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Liver-distributed FXR Agonist TERN-101 Leads to Corrected T1 (cT1) Response and a Population Shift to Lower cT1 Risk Categories in NASH Phase 2a LIFT Study

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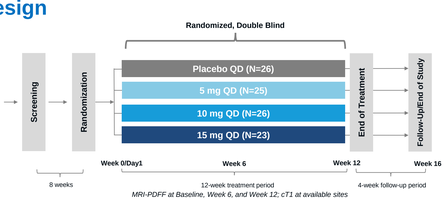
1 • INTRODUCTION •

- FXR is a nuclear hormone receptor that is highly expressed in the liver and small intestine. FXR agonism has demonstrated improvement in histological liver fibrosis without progression of NASH in a late-stage study, demonstrating the potential for FXR agonists for use in the treatment of nonalcoholic steatohepatitis (NASH)[1]
- TERN-101 is a potent, non-steroidal FXR agonist with enhanced liver distribution, being developed for the treatment of NASH. TERN-101 induced robust FXR agonism in rodent liver and significantly reduced steatosis, inflammation, and fibrosis in a NASH rodent model[2,3]
- The Phase 2a LIFT Study (TERN101-2001) assessed 5, 10, or 15 mg TERN-101 vs placebo for 12-weeks in non-cirrhotic patients with presumed NASH and fibrosis based on clinical characteristics or prior biopsy (Figure 1). The primary endpoint was safety, with secondary/exploratory endpoints including liver enzymes, magnetic resonance imaging proton density fat fraction (MRI-PDFF), and corrected (cT1)
- The primary results from the LIFT study are being presented in oral presentation #143[4]
- Here we present a separate analysis of cT1 results from the LIFT Study

Fig. 1 Study Design

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:
F1-3 in last 2 years



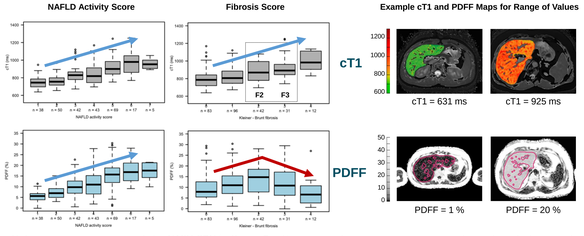
MRI-PDFF at Baseline, Week 6, and Week 12; cT1 at available sites

Magnetic resonance imaging (MRI), proton density fat fraction (PDFF), corrected T1 (cT1); NCT04328077

Corrected T1 (cT1) Overview

- cT1 relaxation time, measured in milliseconds (msec), is an MRI-based test that measures the signal from extracellular water, and is a composite biomarker of inflammation and fibrosis[5]
- Decreases in cT1 relaxation time correlate with histologic improvement in NASH[6]
  - MRI-PDFF (which measures hepatic fat fraction) and cT1 correlate with NAFLD Activity Score
  - cT1, but not MRI-PDFF, correlates with the full range of histological liver fibrosis scoring in NASH (Figure 2)
- cT1 is shown to strongly predict clinical outcomes in patients with chronic liver disease including NAFLD[7]
- Low (<800 msec), elevated (800-875 msec), or high (>875 msec) cT1 values reflect increasing liver fibroinflammation and increased risk of NASH disease progression[8]

Fig. 2 cT1 is Correlated with NAFLD Activity Score and Fibrosis on Liver Histology[6]



Histology was graded according to the NASH-CRN for Kleiner-Brunt fibrosis, hepatocellular ballooning, lobular inflammation, steatosis, and the composite NAFLD Activity Score.

