STATISTICAL ANALYSIS PLAN

Study Title:	A Proof-of-Concept and Dose-Ranging Study Investigating the Efficacy and Safety of HTD1801 in Adult Subjects with Primary Sclerosing Cholangitis (PSC)
Phase:	2
Protocol No.:	HTD1801.PCT003
Protocol Date(s):	Protocol Versions 1.4, 07 January 2019
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STATISTICAL ANALYSIS PLAN REVIEW AND APPROVAL

This Statistical Analysis Plan has been prepared in accordance with team reviewers' specifications.

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1. INTRODUCTION

This document describes the statistical methods and data presentations to be used in the summary and analysis of data from Protocol HTD1801.PCT003. Background information is provided for the overall study design and objectives. The reader is referred to the study protocol and case report forms (CRFs) for details of study conduct and data collection.

1.1. STUDY OVERVIEW

Protocol HTD1801.PCT003 is a Phase 2, randomized, double-blind study which consists of a placebo- and dose-controlled parallel group period, a dose-controlled extension period, and a placebo-controlled randomized withdrawal period with the intent of comparing multiple doses of investigational product (HTD1801) to placebo. Approximately 60 patients with Primary Sclerosing Cholangitis (PSC) will be enrolled as subjects. Upon confirmation of eligibility, subjects will be randomized in Period 1 in a 1:1:1 ratio, stratified by inflammatory bowel disease (IBD) diagnosis and ursodiol (UDCA) status, to one of the following treatment arms:

- **Treatment Arm 1**: HTD1801 500 mg twice daily (BID)
- **Treatment Arm 2**: HTD1801 1000 mg BID
- **Treatment Arm 3**: Placebo BID.

Subjects will receive the treatment to which they are randomly assigned for 6 weeks during the first period.

In response to the COVID-19 pandemic, enrollment into the study was prematurely stopped on 25th March 2020. This impacted 3 subjects who had been randomized but had not yet initiated dosing. There may be additional restrictions associated with COVID-19 that may impact sites' ability to schedule subjects for in-clinic visits and thus, complete all protocol-required assessments. These will be noted as protocol deviations related to COVID-19 should they occur. These measures were put into place following the issuance of the FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Pandemic (March 2020 and April 2020).

See Section 3.2 for additional details on Period 1 randomization.

Following the completion of the first period, subjects are eligible to enroll in Period 2 which is a 6-week extension period. During this period, subjects who were previously randomized to 500 mg or 1000 mg BID in Period 1 will continue to receive the same dose. Subjects who were previously randomized to placebo will be randomized in a 1:1 ratio to receive 6 weeks of either 500 mg or 1000 mg BID. This period will continue to be double-blind.

Following the completion of Period 2, the 6-week treatment extension period, all subjects will be randomized in a 1:1 ratio to either continue on the active treatment they received in the second period or be assigned to placebo.

An independent Data and Safety Monitoring Board (DSMB) will provide additional safety oversight.

1.2. SCHEDULE OF EVENTS

	Screening	Baseline	Initial Dosing Period			Dose-controlled Extension			Randomized Withdrawal			Follow-up
Visit Day	**-28 to -1**	**0**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12**	**Week 14**	**Week 16**	**Week 18**	**Week 22**
Procedures												
Clinic visits	X	X			X			X			X	
Informed consent	X											
Eligibility criteria	X	X										
Demographics	X											
G6PD	X											
IgG4	X											
Urine drug test	X											
HIV/Hepatitis B, C	X											
Medical History	X	X										
Concomitant meds	X	X			X			X			X	X
Physical examination	X	X			X			X			X	
Height/Weight/Vitals	X	X			X			X			X	
ECG	X	X			X			X			X	
Pregnancy testing	X	X									X	
Partial Mayo Score *	X	X			X			X			X	
CBC, CMP**, Lipids	X	X	X	X	X	X	X	X	X	X	X	
INR	X	X			X			X			X	

	Screening	Baseline	Initial Dosing Period			Dose-controlled Extension			Randomized Withdrawal			Follow-up
Visit Day	**-28 to -1**	**0**	**Week 2**	**Week 4**	**Week 6**	**Week 8**	**Week 10**	**Week 12**	**Week 14**	**Week 16**	**Week 18**	**Week 22**
Mayo Risk Score		X										
C-reactive protein *		X			X			X			X	
Fecal calprotectin *		X			X			X			X	
Randomization		X			X			X				
Dosing		X	X	X	X	X	X	X	X	X	X	
Adverse event monitoring		X	X	X	X	X	X	X	X	X	X	X
Telephone contact			X	X		X	X		X	X		X
Discharge											X	

