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Liver-distributed FXR Agonist TERN-101 Demonstrates Favorable Safety and Efficacy Profile in NASH Phase 2a LIFT Study

Presented by Rohit Loomba, MD

Liver-distributed FXR Agonist TERN-101 Demonstrates Favorable Safety and Efficacy Profile in NASH Phase 2a LIFT Study

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Disclosure

Rohit Loomba, MD

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

- Consultant: Aardvark Therapeutics, Altimmune, Anylam/Regeneron, Amgen, Arrowhead Pharmaceuticals, AstraZeneca, Bristol-Myer Squibb, CohBar, Eli Lilly, Galmed, Gilead, Glympse bio, Hightide, Inipharma, Intercept, Inventiva, Ionis, Janssen Inc., Madrigal, Metacrine, Inc., NGM Biopharmaceuticals, Novartis, Novo Nordisk, Merck, Pfizer, Sagimet, Theratechnologies, 89 bio, Terns Pharmaceuticals and Viking Therapeutics.
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Background

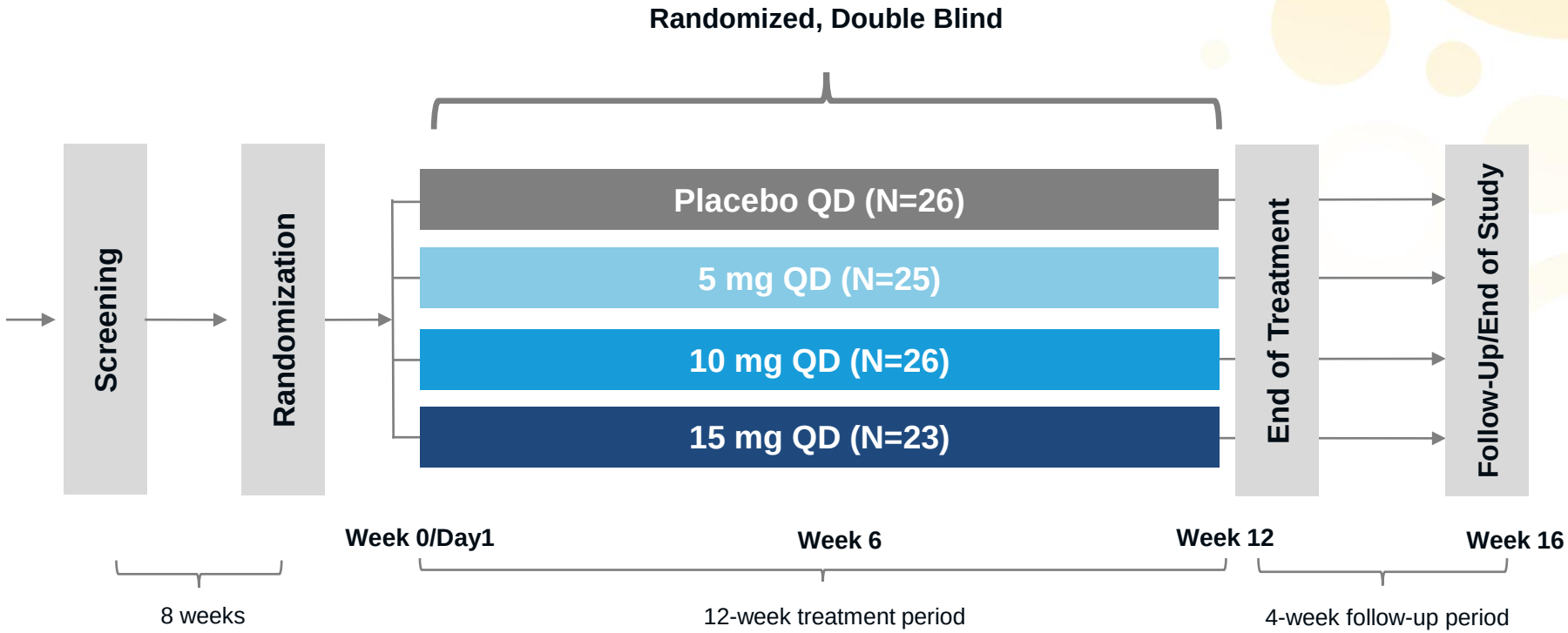
- FXR is a nuclear hormone receptor that is highly expressed in the liver and small intestine
- TERN-101 is a potent, non-steroidal FXR agonist with enhanced liver distribution, being developed for the treatment of NASH
- TERN-101 induced significant reductions in steatosis, inflammation, and fibrosis in a NASH rodent model and induced robust FXR agonism in the liver[1,2]
- We aimed to assess safety and efficacy of several dose levels of TERN-101 versus placebo in patients with NASH

1. Wang Y, et al. Presented at the Liver Meeting 2019 (AASLD). Abstract #2158. Hepatology 2019 Issue S1 188-1382
2. Klucher K. et al. Presented at the International Liver Congress (EASL) Abstract #313. Journal of Hepatology 2019 Vol. 70 Issue 1 Supplement E534

