presented safety data, support the selection of 1, 3, and 6 mg TERN-501 for evaluation in the Phase 2 DUET Study which aims to assess the efficacious dose range of TERN-501 in NASH patients