Novel, first-in-class, fatty acid synthase inhibitor, TVB-2640 versus placebo demonstrates clinically significant reduction in liver fat by MRI-PDFF in NASH

A Phase 2 randomized controlled trial

AASLD 2020

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Disclosure

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.

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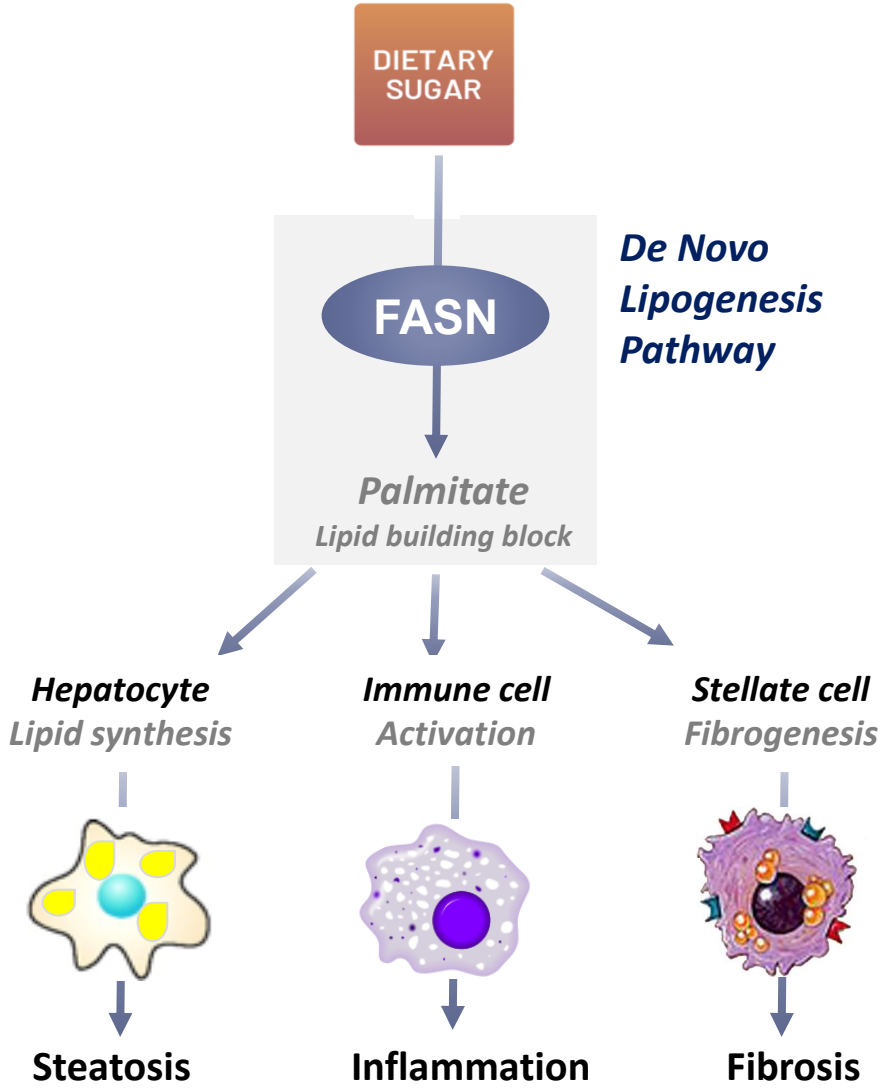
FASN inhibitors targeted to improve NASH and NASH-related fibrosis

- Nonalcoholic steatohepatitis (NASH) is the most common cause of cirrhosis and the second leading cause of liver transplantation in the US
- No FDA-approved therapies
- Increased DNL and lipotoxicity play an important role in NASH pathogenesis
- Fatty acid synthase is an important rate limiting step in fatty acid synthesis and de novo lipogenesis
- FASN/DNL pathway
  - drives steatosis
  - activates pro-inflammatory cells
  - activates stellate cells



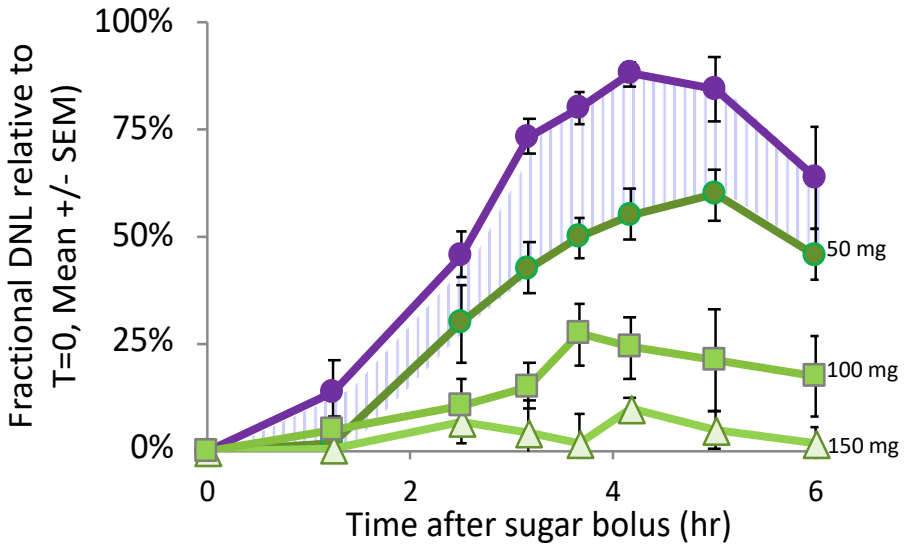
[1]Seyed Abdul et al. 2020, Hepatology 72: 103

