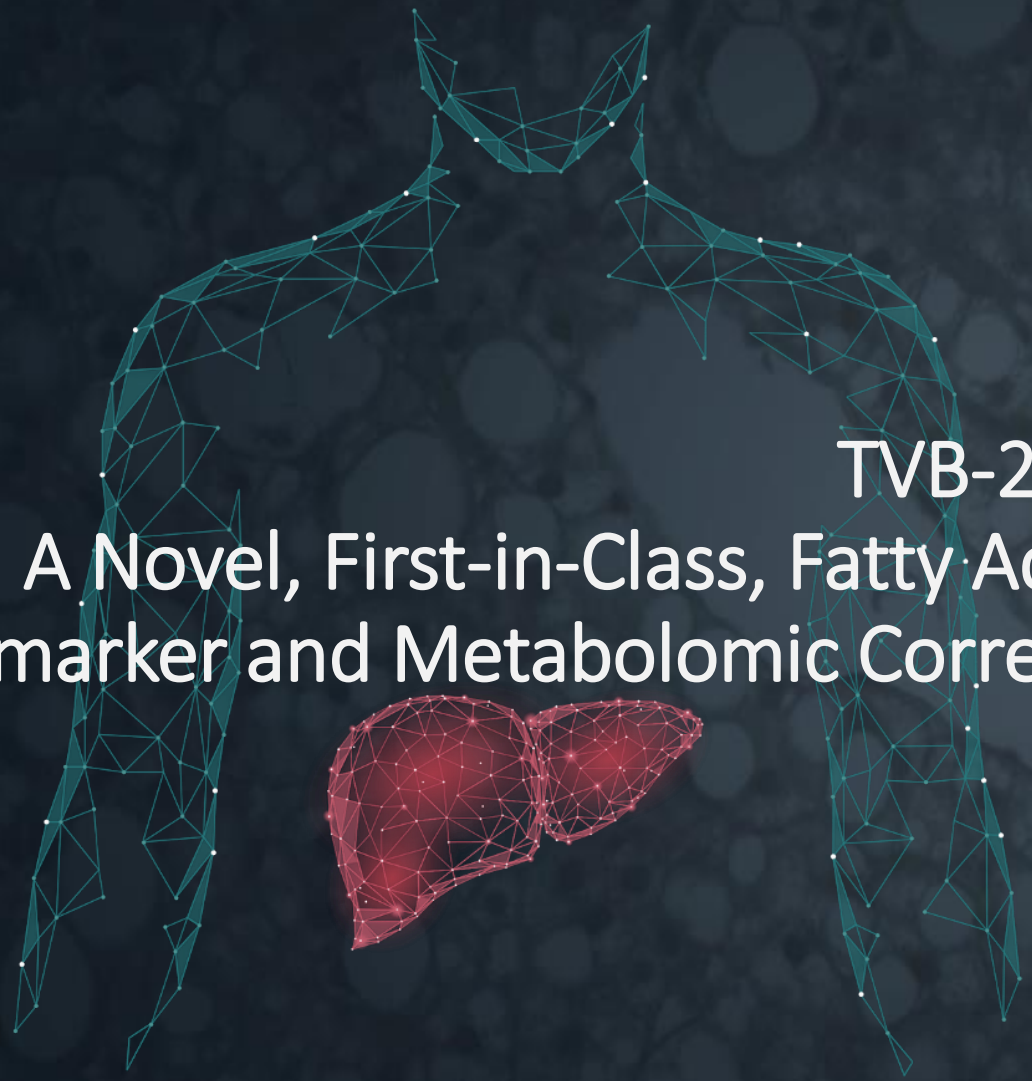


SAGIMET BIOSCIENCES

TVB-2640, A Novel, First-in-Class, Fatty Acid Synthase (FASN) Inhibitor, Biomarker and Metabolomic Correlations With MRI-PDFF Response

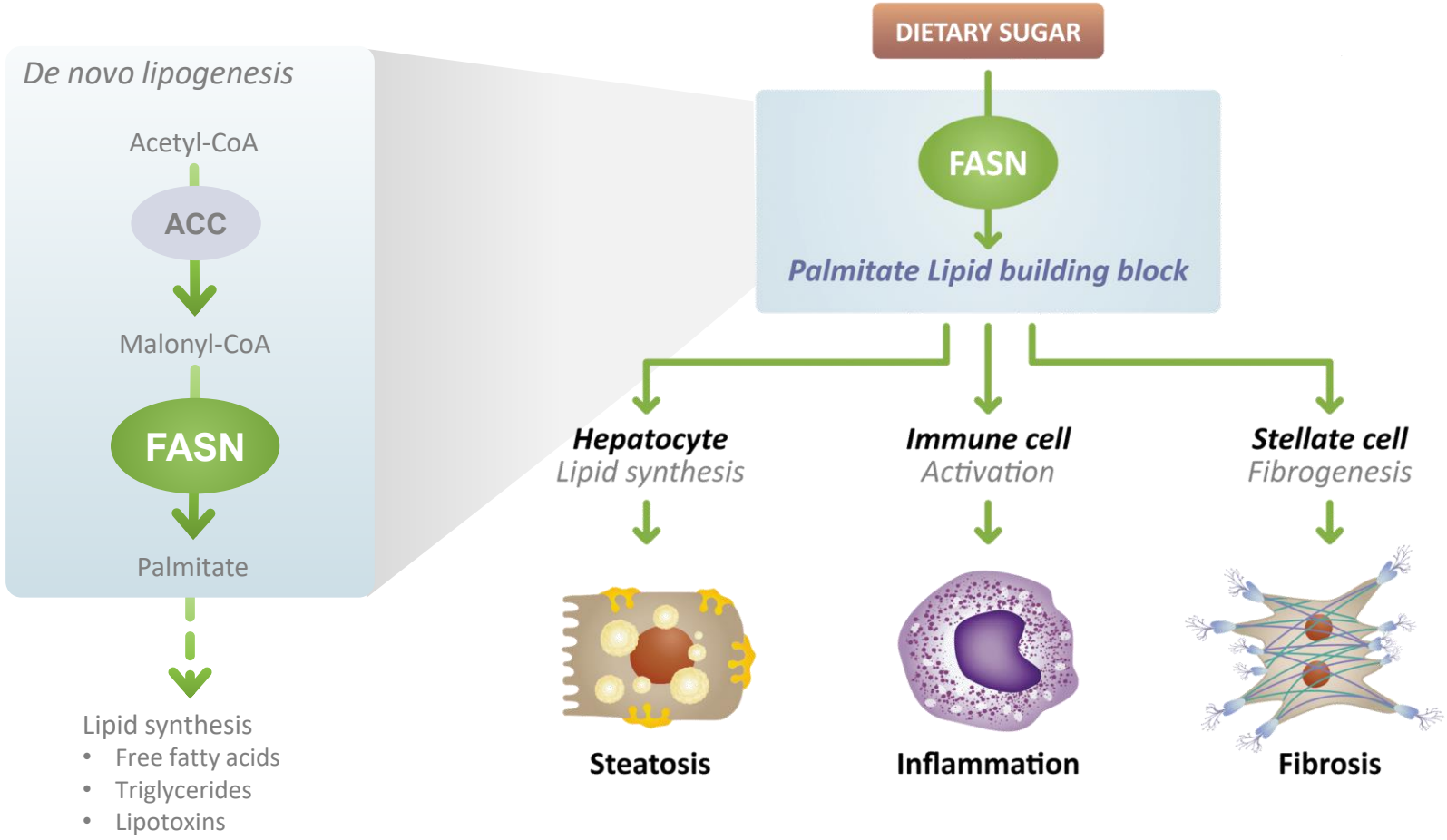
Marie O'Farrell
Vice-President, Research and Development

