Efficacy of Berberine Ursodeoxycholate (HTD1801) in Chinese and Western Patients with T2DM with or without MASH

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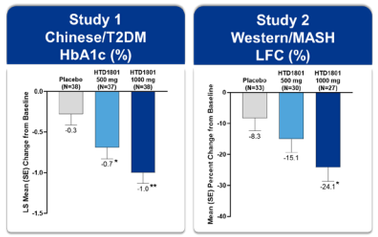
HIGHTIDE

BACKGROUND

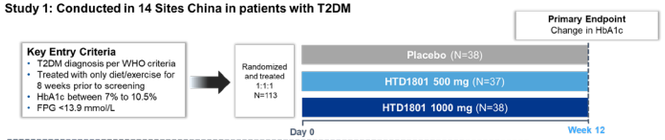
- HTD1801 is active through multiple pathways including activation of AMP kinase and inhibition of the NF-κB signaling pathway
- Patients with multiple metabolic syndromes (e.g. T2DM, MASLD, hyperlipidemia) are at a higher risk of clinical outcomes with each additional syndrome[1-4]
- HTD1801 met the primary endpoint in two placebo-controlled Phase 2 studies:
  - In Study 1, HTD1801 treatment resulted in significant improvements in HbA1c[5]
    - Improvements were also observed in lipids, and liver biochemistry
  - In Study 2, HTD1801 treatment resulted in significant improvements in LFC[6]
    - Improvements were also observed in HbA1c, lipids, and body weight



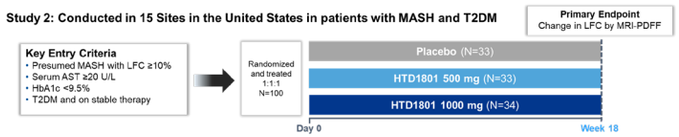
The purpose of this analysis was to compare the effects of HTD1801 in Chinese and Western patients with T2DM +/- MASH

METHODS

Study 1: Conducted in 14 Sites China in patients with T2DM



Study 2: Conducted in 15 Sites in the United States in patients with MASH and T2DM



Both studies utilized twice daily dosing (e.g., 500 mg= 500 mg twice daily)

References

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Abbreviations

ALT: alanine aminotransferase; AMPK: adenosine monophosphate activated protein kinase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase; HbA1c: hemoglobin A1C; LDL-C: low-density lipoprotein cholesterol; LFC: liver fat content; MASLD: metabolic dysfunction-associated steatotic liver disease; MASH: metabolic dysfunction-associated steatohepatitis; T2DM: type 2 diabetes mellitus