TVB-2640 is a potent and selective first-in-human FASN inhibitor

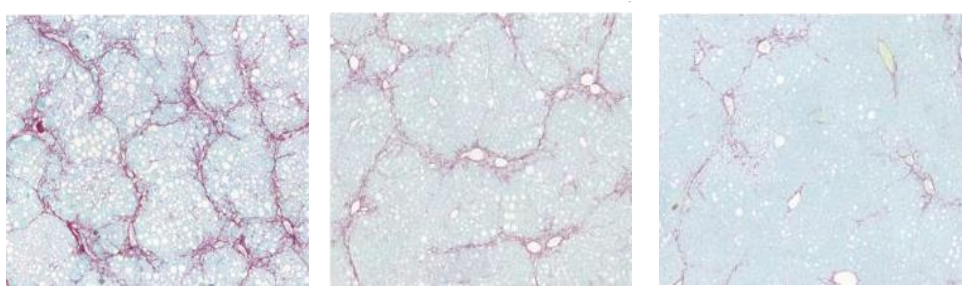
TVB-2640, is a potent and selective first-in-human FASN inhibitor

- ✓ Potent FASN EC_{50} approx. 50 nM
- ✓ Orally-available small molecule
- ✓ Once-daily dosing
- ✓ Excellent PK profile
- ✓ Inhibited hepatic de novo lipogenesis up to 90% in Phase 1b[1]

TVB-2640 reduced DNL in humans



FASN inhibition reverses fibrosis in mice



Vehicle (Placebo) | FASN inhibitor 3mg/kg | FASN inhibitor 10mg/kg

[1]*Seyed Abdul et al. 2020, Hepatology 72: 103*

Introduction

Aim

1. To examine the efficacy of TVB-2640 versus placebo in reducing liver fat by magnetic-resonance-imaging derived proton-density-fat-fraction (MRI-PDFF) in patients with NASH

2. To test the effect of TVB-2640 on exploratory biomarkers of fibrosis, inflammation, metabolic health, and lipidomics including ceramides

Hypothesis

TVB-2640 would be better than placebo in reducing liver fat by MRI-PDFF and in modulating biomarkers in high risk patients with NASH

FASCINATE-1 trial design: TVB-2640 vs placebo

Phase 2a, multicenter, randomized, placebo-controlled trial 1:1:1 (N=99 subjects: 25mg:50mg:placebo)

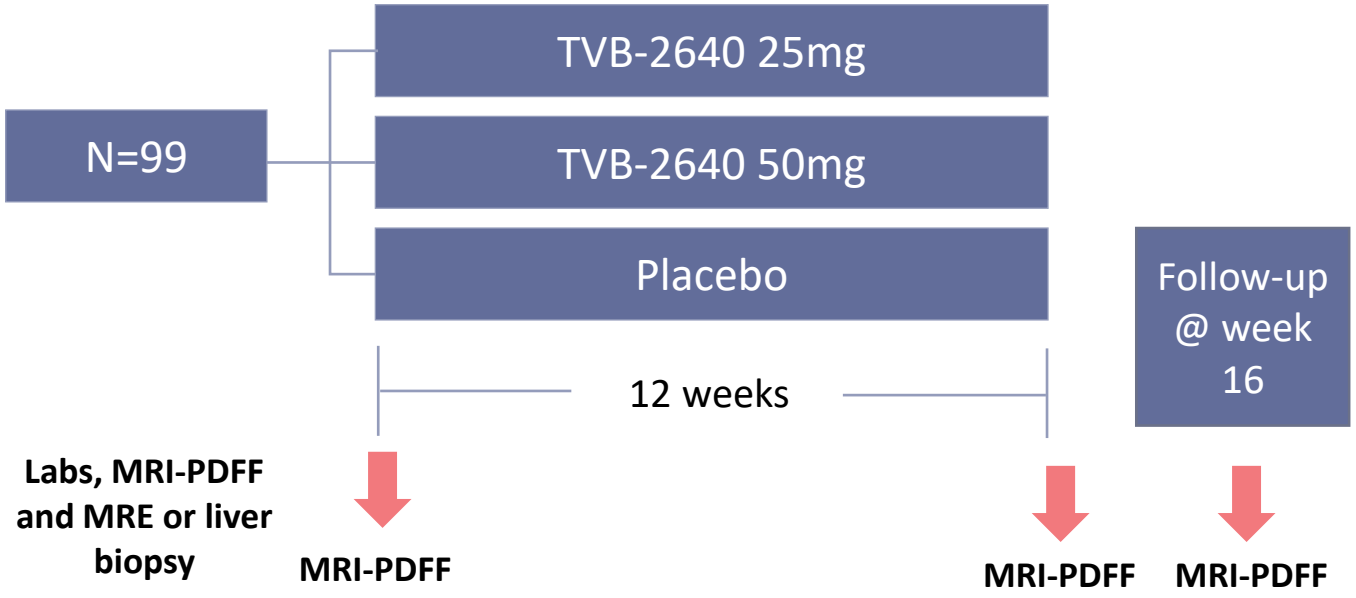
Oral, once-daily, 12 weeks

Criteria

- Inclusion
  - ≥ 8% liver fat
  - MRE ≥ 2.5kPa or recent biopsy
- Exclusion
  - Evidence of cirrhosis
  - Other chronic liver disease

Endpoints

- Primary
  - Liver fat reduction by MRI-PDFF
  - Safety
- Secondary
  - % pts ≥30% reduction of liver fat
  - ALT, AST
  - Biomarkers



