Novel, first-in-class, fatty acid synthase inhibitor, TVB-2640 demonstrates robust clinical efficacy and safety in a global Phase 2 randomized placebo-controlled NASH trial conducted in the US and China

TVB-2640 in FASCINATE-1 Study

AASLD 2021

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Sponsored by SAGIMET BIOSCIENCES

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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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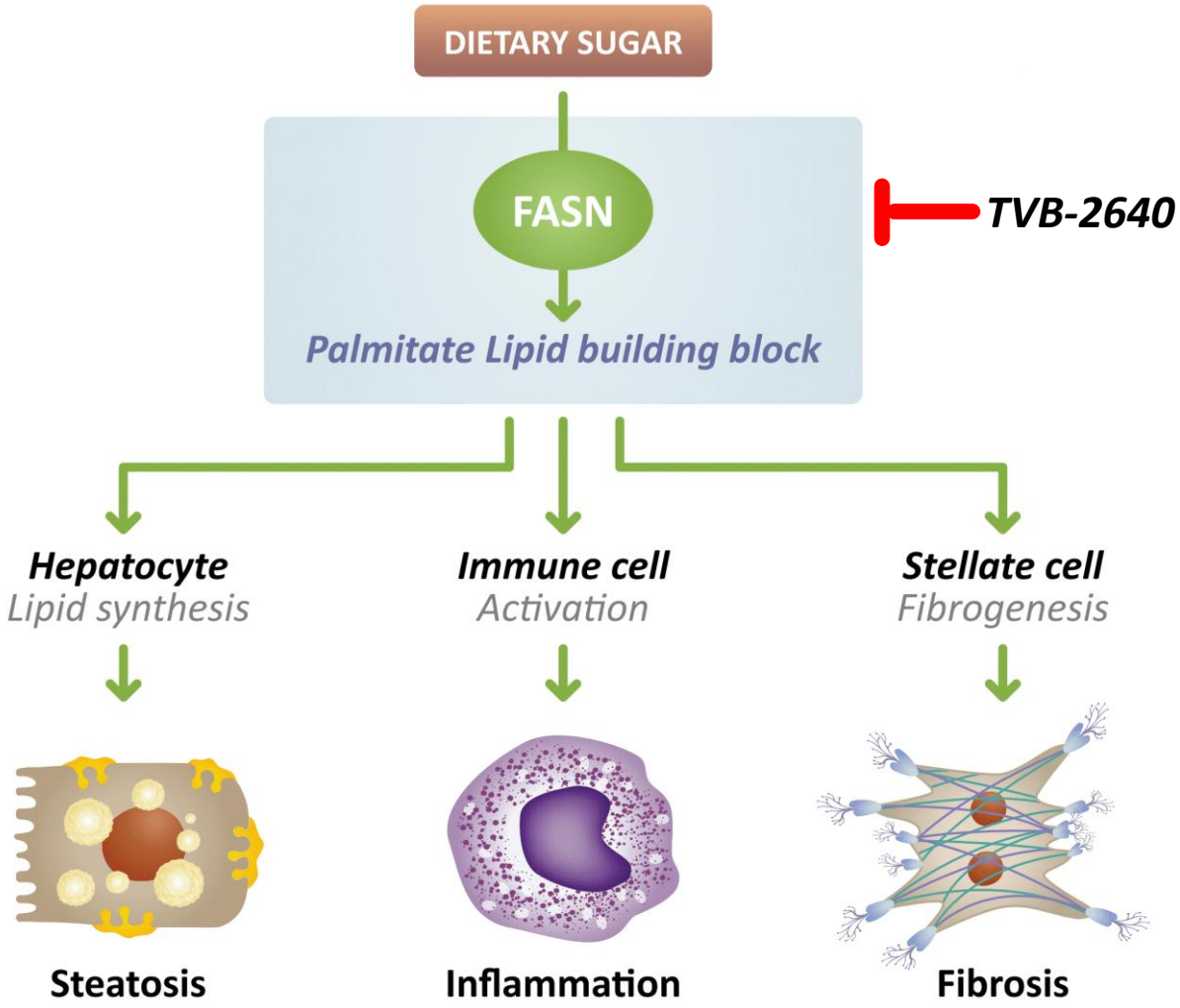
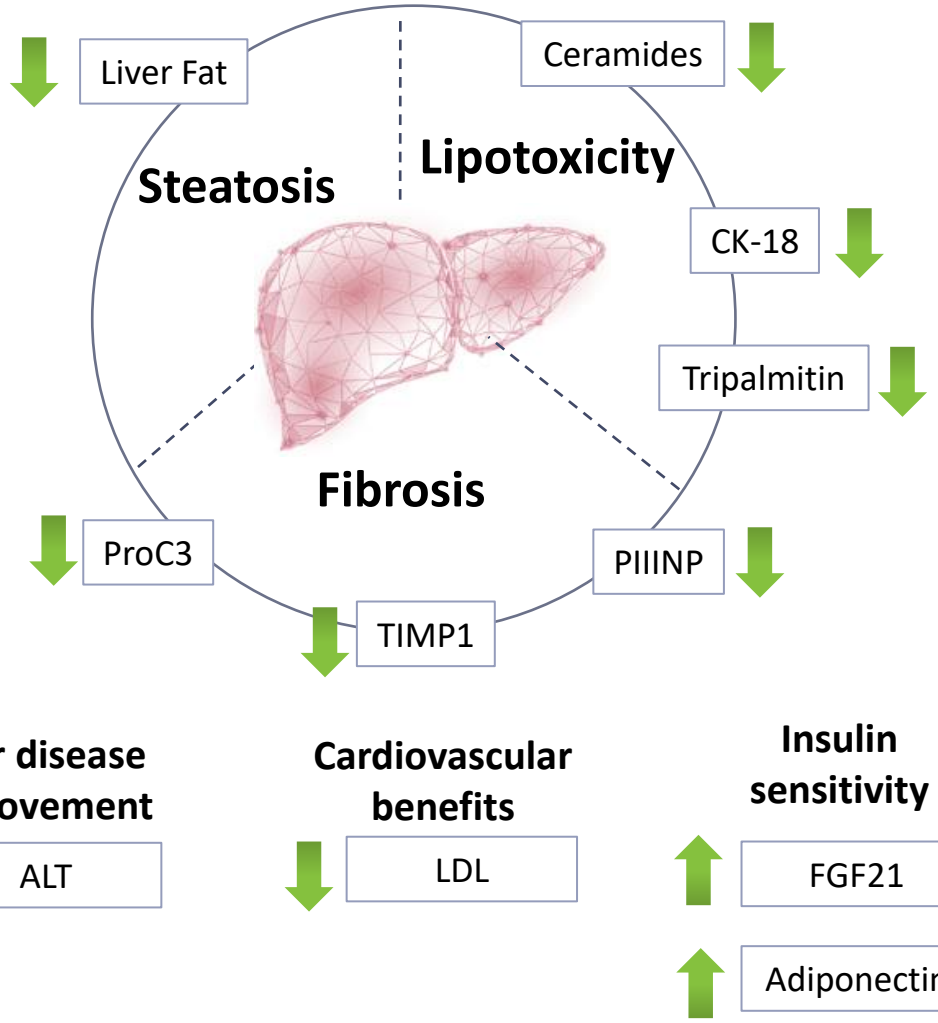
FASN inhibitors targeted to improve NASH and NASH-related fibrosis

