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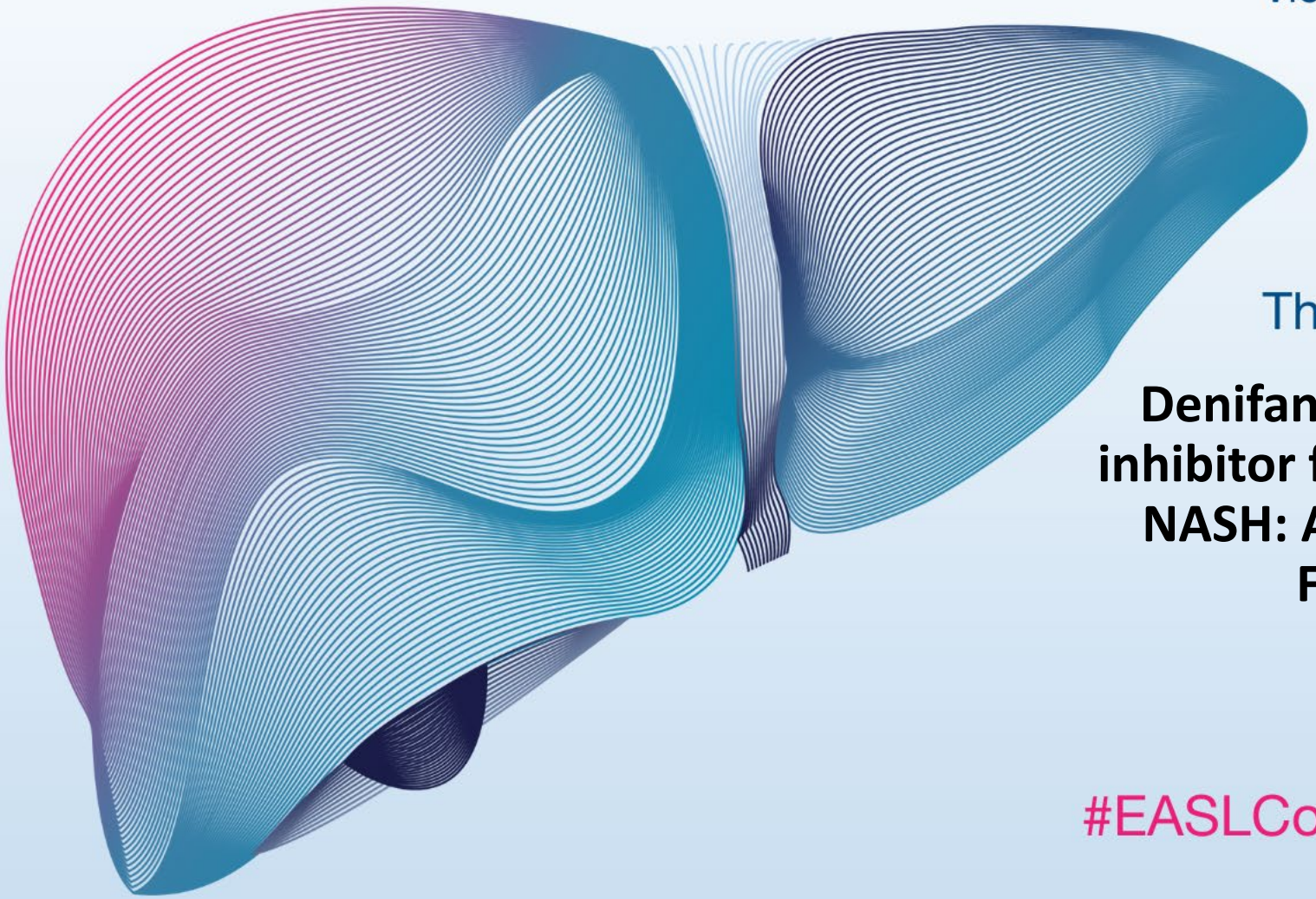
21–24 June
2023



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Denifanstat, a fatty acid synthase (FASN) inhibitor for the treatment of biopsy-proven NASH: A 26-week interim analysis of the FASCINATE-2 Phase 2b trial

