DDW2022 Digestive Disease Week®

MAY 21-24 | SAN DIEGO, CA

NOVEL, FIRST-IN-CLASS, FATTY ACID SYNTHASE (FASN) INHIBITOR TVB-2640 (DENIFANSTAT): EFFICACY, SAFETY AND BIOMARKER RESULTS FROM A GLOBAL PHASE 2 RANDOMIZED PBO-CONTROLLED NASH TRIAL, FASCINATE-1

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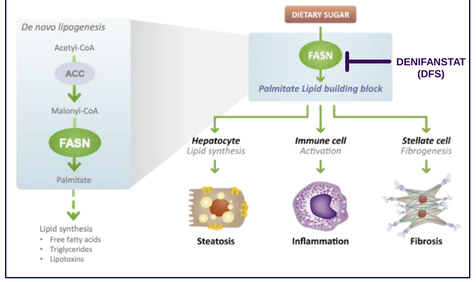
INTRODUCTION

- TVB-2640 (denifanstat; DFS) is a potent and selective FASN inhibitor
- Denifanstat 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)



AIMS

- To assess the safety and efficacy of DFS 50mg in the Phase 2a, multicenter, placebo-controlled FASCINATE-1 study (NCT03938246)
- To identify predictive markers of liver fat reduction in response to DFS 50 mg QD
- To analyze lipid composition changes in response to treatment with DFS 50mg QD

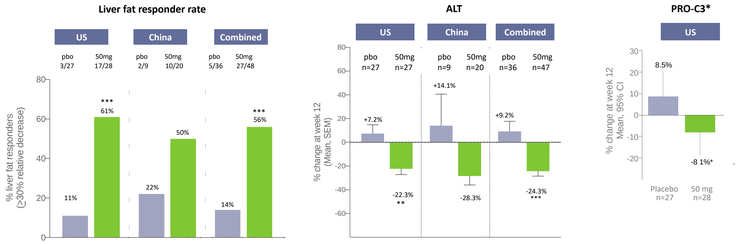
RESULTS

DEMOGRAPHICS AND SAFETY

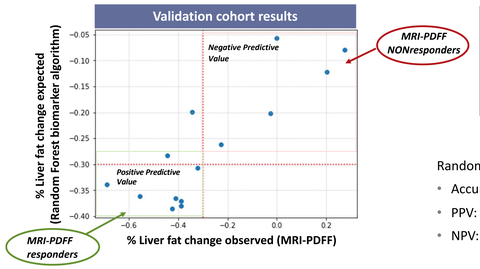
	US		China	
Median (Q1,Q3)	**Placebo (n=31)**	**50mg (n=35)**	**Placebo (n=9)**	**50mg (n=21)**
Age,y	52(46,58)	55(44,62)	34(29,45)	33(28,43)
Male,n(%)	14(45.2)	22(62.9)	6(67)	17(81)
T2D,n(%)	17(54.8)	13(37.1)	1(11)	4(10)
Ethnicity/Asian,(%)	25(80.6)	24(68.6)	9(100)	21(100)
Weight,kg	83.7(74.0,96.8)	92.0(83.0,101.0)	80.0(75.5,94.0)	78.3(72.3,87.5)
BMI(kg/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)
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(124,262)	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)

Treatment Emergent Adverse Event (TEAE) Classification	US Placebo (n=31)	US 50mg (n=35)	China Placebo (n=9)	China 50mg (n=21)
Any TEAE	Gr. 1: 12 (38.7%) Gr. 2: 7 (22.6%)	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	0	0	1 (5%)
Treatment Emergent Serious Adverse Event (SAE)	0	0	0	0
Drug related TEAE	Gr. 1: 3 (9.7%) Gr. 2: 1 (3.2%)	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

DFS POTENTLY REDUCES KEY DRIVERS OF NASH



SERUM METABOLITE SIGNATURE PREDICTS MRI-PDFF RESPONSE TO DFS



- 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%

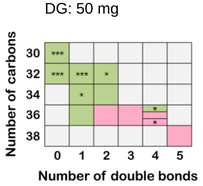
*Data available for US cohorts only.

