# DENIFANSTAT (DEN), A FIRST-IN-CLASS FATTY ACID SYNTHASE (FASN) INHIBITOR, SIGNIFICANTLY REDUCES PLASMA TRIPALMITIN, A MARKER OF DE NOVO LIPOGENESIS, IN NASH PATIENTS IN THE FASCINATE-1 AND FASCINATE-2 CLINICAL STUDIES

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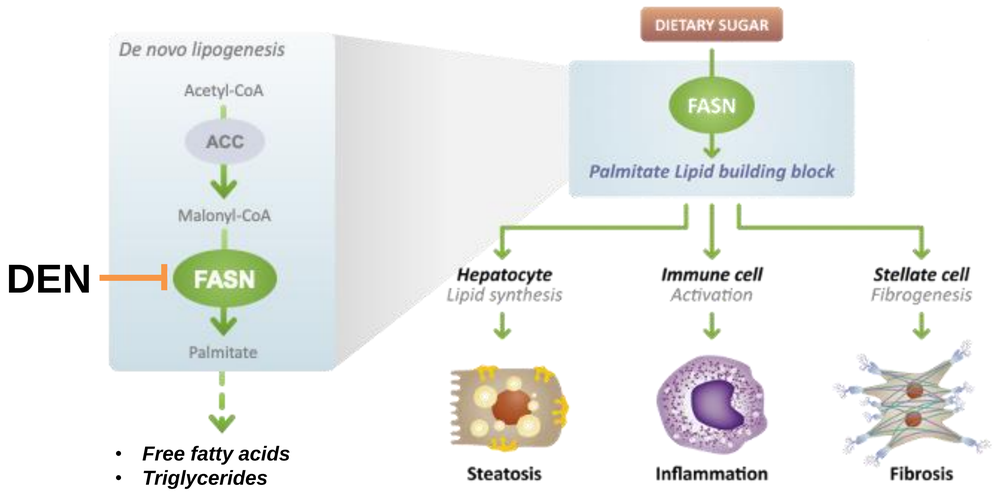
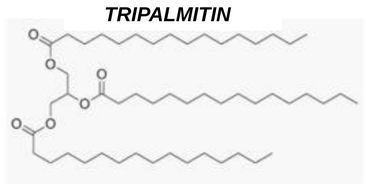
## INTRODUCTION

- **Fatty acid synthase (FASN) produces palmitate, which is further metabolized producing free fatty acids, lipotoxins and triglycerides including *tripalmitin***
- **FASN in NASH patients drives:**
  - **build up of fat in hepatocytes (steatosis)**
  - **activation of immune cells (inflammation)**
  - **activation of stellate cells (fibrogenesis)**
- **Denifanstat (DEN, TVB-2640) is a potent and selective FASN inhibitor**
- **DEN inhibits palmitate synthesis and its products, including *tripalmitin***
- **DEN reduces steatosis, inflammation and fibrotic pathways**




***TRIPALMITIN***



## METHODS

- **FASCINATE-1. A completed Ph2a study that enrolled 99 adults 18 years and older with ≥8% liver fat assessed by MRI-PDFF, and evidence of liver fibrosis by MRE ≥2.5kPa or recent liver biopsy (Loomba, et al, Gastro, 2021).**
- **FASCINATE-2. An ongoing Ph2b study that enrolled 168 adults 18 years and older with a screening biopsy showing F2-F3 fibrosis and a NAFLD activity score (NAS) ≥4 with a score of at least 1 in each of the following parameters: steatosis, ballooning degeneration and lobular inflammation. Changes in plasma tripalmitin after 4 and 13 weeks of dosing were measured in the first 52 patients on study with a baseline MRI-PDFF of ≥8% liver fat; 54% had F3 fibrosis.**

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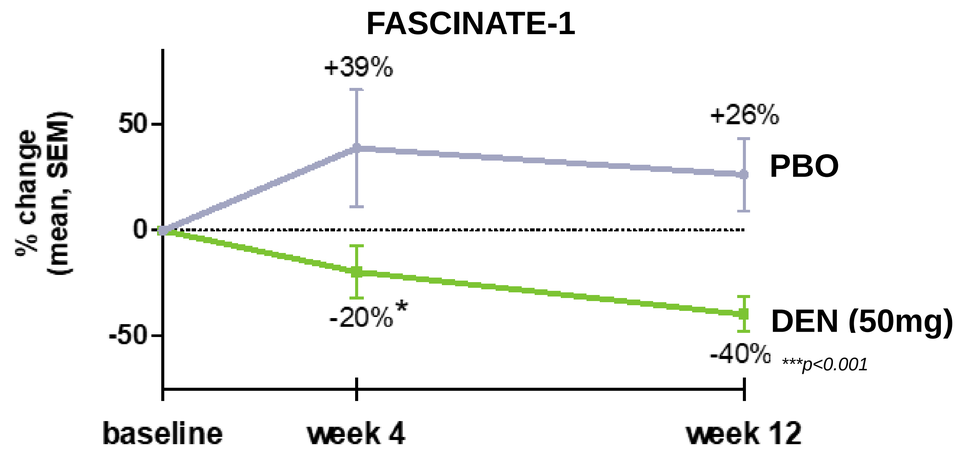
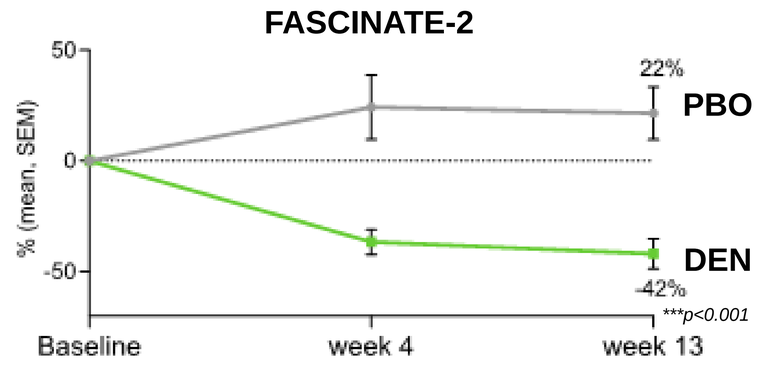
## KEY DEMOGRAPHICS

