DUET

Topline Results from a 12-Week Phase 2a Trial (DUET) Evaluating TERN-501, a Highly Selective Thyroid Hormone Receptor (THR) β Agonist, Either as Monotherapy or in Combination with TERN-101, a Nonsteroidal Farnesoid X Receptor (FXR) Agonist, Demonstrated Significant Reductions in MR-Based Liver Fat Content and Fibroinflammation in Patients with Presumed MASH

Mazen Noureddin[1], Naim Alkhouri[2], Eric Lawitz[3], Kris Kowdley[4], Rohit Loomba[5], William Sanchez[6], Yancicy Gonzalez-Rojas[7], Joseph Kosinski[8], Lois Lee[9], Christopher Jones[9], Erin Quirk[9], Stephen A. Harrison[10]

[1]Houston Methodist Hospital, Houston Research Institute, Houston, TX, USA; [2]Arizona Liver Health, Tucson, AZ, USA; [3]Texas Liver Institute, University of Texas Health, San Antonio, TX, USA; [4]Liver Institute Northwest, Elson S. Floyd College of Medicine, Washington State University, Seattle, Washington, USA; [5]NAFLD Research Center, University of California San Diego, La Jolla, CA, USA; [6]Floridian Clinical Research, Miami Lakes, Florida, USA; [7]Optimus U, Inc., Miami, Florida, USA; [8]Premier Medical Group, Clarksville, Tennessee, USA; [9]Terns Pharmaceuticals, Foster City, CA, USA; [10]Pinnacle Clinical Research, San Antonio, TX, USA

The Liver Meeting; 10-14 November 2023; Boston, MA.

Disclosures

I disclose the following financial relationship(s) with a commercial interest:

- Scientific advisor or consultant for: 89bio, Altimmune, Boehringer Ingelheim, Cytodyn, EchoSens, GSK, Madrigal, Merck, NovoNordisk, Perspectum, Roche diagnostic, Siemens, Takeda, Terns
- Share options: ChronWell, CIMA, Rivus Pharma
- Grant/Research support: Akero, Allergan, Bristol Myers Squibb, Conatus, Corcept, Enanta, Galectin, Genfit, Gilead, GSK, Madrigal, Novartis, NovoNordisk, Shire, Takeda, Terns, Viking, Zydus

Acknowledgements

DUET

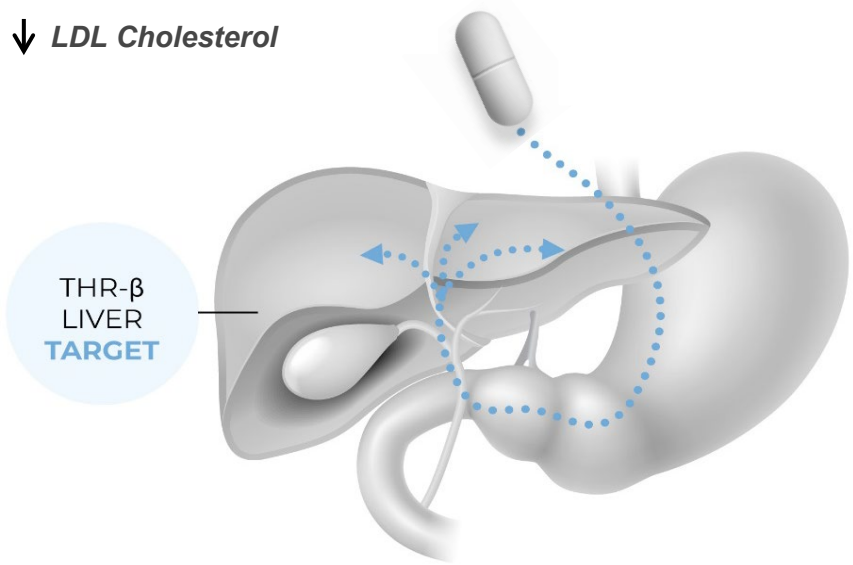
We would like to acknowledge and thank the patients and their families / caregivers, the investigators and their support staff who participated in this work

TERN-501: A Highly Selective THR-β Agonist with Enhanced Metabolic Stability

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

↑ *Sex Hormone Binding Globulin*

↓ *LDL Cholesterol*



- THR-β is the major form of thyroid hormone receptor in liver[1]
  - THR-β agonism can lead to MASH resolution and fibrosis regression as demonstrated in a biopsy-based Phase 3 non-cirrhotic MASH study[2]
- TERN-501 is a potent, highly selective THR-β agonist
  - In a Phase 1 study, once-daily dosing of TERN-501 was safe, well-tolerated, and showed robust target engagement[3,4]
- We conducted the DUET Study, a 12-week clinical trial in presumed MASH, to evaluate TERN-501 as a monotherapy or in combination with TERN-101, a liver directed nonsteroidal FXR agonist

FXR, farnesoid X receptor; LDL low-density lipoprotein; MASH, metabolic dysfunction-associated steatohepatitis; THR-β, thyroid hormone receptor-beta

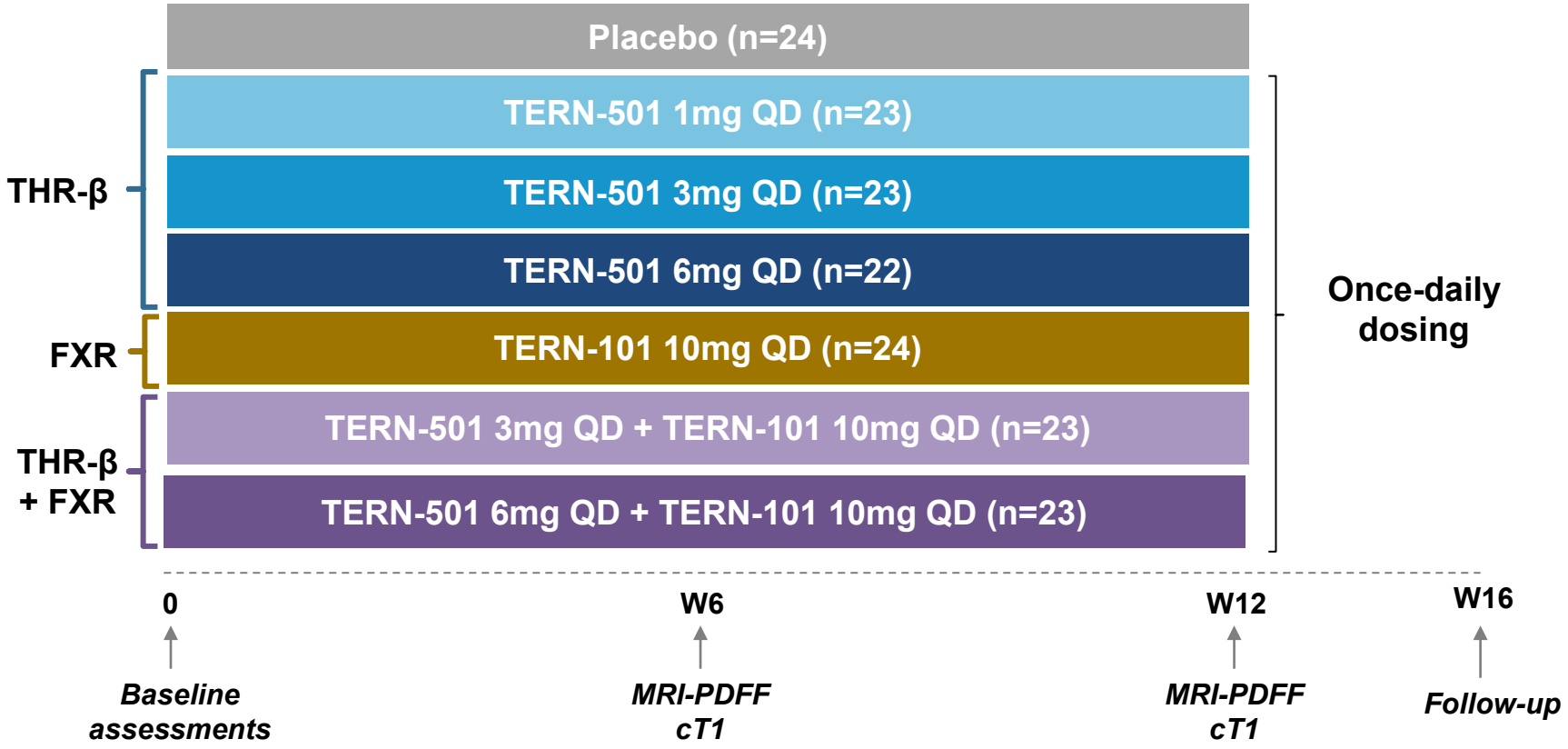
1. Sinha R, et al. *Nat Rev Endocrinol*. 2018;14:259-269. 2. Harrison S, et.al. Abstract GS-001. *J Hep*. 2023; 78 (Suppl. 1). 3. Jones C, et al. Abstract 1889. *Hepatology*. 2021;74 (Suppl.1). 4. Nelson C, et al. Abstract. OS123. *J Hep*. 2022; 77 (Suppl.1).