2 • OBJECTIVES/METHODS •

LIFT Study overall:

- The primary objective of the LIFT Study was to assess the safety and tolerability of 3 dose levels of orally administered TERN-101 versus placebo for 12 weeks in non-cirrhotic presumed NASH patients, based on clinical characteristics or prior biopsy.[4]
  - The secondary endpoint was ALT percent change from baseline to Week 12, and exploratory endpoints included change from baseline in other liver enzymes, MRI-PDFF, and cT1

Current analysis:

- cT1 was collected at baseline, Week 6, and Week 12, at sites with cT1 MRI scanning capability
- The following cT1 exploratory endpoints were prespecified:
  - cT1 change from baseline to Week 6 and to Week 12 by treatment group
  - Patient-level response: percent with cT1 response, defined as a ≥80 msec decrease from baseline
  - Risk level by treatment group: Percent of patients at baseline, Week 6 and Week 12 with low (<800 msec), elevated (800-875 msec), or high (>875 msec) cT1 values, reflecting increasing risk of liver fibrosis/inflammation and disease progression

3 • RESULTS •

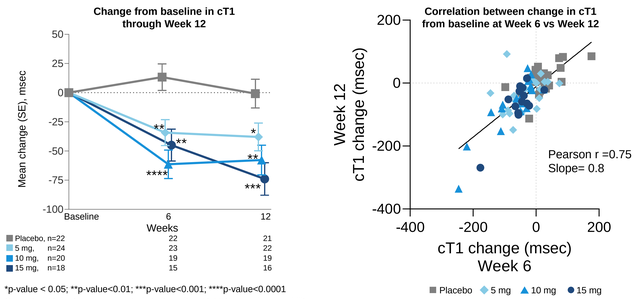
Disposition, Safety, Demographics and Baseline Characteristics

- 100 patients were randomized and received at least one dose of study drug. The numbers (%) of patients completing the treatment period were 26 (100%), 24 (96%), 25 (96.2%), and 21 (91.3%) for the placebo, 5 mg, 10 mg, and 15 mg groups, respectively.
- All dose levels of TERN-101 were overall safe and well-tolerated, with no discontinuations due to adverse events.
- Mean cT1 at baseline was >900 msec in all treatment groups, indicating a patient population with advanced NASH and high levels of fibroinflammation at baseline.
- TERN-101 treatment resulted in significant decreases in ALT, cT1, and MRI-PDFF (Oral presentation #143)[4]

Demographics and Key Baseline Characteristics	Placebo (N=26)	TERN-101 5 mg (N=25)	TERN-101 10 mg (N=26)	TERN-101 15 mg (N=23)
Age, mean (SD) [years]	50.4 (11.0)	48.0 (12.3)	52.5 (13.6)	51.6 (9.5)
Female, n (%)	16 (61.5%)	15 (60.0%)	17 (65.4%)	17 (73.9%)
ALT, mean (SD) [IU/L]	55.5 (23.6)	56.3 (16.3)	60.8 (29.1)	55.8 (26.5)
MRI-PDFF, mean (SD) [%]	21.43 (7.6)	21.08 (8.2)	20.05 (7.1)	22.78 (8.4)
Stiffness by TE, mean (SD) [kPa]	10.4 (2.6)	12.0 (3.6)	9.6 (1.7)	9.8 (2.4)
Patients with cT1 results at baseline[1]	N=22	N=24	N=20	N=18
cT1, mean (SD) [msec]	908.9 (90.9)	925.4 (75.2)	942.0 (143.5)	974.7 (175.3)
> 875 msec, n (%)	13 (59.1%)	18 (75%)	14 (70%)	14 (77.8%)

Transient elastography (TE) conducted in placebo N= 20, 5 mg N=16, 10 mg N=22, 15 mg N=20; [1] cT1 conducted at sites with cT1 MRI scanning capability

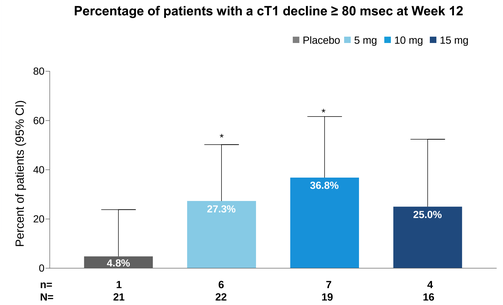
Fig. 3 Mean cT1 values significantly declined from baseline at Weeks 6 and 12 for all TERN-101 doses, and changes in cT1 at Week 6 strongly correlate with changes at Week 12