- NASH is the most common chronic liver disease globally
- Fatty acid synthase (FASN) is an important rate limiting step in de novo lipogenesis (DNL)
- Increased DNL dependent on FASN initiates liver fat accumulation leading to NAFLD/NASH
- FASN inhibition is known to:
  - Reduce steatosis
  - Reduce inflammation
  - Inactivate activated stellate cells

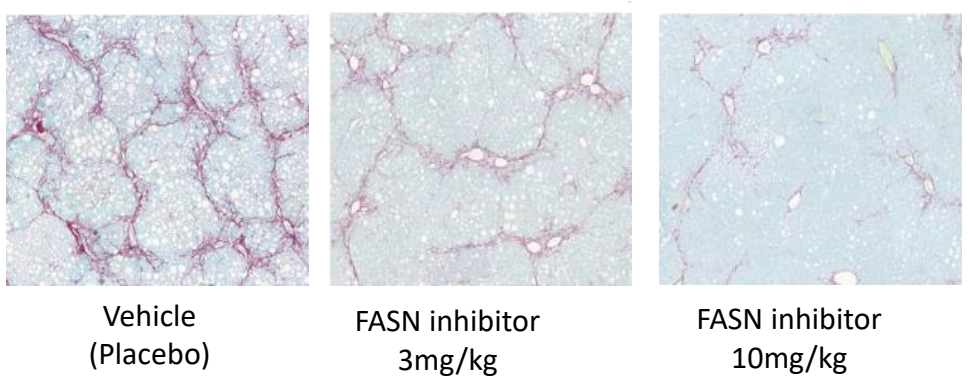


TVB-2640 is a potent and selective first-in-human FASN inhibitor

- ✓ Potent FASN EC_{50} approx. 50 nM
- ✓ Orally-available small molecule
- ✓ Once-daily dosing
- ✓ Excellent PK profile, similar in patients treated in the US and China
- ✓ Inhibited hepatic de novo lipogenesis up to 90% in Phase 1b



FASN inhibition reverses fibrosis in mice



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

Loomba et al., Gastroenterology, 2021, Jul 23, doi: 10.1053/j.gastro.2021.07.025.

Introduction

Aims

1. To compare the efficacy of TVB-2640 versus placebo in reducing liver fat in NASH patients in the US and China, by magnetic resonance imaging proton density fat fraction (MRI-PDFF)

2. To use lipidomics to assess markers that predict MRI-PDFF response

Hypothesis

NASH patients treated in China would respond to TVB-2640 similarly to those treated in the United States with regards to reduction in liver fat by MRI-PDFF

