Berberine Ursodeoxycholate (HTD1801) Improves Key Glycemic and Cardiometabolic Parameters Across the Type 2 Diabetes Disease Spectrum

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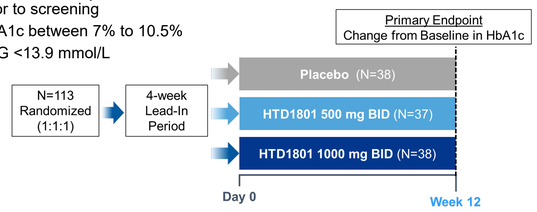
BACKGROUND

- Berberine ursodeoxycholate (HTD1801) is a new molecular entity designed as a gut-liver anti-inflammatory metabolic modulator in development for the treatment of chronic liver and metabolic diseases
- HTD1801 has been previously shown to be safe and versatile in evaluations of hypercholesteremia, metabolic-dysfunction associated steatohepatitis, and primary sclerosing cholangitis[1-3]
- In a Phase 2, placebo-controlled, double-blind study in patients with type 2 diabetes mellitus (T2DM), treatment with HTD1801 for 12 weeks resulted in significant dose-dependent improvements in key glycemic parameters (NCT06411275)[4]

The aim of this study was to evaluate the effectiveness of HTD1801 in patients with T2DM across the disease spectrum

METHODS

Key Entry Criteria
- T2DM diagnosis per WHO criteria
- Treated with only diet/exercise for 8 weeks prior to screening
- HbA1c between 7% to 10.5%
- FPG <13.9 mmol/L

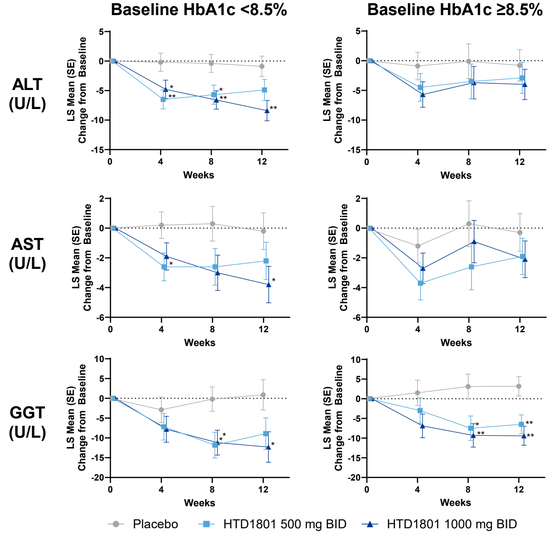


- Secondary endpoints included evaluation of other key parameters including fasting plasma glucose (FPG), lipid metabolism, and liver biochemistry
- For this analysis, patients were assigned to high/low risk disease severity groups based on a baseline HbA1c above/below 8.5%
  - 35% of patients had HbA1c ≥8.5% at baseline
- Change from baseline values are reported as LS Mean (SE)
- P-values and LS Means are derived from a mixed-model of repeated measures
  - *p<0.05, **p<0.01

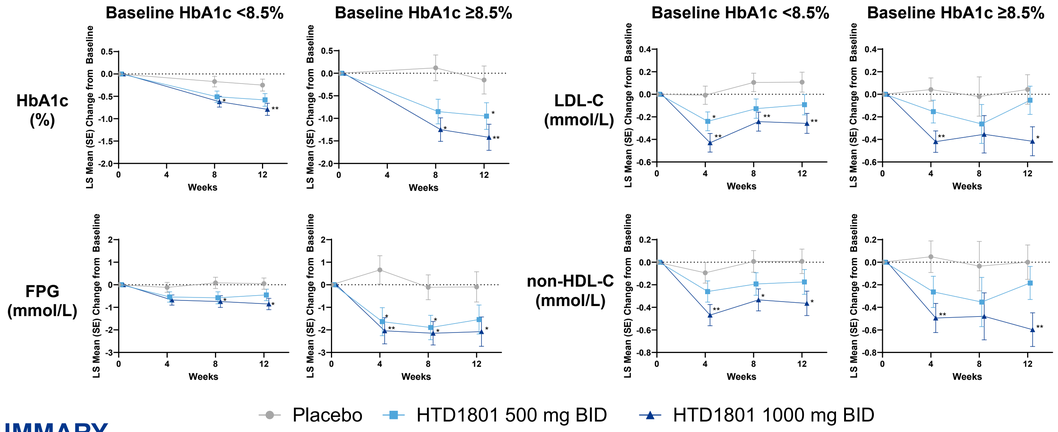
RESULTS

	Baseline HbA1c <8.5%			Baseline HbA1c ≥8.5%		
	Placebo (n=25)	HTD1801 500 mg BID (n=24)	HTD1801 1000 mg BID (n=24)	Placebo (n=13)	HTD1801 500 mg BID (n=13)	HTD1801 1000 mg BID (n=13)
Age, years	52 (10)	55 (11)	56 (10)	53 (13)	54 (9)	54 (12)
Female, n (%)	6 (24)	11 (46)	5 (21)	5 (39)	7 (54)	7 (50)
Weight, kg	72 (13)	65 (8)	71 (11)	66 (11)	69 (12)	69 (13)
T2DM duration, years	2 (2)	2 (2)	3 (3)	2 (2)	3 (2)	3 (3)
CAP, dB/m	273 (48)	270 (50)	257 (66)	267 (75)	267 (53)	266 (47)
HbA1c, %	7.8 (0.3)	7.7 (0.4)	7.7 (0.4)	9.4 (0.6)	9.0 (0.4)	9.1 (0.5)
FPG, mmol/L	8 (1)	8 (1)	8 (1)	11 (3)	10 (3)	10 (2)
HOMA-IR	4 (3)	3 (1)	3 (2)	4 (2)	5 (5)	5 (2)
LDL-C, mmol/L	3 (1)	3 (1)	3 (1)	4 (1)	3 (1)	3 (1)
Non-HDL-C, mmol/L	3 (1)	3 (1)	4 (1)	4 (1)	4 (1)	4 (1)
ALT, U/L	24 (11)	25 (14)	25 (19)	23 (9)	29 (22)	24 (12)
AST, U/L	21 (6)	23 (8)	23 (13)	19 (5)	27 (20)	22 (7)
GGT, U/L	34 (28)	46 (69)	35 (24)	34 (18)	33 (16)	31 (20)

HTD1801 Resulted in Improvements in Liver Biochemistry in Both Disease Severity Groups



HTD1801 Resulted in Significant Improvements in Glycemic Parameters and Lipid Metabolism in Both Disease Severity Groups



SUMMARY

- Regardless of baseline disease severity, HTD1801 treatment for 12 weeks resulted in significant, dose-dependent improvements in key glycemic and cardiometabolic parameters
- While improvements were observed in both subgroups, the magnitude of improvements in cardiometabolic parameters was greater in those with more severe disease based on HbA1c
- Despite most patients having normal liver biochemistry at baseline, improvements in markers of liver injury (ALT, AST) and oxidative stress (GGT) were observed with HTD1801 across the disease spectrum
- HTD1801 shows promise as a new therapy for the treatment of T2DM and continues to be evaluated for T2DM in multiple ongoing Phase 3 studies (NCT06415773, NCT06350890, and NCT06353347)

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; 3. Kowdley K, et al. Am J Gastro. 2022;117:1805-1815; 4. Ji L, et al. Diabetologia. 2023;66(Suppl 1):1-536.

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