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

Corrected T1 (cT1) was conducted at sites with cT1 MRI scanning capability

Fig. 4 A greater proportion of patients in the TERN-101 treatment groups were cT1 responders compared to placebo at Week 12



n is number of patients meeting response criteria; N is total patients with baseline and post-baseline timepoint evaluable scans; *p-value < 0.05

Fig. 5 Greater numbers of patients in the TERN-101 treatment groups had cT1 decreases from baseline, compared to placebo, at Week 12

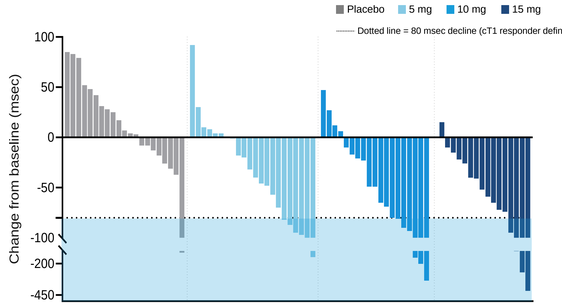


Fig. 6 TERN-101 led to an increased proportion of cT1 low risk patients, and a decreased proportion of high-risk patients, over 12 weeks of dosing

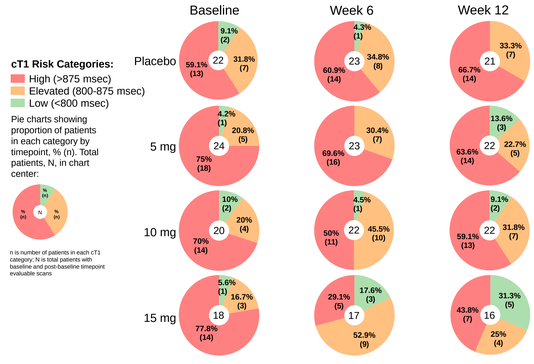
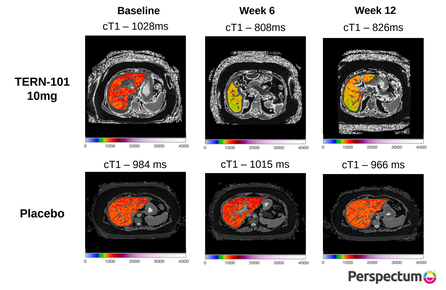


Fig. 7 Patient Case Studies: Changes in cT1



- Images from a LIFT patient with a robust cT1 response alongside a placebo patient are provided, for illustrative purposes.
- High cT1 (depicted by red color), remaining high over the course of treatment in a placebo patient but reducing (depicted by orange-green color) in a patient who received 10 mg TERN-101

4 • CONCLUSIONS •

- TERN-101 was overall safe and well-tolerated in the LIFT Study, and resulted in significant dose-dependent decreases in cT1 at Weeks 6 and 12[4]
- Mean cT1 values significantly decreased from baseline for all TERN-101 doses, and cT1 may serve as a biomarker of TERN-101 treatment response as early as Week 6
  - Decreases in cT1 at Week 6 strongly correlate with decreases at Week 12
- A higher proportion of patients treated with TERN-101 had a cT1 response (decrease ≥80 msec from baseline at Week 12) compared to placebo
- TERN-101 treatment led to study population shifts to cT1 categories associated with lower risk of clinical events in chronic liver disease patients, particularly in the TERN-101 10 and 15 mg dose groups
- Overall cT1 declines in the LIFT Study indicate improvements in fibroinflammation following TERN-101 treatment in NASH patients
- 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

5 • REFERENCES •

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6 • ACKNOWLEDGEMENTS •

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7 • CONTACT •

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