Statistical Analysis Plan

Sponsor:	Enanta Pharmaceuticals, Inc.
Protocol No:	EDP 305-201
PRA Project Id:	ENA30501-30501
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Title:	A Phase 2 Dose Ranging, Randomized, Double Blind, Placebo-Controlled Study Evaluating the Safety, Tolerability, Pharmacokinetics and Efficacy of EDP-305 in Subjects with Primary Biliary Cholangitis (PBC) with or without an Inadequate Response to Ursodeoxycholic Acid (UDCA)
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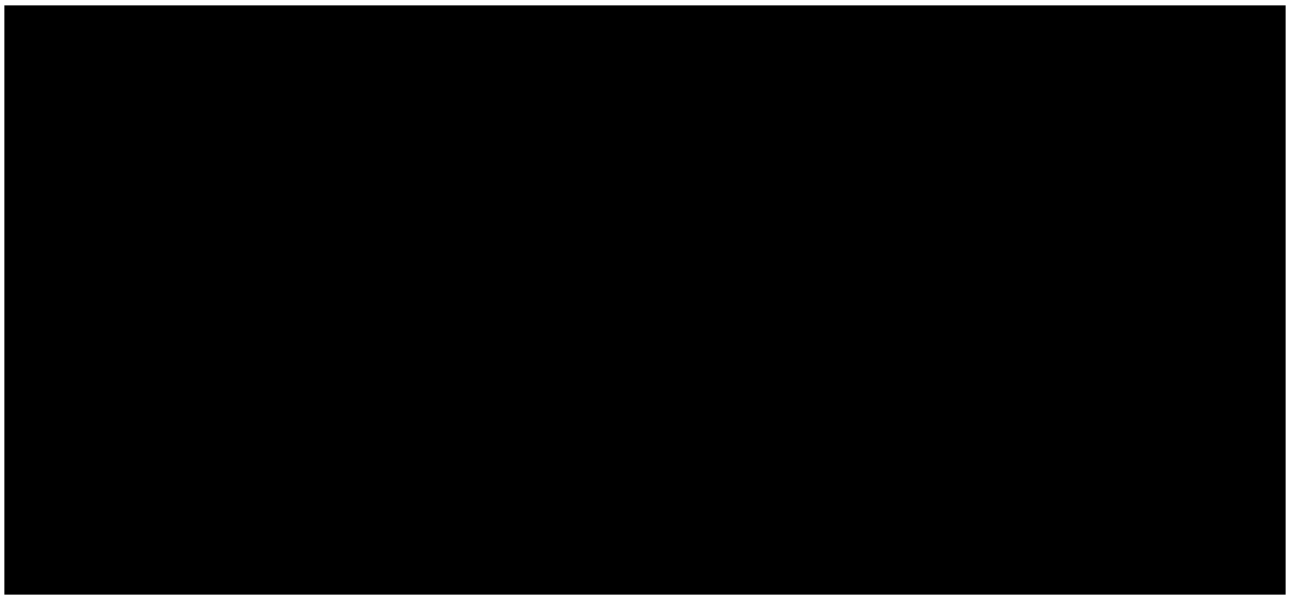

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1 Purpose

The Statistical Analysis Plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under Enanta Pharmaceuticals, Inc. Protocol EDP 305-201.

2 Scope

This plan is a living document that is created during the study start-up. The SAP will be drafted within three months of final CRF and maintained throughout the lifecycle of the study. The SAP will be amended with any changes that occurred during the course of the study and finalized prior to database lock. The SAP and amended SAP will be approved and signed off by the Project Manager and the Sponsor.

The SAP outlines the following:

- Study objectives
- Study design
- Variables analyzed and analysis populations
- Applicable study definitions
- Statistical methods regarding important protocol deviations, study drug exposure, efficacy analysis, concomitant medications, adverse events handling, laboratory data and physical examinations
- Study conduct methods for maintaining blinding of efficacy lab data during the course of the study

3 Introduction

This SAP describes the statistical methods to be used during the reporting and analyses of data collected under Enanta Pharmaceuticals, Inc.'s Protocol EDP 305-201, titled "A Phase 2 Dose Ranging, Randomized, Double Blind, Placebo-Controlled Study Evaluating the Safety, Tolerability, Pharmacokinetics and Efficacy of EDP-305 in Subjects with Primary Biliary Cholangitis (PBC) with or without an Inadequate Response to Ursodeoxycholic Acid (UDCA)." The study protocol provides conduct for a phase 2 randomized, double blind, dose-ranging placebo-controlled study to evaluate the safety, tolerability, efficacy, and pharmacokinetics of compound EDP-305 in subjects with PBC, with or without inadequate response to UDCA. Both males and females may be enrolled in the study, though the condition PBC is mainly found in women (10:1 women versus men). Suspicion of a potential PBC diagnosis is raised by an elevation of alkaline phosphatase (ALP) noted on screening blood tests obtained during routine office visits.

This SAP should be read in conjunction with the study protocol and case report form (CRF). This version of the plan has been developed using the protocol dated 02Apr2018 (Amendment 2.0) and CRF dated 01Aug2018. Any further changes to the protocol or CRF may necessitate updates to the SAP.

Changes following approval of this SAP will be tracked in the SAP Change Log and a final amended version will be issued for Sponsor approval prior to database lock, and subsequent unblinding of treatment codes and efficacy lab data for final study results delivery.

Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the clinical study report.

[redacted]

4 Study Objectives

The primary objective of the study is to evaluate the effect of EDP-305 on alkaline phosphatase (ALP) levels.

The secondary objectives of the study are as follows:

- To evaluate the safety and tolerability of EDP-305

- To evaluate the effects of EDP-305 on bilirubin levels
- To evaluate the effects of EDP-305 on other markers of liver function
- To evaluate the effects of EDP-305 on non-invasive markers of liver fibrosis
- To evaluate the effects of EDP-305 on inflammatory markers
- To evaluate the effects of EDP-305 on lipids
- To evaluate the effects of EDP-305 on pruritus
- To evaluate the effects of EDP-305 on Quality of Life (QoL)
- To evaluate the pharmacokinetics (PK) of EDP-305 and metabolites in plasma
- To evaluate the pharmacodynamics (PD) of EDP-305

5 Study Design

The study is a double blind, placebo-controlled study to compare 2 orally-administered dose levels (1 and 2.5 mg, respectively) of EDP-305 versus placebo for treatment of PBC.
The study is composed of 3 phases or periods:

- Screening period which includes the Screening Visit and may occur over a time period of 28 days prior to the first dose of study drug
- Treatment period which begins with the first dose of study drug on Day 1 and concludes with the End of Treatment (EOT) Visit on Day 84 (Week 12)
- Safety Follow-up period which includes the End of Study (EOS) Visit on Day 112.

Given that knowledge of ALP levels and other laboratory test results may lead to unblinding of treatment assignment, laboratory assessment data will remain blinded to the Enanta and PRA study blinded staff members by exclusion from scheduled data transfers, until after database lock. See Section 6.1.1 for a list of blinded laboratory test parameters.

Total planned enrollment is approximately 119 subjects based on a target of 105 after a 10% discontinuation rate. Enrollment will take place at approximately 90 sites located in the US as well as international locations (Australia, Austria, Belgium, Canada, France, Germany, Netherlands, Spain, and Great Britain).

The total maximum length of time of participation for each subject enrolled in the study will be approximately 20 weeks based on a maximum of 28 days for the Screening Period, 12 weeks for the Treatment Period and 4 weeks for the Follow-up Period.

The planned sample size is approximately 105 subjects. Group sample sizes of 45 in each active arm and 15 in the placebo arm achieve 83.552% power to detect a ratio of the group proportions of 40%. The proportion in the smallest active arm is assumed to be 0.4000 under the null hypothesis and 0.0400 under the alternative hypothesis. The proportion in the placebo arm is 10%. The test statistic used is the two-sided Mantel-Haenszel test. The significance level of the test is 0.05.

To account for a 10% discontinuation rate, 14 additional subjects will be enrolled to attempt to have 105 who complete treatment, bringing the total number of subjects enrolled to 119.

PASS software version 14 was used to calculate the sample size.

Subjects will be asked to participate in the PK/PD substudy. The randomization schedule will be developed to allow for balance between the treatment groups within the substudy. For all non-PK/non-PD analysis purposes, the subjects in the substudy will be combined with the subjects not in the substudy.

In order to achieve this balance subjects will be stratified by:

1) prior use of fibrates

2) prior and/or current use of UDCA

Note that both 1) and 2) may be applicable for a given subject. In addition, a subset of subjects will be included in the PK/PD substudy.

Subjects will be randomized to 3 treatment groups in a 3:3:1 ratio after stratification:

- Treatment Group 1: EDP-305 1 mg orally for 12 weeks
- Treatment Group 2: EDP-305 2.5 mg orally for 12 weeks
- Treatment Group 3: Placebo (PBO) orally for 12 weeks

A minimum of 10 subjects per treatment group will be included in the PK/PD substudy.

Triangle Biostatistics generated the randomization schedule and provided it to Bioclinica as the IWRS vendor, for incorporation into the IWRS

6 Statistical Considerations

All analyses will use SAS version 9.4 or higher.

Continuous and discrete variables will be summarized using an 8-number summary (n, mean, standard deviation, median, 25th quartile, 75th quartile, minimum and maximum values). The median, minimum and maximum values will be displayed to the same level of precision as the raw data, the mean to one additional decimal place and the SD to two additional decimal places.

Categorical variables will be summarized using frequencies and percentages based on the specified population total. Variables will be summarized by treatment group.

Statistical hypothesis testing will be conducted to compare treatment groups, using 2-sided tests at alpha = 0.05.

6.1 Study Analysis Populations

The following analysis populations are planned:

- Safety population: All subjects who received at least one dose of study drug. Subjects will be included in the treatment group that corresponds to the study drug received during the study.
- Full Efficacy (FE) population: All subjects who received at least one dose of study drug. Subjects will be included in the treatment group that corresponds to the planned randomized study drug.
- Per Protocol (PP) population: All subjects who receive at least one dose of study drug; did not have any important protocol deviations (IPDs) during the course of the study; and have ALP data at Baseline and Week 12. Since misallocation of study drug is always an IPD, planned treatment will always match actual treatment received in this population, which these subjects will be grouped according to.
- Pharmacokinetic (PK) Population: All subjects receiving active study drug and having any measurable plasma concentration of study drug at any timepoint. This includes subjects in the PK/PD substudy population.
    - The PK/PD Substudy Population consists of subjects who have additional PK and PD samples at a subset of study sites; and an additional ALP sample will be collected at these timepoints.