DUET: 12-week Phase 2a Trial in Presumed MASH Patients

Key Entry Criteria

- Non-cirrhotic; presumed MASH
- BMI ≥25 kg/m^2
- MRI-PDFF ≥10%
- MRI-cT1 ≥800 msec
- HbA1c ≤ 9.5%
- LDL <150 mg/dL; TG ≤ 500 mg/dL

Randomized, double-blind, placebo-controlled trial (N=162)



NCT05415722

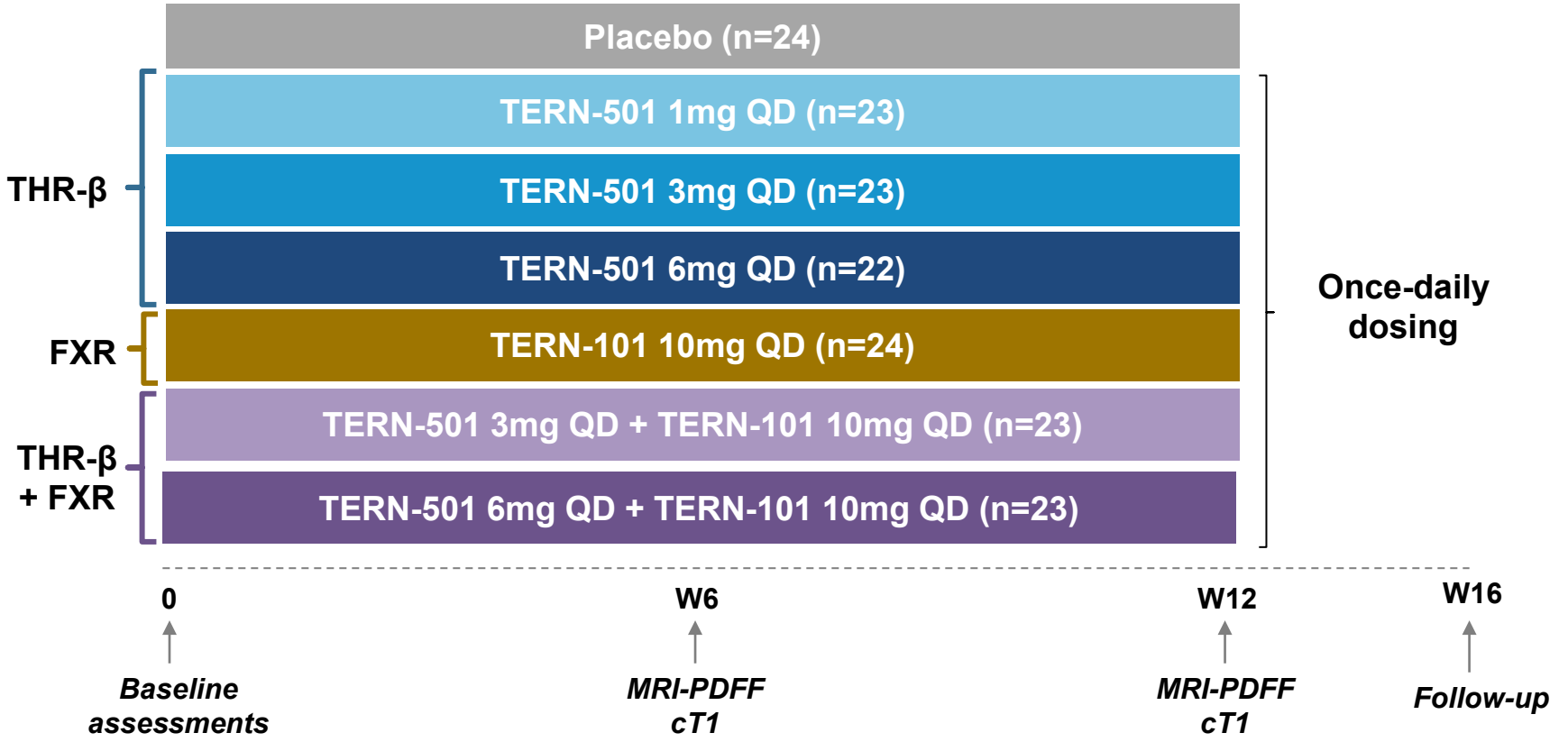
BMI, body mass index; cT1, corrected T1; HbA1c, hemoglobin A1c; MRI-PDFF, magnetic resonance imaging proton density fat fraction; QD, once-daily; TG, triglycerides; W, week

DUET: 12-week Phase 2a Trial in Presumed MASH Patients

Randomized, double-blind, placebo-controlled trial (N=162)

Key Entry Criteria

- Non-cirrhotic; presumed MASH
- BMI ≥25 kg/m^2
- MRI-PDFF ≥10%
- MRI-cT1 ≥800 msec
- HbA1c ≤ 9.5%
- LDL <150 mg/dL; TG ≤ 500 mg/dL



Endpoints At Week 12

Primary Endpoint

- Relative change in MRI-PDFF of TERN-501 vs placebo

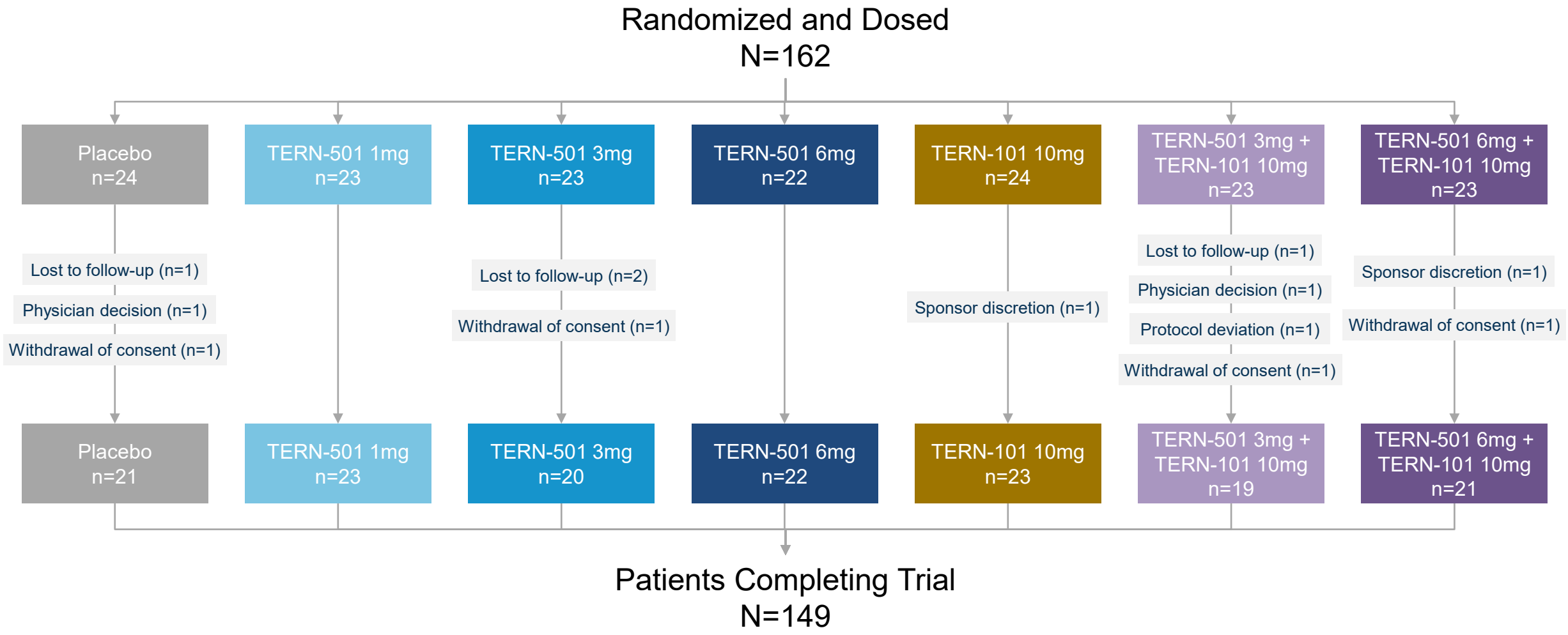
Secondary Endpoints

- Relative change in MRI-PDFF of '501+'101 vs placebo
- Changes in cT1 of TERN-501 vs placebo and of '501+'101 vs placebo
- Safety and tolerability

NCT05415722

BMI, body mass index; cT1, corrected T1; HbA1c, hemoglobin A1c; MRI-PDFF, magnetic resonance imaging proton density fat fraction; QD, once-daily; TG, triglycerides; W, week

>90% Rate of Trial Completion With Similar Frequency of Study Withdrawal Among All Arms



Baseline Characteristics: Balanced Across Arms

		TERN-501			TERN-101	'501 + '101	
	Placebo (N=24)	1mg (N=23)	3mg (N=23)	6mg (N=22)	10mg (N=24)	3mg + 10mg (N=23)	6mg + 10mg (N=23)
Age, mean (SD) [years]	52 (11)	52 (13)	52 (14)	52 (12)	54 (12)	56 (13)	55 (8)
Female	63%	48%	57%	73%	50%	48%	48%
Hispanic	79%	74%	57%	68%	42%	48%	61%
BMI, mean (SD) [kg/m^2]	37 (7)	38 (8)	37 (8)	39 (7)	37 (4)	39 (8)	38 (6)
Type 2 diabetes	46%	35%	44%	27%	29%	57%	57%
GLP-1 agonists	8%	9%	9%	5%	13%	17%	13%
ALT, mean (SD) [IU/L]	44 (19)	42 (25)	39 (22)	38 (24)	39 (16)	43 (28)	50 (33)
AST, mean (SD) [IU/L]	34 (17)	31 (14)	29 (13)	26 (9)	31 (12)	31 (17)	36 (23)
LDL cholesterol, mean (SD) [mg/dL]	87 (29)	102 (32)	102 (27)	99 (30)	85 (27)	89 (30)	93 (24)
MRI-PDFF, mean (SD) [%]	17 (5)	17 (5)	20 (6)	17 (6)	18 (5)	19 (7)	17 (4)
cT1, mean (SD) [msec]	937 (102)	921 (83)	928 (81)	920 (79)	962 (113)	977 (129)	906 (85)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GLP-1, glucagon-like peptide-1; SD, standard deviation

Baseline Characteristics: Balanced Across Arms

		TERN-501			TERN-101	'501 + '101	
	Placebo (N=24)	1mg (N=23)	3mg (N=23)	6mg (N=22)	10mg (N=24)	3mg + 10mg (N=23)	6mg + 10mg (N=23)
Age, mean (SD) [years]	52 (11)	52 (13)	52 (14)	52 (12)	54 (12)	56 (13)	55 (8)
Female	63%	48%	57%	73%	50%	48%	48%
Hispanic	79%	74%	57%	68%	42%	48%	61%
BMI, mean (SD) [kg/m^2]	37 (7)	38 (8)	37 (8)	39 (7)	37 (4)	39 (8)	38 (6)
Type 2 diabetes	46%	35%	44%	27%	29%	57%	57%
GLP-1 agonists	8%	9%	9%	5%	13%	17%	13%
ALT, mean (SD) [IU/L]	44 (19)	42 (25)	39 (22)	38 (24)	39 (16)	43 (28)	50 (33)
AST, mean (SD) [IU/L]	34 (17)	31 (14)	29 (13)	26 (9)	31 (12)	31 (17)	36 (23)
LDL cholesterol, mean (SD) [mg/dL]	87 (29)	102 (32)	102 (27)	99 (30)	85 (27)	89 (30)	93 (24)
MRI-PDFF, mean (SD) [%]	17 (5)	17 (5)	20 (6)	17 (6)	18 (5)	19 (7)	17 (4)
cT1, mean (SD) [msec]	937 (102)	921 (83)	928 (81)	920 (79)	962 (113)	977 (129)	906 (85)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GLP-1, glucagon-like peptide-1; SD, standard deviation

