A Stepwise Screening Approach Using Noninvasive Tests To Identify Phenotypic Metabolic Dysfunction-Associated Steatohepatitis (MASH) Patients With Fibrosis For Clinical Trials

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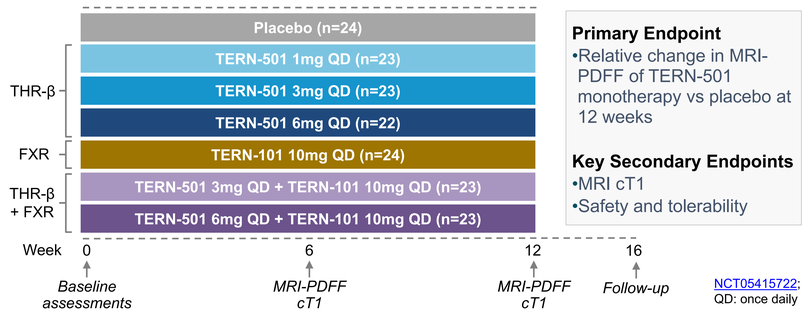
1 BACKGROUND

- Non-invasive tests (NITs) have become essential to help diagnose and stage metabolic dysfunction-associated steatohepatitis (MASH)
- Biopsy-based screen failure (SF) rates are high in MASH trials, which lead to increased cost and extended enrollment durations
- Per 2023 AASLD Practice Guidance on the Clinical Assessment and Management of Nonalcoholic Fatty Liver Disease[1], patients with at least stage 2 fibrosis are at increased risk of cirrhosis and liver-related complications
- Patients with specific comorbidities such as type 2 diabetes mellitus (DM2), obesity and hypertension and biomarkers such as proton density fat fraction (PDFF), corrected T1 (cT1) and other NITs may help define the MASH population
- A stepwise NIT screening approach was implemented in the DUET study to recruit patients likely to have MASH and a high degree of liver fat and fibro-inflammation, likely reflecting F2 and F3 fibrosis without requiring a biopsy

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

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



Primary Endpoint
- Relative change in MRI-PDFF of TERN-501 monotherapy vs placebo at 12 weeks

Key Secondary Endpoints
- MRI cT1
- Safety and tolerability

NCT05415722; QD: once daily

Key Inclusion Criteria

- Age 18-75 years old
- Body Mass Index (BMI) ≥ 25 kg/m^2

MASH participants based on prior biopsy and/or imaging criteria:

- Prior biopsy: F1-3 within 1 year prior to randomization

OR

- Vibration controlled transient elastography (VCTE) 7.6 – 21 kPa
- Controlled attenuation parameter (CAP) > 300 dB/m

All participants:

- MRI-PDFF ≥ 10%
- cT1 ≥ 800msec

Key Exclusion Criteria

- History or clinical evidence of chronic liver diseases other than NAFLD
- History or known clinical evidence of cirrhosis, esophageal varices, hepatic decompensation or other severe liver impairment
- History of liver transplant, or current placement on a liver transplant list
- Current diagnosis or history of pituitary or thyroid disorders - except for patients with primary hypothyroidism on a stable dose of thyroid hormone replacement therapy
- Abnormal TSH or free T4 levels
- Weight loss of > 5% total body weight within 3 months prior to screening
- Uncontrolled diabetes
- Uncontrolled hyperlipidemia
- Unstable cardiovascular disease
- Excessive alcohol consumption

2 METHODS

DUET Study Screening

STEP 1 Screening
- Age 18 – 75 years old
- BMI ≥ 25 kg/m^2
- Laboratory and Clinical Criteria
- VCTE of 7.6 to 21 kPa and CAP > 300 dB/m in patients without prior historical biopsy for fibrotic MASH within 1 year before randomization

STEP 2 Screening
- MRI to assess:
  - Liver fat content eligibility of ≥ 10% by PDFF and
  - Liver fibro-inflammation defined as cT1 ≥ 800 msec

- Common SF reasons were tabulated, multiparametric MRI SF rates were calculated and an analysis of patients with cT1 ≥ 875 was performed
- Baseline criteria of the randomized population were compared to the SF population as well as to the AASLD guidance for identifying patients with MASH

3 RESULTS

- 591 patients were screened and 162 were randomized
- Overall SF rate was 73% and the screening duration was 9 months
- Of the 591 patients, 291 met step 1 eligibility criteria, with a SF rate of 51%
- Of the 291 patients who underwent MRI assessments, 162 met MRI-PDFF and cT1 criteria resulting in a step 2 MRI SF rate of 56%
- The randomized population had higher mean values for ALT and AST and a higher proportion of DM2 patients compared to the SF population (Table 1)
- The majority of the randomized population represent an at-risk MASH population according to the cutoff (≥ 875 msec) provided in the AASLD guidance[2]