6.1.1 Blinded Laboratory Parameters

The following laboratory parameters are considered potentially unblinding (as to study treatment) when values would be viewed, and therefore need to remain unseen and inaccessible by the Enanta and PRA blinded staff until the official unblinding of the study following database lock.

- ALP Levels;
- The Laboratory parameters for Chemistry panel and Hematology panel are listed in the Appendix 6.

6.2 Baseline

For the primary endpoint, baseline will be defined in 3 ways: 1.) the average between the screening and the day 1 visits. If either is missing, the non-missing value will be considered baseline for this approach. This is the primary definition for the study 2.) The Day 1 value or the last value prior to first dose of study drug. 3.) The value from the screening visit as the baseline. The primary endpoint will be evaluated using all 3 baseline calculations. For all secondary and safety endpoints, baseline will be defined using method 2.) above.

6.3 Study Day Windows

The windows for all visits including PK draws appear in table below:

Visit	Target Day	Time window
Screening	Day -1	Day -28 to Day -1
Day 1	Day 1	N/A
Day 3	Day 3	N/A
Week 2	Day 14	Day 4 to Day 21
Week 4	Day 28	Day 22 to Day 42
Week 8	Day 56	Day 43 to Day 70
Week 12	Day 84	Day 71 to less than or equal to End of Treatment+7 days
Treatment-Free Follow-up Week 4	Day 112	Greater than End of Treatment+7 days to last visit

a. Samples at each visit should be obtained at different times postdose relative to each of the other visits (2, 4, and 8)

b. The target day for the screening visit is Day -1 during the period of Day -28 to Day -1

The relative day will be computed for each laboratory, vitals, ECG and PD data point. The relative day will be calculated as visit date-date of first dose+1. For data collected prior to first dose, the relative day will be calculated as visit date-date of first dose. When there are multiple observations within a visit window, the value closest to the target day will be analyzed..

PK/PD Draw Timing

		Population		
Visit	Target Day	PK/PD Substudy (PK, C4, FGF19, BA, and additional ALP samples)	For subjects not substudy	
			PK	PD (FGF19, BA, C4)
Day 1	Day 1	At predose and 2, 6, and 8 hr postdose	at predose and two samples postdose; • First sample collected 1 to 3 hours postdose • Second sample at least 1 hour later	At predose
Week 2	Day 14	at predose and two samples postdose; • First sample collected 1 to 3 hours postdose • Second sample at least 1 hour later	at predose and two samples postdose; • First sample collected 1 to 3 hours postdose • Second sample at least 1 hour later	At predose
Week 4	Day 28	at predose and two samples postdose; • First sample collected 1 to 3 hours postdose • Second sample at least 1 hour later	at predose and two samples postdose; • First sample collected 1 to 3 hours postdose • Second sample at least 1 hour later	At predose
Week 8	Day 56	at predose and two samples postdose; • First sample collected 1 to 3 hours postdose • Second sample at least 1 hour later	at predose and two samples postdose; • First sample collected 1 to 3 hours postdose • Second sample at least 1 hour later	At predose
Week 12	Day 84	At predose and 2, 6, and 8 hr postdose	at predose and two samples postdose; • First sample collected 1 to 3 hours postdose • Second sample at least 1 hour later	At predose

6.4 Multiplicity

No adjustments for multiplicity will be performed.

7 Subject Disposition

7.1 Disposition of Subjects

The number of subjects screened, randomized, randomized and treated, randomized and not treated, and the number of subjects in the analysis populations will be summarized.

The number and percentage of subjects will also be summarized for the following subject disposition categories:

- Completed study drug treatment per protocol
- Discontinued study drug early and the reason for discontinuation
- Completed the study including follow-up period
- Discontinued from the study early and the reason for discontinuation

7.2 Important Protocol Deviations

As a guideline, important protocol deviations (IPDs) are:

- Non-compliance with study drug
- Pregnancy
- Other deviations that violate inclusion or exclusion criteria
- Outside Study Windows

The occurrence of protocol deviations will inform which subjects to include in the Per Protocol population.

The Per Protocol population must be finalized prior to the post-freeze data review meeting (or earlier), prior to database lock

Subjects indicating reason for discontinuation at end of treatment visit as Other Protocol Deviation will be listed along with their deviation reason, demographics and study drug group for inclusion in the CSR based on the deviation data entered into CTMS.

7.3 Extent of Study Drug Exposure and Compliance

Exposure to study drug, number of days dose is taken and compliance with study drug dosing will be summarized by treatment group using the Safety Population. Study drug accountability including bottle types, dispensed tablets and returned tablets will be listed. Study drug not returned will be assumed to have been taken.

Study drug compliance will be calculated using values from the Study Drug Accountability and Exposure – Oral CRF pages as shown below:

(Number of Tablets Dispensed – Number of Tablets Returned) / (End Date – Start Date + 1)

Percentage of subjects meeting Study Drug Compliance will be presented in the following categories: at least 85% of dispensed tablets (coded as yes/no), and, < 80%, ≥ 80% to < 85%, ≥ 85% to < 90%, and ≥ 90%.

8 Demographic and Baseline Characteristics

8.1 Demographic and Baseline Characteristics

Baseline data will be summarized for continuous and categorical variables as applicable.

The following subject demographics and pre-dose values will be summarized in the Full Efficacy population:

- Age, and Age group (< 45 years, 45 to < 65 years, and ≥ 65 years);
- PBC Diagnosis Age, and PBC Diagnosis Age group (<45, ≥45)
  (Age at diagnosis will be calculated as [year of diagnosis] minus [year of birth]. If only the subject's age at screening is available (rather than year of birth), then [year of signing consent (first consent)] minus [age at consent] will be used in place of [year of birth]);
- Duration of PBC, and Duration of PBC category(<7.5 years vs ≥7.5 years);
- Sex, and Females of Child-Bearing Potential;
- Ethnicity, Race;
- Height, Weight, BMI;
- liver stiffness score;
- documented fibrosis stage;
- UDCA usage (Yes/No), UDCA Total Daily Dose (will be derived as the total daily dose recorded immediately prior to first dose of study drug - as an ongoing concomitant medication at that time; any changes in UDCA use are not expected and will not affect the derivation of this baseline characteristic);
- UDCA response status;
- ApoE Isoform (Genomics) as resulted at Day 1, if no Day 1 value is present reported as the next result available in the progression of study visits (i.e. Day 1, Week 2, Week 4, Week 8, Week 12, and EOS);
- Alkaline phosphatase (ALP): screening value, baseline (last pre-dose) value, average of all pre-dose values;
- Alanine Aminotransferase (ALT);
- Conjugated (direct), Unconjugated (indirect), and Total Bilirubin (unconjugated will be derived as total minus conjugated).
- Gamma-Glutamyl Transferase (GGT)

No statistical testing will be performed on the aforementioned demographic data.

8.2 Medical History

Subjects medical history will be summarized by treatment group for all subjects in the safety population. Medical history data will be coded using MedDRA 20.1 and summarized by system organ class and preferred term. No inferential testing will be performed in this section.

8.3 Prior and Concomitant Medications

Subjects taking UDCA at the start of the study must remain on the same dose of UDCA throughout the 12-week dosing period. Subjects who were not taking UDCA at the start of the study will not be allowed to initiate treatment during the study. Subjects will be classified as taking or not taking UDCA.

Medications will be categorized by medication group and subgroup according to WHODRUG (Version Global B3 2017SEP01 DDE+HD (Enhanced + Herbals)). Refer to the Coding Conventions document for this study.

A medication will be considered concomitant if started or continued to be taken after first dose of study drug through 30 days after the last dose of study drug. Otherwise if a medication was stopped prior to first dose of study drug then it will be consider prior.

Prohibited medications are inhibitors and inducers of CYP3A4 and P-gp (taken between 14 days prior to first dose through 30 days after last dose of study drug). Any medication that inhibit or induce the transporter proteins P-gp are also prohibited during the study. Use of a new statin regimen is prohibited from Screening and throughout study duration. Additional details of prohibited medications please see protocol section 5.9. For protocol restrictions other than prohibited medications, please see the protocol section 5.10

In order to flag prohibited medications taken in the study, each medication taken will be compared against a pre-specified list of all prohibited medications. Prior, Concomitant and Prohibited medications will be summarized based on the number and percentage of subjects using each medication along with the number and percentage of subjects using at least one medication within each medication group and subgroup.

Prior, concomitant, and prohibited medications will be summarized for the Safety Population. All medications will be listed per subject.

9 Efficacy Analysis

The variables from the data to be used to produce the analysis of the objectives and corresponding endpoints are presented below. All efficacy endpoints will be evaluated using the Full Efficacy population.

9.1 Primary Endpoint

9.1.1 Definition of Primary Endpoint

The primary endpoint is defined as the proportion of subjects who have either a 20% reduction in ALP from pre-treatment values or normalization of ALP at Week 12. All subjects in the Full Efficacy population will be included in the analysis of the primary endpoint. Meeting either of these conditions will be considered meeting the primary endpoint of ALP response. Subjects who are missing either Baseline or Week 12 ALP results cannot have either condition evaluated, and will therefore be counted as failure (non-responder). Subjects having both Baseline and Week 12 ALP results will each be evaluated as follows:

1. Percent change will be calculated as [(ALP at Week 12 – ALP at Baseline)/ALP at Baseline] *100. The subject will be considered to have successfully achieved 20% reduction in ALP if the result is ≤ -20.
2. The subject will be considered to have successfully achieved ALP normalization if ALP was abnormal at baseline and normal at week 12.

If either condition is met, the subject is a responder (ALP Response = YES); if the subject fails both conditions, the subject is a non-responder (ALP Response = NO). The proportion of subjects with a 'Yes' for ALP Response will be compared among the 3 study treatment groups. The denominator for this calculation is the number of subjects in the Full Efficacy population.

9.1.2 Analysis of Primary Endpoint

For the primary endpoint, the Cochran-Mantel-Haenszel (CMH) test will be used to compare the proportion of subjects with ALP Response = " Yes" (percent improvement < -0.20 and/or normalization at Week 12 from Baseline) for each of the active treatment groups to placebo. The CMH test will be stratified, two-sided with an alpha level at 0.05. For the stratification in this analysis, the two randomization strata (fibrates and UDCA use) will be combined to create one strata variable. The code used to generate the p-value for each active treatment vs the placebo will be (with necessary output steps added):

Proc freq data=*indata;*

Tables strata*treatment*response/cmh;

Run;

The primary analysis of the primary endpoint will be performed using the Full Efficacy population. The analysis will be repeated on the Per-Protocol (PP) population, including only subjects with Baseline and Week 12 ALP results.