TERN-101 LIFT Study: Phase 2a Study in NASH Patients

Key inclusion criteria:
Adults 18-75 years
BMI ≥ 25 kg/m^2
MRI-PDFF ≥ 10%
ALT ≥ 28 IU/L (women) or
≥ 43 IU/L (men)

NASH based on clinical characteristics:
TE 7.6-21 kPa
CAP > 300 dB/m
Or prior biopsy (n= 23):
F1-3 in last 2 years



MRI-PDFF at Baseline, Week 6, and Week 12; cT1 at available sites

Alanine aminotransferase (ALT), body mass index (BMI), corrected T1 (cT1), magnetic resonance imaging (MRI), once daily (QD), proton density fat fraction (PDFF), transient elastography (TE); NCT04328077

Endpoints

Primary:

- Overall safety including treatment-emergent adverse events and laboratory abnormalities

Secondary:

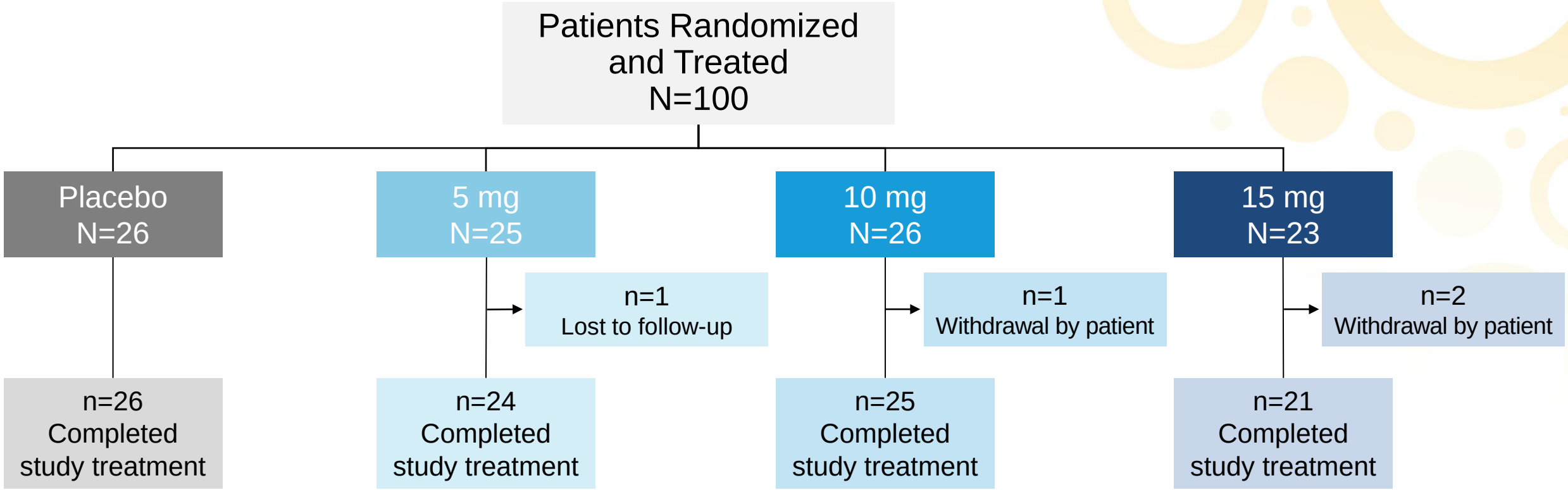
- Percent change from baseline in ALT at Week 12

Exploratory:

- Changes in other liver enzymes
- MRI-PDFF and cT1 change
- Proportion of patients achieving ≥ 30% relative decline in MRI-PDFF
- Proportion of patients achieving ≥ 80 msec decline in cT1

Magnetic resonance imaging (MRI), proton density fat fraction (PDFF), corrected T1 (cT1)

Disposition



- Overall, 96% of patients completed the treatment period
- No patient discontinued due to an adverse event

Overall study completion was similar across groups; one patient in the 5 mg group completed treatment but discontinued study early due to withdrawal by patient.

Patient Demographics

	Placebo (N=26)	5 mg (N=25)	10 mg (N=26)	15 mg (N=23)
Age, mean (SD) [years]	50.4 (11.0)	48.0 (12.3)	52.5 (13.6)	51.6 (9.5)
Sex, n (%)				
Female	16 (61.5%)	15 (60.0%)	17 (65.4%)	17 (73.9%)
Race and Ethnicity, n (%)				
White	21 (80.8%)	23 (92.0%)	21 (80.8%)	21 (91.3%)
Black or African American	2 (7.7%)	1 (4.0%)	2 (7.7%)	0
Hispanic or Latino	20 (76.9%)	17 (68.0%)	16 (61.5%)	17 (73.9%)
BMI, mean (SD) [kg/m^2]	36.5 (5.43)	37.2 (6.44)	36.3 (6.63)	36.2 (4.74)
Baseline statin use*, n (%)	7 (26.9%)	8 (32.0%)	10 (38.5%)	7 (30.4%)
History of diabetes, n (%)	11 (42.3%)	11 (44.0%)	16 (61.5%)	8 (34.8%)

* Per protocol, initiation of statins within 3 months of randomization or dose adjustment expected during study participation is exclusionary.