* IBD subset only

** Including GGT

1.3. GLOSSARY OF ABBREVIATIONS

AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
BID	twice daily
BMI	Body Mass Index
CRF	case report form
CRP	C-reactive Protein
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data and Safety Monitoring Board
ET	Early Termination
FAS	full analysis set
FC	Fecal Calprotectin
GGT	Gamma-Glutamyl Transferase
IBD	Inflammatory Bowel Disease
ITT	Intent-to-treat population
IxRS	interactive web/voice response system
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treat population
MMRM	Mixed Model with Repeated Measures
PP	per protocol
PSC	Primary Sclerosing Cholangitis
PT	Preferred Term
SAE	serious adverse event
SD	standard deviation
SOC	System Organ Classification
TEAE	treatment emergent adverse events
UDCA	ursodeoxycholic acid
WHO	World Health Organization

2. OBJECTIVES

Primary Objective:

The primary objective of this proof-of-concept study is to evaluate the effects of HTD1801 on serum alkaline phosphatase (ALP) levels in adult subjects with PSC.

Secondary Objective:

The secondary objectives of this study are to evaluate:

- the effects on concurrent disease activity of IBD, and
- the safety (inclusive of adverse events, serology, and vital signs) and
- the tolerability of HTD1801 over 18 weeks in adult subjects with PSC.

3. GENERAL STATISTICAL CONSIDERATIONS

3.1. SAMPLE SIZE AND POWER

Results from published clinical trials of PSC patients including Zhu et al., 2015 and Fickert et al., 2017 were reviewed. These publications were used along with consideration of inclusion and exclusion criteria for this study to estimate mean Baseline ALP and to estimate variability. Total sample size was chosen based on balancing consideration of business costs, time to enroll subjects with this rare disease and the mean change which could be detected given the mean Baseline and variability assumptions. The standard deviation for change from Baseline in ALP was assumed to be 200. A total of 90 subjects, 30 subjects per group, is sufficient to detect a mean difference from placebo within a dose group of 147 with 80% power at an alpha of 0.05. Assuming a mean Baseline ALP of 450, this equates to a 32.7% reduction. This study should be adequate to determine if there is a positive signal in ALP during HTD1801 treatment.

While the sample size was originally planned to be 90 subjects, in view of the protracted period necessary to enroll subjects into the study, a strategy session in the fall of 2018 with external consultants advised that the study would be adequately powered by enrolling approximately 60 subjects. Specifically, it was determined that a total of 63 subjects, 21 subjects per group, would be sufficient to detect a mean difference of 180 for each dose group vs. placebo with 80% power for a two-sided t-test with alpha of 0.05. A protocol amendment was deemed unnecessary.

3.2. RANDOMIZATION AND BLINDING

Period 1: Placebo- and dose-controlled, parallel-group period

Subjects will be enrolled in equal numbers to one of the initial three treatment groups (placebo BID, HTD1801 500 mg BID, HTD1801 1000 mg BID) during the initial 6-week, double-blind, placebo- and dose-controlled, parallel-group period. Randomization will be centrally controlled, stratified

according to a co-existing diagnosis of IBD and UDCA status, and subjects will be assigned a pre-packaged and numbered treatment.

Subjects who were currently taking ursodeoxycholic acid (UDCA), or who had taken UDCA during the 6 weeks prior to randomization were to have completed a 6-week washout period before Baseline measurements per Protocol Version 1.2 dated 01 February 2018. The UDCA restriction was modified in Protocol Version 1.3 dated 12 June 2018 since only one subject had been enrolled in the earlier version of the protocol. Subjects on UDCA were eligible as long as the dose of UDCA was stable for at least 6 weeks prior to the Baseline visit.

Following the strategy session in the fall of 2018, an unblinded individual from the CRO, Cato Research, was tasked with determining whether the number of subjects taking UDCA was evenly distributed among the three study groups. This was found not to be so, with one dose cohort having no subjects who had previously been taking UDCA. While at the onset of the study, Period 1 randomization was stratified only by IBD diagnosis, this discovery spurred the inclusion of UDCA status as a stratification factor in an attempt to ensure even distribution between treatment groups for the primary analysis. UDCA status was therefore retroactively applied as a stratification factor to those 42 subjects who had already been randomized to Period 1, and gaps in these new strata were subsequently filled by 17 subjects enrolling from that point forward, with new randomization blocks prospectively added.