Subgroup analysis will be performed for ALP Response for the following subgroups:

- Age (<65 vs ≥65)
- gender
- UDCA strata
- Prior use of Fibrates strata
- ALP baseline categories [1.67xULN,2xULN), [2xULN,3xULN), [3xULN,4xULN), [4xULN,5xULN), and ≥5xULN (categories are data dependent)
- Total Bilirubin baseline categories [1xULN,2xULN), [2xULN,3xULN), ≥3xULN (categories are data dependent)
- ALP/Total Bilirubin/UDCA baseline subgroup (categories are data dependent, cut points should be based on median baseline values)
    - ALP≤3xULN, Total Bilirubin≤2xULN, UDCA usage,
    - ALP≤3xULN, Total Bilirubin>2xULN, UDCA usage
    - ALP>3xULN, Total Bilirubin≤2xULN, UDCA usage,
    - ALP>3xULN, Total Bilirubin>2xULN, UDCA usage
    - ALP≤3xULN, Total Bilirubin≤2xULN, No UDCA usage,
    - ALP≤3xULN, Total Bilirubin>2xULN, No UDCA usage
    - ALP>3xULN, Total Bilirubin≤2xULN, No UDCA usage,
    - ALP>3xULN, Total Bilirubin>2xULN, No UDCA usage

The code used to generate the p-value for each active treatment vs the placebo will be:

Proc freq data=*indata;*

Tables *subgroup**treatment*response/cmh;.

Run;

The subgroup analysis will be performed using the Full Efficacy population

The proportion of responders will be summarized and plotted by Visit.

9.1.3 Imputation of Missing Data

To account for missing data, a sensitivity analysis will be performed using the multiple imputation Markov Chain method.

MMRM Using Multiple imputation (MI)

To assess robustness of the efficacy analysis, sensitivity analysis with missing values imputed by MI will be performed on ALP change from baseline data. In the first stage, missing values will be imputed by Markov Chain Monte Carlo (SAS PROC MI, MCMC) to make the missing pattern monotone (by filling in

imputed values of ALP between 2 non-missing values). In the second stage, monotone linear regression will fill in missing values through Week 12. SAS PROC MI and PROC MIXED will be used to obtain MMRM estimates of treatment difference. SAS PROC MIANALYZE will be used to combine estimates and to generate the average test statistics for hypothesis testing. The Missing at Random method will be used with the following parameters MAR – assume missing at random, number of imputation=100, seed= SEED11 (for MCMC) and SEED12 (for MONOTONE REG) for imputation.

9.1.4 Change from Baseline and Percent Change from Baseline for ALP

A descriptive summary will be provided for ALP values, change from Baseline and percentage change from Baseline using 8-number summary by visit and treatment group.

Change from Baseline and percentage change from Baseline at Week 12 will be analyzed using an ANCOVA model with treatment as fixed effect and the associated baseline value as covariate. Least squares means and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

A by-subject listing will be provided for observed and derived variables.

Mean ± SD ALP values and change from baseline by visit and treatment group will be plotted and also separately for the subgroups of UDCA and Fibrates strata. Scatterplots of the percentage change from baseline in ALP at Week 12 against the baseline ALP will also be produced.

Additional ALP endpoints investigated include:

- Decrease in ALP ≥10% at 12 weeks
- Decrease in ALP ≥15% at 12 weeks
- Decrease in ALP ≥20% at 12 weeks
- Decrease in ALP ≥40% at 12 weeks
- ALP < ULN and Decrease in ALP ≥10% at 12 weeks
- ALP < ULN and Decrease in ALP ≥20% at 12 weeks
- ALP < ULN and Decrease in ALP ≥40% at 12 weeks
- ALP < 1.67xULN and Decrease in ALP ≥10% at 12 weeks
- ALP < 1.67xULN and Decrease in ALP ≥20% at 12 weeks
- ALP < 1.67xULN and Decrease in ALP ≥40% at 12 weeks
- ALP < 2xULN and Decrease in ALP ≥10% at 12 weeks
- ALP < 2xULN and Decrease in ALP ≥20% at 12 weeks
- ALP < 2xULN and Decrease in ALP ≥40% at 12 weeks
- Proportion of subjects at Week 12 with ALP <ULN, ≥ ULN and <1.67xULN, ≥ to 1.67xULN and < 2xULN and ≥2xULN

ALP Shifts from baseline endpoints will also be evaluated as follows:

- Baseline ALP category ([1.67xULN,2xULN), [2xULN,3xULN), [3xULN,4xULN), [4xULN,5xULN), and ≥5xULN) shifting to Normal, [1*ULN,1.67xULN), [1.67xULN,2xULN), and ≥2xULN (baseline categories are data dependent)

9.2 Secondary Efficacy Endpoints

9.2.1 Change from Baseline and Percentage Change from Baseline in Liver-Related Secondary Endpoints

9.2.1.1 Bilirubin

A descriptive summary will be provided for Total, Conjugated and Unconjugated Bilirubin values, change from Baseline and percentage change from Baseline using 8-number summary by visit and treatment group.

Change from Baseline and percentage change from Baseline at Week 12 will be analyzed using an ANCOVA model with treatment as fixed effect and the associated baseline value as covariate. Least squares means and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

Additional endpoints for Bilirubin will include the following:

- Proportion of subjects at Week 12 with Total Bilirubin <ULN, ≥ULN and <1.5xULN, ≥1.5xULN and <2xULN and ≥2xULN.
- Shift in total bilirubin from baseline to Week 12 using the same categories as the endpoint in the previous bullet.

A by-subject listing will be provided for observed and derived variables.

Scatterplots of the change from baseline in total bilirubin versus the baseline total Bilirubin value will be produced.

9.2.1.2 Alanine Aminotransferase

A descriptive summary will be provided for ALT values, change from Baseline and percentage change from Baseline using 8-number summary by visit and treatment group.

Change from Baseline and percentage change from Baseline at week 12 will be analyzed using an ANCOVA model with treatment as fixed effect and the associated baseline value as covariate. Least squares means and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

A by-subject listing will be provided for observed and derived variables.

Mean ± SD and change from baseline for ALT values by visit and treatment group will be plotted.

9.2.1.3 Aspartate Aminotransferase

A descriptive summary will be provided for AST values, change from Baseline and percentage change from Baseline using 8-number summary by visit and treatment group.

Change from Baseline and percentage change from Baseline at week 12 will be analyzed using an ANCOVA model with treatment as fixed effect and the associated baseline value as covariate. Least

squares means and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided α = 0.05.

A by-subject listing will be provided for observed and derived variables.

Mean ± SD and change from baseline for AST values by visit and treatment group will be plotted.

9.2.1.4 Gamma-Glutamyl Transferase

A descriptive summary will be provided for GGT values, change from Baseline and percentage change from Baseline using 8-number summary by visit and treatment group.

Change from Baseline and percentage change from Baseline at week 12 will be analyzed using an ANCOVA model with treatment as fixed effect and the associated baseline value as covariate. Least squares means and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided α = 0.05.

A by-subject listing will be provided for observed and derived variables.

Mean ± SD and change from baseline for GGT values by visit and treatment group will be plotted.

9.2.2 Change from Baseline and percentage change from Baseline of noninvasive liver fibrosis markers (ELF panel) and PRO C3 at Week 12

9.2.2.1 Enhanced Liver Fibrosis (ELF) Panel

The ELF panel combines 3 biomarkers that have been shown to correlated with the level of liver fibrosis assessed by a liver biopsy. These biomarkers include HA, PIIINP, and TIMP 1.

A descriptive summary will be provided for noninvasive liver fibrosis markers (ELF panel) values, change from Baseline and percentage change from Baseline using 8-number summary by visit and treatment group.

Change from Baseline and percentage change from Baseline at week 12 will be analyzed using an ANCOVA model with treatment as fixed effect and the associated baseline value as covariate. Least squares means and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided α = 0.05.

A by-subject listing will be provided for observed and derived variables.

9.2.2.2 PRO C3

A descriptive summary will be provided for PRO C3 values, change from Baseline and percentage change from Baseline using 8-number summary by visit and treatment group.

Change from Baseline and percentage change from Baseline at week 12 will be analyzed using an ANCOVA model with treatment as fixed effect and the associated baseline value as covariate. Least squares means and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided α = 0.05.

A by-subject listing will be provided for observed and derived variables.

9.2.3 Change from Baseline and Percentage Change from Baseline in Fibrosis at Week 12

9.2.3.1 APRI

The APRI will be calculated by the central laboratory using the following formula:

([AST IU/L / AST ULN] / [Platelet count 109/L]) × 100 = APRI

Online calculator can be found at: http://www.hepatitisc.uw.edu/page/clinical-calculators/apri

A descriptive summary will be provided for APRI, change from Baseline and the percentage change from Baseline using 8-number summary by visit and treatment group.

Change from Baseline and percentage change from Baseline at week 12 will be analyzed using an ANCOVA model with treatment as fixed effect and the associated baseline value as covariate. Least squares means and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

A by-subject listing will be provided for observed and derived variables.

9.2.3.2 FIB-4

The FIB-4 score will be calculated using the following formula:

[Age (years) × AST (IU/L)] / [Platelets (109/L) × (√ ALT (IU/L)))]

Online calculator can be found at: http://www.hepatitisc.uw.edu/page/clinical-calculators/fib-4

A descriptive summary will be provided for FIB-4 values, change from Baseline and the percentage change from Baseline using 8-number summary by visit and treatment group.

Change from Baseline and percentage change from Baseline at week 12 will be analyzed using an ANCOVA model with treatment as fixed effect and the associated baseline value as covariate. Least squares means and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

A by-subject listing will be provided for observed and derived variables.

9.2.4 Change from Baseline and percentage change from Baseline in Laboratory Fibrosis Parameter levels by Visit and at Week 12

9.2.4.1 Fibrinogen

A descriptive summary will be provided for fibrinogen levels, change from Baseline and percentage change from Baseline using 8-number summary by visit and treatment group.

Change from Baseline and percentage change from Baseline by visit, with the week 12 will be analyzed using an ANCOVA model with treatment as fixed effect and the associated baseline value as covariate. Least squares means and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

A by-subject listing will be provided for observed and derived variables.

