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

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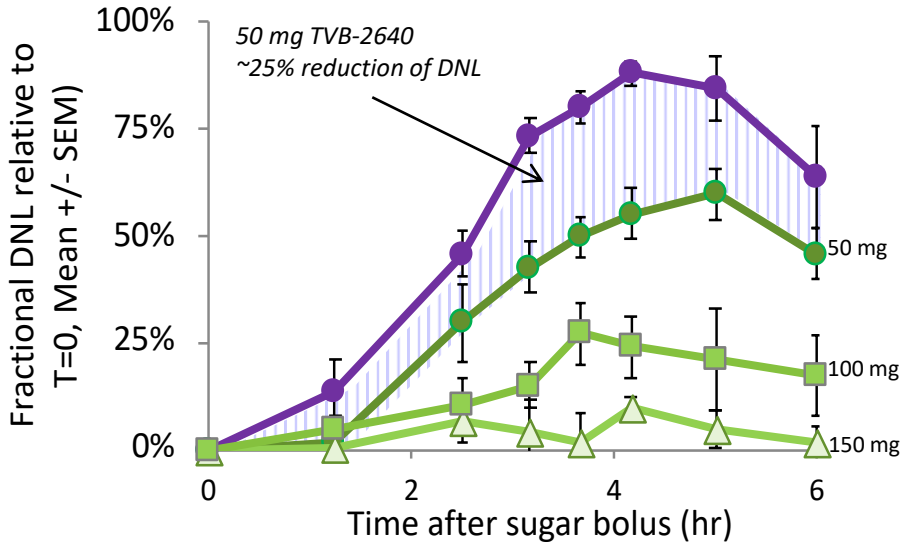
TVB-2640 is a potent and selective first-in-human FASN inhibitor

- Nonalcoholic steatohepatitis (NASH) is the most common cause of cirrhosis and the second leading cause of liver transplantation in the US
- No currently FDA-approved therapies for the treatment of NASH
- Increased DNL and lipotoxicity play an important role in the pathogenesis of NASH
- Reversal of lipotoxicity and reduction of DNL may improve NASH and NASH-related fibrosis

TVB-2640

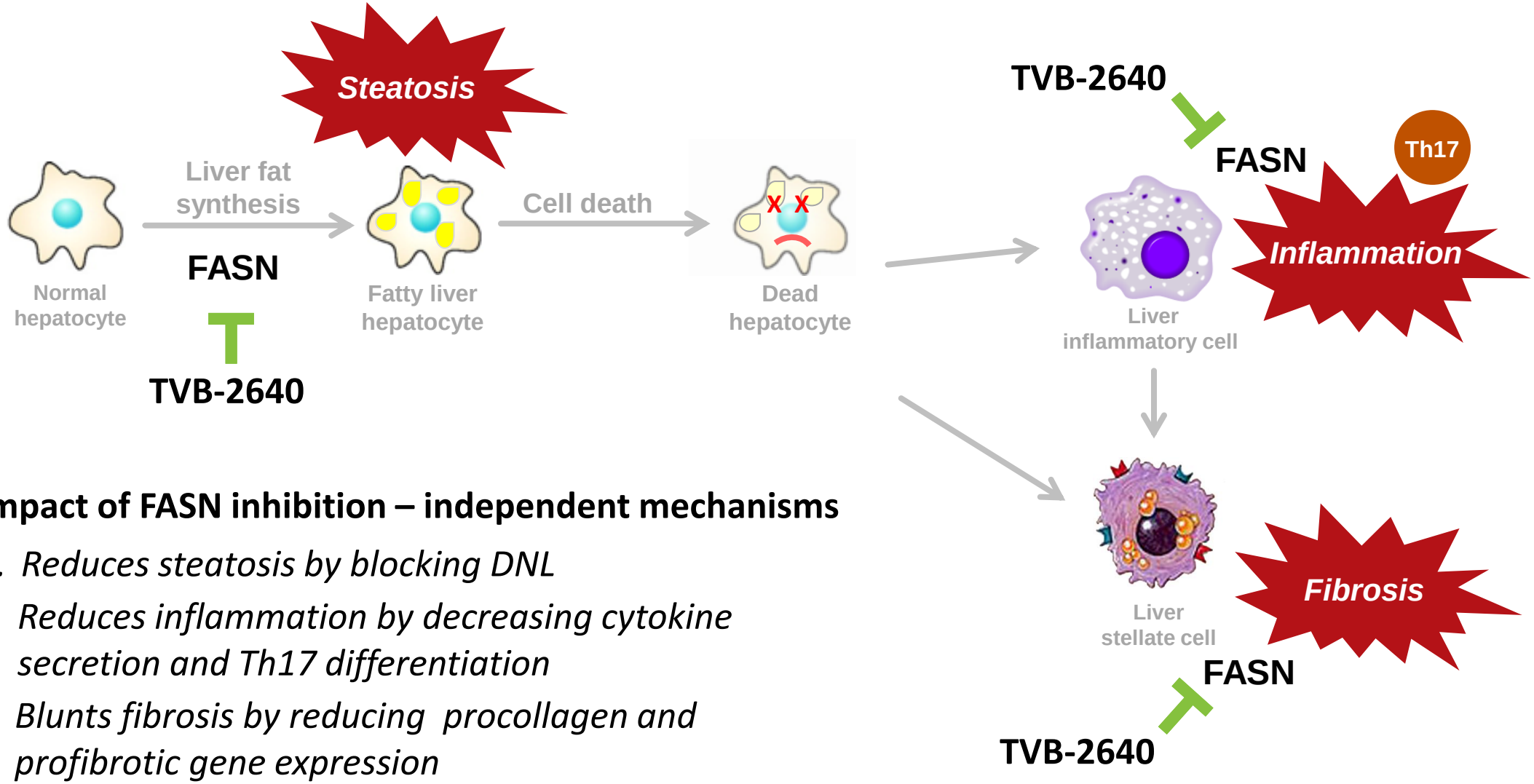
- Orally-available small molecule
- Once-daily dosing
- Excellent and predictable PK profile
- Potent (FASN EC_{50} approx. 50 nM)
- Inhibited hepatic de novo lipogenesis up to 90% in Phase 1b[1]