Key Baseline Characteristics

	Placebo (N=26)	5 mg (N=25)	10 mg (N=26)	15 mg (N=23)
ALT, mean (SD) [IU/L]	55.5 (23.6)	56.3 (16.3)	60.8 (29.1)	55.8 (26.5)
ALT > 60 IU/L, n (%)	7 (26.9%)	8 (32.0%)	11 (42.3%)	6 (26.1%)
AST, mean (SD) [IU/L]	39.5 (18.3)	41.5 (16.2)	45.8 (23.0)	39.3 (17.6)
LDL cholesterol, mean (SD) [mg/dL]	103.4 (30.4)	105.4 (25.2)	99.2 (33.7)	105.8 (26.6)
Hgb A1c, mean (SD) [%]	6.3 (1.2)	6.2 (0.9)	6.5 (0.9)	6.1 (1.0)
CAP by TE, mean (SD) [dB/m]	350.1 (34.0)	356.8 (27.9)	345.1 (29.9)	353.3 (27.8)
Stiffness by TE, mean (SD) [kPa]	10.4 (2.6)	12.0 (3.6)	9.6 (1.7)	9.8 (2.4)
MRI-PDFF, mean (SD) [%]	21.43 (7.6)	21.08 (8.2)	20.05 (7.1)	22.78 (8.4)
cT1, mean (SD) [msec]	908.9 (90.9)	925.4 (75.2)	942.0 (143.5)	974.7 (175.3)

Transient elastography (TE) conducted in placebo N=20, 5 mg N=16, 10 mg N=22, 15 mg N=20
cT1 conducted at sites with this capability, with baseline cT1 values in placebo N=22, 5 mg N=24, 10 mg N=20, 15 mg N=18
Controlled attenuation parameter (CAP); Hemoglobin A1c (Hgb A1c), Transient Elastography (TE), Magnetic resonance imaging proton density fat fraction (MRI-PDFF), Corrected T1 (cT1)

Adverse Event (AE) Summary

- All AEs were mild or moderate except for 2 unrelated Grade 3 events (also considered SAEs)
  - 1 SAE of COVID-19 (placebo) and 1 SAE of UTI requiring hospitalization (TERN-101 15 mg)
- No deaths occurred
- No patient discontinued due to an AE

Patient incidence AEs by category, n (%)	Placebo (N=26)	5 mg (N=25)	10 mg (N=26)	15 mg (N=23)
Any AE, all CTCAE grades	10 (38.5%)	13 (52.0%)	14 (53.8%)	15 (65.2%)
CTCAE Grade 3 or higher AEs	1 (3.8%)	0	0	1 (4.3%)
Serious AE	1 (3.8%)	0	0	1 (4.3%)
AE leading to death	0	0	0	0
AE leading to study or drug discontinuation	0	0	0	0

CTCAE = Common Terminology Criteria for Adverse Events, AE = adverse event, UTI = urinary tract infection; AEs reported refer to treatment-emergent AEs, defined as any AE with a start date on or after the date of first administration of study drug through 30 days after the last administration of study drug or through the Follow-Up Period (Week 16)

Pruritus AE Summary

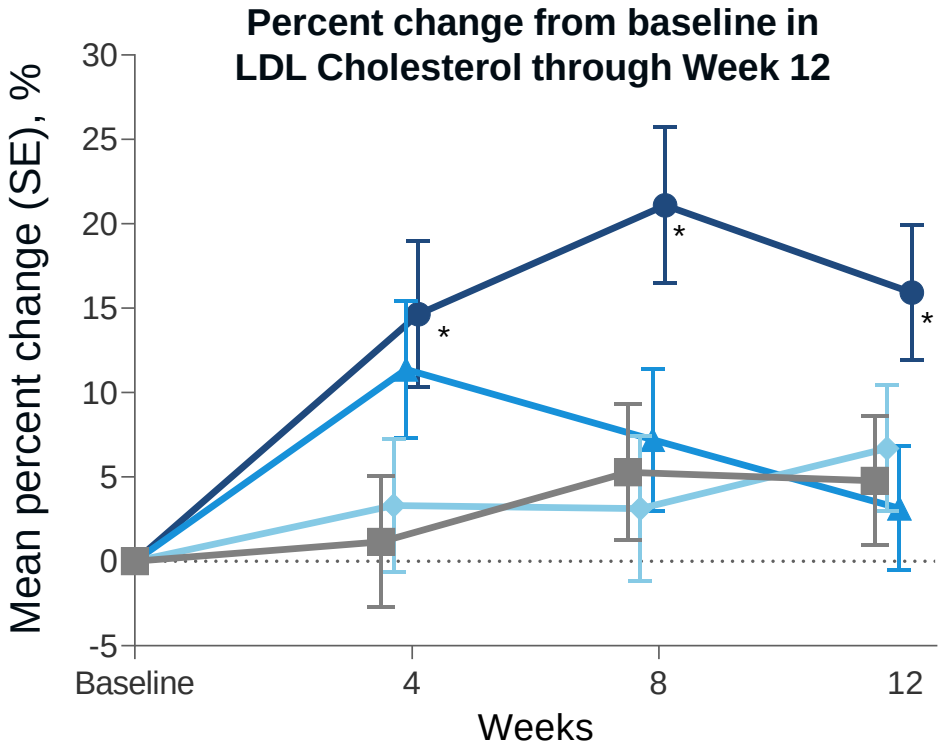
- All pruritus-related AEs* were mild or moderate
- Patient incidence of pruritus was generally balanced across TERN-101 treatment groups
- No patient discontinued study drug due to pruritus
- Most pruritus AEs were mild, self-limited and resolved without treatment interruption