NASH Summit 2021

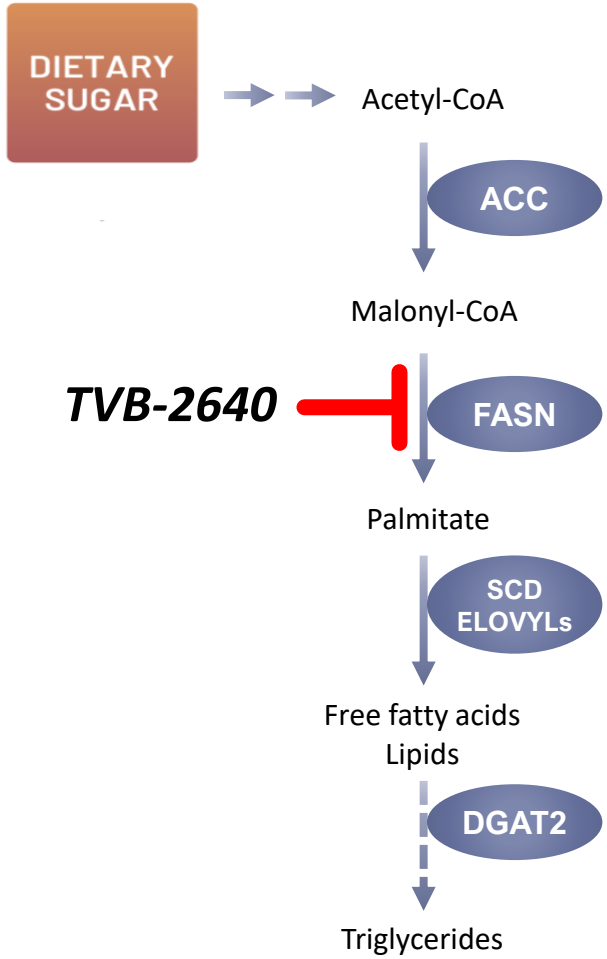
Outline

- FASN background
- Phase 2a FASCINATE-1
  - Efficacy
  - Biomarkers
  - Predictive lipidomics

FASN is a compelling target in NASH
Directly involved in 3 key drivers of the disease



TVB-2640 is designed to be a potent fat synthesis inhibitor

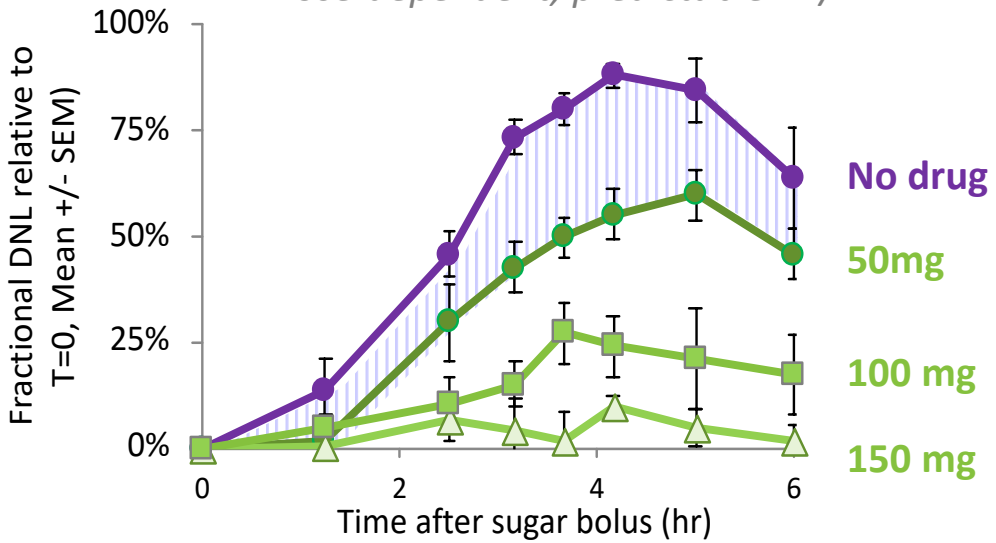


TVB-2640 – first-in-human FASN inhibitor

- Orally-available small molecule (MW=440)
- Once-daily dosing (10-12 hr half-life in blood)
- Efficacy in preclinical NASH models
  - In vitro stellate cells, pro-inflammatory cells, liver microtissues
  - Diet induced mouse models - Gubra
  - FAT-NASH CCl4 mouse model - Scott Friedman

