A BASELINE METABOLOMIC SIGNATURE PREDICTS LIVER FAT (MRI-PDFF) RESPONSE FOR DENIFANSTAT, A FIRST-IN-CLASS, FATTY ACID SYNTHASE (FASN) INHIBITOR: ANALYSIS IN FASCINATE-1 AND FASCINATE-2 CLINICAL STUDIES

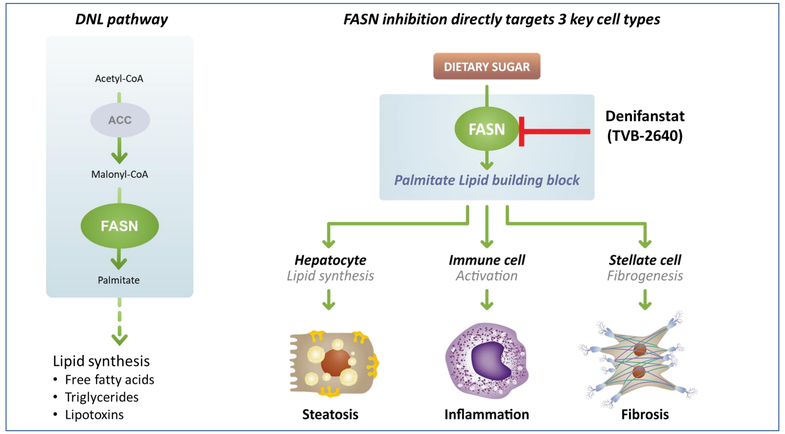
Rohit Loomba[4], Wen-Wei Tsai[1], Katharine Grimmer[1], Alithea Zetter[1], Eduardo B Martins[1], George Kemble[1], Stephen A. Harrison[3], Cristina Alonso[2], Maria E. Blanco[2], Ibon Martinez-Arranz[2], Marie O'Farrell[1]

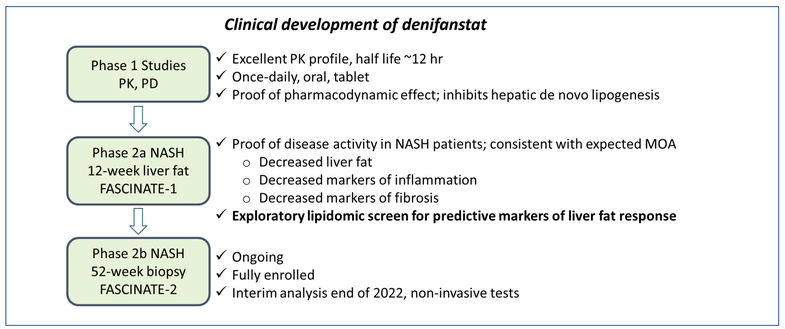
1. Sagimet Biosciences, Inc, San Mateo, CA, USA, 2. OWL Metabolomics, Derio, Bizkaia, Spain, 3. Pinnacle Clinical Research, TX, USA, 4. Division of Gastroenterology, UC San Diego School of Medicine, CA, USA.

DENIFANSTAT IS A POTENT AND SELECTIVE FASN INHIBITOR

Background

- The de novo lipogenesis (DNL) pathway is elevated in NASH patients, and converts dietary sugars to palmitate, the building block for lipid synthesis.
- Fatty acid synthase (FASN) is the last committed step in DNL and therefore provides an approach to target three hallmarks of NASH; steatosis, inflammation and fibrosis (1, 2).
- The FASN inhibitor denifanstat (TVB-2640) is in Phase 2b development for NASH.
- The Phase 2a FASCINATE-1 study showed that denifanstat significantly reduced liver fat in NASH, and decreased disease biomarkers including ALT, CK-18, PRO-C3 and lipotoxins (3). This confirmed the expected mechanism of action.
- NASH is a complex and heterogeneous disease. Enrichment of patients most likely to respond to a specific therapy is a critical part of NASH drug development and has potential to improve response rates and direct patients to the most appropriate treatment.