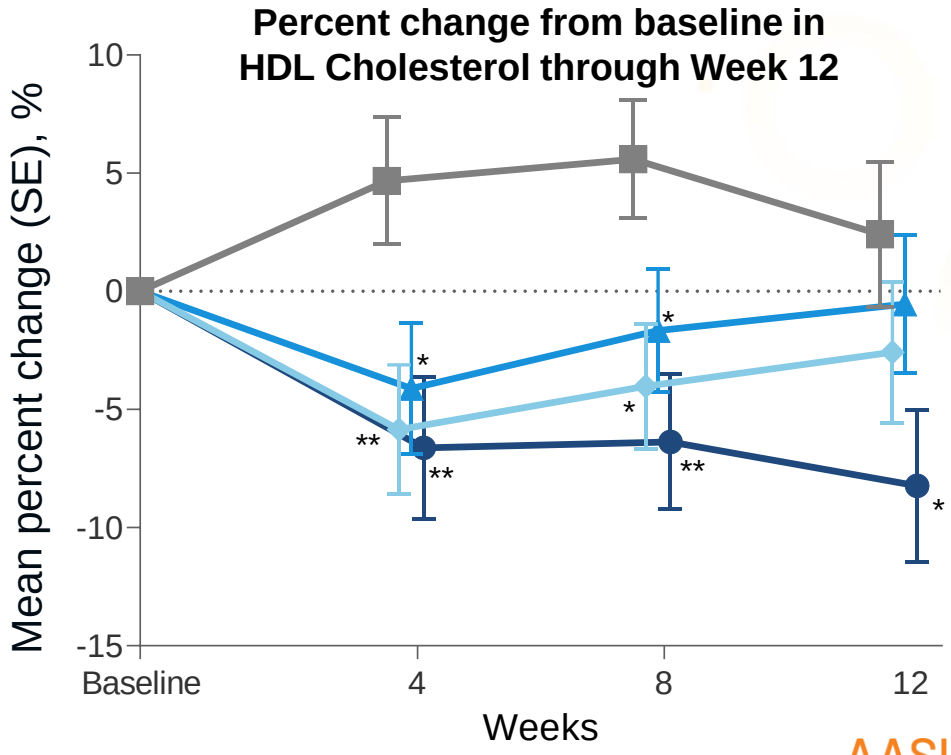
Patient incidence of any pruritus AE, n (%)	Placebo (N=26)	5 mg (N=25)	10 mg (N=26)	15 mg (N=23)
Pruritus, all CTCAE grades*	0	4 (16.0%)	3 (11.5%)	4 (17.4%)
Grade 1	0	4 (16.0%)	1 (3.8%)	3 (13.0%)
Grade 2	0	0	2 (7.7%)	1 (4.3%)
Grade 3	0	0	0	0
Study drug-related pruritus AEs, per Investigator	0	3 (12.0%)	3 (11.5%)	1 (4.3%)
Study drug discontinuation due to pruritus	0	0	0	0

*All preferred terms reflecting pruritis including an event of pruritic rash (5 mg group) were included which was a pre-specified analysis (MedDRA version 23.0)
Grade 1: Mild or localized; topical intervention indicated; Grade 2: Widespread and intermittent; skin changes from scratching; oral intervention indicated; limiting activities of daily living
CTCAE = common terminology criteria for adverse events