Rohit Loomba, MD, MHSc

University of California, San Diego

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Disclosures

Conflict of Interest Disclosure Statement

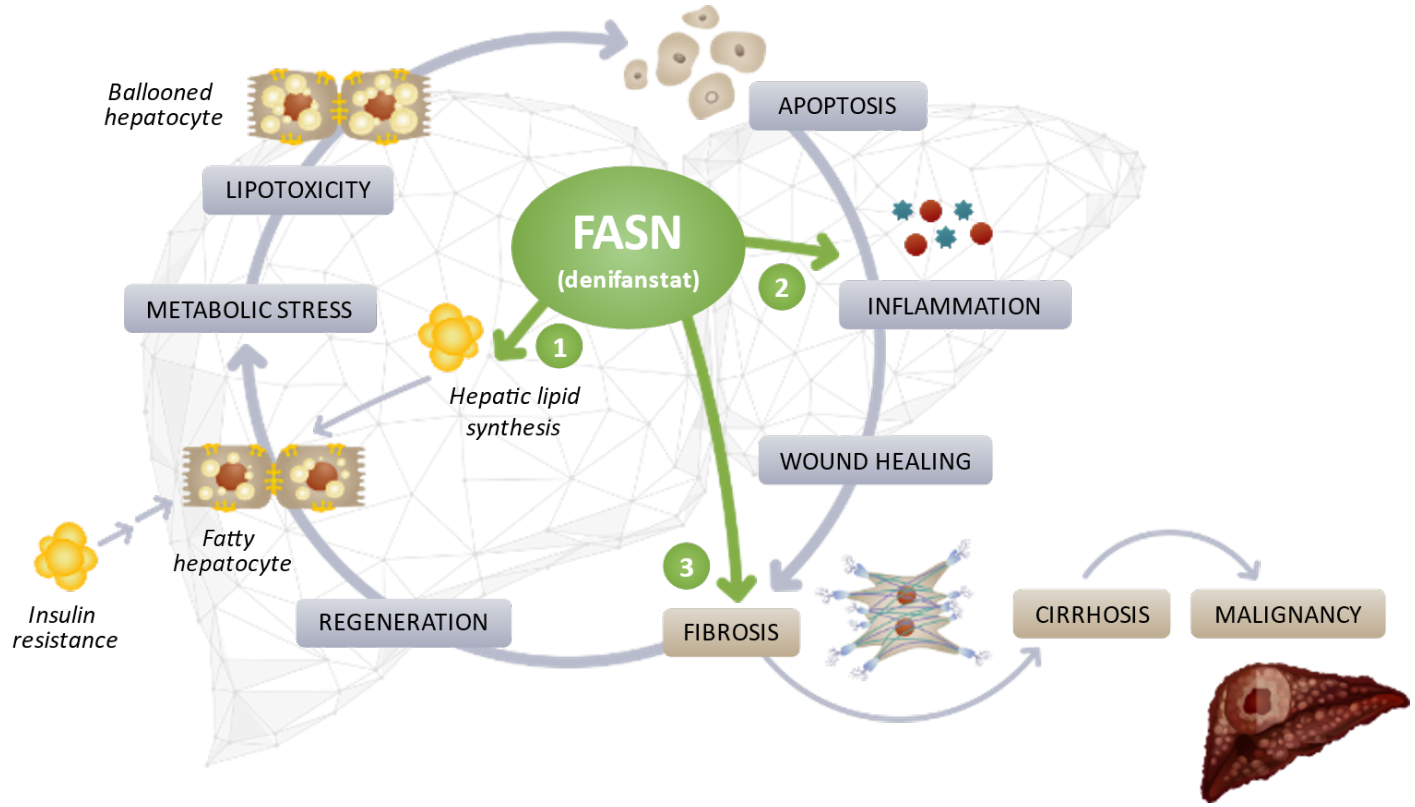
RL serves as chair of the clinical advisory board for Sagimet Biosciences and a consultant or advisory board member for 89bio, Alnylam, Arrowhead Pharmaceuticals, AstraZeneca, Boehringer Ingelheim, Bristol-Myer Squibb, Cirius, CohBar, DiCerna, Galmed, Gilead, Glympse bio, Intercept, Ionis, Metacrine, NGM Biopharmaceuticals, Novo Nordisk, Pfizer, Sagimet and Viking Therapeutics. In addition, his institution has received grant support from Allergan, Boehringer-Ingelheim, Bristol-Myers Squibb, Eli Lilly and Company, Galmed Pharmaceuticals, Genfit, Gilead, Intercept, Inventiva, Janssen, Madrigal Pharmaceuticals, NGM Biopharmaceuticals, Novartis, Pfizer, pH Pharma, and Siemens. He is also co-founder of Liponexus, Inc.

Rohit Loomba, MD, MHSc
Director, NAFLD Research Center
Professor of Medicine, Director of Hepatology and Vice Chief, Division of Gastroenterology
Adjunct Professor, Division of Epidemiology
1W202 ACTRI Building # MC0887
9452 Medical Center Drive
University of California at San Diego
La Jolla, CA, 92093-0887
Ph: 858-246-2201
Fax: 858-246-2255
Email: roloomba@ucsd.edu
Web: http://fattyliver.ucsd.edu

Denifanstat: Differentiated Mechanism Targets Key Drivers of NASH

Denifanstat is a FASN inhibitor

1. Blocks **steatosis** via inhibiting de novo lipogenesis in hepatocytes
2. Reduces **inflammation** via preventing immune cell activation
3. Blunts **fibrosis** via inhibiting stellate cell activation



Adapted from Wegermann et al, Clinical Liver Disease, Vol 11, No 4, April 2018, DOI: 10.1002/cld.709

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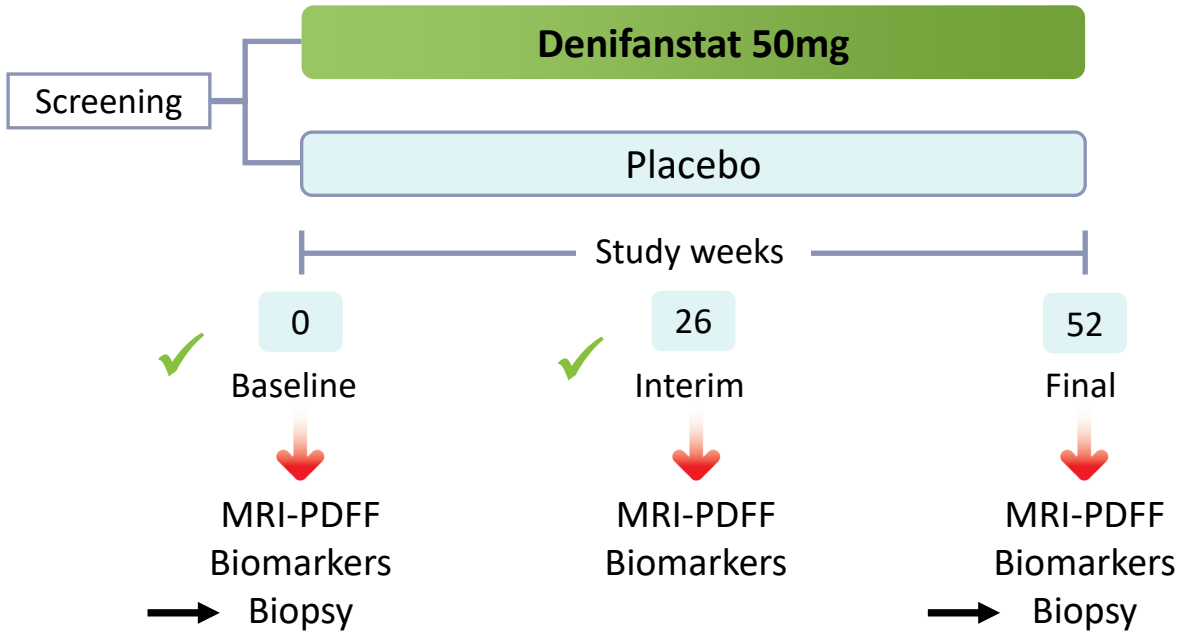
FASCINATE-2 Phase 2b Biopsy Trial: Measuring Histological Improvement

FASCINATE-2 Phase 2b Trial Design

Fully enrolled: 168 patients in U.S., Canada, and Europe



- Biopsy confirmed F2-F3 NASH patients
- 52 weeks, 2:1 50mg or placebo, double-blind

