A stepwise screening approach using noninvasive tests to identify phenotypic nonalcoholic steatohepatitis (NASH) patients with fibrosis for clinical trials

Naim Alkhouri[1*], Rohit Loomba[2], Mazen Noureddin[3], Eric Lawitz[4], Kris Kowdley[5], Hiba Graham[6a], Erin Quirk[6b], Diana Chung[6c†]

[1]Arizona Liver Health, Tucson, Arizona, USA; nalkhouri@azliver.com [2]NAFLD Research Center, University of California at San Diego, La Jolla, California, USA; rloomba@health.ucsd.edu [3]Houston Research Institute, Houston Methodist Hospital, Houston, Texas, USA; NoureddinMD@houstonresearchinstitute.com [4]Texas Liver Institute, University of Texas Health, San Antonio, Texas, USA; lawitz@txliver.com [5]Liver Institute Northwest, Seattle, Washington, USA; kkowdley@liverinstitutenw.org [6]Terns Pharmaceuticals, Foster City, California, USA; [a]hgraham@ternspharma.com; [b]equirk@ternspharma.com; [c]dchung@ternspharma.com *Presenting author †Corresponding author

1 BACKGROUND and OBJECTIVES

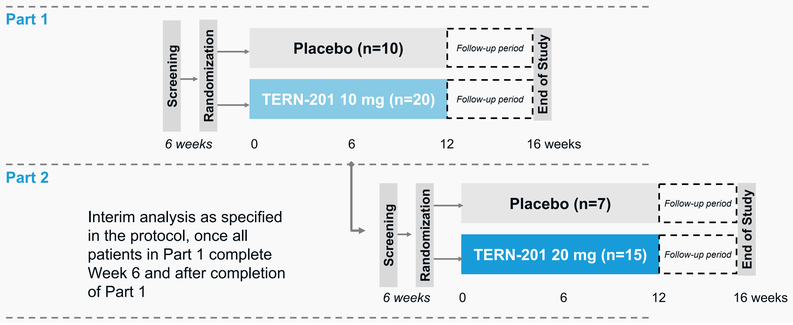
Non-invasive tests (NITs) have become essential to diagnose and stage nonalcoholic steatohepatitis (NASH). Biopsy-based screen failure (SF) rates are high in NASH trials, which lead to increased cost and extended enrollment durations. Both reduction in liver fat content on MRI-PDFF and reduction in liver fibro-inflammation on corrected T1 (cT1) have been proposed as endpoints for early NASH trials to demonstrate efficacy before proceeding to larger trials with histology-based endpoints. High cT1 values (> 875 msec) were shown to predict the presence of fibrotic NASH[1] and liver-related clinical outcomes[2].

LIFT and AVIATION were double-blind, placebo-controlled studies in adults with non-cirrhotic NASH evaluating TERN-101, a potent, nonsteroidal farnesoid X receptor (FXR) agonist with enhanced liver distribution, and TERN-201, a highly specific vascular adhesion protein-1 (VAP-1) inhibitor, respectively. Given that several early NASH trials now require the presence of at least 10% liver fat content on MRI-PDFF or a corrected cT1 value above 800 m sec, the aim of this study was to assess the utility of a simple NIT screening approach to decrease the SF rate in early trials.

A stepwise NIT screening approach was implemented to recruit similar study populations in both trials: patients with presumed NASH and a high degree of liver fat and fibro-inflammation, reflecting F2 and F3 fibrosis.

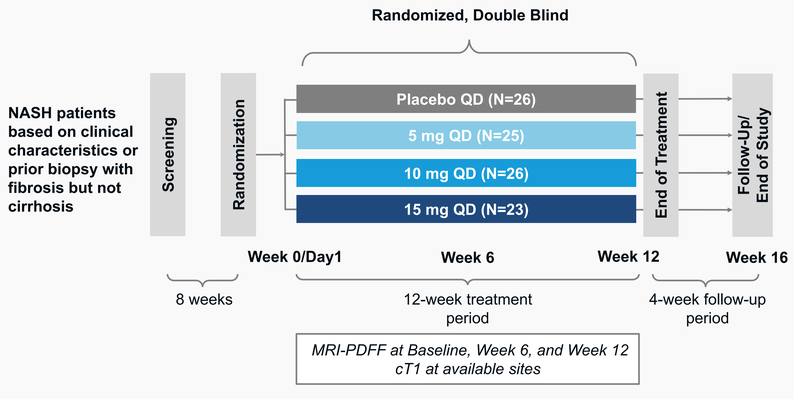
2 STUDY DESIGN

TERN-201 AVIATION Study: Phase 1b Study in NASH patients



Magnetic resonance imaging- proton density fat fraction (MRI-PDFF) and corrected T1 (cT1) at Baseline, Week 6, and Week 12

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



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

ACKNOWLEDGEMENTS

The authors are grateful to the study participants, the research staff and to all the investigators for their participation in the AVIATION and LIFT studies

3 ELIGIBILITY CRITERIA

Combined Key Inclusion Criteria

Key inclusion criteria:

- ✓ Adults aged 18-75
- ✓ Overweight or obese with a BMI ≥ 25 kg/m2

NASH patients based on clinical characteristics:

AVIATION:
- ✓ TE 6.5-21 kPa
- ✓ CAP > 280 dB/m

LIFT:
- ✓ TE 7.6-21 kPa
- ✓ CAP > 300 dB/m

OR
- ✓ Prior biopsy: F1-3 without cirrhosis within 2 years
- ✓ Stable weight (< 5% weight loss) since the time of the biopsy

All patients:
- ✓ ALT ≥ 28 IU/L (women) and ≥ 43 IU/L (men)

AVIATION:
- ✓ MRI-cT1 relaxation time > 800 msec

LIFT:
- ✓ MRI PDFF liver fat content ≥ 10 %

Transient elastography (TE), controlled attenuation parameter (CAP); alanine aminotransferase (ALT); Magnetic resonance imaging (MRI); corrected T1 (cT1)

Combined Key Exclusion Criteria

- × History or clinical evidence of other chronic liver diseases, including but not limited to alcoholic liver disease, hepatitis B, hepatitis C, autoimmune related hepatic disorders, drug-induced hepatotoxicity, Wilson's disease, hemochromatosis or alpha-1-antitrypsin deficiency
- × History or clinical evidence of cirrhosis, hepatic decompensation or other severe liver impairment
- × ALT or AST > 5x ULN
- × Bilirubin > 1.2 mg/dL
- × Uncontrolled diabetes with HbA1c > 9.5%
- × Excessive alcohol average weekly consumption of >21 standard drinks for males and > 14 standard drinks for females over a period of more than 3 consecutive months in the year prior to screening.
- × Unstable cardiovascular disease; uncontrolled hyperlipidemia defined as fasting LDL cholesterol ≥ 150 mg/dL despite treatment or total triglyceride > 300 mg/dL (LIFT)
- × History of serotonin syndrome, seizure disorder, schizophrenia, or bipolar disease (AVIATION)

Alanine aminotransferase (ALT), aspartate aminotransferase (AST), international normalized ratio (INR), alkaline phosphatase (ALP), estimated glomerular filtration rate (eGFR), low-density lipoprotein (LDL)

4 METHODS

- Screening and baseline characteristics from the phase 2a LIFT and phase 1b AVIATION studies were combined.
- In screening step 1, both trials required age ≥ 18, BMI ≥ 25 kg/m2, ALT above the median central laboratory normal range, vibration controlled transient elastography (VCTE) of 7.5 (LIFT) and 6.5 (AVIATION) to 21 kPa, and controlled attenuation parameter (CAP) of 280 (AVIATION) and 300 (LIFT) dB/m within 3 months of screening.
- Neither trial required liver biopsy. Potential subjects remaining eligible after the step 1 screening underwent MRI to assess liver fat content eligibility ≥ 10% by proton density fat fraction (PDFF) for LIFT or corrected T1 (cT1) > 800 msec for AVIATION (Step 2). An analysis of patients with cT1 ≥ 875 was performed. Common SF reasons were tabulated, and multiparametric MRI SF rates were calculated.

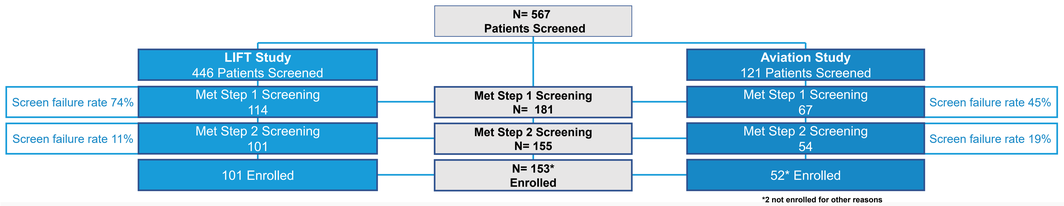
REFERENCES

1. Pavlides M, Banerjee Andersson A, Kelly M, Imajo K, Nakajima A, Fallowfield JA, Hirschfield G, Pavlides M, Sanyal AJ, Noureddin M, Banerjee R, Dennis A, Harrison S. Clinical Utility of Magnetic Resonance Imaging Biomarkers for Identifying Nonalcoholic Steatohepatitis Patients at High Risk of Progression: A Multicenter Pooled Data and Meta-Analysis. Clin Gastroenterol Hepatol. 2022 Nov;20(11):2451-2461.

1. R, Sellwood J, Kelly CJ, Robson MD, Booth JC, Collier J, Neubauer S, Barnes E. Multiparametric magnetic resonance imaging predicts clinical outcomes in patients with chronic liver disease. J Hepatol. 2016;64:308–315. doi: 10.1016/j.jhep.2015.10.009.

5 RESULTS

Screen Failure Flow



- The overall SF rate was 73%. Recruitment durations were 6 and 3 months for LIFT and AVIATION, respectively. Of the 567 patients,181 (32%) met step 1 eligibility criteria, with a SF rate of 68%.
- The most common reason for SF was not meeting the ALT enrollment eligibility threshold value. Of the 181 patients, 155 (86%) met either MRI-PDFF in LIFT or cT1 criteria in AVIATION, resulting in a step 2 MRI SF rate of 14% (26/181; 2 patients not treated for other reasons post step 2).

