Cardiometabolic Effects of HTD1801 (Berberine Ursodeoxycholate) in Subjects with Presumed NASH and Type 2 Diabetes

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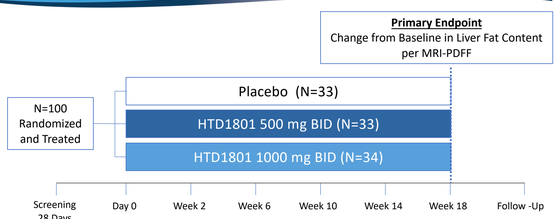
BACKGROUND

- Nonalcoholic steatohepatitis (NASH) is commonly associated cardiovascular disease.
- HTD1801, an ionic salt of berberine and ursodeoxycholic acid, may improve NASH through multiple pathways (improved insulin resistance, activation of AMP kinase, and regulation of lipoprotein metabolism).
- In an 18-week study, HTD1801 significantly improved liver fat content (LFC) assessed by magnetic resonance imaging-estimated proton density fat fraction (MRI-PDFF) and other markers of liver health in subjects with presumed NASH and type 2 diabetes mellitus (T2DM).
- This secondary analysis assessed the cardiometabolic benefits of HTD1801 given the significant co-morbidities of NASH.

Study Design and Methods



- Secondary endpoints: body weight, LDL-C, triglycerides, HDL-C, fasting glucose, HbA1c
  - Glycemic parameters and TG were further evaluated based on baseline subgroups.
- For the primary endpoint, LS Means, standard errors, and p-values are obtained from an ANCOVA model with treatment group as a fixed effect, and Baseline LFC and Baseline ALT as covariates.
- For the secondary endpoints, p-values are obtained from an ANCOVA model with treatment group as a fixed effect, and Baseline value of the given laboratory assessment as a covariate.
- For all endpoints, *p<0.05 and **p<0.01
- Statistical comparisons were not performed for subgroup analyses

Key Entry Criteria

- Presumed NASH with liver fat content ≥10%
- Serum aspartate aminotransferase (AST) ≥20 U/L
- Documented T2DM ≥6 months prior to randomization
- On stable therapy for T2DM for ≥ 90 days
- If on vitamin E, on a stable dose of ≤400 IU for ≥90 days prior to randomization
- Body mass index (BMI) >25 kg/m^2

Results

Table 1. Baseline Demographics and Characteristics

	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 – n (%)			
White	31 (94)	29 (88)	31 (91)
Black	0	3 (9)	2 (6)
Other	2 (6)	1 (3)	1 (3)
Not Hispanic or Latino – n (%)	20 (61)	19 (58)	23 (68)
Weight (kg)	97.5 (22.57)	98.4 (23.05)	101.2 (20.26)
BMI (kg/m^2)	35.0 (6.18)	36.7 (6.88)	36.3 (6.28)
Liver fat content (%)	20.2 (6.23)	18.4 (6.24)	19.4 (6.96)
ALT (U/L)	54 (26.7)	46 (27.6)	62 (31.8)
AST (U/L)	38 (17.3)	36 (15.9)	45 (29.7)
LDL-C (mg/dL)*	99 (35.8)	86 (29.4)	107 (35.3)
Triglycerides (mg/dL)*	197 (83.3)	190 (204.6)	174 (77.1)
HbA1c (%)	7.0 (1.05)	6.9 (0.85)	7.3 (1.16)
Fasting insulin (uIU/mL)	45.7 (34.64)	30.8 (15.74)	32.9 (16.43)
Fasting glucose (mg/dL)	136 (44.1)	140 (39.9)	155 (46.3)

Values are Mean (SD) unless otherwise specified. LDL and triglycerides based on modified efficacy set (Placebo, n=33; HTD1801 500 mg BID, n=31; HTD1801 1000 mg BID, n=30). All other parameters are based on the safety set.

