

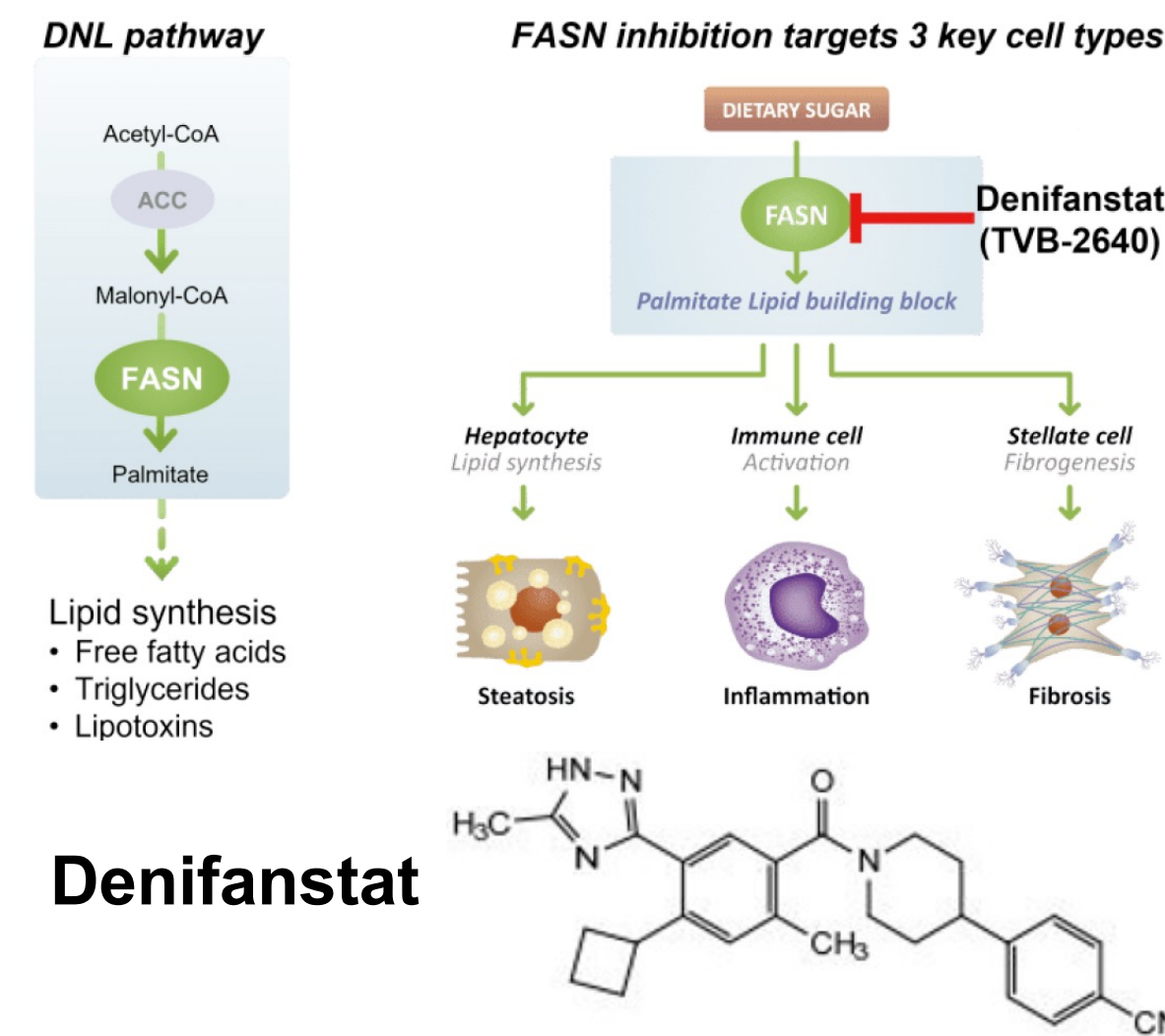
# SERUM PROTEOMIC PROFILING REVEALS THAT THE FATTY ACID SYNTHASE (FASN) INHIBITOR DENIFANSTAT PROVIDES METABOLIC BENEFITS VIA INCREASING FIBROBLAST GROWTH FACTOR 19 (FGF19) AND DECREASING 3-HYDROXY-3-METHYLGLUTARYL-COA SYNTHASE 1 (HMGCS1) IN NASH PATIENTS

