A baseline signature of metabolites involving the gut-liver axis predicts MRI-PDFF response to FASN inhibitor TVB-2640 in NASH patients: results from the FASCINATE-1 study

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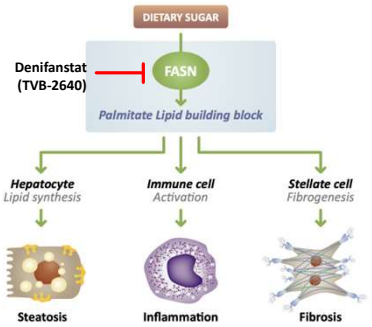
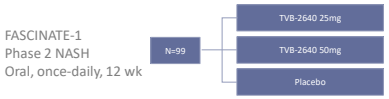
INTRODUCTION

- TVB-2640 is a potent and selective FASN inhibitor
- Directly tackles 3 hallmarks of NASH by acting on hepatocytes, stellate cells, and pro-inflammatory cells



OBJECTIVE

Explore baseline predictive markers of liver fat response in FASCINATE-1



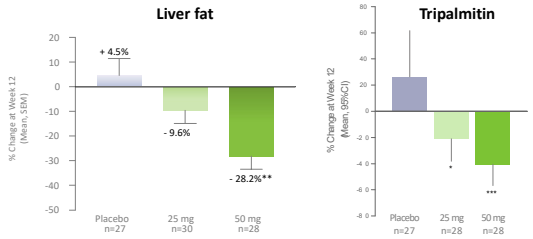
- Multicenter, randomized, placebo-controlled trial
- Primary endpoint: relative liver fat reduction by MRI-PDFF and safety
- Secondary endpoint: % pts ≥30% relative reduction of liver fat
- Serum markers included ALT, AST, tripalmitin, lipidomics, adiponectin, PRO-C3, ELF (results previously described[1])

METHODS

Study design, demographics and results of FASCINATE-1 have previously been described[1]. Population is US cohorts. Baseline blood samples from FASCINATE-1 were profiled for ~470 metabolites by LC/MS/MS. Metabolomic results from the 50mg denifanstat group (n=34) were analysed using nonlinear regression machine learning algorithms to identify a biomarker panel that predicted liver fat response as measured by MRI-PDFF.

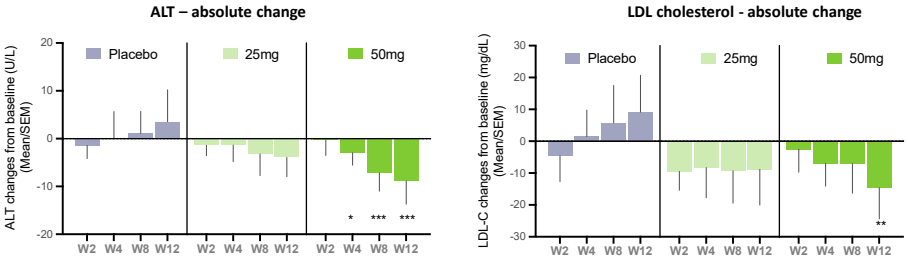
RESULTS

1 Liver fat and tripalmitin decrease with denifanstat treatment



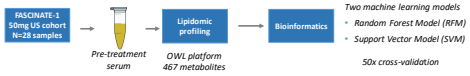
*p<0.05, **p<0.005, ***p<0.001. LSM difference versus placebo for liver fat, ANCOVA.

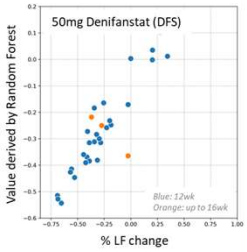
2 ALT and LDL decrease with denifanstat treatment, in a time-dependent manner



*p<0.05, **p<0.005, ***p<0.001. One sample T and Wilcoxon test

3 Baseline metabolomic signature predicts liver fat response to denifanstat





Metabolite	Class
Ursodeoxycholic acid	Bile acid
DL-2-Aminocaprylic acid	Amino Acid Derivative
Sarcosine	Amino Acid
Glycoursodeoxycholic acid	Bile acid
D(-)-2-Aminobutyric acid	Amino Acid derivative
PC(O-18:0/22:4)	Glycerophospholipid

Relative liver fat reduction	≥25%
Sensitivity	0.841
Sensitivity	0.802
Specificity	0.860
PPV	0.733
NPV	0.899

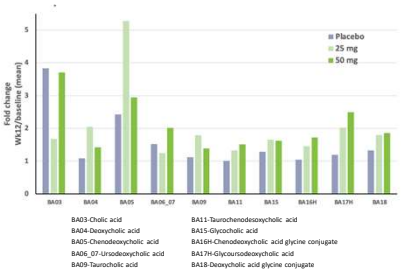
50mg data. PPV; positive predictive value, NPV; negative predictive value

4 Signature components do not change meaningfully with denifanstat treatment

Metabolite	Fold Change Week 12 vs baseline
Ursodeoxycholic acid	2.06 (0.16)
DL-2-Aminocaprylic acid	1.10 (0.13)
Sarcosine	1.30 (0.18)
Glycoursodeoxycholic acid	2.51 (0.17)
D(-)-2-Aminobutyric acid	1.09 (0.14)
PC(O-18:0/22:4)	1.03 (0.16)

Mean (SEM), 50 mg

5 Bile acids do not change meaningfully with denifanstat treatment, although non-significant increases observed



CONCLUSIONS

1. Denifanstat significantly decreased liver fat in FASCINATE-1.
2. ALT and LDL significantly decreased at week 12, in a time dependent manner. This indicates potential for improvement in both hepatic and cardiovascular health with FASN inhibition
3. A predictive metabolomic signature was identified that predicts liver fat response to denifanstat

Denifanstat is currently being tested in FASCINATE-2, a Phase 2b biopsy study in NASH. Baseline samples from FASCINATE-2 will be tested as an independent validation group for the predictive signature of liver fat response. Translation to biopsy results will also be explored.

ACKNOWLEDGEMENTS

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REFERENCES

1. Loomba et al., Gastroenterology 2021, 165, 1475-1486

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