Effects of HTD1801 (Berberine Ursodeoxycholate) on Non-Invasive Fibrosis Markers in Subjects with Presumed NASH and Type 2 Diabetes

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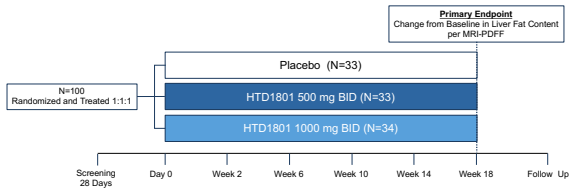
DIGITAL EXPERIENCE

INTRODUCTION

- HTD1801, an ionic salt of berberine and ursodeoxycholic acid, is thought to improve NASH through multiple pathways:
  - Improved insulin resistance
  - Activation of AMP kinase
  - Regulation of lipoprotein metabolism
- A recent phase 2 study of HTD1801 in NASH showed[1]:
  - Reduction in liver fat
  - Improvement in glycemic control
  - Weight loss
  - Reduction in liver-associated enzymes
  - Reduction in serum lipid levels
- Aim: Assess effect of HTD1801 on fibrosis biomarkers

Study Design: Phase 2 Placebo-Controlled Study



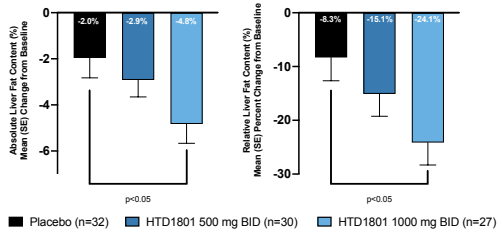
- ELF and Pro-C3 were evaluated prospectively
- AST, ALT and platelets were used to calculate FIB-4 and APRI scores post-hoc.
- Categorial shifts in ALT at Week 18 were assessed as a predictor of fibrosis
- Relevant Entry Criteria:
  - Presumed NASH with liver fat content ≥10%
  - Serum AST ≥20 U/L
  - T2DM ≥6 months, on stable therapy for at least 90 days
  - BMI >25 kg/m^2

RESULTS

Table 1. Baseline Demographics and Characteristics

Values are Mean (SD) or n (%)	Placebo N=33	HTD 1801 500 mg BID N=33	HTD 1801 1000 mg BID N=34
Age (Years)	58 (10.7)	58 (10.2)	53 (12.2)
Female – n (%)	22 (67)	26 (79)	24 (71)
Race – White n (%)	31 (94)	29 (88)	31 (91)
Ethnicity Not Hispanic/Latino n (%)	20 (61)	19 (58)	23 (68)
Body Weight (kg)	97.5 (22.6)	98.4 (23.1)	101.2 (20.3)
BMI (kg/m^2)	35.0 (6.2)	36.7 (6.9)	36.3 (6.3)
Liver Fat Content (%)	20.2 (6.2)	18.4 (6.2)	19.4 (7.0)
ALT (U/L)	54 (27)	46 (28)	62 (32)
AST (U/L)	38 (17)	36 (16)	45 (30)
LDL-c (mg/dL)	99 (36)	86 (29)	107 (35)
Triglycerides (mg/dL)	197 (83)	190 (205)	174 (77)
HbA1c (%)	7.0 (1.0)	6.9 (0.8)	7.3 (1.2)

Figure 1. Significant Reduction in LFC with HTD1801 After 18 Weeks of Treatment



p-values are obtained from an ANCOVA model with treatment group as a fixed effect, and Baseline LFC and Baseline ALT as covariates.

Figure 2. No Significant Differences Between Groups in ELF or Pro-C3

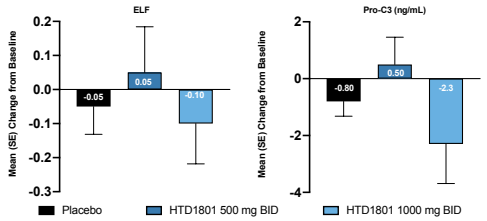
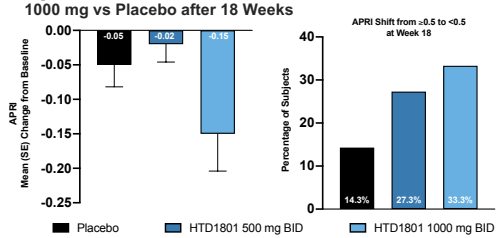
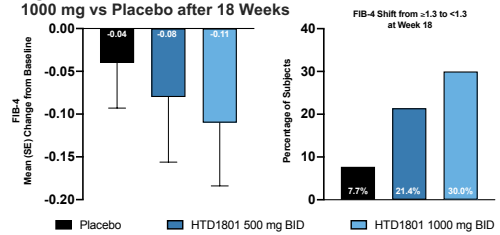


Figure 3. ~3-Fold Greater Reduction in APRI with HTD1801 1000 mg vs Placebo after 18 Weeks



- Treatment with HTD1801 1000 mg vs Placebo showed a ~2-fold greater proportion of subjects showing improvements in APRI to thresholds associated with less severe fibrosis

Figure 4. ~3-Fold Greater Reduction in APRI with HTD1801 1000 mg vs Placebo after 18 Weeks



- Treatment with HTD1801 1000 mg vs Placebo showed a ~2-fold greater proportion of subjects showing improvements in FIB-4 to thresholds associated with less severe fibrosis

Figure 5. A Greater Percentage of Subjects Treated with HTD1801 vs Placebo Achieved ALT Reductions Associated with Histologic Improvement

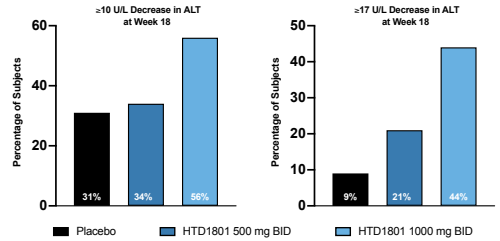


Table 2. TEAEs Occurring in ≥5% of All Subjects

	Placebo (N=33)	HTD1801 500 mg BID (N=33)	HTD1801 1000 mg BID (N=34)
Any TEAE, n (%)	20 (61)	21 (64)	26 (76)
Diarrhea	3 (9)	6 (18)	11 (32)
Nausea	3 (9)	4 (12)	7 (21)
Headache	2 (6)	1 (3)	3 (9)
Upper Respiratory Tract Infection	4 (12)	1 (3)	1 (3)
Abdominal Pain Upper	2 (6)	2 (6)	1 (3)

- Other than GI-related events, which were more common with HTD1801 1000 mg BID compared with HTD1801 500 mg BID and placebo, the incidence of TEAEs was low and generally not different from placebo
- 3 treatment-emergent serious adverse events occurred during the course of the study; all were considered unrelated to study drug
  - Myocardial Infarction (HTD1801 1000 mg BID)
  - Oxygen Saturation Decreased (HTD1801 500 mg BID)
  - Bladder transitional cell carcinoma (Placebo)

CONCLUSIONS

- Treatment with HTD1801 1000 mg for 18 weeks was associated with improvements in some non-invasive fibrosis markers compared to placebo.
- An effect of HTD1801 on histologic fibrosis will be evaluated in a future study.

REFERENCES

1. Harrison SA, Gunn N, Neff GW, Kohli A, Liu L, Flyer A, et al. Nature Communications. 2021;12(1):5503.

DISCLOSURES

Please review the published abstract for a full list of author disclosures

CONTACT INFORMATION

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