Baseline Characteristics: Balanced Across Arms

		TERN-501			TERN-101	'501 + '101	
	Placebo (N=24)	1mg (N=23)	3mg (N=23)	6mg (N=22)	10mg (N=24)	3mg + 10mg (N=23)	6mg + 10mg (N=23)
Age, mean (SD) [years]	52 (11)	52 (13)	52 (14)	52 (12)	54 (12)	56 (13)	55 (8)
Female	63%	48%	57%	73%	50%	48%	48%
Hispanic	79%	74%	57%	68%	42%	48%	61%
BMI, mean (SD) [kg/m^2]	37 (7)	38 (8)	37 (8)	39 (7)	37 (4)	39 (8)	38 (6)
Type 2 diabetes	46%	35%	44%	27%	29%	57%	57%
GLP-1 agonists	8%	9%	9%	5%	13%	17%	13%
ALT, mean (SD) [IU/L]	44 (19)	42 (25)	39 (22)	38 (24)	39 (16)	43 (28)	50 (33)
AST, mean (SD) [IU/L]	34 (17)	31 (14)	29 (13)	26 (9)	31 (12)	31 (17)	36 (23)
LDL cholesterol, mean (SD) [mg/dL]	87 (29)	102 (32)	102 (27)	99 (30)	85 (27)	89 (30)	93 (24)
MRI-PDFF, mean (SD) [%]	17 (5)	17 (5)	20 (6)	17 (6)	18 (5)	19 (7)	17 (4)
cT1, mean (SD) [msec]	937 (102)	921 (83)	928 (81)	920 (79)	962 (113)	977 (129)	906 (85)

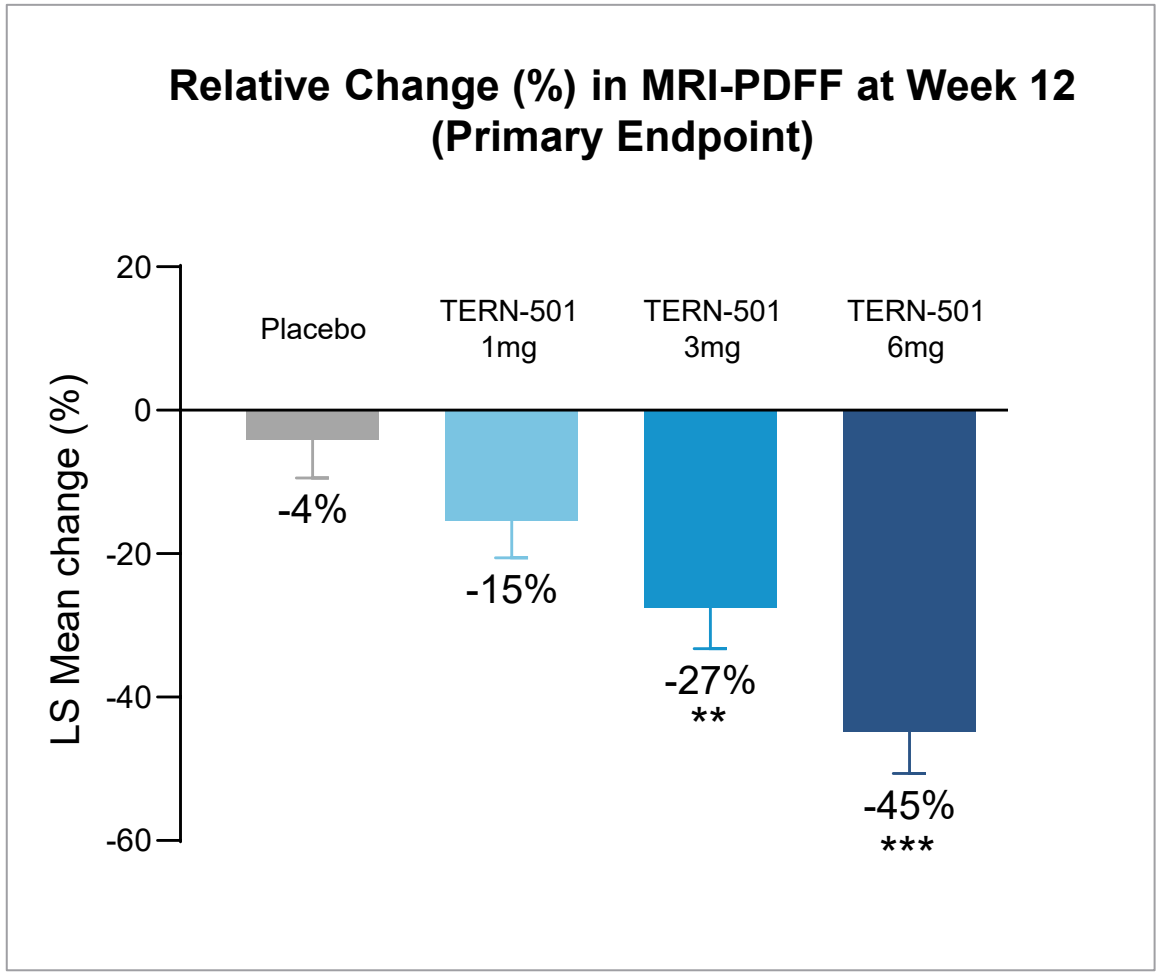
ALT, alanine aminotransferase; AST, aspartate aminotransferase; GLP-1, glucagon-like peptide-1; SD, standard deviation

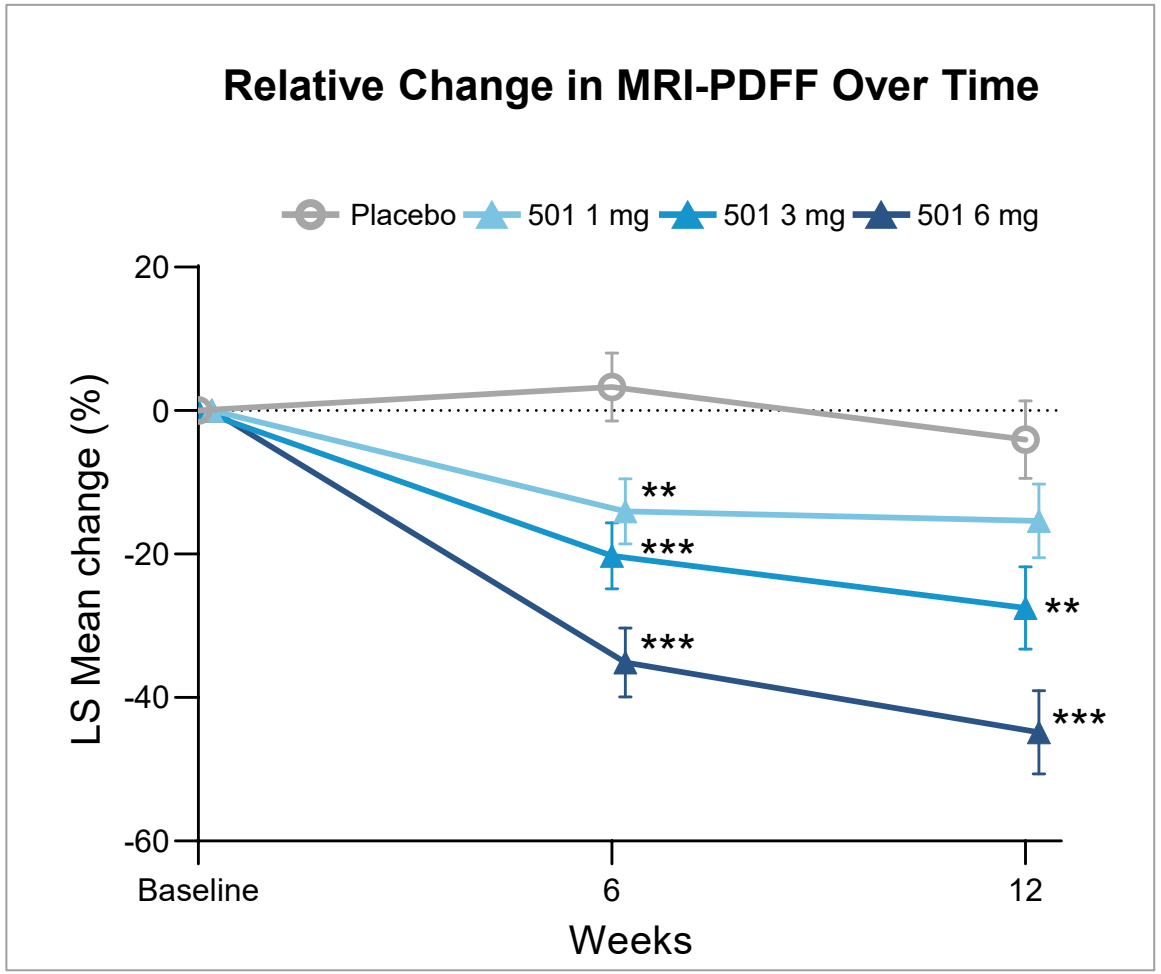
Baseline Characteristics: Balanced Across Arms