| | FASCINATE-1 | | | FASCINATE-2 (Interim cohort) | |
|---|---|---|---|---|---|
| **Median (Q1,Q3)** | **Placebo (n=31)** | **25mg (n=33)** | **50mg (n=35)** | **Placebo (n=22)** | **50mg (n=30)** |
| Age, y | 52(46,58) | 58(53, 62) | 55(44,62) | 58 (9.4) | 56.1 (12.4) |
| Male, n (%) | 14 (45.2) | 18 (54.5) | 22 (62.9) | 8 (36.4) | 13 (43.3) |
| T2D, n (%) | 17 (54.8) | 25 (75.8) | 13 (37.1) | 13 (59.1) | 21 (70.0) |
| BMI (kg/m$^2$) | 31.2 (29.3,35.1) | 34.0 (29.7,38.1) | 32.8 (29.6,35.2) | 35.1 (30.1,37.3) | 33.4 (31.1, 37.0) |
| ALT (U/L) | 25 (16,46) | 28 (23,36) | 29 (24,43) | 56 (44, 78) | 48 (37, 74) |
| AST (U/L) | 21 (15,30) | 21 (17,26) | 23 (20,30) | 36 (27, 70) | 35 (26, 57) |
| MRI-PDFF (%) | 15.3 (11.8,22.2) | 14.3 (10.4,22.3) | 15.8 (12.3,19.6) | 22.1 (17.5, 27.1) | 16.6 (12.9, 20.8) |

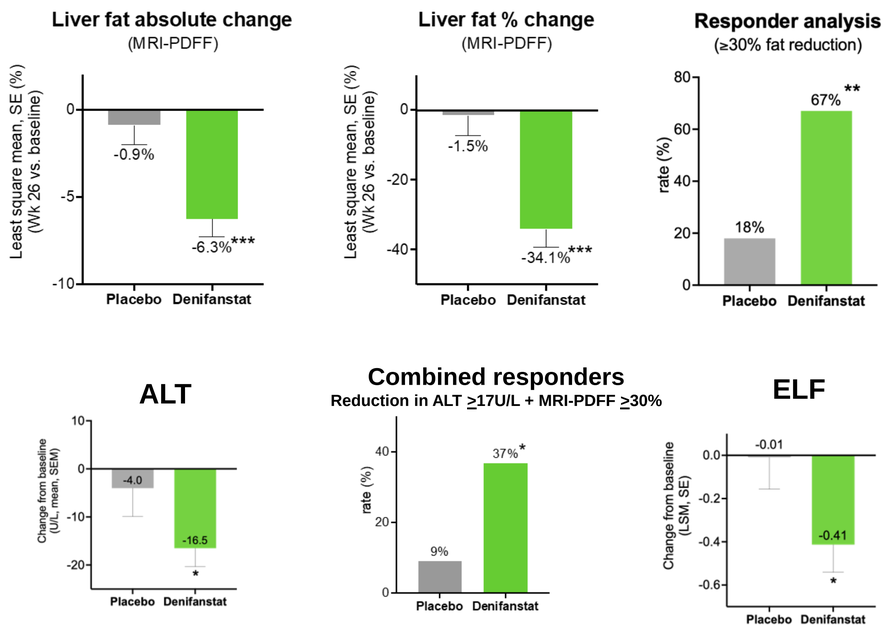
## DEN REDUCES PLASMA TRIPALMITIN – ACROSS STUDIES

**% CHANGE FROM BASELINE**




## DEN INHIBITION OF FASN REDUCES LIVER FAT AND MARKERS OF INFLAMMATION & FIBROSIS - FASCINATE-2 INTERIM ANALYSIS (26 WEEKS)




*p<0.05, **p<0.01, ***p<0.001

- **No treatment related SAEs**
- **Majority of AEs mild to moderate (Grade 1/2)**

## CONCLUSIONS

- **DEN inhibits FASN in NASH patients – measured by decreased tripalmitin**
- **Tripalmitin levels are reduced 4 weeks of treatment – continued decreases observed out to 12-13 weeks**
- **DEN reduces liver fat, liver enzyme, and ELF in biopsy-proven advanced NASH patients (46% F2 / 54% F3)**