TVB-2640 inhibits liver fat synthesis in Phase 1 clinical trial

Dose-dependent, predictable PK/PD



Syed-Abdul et al, 2019 Hepatology https://doi.org/10.1002/hep.31000

FASCINATE-1 Phase 2a Study Design

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

Oral, once-daily, 12 weeks

Primary Endpoints

- Liver fat reduction by MRI-PDFF
- Safety

Secondary Endpoints

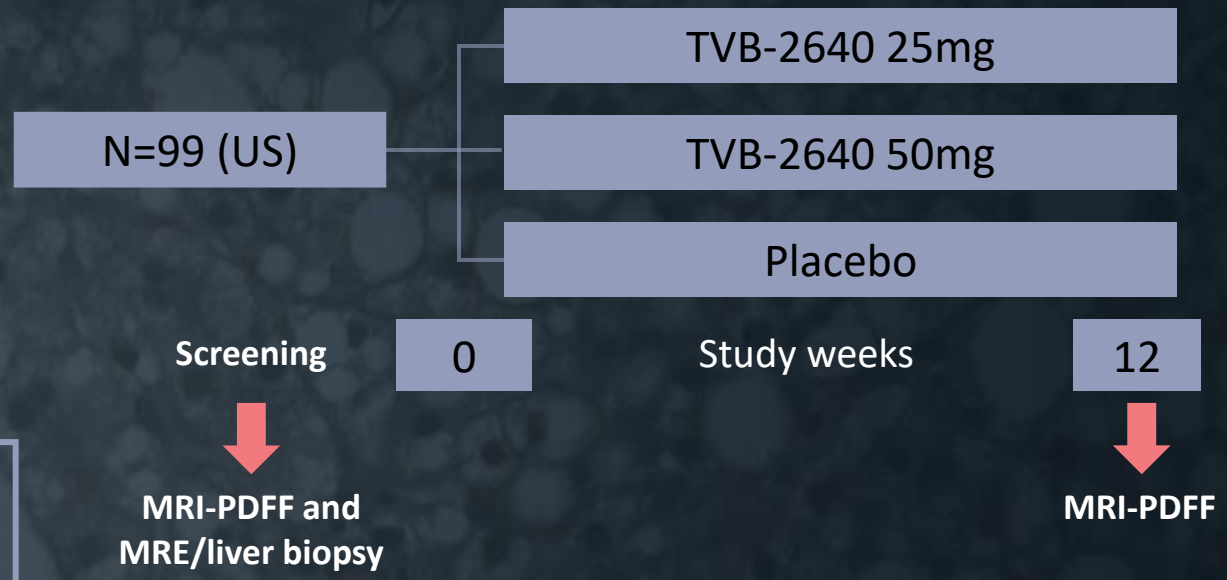
- % pts ≥30% reduction of liver fat
- ALT, AST

Comprehensive biomarkers in US placebo, 25 mg and 50 mg

- **Fibrosis markers**
- **Inflammation markers**
- **Lipidomics**
- **SNPs relevant to NALFD/NASH**

Inclusion criteria

- **≥ 8% liver fat**
- **MRE ≥ 2.5kPa or recent biopsy**



Additional cohorts recently completed

- **China: placebo vs 50 mg**
- **US: 75 mg open label in US**

Biomarker data not available or not feasible

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

SAGIMET BIOSCIENCES

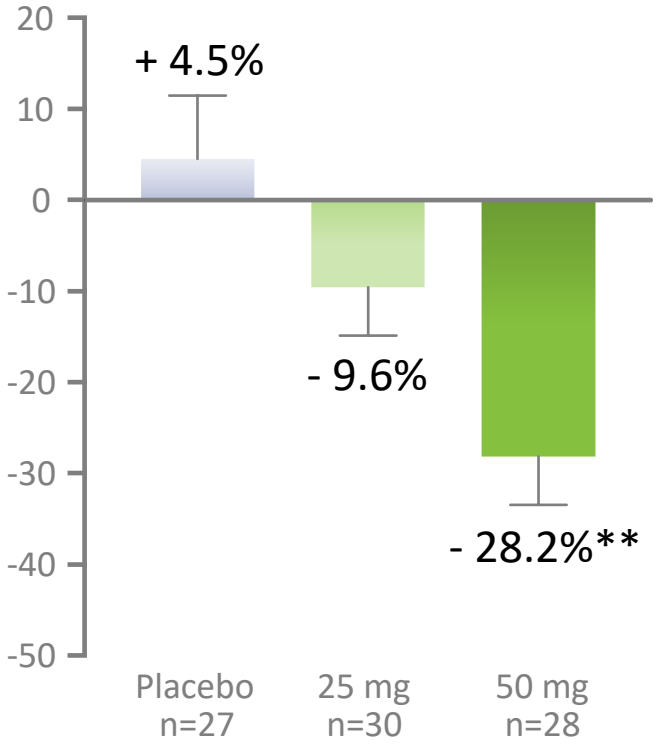
Demography and baseline characteristics

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)

Potent, dose-dependent reduction of liver fat

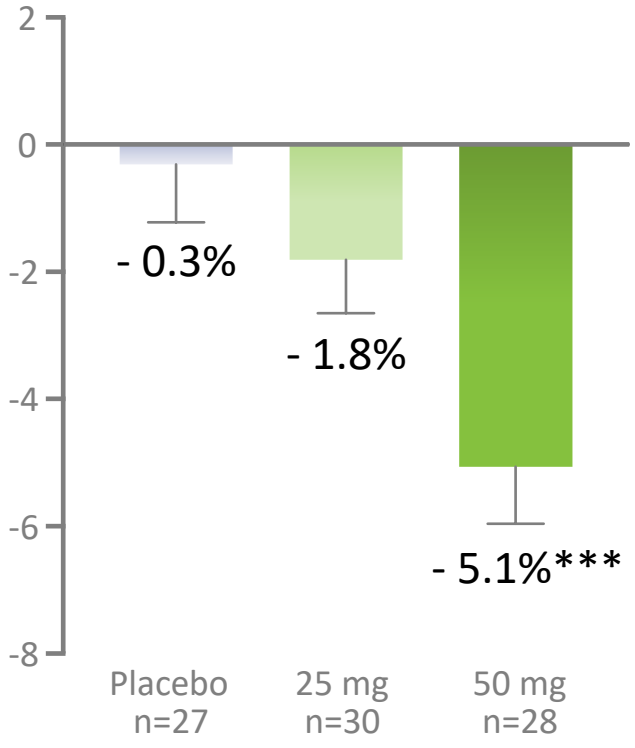
Mean relative liver fat reduction

MRI-PDFF at week 12



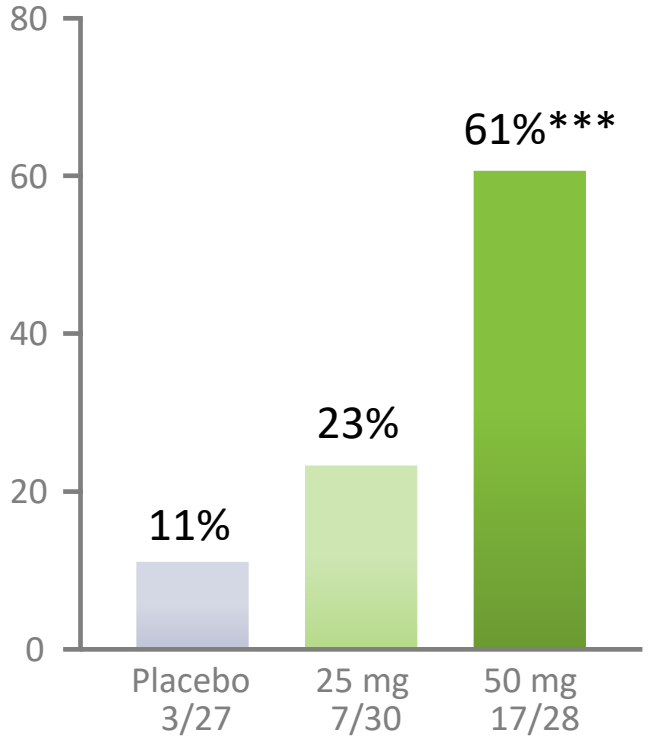
Mean absolute liver fat reduction

MRI-PDFF at week 12



Responder frequency

Patients with ≥30% relative reduction



***p<0.005, ***p<0.001. Mean ±SEM. LSM difference versus placebo for liver fat. Common risk difference for responder frequency*