This new manual randomization process was initiated in November 2019. The autogenerated randomization process in the web-response system was too time consuming and costly to implement. This is managed by Dr. Philip Lavin (Boston Biostatistics Research Foundation, Inc.) in conjunction with an unblinded data base administrator, William Scott (Cato Research Limited). The additional stratification factor of UDCA status will be included in the modeling.

Period 2: Dose-controlled extension

Following their completion of Period 1, subjects will enroll in a 6-week extension period in which subjects previously randomized to 500 mg or 1000 mg BID will continue for 6 more weeks at that previous dose, while subjects previously randomized to placebo will be randomly assigned to receive 6 weeks of either 500 mg or 1000 mg BID.

Period 3: Randomized withdrawal

Following their completion of Period 2, subjects will enroll into a 6-week randomized withdrawal period in which all subjects will be randomly assigned in a 1 to 1 ratio to either continue on the active treatment they received in Period 2, or be assigned to placebo so that 50% of the subjects remain on the experimental treatment at the previous dose, and 50% will receive placebo.

All subjects and study personnel will remain blinded as to the treatment administered throughout the study with the exception of an unblinded statistician who will develop the randomization list with the expanded strata and an unblinded EDC designer who will load the completed randomizations

into the EDC system. All study test drug will be provided in matching white tablets, four to a bottle, two bottles to be administered each day, one in the morning and one in the evening. A 45-day supply will be provided to each subject at each visit to cover the next 6-week period with an additional 3 days of coverage to provide for possible scheduling conflicts.

In this double-blind study, if a medical emergency occurs and a decision about a subject's condition requires knowledge of the treatment assignment in order to properly treat the subject, the study blind may be broken for that specific subject only. Ideally, the decision to break the blind for this one subject should only be made after consultation with the Medical Monitor or Sponsor Representative.

Any broken blind must be clearly justified and explained by a note in the subject's source documents.

3.3. HANDLING OF DATA

3.3.1. Strata and Covariates

Statistical models run for the primary endpoint as well as secondary continuous endpoints in Period 1 will include IBD diagnosis as randomized and UDCA status when entering the study as covariates. Secondary continuous endpoints in Periods 2 and 3 will also include IBD diagnosis and UDCA status as a covariate.

3.3.2. Examination of Subject Subsets

Analysis of the primary endpoint will additionally be presented by IBD diagnosis as randomized and UDCA status when entering the study.

3.3.3. Multiple Testing and Comparisons

All analyses will be conducted without adjustments for multiple comparisons for this proof-of-concept study.

3.3.4. Missing Data

Every effort will be made to obtain required data at each scheduled evaluation from all subjects who have been treated. Missing end dates for dosing in each period will be imputed using the first date of dosing in the next period if available, or the last collected visit date for the period if not. Missing start dates will be imputed as the earliest study drug dispensation date for the period, provided there is a last dose date or multiple dispensations in the period. No other imputations will be used for this analysis except for handling of incomplete dates.

3.3.5. Imputation of Incomplete Dates

An incomplete date is any date for which either the day, month, or year is unknown, but all three fields are not unknown. An incomplete date occurs when the exact date an event occurred or ended cannot be obtained from a subject. For many of the analyses, a complete date is necessary in order

to determine if the event should be included in the analysis (i.e., if the event is treatment-emergent) or to establish the duration of an event. In such cases, incomplete dates will be imputed.

For purposes of imputation, all events with an incomplete end date are assumed to have ended on or before the day the form was completed. In an effort to minimize bias, the project statistician will impute dates in a systematic but reasonable manner, as described below.

For event start dates, if the month/year is the same as the Day 1 month/year then the date will be set to the date of Day 1. In other cases, missing days will be imputed as the day component of Day 1; missing months/years will be imputed as the month/year of Day 1. If the end date is present, then the imputed start date will be set to the end date if the above imputation imputes a date after the end date.

For event end dates, if the month/year is the same as the event start date month/year then the date will be set to the date of the event start date. In other cases, missing days will be imputed as the day component of the event start date, or if missing, then then day component of the treatment start date; missing months/years will be imputed as the month/year of the event start date, or if missing then the months/years of the treatment start date.

