Madrigal Pharmaceuticals

MAESTRO-NASH

Topline Results Webcast

December 19, 2022

Resmetirom is an investigational therapy and has not been approved by the FDA (or any other regulatory authority). Resmetirom is only available for use in a clinical trial setting (ClinicalTrials.gov NCT03900429, NCT04197479, NCT05500222).

NASDAQ: MDGL

Forward Looking Statements

This Current Report includes "forward-looking statements" made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995, that are based on Madrigal's beliefs and assumptions and on information currently available to it, but are subject to factors beyond its control. Forward-looking statements: reflect management's current knowledge, assumptions, judgment and expectations regarding future performance or events; include all statements that are not historical facts; include statements referenced by forward-looking statement identifiers, including the examples in the paragraph below; and include but are not limited to statements or references concerning - the potential efficacy and safety of resmetirom for noncirrhotic NASH patients and cirrhotic NASH patients; possible or assumed future results of operations and expenses, business strategies and plan (including ex-US. Launch/partnering plans); research and development activities, and the timing and results associated with the future development of resmetirom; the timing and completion of projected future clinical milestone events, including enrollment, additional studies, top-line data and open label projections; plans, objectives and timing for making a Subpart H (Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses) submission to FDA; projections or objectives for obtaining accelerated or full approval for resmetirom; Madrigal's primary and key secondary study endpoints for resmetirom and the potential for achieving such endpoints and projections; optimal dosing levels for resmetirom and projections regarding potential NASH or NAFLD and potential patient benefits with resmetirom, including future NASH resolution, safety, fibrosis treatment, cardiovascular effects, lipid treatment, and/or biomarker effects with resmetirom.

Forward-looking statements can be identified by terms such as "accelerate," "achieve," "allow," "anticipates," "appear," "be," "believes," "can," "continue," "could," "demonstrates," "design," "estimates," "expectation," "expects," "forecasts," "future," "goal," "help," "hopeful," "inform," inform," "intended," "intends," "may," "might," "on track," "planned," "planning," "plans," "positions," "potential," "powers," "predicts," "predictive," "projects," "seeks," "should," "will," "will achieve," "will be," "would" or similar expressions and the negatives of those terms.

Forward-looking statements are subject to a number of risks and uncertainties including, but not limited to: the assumptions underlying the forward-looking statements; risks of obtaining and maintaining regulatory approvals, including, but not limited to, potential regulatory delays or rejections; risks associated with meeting the objectives of Madrigal's clinical studies, including, but not limited to Madrigal's ability to achieve enrollment objectives concerning patient numbers (including an adequate safety database), outcomes objectives and/or timing objectives for Madrigal's studies; any delays or failures in enrollment, and the occurrence of adverse safety events; risks related to the effects of resmetirom's mechanism of action; the achievement of enrollment objectives concerning patient number, safety database and/or timing for Madrigal's studies; enrollment and trial conclusion uncertainties, generally and in relation to COVID-19 related measures and individual precautionary measures that may be implemented or continued for an uncertain period of time; market demand for and acceptance of our products; the potential inability to raise sufficient capital to fund ongoing operations as currently planned or to obtain financings on terms similar to those arranged in the past; the ability to service indebtedness and otherwise comply with debt covenants; outcomes or trends from competitive studies; future topline data timing or results; the risks of achieving potential benefits in studies that includes substantially more patients, and patients with different disease states, than prior studies; the timing and outcomes of clinical studies of resmetirom; and the uncertainties inherent in clinical testing. Undue reliance should not be placed on forward-looking statements, which speak only as of the date they are made. Madrigal undertakes no obligation to update any forward-looking statements to reflect new information, events or circumstances after the date they are made, or to reflect the occurrence of unanticipated events. Please refer to Madrigal's submissions filed with the U.S. Securities and Exchange Commission, or SEC, for more detailed information regarding these risks and uncertainties and other factors that may cause actual results to differ materially from those expressed or implied. Madrigal specifically discusses these risks and uncertainties in greater detail in the section appearing in Part I, Item 1A of its Annual Report on Form 10-K for the year ended December 31, 2021, filed with the SEC on February 24, 2022, as updated by the risk factors discussed in Part II, Item 1A of the Quarterly Report on Form 10-Q filed with the SEC on May 9, 2022, as well as in Madrigal's other filings with the SEC.

