INTERIM ANALYSIS OF FASCINATE-2: A PHASE 2B RANDOMIZED, PLACEBO CONTROLLED TRIAL DEMONSTRATES DENIFANSTAT REDUCES CIRCULATING SATURATED DIACYLGLYCEROLS AND TRIACYLGLYCEROLS, MARKERS OF LIPOTOXICITY

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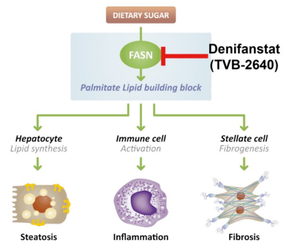
Introduction

- Denifanstat is an oral, once daily, fatty acid synthase (FASN) inhibitor currently in Phase 2b clinical trial for NASH (FASCINATE-2, NCT04906421)
- In the completed 12 week FASCINATE-1 trial, patients with NAFLD treated with denifanstat showed significant reductions in liver fat content and inflammatory and fibrosis biomarkers, including ALT, PRO-C3 and LDL-C[1]
- Increased *de novo* lipogenesis (DNL) is correlated with increased saturated lipids and ceramides, markers of lipotoxicity[2]

DNL pathway

FASN inhibition targets 3 key cell types

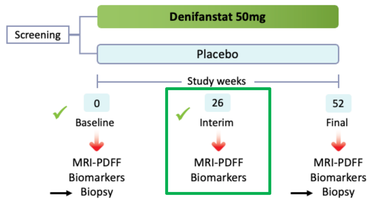


Aim

- Hypothesis: Denifanstat reduced lipotoxic saturated lipids in NAFLD patients[1]. We hypothesize that denifanstat will provide a beneficial circulating lipid profile in NASH patients with F2/F3 fibrosis
- Lipidomics were included in the interim analysis (IA) of FASCINATE-2 to examine if denifanstat can reverse lipid mediators of lipotoxicity by reducing saturated diacylglycerols (DG) and triacylglycerols (TG) and increasing polyunsaturated fatty acid (PUFA) content at week 13, prior to week 52 liver biopsy

Methods

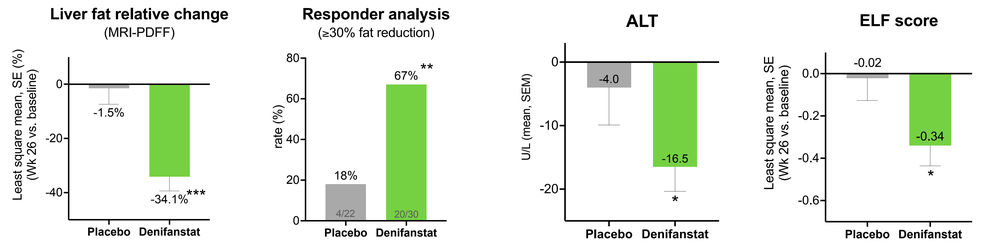
- NASH patients with biopsy confirmed F2-F3 fibrosis and NAFLD Activity Score ≥4 were enrolled in FASCINATE-2 for 52 weeks treatment. The first 52 patients on study for 26 weeks with baseline ≥8% liver fat by MRI-PDFF were included in the IA
- Comprehensive lipidomic analysis was performed for baseline, wk4 and wk13 plasma samples (OWL Metabolomics)



Results (FASCINATE-2 Interim Analysis)

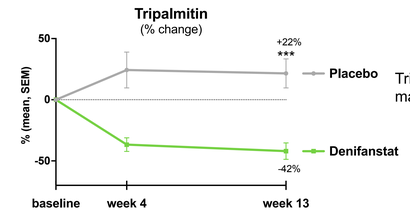
FASCINATE-2 IA population: the first 52 patients on study for 26 weeks with baseline ≥8% liver fat by MRI-PDFF

Denifanstat reduced liver fat and inflammation and fibrosis biomarkers (week 26)