Primary endpoints (biopsy)

- NAS ≥2 points improvement w/o worsening of fibrosis
  OR
  resolution of NASH w/o worsening of fibrosis
- Safety

Secondary endpoints

- Improvement in liver fibrosis ≥1 stage without worsening of NASH (Bx)
- Digital AI pathology
- Interim MRI-PDFF: absolute decrease, % change from baseline, % pts ≥30% (responders)

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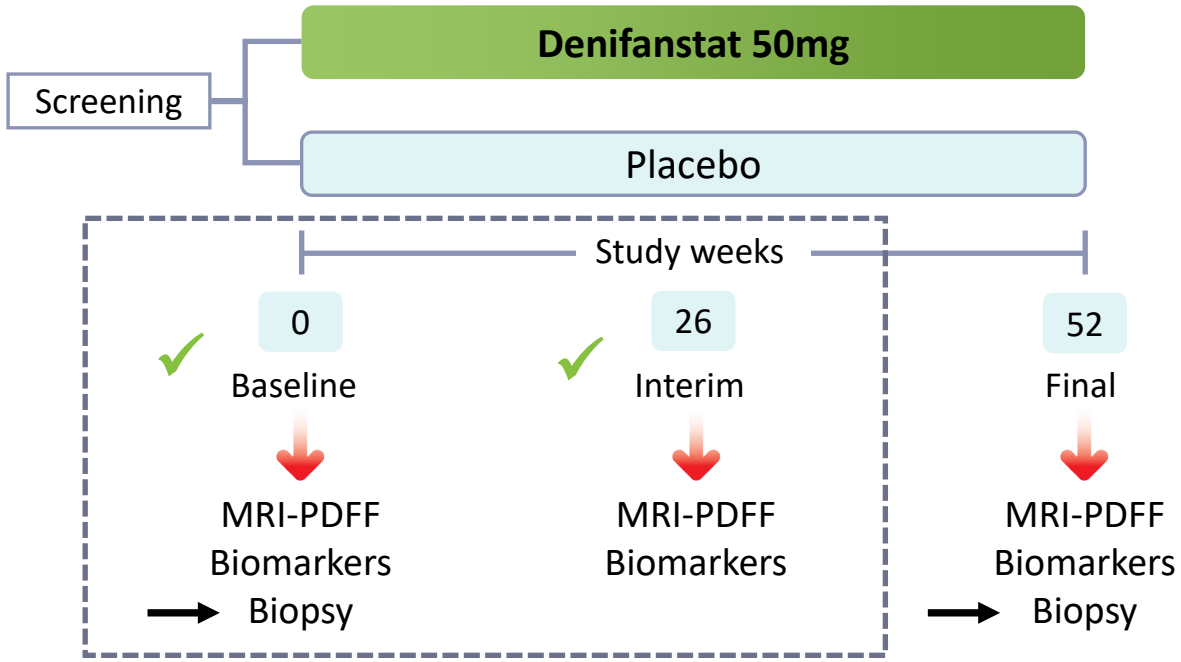
FASCINATE-2: MRI and PD Biomarkers at Week 26 Interim Analysis

FASCINATE-2: IA at Week 26



Aim

To perform an interim analysis of Non-Invasive Tests (NITs) in FASCINATE-2 at week 26

- To examine the efficacy of 50mg once-daily denifanstat versus placebo* in reducing liver fat by MRI-PDFF, as well as biomarkers of inflammation and fibrosis in patients with Stage 2-3 NASH after 26 weeks of treatment

*study team remains blinded to individual patient assignment

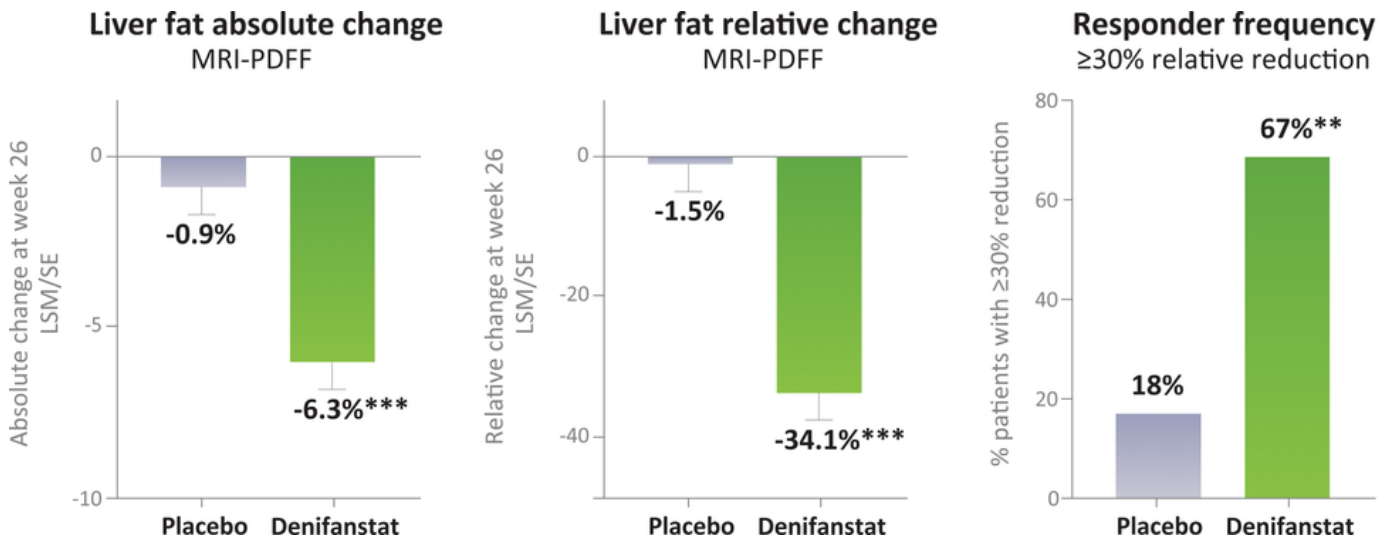
Interim Analysis Cohort Represents Target Patient Population