Cholesterol Percent Change from Baseline

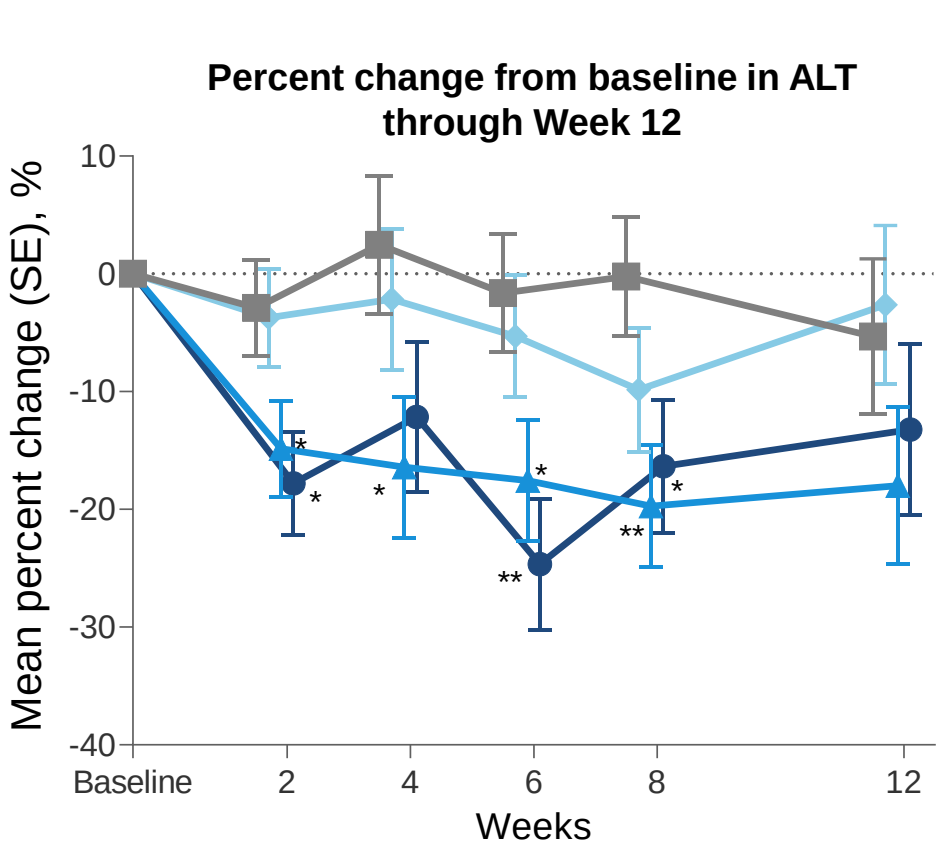
- No difference from placebo in LDL percent change in the TERN-101 5 mg and 10 mg groups
- HDL decreased initially in all TERN-101 groups versus placebo and returned to baseline in the 5 and 10 mg groups
- LDL increased and HDL decreased significantly in the TERN-101 15 mg group versus placebo at Week 12