FASCINATE-1 - Phase 2 Global NASH study

Phase 2a, global, multicenter, randomized, placebo-controlled trial

Oral, once-daily, 12 weeks

50mg tested in separate cohorts in US and China

25mg and 75mg tested in US only

Primary Endpoints

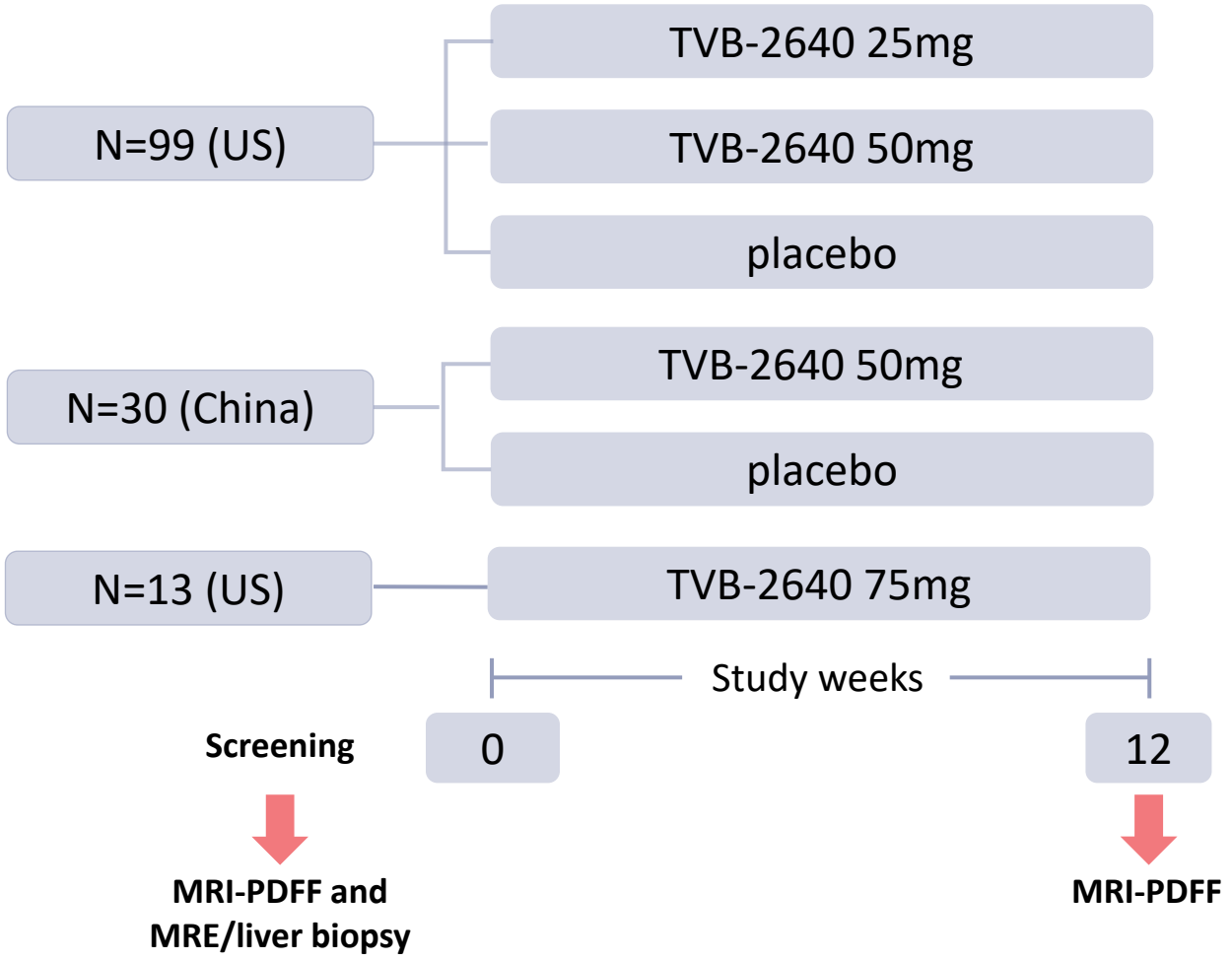
- Liver fat reduction by MRI-PDFF
- Safety

Secondary Endpoints

- % pts ≥30% reduction of liver fat
- ALT, AST
- Biomarkers including lipidomics in US patients

Inclusion criteria

- ≥ 8% liver fat
- MRE ≥ 2.5kPa or recent biopsy (China used biopsy only)



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Baseline demographics and characteristics at 50mg and placebo

	US		China	
Median (Q1,Q3)	**Placebo (n=31)**	**50mg (n=35)**	**Placebo (n=9)**	**50mg (n=21)**
Age,y	52(46,58)	55(44,62)	34(29,45)	33(28,43)
T2D,n(%)	17(54.8)	13(37.1)	1(11)	4(10)
Male,n(%)	14(45.2)	22(62.9)	6(67)	17(81)
Ethnicity/Asian,(%)	25(80.6)	24(68.6)	9(100)	21(100)
Weight,kg	83.7(74.0,96.8)	92.0(83.0,101.0)	80.0(75.5,94.0)	78.3(72.3,87.5)
BMI(kg/m^2)	31.2(29.3,35.1)	32.8(29.6,35.2)	28(26.6,33.5)	27.3(25.8,30)
ALT(U/L)	25(16,46)	29(24,43)	69(44,135)	82(39,143)
AST(U/L)	21(15,30)	23(20,30)	46(34,60)	42(30,67)
HbA1c,%	6.4(5.9, 8.6)	5.8(5.5, 6.4)	5.8(5.3,6.2)	5.3(5.2,5.8)
Insulin(fasting)(μU/mL)	17(15, 24)	22(14, 32)	17(14,21)	10(7,15)
Total Cholesterol(mg/dL)	192(162,229)	189(167,225)	198(175,217)	183(170,192)
LDL(mg/dL)	116(98,139)	114(94,153)	101(96,137)	104(94,123)
HDL(mg/dL)	43(39,53)	44(37,51)	42(30,55)	37(36,46)
Triglycerides(mg/dL)	157(123,248)	163(124,262)	142(124,230)	168(115,265)
MRI-PDFF(%)	15.3(11.8,22.2)	15.8(12.3,19.6)	20.6(11.8,26)	16.8(13.3,19.8)

