Assessment of MRI Response in Patients with NASH and T2DM Treated with HTD1801 (Berberine Ursodeoxycholate) for 18 Weeks

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HIGHTIDE

BACKGROUND

- Berberine ursodeoxycholate (HTD1801), is a first-in-class gut-liver anti-inflammatory metabolic modulator which targets multiple pathways pivotal to metabolic regulation
- In a Phase 2 study in patients with NASH and T2DM HTD1801 significantly reduced LFC and fibroinflammation as determined by MRI-PDFF and MRI-derived cT1, respectively after 18 weeks of treatment (NCT03656744)[1]
- Achieving either of these MRI response criteria have been associated with improvements in liver histology (≥2-point improvement in the NAS and no worsening of fibrosis)
  - A cT1 reduction of ≥80 ms has been correlated with improved histology (a 2-point reduction in NAS)[2]
  - Reductions in LFC of ≥30% have been shown to be predictive of histologic improvement in NASH[3]

The objective of this post-hoc analysis was to evaluate the characteristics and on-treatment changes in patients who achieved either of the MRI response criteria

METHODS

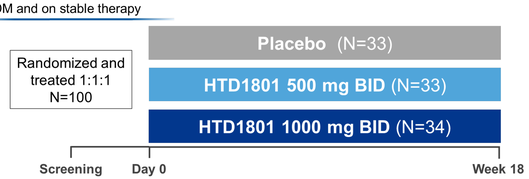
Phase 2a Proof of Concept Dose-Finding Study[4]

Key Entry Criteria

- Presumed NASH with LFC ≥10%
- cT1 ≥830 ms
- Serum AST ≥20 U/L
- T2DM and on stable therapy

Primary Endpoint

Change from baseline in LFC by MRI-PDFF



- MRI response was defined as achieving either ≥30% reduction in LFC by MRI-PDFF or an improvement in fibroinflammation as determined by ≥80 ms reduction in cT1 at 18 weeks
  - MRI-PDFF data was collected prospectively for evaluation of the primary endpoint (LFC)
  - cT1 segmented analysis was evaluated after the completion of the study for patients who had been randomized to HTD1801 1000 mg BID or placebo

RESULTS

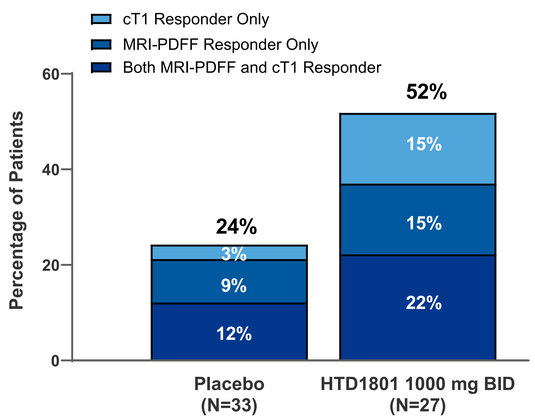
Demographics and Baseline Characteristics

	MRI Responders		MRI Non-Responders	
	Placebo (n=8)	HTD1801 1000 mg BID (n=14)	Placebo (n=25)	HTD1801 1000 mg BID (n=13)
Age, years	57 (9)	50 (13)	58 (11)	53 (10)
Female, n (%)	6 (75%)	11 (79%)	16 (64%)	9 (69%)
White, n (%)	8 (100%)	13 (93%)	23 (92%)	12 (92%)
Hispanic or Latino, n (%)	2 (25%)	5 (36%)	11 (44%)	3 (23%)
Body Weight, kg	95 (18)	104 (21)	98 (24)	99 (23)
LFC, %	21 (10)	19 (7)	20 (5)	20 (8)
cT1, ms	984 (155)	984 (86)	929 (77)	907 (57)
ALT, U/L	40 (14)	76 (38)	59 (28)	50 (24)
FIB-4	1.4 (0.8)	1.4 (0.8)	1.4 (0.7)	1.0 (0.4)
FPG, mg/dL	117 (21)	168 (43)	139 (47)	135 (50)
HbA1c, %	7.4 (0.9)	7.9 (1.0)	6.8 (1.1)	6.7 (1.0)
LDL-C, mg/dL	87 (22)	108 (26)	99 (35)	107 (47)

Values are Mean (SD) unless otherwise noted.
*Baseline cT1 values were reassessed using a segmented analysis as defined by the analysis plan rather than the regional analysis used to determine subject eligibility at screening.