TVB-2640 reduces DNL in Humans



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

Proposed mechanism of action of FASN inhibitor TVB-2640 in NASH related fibrosis



Impact of FASN inhibition – independent mechanisms

1. *Reduces steatosis by blocking DNL*
2. *Reduces inflammation by decreasing cytokine secretion and Th17 differentiation*
3. *Blunts fibrosis by reducing procollagen and profibrotic gene expression*

Introduction

Aim

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

Hypothesis

TVB-2640 would be better than placebo in reducing liver fat by MRI-PDFF in high risk patients with NAFLD

FASCINATE-1 trial design: TVB-2640 vs Placebo

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

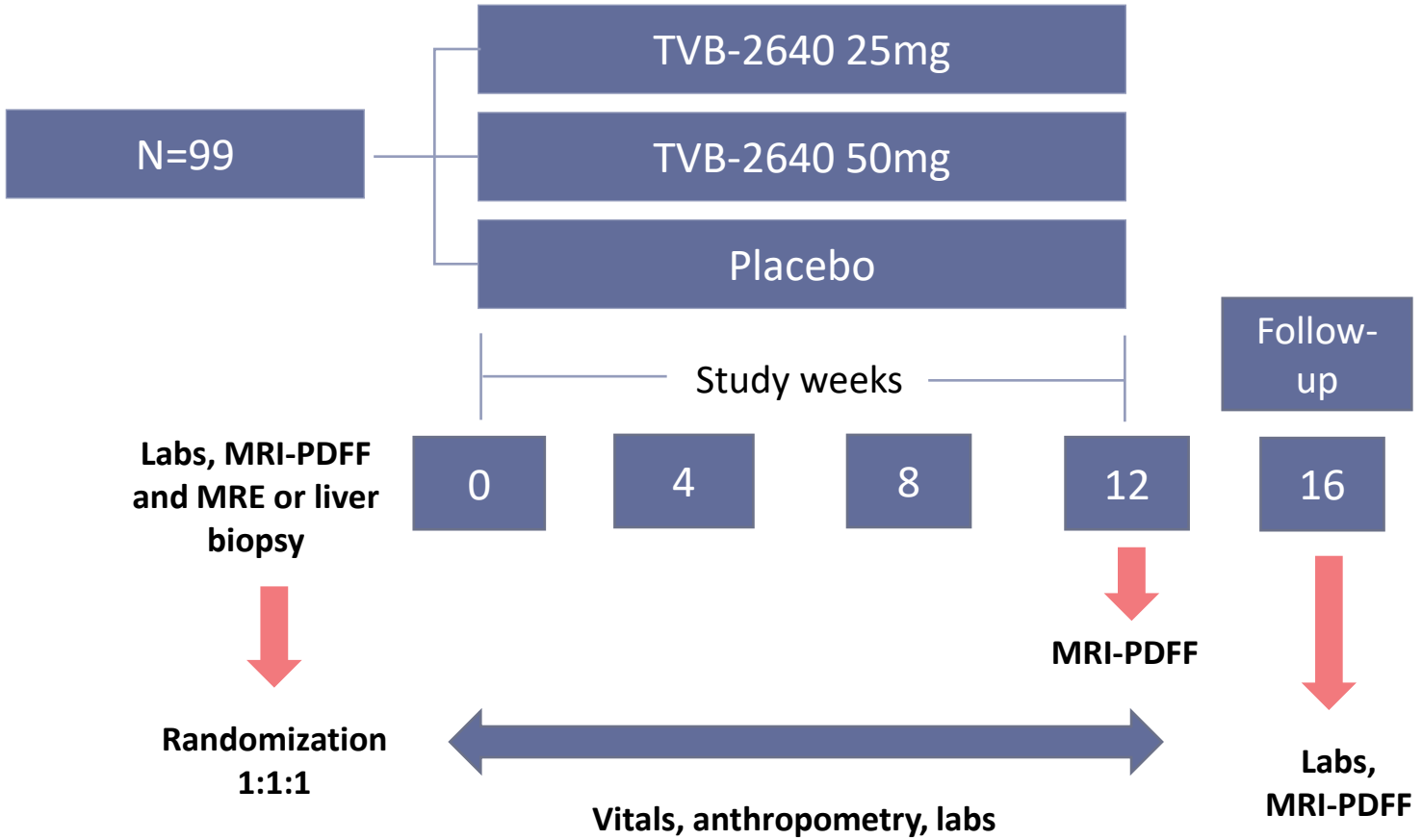
Oral, once-daily, 12 weeks

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
  - Tripalmitin
  - Adiponectin
  - Serum fibrosis markers, including TIMP1



