Symphony 1: A Randomized, Placebo-Controlled Phase 3 Study of Berberine Ursodeoxycholate (HTD1801) as Monotherapy in Patients with Type 2 Diabetes

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BACKGROUND

- HTD1801 is a first-in-class gut liver anti-inflammatory metabolic modulator that activates AMPK and inhibits the NLRP3 inflammasome
- These pathways converge to increase fatty acid oxidation and glucose utilization while reducing insulin resistance and chronic inflammation
- In a Phase 2 study in patients with type 2 diabetes (T2DM), HTD1801 resulted in significant improvements in key glycemic and cardiometabolic parameters and markers of inflammation[1]

The objective of this Phase 3 study was to evaluate the efficacy and safety of HTD1801 compared to placebo in patients with T2DM inadequately controlled with diet and exercise alone

METHODS

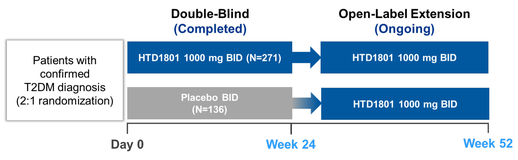
Phase 3 Study Design: Symphony 1 (NCT06350890)

Overview

- Key entry criteria included:
  - Diagnosis of T2DM per WHO criteria
  - HbA1c between 7.0%-10.5%
  - FPG ≤13.9 mmol/L

Primary Endpoint

Change from baseline in HbA1c at Week 24



- A randomized, double-blind, placebo-controlled study conducted at 56 sites in China
- Randomization stratification factors were hs-CRP (≤3 mg/L and >3 mg/L) and HbA1c (<8.5% and ≥8.5%)

Primary Endpoint

- p-values are based on a MMRM analysis with the response variable as the dependent variable; treatment group, measurement time point, interaction term between treatment group and measurement time point, and hs-CRP as independent variables; and the patient's baseline value as the covariate

Secondary Endpoints

- Multiplicity considerations: type 1 error in secondary efficacy measures was controlled using a sequential gatekeeping strategy
- Continuous variables were analyzed similarly to the primary analysis with randomization stratification factors as independent variables
- Dichotomous endpoints were analyzed with a CMH model using the randomization stratification factors in the model

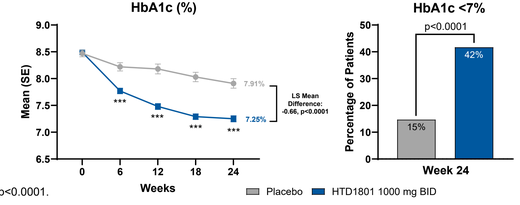
RESULTS

Demographics and Baseline Characteristics

	Placebo (N=136)	HTD1801 1000 mg BID (N=271)
Age, years	55.1 (10.5)	54.5 (10.3)
Female, n (%)	57 (42)	106 (39)
Asian, n (%)	136 (100)	271 (100)
Weight, kg	69.3 (11.0)	71.2 (12.0)
Diabetes duration, years	3.0 (3.4)	2.9 (2.9)
HbA1c, %	8.5 (0.7)	8.5 (0.8)
Fasting glucose, mg/dL	163.4 (27.5)	167.9 (34.3)
2h-PPG, mg/dL	292.0 (48.6)	294.6 (57.9)
hs-CRP, mg/L	1.8 (2.0)	2.4 (7.0)
LDL-c, mg/dL	113.7 (33.9)	112.1 (33.3)
Non-HDL-c, mg/dL	142.1 (36.7)	142.5 (36.1)
GGT,U/L	34.2 (28.9)	33.6 (25.4)

Values are Mean (SD) unless otherwise indicated.