9.2.4.2 CRP

A descriptive summary will be provided for CRP levels, change from Baseline and percentage change from Baseline using 8-number summary by visit and treatment group.

Change from Baseline and percentage change from Baseline in at week 12 will be analyzed using an ANCOVA model with treatment as fixed effect and the associated baseline value as covariate. Least squares means and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

A by-subject listing will be provided for observed and derived variables.

9.2.4.3 IL6

A descriptive summary will be provided for IL6 levels, change from Baseline and percentage change from Baseline using 8-number summary by visit and treatment group.

Change from Baseline and percentage change from Baseline in at week 12 will be analyzed using an ANCOVA model with treatment as fixed effect and the associated baseline value as covariate. Least squares means and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

A by-subject listing will be provided for observed and derived variables.

9.2.4.4 IL1β

A descriptive summary will be provided for IL1β levels, change from Baseline and percentage change from Baseline using 8-number summary by visit and treatment group.

Change from Baseline and percentage change from Baseline in at week 12 will be analyzed using an ANCOVA model with treatment as fixed effect and the associated baseline value as covariate. Least squares means and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

A by-subject listing will be provided for observed and derived variables.

9.2.4.5 TNF-α

A descriptive summary will be provided for TNF-α levels, change from Baseline and percentage change from Baseline using 8-number summary by visit and treatment group.

Change from Baseline and percentage change from Baseline in at week 12 will be analyzed using an ANCOVA model with treatment as fixed effect and the associated baseline value as covariate. Least squares means and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

A by-subject listing will be provided for observed and derived variables.

9.2.4.6 TNF-β

A descriptive summary will be provided for TNF-β levels, change from Baseline and percentage change from Baseline using 8-number summary by visit and treatment group.

Change from Baseline and percentage change from Baseline in at week 12 will be analyzed using an ANCOVA model with treatment as fixed effect and the associated baseline value as covariate. Least squares means and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

A by-subject listing will be provided for observed and derived variables.

9.2.4.7 Haptoglobin

A descriptive summary will be provided for haptoglobin levels, change from Baseline and percentage change from Baseline using 8-number summary by visit and treatment group.

Change from Baseline and percentage change from Baseline levels at week 12 will be analyzed using an ANCOVA model with treatment as fixed effect and the associated baseline value as covariate. Least squares means and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

A by-subject listing will be provided for observed and derived variables.

9.2.4.8 Alpha2 Macroglobulin

A descriptive summary will be provided for alpha2 macroglobulin levels, change from Baseline and percentage change from Baseline using 8-number summary by visit and treatment group.

Change from Baseline and percentage change from Baseline levels at week 12 will be analyzed using an ANCOVA model with treatment as fixed effect and the associated baseline value as covariate. Least squares means and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

A by-subject listing will be provided for observed and derived variables.

9.2.5 Change from Baseline and Percentage Change from Baseline in Lipids by Visit and at Week 12

Lipids will be evaluated using the regular lipid panel obtained in the biochemistry panel from the standard blood draw. In addition, a special LipoProfile assay will be used to further evaluate the number of particles in each of the lipid parameters. This section will describe the parameters obtained from this standard lipid profile.

9.2.5.1 Triglycerides by Visit and Week 12

Triglycerides are captured in the general lab biochemistry panel and also in the LipoProfile panel. Both measurements of triglycerides will be summarized separately.

A descriptive summary will be provided for Triglycerides values, change from Baseline and percentage change from Baseline using 8-number summary by visit and treatment group.

Change from Baseline and percentage change from Baseline at each visit, with week 12 as the visit of primary interest, will be analyzed using an ANCOVA model with treatment as fixed effect and the associated baseline value as covariate. Least squares means and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

By-subject listing will be provided for observed and derived variables.

9.2.5.2 Total Cholesterol by Visit and Week 12

Total cholesterol is captured in the general lab biochemistry panel and also in the LipoProfile panel. Both measurements of total cholesterol will be summarized separately.

A descriptive summary will be provided for total cholesterol values, change from Baseline and percentage change from Baseline using 8-number summary by visit and treatment group.

Change from Baseline and percentage change from Baseline at each visit, with week 12 as the primary visit of interest, will be analyzed using an ANCOVA model with treatment as fixed effect and the associated baseline value as covariate. Least squares means and standard errors will be presented for each visit, p-

value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided α = 0.05.

By-subject listing will be provided for observed and derived variables.

9.2.5.3 hs-CRP by Visit and Week 12

A descriptive summary will be provided for hs-CRP values, change from Baseline and percentage change from Baseline using 8-number summary by visit and treatment group.

Change from Baseline and percentage change from Baseline by visit, with the week 12 being the primary visit of interest, will be analyzed using an ANCOVA model with treatment as fixed effect and the associated baseline value as covariate. Least squares means and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided α = 0.05.

By-subject listing will be provided for observed and derived variables.

9.2.5.4 HDL by Visit and Week 12

HDL is captured in the general lab biochemistry panel and also in the LipoProfile panel (as HDL-C). Both measurements of HDL will be summarized separately.

A descriptive summary will be provided for HDL values, change from Baseline and percentage change from Baseline using 8-number summary by visit and treatment group.

Change from Baseline and percentage change from Baseline at each visit, with the week 12 being the primary visit of interest, will be analyzed using an ANCOVA model with treatment as fixed effect and the associated baseline value as covariate. Least squares means and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided α = 0.05.

By-subject listing will be provided for observed and derived variables.

9.2.5.5 LDL by Visit and Week 12

LDL is captured in the general lab biochemistry panel and also in the LipoProfile panel (as LDL-C). Both measurements of triglycerides will be summarized separately.

A descriptive summary will be provided for LDL values, change from Baseline and percentage change from Baseline using 8-number summary by visit and treatment group.

Change from Baseline and percentage change from Baseline at each visit, with the week 12 being the primary visit of interest, will be analyzed using an ANCOVA model with treatment as fixed effect and the associated baseline value as covariate. Least squares means and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided α = 0.05.

By-subject listing will be provided for observed and derived variables.

9.2.5.6 Total Cholesterol/HDL (CT Ratio) by Visit and Week 12

A descriptive summary will be provided for total cholesterol/HDL Ratio values, change from Baseline and percentage change from Baseline using 8-number summary by visit and treatment group.

Change from Baseline and percentage change from Baseline in total cholesterol/HDL ratio at each visit, with week 12 as the primary visit of interest, will be analyzed using an ANCOVA model with treatment as fixed effect and the associated Baseline value as covariate. Least squares means and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided α = 0.05.

By-subject listing will be provided for observed and derived variables.

9.2.6 Adiponectin

A descriptive summary will be provided for adiponectin values, change from Baseline and percentage change from Baseline using 8-number summary by visit and treatment group.

Change from Baseline and percentage change from Baseline by visit, with the week 12 being the primary visit of interest, will be analyzed using an ANCOVA model with treatment as fixed effect and the associated baseline value as covariate. Least squares means and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

By-subject listing will be provided for observed and derived variables.

9.2.7 ApoA-I

A descriptive summary will be provided for ApoA-I values, change from Baseline and percentage change from Baseline using 8-number summary by visit and treatment group.

Change from Baseline and percentage change from Baseline by visit, with the week 12 being the primary visit of interest, will be analyzed using an ANCOVA model with treatment as fixed effect and the associated baseline value as covariate. Least squares means and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

By-subject listing will be provided for observed and derived variables.

9.2.8 ApoB

A descriptive summary will be provided for ApoB values, change from Baseline and percentage change from Baseline using 8-number summary by visit and treatment group.

Change from Baseline and percentage change from Baseline by visit, with the week 12 being the primary visit of interest, will be analyzed using an ANCOVA model with treatment as fixed effect and the associated baseline value as covariate. Least squares means and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

By-subject listing will be provided for observed and derived variables.

9.2.9 ApoC3

A descriptive summary will be provided for ApoC3 values, change from Baseline and percentage change from Baseline using 8-number summary by visit and treatment group.

Change from Baseline and percentage change from Baseline by visit, with the week 12 being the primary visit of interest, will be analyzed using an ANCOVA model with treatment as fixed effect and the associated baseline value as covariate. Least squares means and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

By-subject listing will be provided for observed and derived variables.

9.2.10 ApoB/A Ratio

A descriptive summary will be provided for ApoB/A ratio values, change from Baseline and percentage change from Baseline using 8-number summary by visit and treatment group.

Change from Baseline and percentage change from Baseline by visit, with the week 12 being the primary visit of interest, will be analyzed using an ANCOVA model with treatment as fixed effect and the associated

baseline value as covariate. Least squares means and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided α = 0.05.

By-subject listing will be provided for observed and derived variables.

Correlation scatterplots for all combinations of Primary (ALP) and Secondary Efficacy variables (sections 9.2.1 through 9.2.10) by visit for each treatment group will be presented.

9.2.11 Pruritis

9.2.11.1 5D-Itch Scale

The 5-D questionnaire (Elman 2010) is a specific tool used to quantify the magnitude of pruritus in PBC (and other diseases). It consists of 5 domains: duration, degree, direction, disability, distribution, as well as the total score. Each of the domains and the total score will be summarized by visit and treatment, with the week 12 visit being considered as the primary visit of interest.

The disability domain will be the highest score obtained from the daily activities of sleep, leisure/social activities, housework/errands, and work/school. The disability domain will only be calculated if at least 3 daily activities are documented.

The distribution domain includes 16 locations of itch and is the categorized to a scale of 0 to 5, based on the sum of the number of affected locations: sum of 0 to 2 = score of 1, sum of 3 to 5 = score of 2, sum of 6 to 10 = score of 3, sum of 11 to 13 = score of 4, sum of 14 to 16 = score of 5.

The total 5D score is obtained by summing up the domain scores and ranges between 5 (no pruritus) and 25 (most severe pruritus). The total score will not be calculated if any of the domain scores is missing.

For each of the domains and the total score, the value at each visit, the change from Baseline and percentage change from Baseline will be summarized for each of the domains. Statistical inference will be tested using an ANCOVA model with treatment as fixed effect and the associated baseline value as covariate. Least squares means and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided α = 0.05.

9.2.11.2 Visual Analog Scale

A descriptive summary will be provided for the VAS values, change from Baseline and percentage change from Baseline using 8-number summary by visit and treatment group.

Change from Baseline and percentage change from Baseline by visit, with the week 12 being the primary visit of interest, will be analyzed using an ANCOVA model with treatment as fixed effect and the associated baseline value as covariate. Least squares means and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided α = 0.05.