Results: demography and baseline characteristics

Median (Q1, Q3)	Placebo (n=31)	25 mg (n=33)	50 mg (n=35)
Age, y	52 (46, 58)	58 (53, 62)	55 (44, 62)
Male, n (%)	14 (45.2)	18 (54.5)	22 (62.9)
T2D, n (%)	17 (54.8)	25 (75.8)	13 (37.1)
Ethnicity/Hispanic, n (%)	25 (80.6)	22 (66.7)	24 (68.6)
Weight, kg	83.7 (74.0, 96.8)	95.4 (84.9, 105.6)	92.0 (83.0, 101.0)
BMI (kg/m^2)	31.2 (29.3, 35.1)	34.0 (29.7, 38.1)	32.8 (29.6, 35.2)
ALT (U/L)	25 (16, 46)	28 (23, 36)	29 (24, 43)
AST (U/L)	21 (15, 30)	21 (17, 26)	23 (20, 30)
ALP (U/L)	82 (72, 98)	76 (62, 92)	74 (58, 103)
GGT (U/L)	33 (22, 58)	32 (22, 40)	39 (25, 49)
Glucose (fasting) (mg/dL)	108 (86, 167)	152 (103, 187)	98 (80, 124)
HbA1c, %	6.4 (5.9, 8.6)	7.1 (6.2, 8.3)	5.8 (5.5, 6.4)
Insulin (fasting) (µU/mL)	17 (15, 24)	23 (13, 37)	22 (14, 32)
Apolipoprotein B (mg/dL)	100 (84,126)	109 (90, 117)	104 (89, 124)
Total Cholesterol (mg/dL)	192 (162, 229)	194 (161, 203)	189 (167, 225)
LDL (mg/dL)	116 (98, 139)	127 (104, 136)	114 (94, 153)
HDL (mg/dL)	43 (39, 53)	40 (36, 54)	44 (37, 51)
Triglycerides (mg/dL)	157 (123, 248)	159 (113, 218)	163 (124, 262)
MRI-PDFF (%)	15.3 (11.8, 22.2)	14.3 (10.4, 22.3)	15.8 (12.3, 19.6)
MRE (kpa)	3.0 (2.7, 3.4)	2.9 (2.7, 3.2)	3.0 (2.8, 3.2)

Safety assessment of TVB-2640 vs placebo

TEAE classification	Placebo n=31	25mg cohort n=33	50mg cohort n=35
Any TEAE	Gr. 1: 11 (35.5%) Gr. 2: 8 (25.8%)	Gr. 1: 18 (54.5%) Gr. 2: 7 (21.2%)	Gr. 1: 11 (31.4%) Gr. 2: 7 (20.0%)
TEAE leading to drug withdrawal	0	2 (6.1%)	0
Treatment Emergent Serious Adverse Event (SAE)	0	0	0
Drug related TEAE	Gr. 1: 3 (9.7%) Gr. 2: 1 (3.2%)	Gr. 1: 10 (30.3%) Gr. 2: 2 (6.1%)*	Gr. 1: 9 (25.7%) Gr. 2: 1 (2.9%)*
TEAE leading to death	0	0	0

**25mg: urinary tract infection and increased appetite; 50mg: shortness of breath; all resolved without dose adjustment*

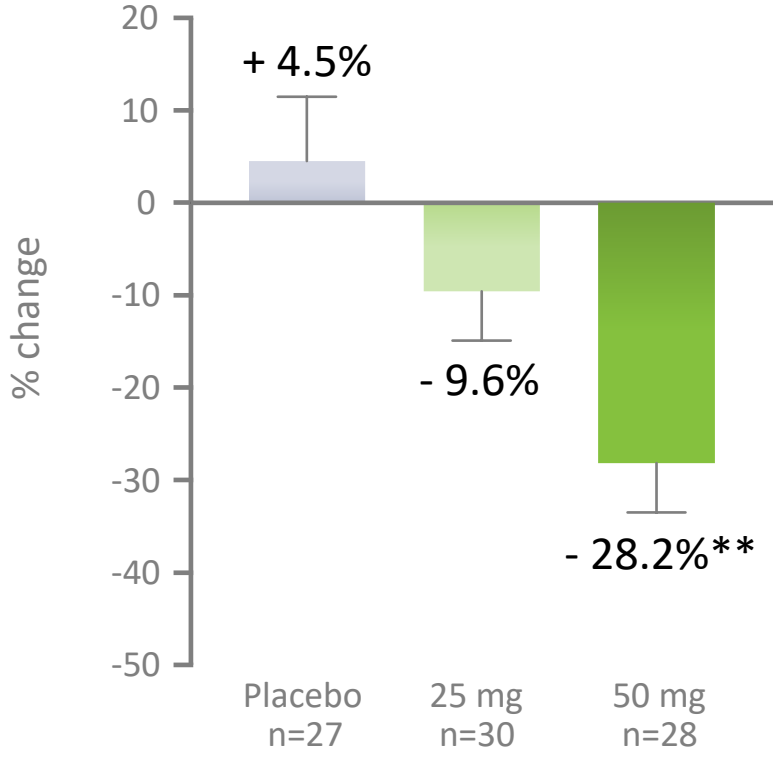
- TVB-2640 appears to be very well tolerated
- No dose related significant adverse events relative to placebo
- Majority of AE's were grade 1 and no grade ≥3 AE's were noted

