STATISTICAL ANALYSIS PLAN

Unique Protocol ID: CB8025-31735

Official Title: A 52-week, placebo-controlled, randomized, Phase 3 study to evaluate the safety and efficacy of seladelpar in subjects with primary biliary cholangitis (PBC) and an inadequate response to or an intolerance to ursodeoxycholic acid (UDCA)

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CymaBay Therapeutics, Inc.

CB8025-31735

A 52-week, placebo-controlled, randomized, Phase 3 study to evaluate the safety and efficacy of seladelpar in subjects with Primary Biliary Cholangitis (PBC) and an inadequate response to or an intolerance to ursodeoxycholic acid (UDCA)

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Abbreviated Statistical Analysis Plan

Version 2.0

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List of Abbreviations

AE	Adverse event
ALT	Alanine aminotransferase
AMA	Anti-mitochondrial antibodies
ANCOVA	Analysis of Covariance
AP	Alkaline phosphatase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BUN	Blood urea nitrogen
CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CK	Creatine kinase
CRF	case report form
CTMS	Clinical Trial Management System
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
ET	Early Termination
GGT	Gamma-glutamyl transferase
HDL-C	High density lipoprotein cholesterol
hs-CRP	High sensitivity C-reactive protein
INR	International normalized ratio
IRT	Interactive Response Technologies
LDH	Lactate dehydrogenase
LDL-C	Low density lipoprotein cholesterol
LOCF	Last observation carried forward
M1, M2, M3	Seladelpar (MBX-8025) metabolites
MedDRA	Medical Dictionary for Regulatory Activities
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NRS	Numerical rating scale
PBC	Primary biliary cholangitis
PPAR	Peroxisome Proliferator-Activated Receptor
PT	Prothrombin time
QoL	Quality of life
RBC	Red blood cells
SAP	Statistical analysis plan
SD	Standard deviation
TEAE	Treatment emergent adverse event
TG	Triglycerides
UDCA	Ursodeoxycholic acid
ULN	Upper limit of normal
UNS	Unscheduled
WBC	White blood cells
WHODD	World Health Organization Drug Dictionary

1. Introduction

This statistical analysis plan (SAP) is an abbreviated SAP which describes the analyses and presentations for the data collected for CymaBay's protocol CB8025-31735 "A 52-week, placebo controlled, randomized, Phase 3 study to evaluate the safety and efficacy of seladelpar in subjects with Primary Biliary Cholangitis and an inadequate response to or an intolerance to ursodeoxycholic acid (UDCA)", referred to as ENHANCE. The study is terminated early due to atypical histological findings from the phase 2 study of seladelpar in patients with nonalcoholic steatohepatitis, NASH (CB8025-21730). Therefore, this abbreviated SAP is created for the summary, analysis, and documentation of the collected safety data on seladelpar. Results of the analyses described in this SAP will be included in the abbreviated clinical study report (CSR).

Primary biliary cholangitis (PBC, formerly known as primary biliary cirrhosis) is a serious and potentially life-threatening autoimmune disease of the liver characterized by impaired bile flow (cholestasis) and accumulation of toxic bile acids (BA). The hallmark of PBC is cholestasis with an accompanying elevation in serum biomarkers including alkaline phosphatase (AP), gamma glutamyl transferase (GGT) and, depending on the severity of the disease, bilirubin and liver transaminases. The first line therapy for PBC is UDCA, a non-cytotoxic BA that has been the mainstay of treatment for more than twenty years (Poupon, et al., 1997). However, up to 40% of subjects have persistent elevation of AP and/or bilirubin despite UDCA and are considered inadequate responders (Corpechot, et al., 2008). Obeticholic acid (OCA), a synthetic analogue of chenodeoxycholic acid (CDCA), was approved under the provisions of accelerated approval regulations in the United States and European Union on 27 May 2016 and 12 December 2016, respectively. The approval was based on OCA's ability to significantly decrease AP levels and maintain a normal total bilirubin when, used as an add-on therapy in PBC patients who are inadequate responders to UDCA or, as a monotherapy in PBC patients who are intolerant to UDCA (Ocaliva, 2016). Despite the previously mentioned therapeutic interventions, it is evident that many PBC patients do not respond adequately to therapy and continues to have a progression of their disease (Kaplan, 2005; Kumagi, 2008; Momah, 2014) and additional treatments are needed. Seladelpar (MBX-8025) is an oral, once-daily administered, potent and selective peroxisome proliferator-activated receptors (PPAR) δ agonist (Bays, 2011; Jones, et al., 2017). Seladelpar is being developed for the treatment of PBC in subjects with inadequate response to UDCA or intolerance to UDCA and in nonalcoholic steatohepatitis.

2. Objective

The primary objective of this abbreviated SAP is to evaluate the safety of two seladelpar regimens (5 mg/day titrated to 10 mg/day and 10 mg/day) over treatment compared with that of the placebo.

3. Investigational Plan

3.1. Overall Study Design and Plan

The ENHANCE study was designed as a Phase 3 international, multicenter, double-blind, randomized, placebo-controlled 52-week dose ranging (placebo, 5/10 mg/day, and 10 mg/day), parallel treatment groups study. Due to the unexpected termination of the study, the actual study duration may vary.

The study planned to enroll approximately 240 subjects. Subjects were randomly assigned to receive placebo, seladelpar 5 mg titrated to 10 mg, or seladelpar 10 mg. Subjects were stratified by AP level (AP < 350 U/L and ≥ 350 U/L) and presence of significant pruritus (pruritus numerical rating scale [NRS] < 4 and NRS ≥ 4).

Study drug (placebo or seladelpar) was taken in a blinded manner orally once a day for a period of 52 weeks. After the first 6 months of treatment, evaluation of the initially assigned dose was performed in a blinded manner. Subjects assigned to the seladelpar 5/10 mg group who were not responders based on composite endpoint (defined as subjects with AP >=1.67 × upper limit of normal (ULN), < 15% decrease in AP, and Total bilirubin > ULN) at Month 6, and were tolerating study drug, were up titrated from seladelpar 5 mg to 10 mg for the remainder of the study. Those subjects initially assigned to placebo or 10 mg did not have their dose changed (see Section 9.3 of the study protocol). To avoid unblinding, all subjects were invited to the Dose Adjustment visit which occurred two weeks after Month 6 visit. See Appendix 11.1 for the schedule of study procedures.