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Agenda

Introduction	Paul Friedman, M.D., Chief Executive Officer
MAESTRO-NASH Data Review	Becky Taub, M.D., Chief Medical Officer and President of R&D Stephen Harrison, M.D., Chairman for both Pinnacle Clinical Research and Summit Clinical Research, San Antonio, Texas, Visiting Professor of Hepatology, Oxford University, and lead Principal Investigator of the MAESTRO studies
Q&A	

Opening Remarks

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MAESTRO-NASH
Topline

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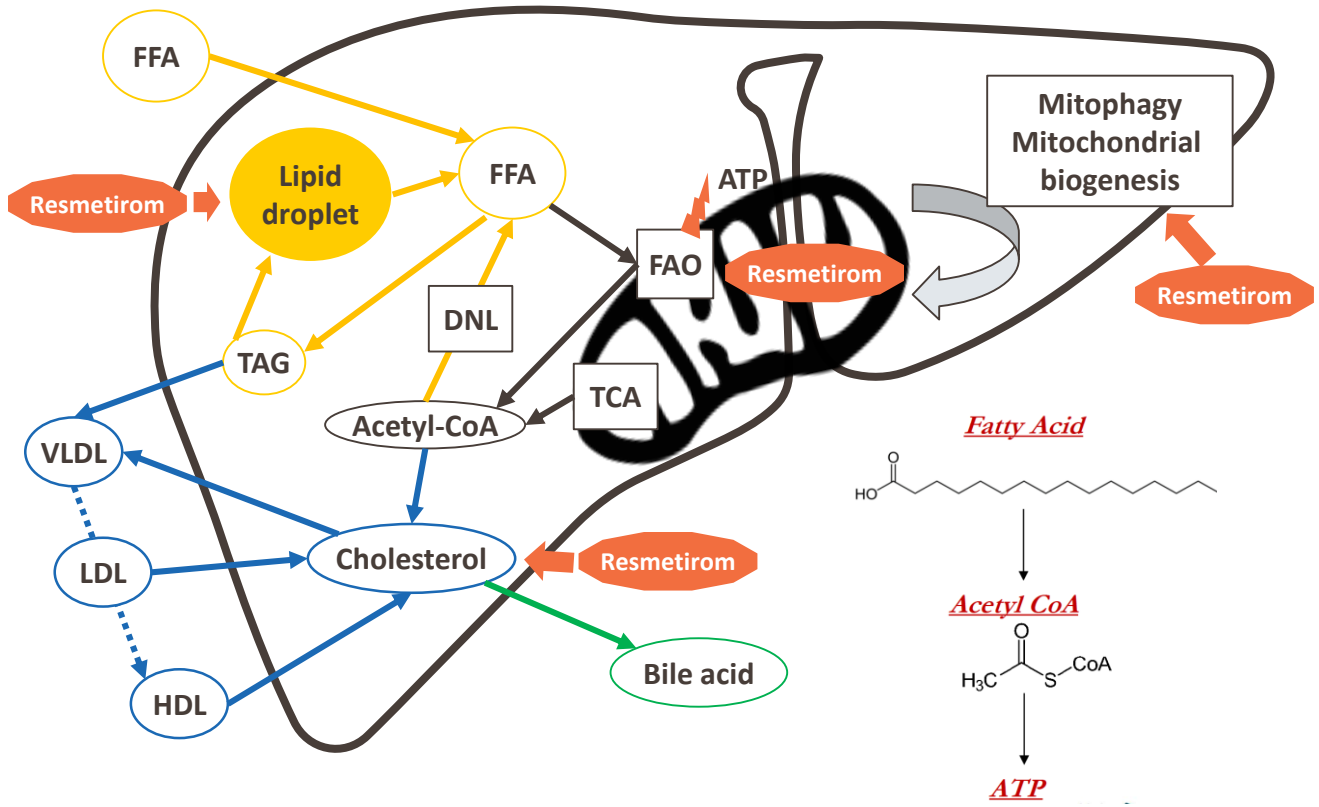
THR-β Pathway Plays a Key Role in Liver Health