Potent, dose-dependent reduction of liver fat, with high responder rate

- Liver fat reduction is independent of T2D, baseline MRE and baseline liver fat

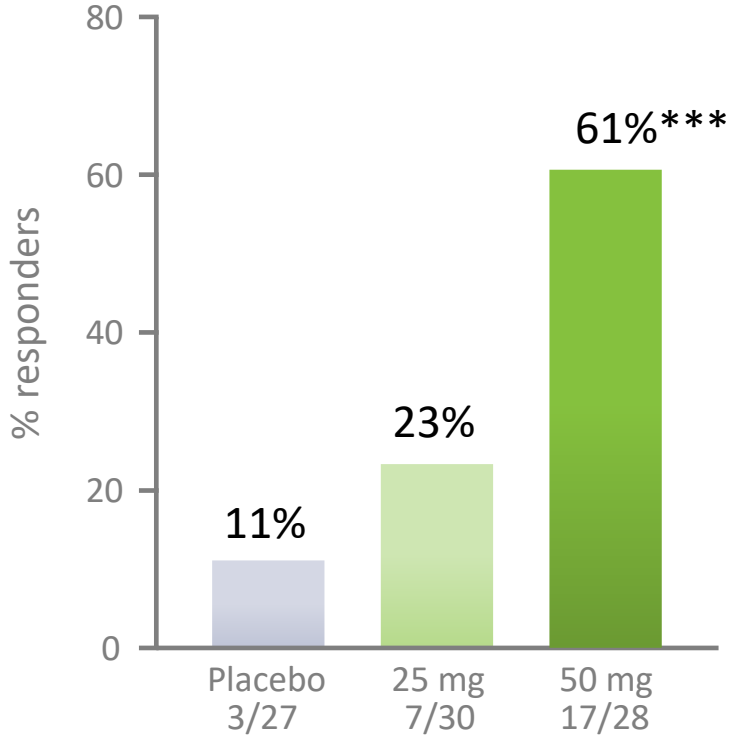
Relative liver fat reduction

MRI-PDFF at week 12



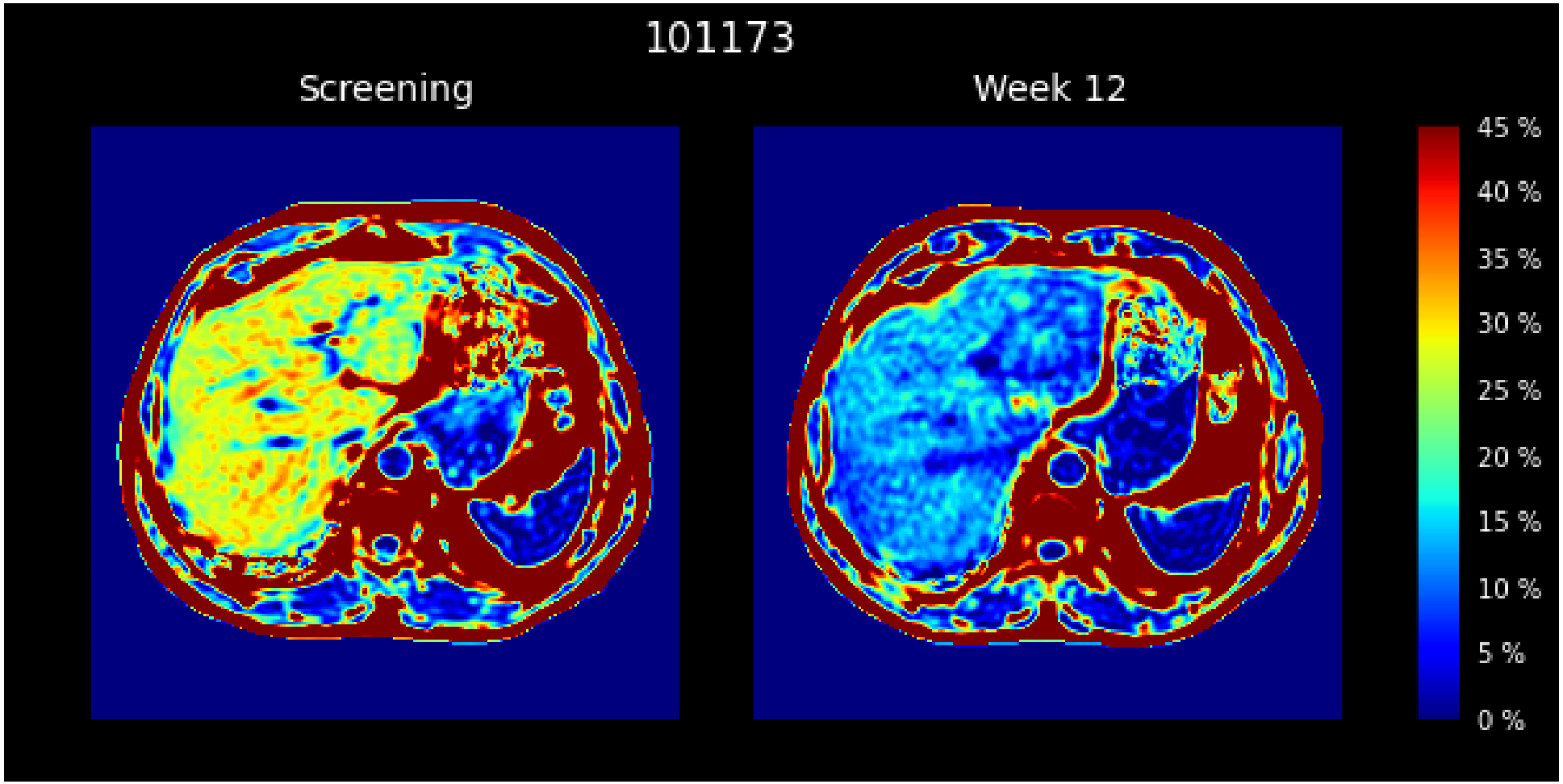
Responder frequency

≥30% relative reduction at week 12



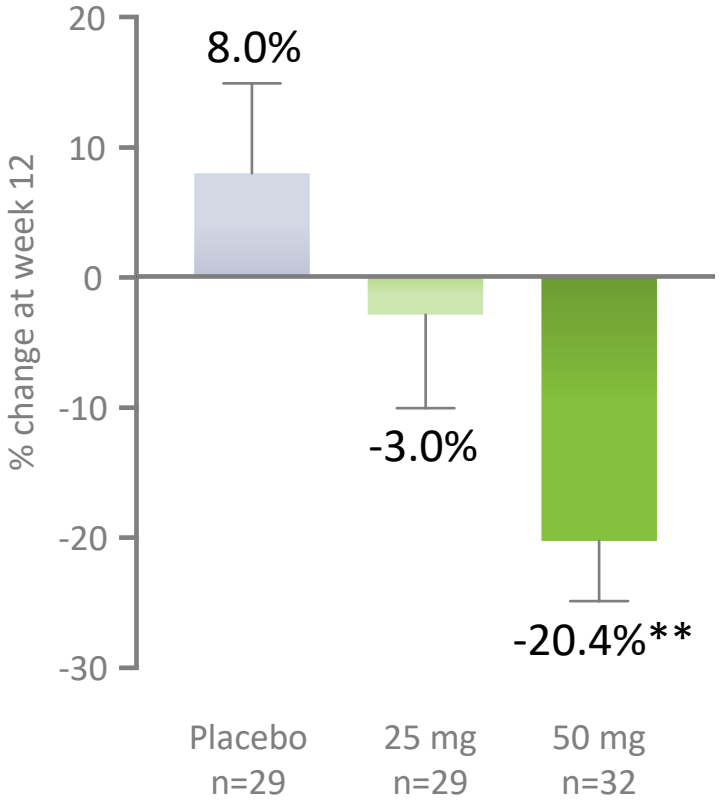
***p<0.005, ***p<0.001. LSM difference versus placebo. mean/SEM. Absolute LF decrease of -0.3%, -1.8% and -5.1% at week 12.*

