Berberine Ursodeoxycholate (HTD1801) Provides a Unique Therapeutic Approach for Patients with Metabolic Liver Disease and Severe Insulin Resistance

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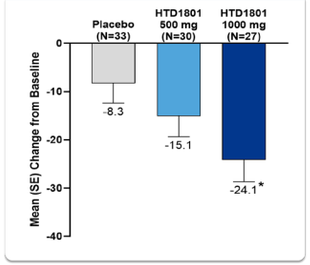
HIGHTIDE

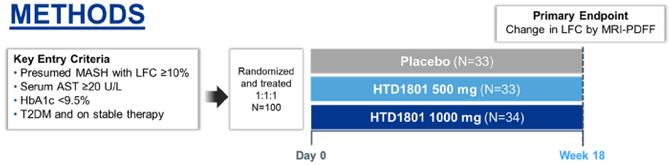
BACKGROUND

- HTD1801 is active through multiple pathways including activation of AMP kinase and inhibition of the NF-κB signaling pathway
- HTD1801 enhances the utilization of glucose and fats, thereby reducing insulin levels and improving insulin resistance
  - Mitigating metabolic complications associated with hyperinsulinemia
- Patients with MASLD and metabolic syndromes are at higher risk of clinical outcomes with each additional syndrome[1,2]
- Hyperinsulinemia is an important risk factor for metabolic diseases, and insulin resistance is a shared pathogenic mechanism[3-5]
- In patients with MASH and T2DM, HTD1801 treatment resulted in significant improvements in LFC, HbA1c, lipids, and body weight (NCT03656744)[6]
- The objective of this post-hoc analysis was to evaluate the effects of HTD1801 response based on degree of insulin resistance

Relative Change in LFC (%) Overall Population



METHODS



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

- Ongoing studies are evaluating doses of HTD1801 1000 mg and higher; therefore, this analysis focused on the 1000 mg dose group compared to placebo
- Patients were then analyzed by subgroups defined by degree of insulin resistance based on baseline fasting insulin (FIN) levels (above and below 40 µIU/mL)
- No adjustments were made for use of exogenous insulin or any other medications for T2DM treatment

References

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3. Weidmann P, et al. J Hypertens Suppl. 1995;13(2)S65-72.
4. Payne JY, et al. Hepatol Commun. 2023;7(1):e0019.
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6. Harrison SA, et al. Nature Commun. 2021;12(1):5503.

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Abbreviations

AMPK: adenosine monophosphate activated protein kinase; LFC: liver fat content; MASLD: metabolic dysfunction-associated steatotic liver disease; MASH: metabolic dysfunction-associated steatohepatitis; MRI-PDFF: magnetic resonance imaging-derived proton density fat fraction; T2DM: type 2 diabetes mellitus

RESULTS

Baseline Characteristics were Generally Similar Across Insulin Subgroups

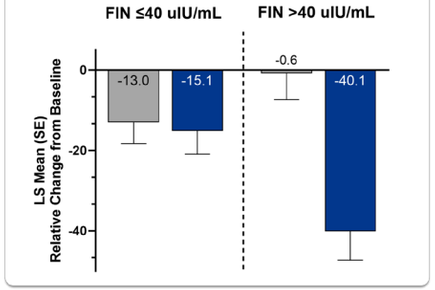
	FIN ≤40 µIU/mL		FIN >40 µIU/mL	
	Placebo (n=20)	HTD1801 1000 mg (n=19)	Placebo (n=12)	HTD1801 1000 mg (n=8)
Age, years	59.1 (10.8)	55.0 (10.5)	54.8 (9.5)	45.6 (12.3)
Female, %	60	68	75	75
Hispanic or Latino, %	30	32	58	38
LFC, %	20.3 (4.9)	20.9 (8.3)	20.2 (8.4)	16.6 (2.2)
HbA1c, %	6.9 (0.9)	7.1 (1.2)	7.0 (1.3)	7.4 (0.9)
Weight, kg	94.6 (16.1)	99.1 (20.1)	104.1 (30.5)	108.1 (25.1)
HOMA-IR	8.6 (3.7)	9.2 (5.7)	33.1 (22.6)	20.6 (4.2)
ALT, U/L	54.8 (27.6)	57.4 (29.7)	54.2 (27.4)	69.8 (37.5)
AST, U/L	39.3 (18.9)	38.9 (21.3)	36.8 (15.3)	62.8 (47.1)
GGT, U/L	89.4 (132.2)	54.1 (43.7)	40.0 (12.6)	114.1 (74.4)
LDL-C, mg/dL	97.6 (36.7)	107.7 (42.6)	94.0 (25.2)	98.1 (28.7)
Triglycerides, mg/dL	174.6 (71.1)	178.9 (88.0)	228.1 (94.6)	185.6 (57.1)
Concomitant Anti-Diabetic Medication Use				
Any Medication, %	100	89	83	100
GLP-1 Receptor Agonists, %	45	16	33	38
SGLT-2 Inhibitors, %	10	16	8	13
Metformin, %	90	79	83	63
Insulin(s), %	30	21	17	25

Values are Mean (SD) unless otherwise noted.

- With the exception of HOMA-IR (which includes insulin in the calculation)
- Concomitant anti-diabetic medications were commonly utilized across all subgroups consistent with patients with T2DM

HTD1801 Resulted in Improvements in Liver Fat Content with Greater Improvements in Patients with Severe Insulin Resistance

Liver Fat Content (%)



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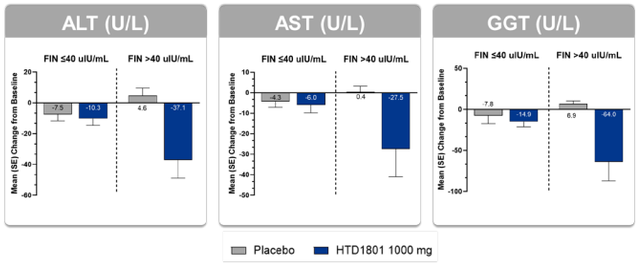
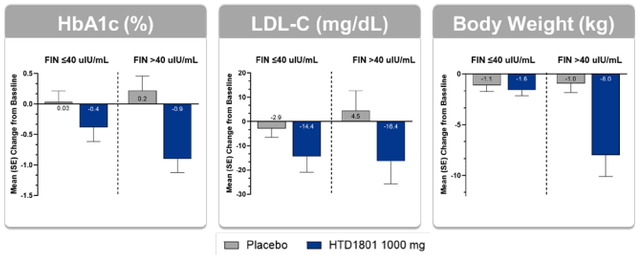
HTD1801 Resulted in Improvements Across Multiple Liver Parameters with Greater Improvements in Patients with Severe Insulin Resistance



HTD1801 Resulted in Improvements in Cardiometabolic Parameters with Greater Improvements in Patients with Severe Insulin Resistance



SUMMARY

- Improvements in liver fat content, markers of liver injury, and cardiometabolic endpoints were observed with HTD1801 regardless of baseline insulin levels
  - Greater improvements were observed in patients with severe insulin resistance
- These data, while limited to a small number of subjects per subgroup, suggest that HTD1801 can alleviate the metabolic inhibitory effects caused by hyperinsulinemia, leading to greater metabolic benefits
- HTD1801 may offer a unique therapeutic approach for individuals with MASH and co-morbid T2DM including those with severe insulin resistance who may be at a greater risk of developing comorbidities
- HTD1801 is currently under evaluation in an ongoing paired biopsy Phase 2b study of MASH and T2DM or prediabetes (NCT05623189) and three ongoing Phase 3 studies of T2DM (NCT06353347, NCT06350890, and NCT06415773)