Improvements in Liver Fibroinflammation (as assessed by Corrected T1 [cT1]) with HTD1801 (Berberine Ursodeoxycholate) Treatment in Patients with Nonalcoholic Steatohepatitis and Type 2 Diabetes Mellitus

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HIGHTIDE

BACKGROUND

- HTD1801 (berberine ursodeoxycholate), a new molecular entity, is a gut-liver anti-inflammatory metabolic modulator
  - Targets multiple pathways pivotal to metabolic regulation, including those associated with metabolic and digestive diseases
- Corrected T1 (cT1) is an MRI-based quantitative metric for assessing liver inflammation and fibrosis
- Previous studies in patients with nonalcoholic steatohepatitis (NASH) have reported that[1]:
  - cT1 improvements are moderately correlated with histologic improvements in NAFLD Activity Score (NAS) and fibrosis
  - cT1 levels are associated with clinical outcomes (liver and cardiovascular disease)
- In a Phase 2 study in patients with NASH and type 2 diabetes mellitus (T2DM), HTD1801 significantly reduced liver fat content (LFC) as determined by MRI-PDFF after 18 weeks of treatment (NCT03656744)[2]

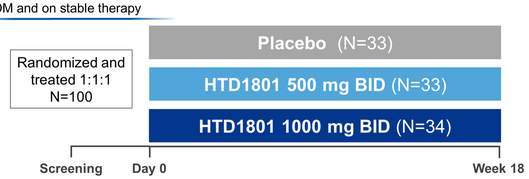
The objective of this post-hoc analysis was to evaluate the effects of HTD1801 on cT1 in patients with NASH and T2DM

METHODS

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

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-PDFF data was collected prospectively for evaluation of the primary endpoint
- cT1 segmented analysis was evaluated after study completion for HTD1801 1000 mg BID or placebo

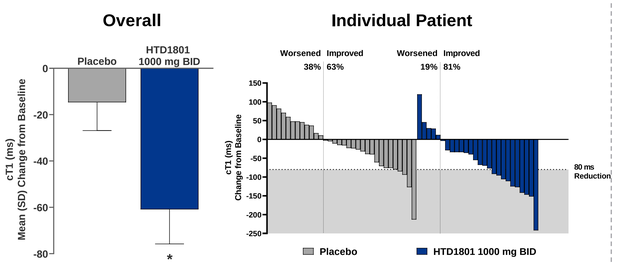
RESULTS

Demographics and Baseline Characteristics

	Placebo (N=33)	HTD1801 1000 mg BID (N=34)
Age, years	58 (11)	53 (12)
Female, n (%)	22 (67)	24 (71)
White, n (%)	31 (94)	31 (91)
Hispanic or Latino, n (%)	13 (39)	11 (32)
BMI, kg/m^2	35 (6)	36 (6)
HbA1c, %	7.0 (1)	7.3 (1)
MRI-PDFF, %	20 (6)	19 (7)
cT1, ms*	938 (98)	942 (91)
ALT, U/L	54 (27)	62 (32)

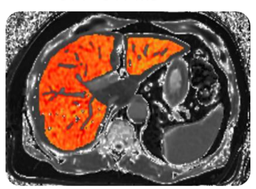
Values are Mean (SD) unless otherwise noted.
*Baseline cT1 values were reassessed using a segmented analysis as defined by the analysis plan rather than the regional analysis used to determine subject eligibility at screening.

Patients Receiving HTD1801 Had A Significant Reduction in Fibroinflammatory Disease as Assessed by cT1

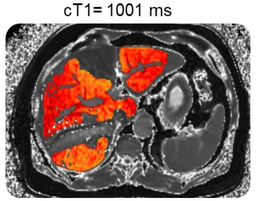


*p<0.05, p-values are obtained from an ANCOVA model with treatment group as a fixed effect, and baseline ALT and baseline cT1 as covariates.

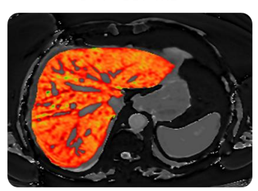
Patient Receiving Placebo
Baseline
cT1= 941 ms



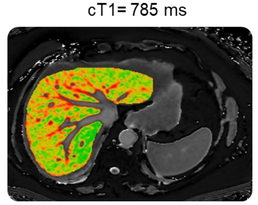
Week 18
cT1= 1001 ms



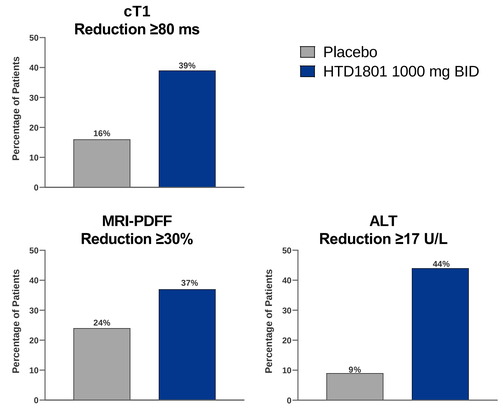
Patient Receiving HTD1801
Baseline
cT1= 937 ms



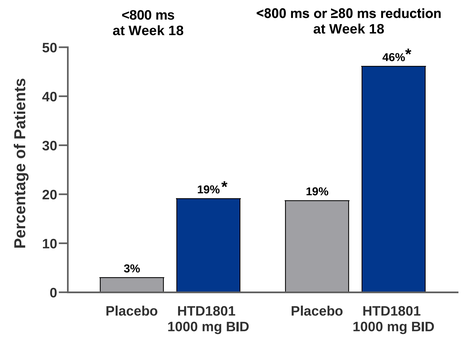
Week 18
cT1= 785 ms



More Patients Treated with HTD1801 Achieved Reductions in Biomarkers Correlated with Histologic Improvement[1,4-5]



A Larger Proportion of Patients Receiving HTD1801 Achieved Clinically Meaningful Thresholds in cT1



*p<0.05, 2-sided p-values are obtained from a chi-square test.

- cT1 <800 ms has been associated with a low likelihood of disease activity[3]
- A cT1 reduction of ≥80 ms has been correlated with improved histology (a 2-point reduction in NAS)[1]
- After 18 weeks:
  - Treatment with HTD1801 resulted in a larger proportion of patients achieving a cT1 <800 ms
  - Twice as many patients treated with HTD1801 compared to placebo achieved either a cT1 <800 ms or ≥80 ms reduction in cT1

TEAEs Occurring in More Than 2 Subjects[2]

	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)

- The incidence of TEAEs was low and events were generally mild in severity
  - The most common TEAEs were GI-related events, which occurred more frequently with HTD1801
- 3 serious adverse events occurred during the study none of which were considered related to study drug
  - Includes myocardial infarction (1000 mg BID) oxygen saturation decreased (500 mg BID); bladder transitional cell carcinoma (placebo)

SUMMARY

- Subjects receiving HTD1801 had significant reduction in fibroinflammatory disease as assessed by cT1
- Across multiple biomarkers, HTD1801 resulted in more patients achieving clinically relevant thresholds correlated with histologic improvement and lower disease activity
- These data suggest that HTD1801 may improve liver histology in patients with NASH and T2DM, warranting further investigation
- A Phase 2b study is currently ongoing to evaluate the histologic effects of HTD1801 in patients with NASH and T2DM or prediabetes (NCT05623189)

References

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