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Study ID: 652-205

Title: PERSEUS: A Phase 2 Proof of Concept Study Investigating the Preliminary Efficacy and Safety of Cenicriviroc in Adult Subjects with Primary Sclerosing Cholangitis (PSC)

Statistical Analysis Plan Date: 12 June 2017

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Protocol 652-205

STATISTICAL ANALYSIS PLAN

Tobira Therapeutics, Inc., a subsidiary of Allergan plc

A Phase 2 Proof of Concept Study Investigating the Preliminary Efficacy and Safety of Cenicriviroc in Adult Subjects with Primary Sclerosing Cholangitis (PSC)

12 June 2017
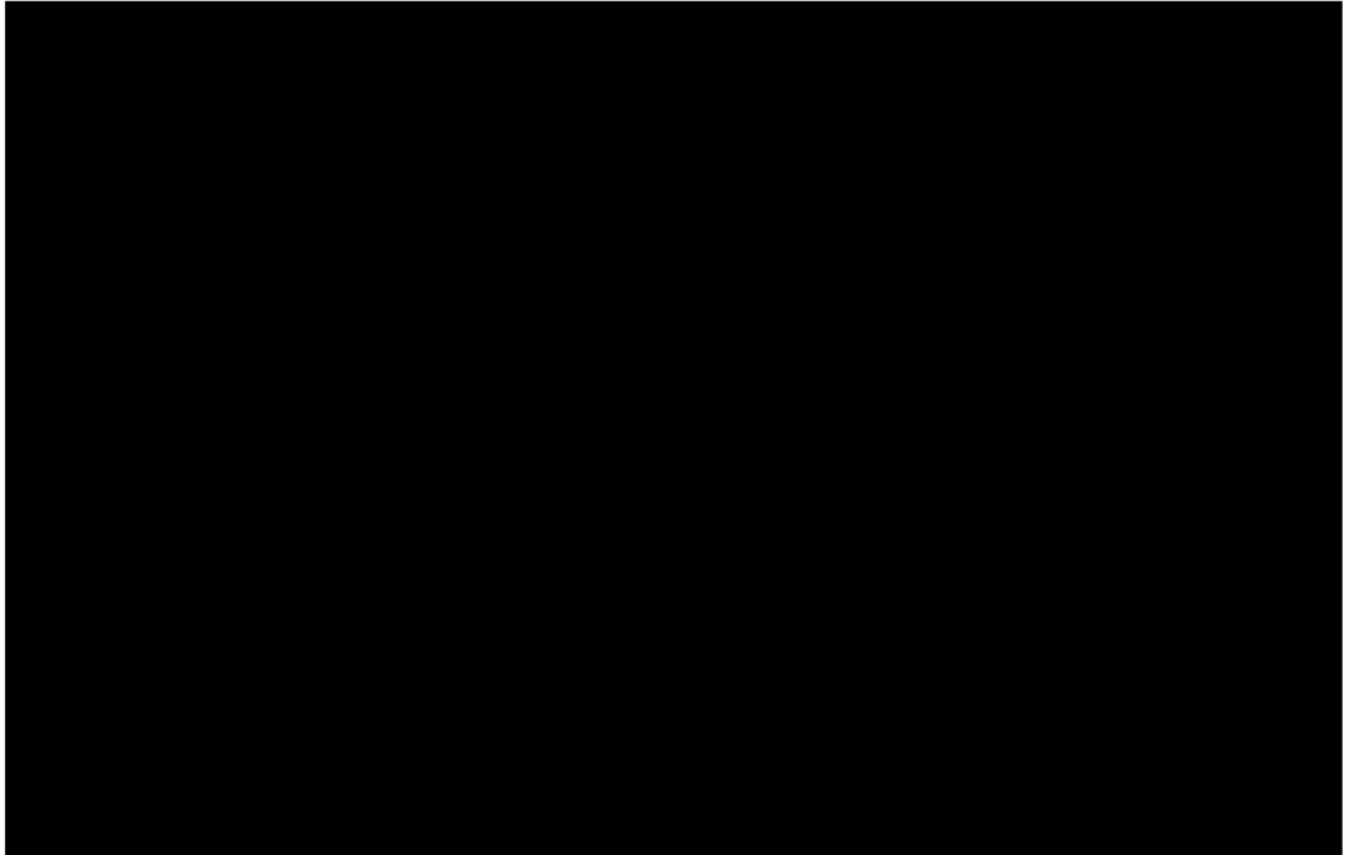
Version 1.0

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APPROVAL SIGNATURES

Title: **Tobira Therapeutics, Inc., a subsidiary of Allergan plc: A Phase 2 Proof of Concept Study Investigating the Preliminary Efficacy and Safety of Cenicriviroc in Adult Subjects with Primary Sclerosing Cholangitis (PSC))**