		TERN-501			TERN-101	'501 + '101	
	Placebo (N=24)	1mg (N=23)	3mg (N=23)	6mg (N=22)	10mg (N=24)	3mg + 10mg (N=23)	6mg + 10mg (N=23)
Age, mean (SD) [years]	52 (11)	52 (13)	52 (14)	52 (12)	54 (12)	56 (13)	55 (8)
Female	63%	48%	57%	73%	50%	48%	48%
Hispanic	79%	74%	57%	68%	42%	48%	61%
BMI, mean (SD) [kg/m^2]	37 (7)	38 (8)	37 (8)	39 (7)	37 (4)	39 (8)	38 (6)
Type 2 diabetes	46%	35%	44%	27%	29%	57%	57%
GLP-1 agonists	8%	9%	9%	5%	13%	17%	13%
ALT, mean (SD) [IU/L]	44 (19)	42 (25)	39 (22)	38 (24)	39 (16)	43 (28)	50 (33)
AST, mean (SD) [IU/L]	34 (17)	31 (14)	29 (13)	26 (9)	31 (12)	31 (17)	36 (23)
LDL cholesterol, mean (SD) [mg/dL]	87 (29)	102 (32)	102 (27)	99 (30)	85 (27)	89 (30)	93 (24)
MRI-PDFF, mean (SD) [%]	17 (5)	17 (5)	20 (6)	17 (6)	18 (5)	19 (7)	17 (4)
cT1, mean (SD) [msec]	937 (102)	921 (83)	928 (81)	920 (79)	962 (113)	977 (129)	906 (85)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GLP-1, glucagon-like peptide-1; SD, standard deviation

Primary Endpoint: TERN-501 Showed Rapid, Dose Dependent, and Significant Reductions in MRI-PDFF



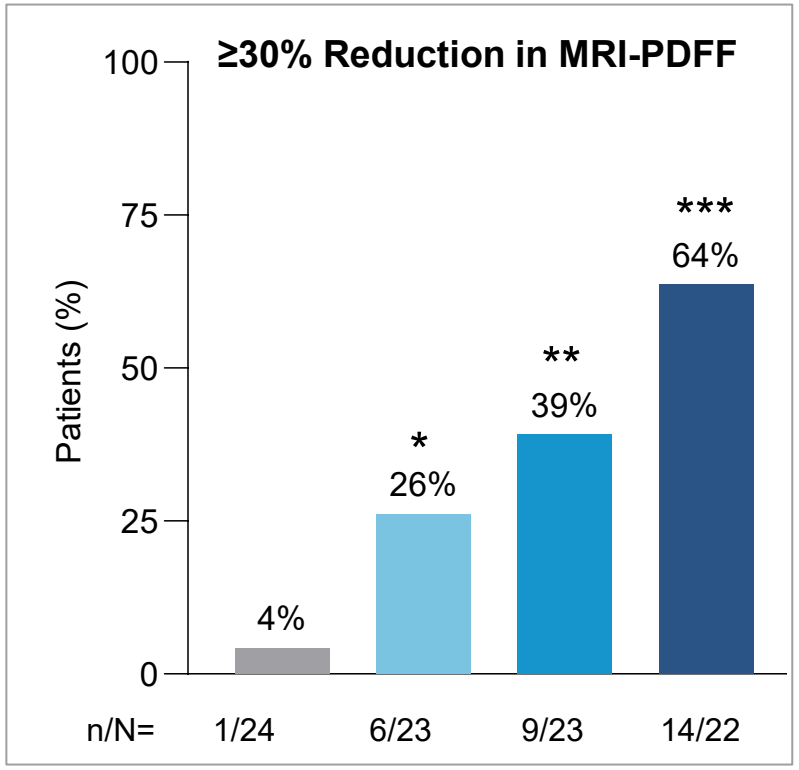


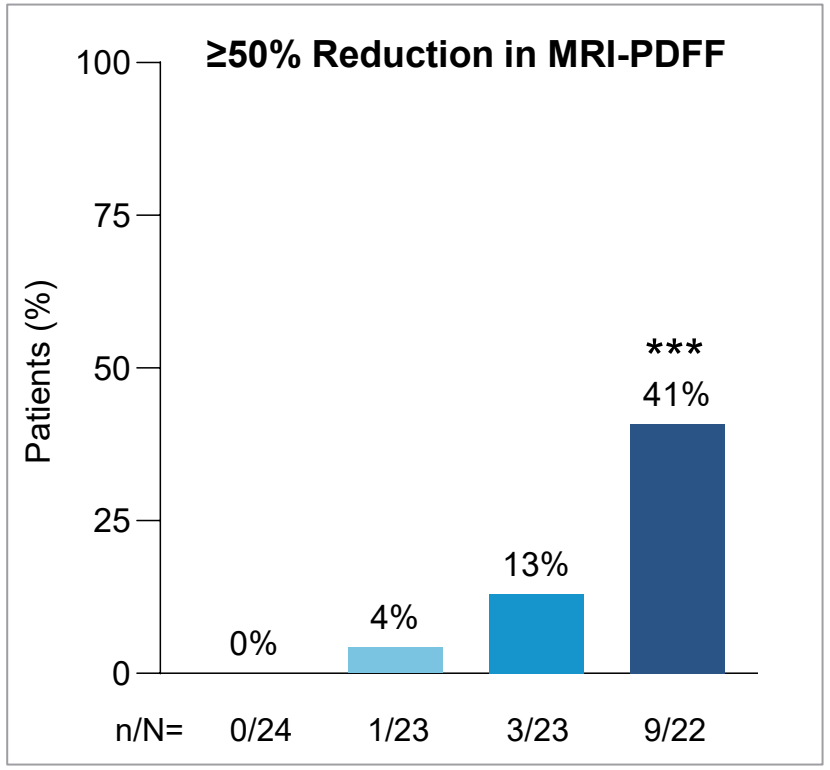
**p-value <0.01; ***p-value <0.001 for TERN-501 monotherapy vs. placebo
Error bars represent standard error
ANCOVA, analysis of covariance; LS Mean, least squares mean from ANCOVA model

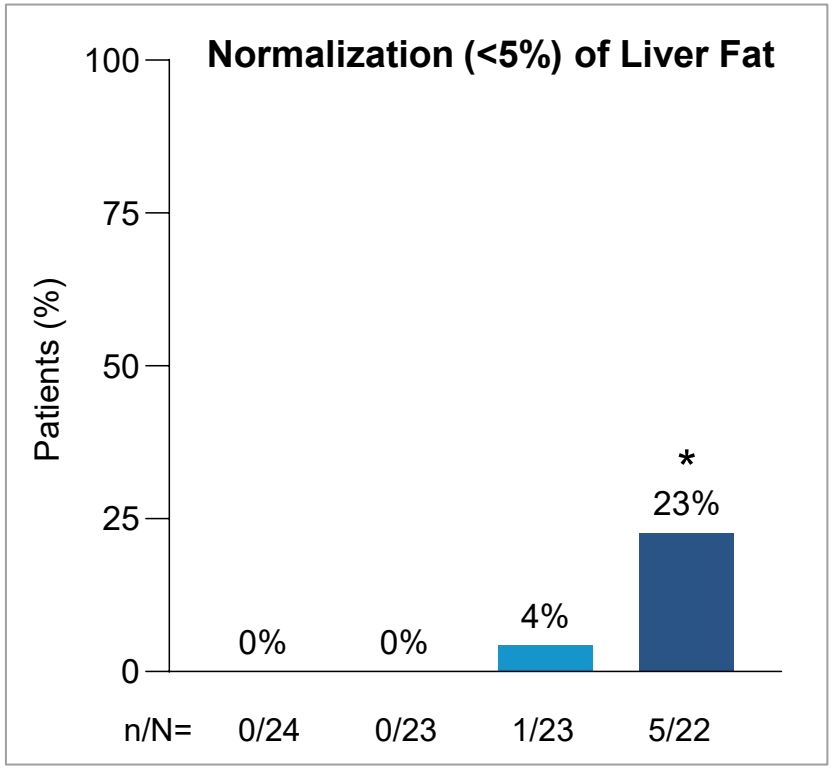
TERN-501 Demonstrated Robust Liver Fat Reduction with High Responder Rates by MRI-PDFF

- 64% of patients with ≥30% liver fat reduction and 23% patients normalized liver fat at Week 12 in the TERN-501 6mg group