By-subject listing will be provided for observed and derived variables.

Mean ± SD and change from baseline for 5D-Itch Scale Total Score and VAS values by visit and treatment group will be plotted.

9.2.12 Quality of Life

9.2.12.1 PBC-40

PBC-40 Quality of Life questionnaire for this study does not collect an overall score. The 40 questions from the PBC-40 questionnaire will be scored from 1-5, with 5 representing the highest impact and 1 the lowest impact of PBC on the quality of life. The direction is reversed to reflect this impact. There will be 6 domains computed from the 40 questions in the following manner:

1.) Symptoms: Sum of questions 1-7. Question 1 will be scored with 'Never'=5 to 'Always'=1. The remaining questions will be scored with 'Never'=1 to 'Always'=5. If 4 or more of the 7 questions are missing, then the domain will be left as missing. If 4 or more questions are answered, any missing answered will be imputed using the median value of the non-missing questions used for this domain. The range of possible scores for this domain are [7,35].

2.) Itch: Sum of questions 8-10. All 3 questions will be scored with 'Never'=1 to 'Always'=5 and 'Did not apply/no itch'=0. If 2 or more of the questions are missing, then the domain will be left as missing, otherwise, all missing values will be imputed using the median of the other non-missing values used in this question. The possible range of scores for this domain are [0,15].

3.) Fatigue: Sum of questions 11-21. All questions will be scored as 'Never'=1 to 'Always'=5. If 6 or more of the 11 questions are missing, then the domain will be left as missing. If 6 or more questions are answered, any missing answered will be imputed using the median value of the non-missing questions used for this domain. The range of possible scores for this domain are [11,55].

4.) Cognition: Sum of questions 22-27. All questions will be scored as 'Never'=1 to 'Always'=5. If 4 or more of the 6 questions are missing, then the domain will be left as missing. If 4 or more questions are answered, any missing answered will be imputed using the median value of the non-missing questions used for this domain. The range of possible scores for this domain are [6,30].

5.) Social: Sum of questions 29, 31, 32, 34, 35, 36, 37, 38, 39, and 40. Questions 29, 31 and 32 will be scored from 'Not at all'=1 to 'Very Much'=5. Questions 29 and 31 will also include 'Does not apply'=0. The remaining questions will be scored from 'Strongly agree'=5 to 'Strongly disagree=1'. If 6 or more of the 10 questions are missing, then the domain will be left as missing. If 6 or more questions are answered, any missing answered will be imputed using the median value of the non-missing questions used for this domain. The range of possible scores for this domain are [8,50].

6.) Emotional: Sum of questions 28, 30, and 33. Questions 28 and 30 will be scored from 'Not at all'=1 to 'Very Much'=5 and 'Does not apply'=0. The remaining question will be scored from 'Strongly agree'=5 to 'Strongly disagree=1'. If 2 or more of the 3 questions are missing, then the domain will be left as missing. If 2 or more questions are answered, any missing answered will be imputed using the median value of the non-missing questions used for this domain. The range of possible scores for this domain are [1, 15].

A descriptive summary will be provided for the domains, the change from Baseline and percentage change from Baseline for each domain, using 8-number summary by visit and treatment group.

Change from Baseline and percentage change from Baseline by visit, with the week 12 being the primary visit of interest, will be analyzed using an ANCOVA model with treatment as fixed effect and the associated baseline value as covariate. Least squares means and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

By-subject listing will be provided for observed and derived variables.

9.3 PK/PD Analysis

9.3.1 Pharmacokinetic (PK) Analysis

For subjects who agree to participate in the PK/PD substudy, PK samples will be drawn at Day 1 and Day 84 (Week 12) at predose, and 2, 6, and 8 hours postdose.

For subjects who are not in the PK/PD substudy, on Day 1 and Day 84 (Week 12), PK samples will be drawn on predose, between 1 to 3 hours postdose and then the last sample at least 1 hour after the second collection, for a total of 3 samples

For all subjects (including those in the PK/PD substudy), at visits on Week 2, 4, and 8, PK sampling will be collected predose, between 1 to 3 hours postdose and then the last sample at least 1 hour after the second collection, for a total of 3 samples at each visit.

9.3.1.1 PK/PD Substudy Analysis (Day 1 and Day 84)

For subjects who agree to participate in the PK/PD substudy, concentration data will be summarized by active treatment arm, visit and hours since last dose for post-baseline visits for EDP-305 and each metabolite. Concentrations that are below the limit of quantitation (BLQ) will be treated as zero for the computation of descriptive statistics. The number of observations, mean, standard deviation, % coefficient of variation, geometric mean, % geometric coefficient of variation, median, minimum, maximum values will be displayed. Figures will be created to display mean (+/- SD) and individual subject EDP-305 concentration time curves in plasma on both a linear and semi-logarithmic scale (for semi-logarithmic plots, no SD will be presented).

The PK parameters listed in Table 4 will be calculated as indicated for plasma EDP-305 and its metabolites, as applicable. PK parameters will be calculated by noncompartmental methods (AUC by linear up/log down method) (only on Day 1 and Day 84).

Plasma PK parameters for each dose level will be calculated from the concentrations of EDP-305 and its metabolites measured in predose and post-dose plasma samples. For each EDP-305 dose level, descriptive statistics (sample size, arithmetic means, geometric means, standard deviation (SD), % coefficient of variation (%CV), %GCV, minimum, median, and maximum) will be presented.

Individual data will be presented in listing.

Table 4: PK/PD Substudy Parameters

PK Parameter	Description
AUC_{last}	The area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration.
C_{max}	Maximum observed concentration.
T_{last}	Time to last quantifiable concentration.
T_{max}	Time to reach Cmax. If the maximum value occurs at more than one timepoint, Tmax is defined as the first time point with this value.

9.3.1.2 Population PK Analysis (Day 1 and Day 84)

For subjects not in the PK/PD substudy, the concentration data will be summarized by active treatment arm, visit and hours since last dose for EDP-305 and each metabolite. Concentrations that are below the limit of quantitation (BLQ) will be treated as zero for the computation of descriptive statistics. The number of observations, mean, SD, % CV, geometric mean, % GCV, median, minimum and maximum values will be displayed. Figures will be created to display mean and individual subject EDP-305 concentration time curves in plasma on both a linear and semi-logarithmic scale (for semi-logarithmic plots, no SD will be presented).

Individual data will be presented in listing.

9.3.1.3 PK Population Analysis

For Week 2, 4, and 8: For all subjects in the PK population (PK/PD substudy subjects and population PK subjects), the concentration data will be summarized by active treatment arm, visit and hours since last dose for post-baseline visits for EDP-305 and each metabolite for visits at Week 2, 4, and 8. Concentrations that are below the limit of quantitation (BLQ) will be treated as zero for the computation of descriptive statistics. The number of observations, mean, SD, % CV, geometric mean, % GCV, median, minimum, maximum values will be displayed. Figures will be created to display mean and individual subject EDP 305 concentration time curves in plasma on both a linear and semi-logarithmic scale (for semi-logarithmic plots, no SD will be presented).

For all visits: A summary plot of the means and standard deviations of the pre-dose concentrations at each visit (Day 1, Week 2, 4, 8, and 12) will be provided by treatment on both a linear and semi-logarithmic scale (for semi-logarithmic plots, no SD will be presented).

Individual data will be presented in listing.

9.3.2 Pharmacodynamic (PD) Analysis

The PD analysis will use the efficacy population and will include active treatment arms and placebo arms.

For subjects who agree to participate in the PK/PD substudy, PD samples (FGF19, C4, bile acids (BA), and ALP) will be drawn at Day 1 and Day 84 (Week 12) at predose, 2, 6, and 8 hours postdose. At visits on Week 2, 4, and 8, PD sampling will be collected predose, between 1 to 3 hours postdose and then the last sample at least 1 hour after the second collection, for a total of 3 samples at each visit.

For subjects who are not in the PK/PD substudy, PD samples (FGF19, C4, bile acids (BA)) will be drawn predose.

9.3.2.1 PD Substudy Analysis (Day 1 and Day 84)

9.3.2.1.1 FGF19

A descriptive summary will be provided for the PD parameters such as AUC_{0-8} and AUC_{2-8} for FGF19 at Day 1 and Day 84 (Week 12), change from Baseline in the AUC values at Week 12 and percentage change from baseline in the AUC values at Week 12 using 8-number summary by visit and treatment group.

Change from Baseline and the percentage change from baseline in the AUC_{0-8} and the AUC_{2-8} for FGF19 at Week 12, will be analyzed using an ANCOVA model with treatment as fixed effect and the associated baseline value as covariate. Least squares means and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

The above analysis will be repeated for the actual FGF19 values (concentrations), the change from Baseline and the percentage change from Baseline values at time point and each visit for the PD substudy subjects.

Individual Plasma Concentrations as well as Mean ± SD and change from baseline for FGF19 values by visit and treatment group will be plotted.

A by-subject listing will be provided for observed and derived variables.

9.3.2.1.2 C4

A descriptive summary will be provided for the PD parameters such as AUC_{0-8} and AUC_{2-8} for C4 at Day 1 and Day 84 (Week 12), change from Baseline in AUC at Week 12 and percentage change from baseline in the AUC at Week 12 values using 8-number summary by visit and treatment group.

Change from Baseline and the percentage change from baseline in the AUC_{0-8} and the AUC_{2-8} for C4 at Week 12, will be analyzed using an ANCOVA model with treatment as fixed effect and the associated baseline value as covariate. Least squares means and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

The above analysis will be repeated for the actual C4 values (concentrations), the change from Baseline and the percentage change from Baseline values at time point and each visit for the PD substudy subjects.

Individual Plasma Concentrations as well as Mean ± SD and change from baseline for C4 values by visit and treatment group will be plotted.

A by-subject listing will be provided for observed and derived variables.

9.3.2.1.3 Bile Acid

A descriptive summary will be provided for the bile acid concentrations, change from Baseline and the percentage change from baseline using 8-number summary by visit and treatment group.

Change from Baseline and the percentage change from baseline in the bile acid for each time point by visit, with the Week 12 visit being considered the primary visit of interest, will be analyzed using an ANCOVA model with treatment as fixed effect and the associated baseline value as covariate. Least squares means and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

Individual Plasma Concentrations as well as Mean ± SD and change from baseline for Bile Acid values by visit and treatment group will be plotted.

A by-subject listing will be provided for observed and derived variables.