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)

Detailed TEAE listing

Most common (>5%) TEAE *(all Grade 1)*	Placebo n=31	25mg cohort n=33	50mg cohort n=35
Diarrhea	1 (3.1%)	2 (6.1%)	0
Headache	1 (3.1%)	4 (12.1%)	1 (2.9%)
Nausea	0	2 (6.1%)	0
Dyspepsia	2 (6.3%)	1 (3.0%)	0
Arthralgia	0	2 (6.1%)	0
Bronchitis	0	2 (6.1%)	0
Abdominal distension	0	2 (6.1%)	0
Peripheral oedema/swelling	0	2 (6.1%)	0
Rash	1 (3.1%)	2 (6.1%)	1 (2.9%)
Upper respiratory infection	0	2 (6.1%)	2 (5.9%)
Urinary tract infection	0	2 (6.1%)	0

No significant dose dependent AE's were observed

Safety assessment of TVB-2640 vs placebo

TEAE classification	Placebo n=31	25mg cohort n=33	50mg cohort n=35
Any TEAE	Gr. 1: 14 (45.1%) Gr. 2: 4 (13.0%)	Gr. 1: 18 (54.5%) Gr. 2: 3 (9.0%)	Gr. 1: 11 (31.4%) Gr. 2: 6 (17.1%)
TEAE leading to drug withdrawal	0	2 (6.1%)	0
Treatment Emergent Serious Adverse Event (SAE)	0	0	0
Drug related TEAE	Gr. 1: 4 (12.9%) Gr. 2: 0	Gr. 1: 9 (27.3%) Gr. 2: 1 (3.0%)*	Gr. 1: 7 (20.0%) Gr. 2: 1 (2.9%)*
TEAE leading to death	0	0	0

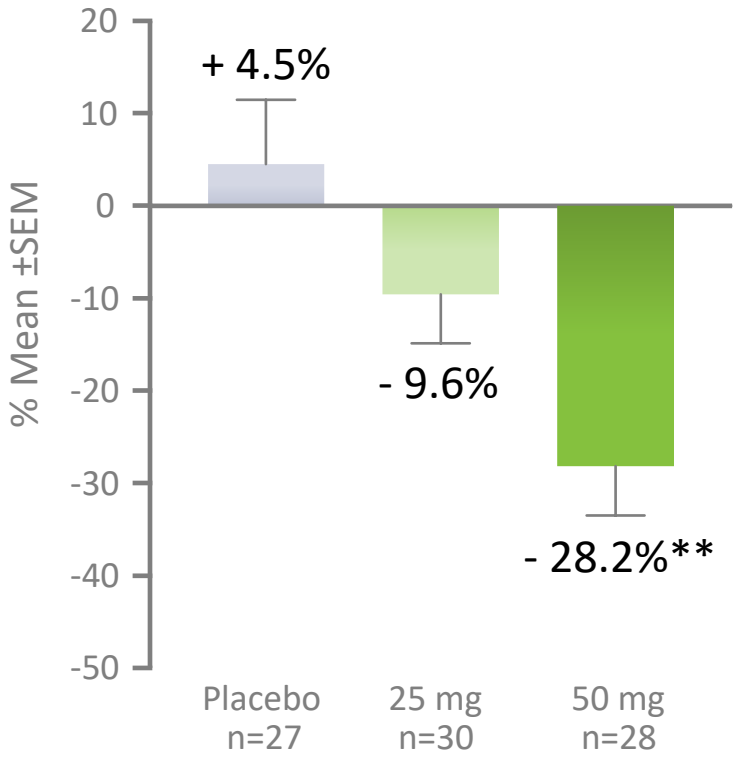
**25mg: urinary tract infection; 50mg: shortness of breath; both resolved without dose adjustment*