- **Selective THR-β agonists without extrahepatic effects**
- THR-β agonists act on multiple hepatic pathways to maintain liver health by controlling[1]:
  - De novo lipogenesis
  - Fatty acid oxidation
  - Mitophagy & mitochondrial biogenesis
  - Cholesterol metabolism
  - Direct anti-inflammatory & anti-fibrotic effects
- In human NASH, the liver has relatively low THR-β activity, exacerbating mitochondrial dysfunction & lipotoxicity
- Potential for hepatic and CV benefits in patients with NASH and liver fibrosis



ATP, adenosine triphosphate; DNL, de novo lipogenesis; FAO, fatty acid oxidation; FFA, free fatty acid; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NASH, nonalcoholic steatohepatitis; TAG, triacylglycerol; TCA, tricarboxylic acid; THR, thyroid hormone receptor; VLDL, very low-density lipoprotein.

1. Sinha RA, et al. *Nat Rev Endocrinol*. 2018;14(5):259-269.

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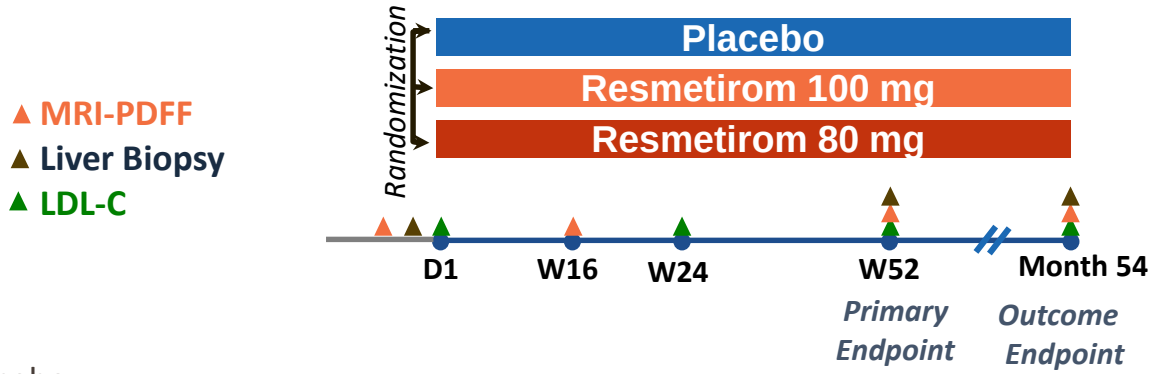
Phase 3 MAESTRO-NASH Study Design: Randomized, Double-Blind, PBO Controlled: Serial Liver Biopsy Study



Comparator/Arms

- 1:1:1 MGL-3196 80, 100 mg , placebo
- >1000 patients enrolled in USA, Europe for primary Week 52 analysis; analysis includes >90% (F1B, F2, F3)
- Up to 2000 patients total enrollment for 54 months
- >150 centers, world-wide

Key Inclusion/Exclusion

- Requires 3 metabolic risk factors (Metabolic Syndrome); FibroScan kPa consistent with F2-F3, CAP≥280
- NASH on liver biopsy: NAS≥4 with fibrosis stage 1A (up to 3%) 1B, total F1 up to 15%; F3, at least 50%, the rest F2
- ≥8% liver fat on MRI-PDFF

Primary Endpoints

- Dual: Resolution of NASH at Week 52 with at least 2 point reduction in NAS with no worsening of fibrosis OR reduction in fibrosis stage by 1-point with no worsening of NAS
  - Key secondary endpoints LDL-C lowering at Week 24
- Composite liver-related outcome at 54 months [histologic evidence of cirrhosis on biopsy, MELD>=15, hepatic decompensation, liver transplant, all cause mortality]

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Baseline Characteristics (ITT)