FASCINATE-2 Phase 2b Interim Analysis Demographics			
Mean (SD)	**Placebo (22)**	**Denifanstat (30)**	**Combined**
Age (years)	56.8 (9.4)	56.1 (12.4)	56.4 (11.1)
Female/Male (%)	14 (63.6%) / 8 (36.4%)	17 (56.7%) / 13 (43.3%)	31 (59.6%) / 21 (40.4%)
Not Hispanic or Latino	16 (72.7%)	24 (80.0%)	40 (76.9%)
Weight (kg)	97.8 (21.9)	100.9 (21.2)	99.6 (21.4)
Diabetes (% T2DM)	13 (59.1%)	21 (70.0%)	34 (65.4%)
F2/F3 (%)	12 (54.5%) / 10 (45.5%)	12 (40.0%) / 18 (60.0%)	24 (46.2%) / 28 (53.8%)
MRI-PDFF (%)	21.78 (5.46)	17.46 (6.36)	19.29 (6.32)
Fibroscan (kPa)	10.67 (4.07)	12.29 (7.33)	11.56 (6.04)
ALT (U/L)	69.77 (42.50)	57.14 (27.55)	62.70 (35.11)
AST (U/L)	51.00 (29.87)	44.43 (22.65)	47.32 (26.00)
LDL (mg/dL)	111.37 (40.6)	96.29 (50.27)	102.86 (46.4)
ELF	9.70 (0.76)	9.73 (0.76)	9.72 (0.75)
PRO-C3 cobas® (ng/mL)	35.72 (15.71)	32.54 (11.19)	33.91 (13.28)

- Typical F2/F3 NASH population
- Middle-aged
- High % of diabetes
- High liver fat by MRI-PDFF
- Elevated liver enzymes: inflammation
- Non-invasive markers of fibrosis consistent with F2/F3

Denifanstat Decreases Liver Fat

Steatosis Biomarker – Liver Fat



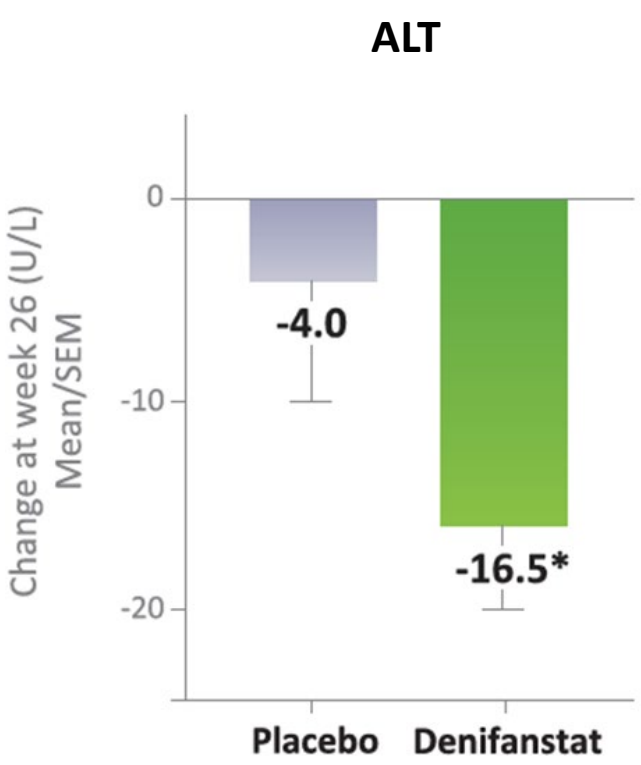
Findings to Date

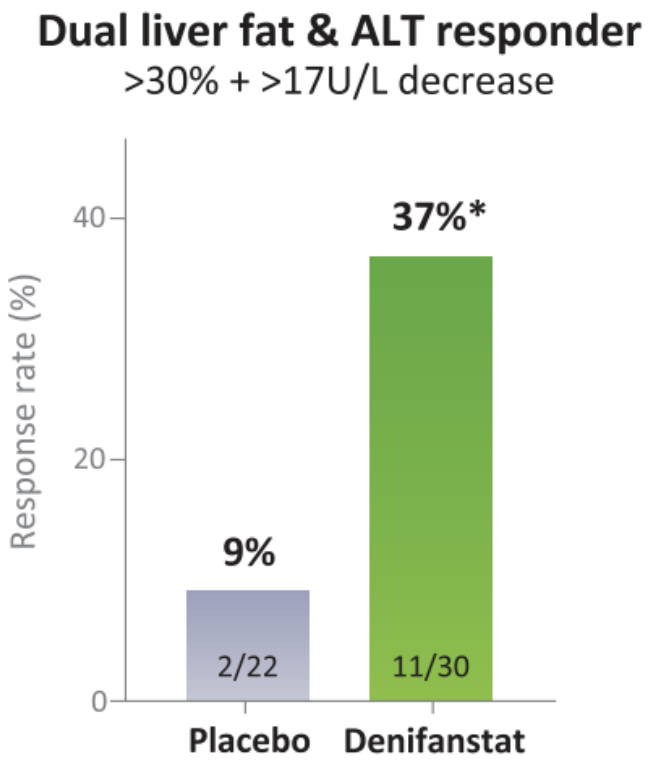
- Denifanstat induced statistically significant reduction of liver fat
- 67% (p<0.001) MRI-PDFF response rate
- About half of responders decreased liver fat by ≥50%
- A relative reduction of liver fat ≥30% by MRI-PDFF has been shown to correlate with liver biopsy response

*** p<0.01, ***p<0.001*

Denifanstat Reduces ALT and Induced Dual Response

ALT and Dual Response





Findings to Date

- ALT decrease suggests a decrease in inflammation with denifanstat
- Denifanstat increased dual liver fat and ALT responder rate, which correlates strongly with liver biopsy response

** p<0.05*

Gastroenterology. 2019 January ; 156(1): 88–95.e5. doi:10.1053/j.gastro.2018.09.021