- TVB-2640 appears to be 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

Primary efficacy endpoint:
Potent, dose-dependent reduction of liver fat

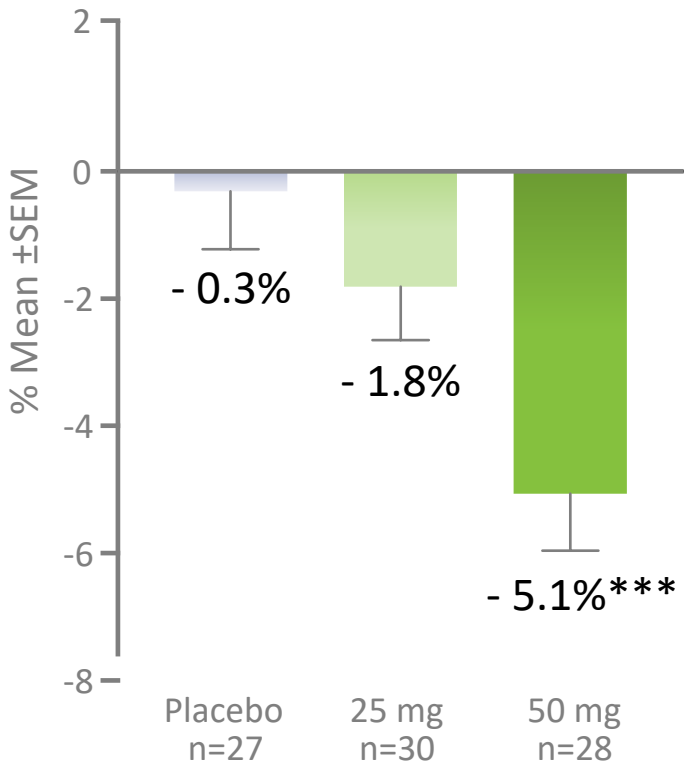
Mean relative liver fat reduction

MRI-PDFF at week 12



Mean absolute liver fat reduction

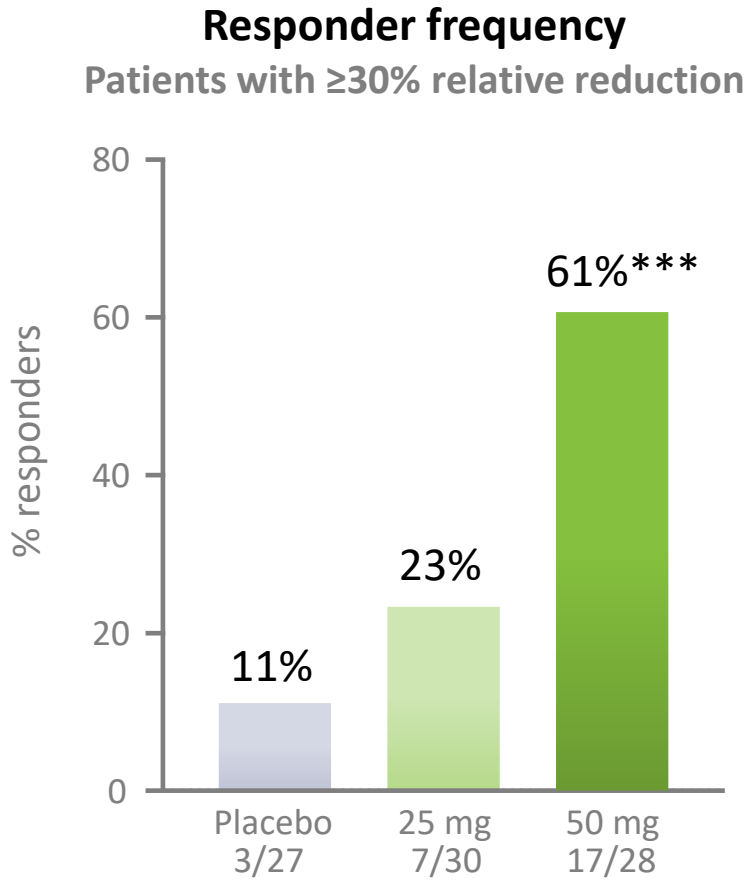
MRI-PDFF at week 12



***p<0.005, ***p<0.001. LSM difference versus placebo*

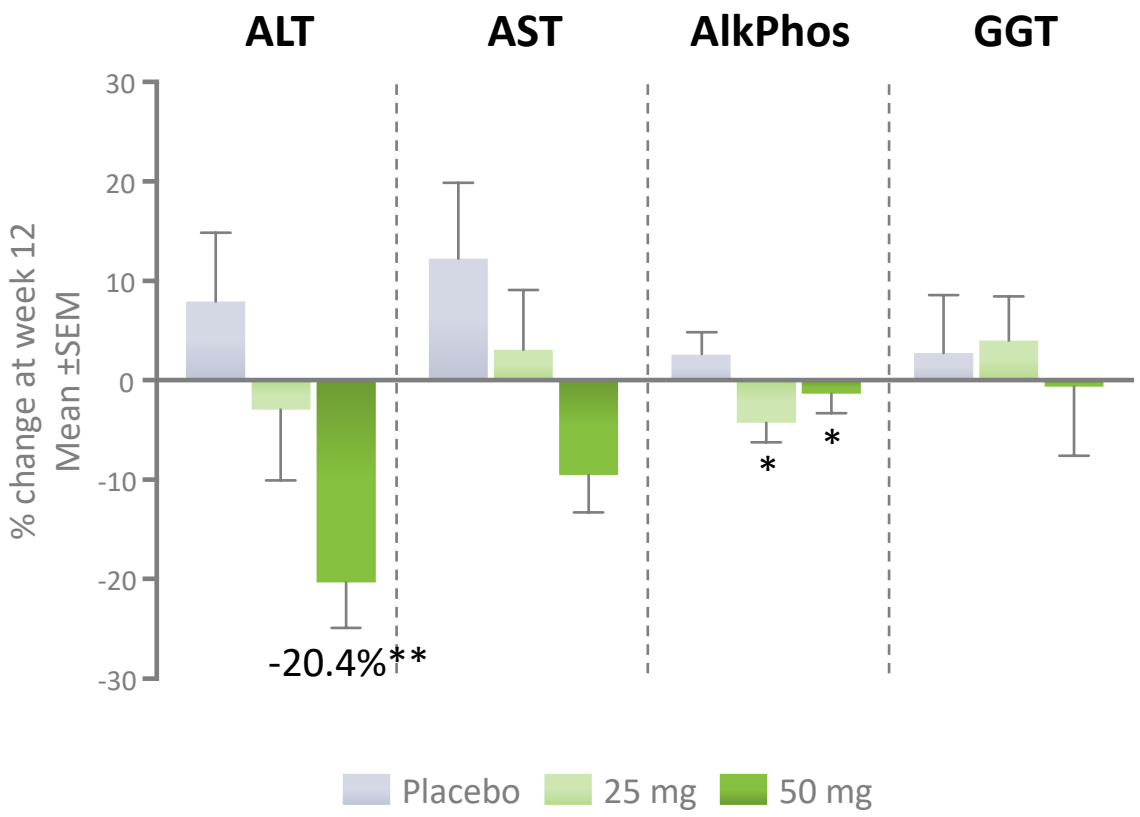
Secondary efficacy endpoint: TVB-2640 showed a dose dependent and robust MRI-PDFF response