TVB-2640 was well tolerated

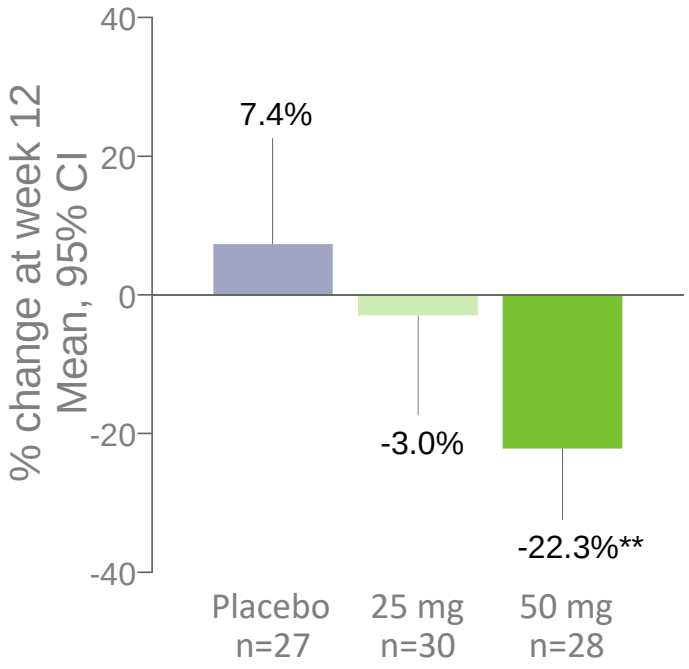
Treatment Emergent Adverse Event (TEAE) Classification	US Placebo N=31	US 25mg N=33	US 50 mg N=35
Any TEAE	Gr. 1: 12 (38.7%) Gr. 2: 7 (22.6%)	Gr. 1: 18 (54.5%) Gr. 2: 7 (21.2%)	Gr. 1: 12 (34.3%) Gr. 2: 6 (17.1%)
TEAE leading to drug withdrawal	0	2 (6.1%)	0
Treatment Emergent Serious Adverse Event (SAE)	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

