Berberine Ursodeoxycholate (HTD1801) Improves Glycemic Control in Patients with Type 2 Diabetes: Double-Blind, Placebo-Controlled, Phase 2 Study

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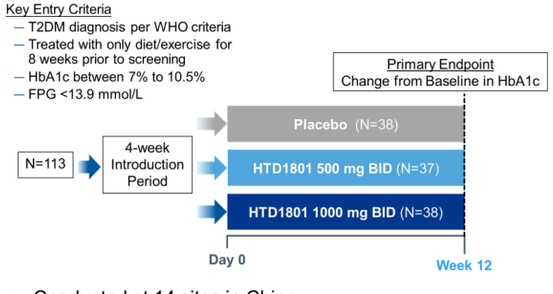
HIGHTIDE

BACKGROUND

- Berberine ursodeoxycholate (HTD1801), is a first-in-class gut-liver anti-inflammatory metabolic modulator which targets multiple pathways pivotal to metabolic regulation
- In patients with obesity and hypercholesteremia HTD1801 treatment for 28 days resulted in reductions in triglycerides and non-high-density lipoprotein cholesterol (non-HDL-C)[1]
- In patients with metabolic dysfunction-associated steatohepatitis (previously known as nonalcoholic steatohepatitis) HTD1801 treatment for 18 weeks resulted in significant decreases in liver fat content along with significant reductions in HbA1c and weight[2]
- Based on these findings, a Phase 2, double-blind, placebo-controlled study evaluating the efficacy and safety of HTD1801 was conducted in Chinese patients with type 2 diabetes mellitus (T2DM) with the primary objective of improving glycemic control

STUDY DESIGN AND METHODS



- Conducted at 14 sites in China
- Patients were randomized 1:1:1 to each of the treatment groups
  - Randomization stratification included HbA1c (above/below 8.5%) and controlled attenuation parameter ([CAP] above/below 274 dB/m)
- LS Means are derived from a mixed-effects model for repeated measures with:
  - Dependent variable: measured value or change from baseline
  - Independent variables: treatment group, measurement time point, and interaction between treatment group and measurement time point
  - Covariates: randomized stratification factors and subject baseline measurements
- For dichotomous endpoints, a CMH model was used and the randomization stratification factor was CAP

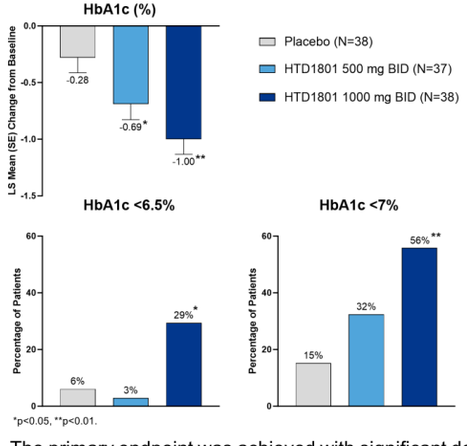
RESULTS

Demographics and Baseline Characteristics

	Placebo (N=38)	HTD1801 500 mg BID (N=37)	HTD1801 1000 mg BID (N=38)
Age, y	52.45 (11.25)	54.86 (10.09)	55.57 (10.47)
Males, n (%)	27 (71.1)	19 (51.4)	26 (68.4)
Han, n (%)	36 (94.7)	36 (97.3)	38 (100.0)
Weight, kg	69.88 (12.37)	66.08 (9.84)	69.97 (11.49)
BMI, kg/m^2	25.49 (3.78)	25.25 (3.92)	25.80 (3.38)
Diabetes duration, y	2.13 (1.96)	2.20 (1.94)	3.08 (2.56)
CAP, dB/m	270.7 (57.98)	268.9 (50.59)	260.5 (59.30)
HbA1c, %	8.32 (0.89)	8.18 (0.73)	8.18 (0.82)
FPG, mmol/L	9.19 (2.24)	8.70 (2.31)	8.87 (1.84)
Fasting insulin, pmol/L	72.33 (58.71)	64.55 (33.88)	62.87 (28.87)
Non-HDL-C, mmol/L	3.57 (0.86)	3.50 (0.90)	3.71 (0.93)
LDL-C, mmol/L	3.08 (0.77)	3.03 (0.73)	3.15 (0.75)
Triglycerides, mmol/L	2.14 (0.92)	2.07 (1.29)	2.17 (1.28)

BMI: body mass index; FPG: fasting plasma glucose; LDL-C: low density lipoprotein cholesterol; Values are Mean (SD) unless otherwise noted.