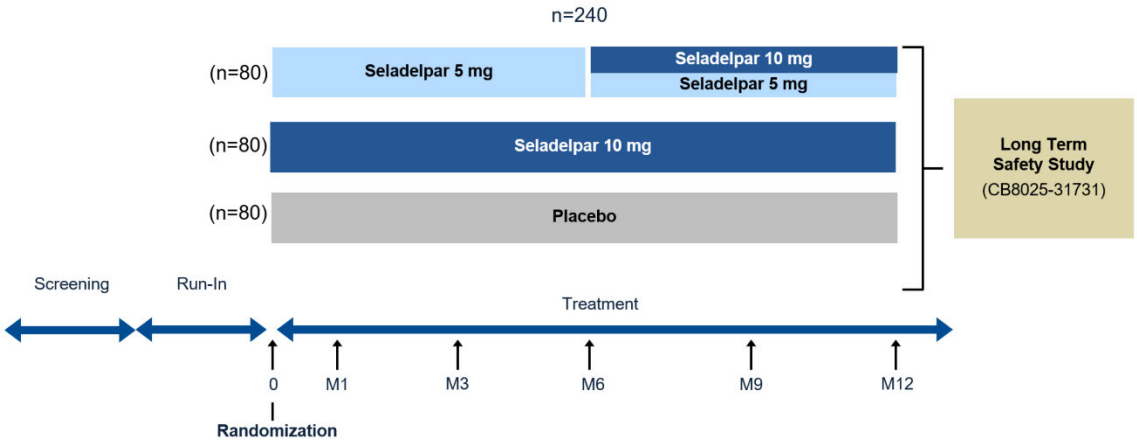
Subjects with an inadequate response to UDCA continued to receive UDCA throughout the study. Study specific UDCA supply was provided and taken during the study participation. UDCA supply was switched from pre-study supply to the study supply at the Screening visit and continued through the Week 52 visit. At the Week 52 visit, UDCA was switched to pre-study supply.

Subjects who met muscle safety monitoring criteria per Section 10.4.2 of the study protocol were eligible for dose-down titration. Subjects initially assigned to the seladelpar 10 mg group were down-titrated to 5 mg. Subjects initially assigned to the seladelpar 5 mg group were down-titrated to placebo and subjects assigned to placebo stayed on placebo.

The planned total duration of the study for each subject was up to 60 weeks. The screening period was up to 2 weeks, the run-in period was 2 weeks, the planned treatment period was 52 weeks with an option to enter the long-term study (CB8025-31731), and the follow-up period was 4 weeks (if not enrolled in the long-term study). Because the study was terminated early, the actual treatment duration varies.

The study design implements safety criteria to monitor subjects with potential drug induced liver injury, muscle injury, renal injury and acute pancreatitis with actions to either stop the study drug, to interrupt the study drug, to down-titrate the study drug or investigate the case prior to actions with the study drug.

The overall study design is illustrated as shown below:



3.2. Study Endpoints

This study was a pivotal study to evaluate the safety and efficacy of seladelpar. Due to the unexpected termination of the study, only limited efficacy and safety will be evaluated by the following endpoints:

Efficacy:

- Response on the composite endpoint of AP and total bilirubin at 6 months:
  - AP < 1.67 × upper limit of normal (ULN),
  - ≥ 15% decrease in AP, and
  - Total bilirubin ≤ ULN
- Proportion of subjects with AP ≤ 1.0 × ULN at 6 months
- Change from baseline in pruritus NRS at 3 and 6 months

Safety:

- Type, frequency, and severity of treatment-emergent adverse events (TEAEs) graded using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, Version 5.0)
- Absolute and change from baseline of laboratory tests including safety laboratory parameters, vital signs, body weight and body mass index values
- Change from baseline of Pruritus NRS on Month 1, 3, 6, 9 and 12
- Liver elastography (at selected centers)
- Abdominal ultrasound

4. General Statistical Considerations

Statistical analysis and generation of tables, figures, subject data listings, and statistical output will be performed using SAS Version 9.4 or higher.

Summary statistics will be displayed to provide an overview of the study results. For categorical parameters, the number and percentage of subjects in each category will be presented. The denominator for percentages will be based on the number of subjects appropriate for analysis.

Statistical tests of efficacy variables will be presented as 2-sided p-values rounded to 4 decimal places. P-values less than 0.0001 will be presented as "<0.0001" and p-values greater than

0.9999 will be presented as ">0.9999." Unless stated otherwise, statistical comparisons will be performed at the 0.05 level of significance.

The following reporting conventions apply generally to tables, listings and figures:

- Confidence intervals (CIs) will be presented as 2-sided 95% CIs unless specified differently for a given analysis.
- Summary statistics will consist of the number and percentage of subjects in each category for discrete variables, and the number of subjects (n), mean, standard deviation (SD), median, minimum, and maximum for continuous variables.
- All mean and median values will be formatted to one more decimal place than the measured value, up to three decimal places. Standard deviation values will be formatted to two more decimal places than the measured value, up to three decimal places. Minimum and maximum will be formatted to the same decimal place as the measured value.
- All percentages will be rounded to one decimal place. The number and percentage will be presented in the form XX (XX.X), where the percentage is displayed in parentheses.
- All listings will be sorted for presentation in order of treatment arm (randomized or actual treatment depending on analysis set of interest), study site, subject, date of procedure or event, and test/parameter name (if applicable).
- All analysis and summary tables will include the analysis set sample size (i.e., number of subjects) in the header.

4.1. Analysis Time Points

Unless specified otherwise, baseline is defined as the arithmetic mean of multiple pre-treatment measurements (Screening, Run-in, Day 1, and unscheduled [UNS] if applicable) preceding the first administration of study drug, or as the last measurement prior to the first administration of study drug if only a single value is available.

For assessments prior to the first date of study drug, the study day will be calculated as:

- Assessment date – date of first dose of study drug

For assessments on or after the first date of study drug, the study day will be calculated as:

- Assessment date – date of first dose of study drug + 1 day

If the assessment date is completely missing or partial, the study day will be missing.