- 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**

Improvement consistent across other key drivers of NASH

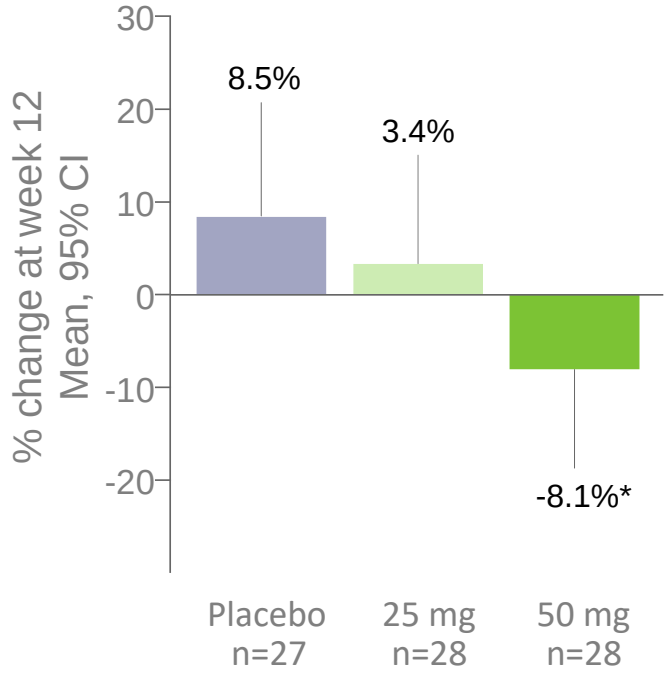
Inflammation

ALT



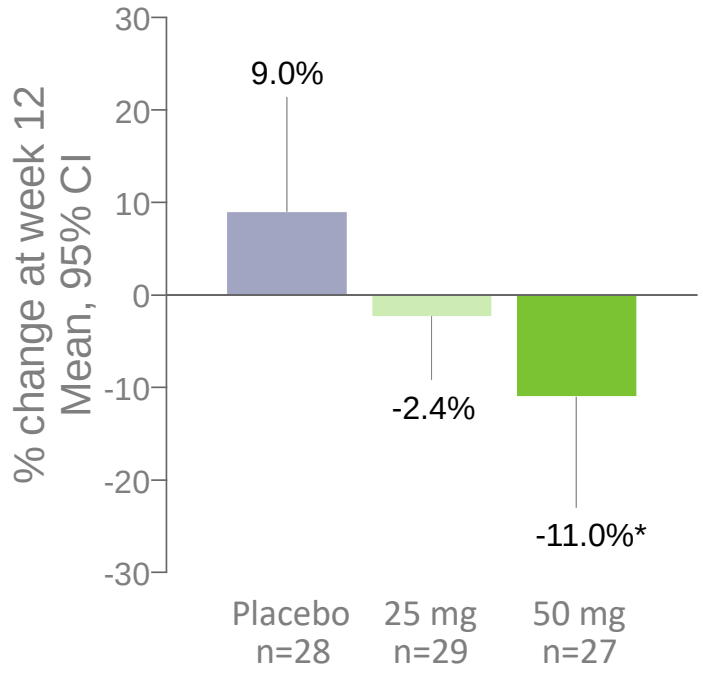
Fibrosis

ProC3



Metabolic health

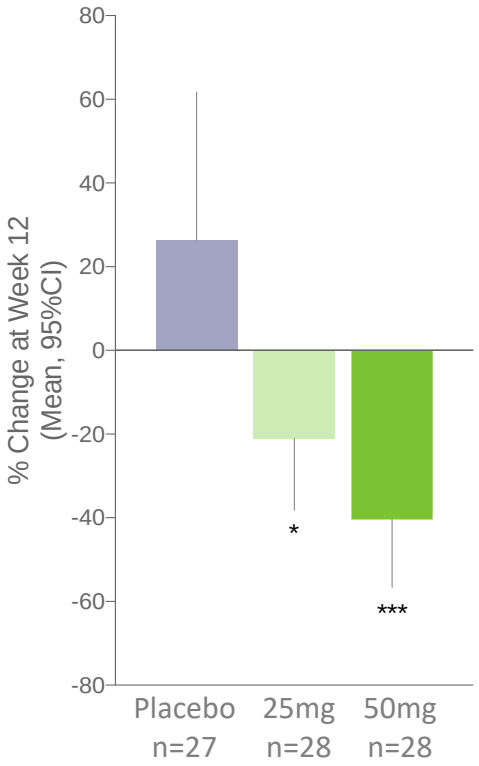
LDL-cholesterol

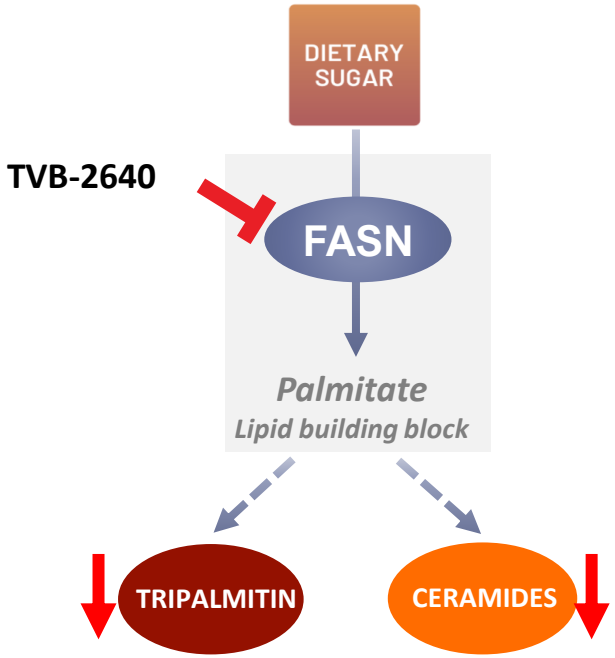


*p<0.05, **p<0.005 ANCOVA model

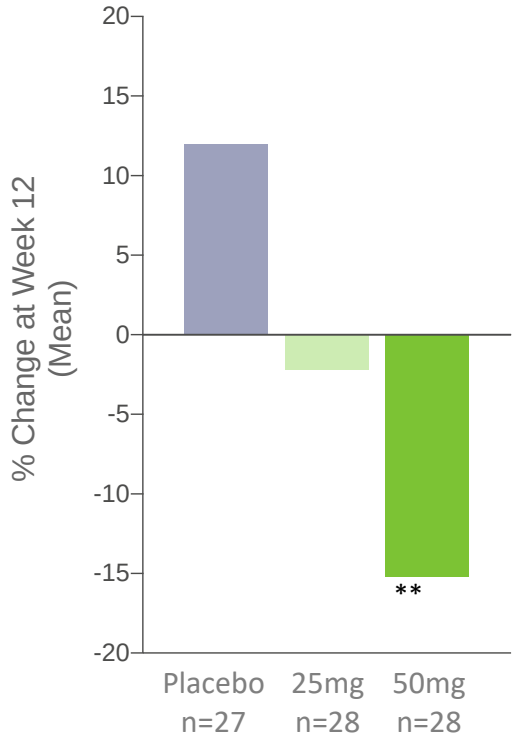
TVB-2640 reduces tripalmitin and significantly reduces lipotoxic ceramides

Tripalmitin
Proof of mechanism



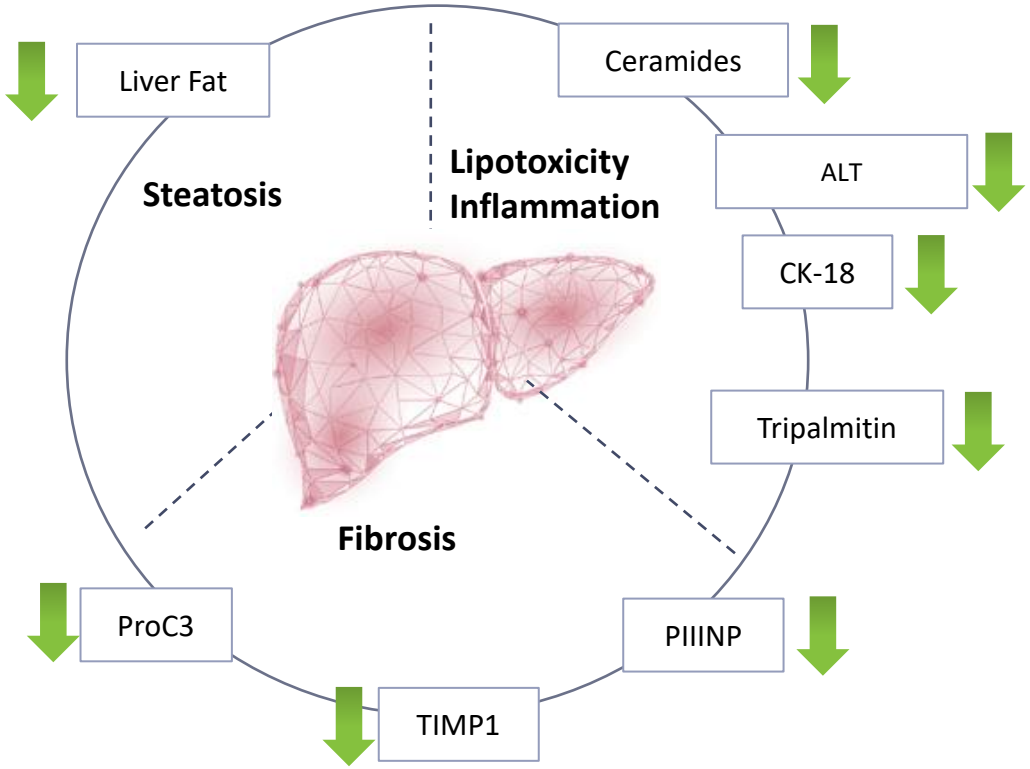


Ceramide C18:1/16:0
Decreased lipotoxins



**p<0.05, **p<0.005, ***p<0.001. Mann Whitney U test vs placebo for tripalmitin. Wilcoxon signed rank test for ceramide.*