	Resmetirom 80 mg (N=322)	Resmetirom 100 mg (N=323)	Placebo (N=321)	Overall (N=966)
Age mean (SD)	56 (12)	57 (11)	57 (11)	57 (11)
Female n, (%)	182 (57)	182 (56)	178 (56)	542 (56)
White n, (%)	291 (90)	291 (90)	281 (88)	863 (89)
Hispanic or Latino n, (%)	71 (22)	81 (25)	52 (16)	204 (21)
BMI mean (SD)	36 (6)	36 (7)	35 (7)	36 (7)
Type 2 Diabetes n, (%)	224 (70)	213 (66)	210 (65)	647 (67)
Hypertension n, (%)	243 (76)	254 (79)	257 (80)	754 (78)
Dyslipidemia n, (%)	230 (71)	236 (73)	223 (70)	689 (71)
Hypothyroid n, (%)	38 (12)	46 (14)	45 (14)	129 (13)
FibroScan VCTE kPa mean (SD)	13 (7)	14 (7)	13(6)	13 (7)
FibroScan CAP mean (SD)	346 (37)	349 (39)	347 (37)	348 (38)
MRI-PDFF mean (SD)	18 (7)	17 (7)	18 (7)	18 (7)
Baseline Liver Biopsy				
NAS >= 5 n, (%)	266 (83)	288 (89)	253 (79)	807 (84)
1B n, (%)	16 (5)	15 (5)	18 (6)	49 (5)
2 n, (%)	107 (33)	100 (31)	112 (35)	319 (33)
3 n, (%)	199 (62)	208 (64)	191 (60)	598 (62)

Biopsy Reads and MAESTRO-NASH ITT Population

- All baseline and Week 52 biopsies were read independently by two central pathologists (glass slides) for the primary analysis read

- Baseline biopsies rescored during the primary read as F1B, F2, F3 by the two central pathologists were the primary population and ITT (n=966) included all patients with at least a baseline biopsy with appropriate fibrosis stage
  - Eligible week 52 biopsies were included if conducted before 60 weeks; patients with biopsies after Week 60 were considered missing, 11 patients with a >Week 60 biopsy due to COVID were removed from the primary analysis population for liver biopsies (mITT, n=955)
  - Biopsies rescored as F1A, C were considered exploratory and will be evaluated separately

Primary and Key Secondary Endpoints

Primary Endpoint	Resmetirom 80 mg (n=316)	p-value	Resmetirom 100 mg (n=321)	p-value	Placebo (n=318)
NASH resolution (ballooning 0, inflammation 0,1) with ≥2-point reduction in NAS and no worsening of fibrosis	26%	<0.0001	30%	<0.0001	10%
≥1-stage improvement in fibrosis with no worsening of NAS	24%	0.0002	26%	<0.0001	14%
Key Secondary Endpoint					
LDL-C lowering (24 weeks)	-12%	<0.0001	-16%	<0.0001	1%

Additional Liver Biopsy Results

- All biopsies were read independently by two central pathologists (glass slides) for the primary efficacy analysis
  - Each pathologist's scores showed a similar statistically significant magnitude of response at both doses for both liver biopsy endpoints
  - The results were combined statistically to generate a single treatment effect

- Biopsy endpoints were achieved independent of baseline fibrosis stage or diabetes status, including similar statistical significance and magnitude of response at both doses in subgroups of F2, F3, and F2/F3 biopsies

- Other secondary liver biopsy endpoints that were achieved at both doses include ≥2 point reduction in NAS with no worsening of fibrosis, ≥2 point reduction in NAS with ≥1-stage improvement in fibrosis, NASH resolution (with ≥2 point reduction in NAS) with ≥1-stage improvement in fibrosis, and a 2-stage reduction in fibrosis without worsening of NAS

- Exploratory and supportive biopsy reviews included reviews of digitized slide images by the central pathologists and two artificial intelligence methodologies

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Safety

- Resmetirom was safe and well-tolerated at both the 80 mg and 100 mg doses
- The frequency of serious adverse events was similar across treatment arms
- The rate of study discontinuation for adverse events was low
- Consistent with previous Phase 2 and Phase 3 data, the most common adverse events reported with greater frequency in the resmetirom groups vs placebo were an excess of generally mild and transient diarrhea and generally mild nausea at the beginning of therapy