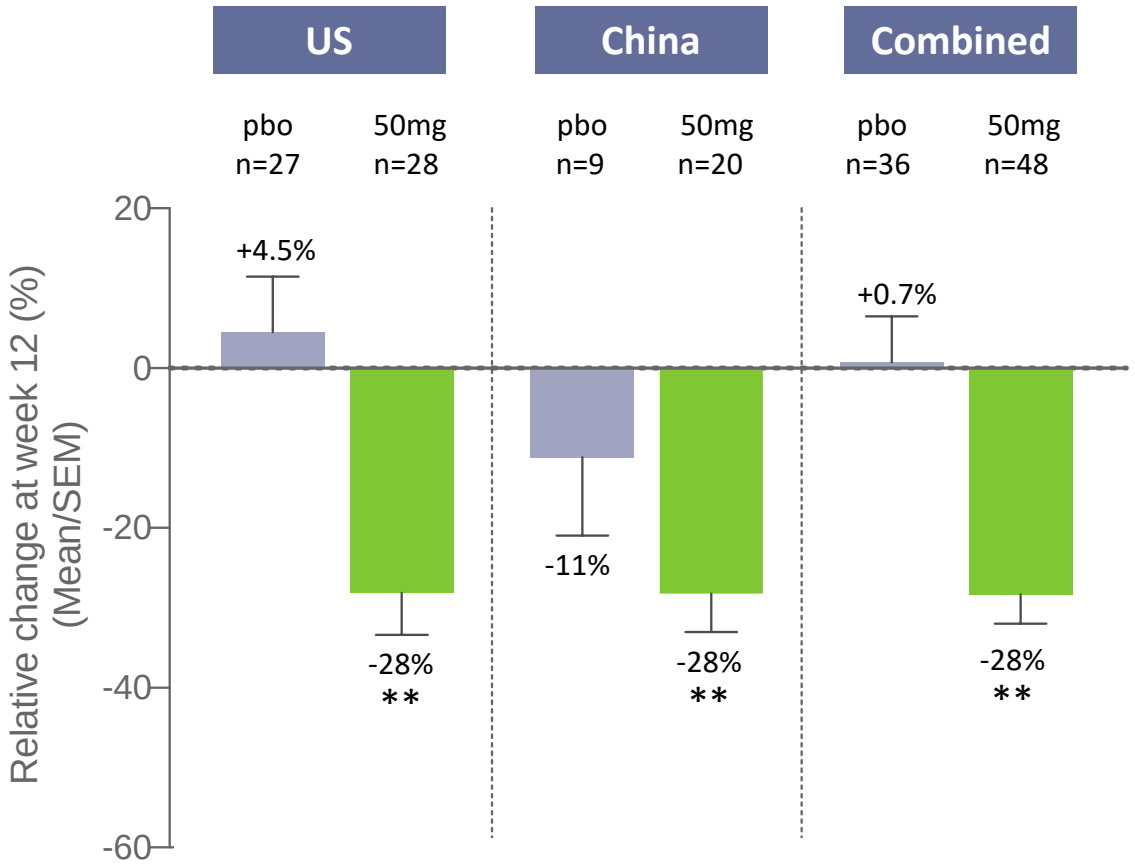
Key Differences

Patients in China were:

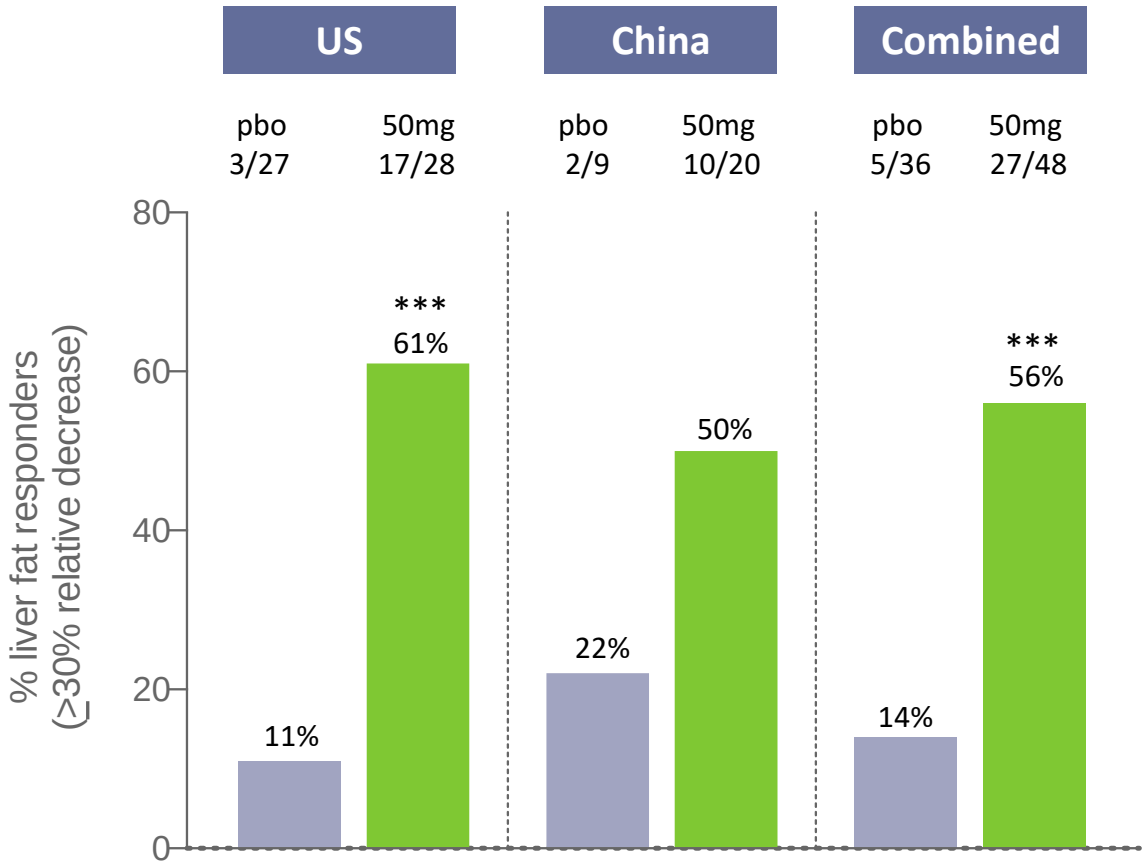
- Younger
- Fewer T2D
- Lower BW
- Higher ALT
- Biopsy: >90% enrolled based on F1-F3 biopsy compared to MRE threshold-based in US patients (2.9kpa)