TVB-2640 showed biomarker improvements in key NASH pathways



Cardiovascular benefits

LDL

Insulin sensitivity

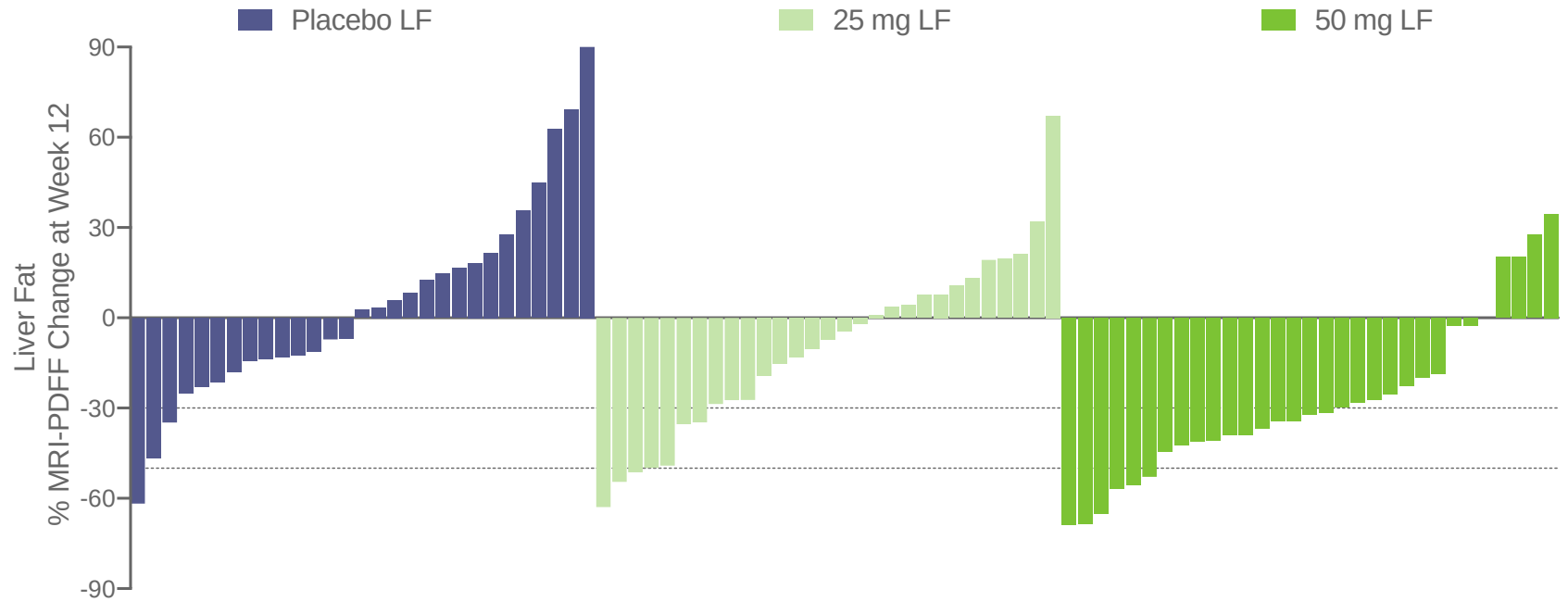
FGF21

Adiponectin

Loomba et al, Gastroenterology, 2021
161(5):1475-1486. doi: 10.1053/j.gastro.2021.07.025.

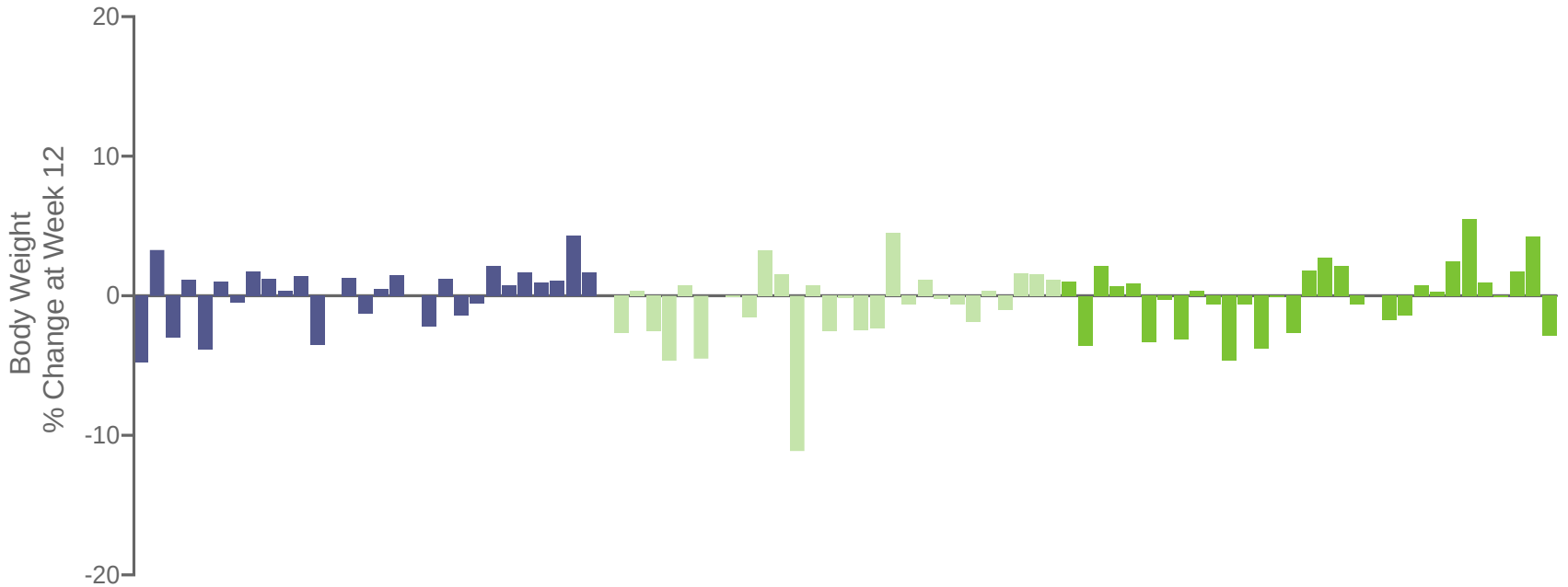
Liver fat

- **Dose-dependent response**



Body weight

- **No meaningful change with treatment (median change at 50 mg of 0.2 kg)**
- **No correlation with liver fat change**
- **Indicates direct effect of TVB-2640 on liver fat as expected**