MRI-PDFF responders were defined as those with ≥ 30% MRI-PDFF decline relative to baseline



***p<0.005, ***p<0.001. Common risk difference for responder frequency*

TVB-2640 showed dose-dependent response in reducing ALT



***p<0.005, *p<0.05. LSM difference versus placebo*

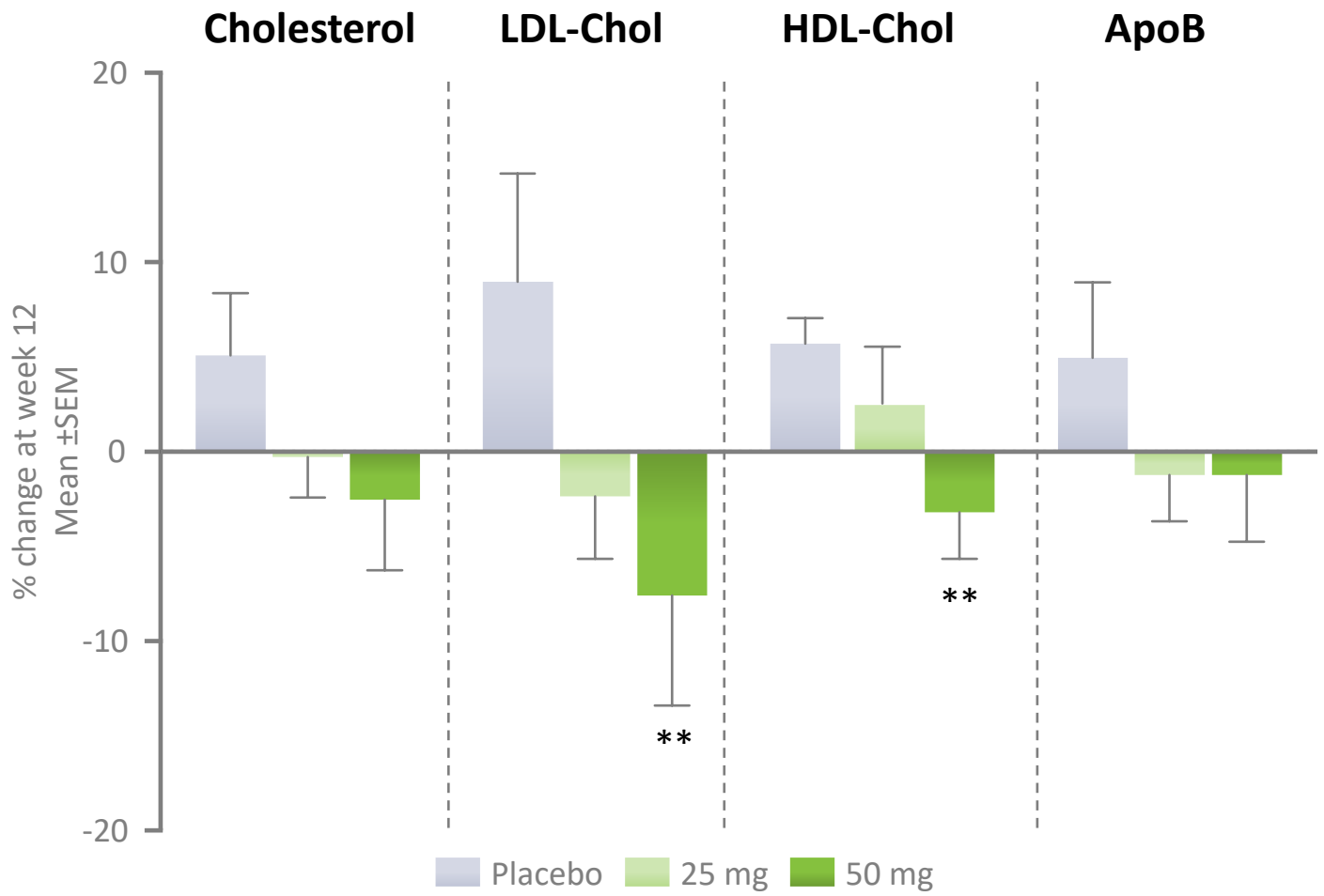
Patients with baseline >ULN ALT only [1]

