Dose-Finding, Positive Proof-of-Concept Study of HTD1801 (Berberine Ursodeoxycholate) In Patients with Primary Sclerosing Cholangitis

#210

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BACKGROUND

- Primary sclerosing cholangitis (PSC) is a progressive, inflammatory, and cholestatic liver disease, without present effective medical therapy
- HTD1801 is an ionic salt of berberine and ursodeoxycholic acid, with predicted enhanced anti-inflammatory, anti-cholestatic, and anti-fibrotic effects
- We report a proof-of-concept randomized, placebo controlled, two-part study of HTD1801 over 18 weeks in patients with PSC and elevated serum alkaline phosphatase (ALP)

AIMS

- To assess the effect of two doses of HTD1801 on serum levels of alkaline phosphatase
- To assess the effect of two doses of HTD1801 on a variety of secondary biochemical endpoints
- To assess safety and tolerability of HTD1801 in patients with PSC

MATERIAL & METHODS

- Subjects were initially randomized into one of three treatment groups:
  1) HTD1801 1000mg BID
  2) HTD1801 500mg BID
  3) Placebo
- The primary endpoint for Part 1 of the study was change in ALP at 6 weeks and differences in serum ALP and other liver-related enzymes among the three groups were compared using Mixed-Effect Model Repeated Measures.
- In Part 2 of the study, HTD1801 was continued for an additional 6 or 12 weeks and safety and biochemical efficacy were evaluated while some subjects were randomized to withdraw from HTD1801.
- Washout of UDCA was initially required but a protocol amendment allowed subjects on UDCA to continue until randomized into this study.

RESULTS

- A total of 59 subjects were enrolled into the study and 55 received at least one dose of study drug.
- At week 6, there was a statistically significant difference in ALP and GGT in both HD1801 treatment groups compared to placebo (Fig 1a). Among the 32 subjects not on UDCA at randomization, ALP reduction was dose dependent (36% with high-dose HTD1801, 27% in low-dose vs 10% in placebo) (Fig 1b).
- In Part 2 of the study, ALP reduction was maintained through 18 weeks of treatment in both HTD1801-treated groups, while ALP and GGT recrudesced substantially among those who crossed over from HTD1801 to placebo.
- HTD1801 was generally well tolerated. Only 4 subjects experienced serious adverse events (motor accident with injury, C. difficile colitis, colostomy hemorrhage, partial SBO respectively), none of which were attributed to study drug.

Table 1: Baseline Demographics and Disease Characteristics

		HTD1801	
	Placebo (n=16)	500 mg (n=15)	1000 mg (n=24)
Mean Age (range, yrs)	40 (21-72)	43 (29-69)	45 (24-75)
Gender (male)	7 (44%)	11 (73%)	14 (58%)
Race			
White	13 (81%)	14 (93%)	19 (79%)
Black or African American	2 (13%)	1 (7%)	4 (17%)
Other	1 (6%)	0	1 (4%)
History of Inflammatory Bowel Disease	10 (63%)	9 (60%)	16 (67%)
Mean ALP (U/L) at Baseline (range)	414 (138-1048)	397 (237-773)	335 (122-882)
Mean GGT (U/L) at Baseline (range)	497 (119-1563)	742 (76-3535)	554 (64-2015)
Mean ALT (U/L) at Baseline (range)	93 (24-166)	153 (35-420)	112 (31-363)
Mean Bilirubin (mg/dL) at Baseline	0.8 (0.4-1.4)	1.1 (0.5-2.6)	0.8 (0.3-1.4)
Prior UDCA (no., %) (Total 22; 3 discontinued >4 weeks prior, 19 continued up until enrollment)	8 (50%)	6 (40%)	8/23 (35%)

Figure 1a (Part 1): There was a statistically significant reduction in ALP levels in both groups receiving HTD1801, compared to placebo, in the first 6 week period.
Figure 1b: In the 32 subjects without prior exposure to UDCA immediately on randomization, a statistically significant reduction in ALP levels was noted in both groups receiving HTD1801, compared to placebo.

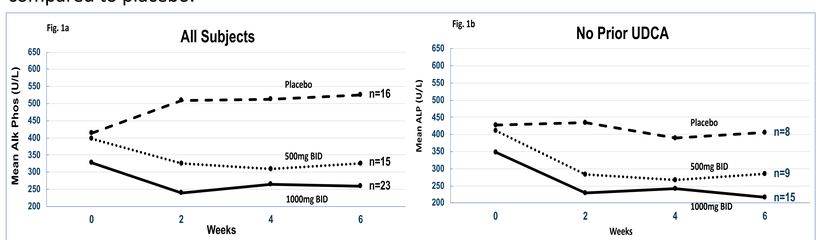

Figure 2a: Improvement in Liver-Related Enzymes in 32 UDCA Naïve Subjects at Week 6
Figure 2b (Part 2): Randomized Withdrawal of HTD1801 at Week 12

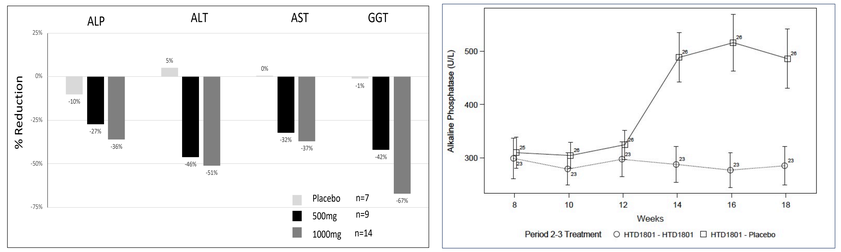

Table 2: Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation by Preferred Term*

		HTD1801	
Preferred Term	Placebo	500 mg	1000 mg
Subjects Who Ever Received Treatment	35	22	31
Number of Subjects with a TEAE Leading to Discontinuation of Study Drug	4 (11%)	1 (5%)	3 (10%)
Serum Alkaline Phosphatase Increased	3 (9%)	0	0
Alanine Aminotransferase Increased	2 (6%)	0	0
Serum Bilirubin Increased	2 (6%)	0	0
Gamma-Glutamyl Transferase Increased	1 (3%)	0	0
Liver Function Test Increased	1 (3%)	0	0
Neutropenia	0	1 (5%)	0
Tachycardia	0	0	1 (3%)
Diarrhea	0	0	1 (3%)
Clostridium Difficile Colitis	0	0	1 (3%)
Pruritus	1 (3%)	0	0

*Summarized according to the treatment taken on the start date of the adverse event. Denominators are the number of subjects receiving the treatment during any period of the study

SUMMARY AND CONCLUSIONS

- HTD1801 significantly improved ALP, ALT, AST and GGT in a dose-dependent manner
- Withdrawals of prior UDCA and HTD1801 were associated with significant elevations in ALP
- HTD1801 was safe for up to 18 weeks

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