TVB-2640 potently reduced liver fat by MRI-PDFF in both US and China cohorts

MRI-PDFF change

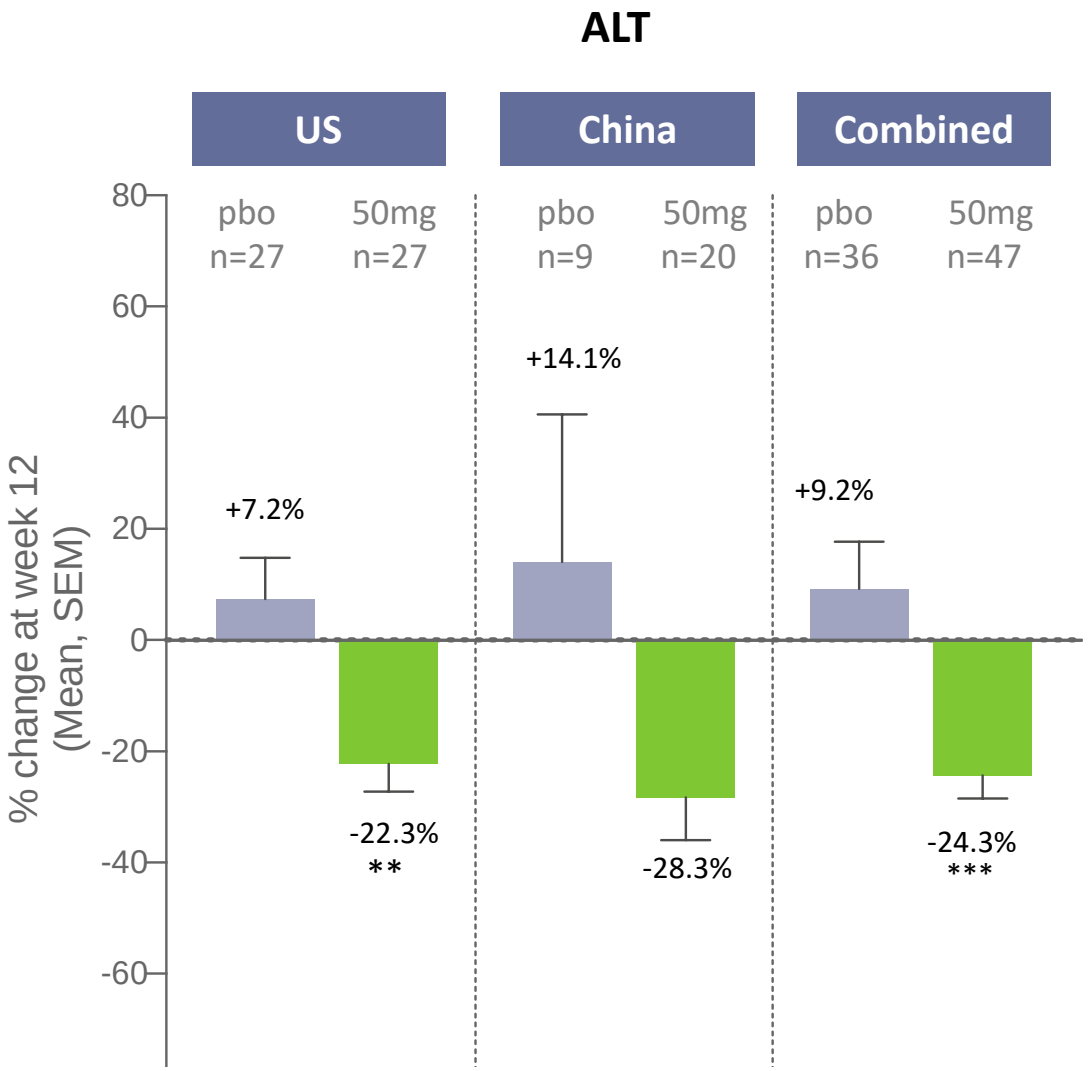


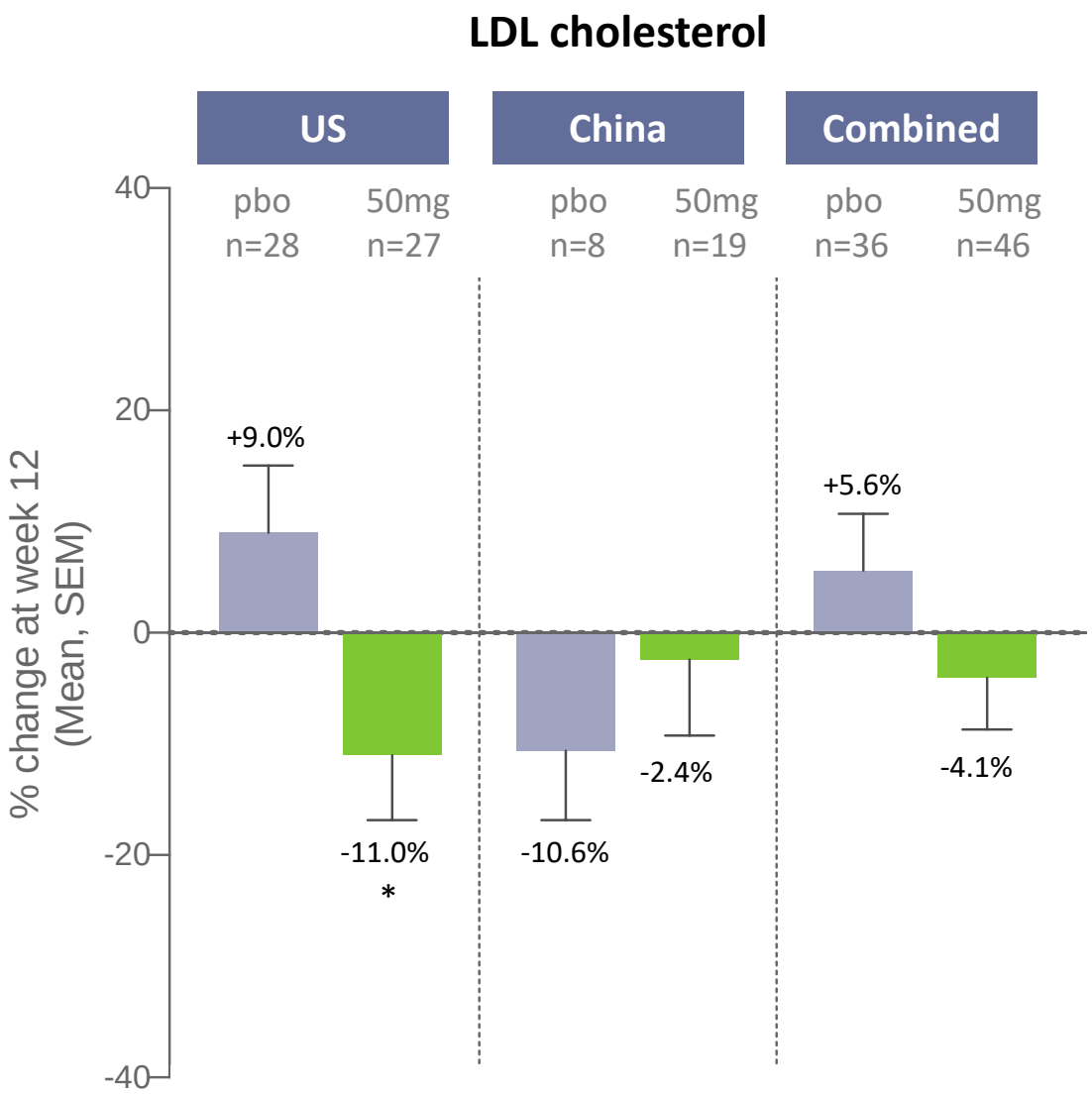
MRI-PDFF responder rate



***p<0.005, LSM difference versus placebo. mean/SEM. *** p<0.001, Common risk difference versus placebo. Combined analysis is post-hoc.*