3.3.6. Presentations by Study Visit

Nominal study visits as obtained from the CRF or laboratory will be utilized for summary displays of efficacy endpoints. Unscheduled and early termination (ET) visits will be windowed based on study day, according to the table below. All assessments will be presented in the listings. If assessments are collected multiple times within a given study visit, the result closest to the scheduled visit date will be used for summary presentations. If two measurements have the same distance to the expected date, the earlier value will be used. If a scheduled assessment and an unscheduled or ET assessment are collected within a given visit, the value from the scheduled assessment will be chosen over the value from the unscheduled assessment.

Study Day	Windowed Study Visit	Additional Details
2 – 20	Week 2	
21 – 34	Week 4	
35 – (date of randomization to Period 2)	Week 6	If subject is not randomized to Period 2, use study day 42 as upper limit
(date of randomization to Period 2) + 1 – 62	Week 8	

63 - 76	Week 10	
77 – (date of randomization to Period 3)	Week 12	If subject is not randomized to Period 3, use study day 84 as upper limit
(date of randomization to Period 3) + 1 – 104	Week 14	
105 – 118	Week 16	
119 – Exit	Week 18	

3.3.7. Definitions and Terminology

Age
The age of a subject is defined as the number of whole years between the subject's birth date and the Period 1 treatment start date.

Day 1 (Baseline)
Day 1 is the earliest day that study drug is initiated in Period 1.

Study Day
Study Day is defined relative to Baseline (Day 1). Thus, the study day of an event is calculated as:

Study Day = event date – date of Day 1 (+ 1 if event date >= date of Day 1).

Study Visit
Study Visit is the nominal visit as recorded on the CRF.

Weeks of Exposure
Weeks of exposure is calculated as the (Last Day on Study Drug – First Day on Study Drug + 1) / 7 within each period.

Treatment Compliance
Treatment compliance is calculated as the Number of Days of Dosing / Expected number of days of dosing within each period.

Baseline Value
For purposes of analysis, the baseline value is defined as the last non-missing value obtained prior to initiation of study drug.

Change from Baseline
Change from baseline for a given endpoint is defined as the Study Day X value minus the Baseline Value.

Adverse Event (AE)
An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of the investigational product, regardless of whether it is considered to be related to the investigational product. All adverse events will be recorded on the Adverse Event CRF.

Treatment-emergent Adverse Event (TEAE)
A TEAE will be an AE that occurred during the study after the first dose of study drug or that was present prior to dosing and exacerbates after the first dose of study drug. Additionally, it is assumed that an Adverse Event which was reported to have started on Day 1 without an associated onset time occurred after the initiation of study drug.

Concomitant Medications
Concomitant medications are those medications taken on or after the initiation of study drug. This definition includes medications started prior to the initiation of study drug but continuing concomitantly with study drug.

Prior Medications
Prior medications are those medications taken prior to the initiation of study drug.

3.4. TIMING OF ANALYSES

The final analysis will be completed after the last subject completes or discontinues the study and the resulting clinical database has been cleaned, quality checked, and locked.

Additionally, safety oversight will be conducted throughout the study under the direction of a DSMB. The timing and frequency for the DSMB will be detailed in a separate DSMB charter.

4. ANALYSIS POPULATIONS

The populations for analysis will include the modified intent-to-treat population (mITT) and safety population.

4.1. MODIFIED INTENT-TO-TREAT POPULATION

The mITT population will consist of all randomized subjects who receive at least one dose of study drug and who have at least one post-dose efficacy assessment. Subjects in this population will be

analyzed according to the treatment group to which they were randomized. This population will be used for analyses of efficacy.

4.2. SAFETY POPULATION

The safety population consists of all subjects who receive at least one dose of study treatment, regardless of whether or not they undergo any study assessments. Subjects in this population will be analyzed according to the treatment which they receive. All safety analyses will be based on this population.

5. STATISTICAL METHODS

Descriptive statistical methods will be used to summarize the data from this study, with hypothesis testing performed for the primary and other selected efficacy endpoints. Unless stated otherwise, the term "descriptive statistics" refers to number of subjects (n), mean, median, standard deviation (SD), minimum and maximum for continuous data and frequencies and percentages for categorical data. Additional statistical methods include mixed model repeated measures (MMRM), Student's t-test (unpaired and paired), and Fisher Exact test. All data collected during the study will be included in data listings. Unless otherwise noted, the data will be sorted first by subject number, and then by Period and date within each subject number.