AE Term	Resmetirom 80 mg (n=316)	Resmetirom 100 mg (n=321)	Placebo (n=318)
SAEs	11.8%	12.7%	12.1%
Study discontinuation for AEs	2.8%	7.7%	3.7%
Diarrhea	28%	34%	16%
Nausea	22%	19%	13%

Additional Analyses

- Multiple secondary endpoints were achieved, including statistically significant reduction from baseline in liver enzymes (ALT, AST and GGT) in resmetirom treatment groups compared to placebo
- Reductions in atherogenic lipids and lipoproteins, fibrosis biomarkers and imaging tests (MRI-PDFF, CAP and liver stiffness measures) were observed in resmetirom treatment arms as compared with placebo
- MAESTRO-NASH included many biomarker and imaging assessments that may be used in real world clinical practice to identify appropriate patients for treatment and monitor response to resmetirom, if approved

Phase 3 MAESTRO Clinical Development Program

Clinical Trial	Status	Primary Outcome
Phase 2 **MGL-3196-05** NCT02912260	**Completed**[1]	Relative change in hepatic fat (by MRI-PDFF) at Week 12
Phase 3 **MAESTRO-NASH**[2] NCT03900429	**Subpart H (52 weeks) – Recruited** **Outcomes (54 months) – Ongoing**	NASH resolution or fibrosis improvement on serial liver biopsy at Week 52 Study continues to outcomes. Composite endpoint includes histologic conversion to cirrhosis, hepatic decompensation events, MELD ≥15, liver transplant, & all-cause mortality
Phase 3 **MAESTRO-NAFLD-1**[3] (presumed NASH) NCT04197479	**Completed (OL Arms Ongoing)** **Ongoing**	Safety & tolerability as measured by incidence of AEs over 52 weeks in >1200 patients Phase 3 **MAESTRO-NAFLD-OLE**[4] (NCT04951219) 52-week extension to MAESTRO-NAFLD-1 in >700 patients: Safety & tolerability by incidence of AEs over 52 weeks
Phase 3 **MAESTRO-NASH-OUTCOMES**[5] NCT05500222	**Initiated**	Event-driven clinical outcome to decompensated cirrhosis in patients with well-compensated NASH cirrhosis

MAESTRO Phase 3 trials provide a comprehensive safety data set in >1500 patients at the top dose of 100 mg and >2000 patients on at least 80 mg to support accelerated approval of resmetirom for the treatment of NASH with liver fibrosis

AE, adverse event; MELD, model for end-stage liver disease; MRI-PDFF, magnetic resonance imaging-proton density fat fraction; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; OL, open-label; OLE, open-label extension.

1. Harrison SA, et al. *Lancet*. 2019;394(10213):2012-2024. 2. ClinicalTrials.gov (NCT03900429). https://clinicaltrials.gov/ct2/show/NCT03900429. Accessed 17Oct2022. 3. ClinicalTrials.gov (NCT04197479). https://clinicaltrials.gov/ct2/show/NCT04197479. Accessed 17Oct2022. 4. ClinicalTrials.gov (NCT04951219). https://clinicaltrials.gov/ct2/show/NCT04951219. Accessed 17Oct2022. 5. ClinicalTrials.gov (NCT05500222). https://clinicaltrials.gov/ct2/show/NCT05500222. Accessed 17Oct2022.

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Q&A

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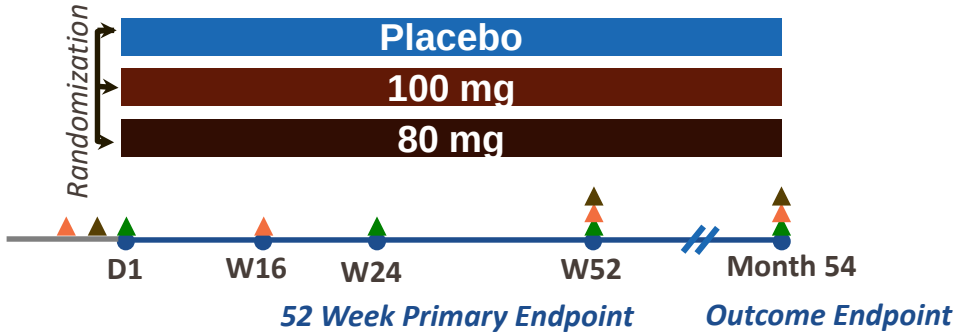
Thank You