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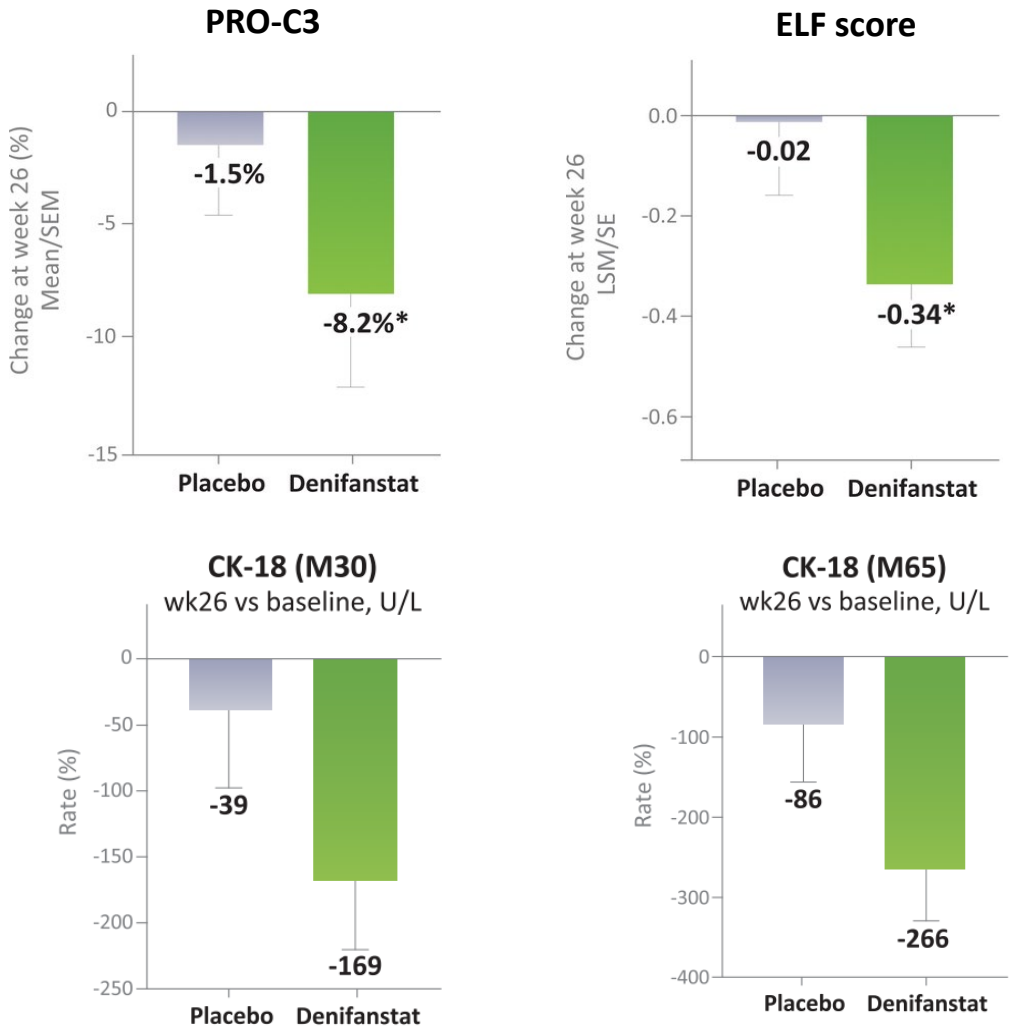
Denifanstat Decreases Markers of Fibrosis and Cell Injury

Fibrosis and Hepatocyte Injury Biomarkers



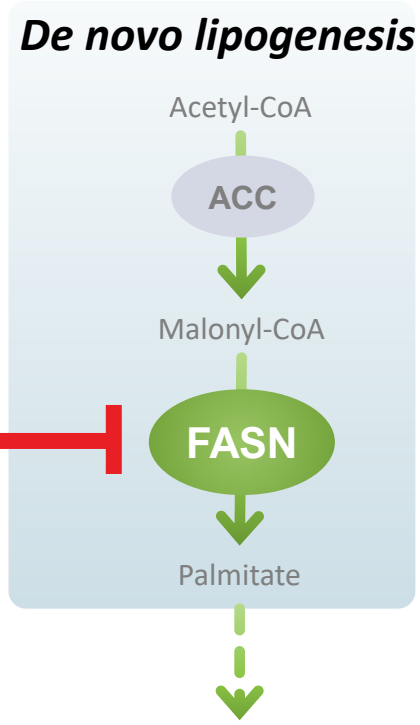
Findings to Date

- PRO-C3 and ELF trends suggest a decrease of liver fibrosis with denifanstat
- ELF score has prognostic value
- CK-18 response suggests reduction in hepatocyte injury

** p<0.05*

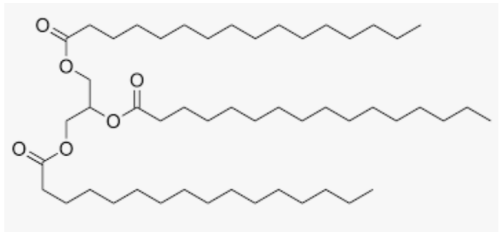
Denifanstat Decreases *De Novo* Lipogenesis