Proportion (%) of Responders Achieving MRI-PDFF Response Criteria at Week 12





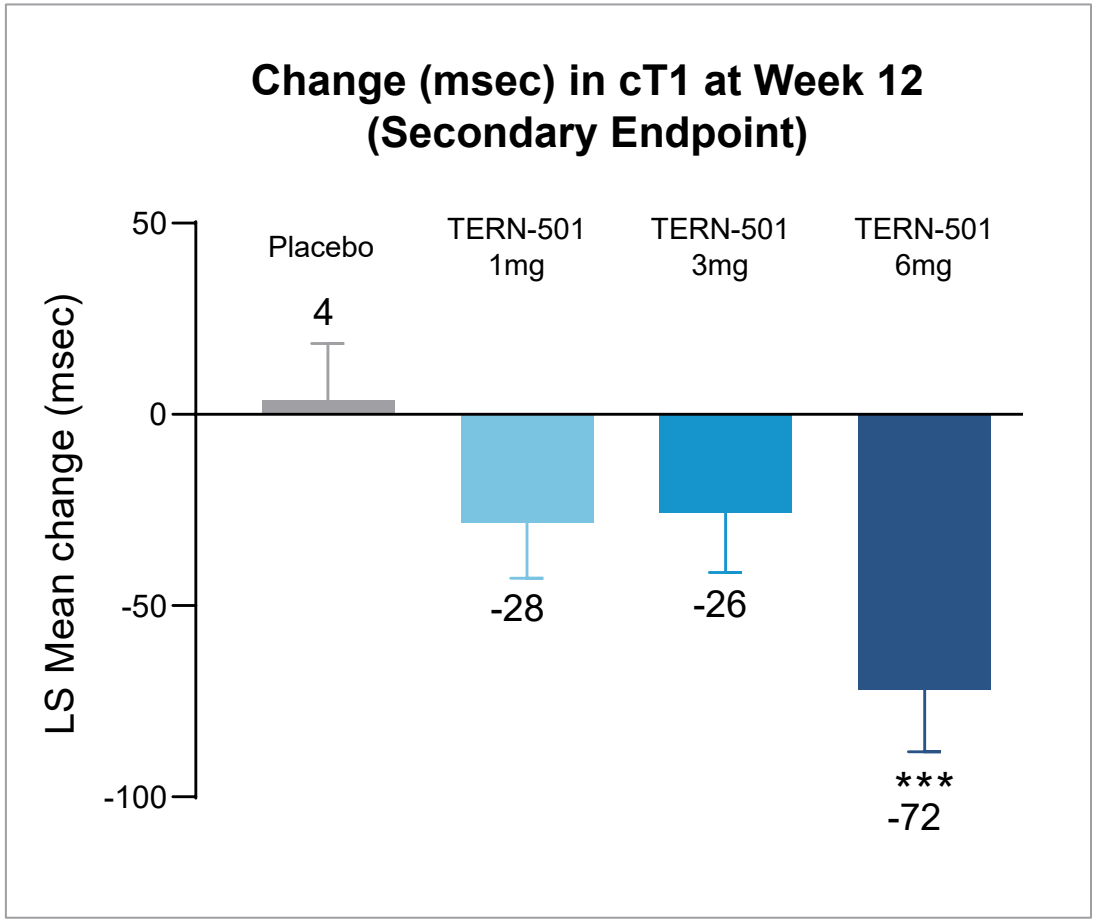


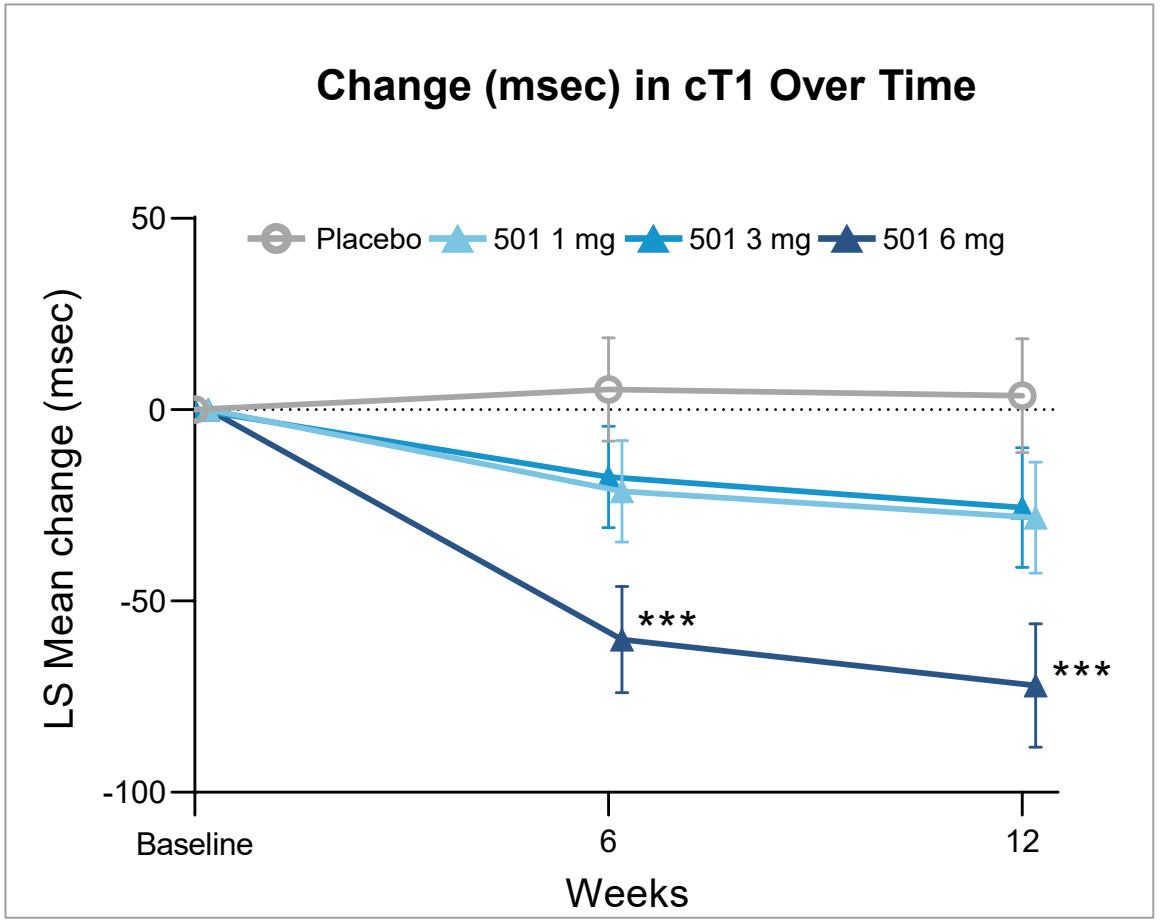
Placebo | 501 1 mg | 501 3 mg | 501 6 mg

*p-value <0.05; **p-value <0.01; ***p-value <0.001 for TERN-501 monotherapy vs. placebo
n=number of responders; N=number of patients in analysis set
Normalization of liver fat = MRI-PDFF <5%

Secondary Endpoint: TERN-501 6 mg Led to Significant and Rapid Improvement in cT1, a Marker of Liver Fibro-Inflammation

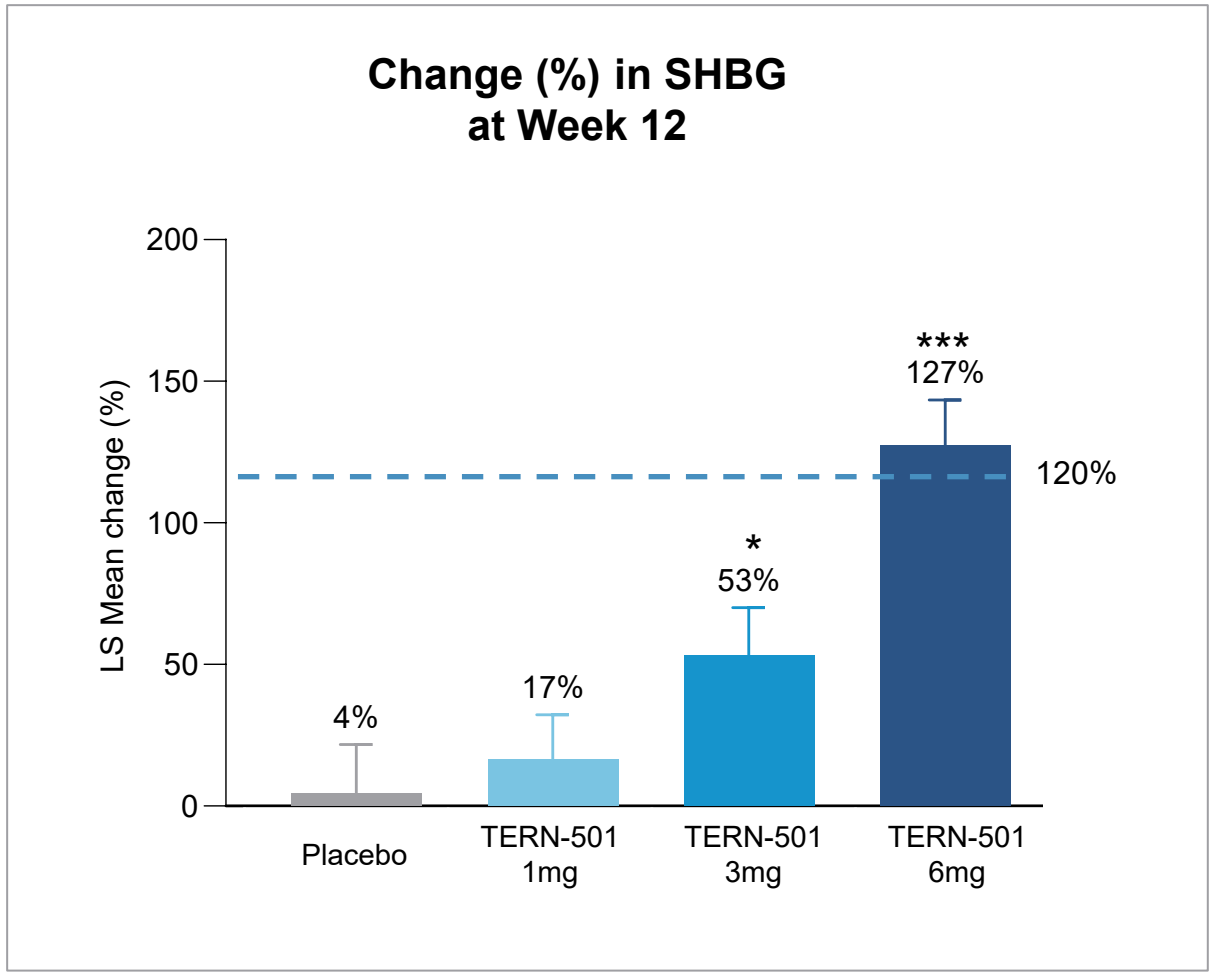
- Significant reduction in cT1 suggests potential antifibrotic effect of TERN-501 and of THR-β class as shown in a Phase 3 trial





***p-value <0.001 for TERN-501 monotherapy vs. placebo
Error bars represent standard error
Harrison S, et.al. Abstract GS-001. *J Hep*. 2023; 78 (Suppl. 1).