The term 'treatment group' refers to all subjects on the same dosing regimen. Efficacy and Safety tables will include only treatment groups that are present in the respective period being summarized. Safety tables will include all treatment groups. The treatment groups will apply for each period:

- Overall – Subjects will be summarized according to the period 1 treatment for demographic and screening information, or according to the actual treatment at the time of event or visit for safety summaries. AE summaries will use this format as well for the by period summaries.
    - Placebo
    - HTD1801 500 mg BID
    - HTD1801 500 mg BID
- Period 1 – Subjects will be summarized according to Period 1 treatment
    - Placebo
    - HTD1801 500 mg BID
    - HTD1801 500 mg BID
- Period 2 – Subjects will be summarized according to the Period 1 and Period 2 treatments
    - HTD1801 500 mg BID to HTD1801 500 mg BID
    - Placebo to HTD1801 500 mg BID
    - All HTD1801 500 mg BID (efficacy only)
    - HTD1801 1000 mg BID to HTD1801 1000 mg BID
    - Placebo to HTD1801 1000 mg BID
    - All HTD1801 1000 mg BID (efficacy only)

- Period 3 – Subjects will be summarized according to the Period 2 and Period 3 treatments
  - HTD1801 500 mg BID to HTD1801 500 mg BID
  - HTD1801 1000 mg BID to HTD1801 1000 mg BID
  - HTD1801 500 mg BID to Placebo
  - HTD1801 1000 mg BID to Placebo
  - All Active to Placebo

All statistical tests will be two-sided with an alpha level of 0.05.

The statistical analyses will be conducted with the SAS® System version 9.4 or higher. All analyses will be subject to formal verification procedures. Specifically, results will be verified utilizing independent programming prior to issuance of the draft statistical report. All documents will be verified by the lead statistician to ensure accuracy and consistency of analyses.

5.1. SUBJECT DISPOSITION, DEMOGRAPHIC AND BASELINE CHARACTERISTICS, AND EXPOSURE

Subject disposition will be presented for all subjects randomized in Period 1. Subjects will be summarized in aggregate for the number of screen failures, the number subjects in the Safety and mITT populations, the number of subjects completing the study and each period, the reasons for early discontinuation at any point, and the number of subjects discontinuing by treatment taken when discontinuation occurred. Disposition and all listings will be presented for the subjects randomized (in Period 1).

Demographic data and baseline characteristics including age, sex, race, height at screening, weight at screening, body mass index (BMI), IBD diagnosis as randomized, UDCA status when entering the study, and protocol version will be summarized using descriptive statistics for the Safety population, and will be presented by treatment group, as treated for Period 1. This information will be reviewed for baseline differences, but no statistical testing will be performed.

Data on drug accountability and total amount of study drug received will be summarized by Period and treatment type according to treatment received in each period. Total study drug exposure within each period will be calculated as the sum of tablets dispensed over the duration of time a subject was on a given study drug within said period – the amount of that study drug returned within said period x the number of mg in the tablets (i.e. 0 mg for Placebo, 125 mg for 500 mg Arm, and 250 mg for 1000 mg Arm). Total exposure over the study period will also be summarized as the sum of the mg taken over all periods.

Weeks of exposure in each period will be calculated as (date of first dose – date of last dose + 1)/7 in the period. Study drug compliance will then be calculated as the number of tablets taken (as defined above) divided by the number of expected tablets to be taken in the period (weeks of exposure x 56) and then x 100 to convert to percentage. Weeks of exposure and study drug compliance will only be presented by period.

Medical history will be mapped to a Medical Dictionary for Regulatory Activities (MedDRA) version 20.1 preferred term (PT) and system organ classification (SOC). Subjects will be summarized in aggregate for the number of subjects with any medical history and the number of subjects by SOC and PT. Subjects with multiple histories mapping to a single SOC or PT will only be counted once within the SOC or PT.

5.2. EFFICACY ANALYSIS

5.2.1. Primary Efficacy Endpoint

The primary endpoint for this study is the absolute change in ALP from Baseline to Week 6 in the double-blind parallel group period (Period 1).