Correlations between liver fat response and other biomarkers

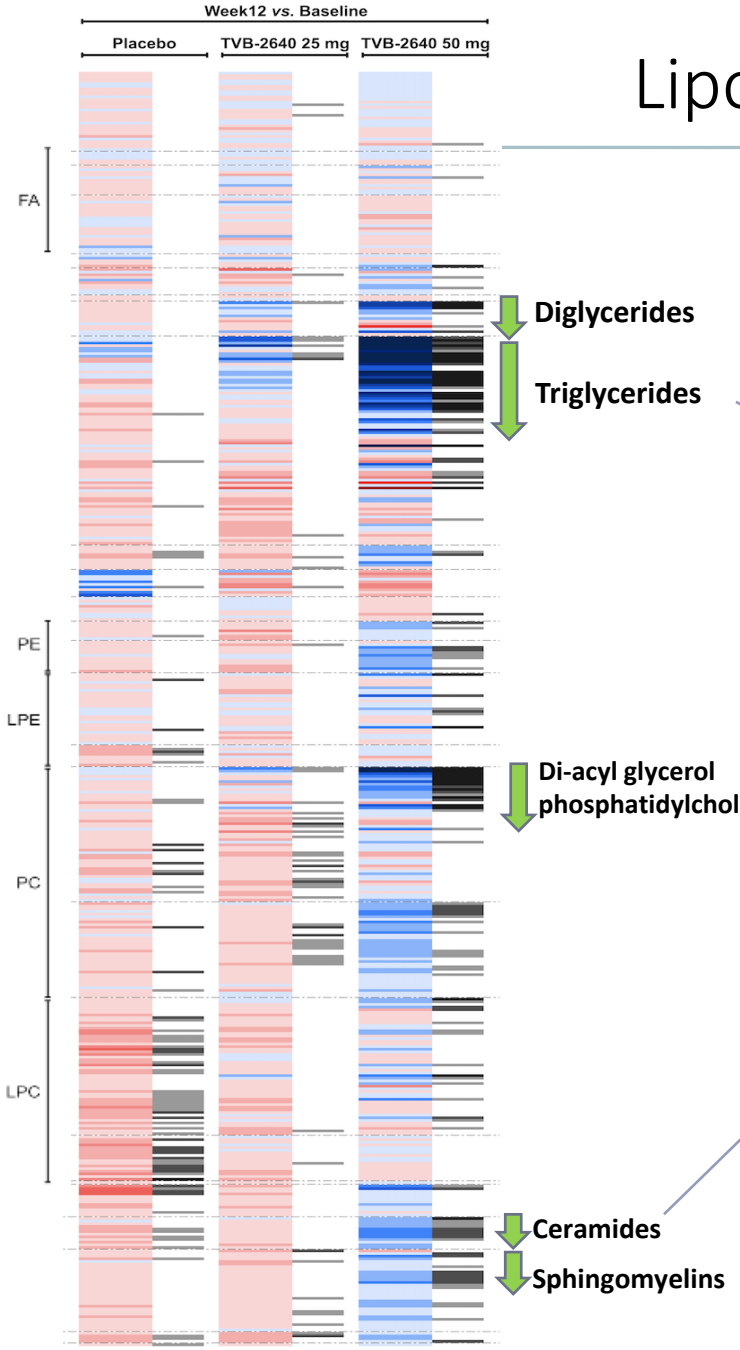
	Placebo		TVB-2640 25mg group				TVB-2640 50mg group			
	Non-Responders		Responders		Non-Responders		Responders		Non-Responders	
	%Change	p-value	%Change	p-value	%Change	p-value	%Change	p-value	%Change	p-value
ALT (U/L)	-7%	0.61	-36%	0.016	3%	0.69	-21%	**0.003**	-13%	0.1
Adiponectin (ug/ml)	-1%	0.63	0%	1	-1%	0.86	19%	0.15	19%	0.13
BW (kg)	1%	0.21	-3%	0.16	0%	0.73	0%	0.6	0%	0.58
ELF Score	-1%	0.96	-6%	0.036	2%	0.24	-3%	0.08	-4%	0.08
FGF21 (pg/ml)	-3%	0.99	-29%	0.31	35%	**0.017**	34%	**0.045**	89%	**0.007**
HA (ng/ml)	1%	0.74	-30%	0.08	27%	**0.016**	-16%	**0.039**	-17%	0.16
IP10 (ng/ml)	-1%	0.24	-29%	0.031	1%	0.49	-1%	0.89	-10%	0.17
PIIINP (ng/ml)	4%	0.39	-22%	0.08	2%	0.95	-11%	0.44	-10%	0.54
ProC3 (ng/ml)	7%	0.21	-1%	0.84	8%	0.28	-8%	0.46	-25%	**0.019**
TIMP1 (ng/ml)	-3%	0.99	-25%	0.016	1%	0.59	-15%	**0.044**	-22%	**0.027**
Tripalmitin	25%	0.56	-53%	0.016	-9%	0.37	-57%	**6.56E-04**	-63%	**0.002**
Linoleic acid	-1%	0.75	28%	0.47	-1%	0.93	-10%	0.31	19%	**0.032**
Palmitic acid	-5%	0.82	-5%	0.81	-1%	0.99	-10%	0.16	-2%	0.32
Palmitoleic acid	2%	0.99	9%	0.69	15%	0.33	-18%	0.22	20%	0.52
TIMP1 (ng/ml)_excluding 101131	-3%	9.88E-01	-25%	1.56E-02	1%	5.95E-01	-18%	4.79E-02	-22%	2.73E-02

p<0.05 **p<0.01** **p<0.001**

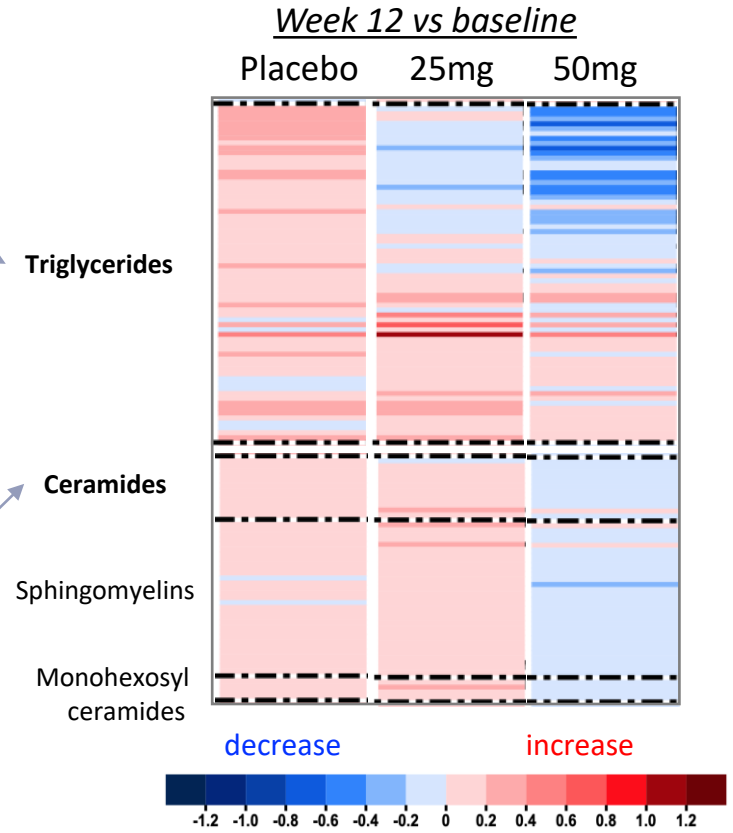
- Follow up analysis – liver fat as a continuous variable
- Expand to additional markers

Paired Wilcoxon signed-rank test p-values are indicated. LF decrease ≥ 30% are "responders". For LF decrease ≥30%/<30%, n of 7/20 (25 mg), 17/11 (50 mg) and 23 (placebo). Placebo >30% LF decrease not included as insufficient number of patients). Greyscale indicates significance.