TVB-2640 reduced ALT and LDL cholesterol

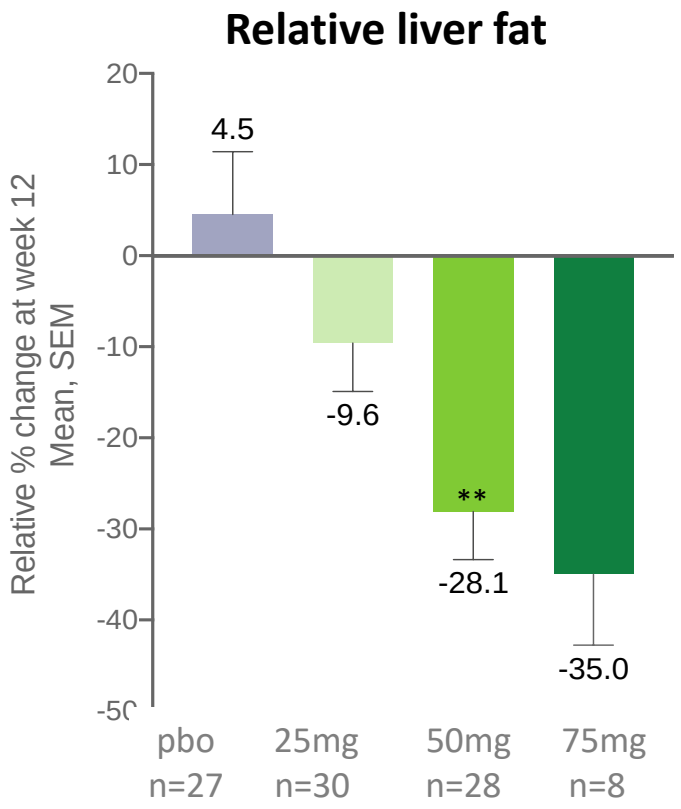


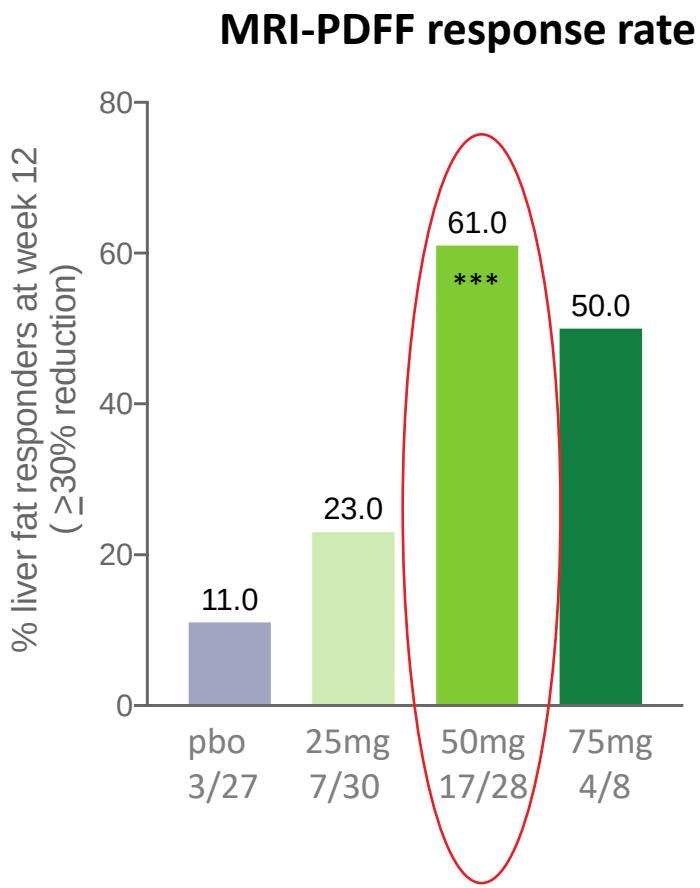


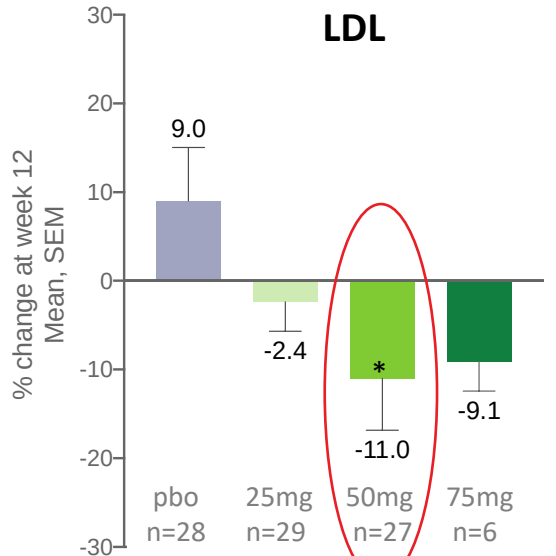
*p<0.05, **p<0.005, *** p<0.001. LSM difference versus placebo. Combined analysis is post-hoc.

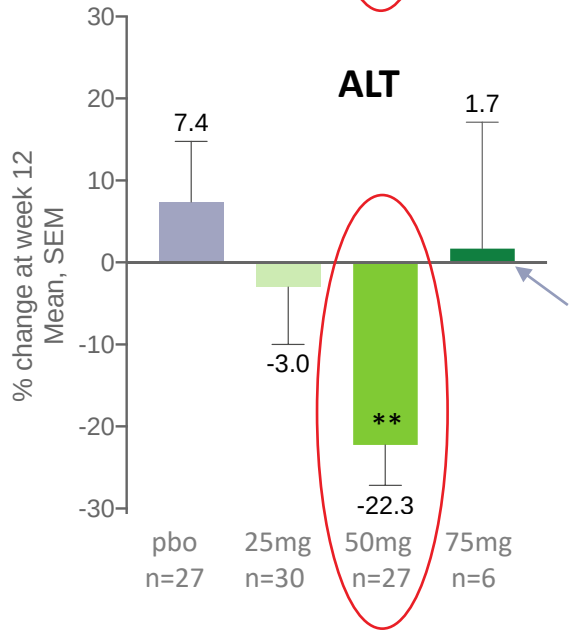
Dose response confirms 50mg as the optimal dose compared to 25mg or 75mg

- Open label 75mg cohort conducted in US, N of 13 pts
- A 75mg dose level did not offer meaningful improvement in efficacy
- Overall, did not offer a meaningful increase in efficacy over 50mg









high variability at wk12
decrease at wk8

**p<0.05, **p<0.005, ***p<0.001. mean/SEM. Statistical analysis not performed for 75mg since open label.*

Safety assessment across all cohorts

Treatment Emergent Adverse Event (TEAE) Classification	US Placebo N=31	US 25mg N=33	US 50 mg N=35	China Placebo N=9	China 50 mg N=21	US 75mg N=13
Any TEAE	Gr. 1: 12 (38.7%) Gr. 2: 7 (22.6%)	Gr. 1: 18 (54.5%) Gr. 2: 7 (21.2%)	Gr. 1: 12 (34.3%) Gr. 2: 6 (17.1%)	Gr.1: 3 (33%) Gr.2: 2 (22%)	Gr.1: 11 (52%) Gr.2: 4 (19%) Gr.3: 2 (10%)	Gr 1: 3 (23%) Gr 2: 6 (46%)
TEAE leading to drug withdrawal	0	2 (6.1%)	0	0	1 (5%)	4 (31%)
Treatment Emergent Serious Adverse Event (SAE)	0	0	0	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%)	0	Gr.1: 9 (43%) Gr.2: 4 (19%)	Gr 1: 1 (8%) Gr 2: 6 (46%)
TEAE leading to death	0	0	0	0	0	0

- TVB-2640 appears to be well tolerated
- No dose related significant adverse events relative to placebo
- **Majority of AEs were Grade 1; no Grade 3 drug-related AEs were reported**