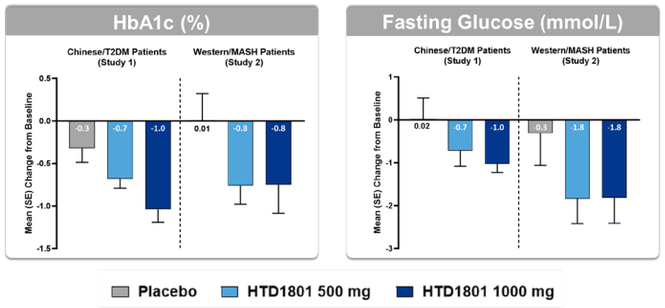
RESULTS

Baseline Characteristics were Generally Comparable Between Populations

Mean (SD)	Chinese/T2DM (Study 1)			Western/MASH (Study 2)		
	Placebo (N=38)	HTD1801 500 mg (N=37)	HTD1801 1000 mg (N=38)	Placebo (N=15)	HTD1801 500 mg (N=16)	HTD1801 1000 mg (N=19)
Age, yrs	52.5 (11.2)	54.9 (10.1)	55.6 (10.5)	56.3 (9.7)	59.5 (7.8)	51.1 (12.0)
Females, n (%)	11 (28.9)	18 (48.6)	12 (31.6)	13 (86.7)	13 (81.3)	16 (84.2)
Diabetes Duration, yrs	2.1 (2.0)	2.2 (1.9)	3.1 (2.6)	8.9 (5.5)	10.7 (5.7)	6.3 (4.6)
Weight, kg	69.9 (12.4)	66.1 (9.8)	70.0 (11.5)	92.8 (16.1)	90.8 (19.4)	102.0 (19.9)
HbA1c, %	8.3 (0.9)	8.2 (0.7)	8.2 (0.8)	7.9 (0.8)	7.6 (0.6)	8.2 (0.6)
FPG, mmol/L	9.2 (2.2)	8.7 (2.3)	8.9 (1.8)	8.2 (3.2)	9.1 (2.2)	10.4 (1.9)
LDL-C, mmol/L	3.1 (0.8)	3.0 (0.7)	3.2 (0.8)	2.5 (1.1)	2.3 (0.9)	3.0 (0.8)
Non-HDL-C, mmol/L	3.6 (0.9)	3.5 (0.9)	3.7 (0.9)	3.5 (1.1)	3.5 (1.9)	4.0 (0.9)
AST, U/L	20.3 (5.6)	24.4 (13.1)	22.6 (11.3)	42.7 (19.0)	35.6 (14.4)	48.7 (33.0)
ALT, U/L	23.8 (10.0)	26.6 (16.8)	24.8 (16.1)	57.7 (28.5)	48.1 (19.2)	62.6 (34.4)
GGT, U/L	34.2 (24.6)	41.4 (56.5)	33.5 (22.6)	60.4 (47.3)	65.6 (49.7)	80.0 (71.0)
Concomitant Anti-Diabetic Medication Use						
Metformin, n (%)	0	0	0	14 (93.3)	13 (81.3)	14 (73.7)
GLP-1RA, n (%)	0	0	0	6 (40.0)	3 (18.8)	3 (15.8)
Insulin(s), n (%)	0	0	0	6 (40.0)	1 (6.3)	4 (21.1)

- To better match the populations, Study 2 was limited to patients with baseline HbA1c ≥7% (N=50)
- Body weight was ~30 kg greater in Western vs Chinese patients; HbA1c was higher in Chinese patients
- As expected with MASH, Western patients had elevated liver biochemistry compared to Chinese patients
- Majority of Western patients were on anti-diabetic medications

HTD1801 Treatment Resulted in Substantial Reductions in Glycemic Parameters Across Both Populations



- Similar, clinically relevant improvements in HbA1c were observed in both study populations
- Greater improvements in fasting glucose were observed in Western patients

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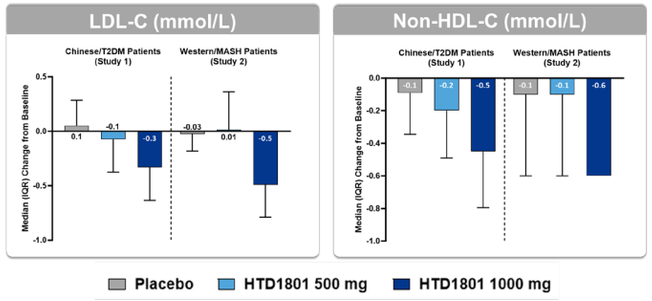
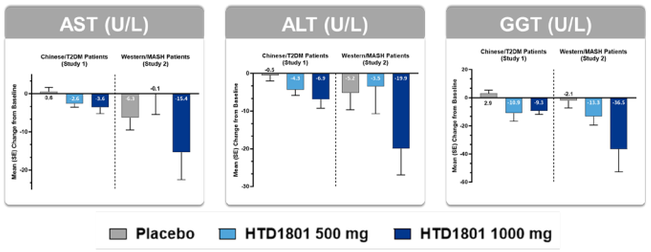
HTD1801 Treatment Resulted in Improvements in Lipid Parameters Across Both Populations



HTD1801 Treatment Resulted in Reductions in Markers of Hepatic Inflammation and Damage Across Both Populations



SUMMARY

- While the two populations are ethnically distinct with related but different diseases (MASH vs T2DM), improvements in key measures of glycemic, cardiometabolic, and hepatic benefit with HTD1801 treatment were observed in both populations
- T2DM and MASH are highly interrelated with the presence of each potentiating risk
  - Patients with both T2DM and MASH are at higher risk of histologic progression in MASH, cardiovascular outcomes, hepatic outcomes, and all-cause mortality
- HTD1801 offers holistic benefits that are observed in both Chinese and Western patients that address core aspects of both T2DM and MASH
- HTD1801 is currently under evaluation in ongoing Phase 3 studies of T2DM (NCT06353347, NCT06350890, and NCT06415773) and a paired biopsy Phase 2b study of MASH and T2DM or prediabetes (NCT05623189)