Efficacy of Berberine Ursodeoxycholate (HTD1801) Compared to Ongoing Use of GLP-1 Receptor Agonists in Patients with MASH and T2DM

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HIGHTIDE

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 shown to significantly reduce liver fat content (LFC) as determined by MRI-PDFF and important cardiometabolic endpoints in an 18-week, placebo-controlled, Phase 2 study in patients with MASH and T2DM (NCT03656744)[1]
- GLP-1 receptor agonists (RA) are widely used for the treatment of T2DM and obesity and are under investigation for treatment of MASH

The purpose of this post-hoc comparative efficacy analysis was to evaluate ongoing GLP-1RA use compared to newly initiated HTD1801 treatment in patients with MASH and T2DM

METHODS

- One hundred patients were randomized and treated with HTD1801 1000 mg BID (N=34), HTD1801 500 mg BID (N=33), or placebo (N=33) for 18 weeks
- Key entry criteria included LFC per MRI ≥10%, BMI ≥25 kg/m^2, and clinically documented diagnosis of T2DM
- The primary endpoint was change in LFC by MRI-PDFF
- Patients were able to continue concomitant therapy for T2DM if they were on a stable dose for ≥90 days prior to randomization
- This analysis compared patients who were randomized to HTD1801 and were not treated concomitantly with GLP-1RAs with patients randomized to placebo receiving GLP-1RAs
  - HTD1801 1000 mg BID: n=28; HTD1801 500 mg BID: n=27; Matching placebo BID + GLP-1RA: n=13

RESULTS

Demographics and Baseline Characteristics

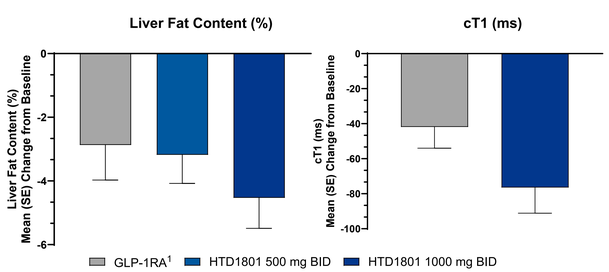
	GLP1-RA[1] (n=13)	HTD1801 500 mg BID (n=27)	HTD1801 1000 mg BID (n=28)
Age, years	53.5 (10.2)	57.9 (11.0)	53.4 (12.2)
Female, n (%)	9 (27)	21 (64)	22 (65)
White, n (%)	12 (36)	23 (70)	26 (77)
Hispanic or Latino, n (%)	5 (15)	8 (24)	8 (24)
Weight, kg	101.1 (19.2)	100.4 (22.5)	99.4 (17.9)
LFC, %	19.7 (5.0)	19.0 (6.6)	19.6 (7.5)
cT1, ms	950.1 (83.6)	-	943.7 (96.8)
ALT, U/L	43.1 (17.0)	46.2 (28.6)	62.7 (34.2)
AST, U/L	32.5 (8.9)	36.7 (17.1)	46.6 (32.0)
HbA1c, %	7.4 (1.0)	6.9 (0.9)	7.3 (1.2)
FPG, mg/dL	133.7 (32.0)	135.7 (29.6)	156.4 (46.3)
LDL-C, mg/dL	80.9 (29.1)	84.6 (26.0)	107.2 (34.8)
Triglycerides, mg/dL	167.9 (74.9)	157.0 (81.8)	184.2 (89.0)

[1]Placebo randomized patients treated concomitantly with GLP-1RAs.
cT1 segmented analysis was evaluated after study completion for HTD1801 1000 mg BID or placebo only.
Values are Mean (SD) unless otherwise noted.

GLP-1RA Medications Utilized

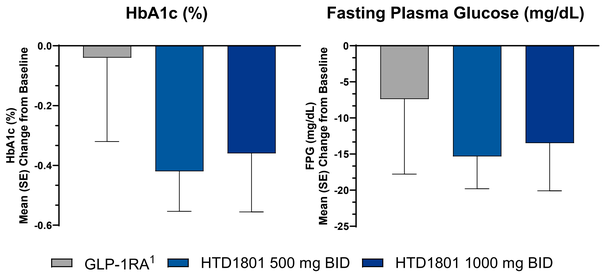
	n (%)
GLP-1 Receptor Agonists	13 (100)
Dulaglutide	6 (46)
Liraglutide	3 (23)
Exenatide	3 (23)
Semaglutide	1 (8)

HTD1801 Resulted in Greater Improvements in LFC (MRI-PDFF) and Fibroinflammation (cT1) Compared to GLP-1RAs



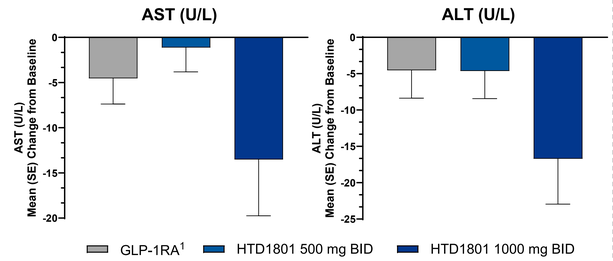
[1]Placebo randomized patients treated concomitantly with GLP-1RAs.
cT1 segmented analysis was evaluated after study completion for HTD1801 1000 mg BID or placebo only.

HTD1801 Resulted in Greater Improvements in Glycemic Control Compared to GLP-1RAs



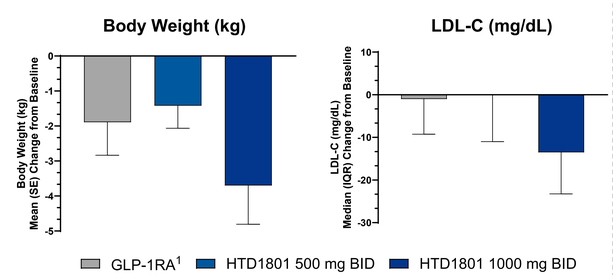
[1]Placebo randomized patients treated concomitantly with GLP-1RAs.

HTD1801 1000 mg BID Resulted in Greater Improvements in AST and ALT Compared to GLP-1RAs



[1]Placebo randomized patients treated concomitantly with GLP-1RAs

HTD1801 1000 mg BID Resulted in Substantial Weight Loss and Reduction of LDL-C Compared to GLP-1RAs



[1]Placebo randomized patients treated concomitantly with GLP-1RAs.

SUMMARY

- GLP-1RAs are widely used for the treatment of T2DM and obesity and are under investigation for the treatment of MASH
- Utilization of GLP-1RAs continues to grow and may be confounding in studies of MASH
  - As observed in this analysis, the presence of background GLP-1RA use may result in a significant placebo response, diminishing the observed placebo-adjusted efficacy of investigational compounds
    - This may impede the advancement of compounds through clinical development and result in inappropriate study designs/sample size assumptions for future studies
  - This has resulted in their exclusion from some new studies of MASH which is unlikely to be reflective of real-world use
- These data suggest HTD1801 may be a viable treatment option for patients with MASH and T2DM, providing greater benefit to ongoing GLP-1RA use, including greater improvements in glycemic control, weight loss, lipids, and markers of liver injury/inflammation
- Based on the positive findings from this study, a Phase 2b study evaluating liver histology is ongoing (NCT05623189)
  - To reflect real world use, GLP-1RA utilization is a stratification factor in the ongoing study

References

1. Harrison SA, et al. Nature Commun. 2021;12(1):5503.

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