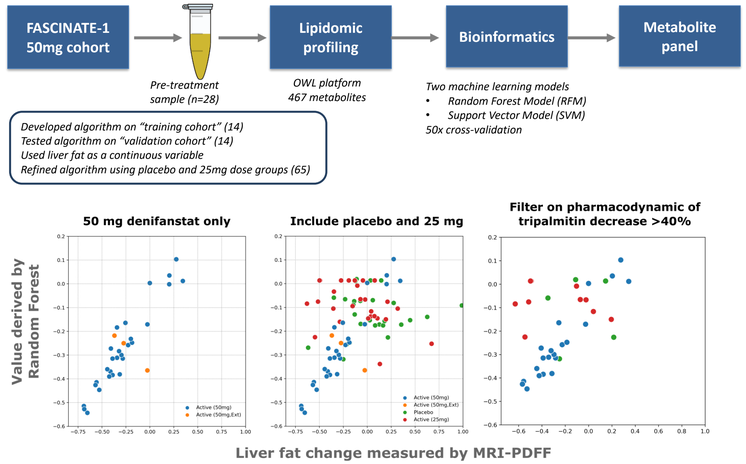




BASELINE METABOLOMIC SIGNATURE PREDICTS LIVER FAT RESPONSE TO DENIFANSTAT

Objectives

- To evaluate baseline lipidomic markers that predict liver fat response to denifanstat.
- To explore the effect of denifanstat on the circulating lipidome.



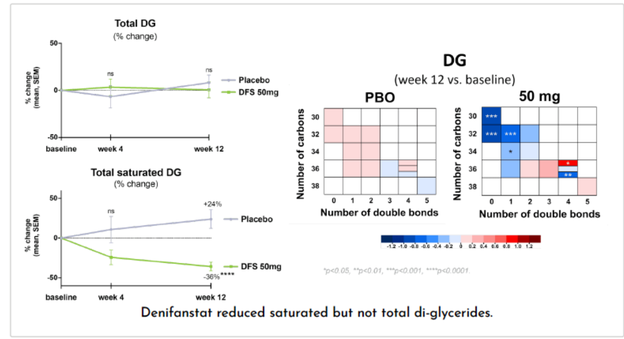
Metabolite	Class
Ursodeoxycholic acid	Bile acid
DL-2-Aminocaprylic acid	Amino Acid Derivative
Sarcosine	Amino Acid
Glycoursodeoxycholic acid	Bile acid
D(-)-2-Aminobutyric acid	Amino Acid derivative
PC(O-18:0/22:4)	Glycerophospholipid

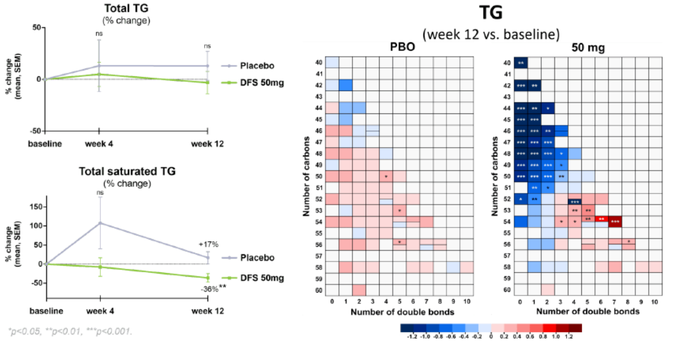
Relative liver fat reduction ≥25%	
Sensitivity	0.802
Specificity	0.860
PPV	0.733
NPV	0.899

Methods

Study design and results of the Phase 2a FASCINATE-1 study have been previously described (3). Baseline blood samples were profiled by LC/MS/MS for ~470 metabolites at OWL laboratories. Results from denifanstat 50 mg were analyzed by two different nonlinear regression machine learning algorithms (Random Forest and Support Vector Machine) to identify a biomarker panel that predicted liver fat response by MRI-PDFF. Samples were split into training and validation cohorts with 50x cross-validation using liver fat as a continuous variable. Blood samples collected at 4 and 12 weeks of denifanstat treatment were also profiled to evaluate changes in the lipidome with denifanstat treatment.

DENIFANSTAT REDUCES SATURATED DI- AND TRI-ACYLGLYEROLS AND INCREASES LONG CHAIN POLYUNSATURED FATTY ACID CONTENT





SUMMARY

- A preliminary predictive lipidomic marker panel was identified that predicts liver fat response to denifanstat. This panel will be prospectively used to predict liver fat response in Phase 2b, including week 26 interim expected by end 2022, and subsequent week 52 liver biopsy results
- Denifanstat has a favorable effect on fatty acid composition and cholesterol, indicative of cardiovascular benefit

References
(1) O'Farrell et al., 2022. Scientific Reports. doi.10.1038/s41598-022-19459-z
(2) Seyed et al., 2019. Hepatology. doi.org/10.1002/hep.31000
(3) Loomba et al., 2021.Gastroenterolog. doi:10.1053/j.gastro/2021.07.025

Acknowledgements
We are grateful to the clinical site teams and patients for participation in denifanstat clinical studies..

contact: marie.ofarrell@sagimet.com