Demographics

Parameter	Statistic	Lift Randomized (N= 101)	AVIATION Randomized (N= 52)	Combined Randomized (N= 153)	Combined Screen Fail (N= 414)	Step 2 Screen Fail (N= 26)
Age (years)	Mean (SD)	50.4 (11.9)	51.8 (11.6)	50.9 (11.8)	53.7 (10.9)	55.8 (11.2)
	Median (Min, Max)	54.0 (20.0, 72.0)	50.5 (27.0, 72.0)	53.0 (20.0, 72.0)	55.0 (22.0, 76.0)	56.5 (33.0, 73.0)
Diabetes	No	55 (54.5%)	31 (59.6%)	86 (56.2%)	**414 (100%)**	**26 (100%)**
	Yes	46 (45.5%)	21 (40.4%)	67 (43.8%)	0	0
Ethnicity	HISPANIC OR LATINO	70 (69.3%)	34 (65.4%)	104 (68.0%)	292 (70.5%)	14 (53.8%)
	NOT HISPANIC OR LATINO	27 (26.7%)	16 (30.8%)	43 (28.1%)	119 (28.7%)	11 (42.3%)
	NOT REPORTED	1 (1.0%)	2 (3.8%)	3 (2.0%)	2 (0.5%)	0
	UNKNOWN	3 (3.0%)	0	3 (2.0%)	1 (0.2%)	1 (3.8%)
Sex	Female	66 (65.3%)	35 (67.3%)	101 (66.0%)	224 (54.1%)	14 (53.8%)
	Male	35 (34.7%)	17 (32.7%)	52 (34.0%)	190 (45.9%)	12 (46.2%)
Race	AMERICAN INDIAN OR ALASKA NATIVE	0	2 (3.8%)	2 (1.3%)	0	0
	ASIAN	3 (3.0%)	2 (3.8%)	5 (3.3%)	7 (1.7%)	2 (7.7%)
	BLACK OR AFRICAN AMERICAN	5 (5.0%)	2 (3.8%)	7 (4.6%)	17 (4.1%)	2 (7.7%)
	WHITE	87 (86.1%)	43 (82.7%)	130 (85.0%)	377 (91.1%)	19 (73.1%)
	Other/ Not reported	6 (5.9%)	3 (5.9%)	9 (5.8%)	13 (3.1%)	3 (11.5%)

Baseline Characteristics

Parameter	Statistic	Lift Randomized (N= 101)	AVIATION Randomized (N= 52)	Combined Randomized (N= 153)	Combined Screen Fail (N= 414)	Step2 Screen Fail (N= 26)
CT1 (msec)	n	85	52	137	26	10
	Mean (SD)	938.3 (125.1)	903.3 (104.3)	**925.0 (118.5)**	**854.5 (75.2)**	820.7 (82.9)
	Median (Min, Max)	921.0 (721.0, 1461)	883.0 (803.0, 1418)	898.0 (721.0, 1461)	860.0 (735.0, 1010)	825.0 (735.0, 1010)
CT1 (msec) >/= 875		(n=85)	(n=52)	(n=137)	(n=26)	(n=10)
	< 875	25 (29.4%)	23 (44.2%)	48 (35.0%)	14 (53.8%)	9 (90.0%)
	≥875	**60 (70.6%)**	**29 (55.8%)**	**89 (65.0%)**	12 (46.2%)	1 (10.0%)
MRI-PDFF (%)	N	101	52	153	36	13
	Mean (SD)	21.3 (7.7)	18.3 (7.1)	**20.3 (7.6)**	**15.8 (12.0)**	7.4 (1.2)
	Median (Min, Max)	20.0 (10.0, 48.2)	17.3 (6.0, 34.4)	18.7 (6.0, 48.2)	10.4 (1.3, 44.8)	7.4 (5.3, 9.5)

Note: Screen Fails are those Screened and not randomized. Certain data collected at screening but not recorded in EDC for screen fails.

Despite the small N values due to limited data availability for screen fail patients, randomized patients had a higher cT1, a higher percentage had cT1 ≥ 875 msec and a higher PDFF %. As expected, the majority of those randomized were diabetic and interestingly, none of the screen failure patients were diabetic.

6 CONCLUSIONS

- A stepwise screening approach first using clinical assessments, laboratory tests and VCTE with CAP allowed for screening of patients that were more likely to meet the MRI eligibility criteria.
- As a result, this reduced the number of MRI assessments that were required which reduced overall costs and the need for patients to be scheduled for a separate imaging visit.
- These NIT-guided studies recruited efficiently and enrolled subjects likely to have presumed NASH. These biomarkers, including cT1 and MRI-PDFF, may be used in combination with medical history to identify phenotypic at-risk NASH patients in a noninvasive fashion in these trials to enable clinical trials of experimental NASH therapies.