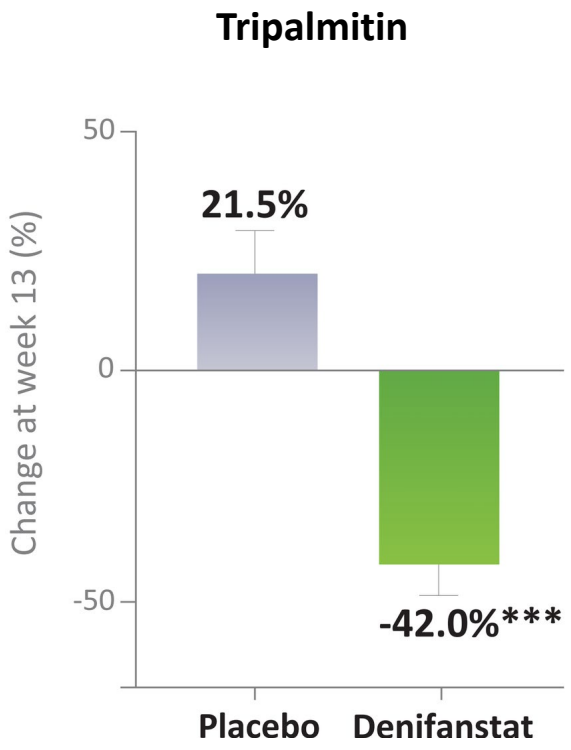
Pharmacodynamic Biomarker



Denifanstat

Tripalmitin





Findings to Date

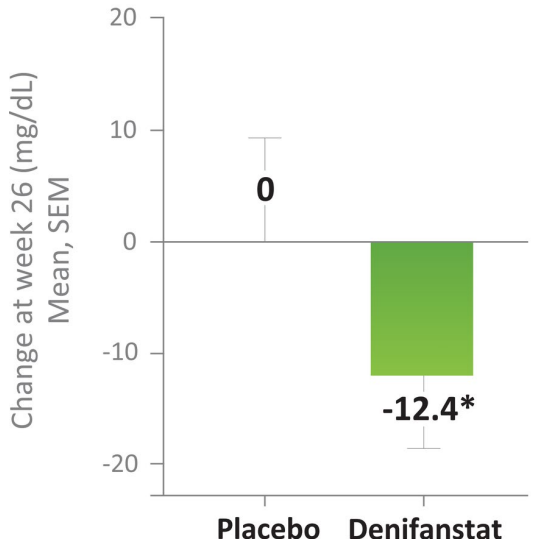
- Tripalmitin is a triglyceride containing three molecules of palmitate, the fully saturated fatty acid product of FASN
- Tripalmitin decrease shows consistent target engagement by denifanstat

****p<0.001*

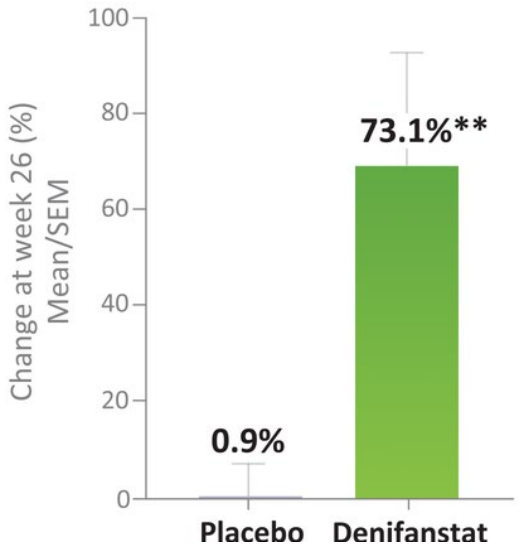
Denifanstat Improves Metabolic Health

Metabolic Health

LDL-C



FGF21



Findings to Date

- LDL-cholesterol decrease suggests cardiovascular benefit
- FGF21 increase indicates denifanstat may improve insulin sensitivity

** p<0.05, ** p<0.01*

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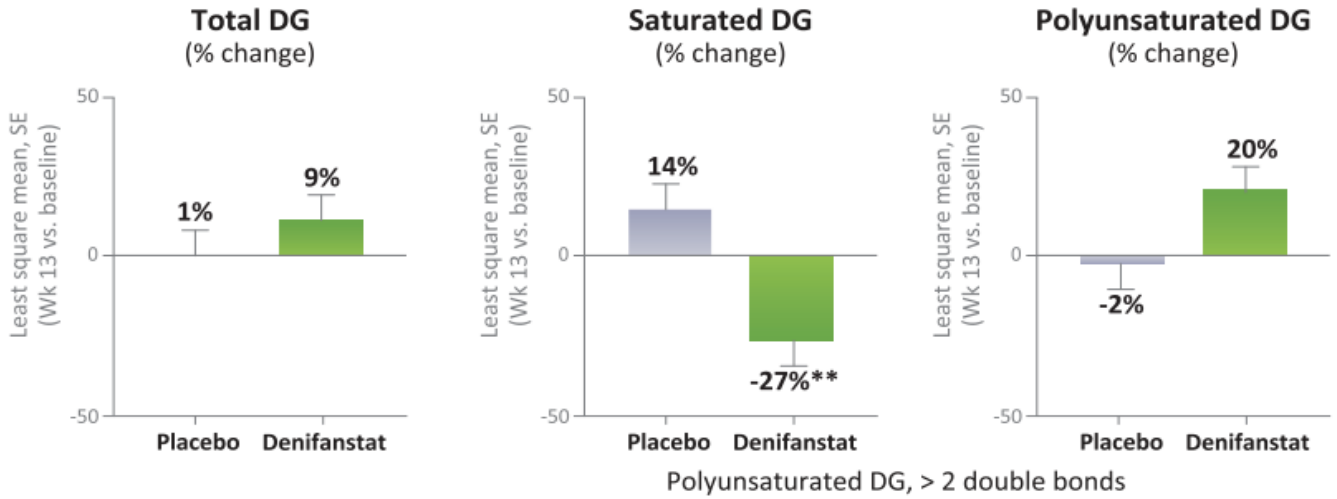
Denifanstat Favorably Changes Circulating Lipid Composition

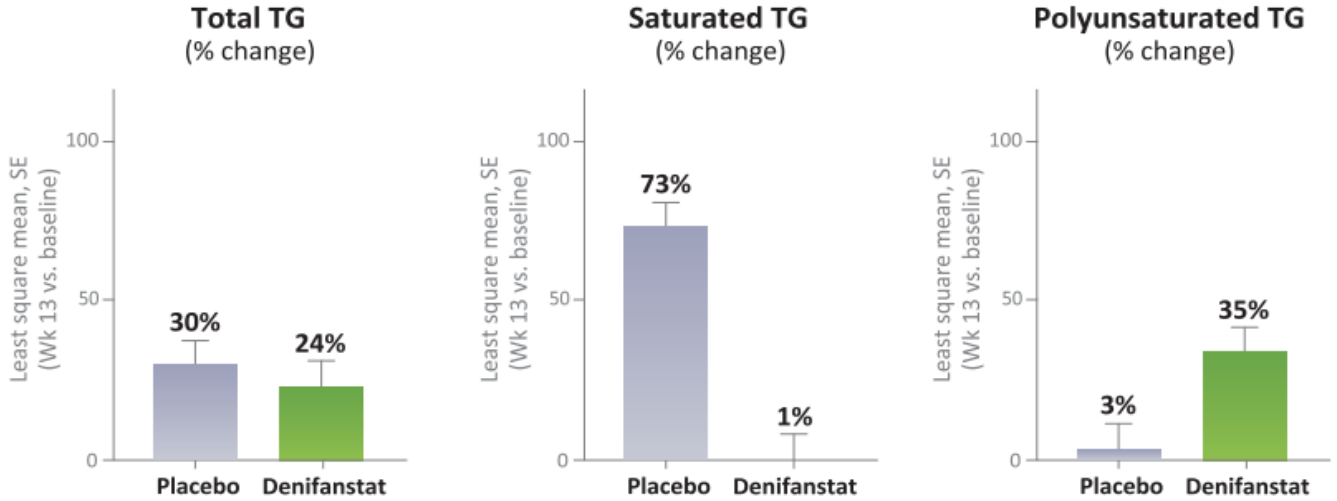
Saturated di- and tri-glycerides are upregulated in NASH