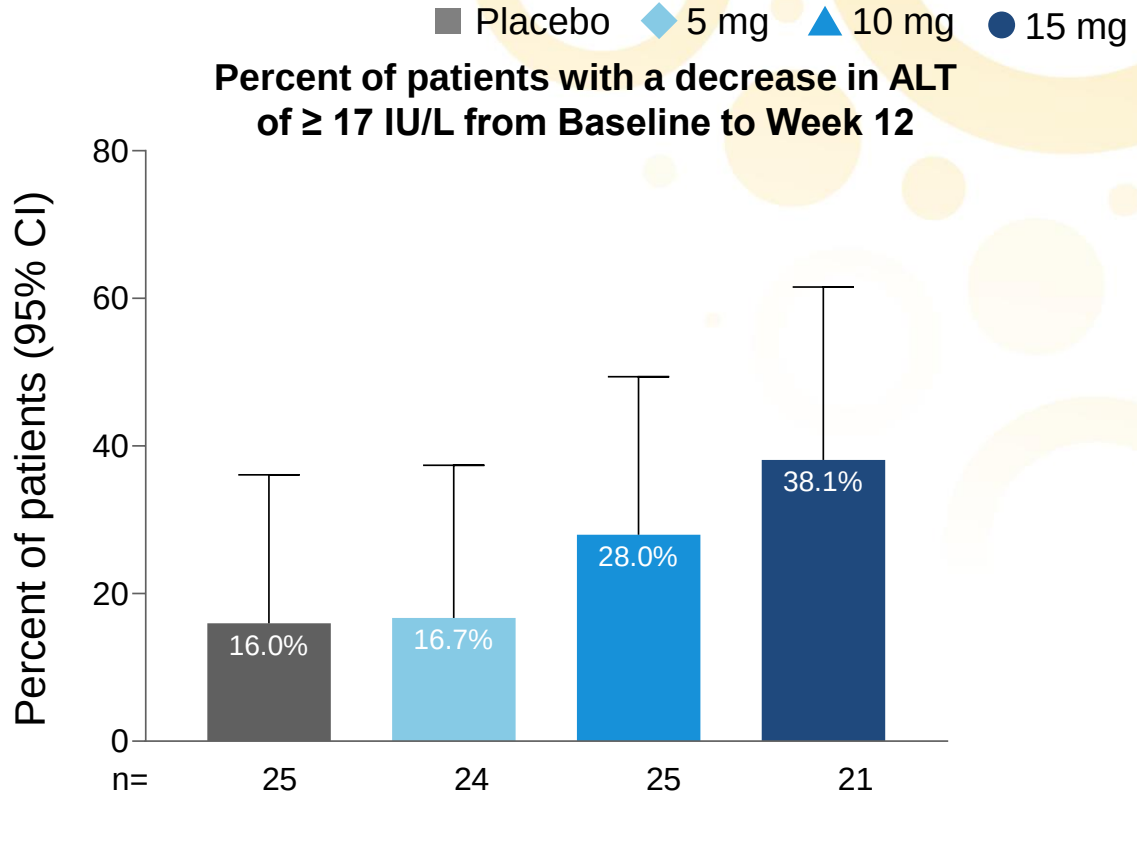




p-value: *< 0.05, **< 0.01

ALT Percent Change from Baseline and Responder Analysis



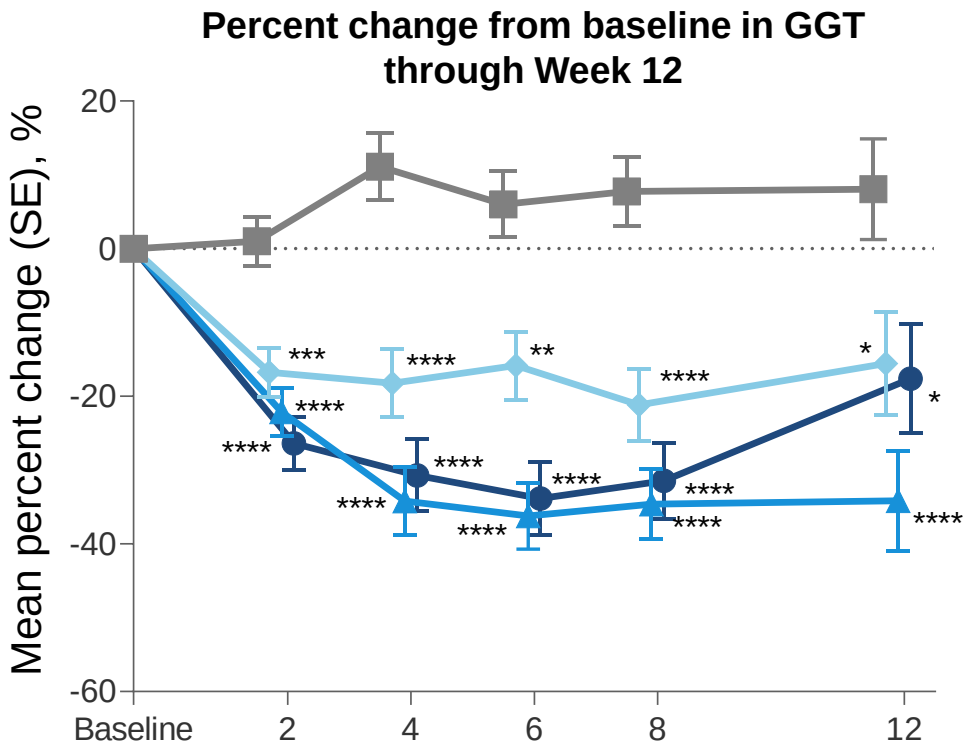


- Significant ALT percent decreases in the TERN-101 10 mg and 15 mg groups compared to placebo as early as Week 2

- Numerically more patients with ≥ 17 IU/L decline from baseline in TERN-101 10 mg and 15 mg groups than placebo and TERN-101 5 mg

