NOVEL, FIRST-IN-CLASS, FATTY ACID SYNTHASE (FASN) INHIBITOR TVB-2640 DEMONSTRATES ROBUST CLINICAL EFFICACY AND SAFETY IN A GLOBAL PHASE 2 RANDOMIZED PLACEBO-CONTROLLED NASH TRIAL (FASCINATE-1)

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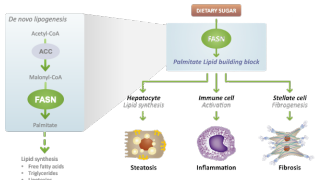
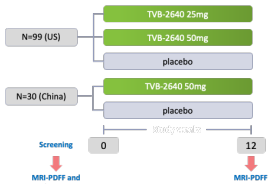
INTRODUCTION

- TVB-2640 is a potent and selective FASN inhibitor
- Directly tackles 3 hallmarks of NASH: inhibits liver fat accumulation (hepatocytes), inhibits fibrosis (stellate cells require DNL for activation) and decreases inflammation (inflammasome activation by palmitate)



METHODS

- Phase 2a, multicenter, placebo-controlled study assessed efficacy and safety of TVB-2640 in the US and China (NCT03938246)
- Subjects with MRI-PDFF ≥8% and fibrosis (MRE ≥2.5 kPa or biopsy F1-F3) were randomized 2:1 to TVB-2640 or pbo once daily (US N=99; China N=30) for 12 weeks. Response was defined as a ≥30% relative reduction in PDFF at W12. Here, we report safety, efficacy and biomarker results.



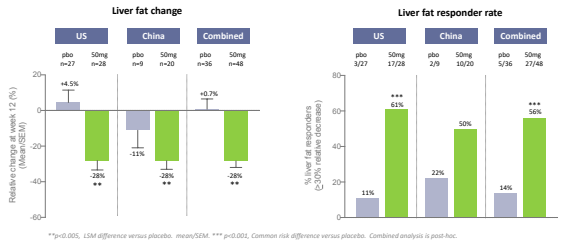
DEMOGRAPHICS

	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)
Male,n(%)	14(45.2)	22(62.9)	6(67)	17(81)
T2D,n(%)	17(54.8)	13(37.1)	1(11)	4(10)
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/m²)	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)
ALP(U/L)	82(72,98)	74(58,103)	79(72,87)	76(64,96)
GGT(U/L)	33(22,58)	39(25,49)	53(37,79)	53(38,65)
Glucose(fasting)(mg/dL)	108(86,167)	98(80,124)	110(103,117)	99(95,110)
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)
Apolipoprotein B (mg/dL)	100(84,126)	104(89,124)	103(94,129)	103(90,114)
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(124,282)	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)

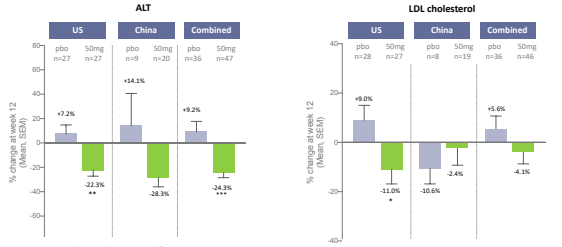
SAFETY

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
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%)
TEAE leading to drug withdrawal	0	2 (6.1%)	0	0	1 (5%)
Treatment Emergent Serious Adverse Event (SAE)	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%)
TEAE leading to death	0	0	0	0	0

EFFICACY



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

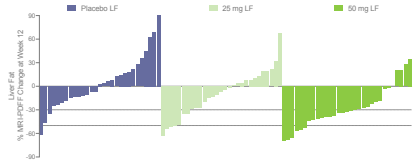


*p<0.05, **p<0.005, *** p<0.001. LSM difference versus placebo. Combined analysis is post-hoc.

EFFICACY CONT.

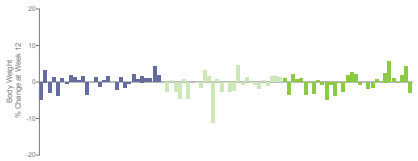
Liver fat*

- 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



*US cohorts only.

LIVER FAT RESPONSE AND BIOMARKERS CORRELATION*

	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%	0.89	-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
Tripeptin	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

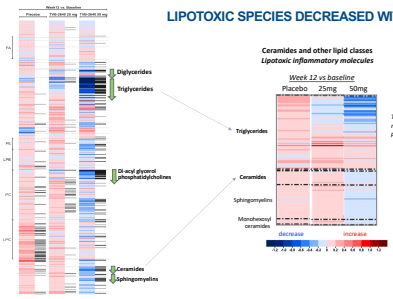
p<0.05 p<0.01 **p<0.001**

- 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.

*Data available for US cohorts only.

LIPOTOXIC SPECIES DECREASED WITH TVB-2460 TREATMENT*



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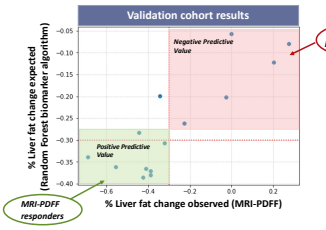
BASELINE METABOLITE PROFILE PREDICTS LIVER FAT CHANGES*



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

Random Forest/Support Vector Models

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

*Data available for US cohorts only.

CONCLUSIONS

- TVB-2640 is a potent and selective FASN inhibitor
- Demonstrated proof-of-concept in robust FASCINATE-1 Ph2a program
- Similar efficacy in two diverse patient populations – US and China
- Liver fat relative reduction of 28% over 12 weeks
  - 61% patients in US and 50% in China achieved ≥30% reduction
- 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
- Preliminary serum metabolite signature correlated to liver fat change at 50 mg in US patients
- FASCINATE-2 Ph2b biopsy study recently initiated
- FASN inhibitor has potential to be a foundational treatment for NASH

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