TERN-501 Showed Robust, Dose Dependent Increases in SHBG

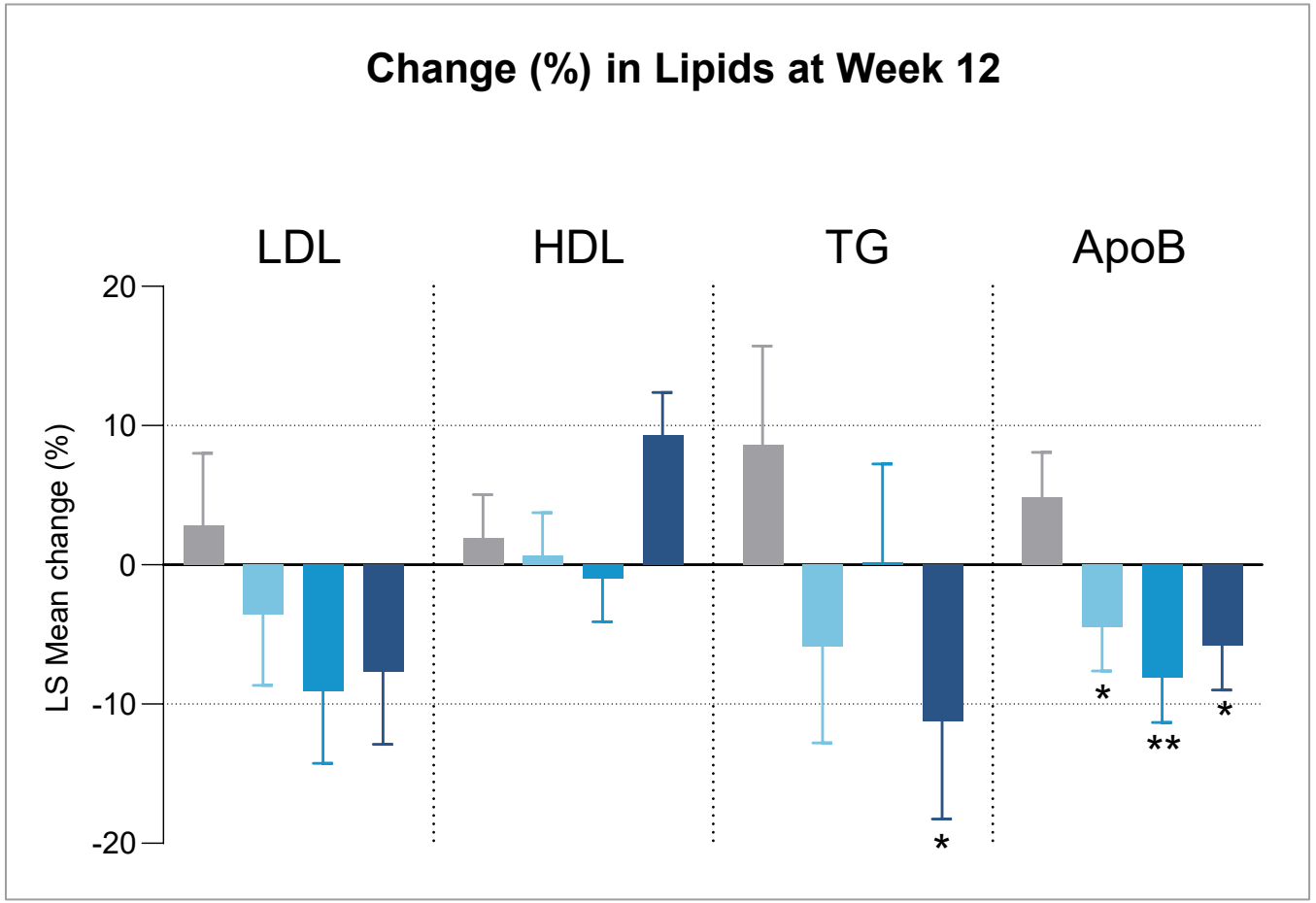


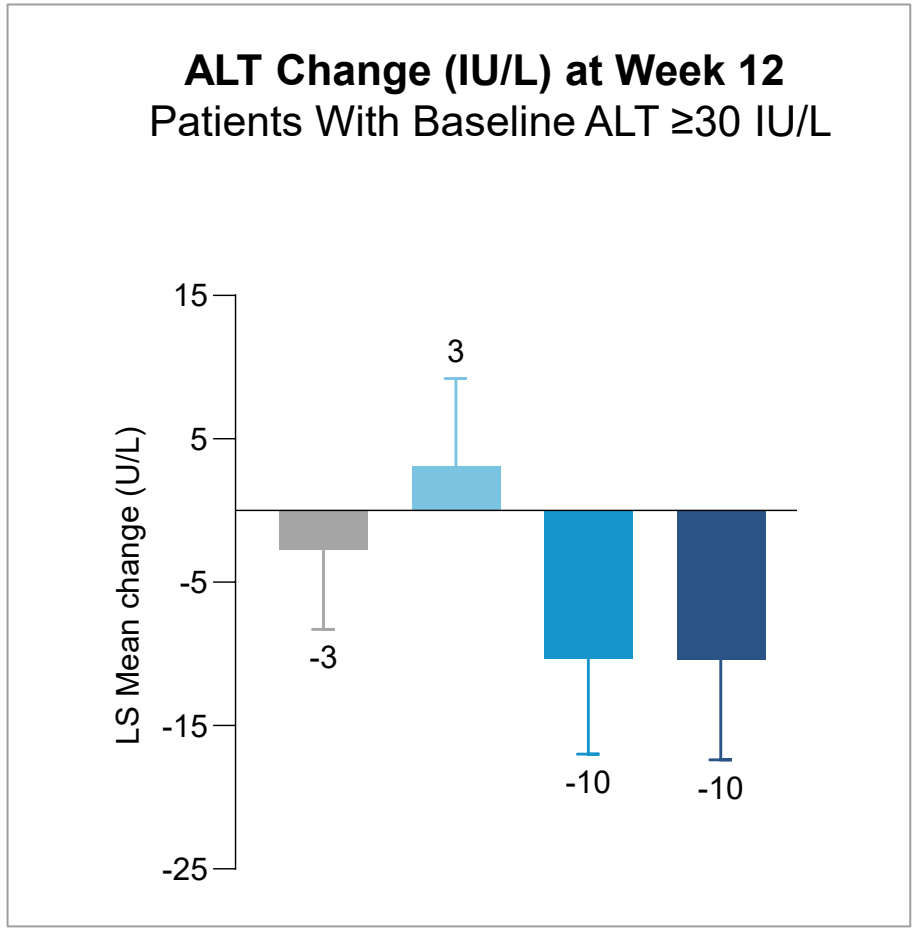
- SHBG is an important marker of THR-β agonism in the liver
- SHBG increase ≥120% has been associated with histological MASH improvement and liver fat reduction in Phase 3 THR-β agonist trials[1,2]

*p-value <0.05; ***p-value <0.001 for TERN-501 monotherapy vs. placebo
SHBG, sex hormone binding globulin
1. Loomba et al. Abstract 149. *Hepatology.* 2023;78(Suppl. 1):S155. 2. Harrison et al. *Nat Med.* 2023 Oct 16. doi: 10.1038/s41591-023-02603-1.

TERN-501 Improved Atherogenic Lipids and ALT at Week 12

- All TERN-501 monotherapy doses achieved statistically significant reductions in ApoB