- Across treatment groups, baseline LFC was balanced between MRI responders and non-responders, but cT1 was elevated in MRI responders
- Baseline biochemical characteristics of HTD1801-treated MRI responders were indicative of more severe disease compared to non-responders
  - Placebo-treated MRI responders had less severe disease by biochemistry

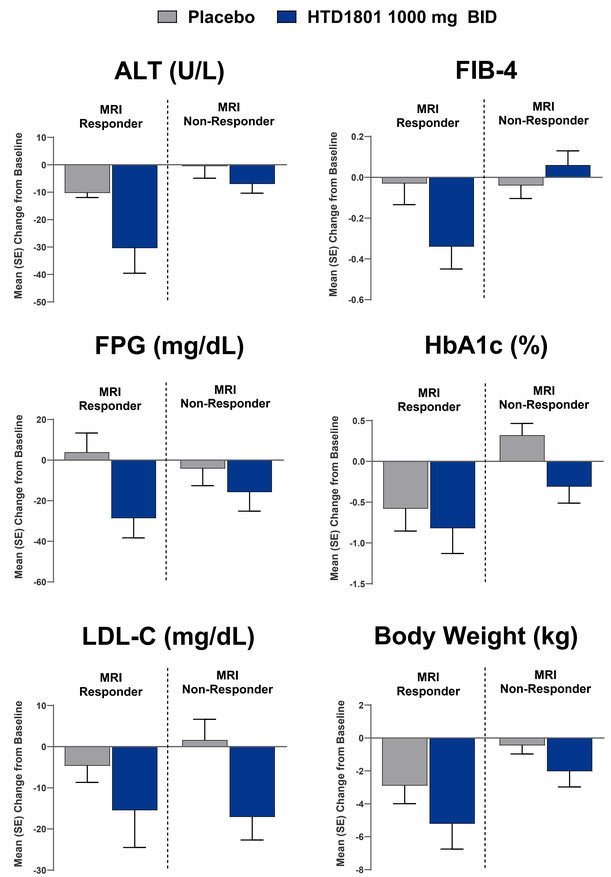
MRI Response Criteria was Achieved by 2-fold More Patients Treated with HTD1801 vs Placebo



- 22% of all patients receiving HTD1801 vs 12% with placebo achieved both improvements in LFC and fibroinflammation after 18 weeks of treatment

HTD1801 Treatment Resulted in Improvements Across Multiple Efficacy Measures

- HTD1801-treated MRI responders had substantial improvements in ALT, FIB-4, FPG, HbA1c, LDL-C, and body weight
- In MRI non-responders, modest improvements in ALT, FPG, HbA1c, LDL-C, and body weight were observed with HTD1801 compared to no change with placebo



Incidence of TEAEs Was Low and Generally Mild[4]

	Placebo (N=33)	HTD1801 1000 mg BID (N=34)
Any TEAE, n (%)	**20 (61)**	**26 (76)**
Diarrhea	3 (9)	11 (32)
Nausea	3 (9)	7 (21)
Headache	2 (6)	3 (9)
Upper Respiratory Tract Infection	4 (12)	1 (3)
Abdominal Pain	3 (9)	1 (3)

TEAEs occurring ≥2 patients.

- The most common TEAEs were GI-related events, which occurred more frequently with HTD1801
- Three serious adverse events occurred during the study all of which were considered not related
  - Myocardial infarction (1000 mg BID) oxygen saturation decreased (500 mg BID); bladder transitional cell carcinoma (placebo)

SUMMARY

- Twice as many patients achieved a meaningful reduction in LFC or fibroinflammation with HTD1801 compared to placebo
- Suggests that HTD1801 may improve liver histology in patients with NASH and T2DM warranting further investigation
- Improvements were observed with HTD1801 in liver biochemistry and key cardiometabolic parameters in both MRI responders and non-responders
- A Phase 2b study is currently ongoing to evaluate the histologic effects of HTD1801 in patients with NASH and T2DM or prediabetes (NCT05623189)

Abbreviations

ALT: alanine aminotransferase; BID: twice daily; cT1: corrected T1; FPG: fasting plasma glucose; HbA1c: hemoglobin A1C; GI: gastrointestinal; LDL-C: low-density lipoprotein cholesterol; LFC: liver fat content; MRI: magnetic resonance imaging; NAS: NAFLD Activity Score; NASH: nonalcoholic steatohepatitis; PDFF: proton density fat fraction; T2DM: type 2 diabetes mellitus; TEAE: treatment-emergent adverse event.

References

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Disclosures

Please review the published abstract for a full list of author disclosures.

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