Unless otherwise noted, all references to Day 1 refer to the day of study drug initiation for analytical purposes. Unless otherwise noted, all references to the last dose of study drug refer to the last dose of study drug taken across all study periods.

4.2. Analysis Visits

Data will be presented and analyzed according to the visit recorded in the database. In general, only those assessments which are assigned to an analysis visit will be included in the summary tables and figures and will be presented by visit.

As subjects do not always adhere to the protocol visit schedule, the following rules are applied to assign actual visits to protocol visit unless specified otherwise in analysis sections.

If a subject has 2 or more actual visits in one visit window, the visit closest to the target day will be used as the protocol visit for that visit window. If 2 actual visits are equidistant from the target day within a visit window, the later visit is used. If a visit window has no scheduled visits but does have unscheduled visits, then the unscheduled visit closest to the target day will be used.

The visit windows and the target days for each analysis visit are listed below.

Scheduled Visit	Target Day	Study Day Analysis Visit Window Range
Month 1 (Week 4)	Day 28	Days 2 - 56
Month 3 (Week 12)	Day 84	Days 57 - 133
Month 6 (Week 26)	Day 182	Days 134 - 189
Dose Adjust (Week 28)	Day 196	Days 190 - 235
Month 9 (Week 39)	Day 273	Days 236 - 319
Month 12 (Week 52)	Day 364	Days 320 - 378
Safety Follow-up (10 Days after EOT)	Day 10 after last dose	Day 3 - 14 after last dose
Safety Follow-up (4 Weeks after EOT)	Day 28 after last dose	> 14 days after last dose

Study days are relative to Day 1 (which is the day of study drug initiation).

For Visits Month 1 to Month 12, all scheduled and unscheduled assessments before or within 2 days after the last dose will be considered.

For two safety follow-up visits within one visit window, the above rules of the selection of two or more actual visits within one visit window will still apply.

4.3. Sample Size

Approximately 240 subjects from about 140 investigational sites worldwide were planned to be dosed in this study.

For the composite endpoint, the placebo group responder rate is estimated at less than 15% (Nevens et al., 2016). The seladelpar 10 mg dose group responder rate is estimated at 40%. With the use of a 2-sided test of equality of binomial proportions based on the Pearson chi-square test at the 5% level of significance, a sample size of 64 subjects per group provides greater than 90% power to detect a difference of 25% between the 10 mg seladelpar group and the placebo group.

The efficacy analysis of normalization of AP is estimated to have a placebo response rate of 5%. A 2-sided test of equality of binomial proportions based on the Pearson chi-square test at the 5% level of significance yields a sample size of 80 subjects per group. This sample size provides more than 90% power to detect a difference of 30% between the 10 mg seladelpar and placebo groups.

The efficacy analysis of change in pruritus NRS sample size calculation is based on a 2-sample 2-sided t-test at the 5% alpha level. The standard deviation is 3 (Lai, 2017). Under these assumptions, a total of 23 subjects per group provides ≥ 90% power to detect a treatment difference of ≥ 3 between the 10 mg seladelpar and placebo groups.

To account for subject dropout rate of > 15%, the planned number of study subjects for an adequately powered study is 240 subjects, or 80 subjects per treatment group. Randomization were centralized to ensure adequate blinding of the study.

4.4. Randomization, Stratification, and Blinding

Subjects were randomized in a blinded manner to placebo or seladelpar in a 1:1:1 scheme (placebo: seladelpar 5/10mg: seladelpar 10 mg). In addition, randomized subjects were stratified by AP level (AP < 350 U/L and ⩾ 350 U/L) and pruritus status (pruritus NRS < 4 and pruritus NRS ⩾ 4).

Randomization was performed centrally via Interactive Response Technologies (IRT) system at the Day 1 visit. A subject was considered formally enrolled in the study at the time of randomization and begin study drug dosing.

4.5. Analysis Set

4.5.1. Modified Intent-to-Treat (mITT)

The Modified Intent-to-Treat (mITT) set includes any subject who is randomized into the study and receives at least one dose of study drug. The mITT set will be used as the analysis set for the efficacy analysis and will be analyzed based on randomized treatment.

4.5.2. Safety Set

The Safety set includes any subject who receives at least one dose of study drug. Tables, listings, and figures based on the Safety set will be based on actual treatment in the event that it differs from the randomized treatment assignment. All safety analyses will be completed using the Safety set.

5. Subject Disposition

5.1. Disposition

The number and percentage of subjects who were randomized and treated, completed treatment, discontinued treatment with reason for treatment discontinuation, completed study, discontinued study with reasons of discontinuation, completed treatment and completed follow-up period, completed treatment and did not complete follow-up period, completed treatment and entered the long-term study (CB8025-31731), completed treatment and did not enter the long-term study will be summarized by treatment group and overall for the Safety set.

The primary reasons for treatment discontinuation are collected in the End of Treatment CRF and will be summarized with the following categories:

- Safety reason
  - Liver safety monitoring
  - Muscle safety monitoring
  - Serum creatinine monitoring
  - Pancreatic safety monitoring
  - Adverse events other than safety monitoring criteria

- Entered the study in violation of inclusion/exclusion criteria
- Required the use of prohibited concomitant medications
- Withdrawal of informed consent
- At the discretion of the Investigator for medical reasons
- Pregnancy
- At the discretion of the Investigator or Sponsor for non-compliance
- Significant protocol deviation
- Administrative decision by the Investigator or Sponsor or designee
- Lost to follow-up
- Death
- Other

The decision to terminate the study was communicated to participating sites on 24 November 2019. Due to sites utilizing different categories to capture the information (under Administrative decision or Other), an additional count of subjects that discontinued treatment on or after 24 November 2019 will be provided under 'Study Closure' category.

The primary reasons for study discontinuation are collected in the End of Study CRF and will be summarized with the following categories:

- Adverse event
- Withdrawal of informed consent
- Lost to follow-up
- Death
- Pregnancy
- Other

Similar to treatment disposition, an additional count of subjects that discontinued study on or after 24 November 2019 will be provided under 'Study Closure' category.

5.2. Protocol Deviations/Violations

Protocol deviations/violations will be recorded within the PPD Clinical Trial Management System (CTMS) and undergo cross-functional team review prior to database lock. The Study Deviation Guidance Document contains all potential protocol deviations, classified by CTMS subtype.