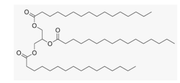


Placebo n=22, denifanstat n=30; **p<0.05, **p<0.01, ***p<0.001.*

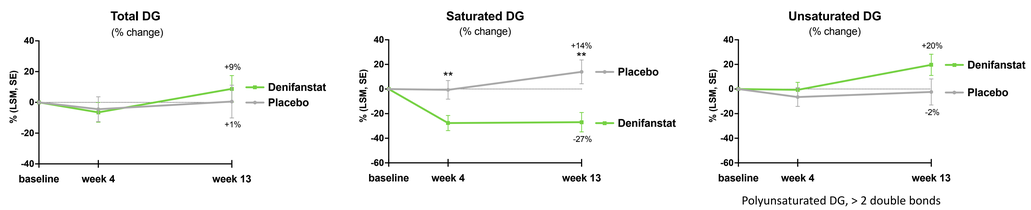
Denifanstat rapidly decreased tripalmitin



Tripalmitin: a target engagement marker for FASN inhibition

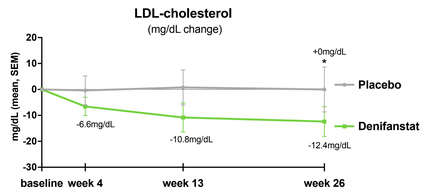


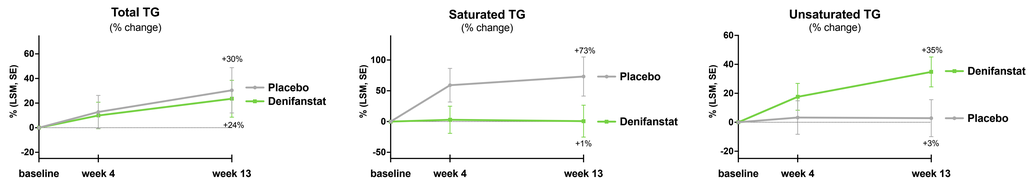
Denifanstat decreased saturated DG/TG and increased unsaturated DG/TG



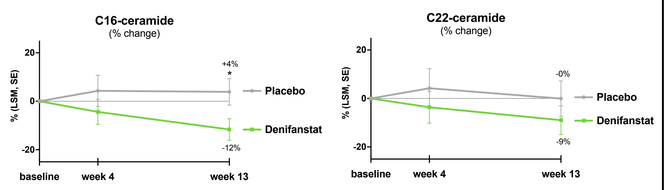
Polyunsaturated DG, > 2 double bonds

Denifanstat decreased circulating lipids associated with cardiovascular risk





Polyunsaturated TG, > 3 double bonds



Placebo n=17-18, denifanstat n=26-27 for lipid biomarkers; **p<0.05, **p<0.01, ***p<0.001.*

Conclusions

- Denifanstat showed strong improvement of key disease markers in FASCINATE-2 interim analysis
- Lipidomic results show that denifanstat was associated at week 13 with changes in circulating lipid compositions rather than altering total lipids. Reduction of saturated DG/TG and ceramides and increased incorporation of PUFA in DG/TG could potentially reduce lipotoxic drive and decrease cardiovascular risk in denifanstat-treated NASH patients
- This concordance of non-invasive metrics together with previously demonstrated biomarker changes suggest that denifanstat could have a positive impact on histological endpoints
- The FASCINATE-2 Phase 2b clinical trial of denifanstat in liver biopsy-confirmed F2-F3 NASH patients is fully enrolled and week 52 topline results, including liver biopsy, are expected in the first quarter of 2024

Acknowledgements

1) We are grateful to the patients and clinical site teams for participation in denifanstat clinical studies
2) Dr. Loomba and Dr. Harrison are scientific advisors to Sagimet Biosciences

References

1) Loomba et al., 2021. Gastroenterology. doi.org/10.1053/j.gastro.2021.07.025
2) O'Farrell et al., 2022. Scientific Reports. doi.10.1038/s41598-022-19459-z