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LIST OF ABBREVIATIONS

ADL	activities of daily living
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
████	████████████████████████
AST	aspartate aminotransferase
BMI	body mass index
████	█████████████████
CRF	case report form
CPK	creatine phosphokinase
CVC	cenicriviroc
DC	discontinuation
ECG	electrocardiogram
ELF	enhanced liver fibrosis
████	██████████████████
IBD	inflammatory bowel disease
ICF	Informed Consent Form
████	████████████
INR	international normalized ratio
ITT	intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
PK	pharmacokinetic
PoC	proof of concept
PP	per protocol
PSC	primary sclerosing cholangitis
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
TEAE	treatment-emergent adverse event
Tobira	Tobira Therapeutics, Inc., a subsidiary of Allergan plc
UDCA	ursodeoxycholic acid
ULN	upper limit of normal
US	United States
UV	Ultraviolet
WHO DDE	World Health Organization Drug Dictionary Enhanced

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1.0   STUDY INTRODUCTION

1.1   STUDY OBJECTIVES

The primary objective is to evaluate effects of cenicriviroc (CVC) on serum alkaline phosphatase (ALP) over 24 weeks of treatment in adult subjects with primary sclerosing cholangitis (PSC).

The secondary objective is to evaluate the safety and tolerability of CVC over 24 weeks in adult subjects with PSC.

1.2   BACKGROUND

CVC is a novel, once-daily, orally active, and potent inhibitor of ligand binding to chemokine receptor type 2 (CCR2) and chemokine receptor type 5 (CCR5). It is currently being developed for the treatment of nonalcoholic steatohepatitis in adult subjects with liver fibrosis, and in obese subjects with prediabetes or type 2 diabetes mellitus with suspected nonalcoholic fatty liver disease. Given the evidence supporting the role of CCR2 and CCR5 in inflammatory- and fibrotic-related liver diseases, this study will evaluate CVC in adult subjects with PSC by assessing the effects on ALP over 24 weeks.

PSC is a life-threatening idiopathic chronic cholestatic disease that affects the intrahepatic or extrahepatic bile ducts of the liver and that cannot be ascribed to another cause, thus differentiating it from secondary sclerosing cholangitis. Inflammation and fibrosis of the bile ducts leading to formation of a beaded pattern and multifocal bile duct strictures are the hallmark of this progressive disease, thereby resulting in destruction of the bile ducts, fibrosis, cirrhosis, portal hypertension, and ultimately hepatic decompensation resulting in liver failure.

There are currently no approved effective therapies for PSC, with drug therapy being used to manage complications and treat symptoms. Several drugs have been used in an attempt to control the disease process but have not shown significant benefit. The stage and degree of progression of the disease dictate the extent of care, with liver transplantation being the only option that can alter outcome and survival. Ursodeoxycholic acid (UDCA) has been shown to improve the liver function profile in some patients; however, improvement in long-term survival has not been proven.

The established safety profile of CVC combined with the well-defined anti-inflammatory and antifibrotic properties associated with CCR2/CCR5 blockade, along with the results from the nonclinical studies, provide a medically plausible rationale for development of CVC for PSC.

The open-label, single-arm, proof of concept (PoC) study aims to evaluate for the first time the effects of CVC in adults with PSC by assessing changes in ALP for up to 24 weeks. Furthermore, this study will evaluate the safety and tolerability of CVC in this population. Findings from this study are expected to expand the understanding of CVC activity in PSC, for which there are no effective treatments available, and also will determine if further controlled studies are warranted in this orphan disease.

1.3   STUDY DESIGN

This is a Phase 2, single-arm, open-label, PoC study of CVC in approximately 25 adult subjects with PSC. The main objective of this PoC study is exploratory in nature and will assess changes in ALP both individually and as a group. A dose of 150 mg of CVC (DP7 formulation) will be evaluated.