Major protocol violations can be related but not limited to study inclusion/exclusion criteria, trial conduct, use of prohibited medications, accidental unblinding during the treatment period, subject dosing compliance, or subject missing assessments.

A listing of protocol deviations and violations will be provided.

6. Demographics and Baseline Characteristics

The demographics, baseline characteristics and medical histories will be summarized for the Safety sets.

6.1. Demographics

Summary statistics will be provided by treatment group for the following continuous variables:

- Age (years)
- Weight (kg)
- Height (cm)
- Body mass index (BMI; kg/m^2)

Number and percentage will be provided by treatment group for the following categorical variables:

- Age group (< 65, ≥ 65 years)
- Sex (male, female)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino, Unknown)
- Region (North America, Latin America, EMEA, APAC)

6.2. Baseline Characteristics

The following variables indicated below will be summarized descriptively:

- Duration of PBC (time [in years] from diagnosis date to the informed consent date)
- MELD score (<12, 12-15, >15)
- Liver stiffness (kPa)
- Fibrosis Score derived from liver Stiffness (>=F1 to <F2, >=F2 to <F3, >=F3 to <F4, =F4, where the cut-off values for F1, F2, F3, and F4 are 7.1, 8.8, 10.7 and 16.9, respectively)
- Liver biopsy performed within 1 year from Day 1 (yes, no)
- Liver biopsy performed during run-in (yes, no)
- UDCA usage (yes, no)
- Total daily UDCA dose (mg, and mg/kg)
- Duration of prior UDCA usage (years)
- AP concentration (U/L)
- AP level (< 350 U/L and ≥ 350 U/L)
- Total bilirubin (TB) concentration (mg/dL)
- Total bilirubin level (≤1xULN, >1 - ≤2xULN, > 2xULN)
- ALT (U/L)
- AST (U/L)
- GGT (U/L)
- Platelet (counts/uL)
- INR
- Albumin (g/dL)
- Pruritus NRS (observed value, and categories < 4 and ≥ 4)
- AMA status (positive, negative, equivocal)

6.3. Medical History

A detailed medical history will be coded by System Organ Class (SOC) and Preferred Term (PT) using Medical Dictionary for Regulatory Activities (MedDRA). The dictionary version used for reporting the study will be described in the relevant table and listing footnotes. The number and percentage of subjects with any medical history will be summarized overall and for each system organ class (SOC) and preferred term (PT) for the Safety set. PBC history will be summarized for the Safety set.

7. Treatments and Medications

7.1. Prior and Concomitant Medications

Concomitant medications are defined as any medications ongoing at the start of study treatment or with a start date on or after the date of the first dose of study treatment. Prior medications are defined as medications with a stop date prior to the date of the first dose of study treatment.

Medications reported on the Prior and Concomitant medications case report form (CRF) pages will be coded by the World Health Organization Drug Dictionary (WHODD) version March 2018 format B3 and will be summarized by Anatomical Therapeutic Chemical (ATC) coding system class, generic name by treatment group for the Safety set. Subjects taking more than one medication in the same generic name or ATC class will be counted once. The dictionary version used for reporting the study will be described in the relevant table and listing footnotes.

For the purpose of inclusion in prior and/or concomitant medication tables, incomplete medication start and stop dates will be imputed. Additional details are provided in Appendix 11.2.

7.2. Concomitant Procedures

Concomitant procedures are defined as any therapeutic intervention (e.g. surgery/biopsy, physical therapy) or diagnostic assessment (e.g. blood gas measurement, bacterial cultures) performed during a subject's participation in this trial.

The number and percentages of subjects who had any concomitant procedures will be summarized by procedure and treatment group based on the Safety set.

7.3. Study drug and Extent of Exposure

Seladelpar was supplied in a blinded fashion as 5 mg and 10 mg capsules. Matching placebo was provided. The study drug (seladelpar or placebo) was administered orally, once daily for the duration of up to 52 weeks.

Exposure to study drug will be summarized by treatment group using descriptive statistics. Exposure (days) is defined as the date of the last dose of study drug – date of the first dose of study drug + 1. The numbers and percentage of subjects with the following exposure categories will be summarized:

- 1 to ⩽ 4 weeks (1 – 28 days)
- > 4 to ⩽ 8 weeks (29 – 56 days)
- > 8 to ⩽ 12 weeks (57 – 84 days)
- > 12 to ⩽ 26 weeks (85 – 182 days)
- > 26 weeks to ⩽ 39 weeks (182 – 273 days)
- > 39 weeks to ⩽ 52 weeks (274 – 364 days)
- > 52 weeks (> 364 days)

The total cumulative dose will be defined as the sum of the actual dose received across all study days. Average daily dose is cumulative dose divided by total days on study (from End of Study CRF). The average daily dose and cumulative dose will be summarized using descriptive statistics over the treatment period, using the formula as below:

Cumulative dose = sum of actual dose received from all segmented periods where for each segment, actual dose = actual dosage (mg/day) × [end day using the dosage – start day using the dosage + 1]. Titration date and dose interruption date will be used for calculation of the end/start day.

Average daily dose in each time period = cumulative dose in the treatment period/ [exposure days].

Exposure to UDCA will also be summarized by treatment group using descriptive statistics.

7.4. Treatment Modifications

7.4.1. Dose Up-Titration

During the study participation subjects might go through dose titration (see Section 3.1). For subjects who have safety concerns limiting up-titration, the dose adjustment visit (see Appendix 11.1) will still occur to evaluate subjects' status. Subjects will have a dose evaluation performed at the Month 6 visit to determine if dose up-titration is necessary. Dose evaluation and up-titration will be done in a double-blind manner.
The double-blind dose up-titration will occur if the following criteria are met:

No safety concerns limiting up-titration	AND	One of the following criteria: • AP ⩾ 1.67 x ULN, OR • < 15% decrease in AP comparing to baseline value, OR • Total bilirubin > 1 x ULN

Subjects who meet the criteria received the up-titrated dose at the Dose Adjustment visit. Subjects on 5 mg were up-titrated to 10 mg; subjects on 10 mg continued 10 mg; and subjects on placebo continued placebo.