Dramatic decrease in liver fat at week 12

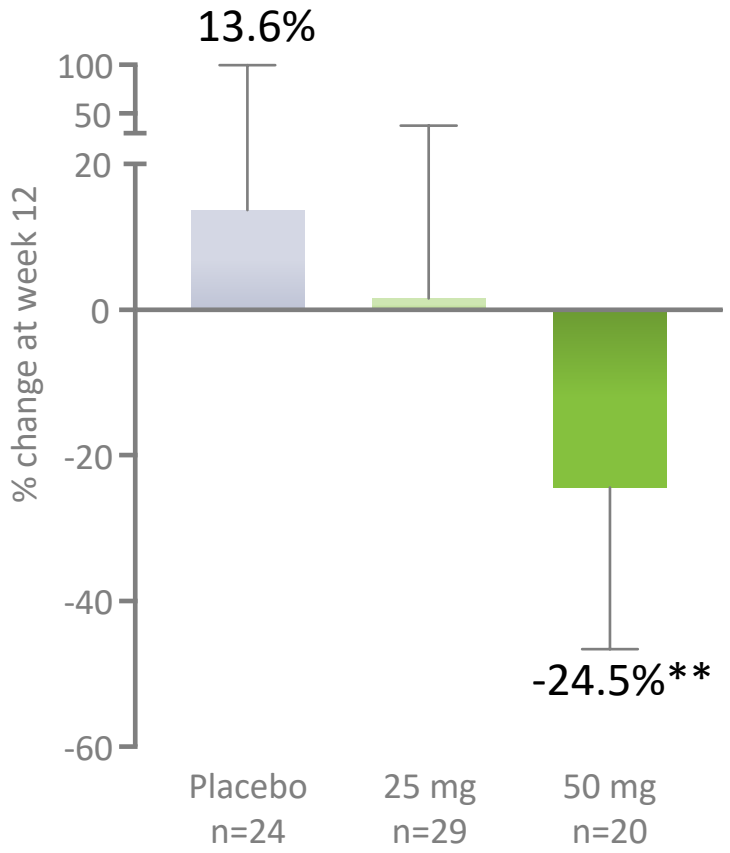


TVB-2640 showed dose-dependent and significant reduction of ALT, Cytokeratin and LDL cholesterol

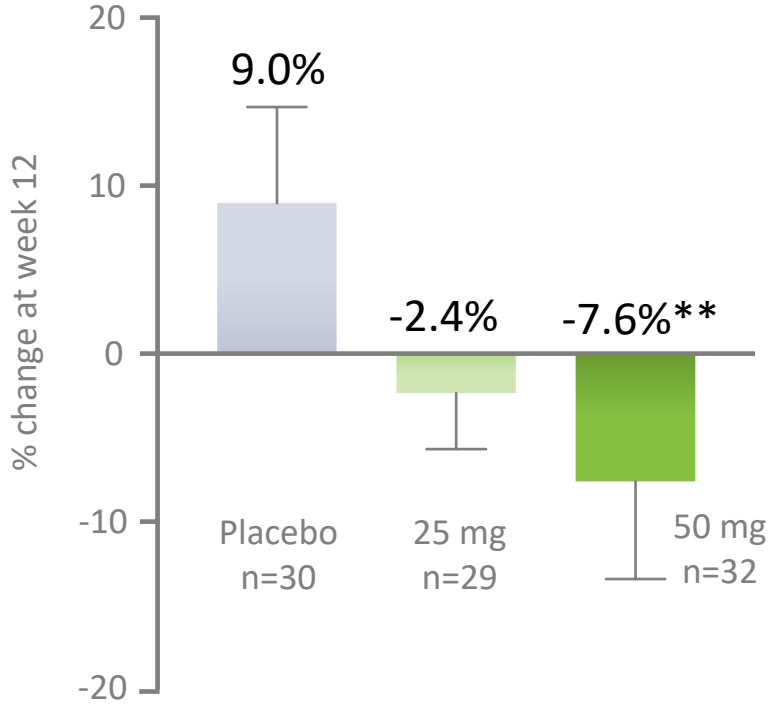
ALT



Cytokeratin-18 (M30)