Lipidomics approach initiated to identify predictive response markers

FASCINATE-1
50mg US cohort
N=28 samples

Pre-treatment serum

Lipidomic profiling

OWL platform
467 metabolites

Bioinformatics

Two machine learning models

- *Random Forest Model (RFM)*
- *Support Vector Model (SVM)*

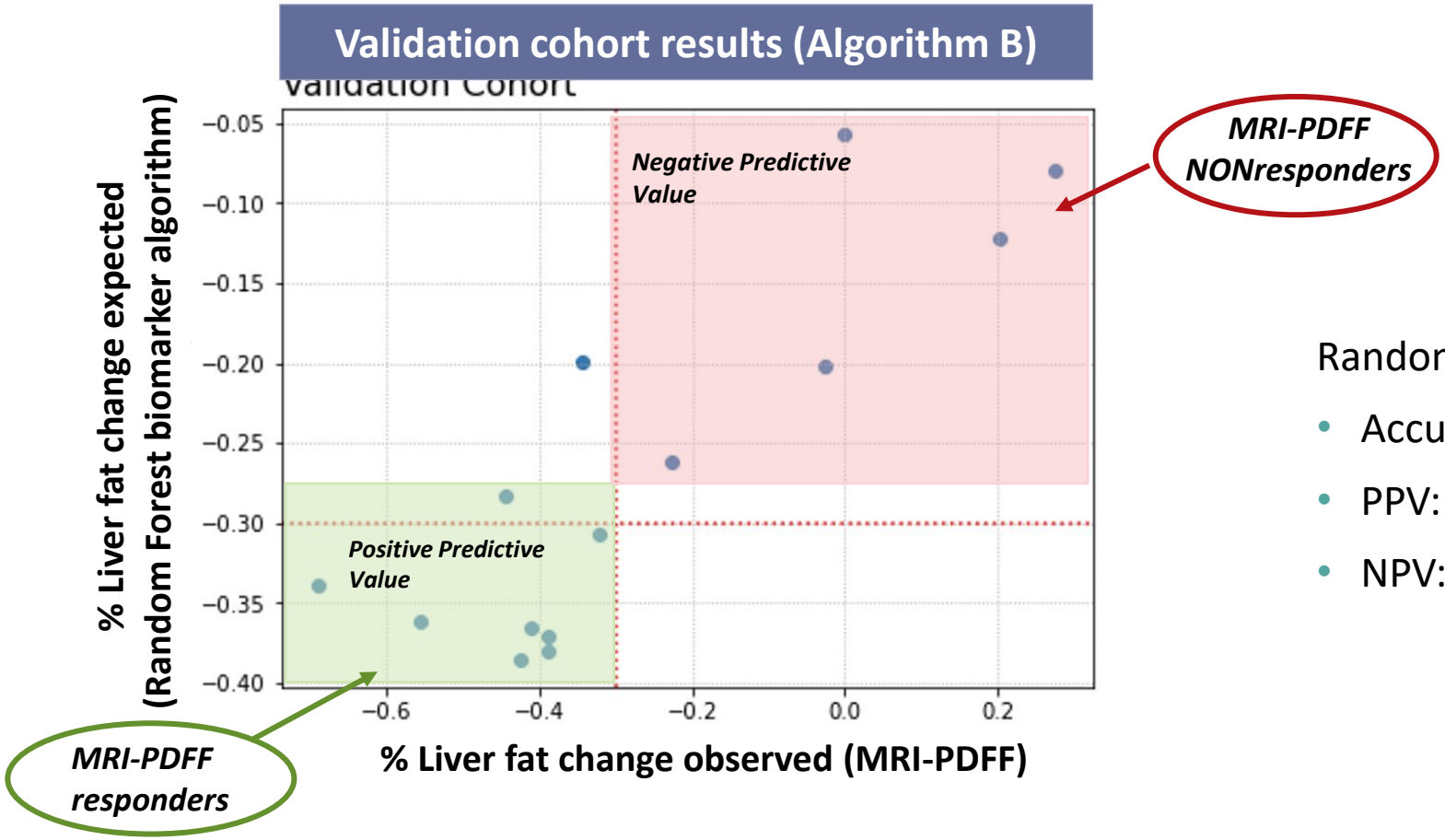
cross-validation process for small sample size

Developed algorithm on “training cohort” (14)
Tested algorithm on “validation cohort” (14)
Used liver fat as a continuous variable

Metabolite panel
Ursodeoxycholic + Hyodeoxycholic acid
DL-2-Aminocaprylic acid
Sarcosine
Glycoursodeoxycholic acid
D(-)-2-Aminobutyric acid
PC(O-18:0/22:4)

A baseline metabolite profile predicts liver fat changes in the 50mg US cohort of FASCINATE-1

- A panel including bile acids, amino acid derivatives and glycerophospholipids, may identify patients who respond to TVB-2640
- Data to be validated in larger Phase 2b study



Random Forest/Support Vector Models

- Accuracy: 79/86%
- PPV: 88%/88%
- NPV: 63/80%

Summary – TVB-2640 potential for promising NASH therapy

- TVB-2640 had similar efficacy in two diverse patient populations – US and China
- TVB-2640 was well tolerated with predominantly Grade 1 AEs at the highest dose tested
- Biomarker improvement in several key NASH pathways: steatosis, inflammation, fibrosis and metabolism
- Novel serum metabolite signature may be able to identify patients who are likely to respond to TVB-2640
  - These data require further validation
- 50mg has been selected based on its potent efficacy and excellent safety profile as the optimal dose for further development
- FASCINATE-2 Ph2b biopsy study recently initiated
- FASN inhibitor has potential to be a promising treatment for NASH

Acknowledgements

- The patients and their families
- Clinical sites in US and China
- Ascletis Pharma Inc
- OWL Metabolomics
- Dr. William McCulloch