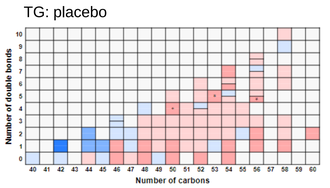
DFS DECREASES SATURATED AND MONOUNSATURATED, AND INCREASES POLYUNSATURATED DI- AND TRIACYLGLYCEROLS

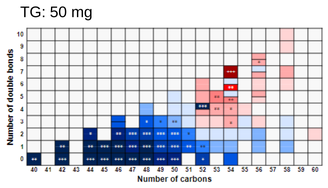
		Week 12 *vs.* Baseline	
	Class	**log$_2$(fc)**	***p*-value**
DG	Diacylglycerols (total)	-0.076	1.13E-01
	Saturated Diacylglycerols	-0.524	3.01E-05
	Unsaturated Diacylglycerols	-0.021	3.42E-01
	Monounsaturated (1sat) Diacylglycerols	-0.169	1.21E-02
	Polyunsaturated (>2sat) Diacylglycerols	0.061	8.92E-01
TG	Triacylglycerols (total)	-0.093	4.20E-02
	Saturated Triacylglycerols	-0.449	1.03E-05
	Unsaturated Triacylglycerols	-0.041	2.06E-01
	Monounsaturated (1sat) Triacylglycerols	-0.243	5.83E-04
	Polyunsaturated (>3sat) Triacylglycerols	0.074	3.70E-01

≤-4 -4 -3 -2 -1 1 2 3 4 ≥4

Logarithmic transformation of the data. Log2 (fold-change) and paired Student's t-test p-values are indicated. Green means decrease and red means increase.







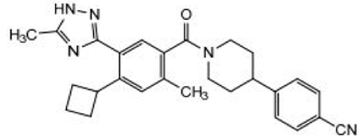
*The color code represents the transformed ratios between means of the groups [log2(fold-change)]. The x axis denotes the number of carbons and the y axis denotes the number of double bonds. Blue means decrease and red means increase. Student's t test p-values (or Welch's t test where unequal variances were found): *p<0.05, **p<0.01, ***p<0.001.*

Top left: changes in metabolic classes related to diglycerides (DG) and triglycerides (TG) for the comparisons Week 12 vs. Baseline in patients randomized in the US cohort DFS (50mg) arm

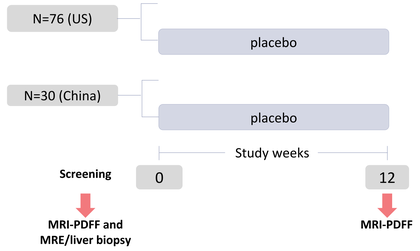
Top right and lower panels: heatmap representation of the influence of the number of carbons and double bond content in the increment or decrement of DG (upper panel) and TG in Week 12 compared to baseline

METHODS

- Phase 2a, multicenter, placebo-controlled study of DFS in patients with NASH in the US and China (NCT03938246). Here we present data from the 50mg dose level
- Subjects with MRI-PDFF ≥8% and fibrosis (MRE ≥2.5 kPa or biopsy F1-F3) were randomized 2:1 to DFS or placebo once daily (US N=99; China N=30) for 12 weeks. Response was defined as a ≥30% relative reduction in MRI-PDFF at W12
- Lipidomic and metabolite analyses were performed in the US cohorts by OWL (Bilbao, Spain)



DENIFANSTAT (DFS)



CONCLUSIONS

- DFS is a potent and selective first-in-class FASN inhibitor
- Similar efficacy in two diverse patient populations – US and China
  - 61% patients in US and 50% in China achieved ≥30% reduction
- DFS was well tolerated with predominantly Grade 1 AEs
- Preliminary baseline serum metabolite signature correlated to liver fat change at 50 mg in US patients
- DFS treatment had a favorable effect on fatty acid composition
  - Decreased lipotoxic saturated di- and triacylglycerols
  - Increased long chain polyunsaturated fatty acid content, that is associated with cardiovascular benefit
- FASCINATE-2 Ph2b biopsy study ongoing with patients receiving DFS 50mg QD; interim analysis expected in 2H 2022
- DFS has potential to be a foundational treatment for NASH