Wen-Wei Tsai<sup>1</sup>, Katharine Grimmer<sup>1</sup>, Alithea Zetter<sup>1</sup>, William Beckwith<sup>2</sup>, Penn Whitley<sup>3</sup>, Eduardo B Martins<sup>1</sup>, George Kemble<sup>1</sup>, Stephen A. Harrison<sup>4</sup>, Rohit Loomba<sup>5</sup>, Marie O'Farrell<sup>1</sup>

1. Sagimet Biosciences, Inc, San Mateo, CA, USA, 2. SomaLogic, Inc, CO, USA, 3. Boulder BioConsulting, Inc, CO, USA, 4. Pinnacle Clinical Research, TX, USA, 5. Division of Gastroenterology, UC San Diego School of Medicine, CA, USA.

## Introduction

- Denifanstat (TVB-2640) 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)<sup>1</sup>

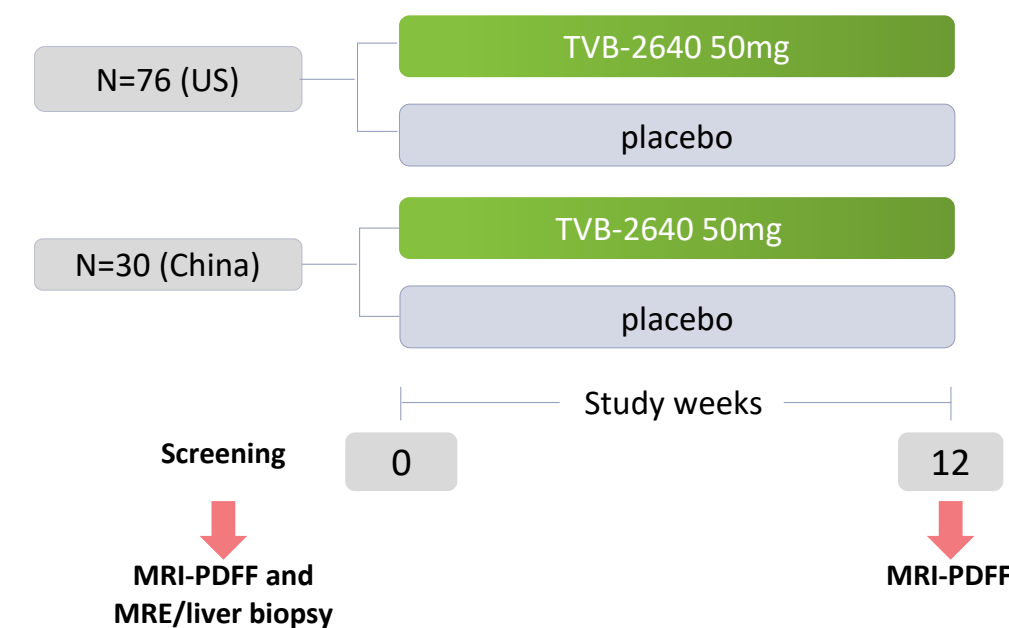


## Aims

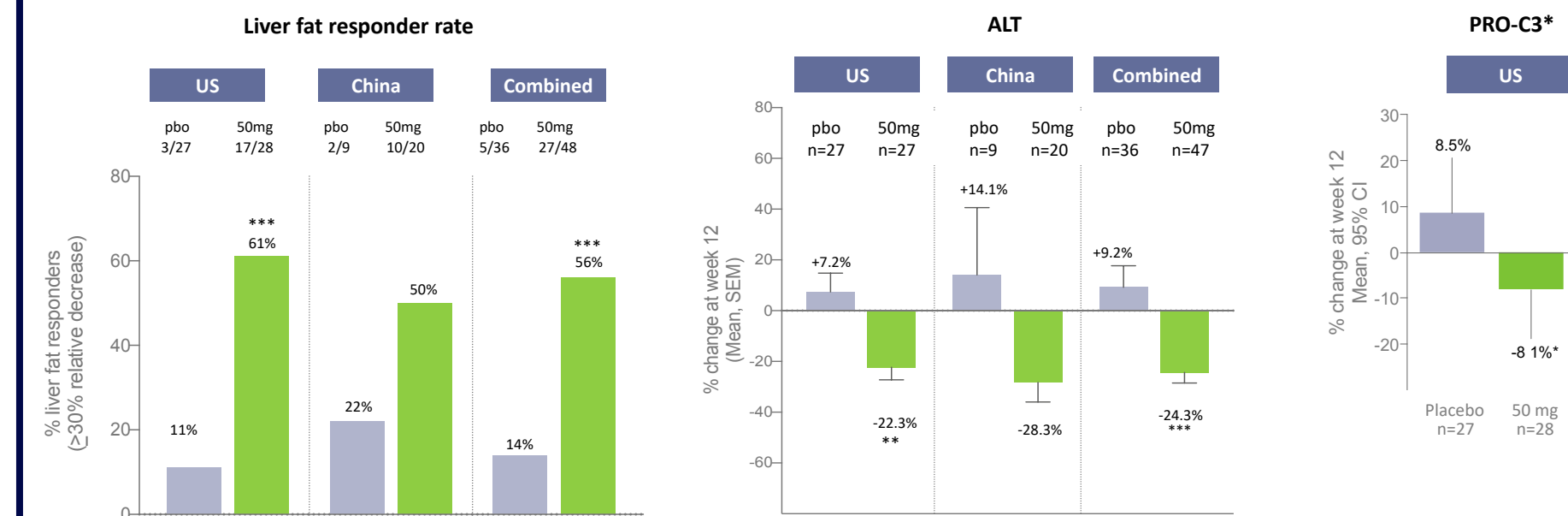
- To assess the safety and efficacy of denifanstat in a Phase 2a FASCINATE-1 study (NCT03938246)<sup>2</sup>
- To determine changes of serum proteins in response to denifanstat treatment

## Methods

- Phase 2a, multicenter, placebo-controlled study of denifanstat in patients with NASH in the US and China<sup>2</sup>
- Subjects with MRI-PDFF ≥8% and fibrosis (MRE ≥2.5 kPa or liver biopsy F1-F3) were randomized 2:1 to denifanstat 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
- Serum proteomic analysis (SomaScan assay) was performed by SomaLogic (Boulder, USA) for placebo and denifanstat 50mg-treated groups in the US cohort