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

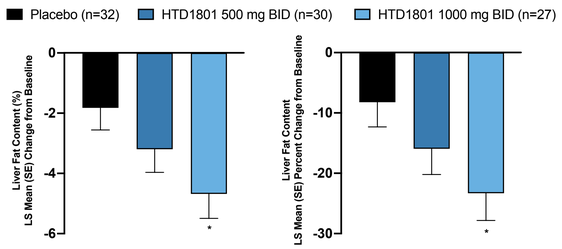
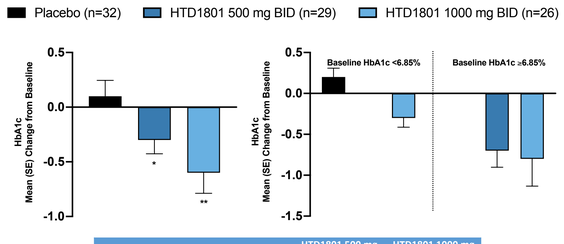


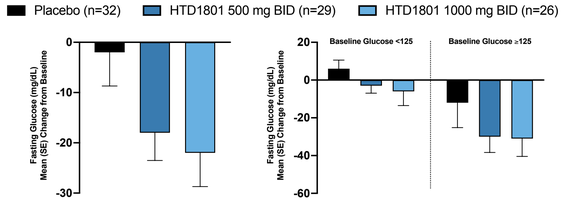
Figure 2. Significant Reduction in HbA1C with HTD1801 at 18 Weeks



Baseline Values	Placebo		HTD1801 500 mg BID		HTD1801 1000 mg BID	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Baseline HbA1c <6.85	15	6.3 (0.6)	16	6.2 (0.4)	13	5.9 (0.4)
Baseline HbA1c ≥6.85	17	7.7 (1.6)	13	6.7 (0.8)	14	7.4 (1.3)

- The magnitude of HbA1c reduction was greater in subjects with elevated baseline HbA1c

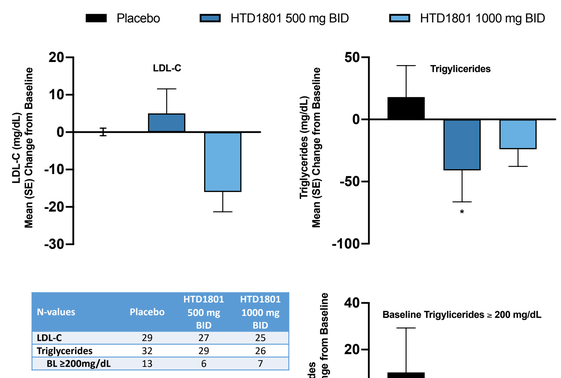
Figure 3. Reduced Fasting Glucose with HTD1801 at 18 Weeks



Baseline Values	Placebo		HTD1801 500 mg BID		HTD1801 1000 mg BID	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Baseline Glucose <125 mg/dL	17	114 (20)	13	105 (15)	11	100 (25)
Baseline Glucose ≥125 mg/dL	15	151 (50)	16	132 (32)	16	149 (39)

- The magnitude of glucose reduction was greater in subjects with elevated baseline glucose

Figure 4. Change from Baseline to Week 18 in Lipids



N-values	Placebo	HTD1801 500 mg BID	HTD1801 1000 mg BID
LDL-C	29	27	25
Triglycerides	32	29	26
BL ≥200mg/dL	13	6	7

- No changes observed in HDL-C across treatment groups

Figure 5. Significant Weight Loss with HTD1801 1000 mg at 18 Weeks

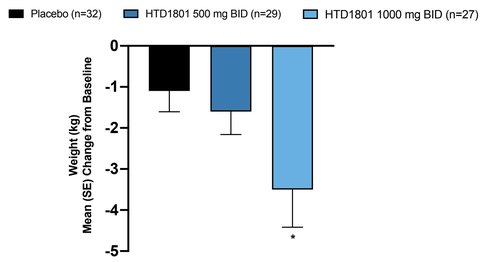


Table 2. Treatment-Emergent Adverse Events Occurring in ≥5% of All Subjects

	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 1000mg BID compared with HTD1801 500mg BID and placebo, the incidence of treatment-emergent adverse events (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 for 18 weeks reduced LFC and showed improvements in markers of cardiovascular risk.
- HTD1801 was safe and generally well tolerated
- The pleiotropic effects of HTD1801, including hepatic and metabolic effects, make it a promising and novel therapeutic agent for the treatment of NASH
- Future trials to further evaluate the benefit of HTD1801 in subjects with NASH are warranted.

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