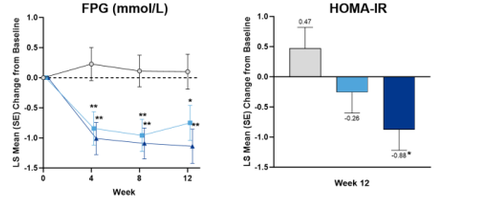
Treatment with HTD1801 Resulted in Significant Improvements in HbA1c Compared to Placebo



*p<0.05, **p<0.01.

- The primary endpoint was achieved with significant dose-dependent reductions in HbA1c after 12 weeks of treatment with HTD1801 compared to placebo
  - Baseline HbA1c levels were 8.3%, 8.2%, and 8.2% for placebo, HTD1801 500 mg BID and 1000 mg BID, respectively; Week 12 levels were 8.0%, 7.2%, and 6.8%
- At Week 12, 56% of patients treated with HTD1801 1000 mg BID achieved HbA1c <7% and 29% achieved HbA1c <6.5%

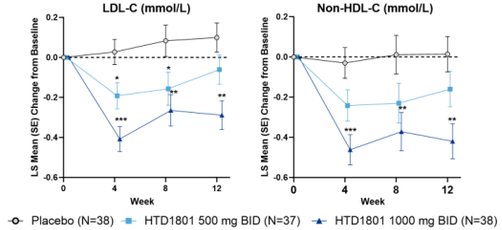
Significant Reductions in Fasting Plasma Glucose and HOMA-IR with HTD1801 Treatment



*p<0.05, **p<0.01.

- Significant improvements in fasting plasma glucose (FPG) were observed as early as Week 4 with HTD1801 in contrast to worsening/no change with placebo
- HOMA-IR was reduced significantly compared to placebo at Week 12 and reduced by 24% compared with baseline

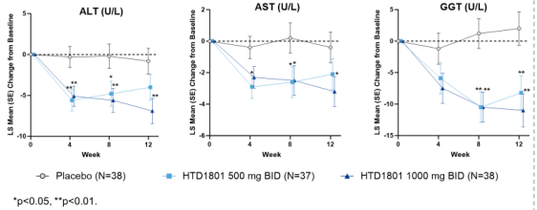
Significant Reductions in LDL-C and Non-HDL-C with HTD1801 Treatment



*p<0.05, **p<0.01, ***p<0.0001.

- Significant dose-dependent improvements in LDL-C and non-HDL-C were observed as early as Week 4 with HTD1801 in contrast to worsening/no change with placebo

Significant Reductions in ALT, AST, and GGT with HTD1801 Treatment



*p<0.05, **p<0.01.

- Significant improvements in ALT, AST, and GGT were observed as early as Week 4 with HTD1801 in contrast to worsening/no change with placebo

Incidence of TEAEs was Low and Events Were Generally Mild in Severity

Preferred Term, n (%)	Placebo (N= 38)	HTD1801 500 mg BID (N=37)	HTD1801 1000 mg BID (N=38)
Subjects with ≥1 TEAE	**15 (39.5)**	**17 (45.9)**	**27 (71.1)**
Hyperlipidemia	2 (5.3)	3 (8.1)	3 (7.9)
Sinus bradycardia	1 (2.6)	2 (5.4)	3 (7.9)
Proteinuria	1 (2.6)	0	3 (7.9)
Ventricular extrasystoles	1 (2.6)	0	3 (7.9)
Upper respiratory tract infection	1 (2.6)	2 (5.4)	2 (5.3)
Hyperuricemia	0	1 (2.7)	2 (5.3)
Constipation	0	1 (2.7)	2 (5.3)
Supraventricular extrasystoles	0	0	2 (5.3)
Hyponatremia	0	2 (5.4)	0
Urinary tract infection	0	2 (5.4)	0

Treatment-emergent adverse events (TEAEs) occurring ≥2 patients.

- The occurrence of hypoglycemia, nausea, and diarrhea was rare, with only one instance of each reported
- One SAE occurred during the study: an event of retinal hemorrhage in a patient randomized to HTD1801 500 mg BID deemed unlikely related to treatment

SUMMARY

- The primary endpoint was achieved with significant dose-dependent reductions in HbA1c after 12 weeks of treatment with HTD1801
- Reductions in HbA1c were paralleled by significant improvements in FPG and HOMA-IR after treatment with HTD1801
- HTD1801 treatment resulted in improvements in lipids that were observed as early as Week 4 and sustained through the duration of treatment
- HTD1801 was found to be generally safe and well tolerated
- This proof-of-concept study supports HTD1801 as a novel oral treatment option for management of glycemic control
- These findings will be further evaluated in Phase 3 studies in patients with T2DM

References

1. Di Bisceglie AM, et al. Lipid Health Dis. 2020;19(1):1-10.
2. Harrison SA, et al. Nat Commun. 2021;12(1):5503.

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