7.4.2. Dose Down-Titration

Subjects who meet muscle safety monitoring criteria per protocol Section 10.4.2 are eligible for the dose down-titration: subject who initially assigned to 10 mg were down-titrated to 5 mg; subjects initially assigned to 5 mg, were down-titrated to placebo. Subjects initially assigned to placebo stayed on placebo. Dose down-titration was performed in a blinded manner.

A listing of Safety set subjects who experienced dose-down or interruptions due to safety monitoring or withdrawal criteria will be provided. Additional details on the dose-down titration analysis can be found in Section 8.2.

8. Efficacy Analysis

All efficacy analyses will be performed using the mITT analysis set. Statistical comparisons will be made using 2-sided tests and the overall significance level will be maintained at 0.05.

8.1. The 1st Efficacy Endpoint

The 1st efficacy endpoint is the number of responders on the composite endpoint of AP and total bilirubin at 6 months. A subject is designated as a responder if all three of the following conditions are met:

- AP < 1.67 × ULN at Month 6
- ≥ 15% decrease in AP at Month 6
- Total bilirubin ≤ ULN at Month 6

Subjects who discontinue treatment or do not provide an assessment at the specified timepoint for defining response will be considered as a non-responder.
The proportion of responders will be reported with its associated 95% exact (Clopper-Pearson) CI for each treatment group. Cochran-Mantel-Haenszel (CMH) test adjusted for both randomization stratification variables (AP level: < 350 U/L and ≥ 350 U/L; pruritus NRS: < 4 and ≥ 4) will be used to test the association between the treatment groups and p-value will be provided. CMH test will be performed for the comparison of 10 mg vs. placebo and 5 mg/10 mg vs. placebo separately.

If assumptions required for the CMH test, including but not limited to, small cell counts or all responses within a stratum are the same for both treatment groups, a continuity correction may be applied. In addition, Breslow-Day test will be used to detect whether the stratification variable is significant.

8.2. The 2nd Efficacy Endpoint

The 2nd efficacy endpoint is the number of responders that achieve normalization of AP at 6 months and will be conducted using the same approach specified for the 1st efficacy analysis.

8.3. The 3rd Efficacy Endpoint

The 3rd efficacy endpoint consists of the change from baseline in pruritus NRS at 3 and 6 months and its efficacy analysis is described in conjunction with its safety analysis in Section 9.8.

9. Safety Analysis

The purpose of this section is to describe the safety analyses for the study. All summaries of safety data will be based on the Safety set which reflects the actual treatment received by each subject.

9.1. Adverse Events

An AE includes any condition resulting from concomitant illnesses, reactions to concomitant medications, or progression of disease states. Pregnancy should be documented as an AE and should be reported to the clinical monitor and to the Sponsor immediately upon learning of the event. Pregnancies will be followed up through delivery or termination of the pregnancy.

Adverse events will be analyzed in terms of treatment-emergent adverse events (TEAEs), defined as any AE that newly appeared, increased in frequency, or worsened in severity after initiation of the study drug and up to 30 days after the last study medication administration. For AE reporting purposes, UDCA is not considered as a study drug. For the summaries of treatment-related AEs, a treatment-related TEAE is defined as an AE which was considered to be related (reported as “possible”, “probably”, or “definite” on the Adverse Events CRF page) to any study drug. AEs with a missing relationship will be presented in the summary table as a relationship category of “treatment-related”.

Adverse events will be coded by SOC and PT using MedDRA. The dictionary version used for reporting the study will be described in the relevant table and listing footnotes. The severity of AEs will be graded based on NCI CTCAE, Version 5.0, November 2017.

An overall summary of the number and percentage of subjects with any TEAE, serious TEAE, Grade 3 or above TEAE, treatment-related TEAE, treatment-related serious TEAE, treatment-related Grade 3 or above TEAE, TEAE leading to permanent withdrawal of study drug, treatment-related TEAE leading to permanent withdrawal of study drug, TEAE leading to study discontinuation, treatment-related TEAE leading to study discontinuation, TEAEs leading to dose interruptions, TEAEs leading to death, and treatment-related TEAE leading to death, will be provided by treatment group.

Tables summarizing the incidence of TEAEs in the Safety set will be generated for each of the following:

- TEAEs by MedDRA SOC and PT;
- TEAEs (Grade 3 or higher) by MedDRA SOC, PT and CTCAE grade;
- Treatment-related TEAEs by SOC and PT;
- Treatment-related TEAEs (Grade 3 or higher) by SOC, PT and CTCAE grade;
- TEAEs presented by PT;

- Serious TEAEs presented by SOC and PT.

Incidence tables will present TEAEs by SOC, PT, sorted by SOC by decreasing frequency of the number (n) and percentage of subjects (%) in the "All Seladelpar" group (then the 10 mg group, the 5/10 mg group and placebo group, if applicable). Counting of AEs will be by subject, and subjects will be counted only once within each SOC or PT. For tables categorized by severity, subjects with multiple events within a particular SOC or preferred term will be counted under the category of their most severe event with that SOC or preferred term. If the severity is missing for all occurrences of the AE, the subject will be counted only once in the 'Missing' category for severity.

For the purpose of inclusion in TEAE tables, incomplete AE onset will be imputed. Additional details are provided in Appendix 11.2.

Listings will be presented including the verbatim term, preferred term, and SOC as well as full details of TEAEs and serious AEs for all subjects in the Safety set.

9.2. Safety Monitoring Criteria and Withdrawal Criteria

Subjects who meet muscle safety monitoring criteria may be eligible for dose down-titration: subjects initially assigned to 10 mg will be down – titrated to 5 mg; subject initially assigned to 5 mg will be down-titrated to placebo; and subjects initially assigned to placebo will stay on placebo. Subjects with lab abnormalities will be monitored closely and may interrupt study drug or discontinue study drug if the criteria are met. A detailed description of the safety monitoring and withdrawal criteria including decision rules can be found in Appendix 11.3.

A listing of safety monitoring criteria met by subjects in Safety set will be provided.

9.3. Clinical Laboratory Evaluations

Clinical laboratory values from the central laboratory will be graded according to NCI CTCAE version 5.0 for selected tests. Summary tables will be presented for clinical laboratory tests with numeric values by treatment group for subjects in the Safety set.