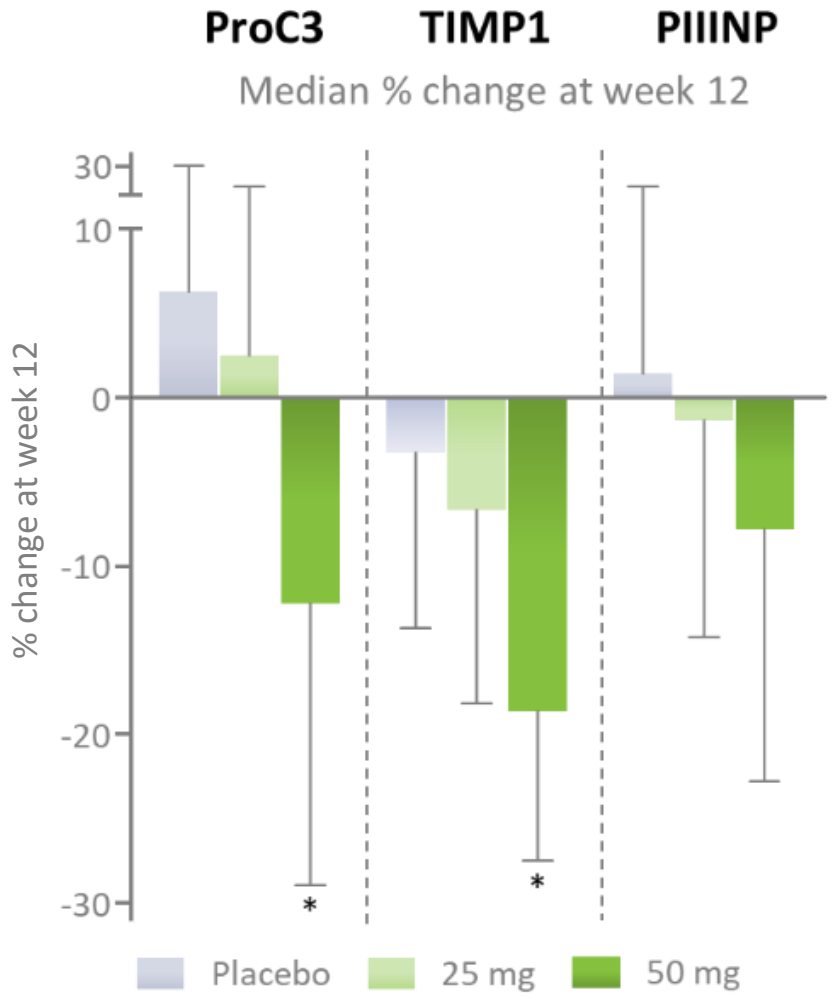


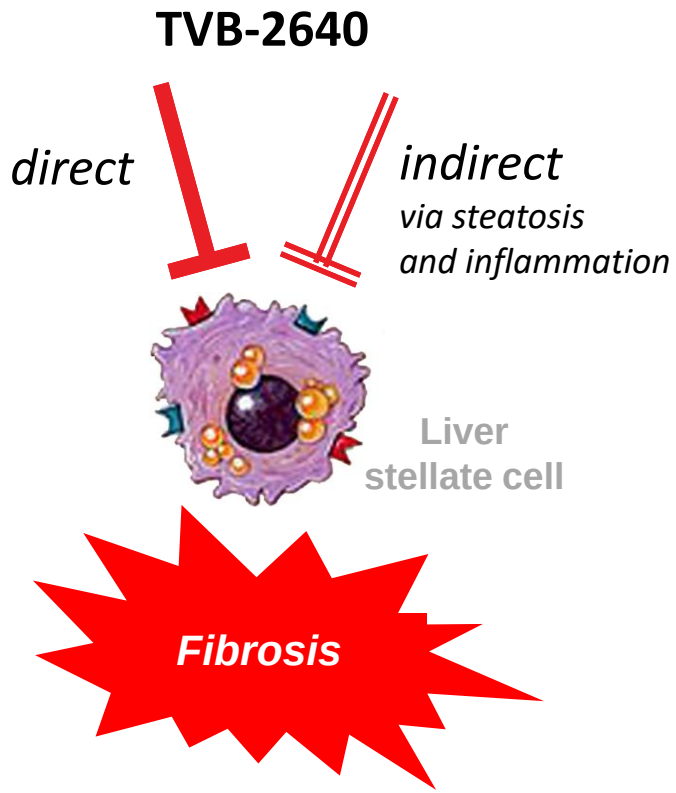
LDL cholesterol



***p<0.005 LSM difference versus placebo. Primary analysis 12-week data cut. ALT and LDL; mean/SEM for ALT, LDL; median/IQR for CK-18*

TVB-2640 decreases fibrosis markers at 12 weeks

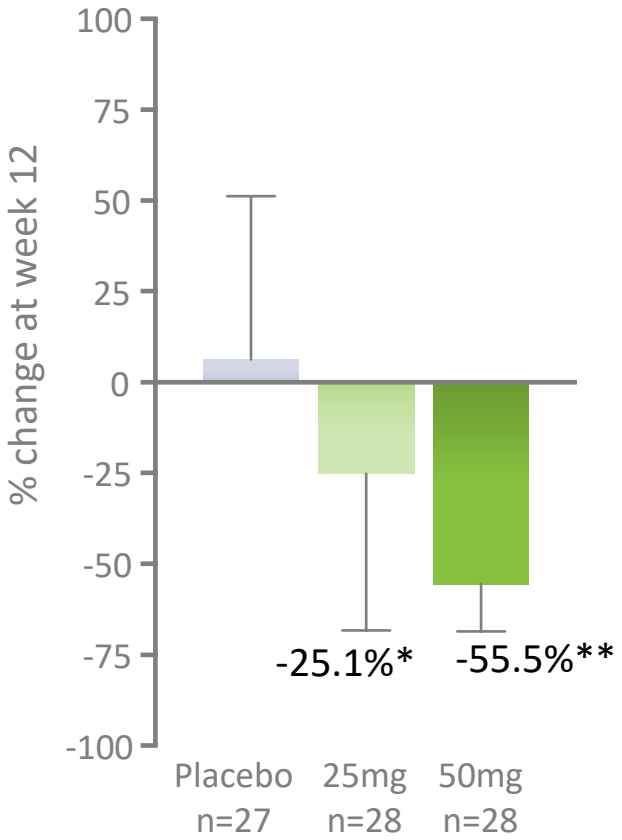


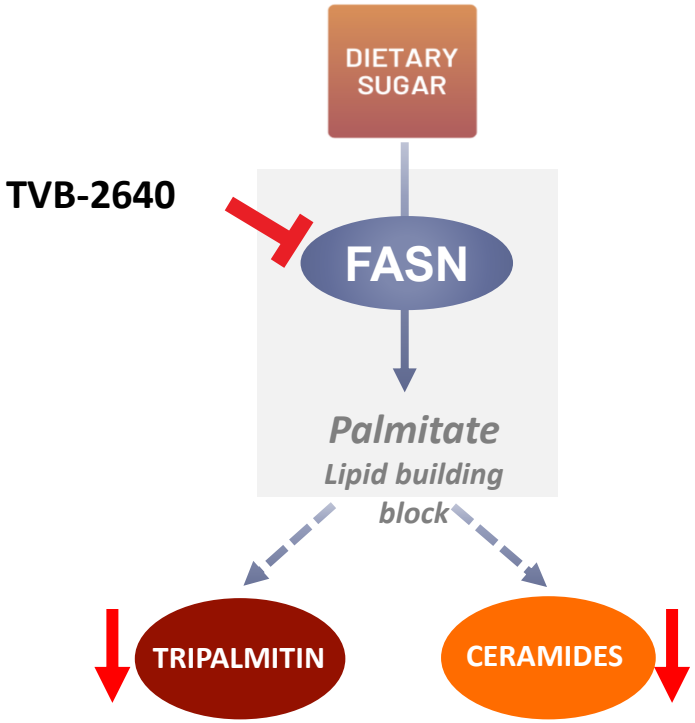


*p<0.05, Mann-Whitney U test versus placebo.
TIMP1 – tissue inhibitor of metalloproteinase 1, PIIINP – procollagen III amino terminal peptide. median/IQR.