5.2.2. Primary Efficacy Analysis

ALP values and absolute change from Baseline will be presented by treatment group and study visit within Period 1. A mixed model with repeated measures (MMRM) will be fit to the data testing absolute change from Baseline, and this model will include fixed effects for treatment, IBD diagnosis, UDCA status, visit and treatment by visit interaction, with Baseline ALP value as a covariate. An unstructured covariance matrix will be used to model the repeated assessments over time. Denominator degrees of freedom will be adjusted using Kenward-Roger's method. Least Square (LS) Means and corresponding standard errors and 95% confidence intervals resulting from the model described will be presented at each visit. Differences in LS Means and corresponding two-sided 95% confidence intervals will be calculated at each Week 6 comparing each active arm to placebo as well as comparing the HTD1801 1000 mg BID treatment group to the HTD1801 500 mg BID treatment group.

The mean ALP will additionally be represented graphically via a line chart for all scheduled visits in Period 1. Each treatment group by UDCA status combination will be presented on a page, with a line for each subject within the group charted individually, and with one line for the overall group.

5.2.3. Additional Analyses of the Primary Endpoint

Subgroup analyses will be performed based on the IBD diagnosis as randomized and UDCA status when entering the study. For each subgroup, the ALP values and change from Baseline will be presented separately by treatment group and study visit within Period 1.

5.2.4. Secondary Efficacy Endpoints

- Relative change in ALP from Baseline to Week 6
- Absolute change in ALP from Week 6 to Week 12
- Change in ALP from Week 12 to Week 18 for all subjects following the randomized withdrawal
- Proportion of subjects who achieve ALP of < 1.5 x ULN at the end of each period for each treatment group

- Proportion of subjects who achieve at least a 50% decrease in ALP at the end of each period for each treatment group
- Proportion of subjects who normalize ALP at the end of each period for each treatment group
- Absolute change in Gamma-Glutamyl Transferase (GGT) from Baseline to Week 6
- Relative change in GGT from Baseline to Week 6
- Absolute change in GGT from Week 6 to Week 12
- Change in GGT from Week 12 to Week 18 for all subjects following the randomized withdrawal
- Absolute change in serum total bilirubin at the end of each period for each treatment group
- In subjects with IBD, absolute change in fecal calprotectin (FC) from Baseline to Week 6
- In subjects with IBD, absolute change in FC from Week 6 to Week 12
- In subjects with IBD, absolute change in FC from Week 12 to Week 18 for all subjects following the randomized withdrawal
- In subjects with IBD who have elevated FC, the proportion of subjects who normalize FC at Weeks 6, 12, and 18 for each treatment group
- In subjects with IBD, absolute change in C-reactive Protein (CRP) from Baseline to Week 6
- In subjects with IBD, absolute change in CRP from Week 6 to Week 12
- In subjects with IBD, absolute change in CRP from Week 12 to Week 18 for all subjects following the randomized withdrawal
- In subjects with IBD who have elevated CRP, the proportion of subjects who normalize CRP at Weeks 6, 12, and 18 for each treatment group
- In subjects with IBD, absolute change in Mayo scores from Baseline to Week 6
- In subjects with IBD, absolute change in Mayo scores from Week 6 to Week 12
- In subjects with IBD, absolute change in Mayo scores from Week 12 to Week 18 for all subjects following the randomized withdrawal
- In subjects with IBD who have Baseline Partial Mayo score above 0, absolute change in Mayo scores from Baseline to Week 6
- In subjects with IBD who have Baseline Partial Mayo score above 0, absolute change in Mayo scores from Week 6 to Week 12
- In subjects with IBD who have Baseline Partial Mayo score above 0, absolute change in Mayo scores from Week 12 to Week 18 for all subjects following the randomized withdrawal

5.2.5. Secondary Efficacy Analysis

All secondary endpoints will be summarized descriptively by treatment group and visit as defined for each period. Continuous endpoints will present baseline and actual value summaries and change from baseline (Period 1), Week 6 (Period 2), or Week 12 (Period 3) as appropriate. Proportions will be presented with denominators based on the number of subjects randomized to each treatment group.

The mean ALP values will additionally be represented graphically via a line chart for Period 2 and Period 3, with one page for each treatment group, with a line for each subject within the group charted individually, and with one line for the overall group. Period 2 will graph values for all scheduled visits from Baseline through Week 12 and Period 3 will graph values for all scheduled visits from Baseline through Week 18.