Lipotoxic species decreased with TVB-2640 treatment



Ceramides and other lipid classes
Lipotoxic inflammatory molecules



TGs: decreased shorter chain saturated or monounsaturated fa, while some polyunsaturated increased

Lipidomics approach initiated to identify predictive response markers

FASCINATE-1
50mg cohort
N=28 samples

Pre-treatment serum

Lipidomic profiling

OWL platform
467 metabolites

Bioinformatics

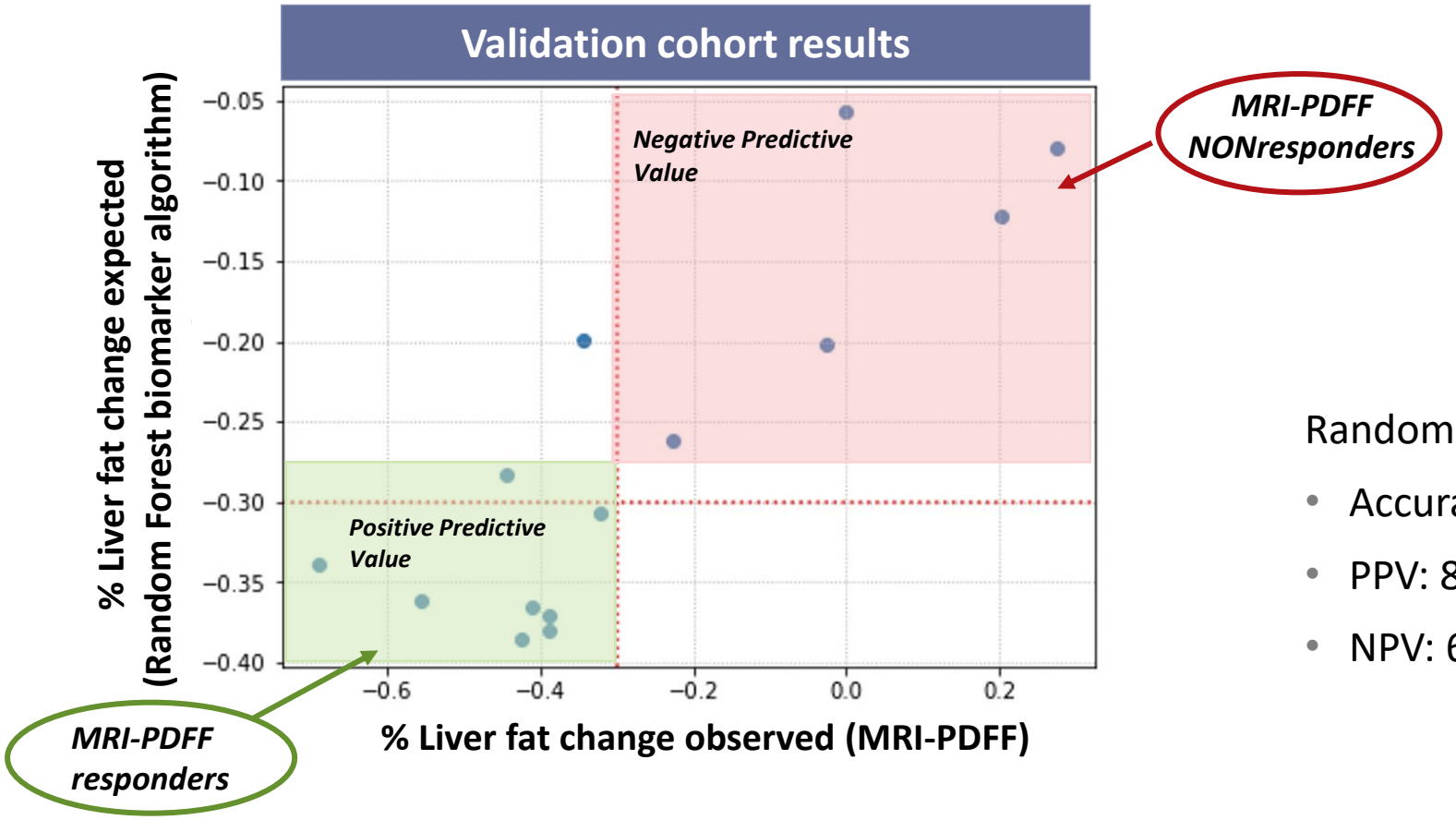
Two machine learning models
- *Random Forest Model (RFM)*
- *Support Vector Model (SVM)*

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 acid
DL-2-Aminocaprylic acid
Sarcosine
Glycoursodeoxycholic acid
D(-)-2-Aminobutyric acid
PC (0-18:0/22:4)

A baseline metabolite profile predicts liver fat changes in the 50mg cohort



Random Forest/Support Vector Models

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

Components of predictive signature suggest role for gut-liver axis

Marker	Class	Function
Ursodeoxycholic acid	*Bile acid derivative*	Secondary bile acid made from chenodeoxycholic acid via epimerization of the 7-alpha>7 beta-hydroxy group by gut bacteria
Glycoursodeoxycholic acid	*Bile acid derivative*	Glycine conjugated secondary bile acid
DL-2-Aminocaprylic acid	*Alpha Amino Acid Derivative*	Aminooctanoic acid
Sarcosine	*Alpha Amino Acid Derivative*	N-methyl glycine, naturally found in muscles and other body tissues; intermediate in metabolism of choline to glycine.
D(-)-2-Aminobutyric acid	*Alpha Amino Acid Derivative*	Function not well defined –can activate AMPK, modulates glutathione homeostasis
PC(O-18:0/22:4)	*Glycerophospholipid*	Function in membranes, metabolism, signaling

Summary

- **Demonstrated proof-of-concept in robust FASCINATE-1 Ph2a program**
  - Liver fat relative reduction of 28% over 12 weeks
  - 61% patients achieved ≥30% reduction
- **Biomarker improvement in several key NASH pathways**
  - Validates expected mechanism of action: impacts steatosis, inflammation/lipotoxicity and fibrosis
- **Biomarker for patient selection**
  - Preliminary serum metabolite signature correlated to liver fat change at 50 mg
- **FASCINATE-2 Ph2b biopsy study recently initiated**
  - Expand biomarker analyses and extend to histology endpoints
- **TVB-2640 has potential to be a foundational NASH therapy**

Acknowledgements

The patients and their families

Clinical sites in US and China

OWL lipidomic team

Ascletis team

Sagimet team