Phase 3 MAESTRO-NASH Study Design: Randomized, Double-Blind, Placebo-Controlled Serial Liver Biopsy Study

All MAESTRO trials have a similar 52 week design of biomarker and imaging collection leading to a robust data set in F1 to F4 NASH patients

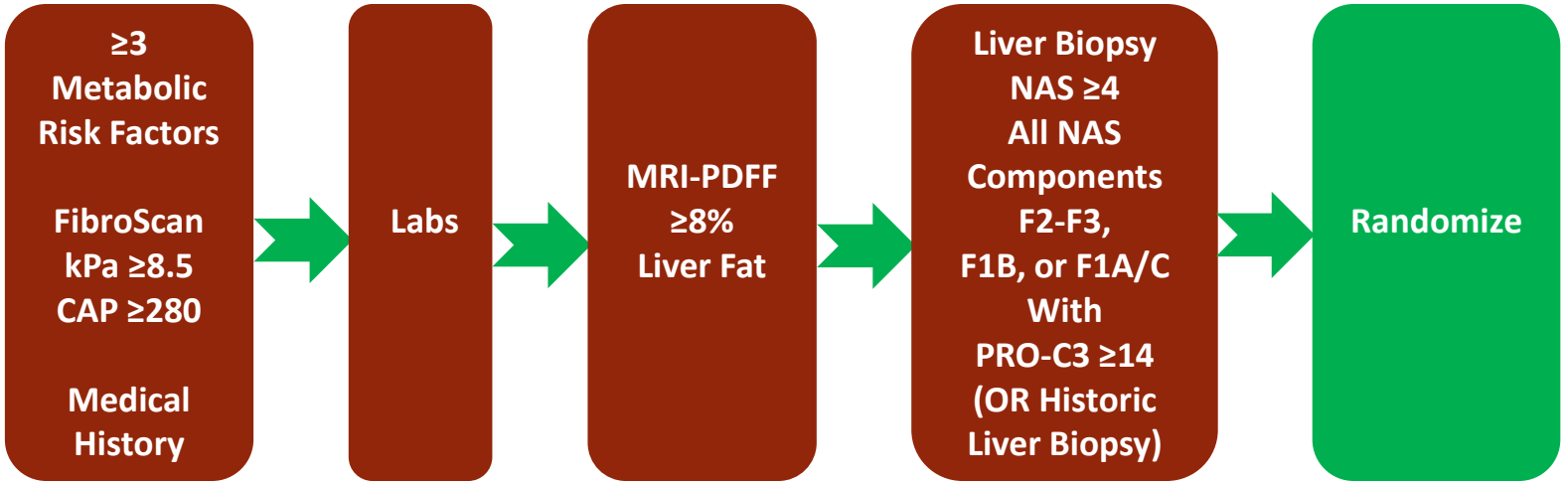
▲ MRI-PDFF
▲ Liver Biopsy
▲ LDL-C



Risk Factors of Significant Fibrosis?

- Age >50 years
- BMI >30 kg/m^2
- Elevated liver enzymes (AST >20 U/L, AST/ALT ≥1)
- T2D
- Hypertension
- Dyslipidemia
- Metabolic Syndrome components (obesity, insulin resistance)
- Historical FibroScan >8.5 kPa, CAP >280 dB/M (Ideally 300)

MAESTRO-NASH 8-Week Screening Process



Screening paradigm led to ~80% of screening biopsies showing at-risk NASH (F2-F4 NAS ≥3) of which 65-70% met all eligibility criteria

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CAP, controlled attenuation parameter; LDL-C, low-density lipoprotein cholesterol; MRI-PDFF, magnetic resonance imaging-proton density fat fraction; NAFLD, nonalcoholic fatty liver disease; NAS, NAFLD activity score; NASH, nonalcoholic steatohepatitis; PRO-C3, N-terminal type III collagen propeptide; T2D, type 2 diabetes

ClinicalTrials.gov (NCT03900429): https://clinicaltrials.gov/ct2/show/NCT03900429