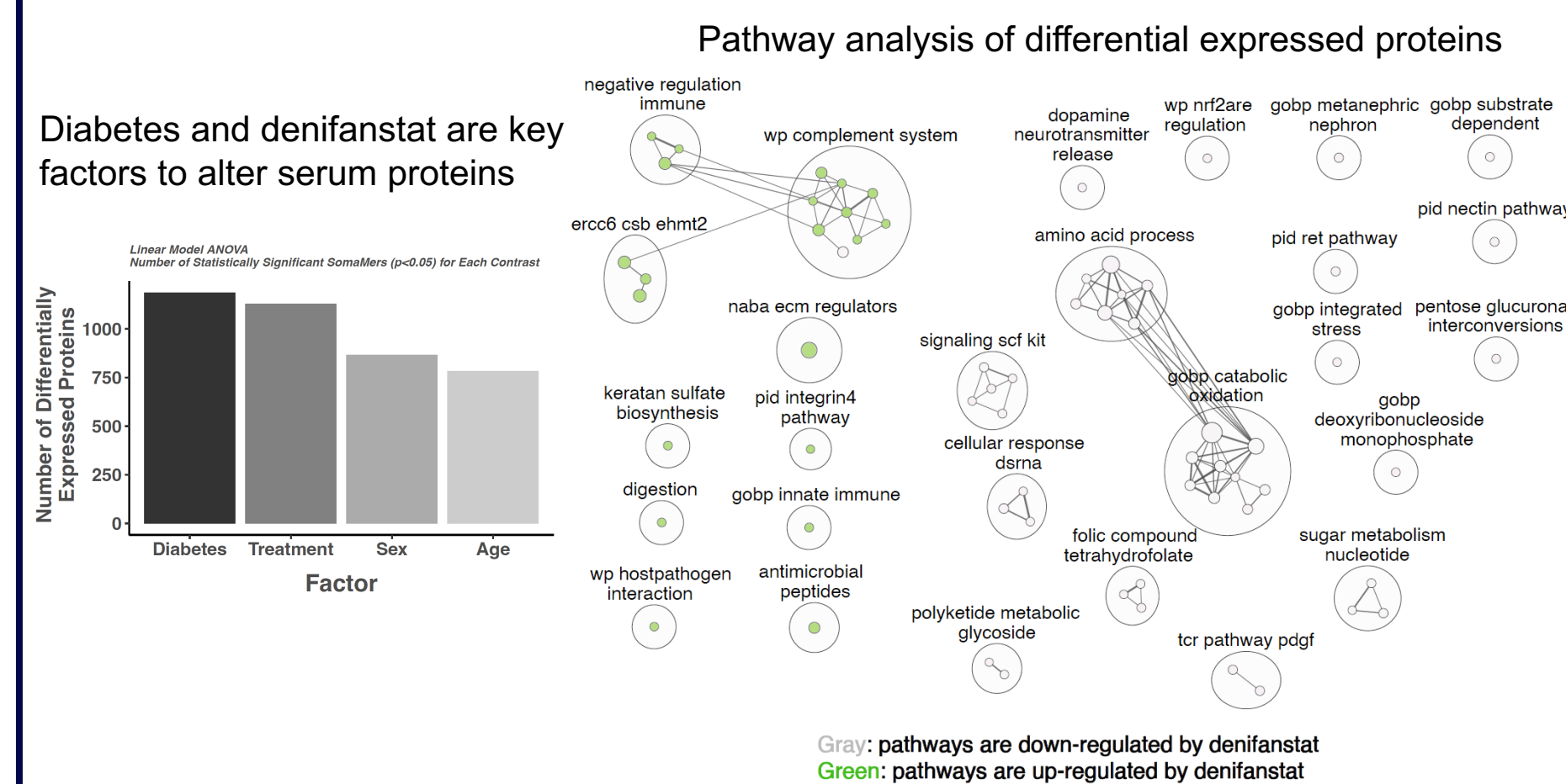


## Denifanstat potently reduced key drivers of NASH