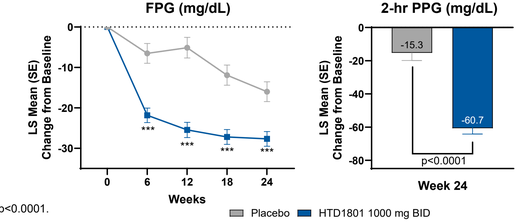
The Primary Endpoint Was Achieved with Significant Improvement in HbA1c with HTD1801 Compared to Placebo



***p<0.0001.

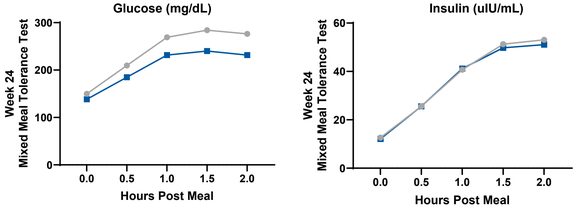
- Significant reductions in HbA1c were observed as early as Week 6 with HTD1801 and continued to improve through Week 24
- At Week 24, nearly 3x as many patients achieved HbA1c less than 7% with HTD1801 compared to placebo

Significant Improvements in Fasting and Postprandial Glucose were Observed with HTD1801 Compared to Placebo



***p<0.0001.

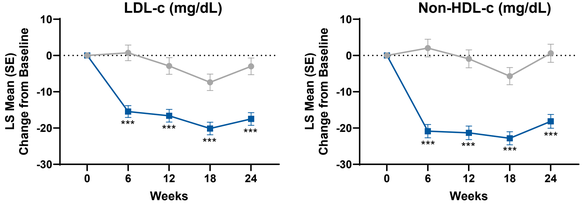
HTD1801 Effectively Lowered Postprandial Glucose Without Increasing Insulin



Based on an ANCOVA analysis.

Placebo HTD1801 1000 mg BID

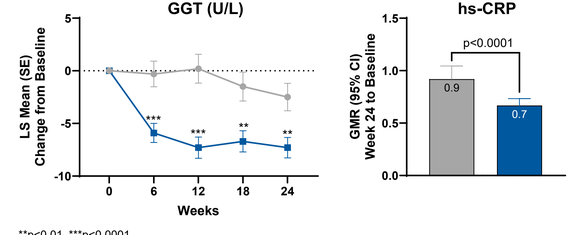
Significant Reductions in LDL-c and non-HDL-c were Observed with HTD1801 Compared to Placebo



***p<0.0001.

Placebo HTD1801 1000 mg BID

Significant Improvements in Markers of Inflammation were Observed with HTD1801 Compared to Placebo[2,3]



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

Placebo HTD1801 1000 mg BID

HTD1801 was Safe and Generally Well Tolerated

- 10% and 20% of TEAEs were deemed related to placebo or HTD1801
- One HTD1801-treated patient experienced a mild TEAE of hypoglycemia
- SAEs were infrequent with a greater incidence with placebo (5.9%) versus HTD1801 (2.6%)*
- No deaths occurred in this study

TEAEs Occurring in ≥5% of Patients

Preferred Term, n (%)	Placebo (N=136)	HTD1801 1000 mg BID (N=271)
Any TEAE	91 (66.9)	203 (74.9)
Diarrhea	1 (0.7)	25 (9.2)
Hyperlipidemia	12 (8.8)	23 (8.5)
Sinus bradycardia	9 (6.6)	19 (7.0)
Nephrolithiasis	11 (8.1)	17 (6.3)
Hyperuricemia	7 (5.1)	17 (6.3)
Upper respiratory tract infection	7 (5.1)	17 (6.3)
Hypertriglyceridemia	10 (7.4)	12 (4.4)
Urinary tract infection	9 (6.6)	10 (3.7)

*SAEs occurred in the following SOC: Cardiac disorders (3 [0.7%]); Infections and infestations (3 [0.7%]); Nervous System disorders (3 [0.7%]); Injury, poisoning and procedural complications (2 [0.5%]); Ear and labyrinth disorders (1 [0.2%]); and Musculoskeletal and connective tissue disorders (1 [0.2%]).

SUMMARY

- The primary endpoint was achieved with HTD1801-treated patients achieving a statistically significant and clinically meaningful improvement in HbA1c compared to placebo
  - Reductions in HbA1c were paralleled by significant improvements in both FPG and PPG
  - Improvements in PPG are likely through improved insulin sensitivity rather than increases in insulin
- Beyond glucose control, significant improvements in lipid metabolism and inflammatory parameters were also observed, demonstrating the broad metabolic benefits of HTD1801
- HTD1801 was found to be safe and generally well tolerated
- The open-label extension phase of Symphony 1 is ongoing to confirm the longer-term benefits and safety of HTD1801

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