Absolute change in GGT from Baseline to Week 6 will be tested using a mixed model with repeated measures (MMRM) analogous to the primary endpoint (Section 5.2.2). This model will include fixed effects for treatment, IBD diagnosis, UDCA status, visit and treatment by visit interaction, with Baseline GGT value as a covariate. An unstructured covariance matrix will be used to model the repeated assessments over time. Denominator degrees of freedom will be adjusted using Kenward-Roger's method. Least Square (LS) Means and corresponding standard errors and 95% confidence intervals resulting from the model described will be presented at each visit. Differences in LS Means and corresponding two-sided 95% confidence intervals will be calculated at each visit comparing each active arm to placebo as well as comparing the HTD1801 1000 mg BID treatment group to the HTD1801 500 mg BID treatment group. The primary comparison of these treatment groups will be at Week 6.

Absolute change in GGT from Baseline to Week 6 will also be summarized by the subgroups as detailed in Section 5.2.3.

5.3. SAFETY

5.3.1. Adverse Events

AEs will be mapped to a Medical Dictionary for Regulatory Activities (MedDRA) version 20.1 preferred term (PT) and system organ classification (SOC). If a subject experiences multiple events that map to a single preferred term, the greatest severity grade according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 will be assigned to the preferred term for the appropriate summaries. Should an event have a missing severity or relationship, it will be classified as having the highest severity and/or assumed related to study medication. The overall occurrence of any TEAEs, TEAE related to study drug, severe TEAEs, serious TEAEs, TEAE leading to discontinuation of study drug, and TEAE leading to death, alongside individual counts of each respective TEAE. The occurrence of TEAEs will be summarized by treatment group by SOC, and PT based on the treatment taken at AE start date. Summaries of the total number of subjects receiving each treatment and the average weeks of exposure for each treatment will be provided for context.

Separate summaries of each TEAE by period, TEAEs leading to the discontinuation of study, TEAEs related to study drug, and serious TEAEs will be generated and summarized by SOC and PT. The occurrence of TEAEs will be summarized by treatment group by SOC, PT, and Severity will also be summarized.

All adverse events reported will be listed for individual subjects showing verbatim term, PT and SOC. All AEs that occurred prior to the initiation of study treatment will be excluded from the tables but will be included in the listings.

Missing onset dates will be imputed as previously outlined in Section 3.3.5 as required to determine treatment-emergent events.

5.3.2. Clinical Laboratory Assessments, Vital Signs, Height, and Weight

Descriptive summaries of selected (quantitative) clinical laboratory results and change from Baseline will be presented by time point and overall treatment groups. Baseline will be the last value observed prior to dosing in Period 1. For more detail on how safety tables will be presented, see Section 3.3.6.

Shift tables (low, normal, high) for change from Baseline to Week 6 in Period 1, and from Week 6 to Week 12 in Period 2 will be presented for all appropriate clinical laboratory parameters by treatment group in Period 1 and Period 2 (excluding efficacy only groups).

Descriptive summaries and change from Baseline in vital signs data, as well as height and weight, will be presented by time point and overall treatment groups, similar to the presentation of clinical laboratory assessments.

Values for all safety variables will be listed by subject and visit (as applicable).

5.3.3. Concomitant Medications

Previous and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary Enhanced September 2017 version. Previous and concomitant medications will be presented in a data listing. Concomitant medications will additionally be summarized by aggregate treatment group.

Missing end dates will be imputed as previously outlined in Section 3.3.5 as required to determine concomitant medications, and all ongoing medications will be considered concomitant.

6. PROTOCOL DEVIATIONS

Possible protocol deviations will be identified and displayed in a data listing and sorted by subject, Period, and study day (where applicable). An additional listing of those deviations deemed Major during the blinded review will be provided.

7. CHANGES IN THE PLANNED ANALYSES

The following secondary endpoints listed in the protocol were removed, with replacements noted in parenthesis.

- Change in serum ALP between Baseline and Weeks 12 or 18, dependent upon the length of continuous treatment, compared to the placebo response during Period 1 (replaced with change from Week 6 to Week 12, and Week 12 to Week 18;

endpoint will be evaluated from descriptive summaries, but no statistical testing will be performed)