Screening will occur within 6 weeks before the baseline visit. At the baseline visit, subjects who have signed the informed consent form (ICF) and meet all the eligibility criteria will be enrolled in the study and begin treatment with CVC. Subjects will return to the study site for on-treatment evaluations at Weeks 2, 4, 8, 12, 16, and 24. Approximately 4 weeks after the last dose of study drug (Week 28), subjects will undergo follow-up evaluations. Subjects who discontinue study drug before completion of 24 weeks of treatment will be required to return to the clinic for an early discontinuation visit.

The dosing regimen and schedule for this study are shown in Figure 1.

Figure 1   Study design schematic.
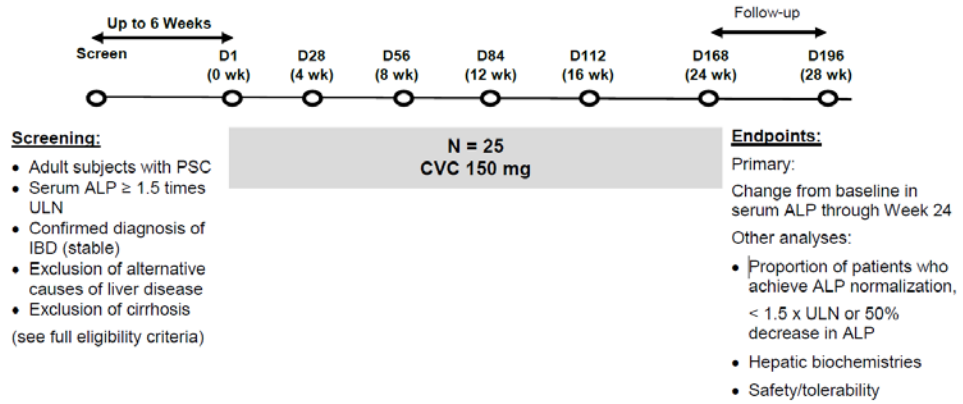
ALP = alkaline phosphatase; CVC = cenicriviroc; IBD = inflammatory bowel disese; PSC = primary sclerosing cholangitis; ULN = upper limit of normal.

1.4   SAMPLE SIZE

Approximately 25 subjects in total are planned for enrollment, all of whom will be treated with open-label CVC.

Each patient will serve as his or her own control when observing ALP relative to baseline.
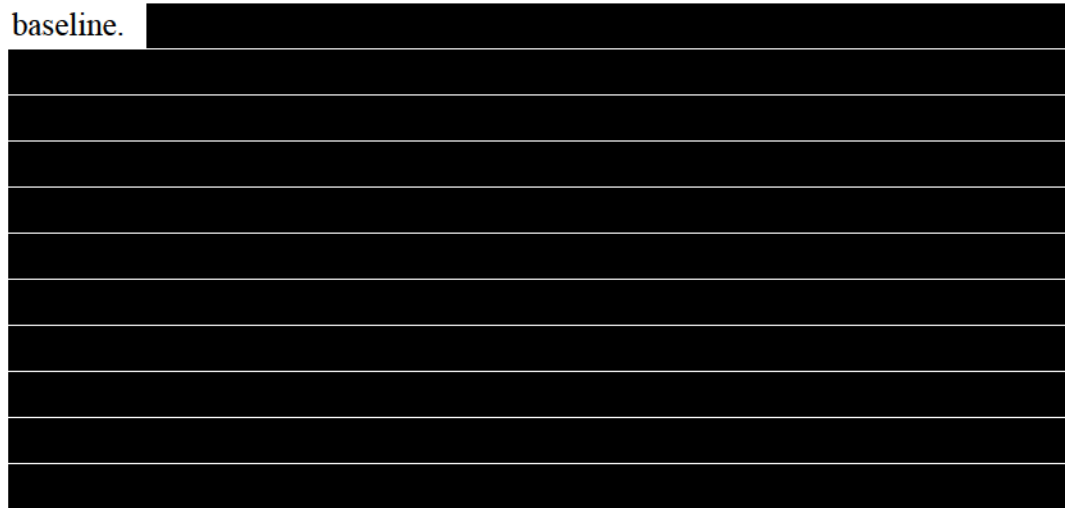
1.5   RANDOMIZATION

Since this is a single-arm study, no randomization will be used.