Denifanstat reverses this abnormality by reducing saturated DG/TG and increasing polyunsaturated DG/TG

FASCINATE-2 lipidomic data reproduced Phase 2a findings



Polyunsaturated DG, > 2 double bonds



Polyunsaturated TG, > 3 double bonds

** p<0.01

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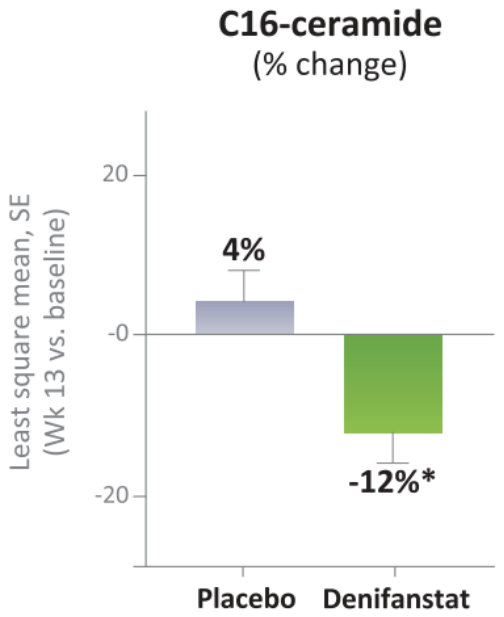
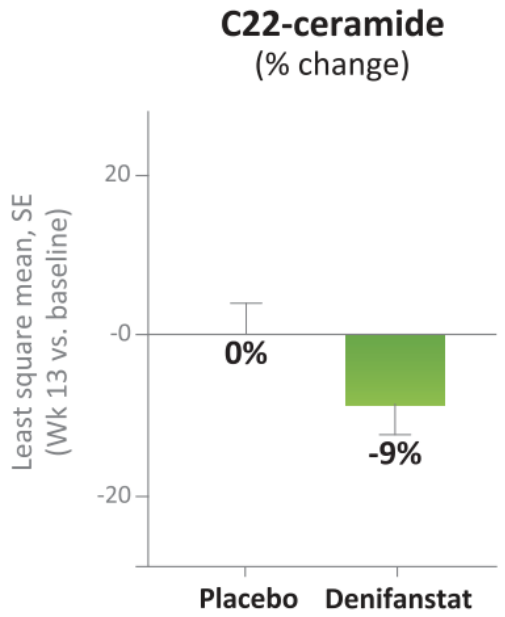
Denifanstat Reduces Lipotoxic Ceramides

Ceramides are associated with CVD risk and elevated in NASH: denifanstat reverses this abnormality

Denifanstat reverses this abnormality by reducing ceramides





Improvements across multiple lipotoxic species are pronounced with denifanstat: this is a unique lipidomic signature that could be beneficial in reducing CVD risk

** p<0.05*

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Denifanstat Was Well Tolerated in the Interim Population

Interim analysis patients – across both active and placebo groups:

- Majority of adverse events were Grade 1 or 2; no Grade ≥3 drug-related AEs
- No treatment related SAEs, no fatal SAEs

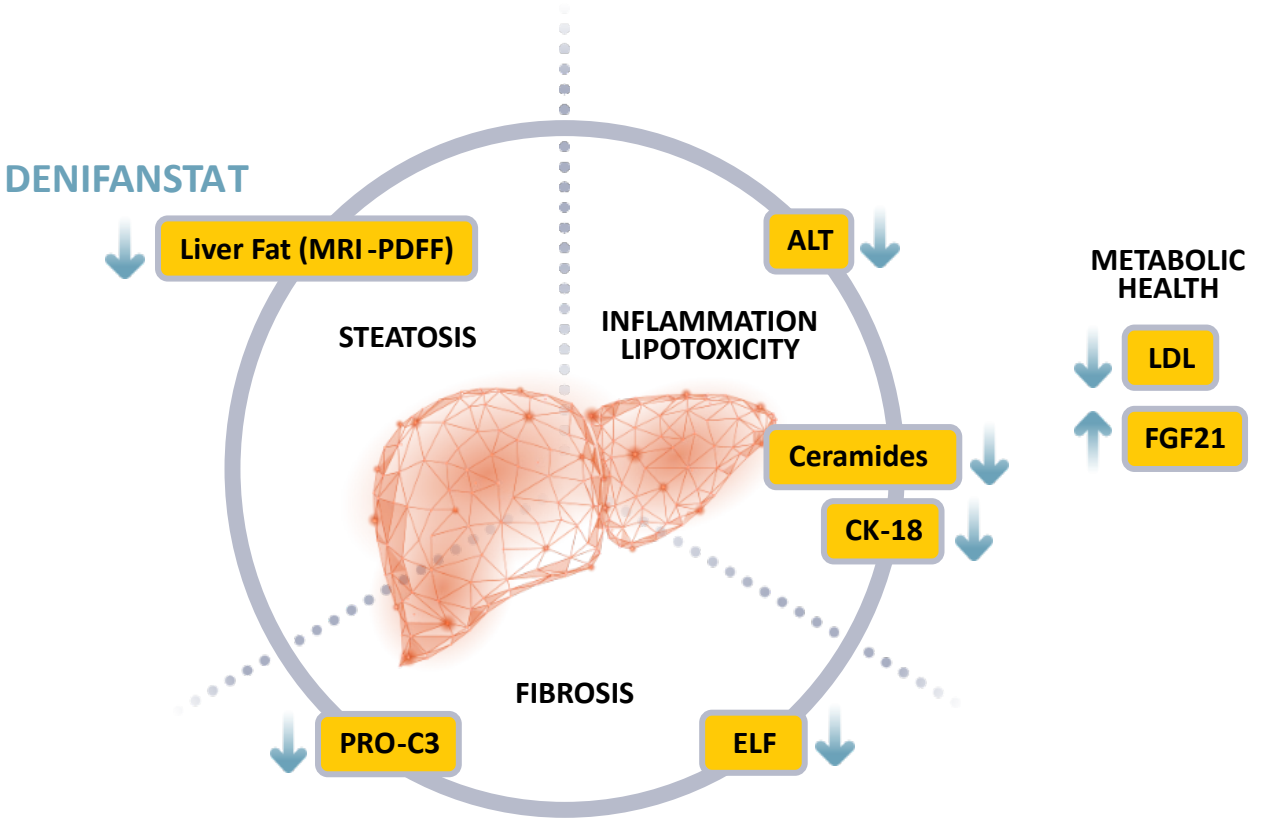
FASCINATE-2 Phase 2b – Interim analysis data set			
Treatment Emergent Adverse Event (TEAE) Classification	**Denifanstat 50mg (n = 30)**	**Placebo (n =22)**	**Combined (n = 52)**
TEAE Related to Study Treatment	14 (46.7%)	6 (27.3%)	20 (38.5%)
TEAE Leading to Treatment Discontinuation	2 (6.7%)	1 (4.6%)	3 (5.8%)
TEAE with CTCAE Grade 3 or Higher (all reported ***unrelated*** to study treatment)	3 (10.0%)	1 (4.6%)	4 (7.7%)