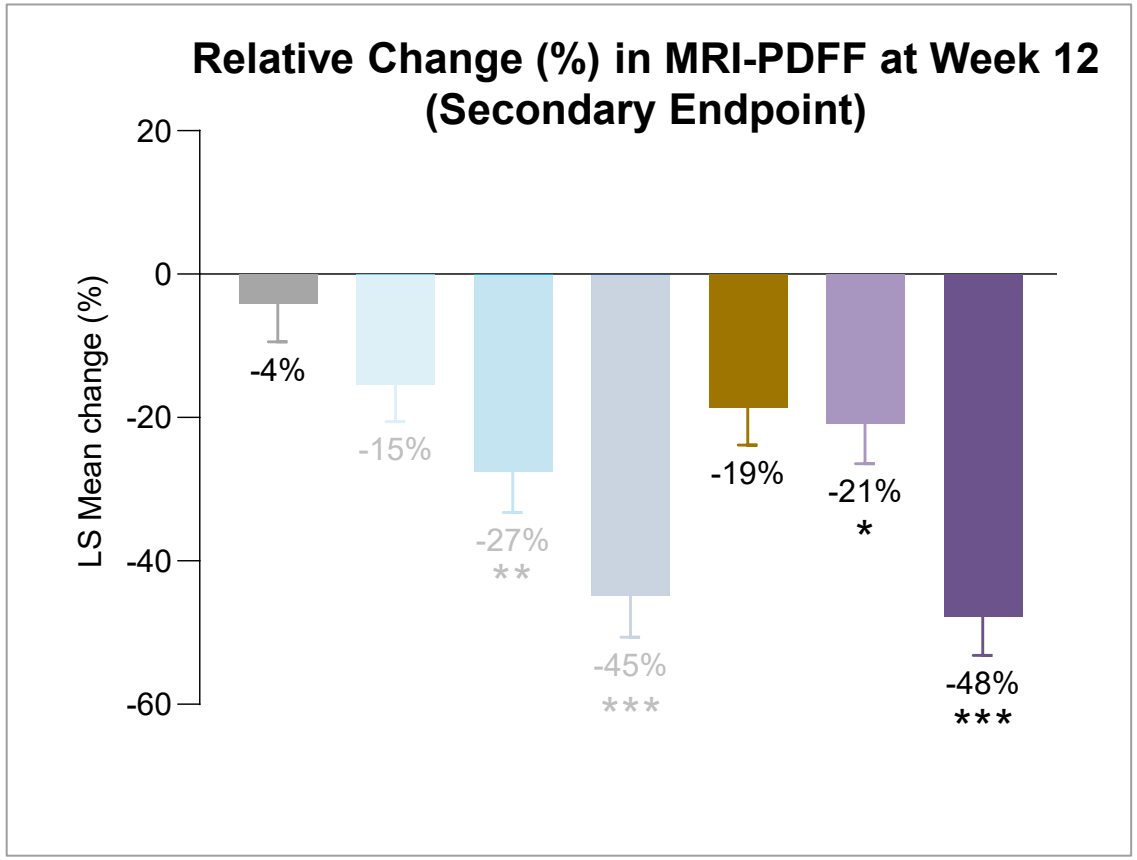


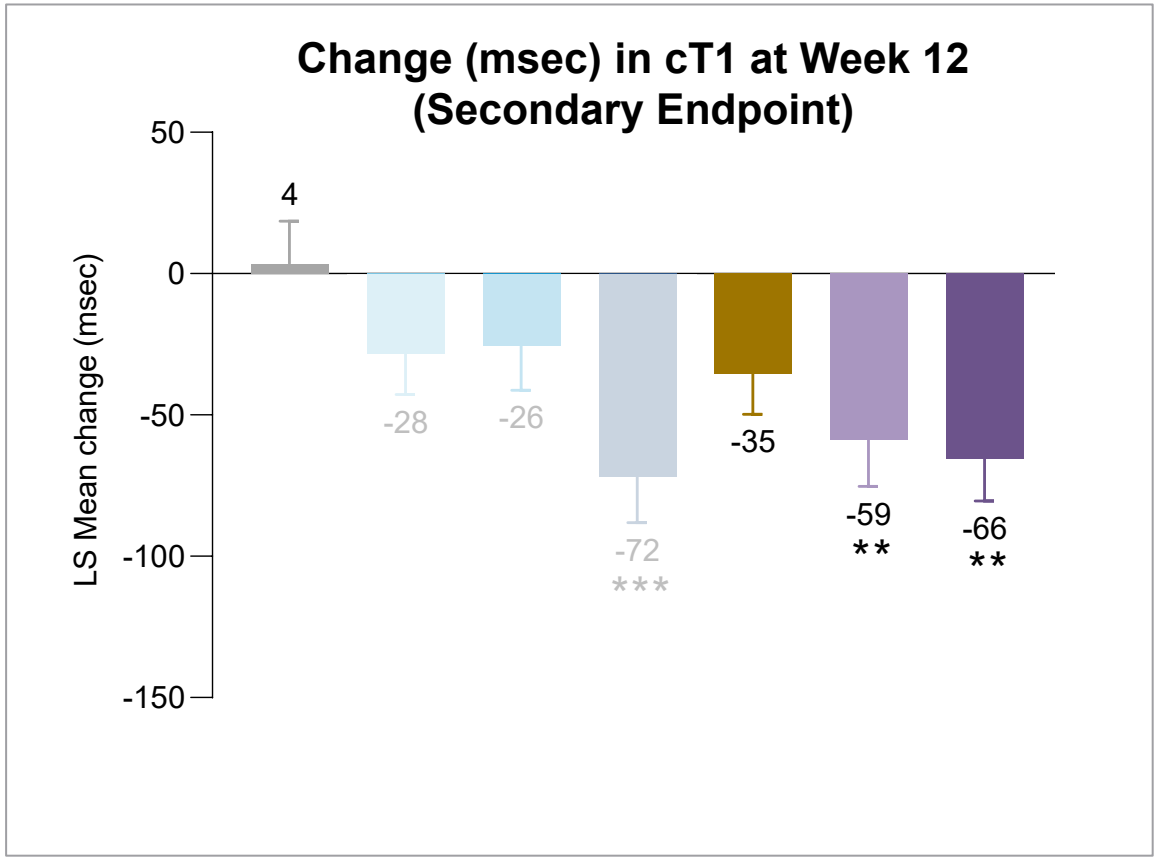
Placebo | 501 1 mg | 501 3 mg | 501 6 mg

*p-value <0.05; **p-value <0.01 for TERN-501 monotherapy vs. placebo
ApoB, apolipoprotein B; HDL, high-density lipoprotein
Lower apolipoprotein B levels associated with reduced cardiovascular risk. (Sniderman et al *JAMA Cardiology* 2019;4(12):1287-1295)

Secondary Endpoints: TERN-501+TERN-101 Showed Significant Reduction in MRI-PDFF and cT1

- First study of a THR-β agonist combined with another mechanism of action for the treatment of MASH





Placebo | 501 1mg | 501 3mg | 501 6mg | 101 10mg | 501 3mg + 101 10mg | 501 6mg + 101 10mg

*p-value <0.05; **p-value <0.01; ***p-value <0.001 for TERN-501 monotherapy or combination therapy vs. placebo

Favorable Safety Profile with No Drug Related AEs Grade 3 or Higher

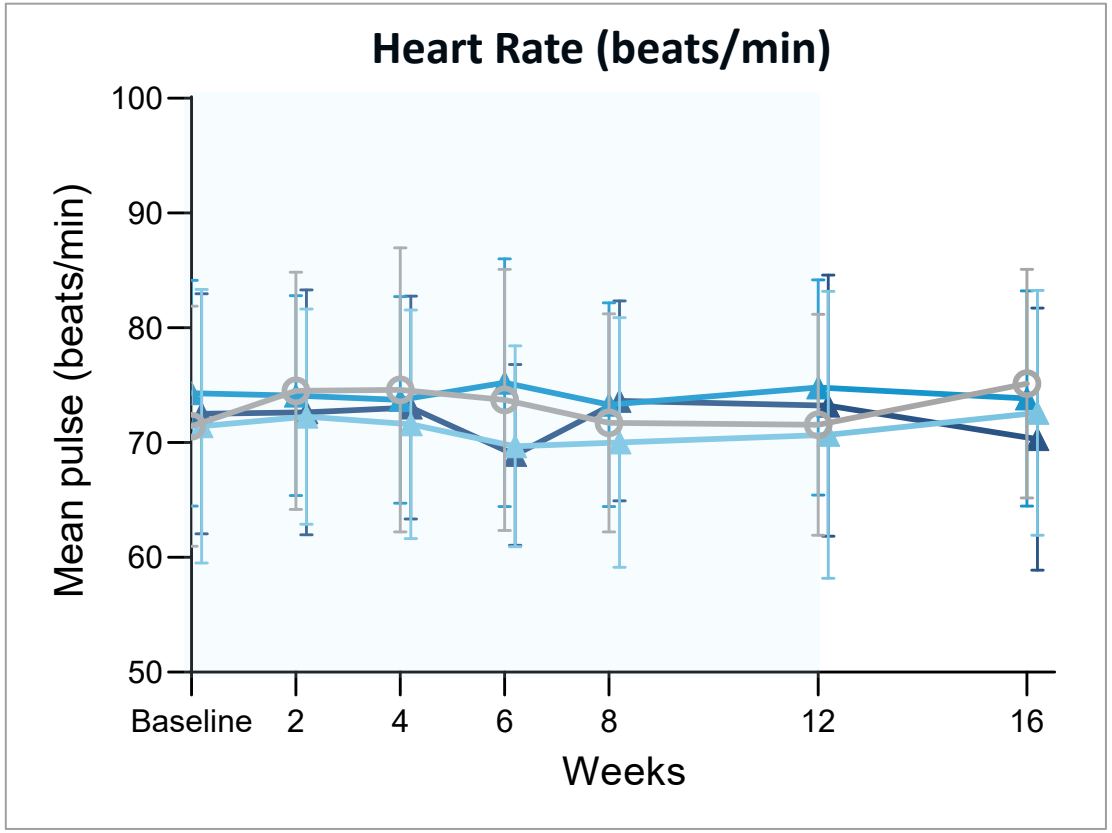
Patient Incidence, n (%)	Placebo (N=24)	TERN-501 1mg (N=23)	TERN-501 3mg (N=23)	TERN-501 6mg (N=22)	TERN-101 10mg (N=24)	'501 + '101 3mg + 10mg (N=23)	'501 + '101 6mg + 10mg (N=23)
Treatment Related Adverse Events (AEs)							
Overall, Any Grade	5 (21%)	1 (4%)	4 (17%)	4 (18%)	2 (8%)	6 (26%)	4 (17%)
Grade 3 or Higher	0	0	0	0	0	0	0
Serious Adverse Event	0	0	0	0	0	0	0
Leading to Treatment Discontinuation	1 (4%)	0	1 (4%)	1 (5%)	0	1 (4%)	1 (4%)
Treatment Related AEs Occurring in >1 Patient in Any Arm							
Pruritus	2 (8%)	0	1 (4%)	2 (9%)	1 (4%)	4 (17%)	2 (9%)
Diarrhea	1 (4%)	1 (4%)	2 (9%)	1 (5%)	1 (4%)	1 (4%)	0

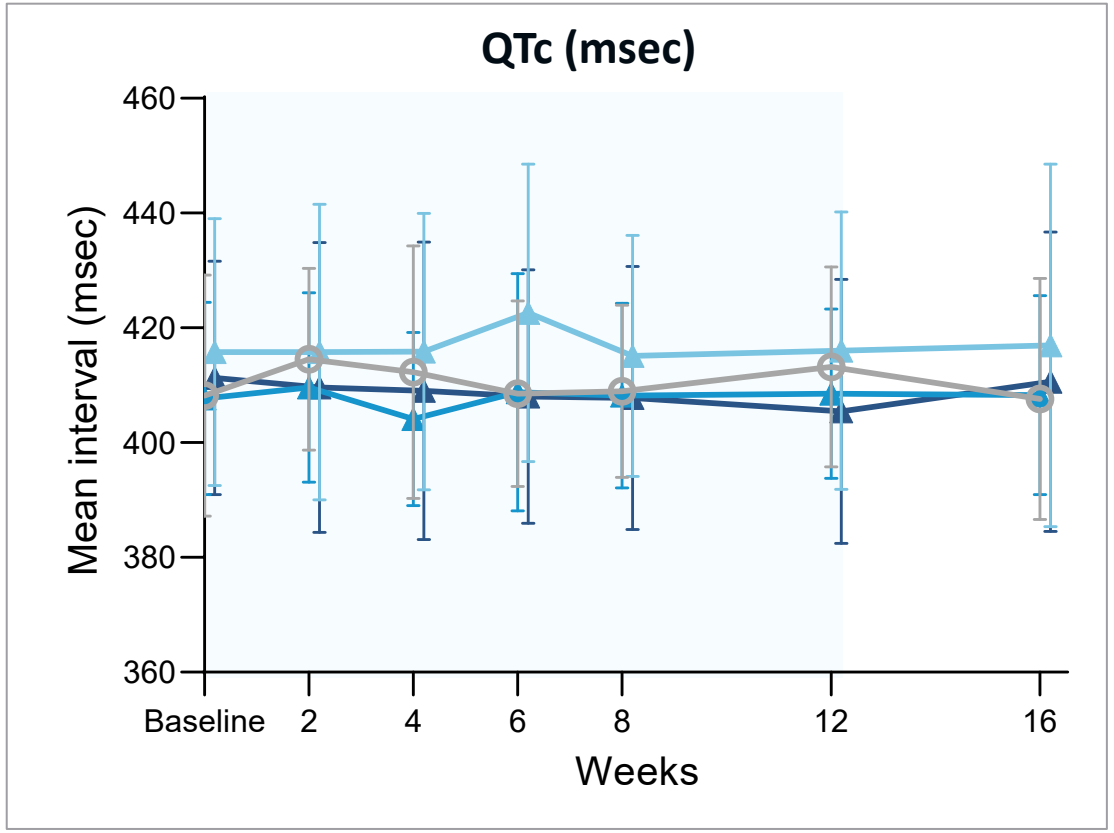
- Treatment related nausea was not seen in more than 1 patient in any arm
- Adverse events in the combination arms were comparable to the TERN-501 monotherapy groups and placebo