9.3.2.2 Population PD Analysis (Day 1 and Day 84)

9.3.2.2.1 FGF19

A descriptive summary will be provided for FGF19 concentrations, change from Baseline and the percentage change from baseline using 8-number summary by visit and treatment group.

Change from Baseline and the percentage change from baseline in the FGF19 for each time point by visit, with the week 12 visit being considered the primary visit of interest, will be analyzed using an ANCOVA model with treatment as fixed effect and the associated baseline value as covariate. Least squares means and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

Mean ± SD and change from baseline for FGF19 values by visit and treatment group will be plotted.

A by-subject listing will be provided for observed and derived variables.

9.3.2.2.2 C4

A descriptive summary will be provided for C4 concentrations, change from Baseline and the percentage change from baseline using 8-number summary by visit and treatment group.

Change from Baseline and the percentage change from baseline in the C4 for each time point by visit, with the week 12 visit being considered the primary visit of interest, will be analyzed using an ANCOVA model with treatment as fixed effect and the associated baseline value as covariate. Least squares means and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

Mean ± SD and change from baseline for C4 values by visit and treatment group will be plotted.

A by-subject listing will be provided for observed and derived variables.

9.3.2.2.3 Bile Acid

A descriptive summary will be provided for bile acid concentrations, change from Baseline and the percentage change from baseline using 8-number summary by visit and treatment group.

Change from Baseline and the percentage change from baseline in the bile acid for each time point by visit, with the week 12 visit being considered the primary visit of interest, will be analyzed using an ANCOVA model with treatment as fixed effect and the associated baseline value as covariate. Least squares means and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

Mean ± SD and change from baseline for Bile Acid values by visit and treatment group will be plotted.

A by-subject listing will be provided for observed and derived variables.

9.3.2.3 PD Population Analysis (Weeks 2, 4, 8 and 12)

9.3.2.3.1 FGF19

A descriptive summary will be provided for FGF19 concentrations, change from Baseline and the percentage change from baseline using 8-number summary by visit and treatment group.

Change from Baseline and the percentage change from baseline in the FGF19 for each time point by visit, with the week 12 visit being considered the primary visit of interest, will be analyzed using an ANCOVA model with treatment as fixed effect and the associated baseline value as covariate. Least squares means and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

Mean ± SD and change from baseline for FGF19 values by visit and treatment group will be plotted.

A by-subject listing will be provided for observed and derived variables.

9.3.2.3.2 C4

A descriptive summary will be provided for C4 concentrations, change from Baseline and the percentage change from baseline using 8-number summary by visit and treatment group.

Change from Baseline and the percentage change from baseline in the C4 for each time point by visit, with the week 12 visit being considered the primary visit of interest, will be analyzed using an ANCOVA model with treatment as fixed effect and the associated baseline value as covariate. Least squares means and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

Mean ± SD and change from baseline for C4 values by visit and treatment group will be plotted.

A by-subject listing will be provided for observed and derived variables.

9.3.2.3.3 Bile Acid

A descriptive summary will be provided for bile acid concentrations, change from Baseline and the percentage change from baseline using 8-number summary by visit and treatment group.

Change from Baseline and the percentage change from baseline in the bile acid for each time point by visit, with the week 12 visit being considered the primary visit of interest, will be analyzed using an ANCOVA model with treatment as fixed effect and the associated baseline value as covariate. Least squares means

and standard errors will be presented for each visit, p-value and 2-sided 95% confidence interval for treatment differences will be presented for each visit. Significance tests will be based on least-squares means using a two-sided $\alpha = 0.05$.

Mean ± SD and change from baseline for Bile Acid values by visit and treatment group will be plotted.

A by-subject listing will be provided for observed and derived variables.

9.3.3 PK/PD Analysis at Week 12 (Correlations)

Scatterplots (including correlations) will be generated comparing the PD parameters or concentration to the PK parameter or concentration data or relevant lab data by treatment group.

9.3.3.1 PK/PD Subgroup Analysis

This will be done for all subjects in the PK/PD substudy. The following scatterplots with one regression line and additional plots will be generated:

- AUC_{0-8} in FGF19 with PK parameter AUC_{last} (Day 1 and Day 84)
- AUC_{2-8} in FGF19 with PK parameter AUC_{last} (Day 1 and Day 84)
- AUC_{0-8} in C4 with PK parameter AUC_{last} (Day 1 and Day 84)
- AUC_{2-8} in C4 with PK parameter AUC_{last} (Day 1 and Day 84)
- Percentage change from Baseline in AUC_{0-8} FGF19 with PK parameter, AUC_{last} (Week 12)
- Percentage change from Baseline in AUC_{2-8} FGF19 with PK parameter AUC_{last} (Week 12)
- Percentage change from Baseline in AUC_{0-8} C4 with PK parameter AUC_{last} (Week 12)
- Percentage change from Baseline in AUC_{2-8} C4 with PK parameter AUC_{last} (Week 12)
- Percentage change from Baseline in Bile Acid (predose Week 12) with PK parameter AUC_{last} (Week 12)
- Percentage change from Baseline in ALT (predose Week 12) with percentage change from Baseline in AUC_{0-8} FGF19 (Week 12)
- Percentage change from Baseline in ALT (predose Week 12) with percentage change from Baseline in AUC_{2-8} FGF19 (Week 12)
- Percentage change from Baseline in ALT (predose Week 12) with percentage change from Baseline in AUC_{0-8} C4 (Week 12)
- Percentage change from Baseline in ALT (predose Week 12) with percentage change from Baseline in AUC_{2-8} C4 (Week 12)
- Percentage change from Baseline in ALT (predose Week 12) with percentage change from Baseline in PK parameter AUC_{last} (Week 12)

- Percentage change from Baseline in FGF19 (predose Week 12) with PK parameter C_{max} (Week 12)
- Percentage change from Baseline in C4 (predose Week 12) with PK parameter C_{max} (Week 12)
- Percentage change from Baseline in Bile Acid (predose Week 12) with PK parameter C_{max} (Week 12)
- Box Plot Comparison of EDP-305 AUC_{last} and C_{max} at Day 1 and Week 12 by Pruritus Status
- Box Plot Comparison of Percent Change from Baseline in C4 AUC_{0-8} by Pruritus Status
- Box Plot Comparison of Percent Change from Baseline in C4 AUC_{2-8} by Pruritus Status

9.3.3.2 PK/PD Population Analysis

This will be done for all subjects (PK/PD substudy and population PK/PD). The following scatterplots with one regression line will be generated:

- Percentage change from Baseline in ALT (Predose Week 12) with the percentage change from Baseline in FGF19 (Predose Week 12)
- Percentage change from Baseline in ALT (Predose Week 12) with the percentage change from Baseline in C4 (Predose Week 12)
- Percentage change from Baseline in ALT (Predose Week 12) with the percentage change from Baseline in Bile Acid (Predose Week 12)
- Percentage change from Baseline in ALT (Predose Week 12) with EDP-305 concentration value (predose at Week 12)
- Percentage change from Baseline in AST (Predose Week 12) with the percentage change from Baseline in FGF19 (Predose Week 12)
- Percentage change from Baseline in AST (Predose Week 12) with the percentage change from Baseline in C4 (Predose Week 12)
- Percentage change from Baseline in AST (Predose Week 12) with the percentage change from Baseline in Bile Acid (Predose Week 12)
- Percentage change from Baseline in AST (Predose Week 12) with the EDP-305 concentration value (Predose Week 12)
- Percentage change from Baseline in GGT (Predose Week 12) with the percentage change from Baseline in FGF19 (Predose Week 12)
- Percentage change from Baseline in GGT (Predose Week 12) with the percentage change from Baseline in C4 (Predose Week 12)

- Percentage change from Baseline in GGT (Predose Week 12) with the percentage change from Baseline in Bile Acid (Predose Week 12)
- Percentage change from Baseline in GGT (Predose Week 12) with EDP-305 concentration value (Predose Week 12)
- Percentage change from Baseline in Total Bilirubin (Predose Week 12) with the percentage change from Baseline in FGF19 (Predose Week 12)
- Percentage change from Baseline in Total Bilirubin (Predose Week 12) with the percentage change from Baseline in C4 (Predose Week 12)
- Percentage change from Baseline in Total Bilirubin (Predose Week 12) with the percentage change from Baseline in Bile Acid (Predose Week 12)
- Percentage change from Baseline in Total Bilirubin with (Predose Week 12) EDP-305 concentration value (Predose Week 12)
- Percentage change from Baseline in Alkaline Phosphatase (Predose Week 12) with the percentage change from Baseline in FGF19 (Predose Week 12)
- Percentage change from Baseline in Alkaline Phosphatase (Predose Week 12) with the percentage change from Baseline in C4 (Predose Week 12)
- Percentage change from Baseline in Alkaline Phosphatase (Predose Week 12) with the percentage change from Baseline in Bile Acid (Predose Week 12)
- Percentage change from Baseline in Alkaline Phosphatase (Predose Week 12) with EDP-305 concentration value (Predose Week 12)
- Percentage change from Baseline in FGF19 (Predose Week 12) with the percentage change from Baseline in C4 (Predose Week 12)
- Percentage change from Baseline in FGF19 (Predose Week 12) with the percentage change from Baseline in Bile Acid (Predose Week 12)
- Percentage change from Baseline in FGF19 (Predose Week 12) with EDP-305 concentration value (Predose Week 12)
- Percentage change from Baseline in C4 (Predose Week 12) with the percentage change from Baseline in Bile Acid (Predose Week 12)
- Percentage change from Baseline in C4 (Predose Week 12) with EDP-305 concentration value (Predose Week 12)
- Percentage change from Baseline in Bile Acid (Predose Week 12) with EDP-305 concentration value (Predose Week 12)

- Percentage change from Baseline in Cholesterol (Predose Week 12) with EDP-305 concentration value (Predose Week 12)
- Percentage change from Baseline in HDL (Predose Week 12) with EDP-305 concentration value (Predose Week 12)
- Percentage change from Baseline in LDL (Predose Week 12) with EDP-305 concentration value (Predose Week 12)
- Percentage change from Baseline in triglycerides (Predose Week 12) with EDP-305 concentration value (Predose Week 12)
- Correlation between Week 12 Predose EDP-305 concentrations and Adverse events occurring in at least 5% of the combined active subjects.