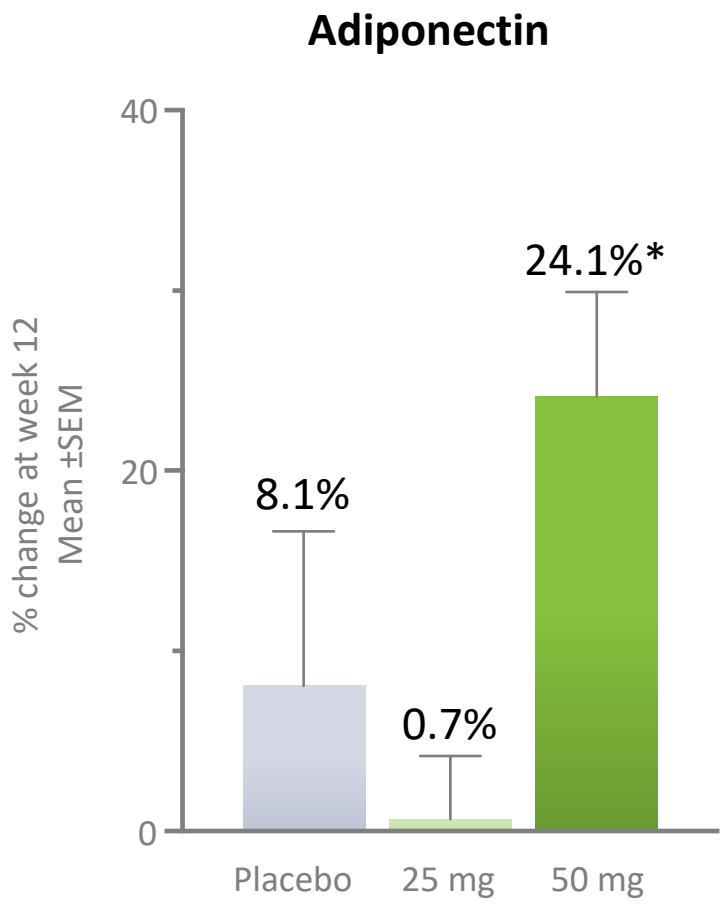
	Mean ALT change at week 12		≥17 U/L decrease at week 12		Normalization at week 12	
	n	%, absolute	N	% pts	n	% pts
placebo	11	+15%, +10 U/L[2]	2/11	18%	3/11	27%
25 mg	9	-16%, -6 U/L	3/9	30%	3/9	33%
50 mg	12	**-24% , -19U/L**	**6/12**	**50%**	**7/12**	**58%**

Patients with high baseline ALT show clear decrease with TVB-2640

[1] *male ULN 41, female ULN 33 U/L*
[2] *median placebo change of -5% and +1U/L*