Screen Failure Flow

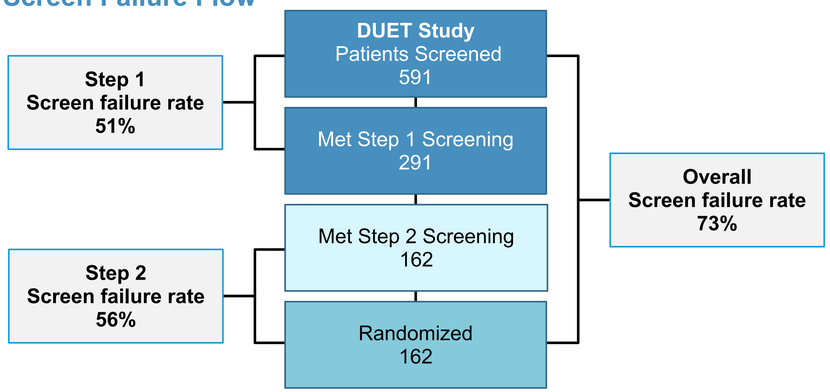


Table 1- Demographics/Baseline Characteristics

	Statistic	Randomized (N= 162)	Overall SF (N= 429)	SF (MRI-PDFF< 10%) (N= 99)	SF (cT1< 800ms) (N= 72)	SF (Less MRI-PDFF SF) (N= 330)	SF (MRI-PDFF or cT1) (N= 127)
Age (years)	Mean (SD)	53.3 (11.8)	54.3 (12.2)	54.7 (11.7)	55.8 (12.0)	54.2 (12.4)	55.3 (11.6)
Ethnicity	Hispanic or Latino	61%	60%	68%	64%	57%	66%
Sex	Female	55%	54%	55%	49%	54%	54%
BMI (kg/m^2)	n	162	373	91	63	282	116
	Mean (SD)	37.8 (6.9)	37.5 (7.1)	36.8 (6.9)	33.9 (5.9)	37.7 (7.1)	36.4 (6.8)
Diabetes [1]	Yes	42%	32%	32%	25%	31%	30%
ALT (U/L)	n	162	376	98	72	278	126
	Mean (SD)	42.2 (24.1)	40.5 (30.5)	27.1 (17.8)	32.5 (22.3)	45.2 (32.5)	29.9 (20.5)
AST (U/L)	n	162	377	98	72	279	126
	Mean (SD)	31.2 (15.6)	31.7 (21.8)	24.2 (13.7)	27.3 (16.8)	34.4 (23.4)	26.1 (16.2)
TE (kPa)	n	162	406	98	71	308	126
	Mean (SD)	10.6 (2.97)	10.6 (4.1)	10.2 (3.3)	10.1 (3.3)	10.7 (4.4)	10.5 (3.5)
CAP(dB/m)	n	162	406	98	71	308	126
	Mean (SD)	339.9 (31.5)	338.6 (34.4)	330.0 (33.3)	329.7 (36.0)	341.3 (34.4)	331.6 (32.6)

Note: Percentages based on number of non-missing per parameter within population.; SF=Screen Failures; TE: Transient elastography

[1] Only using the preferred term Type 2 diabetes mellitus

Table 2- Baseline Characteristics

	Statistic	Randomized (N= 162)	SF (MRI-PDFF< 10%) (N= 99)	SF (cT1< 800ms) (N= 72)	SF (MRI-PDFF or cT1) (N= 127)
MRI-PDFF (%)	n	162	99	72	127
	Mean (SD)	17.74 (5.5)	6.57 (2.1)	8.72 (4.3)	8.05 (3.5)
	Median (Min, Max)	16.6 (10.0, 34.8)	6.4 (0.9, 9.9)	7.5 (0.9, 18.2)	7.6 (0.9, 18.2)
cT1 (msec)	n	162	99	72	127
	Mean (SD)	936.17 (98.8)	809.37 (71.7)	752.83 (38.8)	799.35 (67.6)
	Median (Min, Max)	915 (802, 1394)	809 (623, 1027)	763.5 (623, 799)	791.0 (623, 1027)
cT1 (msec)	≥875 msec	72%	17%	NA	13%
	<875 msec	28%	83%	100%	87%

Note: Percentages based on number of non-missing per parameter within population

Overall, randomized patients were more likely to be diabetic and the screen failed due to MRI-PDFF and/or cT1 population had a lower mean baseline ALT

4 CONCLUSION

- A stepwise screening approach beginning with clinical assessments and laboratory tests followed by MRI identified patients that were more likely to meet the eligibility criteria as suggested by a lower Step 2 screen failure rate (56%) versus overall screen failure (73%)
- As a result, fewer MRI assessments were required to fully enroll the study, reducing costs and the need for patients to be scheduled for a separate imaging visit

REFERENCES

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