- Summary of Week 12 Predose EDP-305 concentrations for subjects with Grade 3 of Higher Adverse Events or Serious Adverse Events

- Summary of Week 12 Predose (or last predose) EDP-305 concentrations for subjects with week 12 completion by pruritus status
- Summary of Week 12 Predose (or last predose) EP-022679 concentrations subjects with week 12 completion by pruritus status
- Summary of Week 12 Predose (or last predose) EDP-305 concentrations for all subjects by pruritus status
- Summary of Week 12 Predose (or last predose) EP-022679 concentrations for all subjects by pruritus status

[redacted]

10 Safety Analyses

All safety analyses will be performed using all subjects in the safety population.

10.1 Treatment Emergent Adverse Events

Adverse events will be coded using MedDRA 20.1 (September 01, 2017) and graded by CTCAE version 5 (November 27, 2017). All safety analyses and listings will be reported using the safety population. An AE will be considered a Treatment-emergent AE (TEAE) if it first occurs or begins previous to and worsens on or after the first dose date and before the last dose date + 30 days. All TEAEs will be classified as being during the on-treatment period or during the follow-up period as follows:

- Events that occurred between first dose and 7 days after last dose are classified as on-treatment;
- Events occurring between 8-30 days after last dose are classified as follow-up.

Adverse Events will be summarized for the safety population by both on-treatment period and follow-up period separately by dose group.

The following events will not be identified as AEs in this study:

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, etc.). The condition (the "triggering event") that leads to the procedure are adverse events and will be reported as such.
- Pre-existing conditions present or detected prior to the first dose of study drug that do not worsen during the study.

Summaries of Adverse Events will include the following:

- AEs that occur during the screening period will be listed in the Medical History for each subject.
- An overall summary of all TEAEs. The number of events and the number and percentage of subjects reporting at least one TEAE will be reported
- The number and percentage of subjects reporting each TEAE, categorized by MedDRA system organ class and preferred term. Note that frequencies will be by subject not event.
- The number and percentage of subjects reporting each TEAE, categorized by MedDRA system organ class, preferred term and maximum CTCAE grade
- TEAEs experienced by ≥ 5% of Subjects will be summarized by preferred term
- TEAE experienced by ≥ 5% of Subjects categorized by MedDRA system organ class, preferred term and maximum CTCAE grade
- Treatment Related Adverse Events categorized by MedDRA system organ class and preferred term
- The number and percentage of TEAEs with outcome of death
- Serious TEAEs categorized by MedDRA system organ class and preferred term
- Serious TEAEs categorized by relationship to study drug, subjects with multiple events within each SOC or preferred term will be counted under the category of their most drug-related event within that SOC or preferred term
- TEAEs leading to study drug discontinuation categorized by MedDRA system organ class and preferred term

- Treatment Related TEAEs leading to study drug discontinuation categorized by MedDRA system organ class and preferred term
- Treatment Related TEAEs experienced by ≥ 5% of Subjects will be summarized by preferred term
- Treatment Related TEAE experienced by ≥ 5% of Subjects categorized by MedDRA system organ class, preferred term and maximum CTCAE grade

All adverse events (including non-treatment-emergent events) recorded on the eCRF will be listed for the Safety population

A summary of the number of subject deaths will be presented by treatment group. All death data will be listed.

10.2 Laboratory Data

Laboratory test results for Baseline, Week 12 visits, change from Baseline at Week 12 and change to abnormal status of either below LLN ("Low") or above ULN ("High") from Baseline at Week 12 for all Safety Lab tests (Appendix 6) will be summarized by treatment groups. Shift tables will be used to present change in status (normal to abnormal or abnormal to normal) from Baseline at Week 12. All lab values will be listed and all test values outside the normal range will be flagged. Urinalysis results will be summarized separately for continuous and categorical variables. Pregnancy test results will be listed only.

The pre-dose laboratory test results only within the time window will be considered for analyses safety laboratory data summaries.

For average baseline, it is considered the average of the latest (closest to the target day Day -1) laboratory test result in the screening window (from Day -28 to Day -1) and the pre-dose Day 1 laboratory test result.

For Day 1 value or the latest value prior to the first dose of study drug as baseline, it is considered the laboratory test result in the screening window (from Day -28 to Day -1) not beyond Day -28 laboratory test result.

For screening visit as baseline, it is considered the laboratory test result in the screening window (from Day -28 to Day -1) and the latest laboratory test result.

If the recorded the laboratory test result (<XX.xx) is below the lower limit, then the value 0.0 is considered for the laboratory test result.

If the recorded laboratory test result (>XX.xx) is above the upper limit, then the value of the (XX.xx) is considered for the laboratory test result.

For the purposes of summarization in both the tables and listings, all laboratory values will be converted to standardized units. Reference Covance Lab Manual for schedule of testing.

10.2.1 Subject Safety Monitoring

Subjects will be monitored throughout the study for the following:

- ALT or AST increase to >5 x Baseline
- ALT or AST increase >2 × Baseline AND the increase is accompanied by a concomitant Total Bilirubin increase to >2 × Baseline OR the INR (prothrombin time / partial thromboplastin time) concomitantly increases from Baseline by >0.2
- Elevated Baseline liver chemistry (AST or ALT elevations 2 × Baseline) will require subjects to be reassessed promptly (within 48–72 hours) with full liver biochemistry and physical exam

- Elevations of ALT/AST accompanied by preferred terms indicating: signs or symptoms of right upper quadrant abdominal pain, anorexia, nausea, vomiting fever, eosinophilia, and/or rash

Incidence of these safety categories will be summarized by treatment group and identified on the listings with laboratory data parameters

10.3 Vital Signs

Vital signs will include heart rate (HR), respiratory rate (RR), blood pressure (BP) and oral temperature. Vital signs results will be summarized by timepoint where it shows change from Baseline, and significant changes in vital signs by treatment. Significant vital signs to be included are:

Pulse Rate
< 50 bpm
> 120 bpm
≥ 30 bpm increase from Baseline
≥ 30 bpm decrease from Baseline

Blood Pressure
SBP > 150 mmHg or DBP > 100 mmHg
SBP > 200 mmHg or DBP > 110 mmHg

Respiration Rate
< 8 breaths/min
> 40 breaths/min

Temperature
> 38.3°C
≥ 1.1°C increase from Baseline (Baseline > 36.8°C)

Change in Weight
≥ 5% increase from Baseline
≥ 5% decrease from Baseline

All vital sign results will be listed.

Weight may be collected in kilograms (kg) or pounds (lb) and height may be collected in centimeters (cm) or inches (in). BMI will be reported in kg/m^2.

For metric measurements kg and cm:

$BMI = Weight/[(Height*100)^2]$.

For English measurements lb and in:

$BMI = [Weight/(Height)^2] \times 703$.

10.4 Physical Exam Data

All physical exam results will be listed along with descriptions of any abnormality.

10.5 ECG Results

ECG results including PR, QRS, QT, RR, and QTc (QTcF) intervals will be summarized by timepoint where it shows change from Baseline with a summary for defined thresholds:

QTcF Maximum value
≤ 450 msec
> 450 to ≤ 480
> 480 to ≤ 500 msec
> 500 msec

QTcF Maximum change from Baseline
≤ 30 msec
> 30 to ≤ 60 msec
> 60 msec

Females with Screening or Baseline < 470 msec
Males with Screening or Baseline < 450 msec

ECG results will be listed for all timepoints and clinically significantly results will be flagged. The ECG parameter, QT interval (msec) will be adjusted for the length of the RR interval (msec) using the Fridericia correction (QT interval length divided by cube root of the interval from the onset of one QRS complex to the next) as follows:

QTcF= QT / cube root(RR).

RR will be converted to seconds for the calculation.

11 Interim Analyses

An administrative interim analysis may be conducted after approximately 25% of the planned total number of subjects (~30 subjects) have been enrolled and completed 12 weeks of treatment.

No study stopping rules have been established and no inferential testing will be performed.

Reporting for interim analysis will include the subject disposition, demographics, the primary endpoint, and secondary efficacy variables. See Appendix 4 for the list of outputs.

Results of the interim analysis will remain blinded to all blinded team members at Enanta and PRA. PRA will create the reporting with blinded treatment codes, and an unblinded PRA team will merge the data with the actual treatment codes for delivery of the unblinded interim analysis to the appropriate members of the Enanta management.

12 Data Safety Monitoring Board

The DSMB will meet on a periodic basis to review safety data. Refer to the DSMB charter for this study for information on the content and conduct for these meetings. Data review meetings will occur after groups of 20 subjects have completed 4 weeks of study drug treatment. The DSMB will receive fully unblinded results. The same team described in the above section will be responsible for providing unblinded outputs to the DSMB independent, unblinded statistician who will distribute the results to the DSMB members.

See Appendix 4 for the list of outputs.

13 References

1. ICH Harmonized Tripartite Guideline. Statistical Principles for Clinical Studys E9. International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use. 05 February 1998. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/Step4/E9_Guideline.pdf
2. ICH Harmonized Tripartite Guideline. Structure and Content of Clinical Study Reports E3. International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use. 30 November 1995. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/E3_Guideline.pdf

Appendix 1 Glossary of Abbreviations

Glossary of Abbreviations:	
AE	Adverse event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
APRI	AST to Platelet Ratio Index
AST	Aspartate Aminotransferase
ATC	Anatomic Therapeutic Classification
AUC_{last}	Area Under the Concentration-time curve at last measurement
BP	Blood Pressure
C_{max}	Maximum concentration
CMH	Cochran-Mantel-Haenszel (test to compare proportions)
CRF	Case Report Form
CSR	Clinical Study Report
CTMS	Clinical Study Management System
CYP450, CYP3A4	Cytochrome P450, Cytochrome P450 3A4
CYP7A1	Cholesterol 7α-hydroxylase
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
EDC	Electronic Data Capture
EOT	End of Treatment
FIB-4	Fibrosis 4 Index
GGT	Gamma-Glutamyl Transferase
HP	High Panic Laboratory test value indicating “potentially critical implications“
HR	Heart Rate
HT	High Telefacsimile Laboratory test value indicating “warrants notification”
IVRS	Interactive Voice Response System
LLN	Lower Limit of Normal
LP	Low Panic Laboratory test value indicating “potentially critical implications“
LT	Low Telefacsimile Laboratory test value indicating “warrants notification”
PBC	Primary Biliary Cholangitis
PD	Pharmacodynamics

PBO	Placebo
P-gp	p-glycoprotein
PK	Pharmacokinetics
PP	Per Protocol
QoL	Quality of Life
QTcF	QT interval, Fridericia correction
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SD	Standard Deviation
TEAE	Treatment Emergent Adverse Event
TFL	Table, Figure and Listing
T_{max}	time to maximum concentration
UDCA	Ursodeoxycholic Acid
ULN	Upper Limit of Normal
VAS	Visual Analog Score
WHODRUG	World Health Organization Drug Dictionary

Appendix 2 Adverse Event Start/Stop Date Imputation

Imputation Rules for Partial Dates (D = day, M = month, Y = year)

Parameter	Missing	Additional Conditions	Imputation
Start date for AEs	D	M and Y same as M and Y of first dose of study drug	Date of first dose of study drug
		M and/or Y not same as date of first dose of study drug	First day of month
	D and M	Y same as Y of first dose of study drug	Date of first dose of study drug
		Y prior to Y of first dose of study drug but same as Y of screening date	Date of screening date
	D, M, Y	None - date completely missing	Date of first dose of study drug
Stop date for AEs	D	M and Y same as M and Y of last dose of study drug	Date of last dose of study drug
		M and/or Y not same as date of last dose of study drug	Use last day of month
	D and M	Y same as Y of last dose of study drug	Date of last dose of study drug
		Y not same as Y of last dose of study drug	Use Dec 31
	D, M, Y	None - date completely missing	No imputation, but assume ongoing

Note: In all cases, if an estimated start date is after a complete stop date, use the first day of the stop date month.
Similarly, if the estimated stop date is before a complete or imputed start date, use the last day of the start day month.