AE data as of Oct 2022 – interim data cut

FASCINATE-2 Interim Results Consistent with Comprehensive Positive Readouts from FASCINATE-1

Interim Results to date show:

- Significant reduction in MRI-PDFF
- Consistent dual response of liver fat & ALT; associated with NASH resolution
- Improvements observed in multiple biomarkers of cardio metabolic health
  - Decrease in LDL-cholesterol
  - Lipid composition improved: decreases in saturated and increases in polyunsaturated di- and triglycerides
  - FGF-21 increase: suggests improved insulin sensitivity
- Improved biomarkers of inflammation
  - Lipotoxic ceramides
  - CK-18
- Improved biomarkers of fibrosis
  - ProC3 and ELF
- Predictive biomarker program ongoing



Highlighted biomarkers replicated in FASCINATE-2

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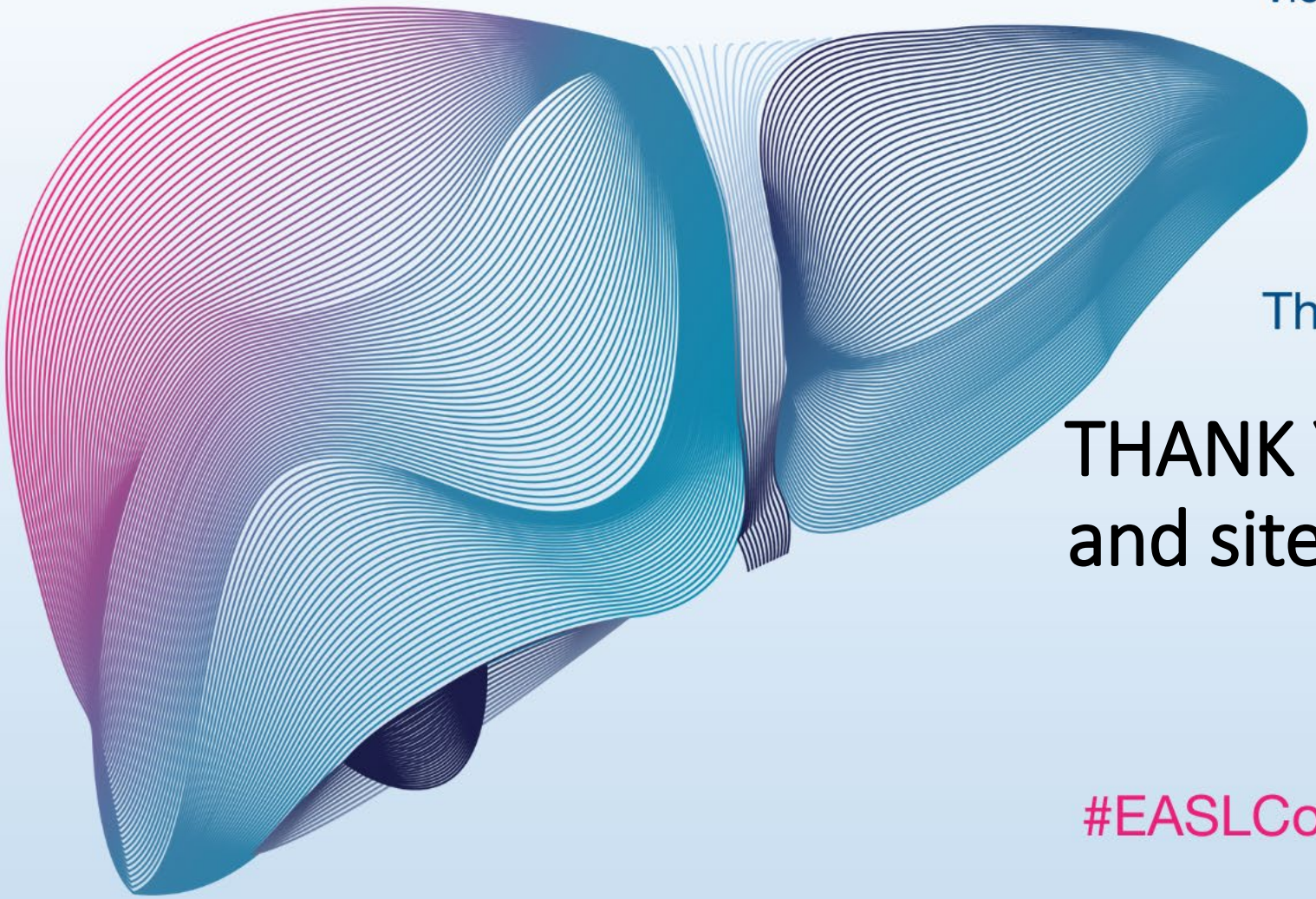

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THANK YOU to our investigators and site staff, patients and their families!

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