Changes in cholesterol and adiponectin levels

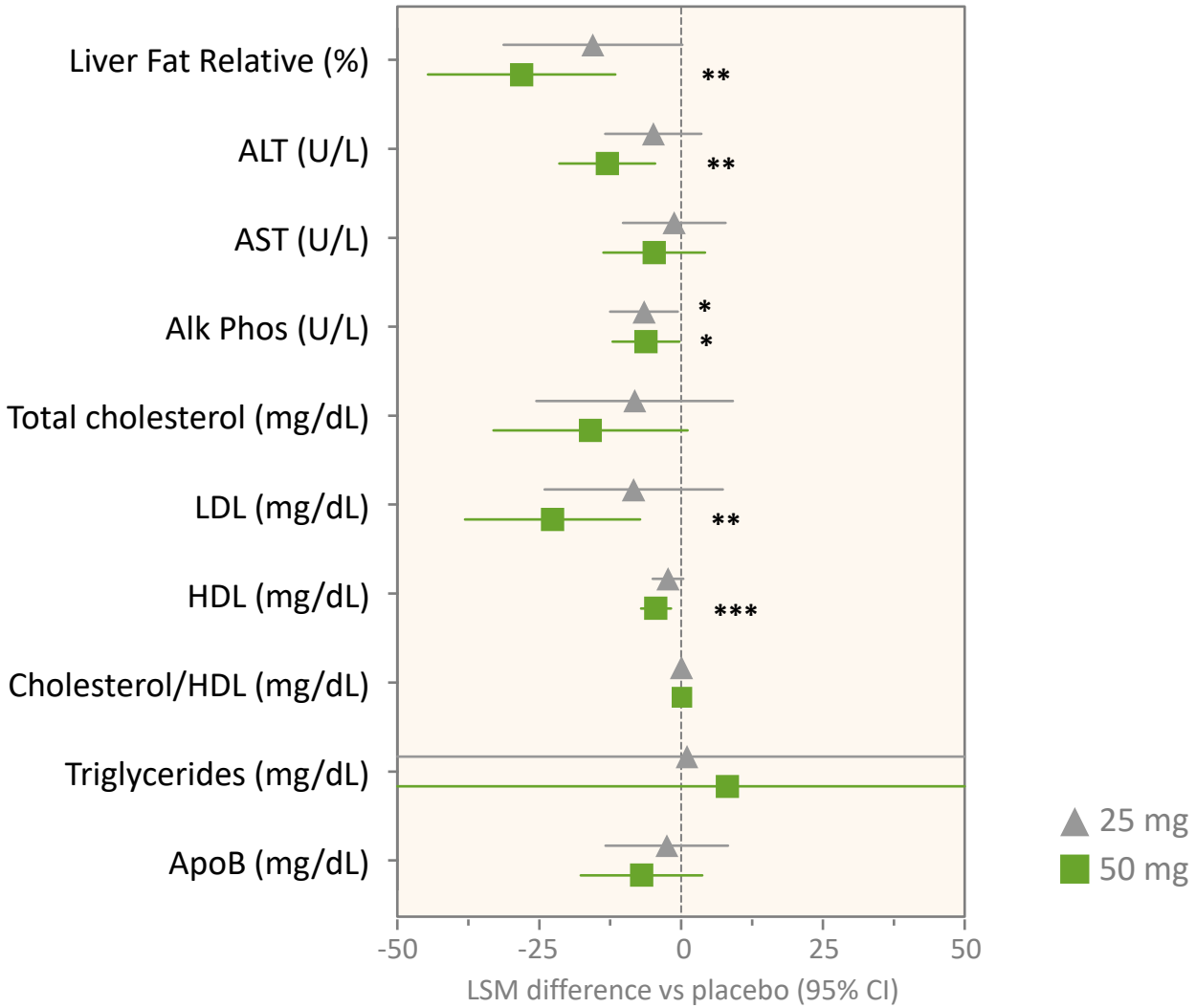




*p<0.05, **p<0.005. LSM difference versus placebo

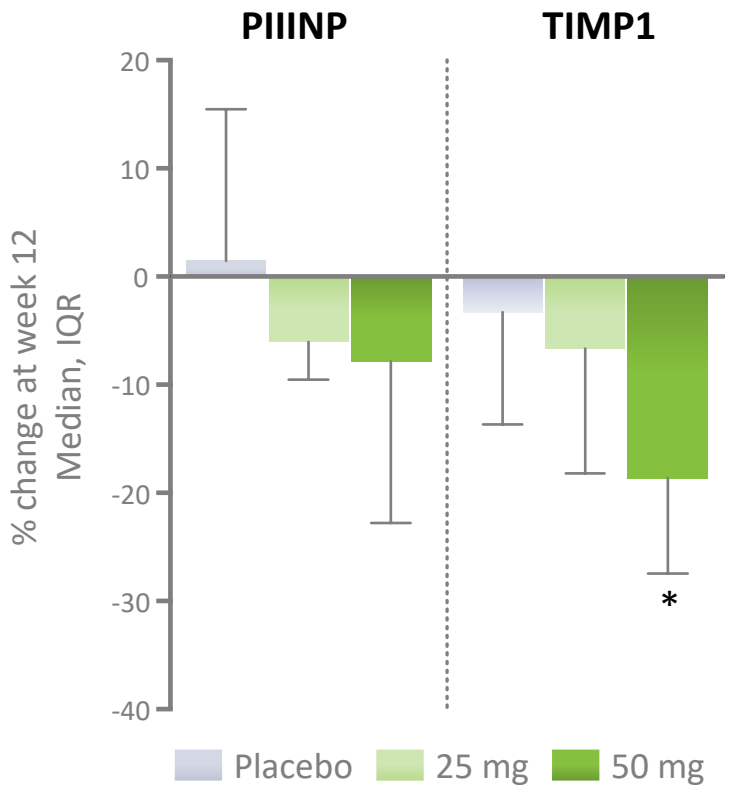
*p<0.05. Mann-Whitney U test versus placebo

Analysis across key readouts versus placebo



** p<0.05, ** p<0.005, ***p<0.001. LSM difference versus placebo. Pairwise comparisons based on a linear mixed effects model for repeated measures within the stratification factor (diabetes, treatment group, etc.)*

TVB-2640 decreases fibrosis markers



TIMP1 (ng/mL)

Absolute change at week 12
Mean (SD)

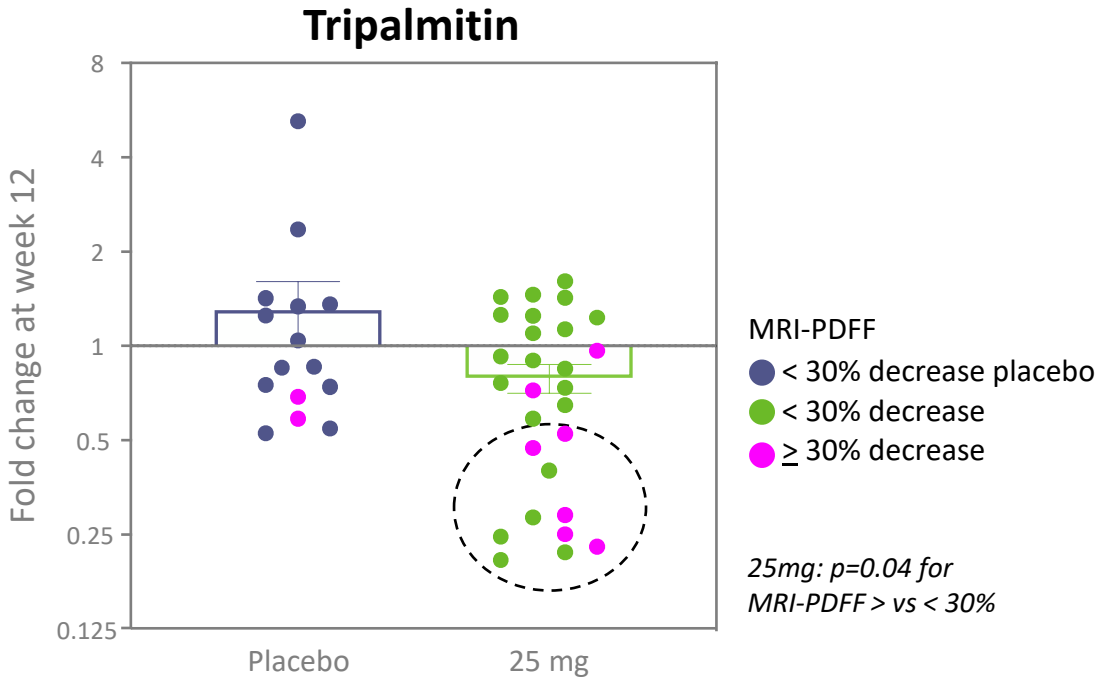
placebo	4.99 (44.9)
25 mg	**-18.11** (37.9)
50 mg	**-26.36** (56.7)