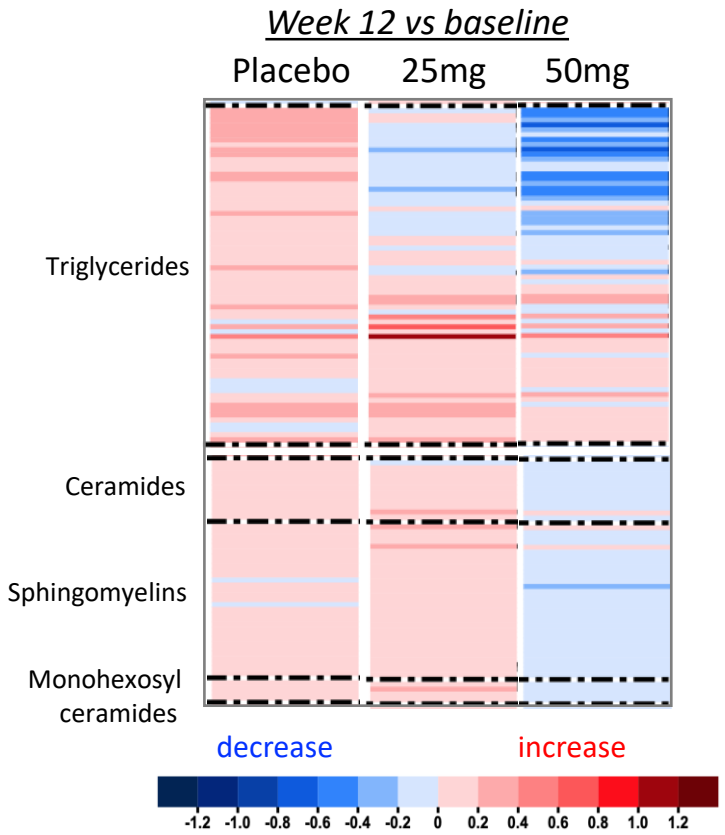
TVB-2640 reduces tripalmitin and significantly reduces lipotoxic ceramides

Tripalmitin
Proof of MOA



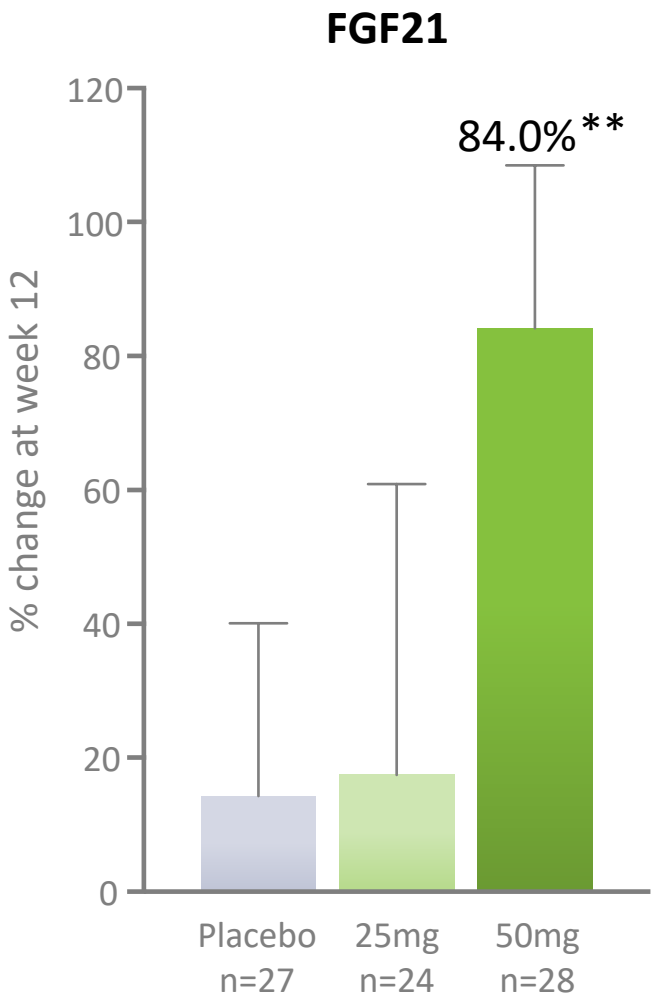


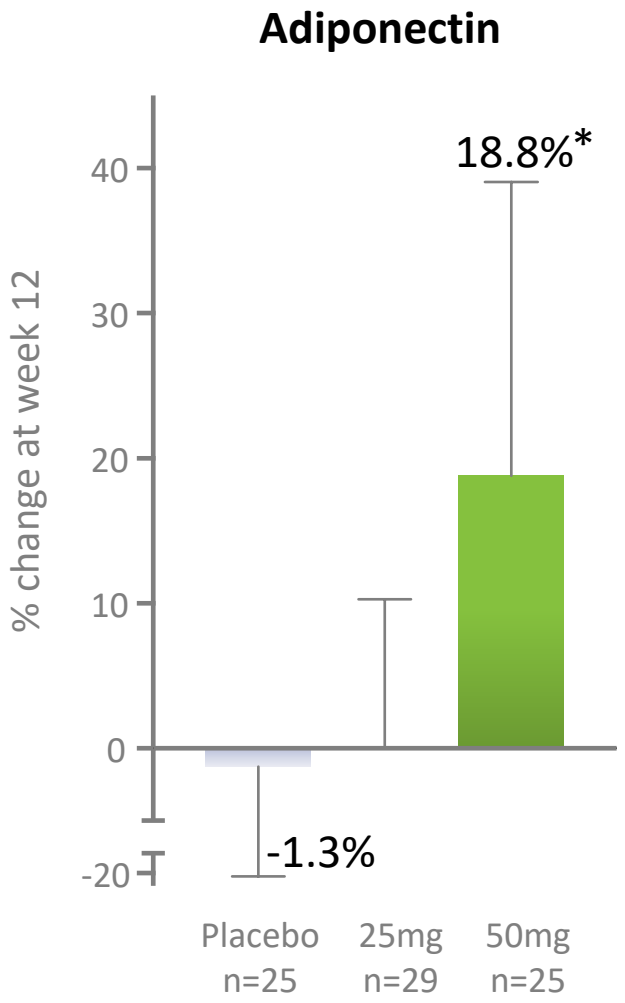
Ceramides and other lipid classes
Lipotoxic inflammatory molecules