- Change in serum ALP between a new baseline at Week 6 and the final value at Weeks 12 for those subjects who received placebo during Period 1, compared to their initial 6-week placebo response (endpoint will be evaluated from descriptive summaries, but no statistical testing will be performed)
- Change in serum ALP between a new baseline at Week 6 and the final value at Weeks 12 for those subjects who received placebo during Period 1, compared to the similar change in the 500 mg and 1,000 mg treatment groups (endpoint will be evaluated from descriptive summaries, but no statistical testing will be performed)
- Change in serum ALP between a new baseline at Week 12 and the final value at Weeks 18 for all subjects following the randomized withdrawal (endpoint will be evaluated from descriptive summaries, but no statistical testing will be performed)
- Proportion of patients who achieve ALP of <1.5 x ULN (endpoint will be evaluated from descriptive summaries, but no statistical testing will be performed)
- Proportion of patients who achieve a 50% decrease in ALP (endpoint will be evaluated from descriptive summaries, but no statistical testing will be performed)
- The proportion of patients who normalize ALP (endpoint will be evaluated from descriptive summaries, but no statistical testing will be performed)
- Change in AST/ALT ratio (endpoint replaced with change in GGT)
- Change in serum bilirubin (endpoint will be evaluated from descriptive summaries, but no statistical testing will be performed)
- In subjects with IBD who have elevated fecal calprotectin (FC), change in FC compared to Baseline at Weeks 6 and 12, and the proportion of subjects who normalize FC at Weeks 6 and 12 (change in FC will be evaluated for all subjects with IBD, not just those with elevated FC; both endpoints will evaluated from descriptive summaries but no statistical testing will be performed)
- For subjects who have elevated CRP at Baseline (for all subjects In the IBD subset): change from Baseline in CRP at Weeks 6 and 12, and normalization of CRP at Weeks 6 and 12 (change in CRP will be evaluated for all subjects with IBD, not just those with elevated CRP; both endpoints will evaluated from descriptive summaries but no statistical testing will be performed)
- For subjects with IBD who have Partial Mayo score above 0: Change from Baseline in Mayo scores at Weeks 6 and 12. (For Week 12, change from Week 6 will replace change from baseline; endpoint will evaluated from descriptive summaries but no statistical testing will be performed)

8. PROGRAMMING CONVENTIONS

- Page orientation, margins, and fonts: Summary tables, listings, and figures will appear in landscape orientation. There should be a minimum of a 1.25" boundary on the upper (bound) edge, and a minimum of a 1.0" boundary on the remaining three edges. Output should be printed in Courier New with a point size of 8. Titles may be printed using a larger font (e.g., Arial point size 10).
- Identification of analysis population: Every summary table and figure should clearly specify the analysis population being summarized. Listings will be prepared for all subjects.
- Group headers: In the summary tables, the group headers will identify the summary group and the sample size for the indicated analysis population. Of note, the header's sample size does not necessarily equal the number of subjects actually summarized within any given summary module; some subjects in the analysis population may have missing values and thus may not be summarized.
- Suppression of percentages corresponding to null categories: When count data are presented as category frequencies and corresponding percentages, the percent should be suppressed when the count is zero in order to draw attention to the non-zero counts.
- Presentation of sample sizes: Summary modules should indicate, in one way or another, the number of subjects actually contributing to the summary statistics presented in any given summary module. As mentioned above, this may be less than the number of subjects in the analysis population due to missing data.
    - In the quantitative modules describing continuous variables (and thus presenting sample size, means, and standard deviations), the sample size should be the number of non-missing observations. The number of missing observations, if any, will be noted.
    - For categorical variables that are presented in frequency tables, the module should present the total count in addition to the count in each category. Percentages should be calculated using this total as the denominator, and the percentage corresponding to the sum itself (that is, 100%) should be presented so as to indicate clearly to a reviewer the method of calculation. The number of missing observations, if any, will be noted.
- Sorting: Listings will be sorted by treatment group, subject number, and date, if applicable. If a listing is sorted in a different manner, a footnote will indicate as such.
- General formatting rules: Rounding for all variables will occur only as the last step, immediately prior to presentation in listings, tables, and figures. No intermediate rounding will be performed on derived variables. The standard rounding practice of rounding numbers ending in 0-4 down and numbers ending in 5-9 up will be employed.
- Numerical Values: The presentation of numerical values will adhere to the following guidelines:
    - Raw measurements will be reported to the number of significant digits as captured electronically or on the CRFs.

- Standard deviations will be reported to one decimal place beyond the number of decimal places the original parameter is presented.
- Means will be reported to the same number of significant digits as the parameter.
- Calculated percentages will be reported with no decimals.

- Dates will be formatted as DDMMMYYYY. Partial dates will be presented on data listings as recorded on CRFs.
  - Time will be presented according to the 24-hour clock (HH:MM).