Hematology and Biochemistry will be assessed at all visits including early termination (ET) and UNS, if applicable. Hepatitis B and C testing, and urine drug screen will only be assessed at the screening visit.

Conventional units and ranges will be used for reporting. Changes from baseline by each scheduled post-baseline visit will be presented.

A listing of subjects with lab CTCAE Grade 2 or above will be presented by subject, visit, date, and lab tests.

9.3.1. Hematology

Erythrocyte count (RBC), hemoglobin, hematocrit, leukocyte count (WBC), WBC differentials (%), neutrophils, lymphocytes, eosinophils, monocytes, will be collected at Screening, Run-in, Day 1 and every study visit as noted in the schedule of assessments

(Appendix 11.1). Platelets, prothrombin time (PT), and international normalized ratio (INR) will also be performed locally at those above visits if deemed necessary by the investigator. Hematology results and change from baseline will be summarized by treatment and visit for the Safety set.

9.3.2. Biochemistry

AP, albumin, ALT, AST, GGT, protein, total bilirubin, direct/indirect bilirubin, aldolase, sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN)/urea, serum creatinine, estimated glomerular filtration rate (eGFR), cystatin C, CK, venous glucose, troponin I, LDH, TG, total cholesterol, HDL-C, LDL-C, amylase, lipase, and MELD will be collected at Screening, Run-in, Day 1 and every study visit as noted in the schedule of assessments (Appendix 11.1).

Biochemistry parameters of special interest (ALT, AST, total bilirubin, creatinine, CK, amylase, lipase, and albumin), along with platelets from hematology, will be graded according to NCI CTCAE version 5.0. For these biochemistry parameters of special interest, a shift table representing the shift from the baseline grade to the most severe grade during treatment will be provided by treatment group for each of these laboratory tests.

Model for End-Stage Liver Disease (MELD) score will be summarized descriptively.
MELD Score is defined in the following.
MELD(i) score = 10*[0.957 x LN(creatinine mg/dL) + 0. 378 x LN(bilirubin mg/dL) + 1.120 x LN (INR) + 0.643].
All laboratory values are rounded to 10th decimal place when calculating the score, and MELD(i) is rounded to the nearest whole number.
All laboratory values less than 1.0 will be set to 1.0 when calculating a candidate's MELD(i) score. Laboratory values for creatinine greater than 4.0mg/dL will be set to 4.0 mg/dL; sodium values less than 125 mmol/L will be set to 125 and sodium values greater than 137 mmol/L will be set to 137.
If MELD(i) is less than or equal to 11 then MELD = MELD(i).
If MELD(i) is greater than 11 then MELD = MELD(i) + (1.32 *(137 - (Na)) – (0.033*MELD(i)*(137 – Na))

9.4. Abdominal Ultrasound

Subjects had two abdominal ultrasound exams at Run-In and at Week 52, or ET (if applicable). A listing of abdominal ultrasound results will be provided.

9.5. Liver Elastography

Liver elastography exam will be used to evaluate liver fibrosis through a noninvasive imaging technique. Subjects had three liver elastography exams at select centers at Run-In, Month 6, Month 12 visits, and ET visit (if applicable).

Most liver elastography exams were performed using transient elastography. A table summary for transient elastography results and change from baseline will be presented by

treatment and visit for the Safety set. A listing of all liver elastography results in company with each subject's cirrhosis status at baseline will be provided by subject.

9.6. Vital Sign and Weight Measurements

Vital signs were recorded at Screening, Run-in, Day 1 and every study visit as noted in the schedule of assessments (Appendix 11.1). Systolic and diastolic blood pressure, heart rate, respiratory rate, temperature and weight will be collected.

Summary tables presenting observed values and changes from baseline will be presented for vital sign data, including systolic blood pressure, diastolic blood pressure, temperature, heart rate, respiration, weight, and body mass index (body mass index will be derived from weight and height) at each applicable post-baseline visit by treatment group for subjects in the Safety set. Changes from baseline to each scheduled post-baseline visit will be presented. International System of Units will be applied in presenting the results.

9.7. Electrocardiogram

A 12-lead electrocardiogram (ECG) were obtained in supine position after at least 5 minutes of rest at Screening, Day1, Month 6, Month 12, Follow-up, ET and UNS, if applicable. Heart rate (beats/minute), PR interval, RR interval, QRS interval, QT interval, QTcB interval, QTcF interval and ECG interpretation will be collected. For ECGs which are abnormal, the abnormality should be specified.

For the Safety set, a shift table from baseline to the worst post-baseline record will be presented for ECG interpretation results.

9.8. Pruritus NRS

The weekly pruritus score will be calculated by recording the daily pruritus score each day for seven days and then taking the mean value of the seven days' daily recorded data. If any data are available for a given week, the available NRS results will be used for the calculation of the weekly mean. Only assessments before or within 2 days after the last dose will be used. The following analysis windows will be applied to calculate weekly means:

Month (Week)	Days used in calculation of weekly mean
Month 1 (Week 4)	Days 22 - 28
Month 3 (Week 12)	Days 78 - 84
Month 6 (Week 26)	Days 176 - 182

Baseline pruritus NRS is defined as the mean of the all daily recorded scores during run-in. Change from baseline in the weekly averaged pruritus NRS for Month 1, 3, and 6 together with the baseline pruritus NRS, will be summarized for the Safety set by treatment and visit using observed cases. The summary will be repeated in subjects with baseline NRS>=4.

Pruritus NRS change from baseline at 3 and 6 months will be evaluated using an analysis of covariance (ANCOVA) model with term for treatment factor and baseline pruritus score as

covariate. The LS means for the change by treatment and the associated SE, the LS means for the difference between treatment groups and associated 2-sided 95% CIs and 2-sided p-values will be derived from the model. The analysis will be repeated in subjects with baseline NRS>=4.

10. Interim Analysis

No formal or informal interim analysis for determination of efficacy is planned for this study.

11. Modifications from Approved Analysis Plan

This version 2.0 is an amendment of the approved version 1.0, to include a small degree of efficacy analysis.