p-value: *< 0.05, **< 0.01

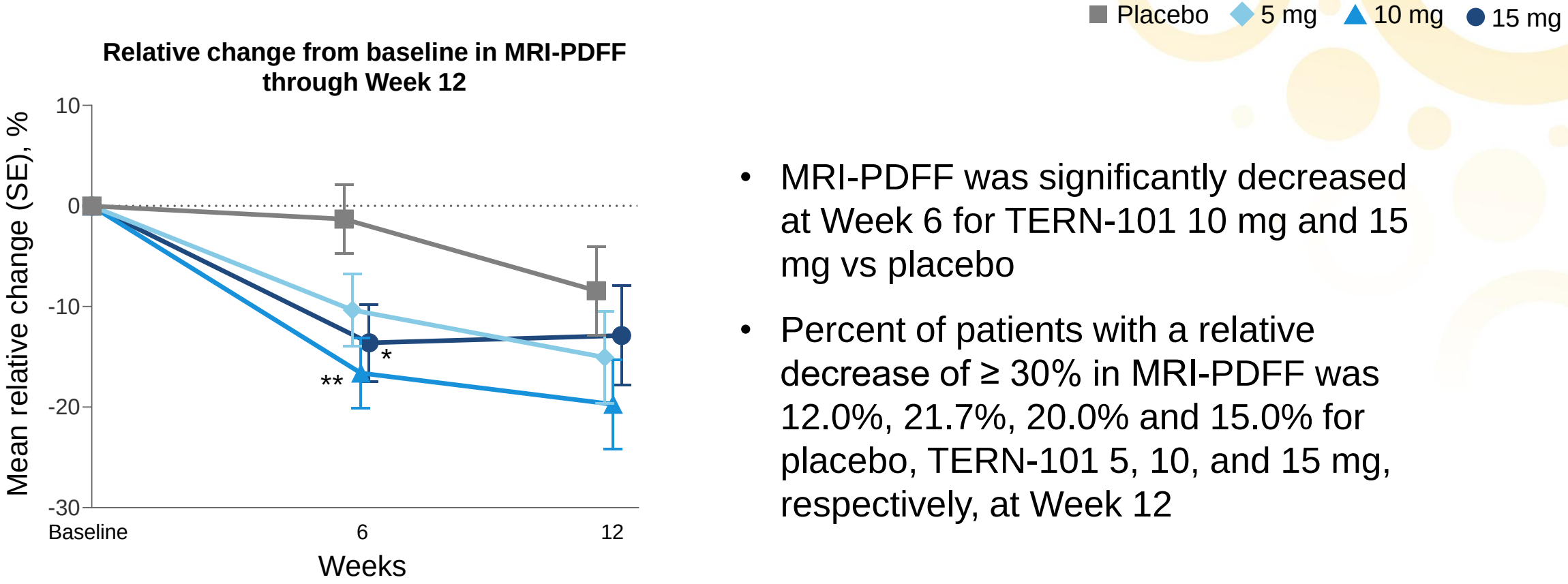
GGT Percent Change from Baseline



- Statistically significant GGT declines occurred in all TERN-101 groups vs placebo at all timepoints
- Magnitude of GGT decreases similar in TERN-101 10 mg and 15 mg groups

*p-value < 0.05; **p-value<0.01; ***p-value<0.001; ****p-value<0.0001

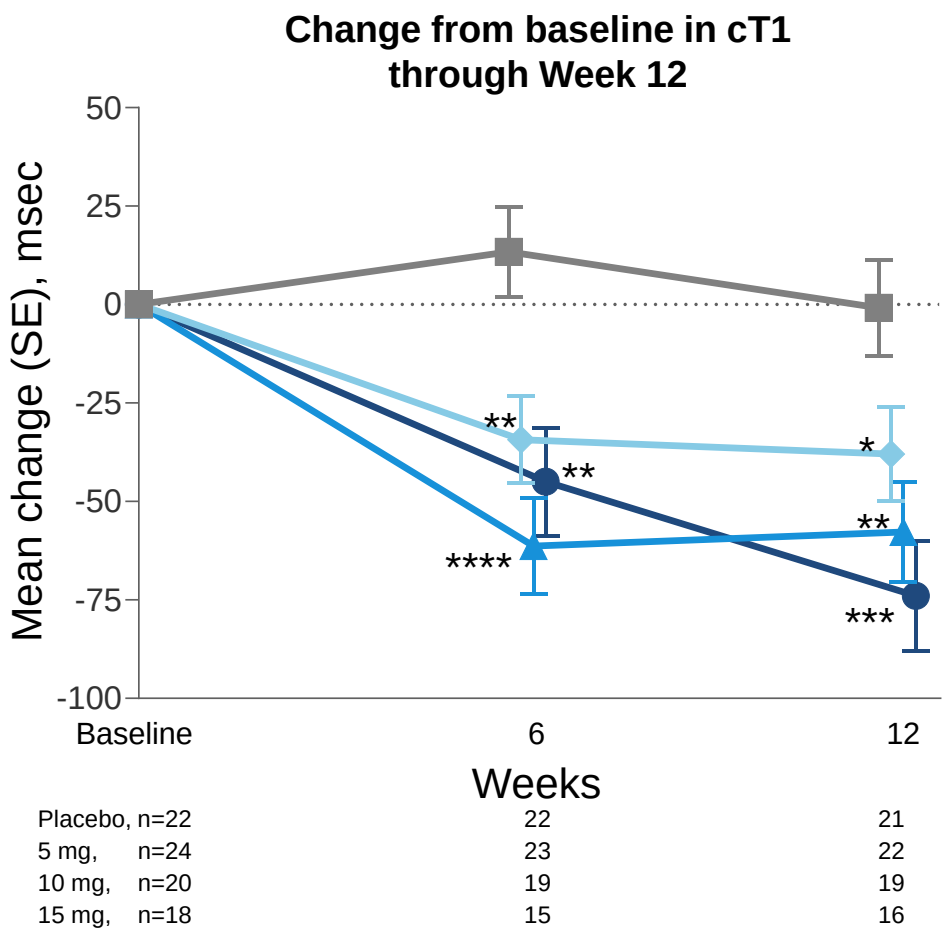
MRI-PDFF Relative Change from Baseline



- MRI-PDFF was significantly decreased at Week 6 for TERN-101 10 mg and 15 mg vs placebo
- Percent of patients with a relative decrease of ≥ 30% in MRI-PDFF was 12.0%, 21.7%, 20.0% and 15.0% for placebo, TERN-101 5, 10, and 15 mg, respectively, at Week 12