AEs, adverse events
Related AEs: AEs deemed by study investigator as related or possibly related to study drug

No Cardiovascular Safety Signals Observed

- No drug-related cardiovascular adverse events were reported
- There were no differences from placebo in mean heart rates, QTc intervals, and blood pressure in any TERN-501 containing arms (monotherapy and combination [not shown])
  - No clinically significant ECG abnormalities were reported

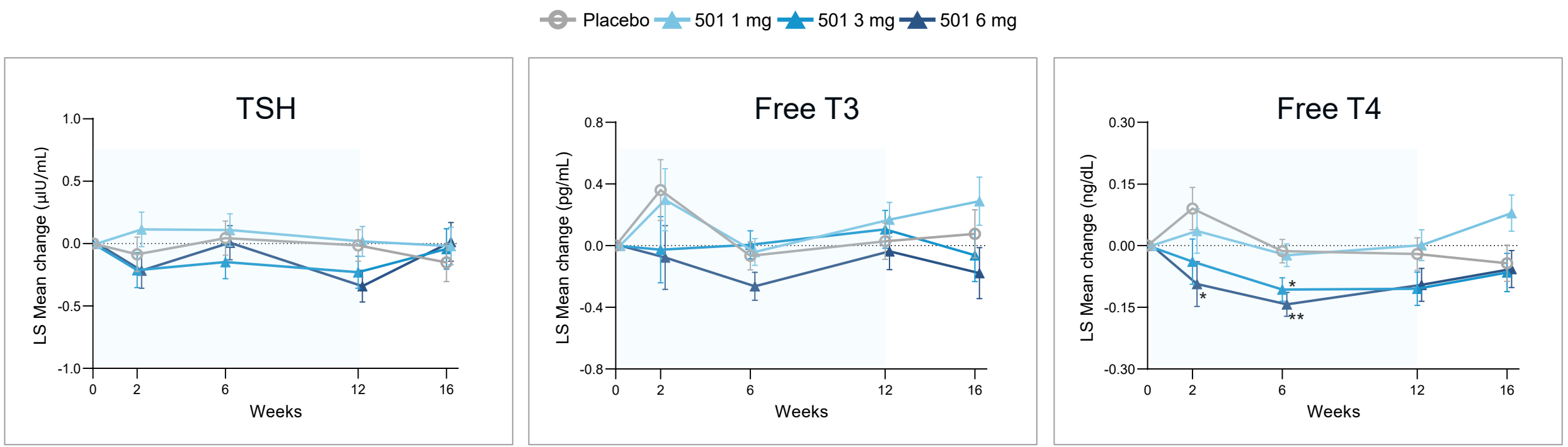




Placebo 501 1 mg 501 3 mg 501 6 mg

The blue shaded area indicates treatment period
ECG, electrocardiogram; QTc, QT interval corrected using Fridericia's formula

No Evidence of Central Thyroid Axis Modulation Observed

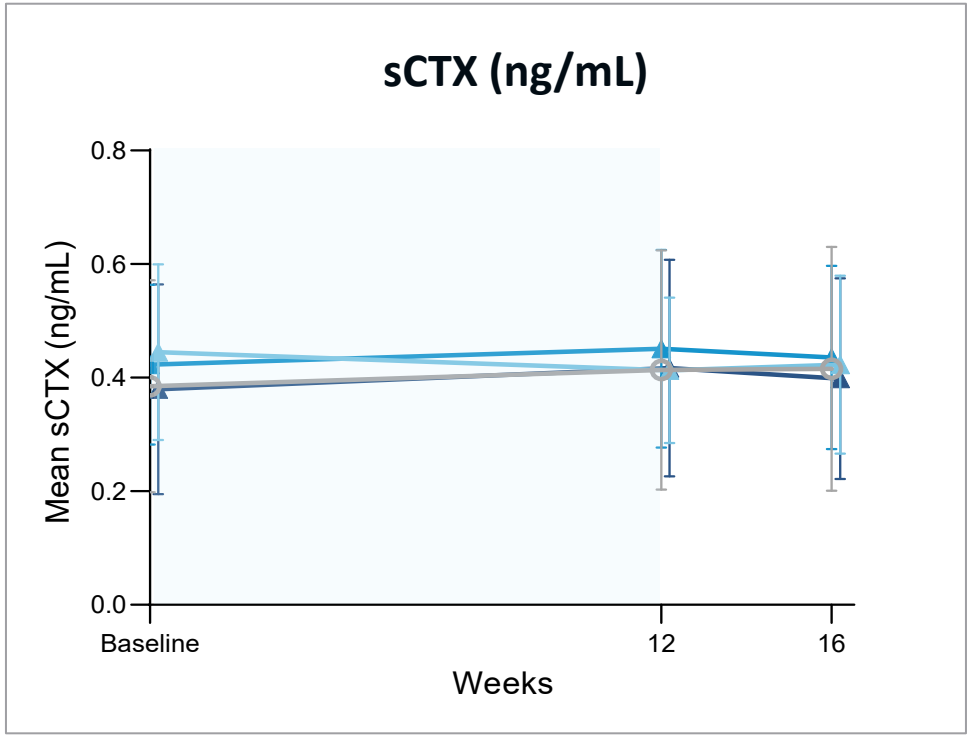


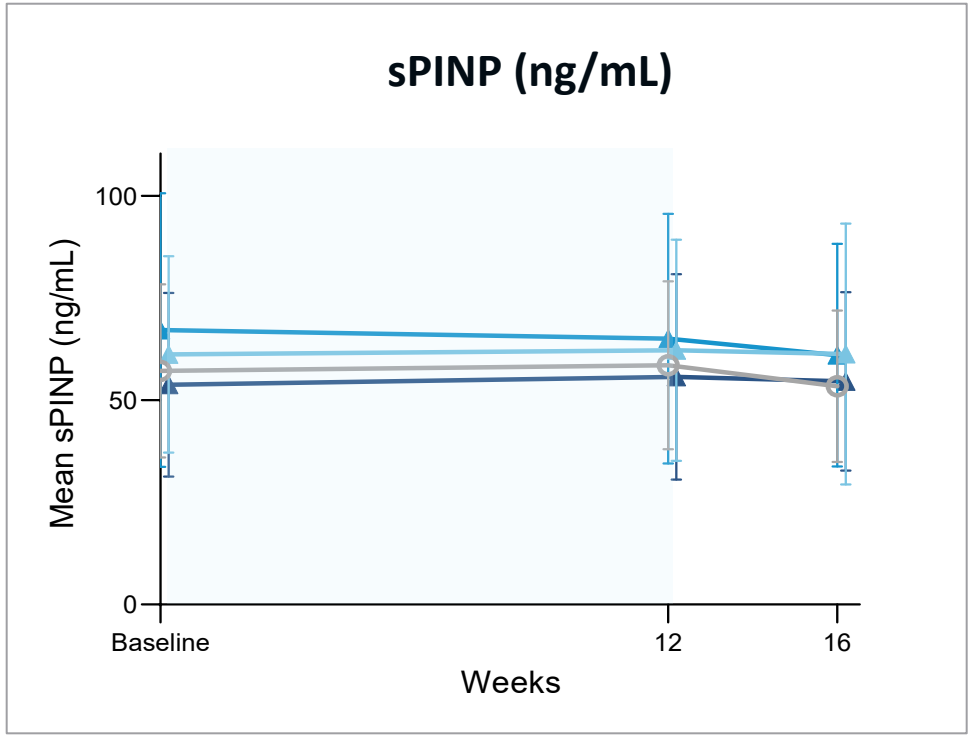
- Mean changes in thyroid axis hormones (TSH, free T3, and free T4) at Week 12 were similar to placebo and remained within normal limits in all TERN-501 containing arms (monotherapy and combination [not shown])
  - No difference from placebo in TSH and free T3 at any time point
  - Initial transient decreases in free T4 up to Week 6 in TERN-501 3 mg and 6 mg arms, as observed with other THR-β agonists; no difference from placebo at Week 12

*p-value <0.05; **p-value <0.01 for monotherapy vs. placebo
The blue shaded area indicates treatment period
T3, triiodothyronine; T4, thyroxine; TSH, thyroid stimulating hormone
Taub et al. *Atherosclerosis*. 2013 Oct;230(2):373-80. Harrison et al. *Lancet*. 2019 Nov 30;394(10213):2012-2024. Lian et al. *Meeting of the American College of Cardiology*. 2016. Charfi et al. *Hepatology* 2022 Oct; 76:S638

No Significant Increase in Serum Bone Turnover Markers

- No apparent mean changes were observed during the dosing period in sCTX (a marker of bone resorption) or sPINP (a marker of bone formation) in any TERN-501 containing arm (monotherapy and combination [not shown])





Placebo 501 1 mg 501 3 mg 501 6 mg

The blue shaded area indicates treatment period
sCTX, serum C terminal cross-linking telopeptide of type I collagen; sPINP, serum procollagen type I N-propeptide

Conclusions

- In this Phase 2a study in MASH population, 12 weeks of TERN-501 treatment demonstrated:
  - **Rapid, significant, and dose-dependent reductions** in **both liver fat content** (by MRI-PDFF) **and fibroinflammation** (by cT1), meeting **all primary and secondary efficacy endpoints**
  - **Robust hepatic target engagement** with significant, dose-dependent increases in SHBG and decreases in atherogenic lipids including ApoB
  - **A highly THR-β selective safety profile** with **no apparent safety signals**
    - Generally mild AEs evenly distributed across arms, including placebo
    - No dose related AEs or SAEs
    - No adverse cardiovascular or gastrointestinal effects
    - No clinically significant changes in thyroid axis hormones or serum bone markers
- When TERN-501 was combined with TERN-101, efficacy was generally maintained or modestly improved without additional safety findings, demonstrating **combinability of TERN-501**
- Collectively, these data warrant further investigation of TERN-501 as a monotherapy or in combination with other mechanisms of action for MASH