12. References

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13. Appendices

13.1. Schedule of Study Procedures

Visit	Screening	Run-In	Randomization	Month 1	Month 3	Contact 1[1]	Month 6	Dose Adjust	Contact 2[1]	Month 9	Contact 3[1]	Month 12[12]	Follow Up	ET	UNS
Target Day	W -4 to -2	W -2	Day 1	W 4	W 12	W 19	W 26	W 28	W 32	W 39	W 45	W 52	4 weeks fter W 52		
Informed Consent	X														
Demographics															
Eligibility	X														
Randomization			X												
Dose Evaluation[2]							X								
Up-Titration								X							
Medical History[3]	X														
AE		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior and Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs and Weight	X	X	X	X	X		X	X		X		X	X	X	
Height	X														
Physical Exam	X	X[4]	X	X[4]	X[4]		X	X[4]		X[4]		X	X	X	X[4]
ECG	X		X				X					X	X	X	
Hematology[5,6]	X	X	X	X	X		X	X		X		X	X	X	X
Biochemistry[5]	X[7]	X	X	X	X		X	X		X		X	X	X	X
Exploratory Measures[5]	X[8]	X	X[8]	X	X		X	X		X		X[8]	X	X[8]	
Hepatitis B and C	X														
Serum Pregnancy Test[9]	X	X	X	X	X		X			X		X	X	X	
Back-up Blood Sample[5]		X	X	X	X		X			X		X	X	X	
Urine Drug Screen	X														
Pruritus NRS[10]	X	X	X	X	X		X			X		X		X	
5D-itch[10]		X	X	X	X		X			X		X		X	
PBC-40 QoL[10]		X	X	X	X		X			X		X		X	
PGI-S[10]		X	X	X	X		X			X		X		X	
PGI-C[10]				X	X		X			X		X		X	
Abdominal Ultrasound		X										X		X	
Liver Elastography (selected sites)			X				X					X		X	
Liver Biopsy[11]			X												
UDCA Dispense	X		X		X		X			X					

Study Drug Dispense			X		X		X	X		X					
Study Drug Compliance and Accountability				X	X	X[13]	X	X	X[13]	X	X[13]	X		X	
UDCA Accountability		X	X	X	X		X			X		X		X	

Abbreviation: AE=adverse events; AMA=anti-mitrochondrial antibodies; ECG=electrocardiogram; ET=Early Termination; NRS=numerical rating scale; PBC=primary biliary cholangitis; PGI-C=patient global impression of change; PGI-S=patient global impression of severity; QoL=quality of life; UDCA=ursodeoxycholic acid; UNS=Unscheduled visit; W=week.

1. Subject contact will be performed over phone or email communication.
2. All subjects will be evaluated for dose up-titration in a blinded manner. For subjects who met the up-titration criteria, dose up-titration will requested. Dose up-titration will occur at Dose Adjustment visit.
3. Including PBC history, liver biopsy, liver elastography, alcohol consumption, evidence of other form of liver disease, and HIV.
4. Symptoms-directed (brief) physical examination.
5. Blood will be collected after at least an 8-hour overnight fast. If the subject forgets to fast prior to the blood collection, the site will record it in the source document and continue to draw labs.
6. PT and INR will also be performed locally at the Screening visit, Run-In, and during the treatment period if deemed necessary by the Investigator.
7. If at screening and unexpected abnormal CK level is observed, re-test the subject to confirm eligibility.
8. Screening visit: only AMA will be performed. Fat-soluble vitamins will be performed at Day 1, Week 52 and ET (if applicable) only.
9. Serum pregnancy test will be performed in women of childbearing potential only. Additional on-treatment pregnancy testing may be performed at the investigator's discretion or per local regulatory requirements.
10. Pruritus NRS, 5-D itch, PBC-40, and PGI-S and PGI-C data will be collected via e-diary. Subjects will be asked to complete (1) pruritus NRS: on a daily basis up from Run-In Visit and through the first 6 months of treatment. After six months NRS will be collected for seven consecutive days during each month up to the Month 12 visit. (2) 5-D itch will be collected bi-weekly from Run-In Visit up until the Month 6 visit; after Month 6, 5-D itch will be collected at clinic visit only. 3) PBC-40, PGI-S, PGI-C will be collected during the clinic visits only.
11. Only subjects willing to undergo liver biopsy. PT and INR must be performed within 2 weeks prior to liver biopsy. If a subject had liver biopsy performed within 1 year from Day 1, sites will attempt to collect biopsy material. A follow up liver biopsy will be performed after 3 years (± 3 months) of treatment during long-term study (CB8025-31731).
12. Subjects will be invited to participate in the long-term study (CB8025-31731). Subjects who consent to participate in CB8025-31731 will have the Month 12 visit combined with the Day 1 visit in the CB8025-31731 study and continue dosing.
13. Only study drug compliance to be evaluated.

13.2. Date Imputation Guideline

If dates are missing or incomplete for an AE (including deaths) or prior/concomitant medications, the following rules will apply:

Incomplete Start Date:

If the stop date is not missing, and the imputed start date is after the stop date, the start date will be imputed by the stop date.

Missing day and month

- If the year is the **same** as the year of the first dosing date, then the day and month of the first dosing date will be assigned to the missing fields.
- If the year is **prior to** the year of first dosing date, then December 31 will be assigned to the missing fields.
- If the year is **after** the year of first dosing, then January 1 will be assigned to the missing fields.

Missing day only

- If the month and year are the **same** as the year and month of first dosing date, then the first doing date will be assigned to the missing day.
- If either the year of the partial date is **before** the year of the first dosing date or the years of the partial date and the first dosing date are the same but the month of partial date is **before** the month of the first dosing date, then the last day of the month will be assigned to the missing day.
- If either the year of the partial date is **after** the year of the first dosing date or the years of the partial date and the first dose date are the same but the month of partial date is **after** the month of the first dosing date, then the first day of the month will be assigned to the missing day.
- If the stop date is not missing, and the imputed start date is after the stop date, the start date will be imputed by the stop date, i.e. set to the stop date.

Missing day, month, and year

- No imputation is needed; the corresponding AE will be included as TEAE provided the end date of the AE is after the first dose date or the end date is also missing.

Incomplete Stop Date:

If the imputed stop date is before the start date, then the imputed stop date will be equal to the start date.