*p-value < 0.05; **p-value<0.01 Magnetic resonance imaging proton density fat fraction (MRI-PDFF)

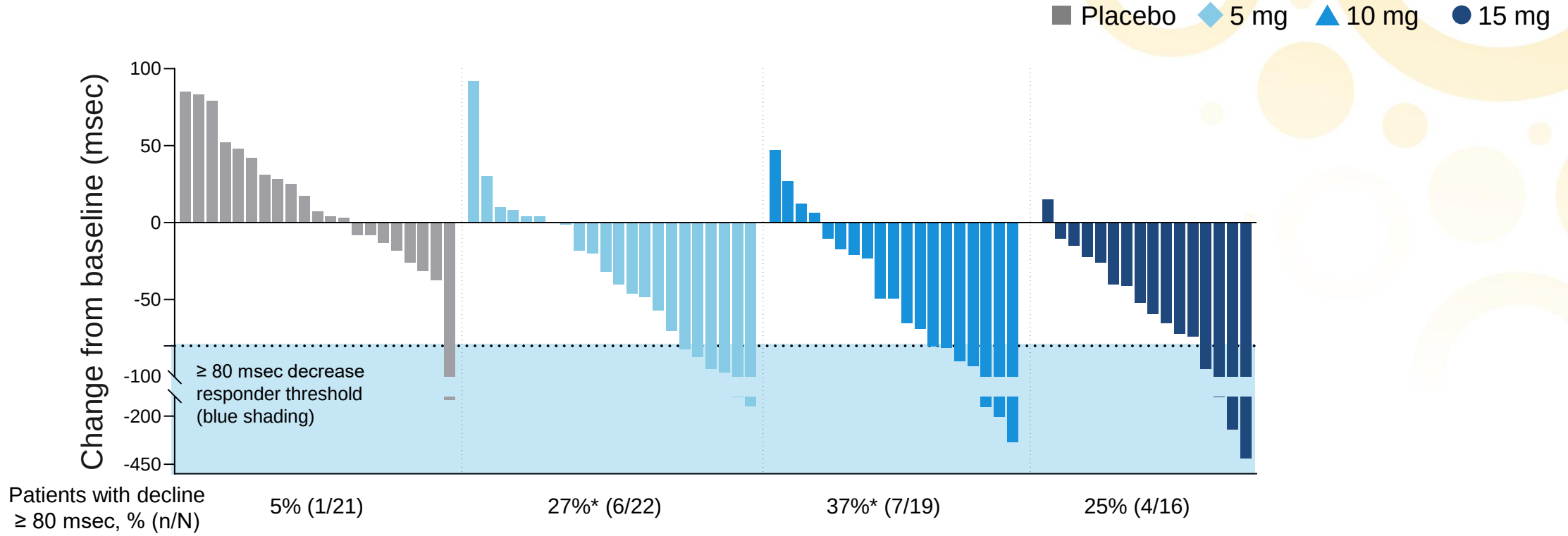
cT1 Change from Baseline



- cT1 declined significantly as early as Week 6 in all TERN-101 groups
- Significant mean cT1 declines persisted at Week 12 in all TERN-101 groups compared to placebo

*p-value < 0.05; **p-value<0.01; ***p-value<0.001; ****p-value<0.0001
Corrected T1 (cT1) was conducted only at available sites.

cT1 Change from Baseline to Week 12: Individual Patient Responses



- cT1 values decreased for majority of TERN-101 patients
- Significantly greater proportion of patients with decrease of ≥ 80 msec in the TERN 101 5 mg and 10 mg groups compared to placebo

*p-value < 0.05; corrected T1 (cT1)

Conclusions

- TERN-101 is highly liver-distributed FXR agonist that was overall safe and well-tolerated at all doses studied in patients with biopsy-diagnosed or presumed NASH
  - No discontinuations due to AEs or treatment-related SAEs
  - No differences from placebo in LDL and HDL percent change from baseline to Week 12 in the TERN-101 5 mg and 10 mg groups
- TERN-101 10 mg and 15 mg showed a numerical reduction in ALT and MRI-PDFF, and a significant reduction in GGT
- Significant decreases in cT1 as early as Week 6 and through Week 12 suggest that TERN-101 decreases fibro-inflammation (additional cT1 results presented in Abstract #1875)
- Further clinical studies of TERN-101 for the treatment of NASH, either alone or in combination with other agents, are warranted
  - A clinical trial of TERN-101 co-administered with the thyroid hormone receptor beta agonist TERN-501 (Abstract #1889) is planned to initiate in the first half of 2022

Acknowledgements

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Thank you!

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