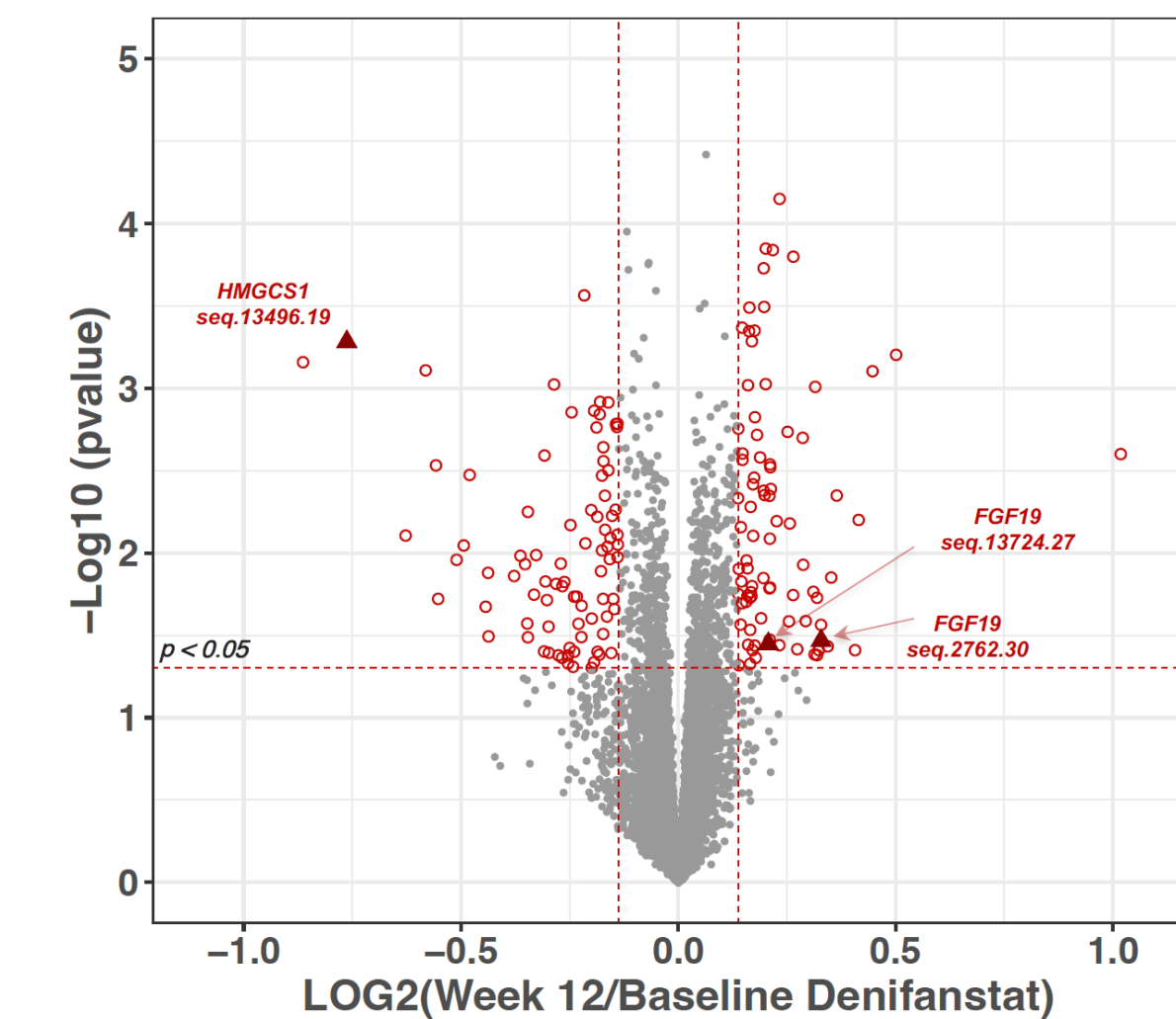
Denifanstat was well tolerated with predominantly Gr1 AE (Loomba et al., Gastroenterology, 2021)