Missing day and month

- If the year of the incomplete stop date is the **same** as the year of the last dosing date, then the day and month of the last dosing date will be assigned to the missing fields.
- If the year of the incomplete stop date is **prior to** the year of the last dosing date and prior to the year of the first dosing date, then December 31 will be assigned to the missing fields.
- If the year of the incomplete stop date is **prior to** the year of the last dosing date but is the same as the year of the first dosing date, then the first dosing date will be assigned to the missing date.
- If the year of the incomplete stop date is **after** the year of the last dosing date, then January 1 will be assigned to the missing fields.

Missing day only

- If the month and year of the incomplete stop date are the same as the month and year of the last dosing date, then the day of the last dosing date will be assigned to the missing day.
- If either the year of the partial date is not equal to the year of the last dosing date or the years of the partial date and the last dosing date are the same but the month of partial date is not equal to the month of the last dosing date, then the last day of the month will be assigned to the missing day.

13.3. Safety Monitoring Criteria and Withdrawal Criteria

Liver Safety Monitoring

1. Elevation of ALT/AST

Normal ALT/AST at baseline

- ALT/AST > 5 × ULN and total bilirubin ≤ 1 × ULN: **Interrupt study drug.** Repeat AST, ALT, total bilirubin, and INR within 3 days and closely follow the subject (see Appendix B of the protocol). Study medication can be restarted only if a firm competing etiology is identified and liver tests return to baseline.
- ALT/AST > 5 ULN and total bilirubin > 1 × ULN:
    - Subjects with normal total bilirubin at baseline: **Stop study drug.** Repeat AST, ALT, total bilirubin, and INR within 3 days and closely follow the subject (see Appendix B of the protocol).
    - Subjects with elevated total bilirubin at baseline:
        - Total bilirubin > 1.5 × baseline: **Stop study drug.** Repeat AST, ALT, total bilirubin, and INR within 3 days and closely follow the subject (see Appendix B of the protocol).
        - Total bilirubin ⩽ 1.5 × baseline： **Interrupt study drug.** Repeat AST, ALT, total bilirubin, and INR within 3 days and closely follow the subject (see Appendix B of the protocol). Study medication can be restarted only if a firm competing etiology is identified and liver tests return to baseline.

Elevated ALT/AST at baseline:

- ALT/AST > 3 × baseline AND INR ≤ 1.5 × ULN AND no liver-related symptoms (e.g., nausea, vomiting, right upper quadrant pain, loss of appetite, dark urine, or jaundice): **Continue study drug.** Repeat AST, ALT, total bilirubin, and INR within 3 days. Closely follow the subject (see Appendix B of the protocol).
- ALT/AST > 3 × baseline AND INR > 1.5 × ULN AND no liver-related symptoms (e.g., nausea, vomiting, right upper quadrant pain, loss of appetite, dark urine, or jaundice): **Interrupt study drug.** Repeat AST, ALT, total bilirubin, and INR within 3 days and closely follow the subject (see Appendix B of the protocol). Study drug can be restarted only if a firm competing etiology is identified and liver tests return to baseline.

2. Liver-related symptoms (e.g., nausea, vomiting, right upper quadrant pain, loss of appetite, dark urine, or jaundice) AND ALT/AST > 3 × baseline (irrespective of baseline levels): **Interrupt study drug.** Repeat AST, ALT, total bilirubin, and INR within 3 days. Closely follow the subject (see Appendix B of the protocol). Study drug can be restarted only if a firm competing etiology is identified and liver tests return to baseline.
3. Elevation of total bilirubin > 1.5 × baseline, regardless of ALT or AST levels, AND indicators of immunological reaction (e.g., rash, eosinophilia > 5%) OR liver-

related symptoms (e.g., nausea, vomiting, right upper quadrant pain, loss of appetite, dark urine, or jaundice): **Interrupt study drug**. Repeat AST, ALT, total bilirubin, and INR within 3 days and closely follow the subject (see Appendix B of the protocol). Study drug can be restarted only if a firm competing etiology is identified and liver tests return to baseline.

4. Hepatic decompensation (e.g., decompensated cirrhosis with gastro-esophageal variceal bleeding, ascites, or hepatic encephalopathy) during the study: **Stop study drug** and closely follow the subject (see Appendix B of the protocol).
5. Close monitoring of a subject is not possible (see Appendix B of the protocol): **Stop study drug**.

Muscle Safety Monitoring

1. CK > 5 × ULN with musculoskeletal symptoms: **Stop study drug**. Repeat the test within 3 days. Follow the subject weekly until resolution or stabilization.
2. CK > 5 × ULN without musculoskeletal symptoms: repeat the test within 3 days. If on repeat test CK is > 2.5 × ULN, stop study drug. Follow the subject weekly until the event resolution or stabilization.
3. CK > 2.5 × ULN and ⩽ 5 × ULN regardless to musculoskeletal symptoms: repeat the test within 3 days. If the test is confirmed, **study drug will be continued at a decreased dose**. For subjects on 5 mg, the study drug will be switched to placebo.

Serum Creatinine Monitoring

1. Serum creatinine > 2.0 × ULN: Stop study drug. The subject should be monitored weekly until resolution or stabilization.
2. Serum Creatinine > 1.5 × ULN and ⩽ 2.0 × ULN: Interrupt study drug. Repeat the test within 3 days. If the test is confirmed and no alternative etiology is identified, stop study drug. If alternative etiology is identified, study drug may be restarted after serum creatinine returns to baseline values. The subject should be monitored weekly until event resolution.

Pancreatic Safety Monitoring

1. Amylase > 3 × ULN and/or lipase > 3 × ULN without clinical symptoms of acute pancreatitis: repeat the test within 3 days. If the test confirms suspicion, interrupt study drug. Abdominal imaging is to be performed to exclude an alternative cause for the event. Study drug might be restarted only if a firm competing etiology of acute pancreatitis is identified.
2. Amylase > 3 × ULN and/or lipase > 3 × ULN with clinical symptoms of acute pancreatitis: interrupt study drug. Repeat the test within 3 days. Abdominal imaging is to be performed to exclude an alternative cause for the event. Study drug might be restarted only if a firm competing etiology of acute pancreatitis is identified.