Appendix 3 Prior and Concomitant Medication Start/Stop Date Imputation

Imputation Rules for Partial Dates (D = day, M = month, Y = year)

Parameter	Missing	Additional Conditions	Imputation
Start date for con meds	D only	M and Y same as M and Y of first dose of study drug	Date of first dose of study drug
		M and/or Y not same as date of first dose of study drug	First day of month
	M and D	Y same as Y of first dose of study drug	Date of first dose of study drug
		Y not same as Y of first dose of study drug	Use Jan 01 of Y
	M, D, and Y	None - date completely missing	Day prior to date of first dose of study drug
Stop date for con meds	D only	M and Y same as M and Y of last dose of study drug	Date of last dose of study drug
		M and/or Y not same as date of last dose of study drug	Last day of month
	M and D	Y same as Y of last dose of study drug	Date of last dose of study drug
		Y not same as Y of last dose of study drug	Use Dec 31 of Y
	M, D, and Y	None - date completely missing and NOT ongoing	Date of last dose of study drug

Note: In all cases, if an estimated start date is after a complete stop date, use the first day of the stop date month.
Similarly, if the estimated stop date is before a complete or imputed start date, use the last day of the start day month.

Appendix 5 Schedule of Assessments (SoA)

Study Event	Scr.[1]	Study Assessments per Planned Study Day						EOS
Visit Day	(D-28	D1[2]	D3	D14±2	D28±2	D56±2	D84[3]±2	D112±2
Treatment Week[4]	to -1)			W2	W4	W8	EOT[5]/W12	W16
ICF[6]; Demography; Medical History	x							
Inclusion/Exclusion	x							
FSH[7]; HIV/HCV/HBV	x							
AMA/M2/PBC-ANAb[8]	x							
Pregnancy Test[9]	x	x			x	x	x	x
Height[10], Weight, BMI	x							x
PT/PTT and INR	x							x
Oral Temperature	x	x						x
Physical Exam[11]	x	x	x	x	x	x	x	x
Vital Signs[12]	x	x	x	x	x	x	x	x
ECG	x	x	x		x		x	
Safety Lab. Tests[13]	x	x	x	x	x	x	x	x
PBC-40 QoL		x			x	x	x	x
VAS and 5-D Itch		x			x	x	x	x
Biomarkers (FGF19, C4, BA)[14]		x		x	x	x	x	
CV Markers[15]		x		x	x	x	x	x
Fibroscan	x							
ELF panel, PRO-C3, Inflammatory Markers[16]	x	x					x	
APRI, FIB-4		x					x	
PK/PD Substudy (PK, C4, FGF19, BA, ALP)[17]		x		x	x	x	x	
Population PK Samples[18]		x		x	x	x	x	
Dispense Study Drug		x			x	x		
Study Drug Dosing[19]		daily dosing						
Drug Accountability			x	x	x	x	x	
AEs & Con Meds[20]	x	x	x	x	x	x	x	x

1 Screening assessments should be conducted within 28 days prior to the first dose of study drug (i.e., Study Days -28 to -1)
2 On Day 1, all samples are to be collected predose with the exception of respective post-dose PK and PD samples
3 Subjects should discontinue drug on Day 84. Subjects who return for their EOT Visit after Day 84, should stop dosing on Day 84.
4 For the treatment phase, indicates number of completed weeks of treatment
5 Subjects who discontinue treatment early should complete the EOT procedures as soon as possible and return 4 weeks later for the EOS visit
6 Informed consent must be obtained prior to conducting any study-specific procedures or assessments
7 For post-menopausal women only
8 Only if historical values are not available; one test must be positive for study entry to confirm PBC diagnosis (see Inclusion Criterion #3)
9 Serum pregnancy test at Screening and Baseline, and urine pregnancy testing at Baseline and all other visits. If the urine pregnancy test is positive, a serum pregnancy test should be obtained as soon as possible to confirm.
10 Height should only be measured at Screening
11 Full PE at Screening and EOS; all other exams should be targeted to review of new signs and symptoms
12 Vital Signs include HR, respiratory rate, and BP and will be measured once in the morning before the morning dose of study drug
13 Safety laboratory tests include chemistry (including liver function tests), hematology, and urinalysis and should be collected predose at all visits; See Section 12.6.3.2 for details

14 Biomarkers include fasting plasma FGF19, fasting serum bile acids, fasting C4 (7 α-OH-4-cholesten-3-one). Samples should be collected after a minimum 8 hr fast and before the subject takes the daily dose of study drug
15 Lipids and CV risk markers to be collected are detailed in Section 12.6.3.2
16 Markers of inflammation include fibrinogen, CRP, IL6, IL1 β, TNF-α, TNF-β, alpha2 macroglobulin and haptoglobin see Section 12.6.3.2
17 Collect PK/PD samples after a minimum 8 hr fast and before the daily dose of study drug. PK/PD samples on Days 1 and 84 (Week12) collected predose and 2, 6, and 8 hr postdose; Weeks 2, 4 and 8 at predose and two samples postdose; the first sample collected 1 to 3 hours postdose and the second sample at least 1 hour later.
18 PK predose samples should be collected after a minimum 8 hr fast before the daily dose of study drug. PK samples collected Day 1, Weeks 2, 4, 8 and 12 at predose and two samples postdose; the first sample collected 1 to 3 hours postdose and the second sample at least 1 hour later.
19 Study drug given in the clinic on days where subject is seen in the clinic
20 Additional samples may be collected to further assess safety events e.g. pruritus

[redacted]

Appendix 6 Laboratory Evaluations

Chemistry Panel

- Alanine Aminotransferase (ALT/SGPT)
- Albumin, Serum
- Albumin/Globulin (A/G) Ratio (calculation)
- Alkaline Phosphatase, Serum
- Amylase
- Aspartate Aminotransferase (AST/SGOT)
- Bilirubin, Total and Direct
- BUN
- BUN/Creatinine Ratio (calculation)
- Calcium, (Serum)
- Creatine Kinase
- Creatinine, Serum (creatinine clearance)
- Uric Acid
- Electrolyte Panel (Na+, K+, Cl-, Bicarb.)
- Phosphorus
- Gamma Glutamyl Transferase (GGT)
- Globulin, Total
- Glucose, Serum
- Cholesterol, serum
- Lactate Dehydrogenase (LDH)
- Lipase
- Protein, Total, Serum
- TG (triglycerides)
- HDL Cholesterol 1
- LDL Cholesterol 1
- Apolipoprotein E (ApoE)

Hematology Panel

- Hemoglobin
- Hematocrit
- Differential WBC Count (percentage and absolute): Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils
- MCH
- MCHC
- MCV
- Platelets
- Red Blood Count
- RBC Morphology
- White Blood Count
- Absolute Neutrophil count)

Urinalysis Panel

- Color and appearance
- PH
- SG
- Bilirubin
- Glucose
- Ketones
- Leukocytes
- Nitrite
- Occult blood
- Protein
- Urobilinogen
- Microscopic (including RBCs and WBCs)
- Bacteria
- Leukocyte Esterase

Coagulation

- INR
- PT
- PTT

Safety Monitoring

- Liver Enzymes
  - Total Bilirubin, Direct Bilirubin, Alkaline Phosphatase, ALT(SGPT), AST(SGOT), GGT
- Liver Hematology
  - RBC, Neutrophils(abs, %), Lymphocytes(abs, %), Monocytes(abs, %), Eosinophils(abs,%), Basophils(abs,%), Platelets
- Elevated Liver Coagulation
  - INR, PT
- Albumin

Appendix 7 Markers of CV Risks and Lipids and Markers of Fibrosis and Inflammation

Markers of CV Risks and Lipids	Markers of Fibrosis and Inflammation

• hs-CRP
• HDL-P
• LDL-P
• apoA-I
• apoB
• apoB/A Ratio
• apoC3
• apoE isoforms (E2, E3, E4)
• Total Cholesterol (TC)
• High Density Lipoprotein – Cholesterol (HDL-C)
• Low-Density-Lipoprotein – Cholesterol (LDL-C)
• TG (triglycerides)
• Total /HDL Cholesterol (CT) Ratio
• Adiponectin
	• Enhanced Liver Fibrosis (ELF) Panel
	  ○ Hyaluronic acid (HA),
	  ○ Procollagen III amino terminal peptide (PIIINP)
	  ○ Tissue inhibitor of metalloproteinase 1 (TIMP-1)
	• PRO-C3
	• Fibrinogen
	• CRP
	• alpha2 macroglobulin
	• haptoglobin
	• TNF-α
	• TNF-β
	• IL-6
	• IL1β
	• AST to Platelet Ratio Index (APRI)
	• Fibrosis 4 (FIB-4) Index

Statistical Analysis Plan

Sponsor:	Enanta Pharmaceuticals, Inc.
Protocol No:	EDP 305-201
PRA Project Id:	ENA30501-30501
Version Date:	09-MAR-2020
Version No.:	7.0

Title:	A Phase 2 Dose Ranging, Randomized, Double Blind, Placebo-Controlled Study Evaluating the Safety, Tolerability, Pharmacokinetics and Efficacy of EDP-305 in Subjects with Primary Biliary Cholangitis (PBC) with or without an Inadequate Response to Ursodeoxycholic Acid (UDCA)
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