## Enriched pathways are associated with denifanstat

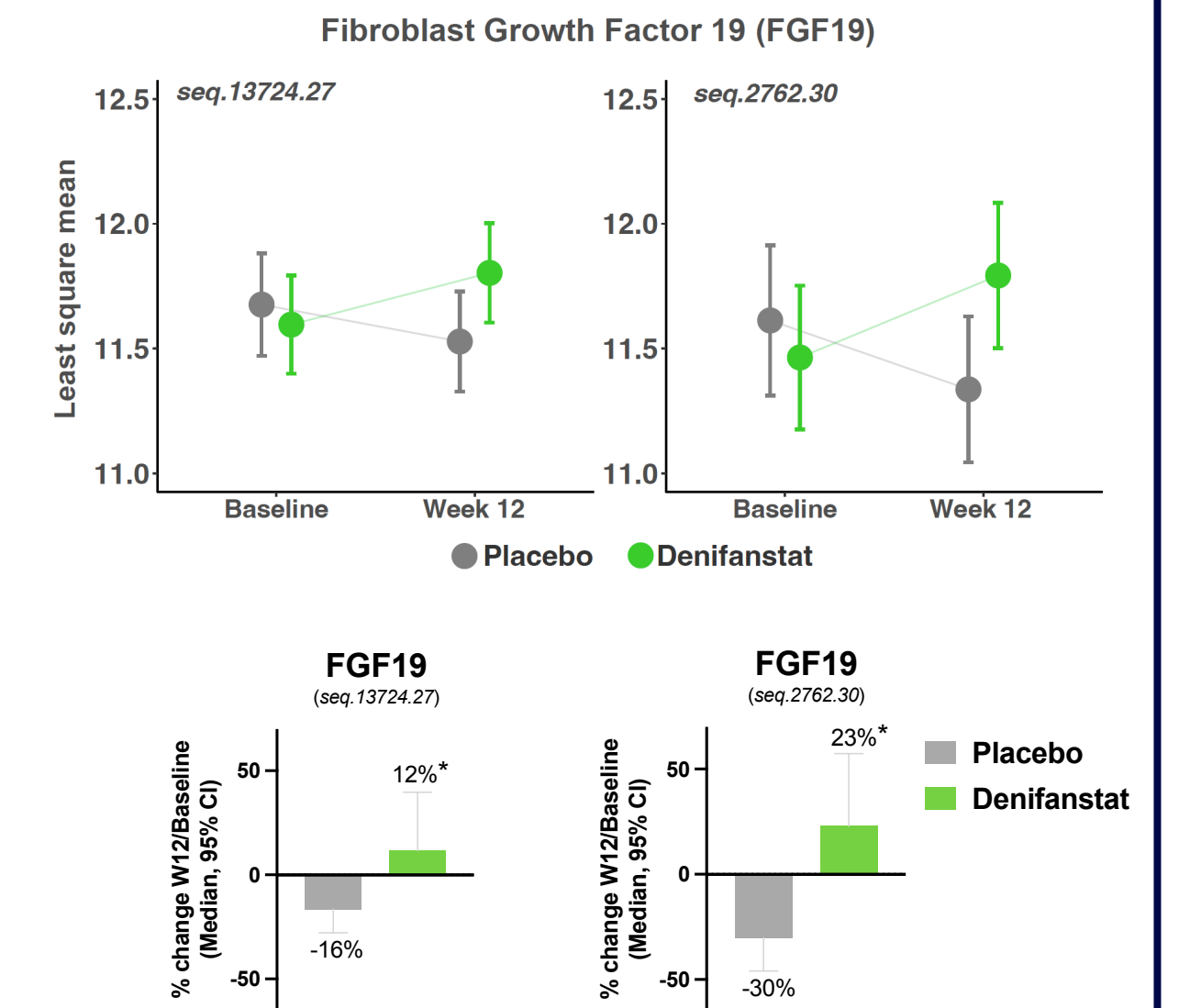


## Results

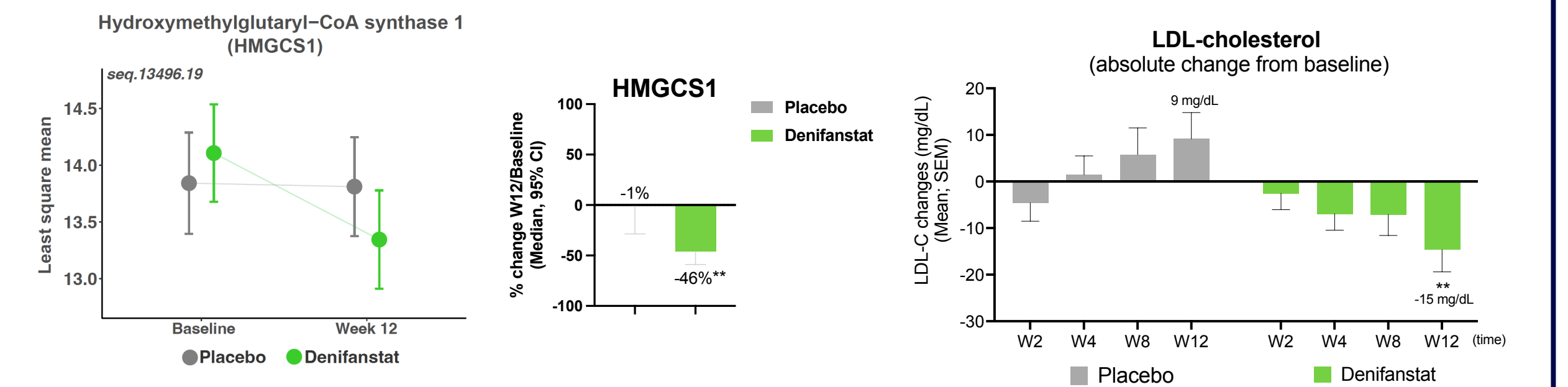
### Serum proteins changed by denifanstat



### Denifanstat increased serum FGF19



### Denifanstat reduced serum HMGCS1 proteins and LDL-cholesterol



## Conclusions

- FASCINATE-1 showed similar efficacy in two diverse patient populations: US and China
  - 61% patients in US and 50% in China achieved ≥30% reduction in liver fat
- Serum proteomic analysis revealed that FGF19 was increased by denifanstat in NASH patients in the US cohort, suggesting that denifanstat may play a role in regulating bile acid synthesis, glucose and lipid metabolism through FGF19/FGFR4 signaling
- Serum HMGCS1 was decreased by denifanstat, concomitant with reduced circulating cholesterol and LDL-C, suggesting that denifanstat decreased HMGCS1 proteins in the liver, thereby reducing cholesterol synthesis
- FASCINATE-2 Ph2b biopsy study is ongoing with NASH patients receiving denifanstat 50mg QD; interim analysis expected in Q4 2022
- Denifanstat has potential to be a foundational treatment for NASH

## References

- O'Farrell et al., 2022. Scientific Reports. doi.10.1038/s41598-022-19459-z
- Loomba et al., 2021. Gastroenterology. 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