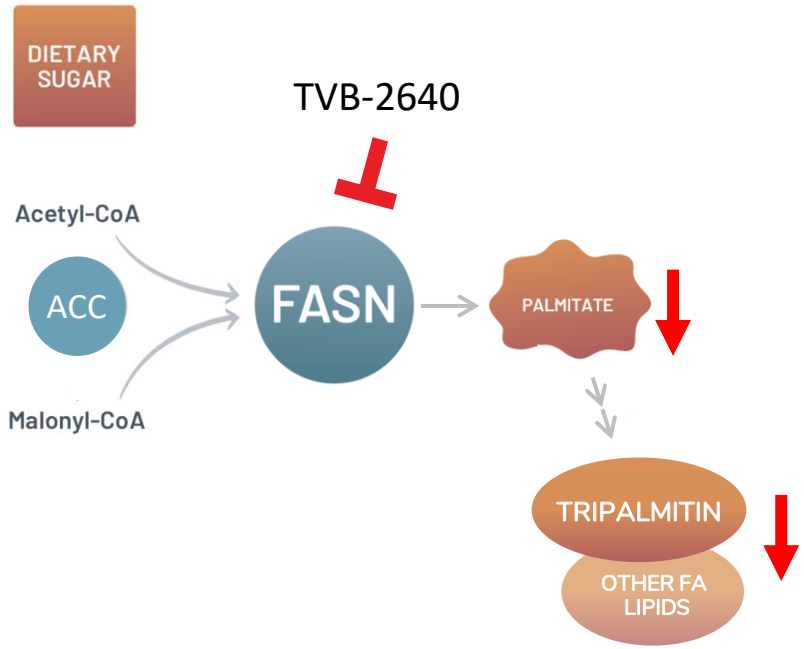
**p<0.05, Mann-Whitney U test versus placebo*
TIMP1 – tissue inhibitor of metalloproteinase 1, PIIINP – procollagen III amino terminal peptide

Tripalmitin decrease confirms FASN inhibition

Significant decrease of plasma tripalmitin in liver fat responders (25 mg dose)

- Biomarker of DNL
- Mean of all 25 mg patients decreased vs placebo





Mean +/- SEM, Mann-Whitney U test vs placebo
n=28 (25 mg), n=15 (placebo). Preliminary data.

Efficacy and safety profile of TVB-2640 in NASH therapy

- Once-daily, oral tablet
- Well tolerated safety profile at 25 & 50mg
  - No pruritus, no thrombocytopenia, no hypertriglyceridemia
  - Decreases LDL
- This RCT in high risk patients with NAFLD demonstrates that TVB-2640
  - Induces dose-dependent, robust reduction in liver fat along with serum ALT reduction
  - Inhibits DNL as evidenced by reduction in tripalmitin
  - Improves fibrosis marker such as TIMP1, PIIINP
  - Improves adiponectin
- These data provide justification for examining the efficacy of TVB-2640 in improving NASH resolution and fibrosis in biopsy-proven NASH patient

THANK YOU

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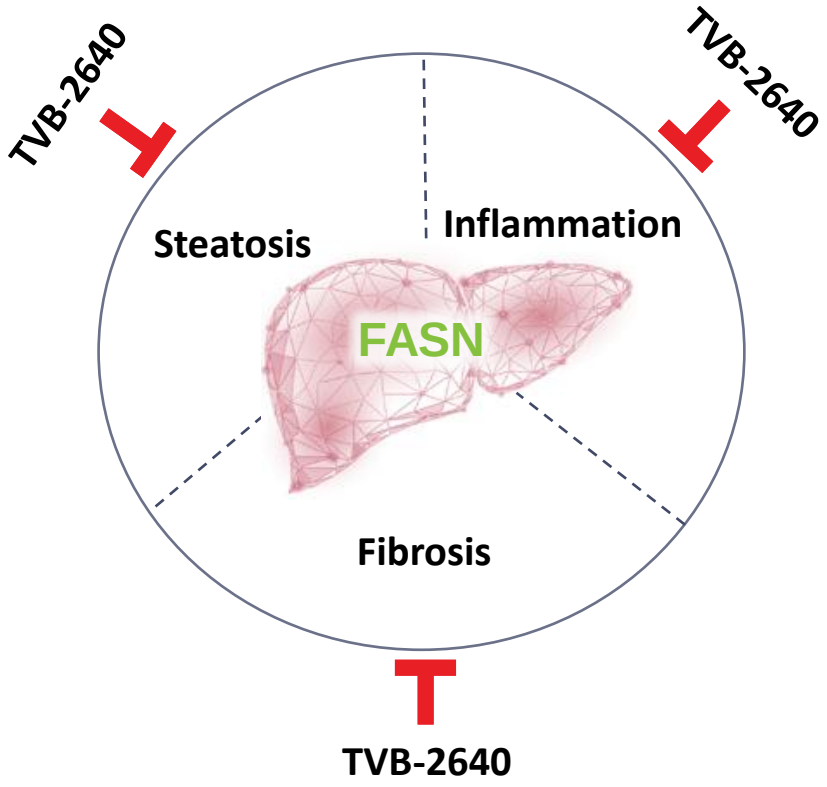
On behalf of all FASCINATE-1 investigators and their teams, thank you to our patients and their families



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