*p<0.05, **p<0.005. Mann Whitney U test vs placebo. median/IQR

TVB-2640 improves markers of hepatic insulin sensitivity

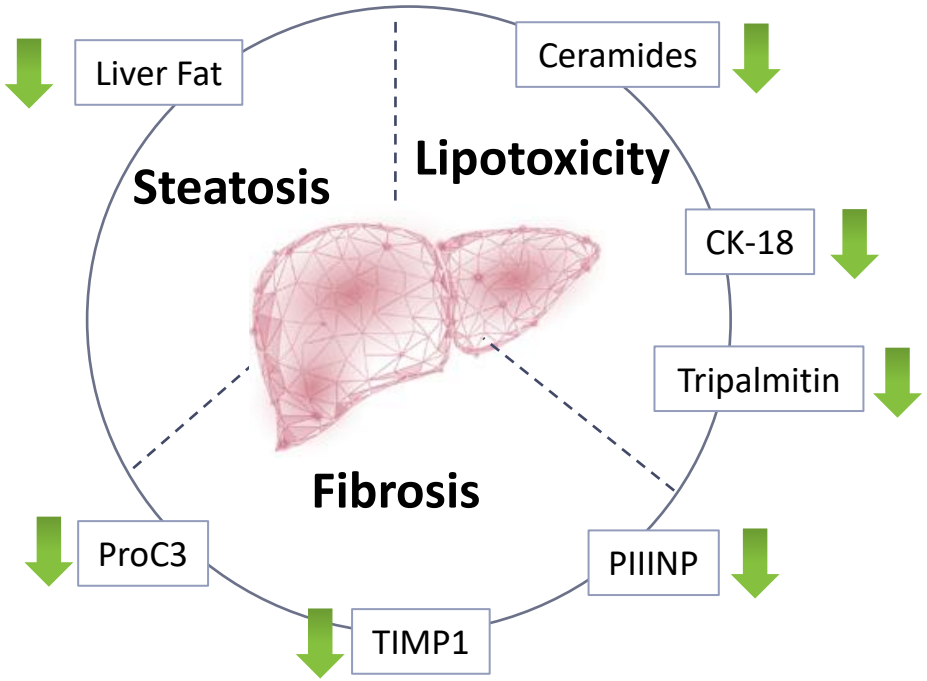




*p<0.05, **p<0.005. Mann Whitney U test vs placebo. median/IQR

TVB-2640 is a compelling agent for development in NASH

- Biomarker changes in FASCINATE-1 indicate improvement in several key nodes of NASH pathology
- FASNi therapy affects steatosis, inflammation, fibrosis and metabolism



Liver disease improvement

ALT

Cardiovascular benefits

LDL

Insulin sensitivity

FGF21

Adiponectin

THANK YOU

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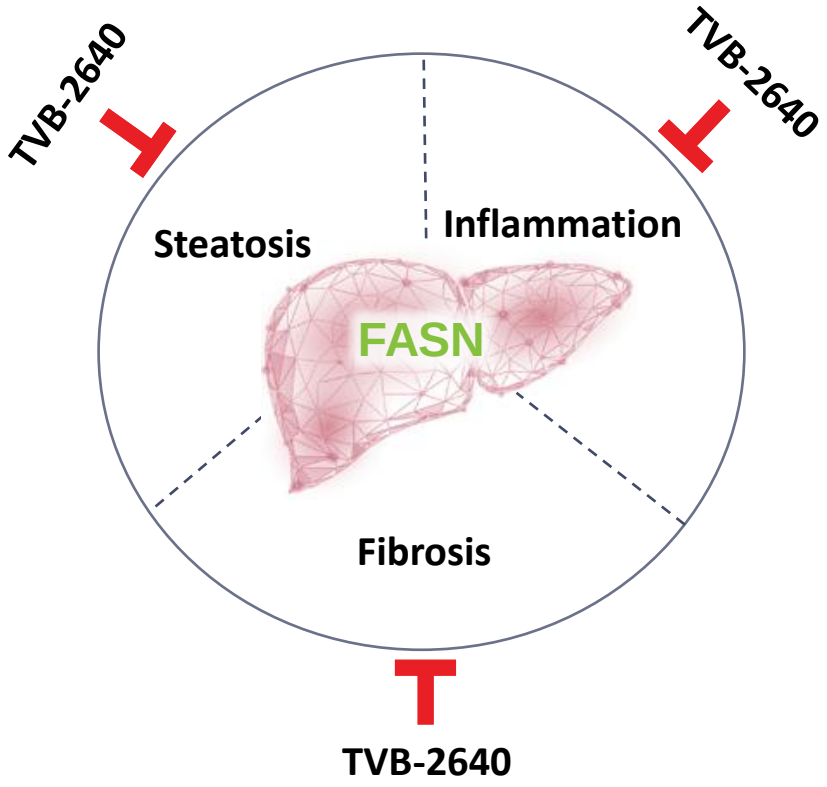
On behalf of all FASCINATE-1 investigators and their teams, thank you to our patients and their families



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