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1.6   STUDY PROCEDURES

Screening will occur within 6 weeks before the baseline visit. Subjects enrolled under Amendments 1 and 2 were also required to have a pre-baseline visit, which was removed in Amendment 3. Eligible subjects will be seen at baseline (Day 1), (Week 2), Week 4, Week 8, Week 12, Week 16, and Week 24. A safety follow-up visit will be conducted at Week 28 (±3) days (i.e., 4 weeks after last intake of study medication) or at the time of early termination (if a subject discontinues the study early). On visit days, subjects will be asked to come in to the clinic while fasting. Blood samples will be collected before dosing. Subjects will be required to bring in study medication on the days of clinic visits, and dosing will be conducted on-site with a morning snack.

Data will be collected as follows:

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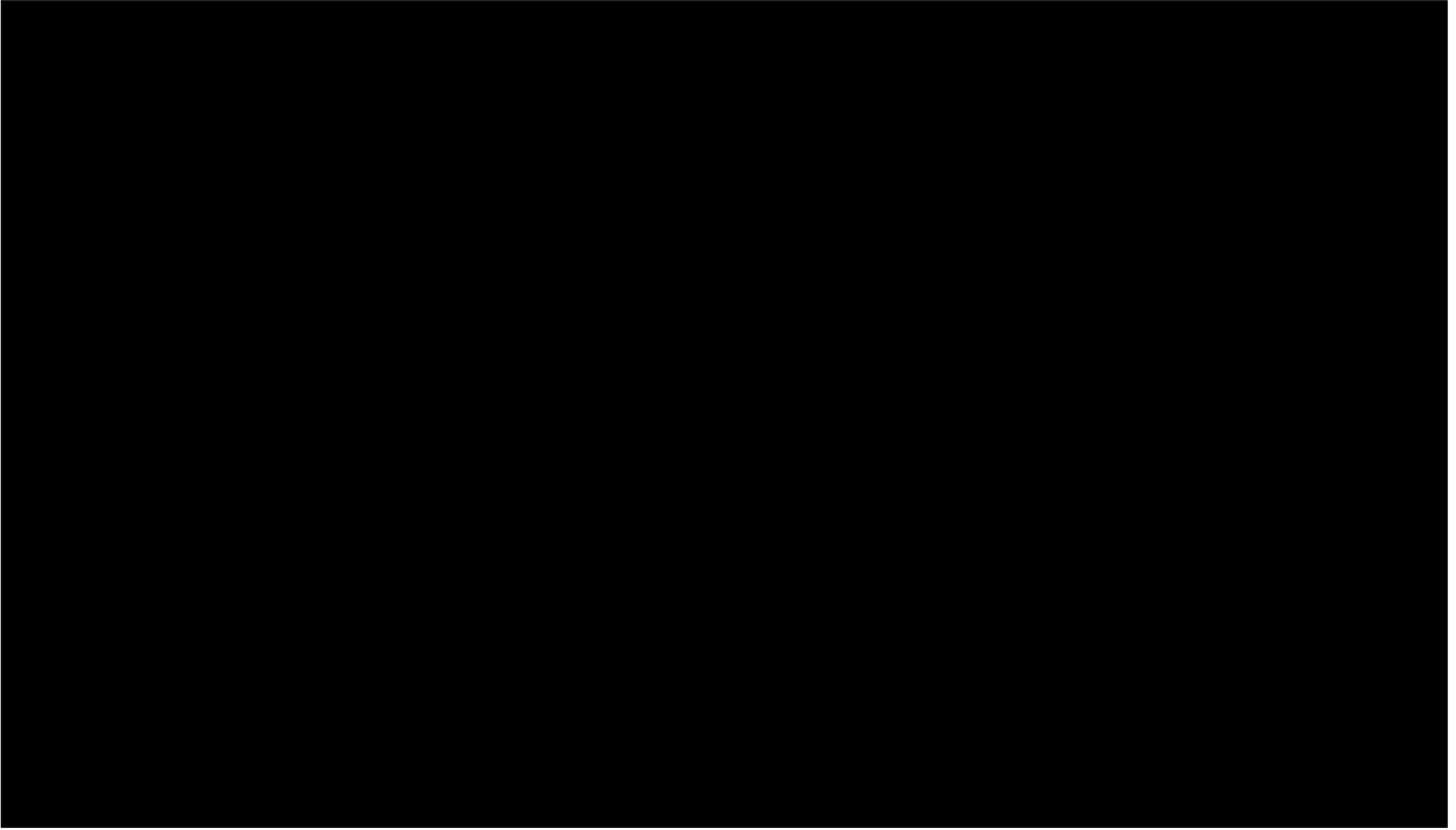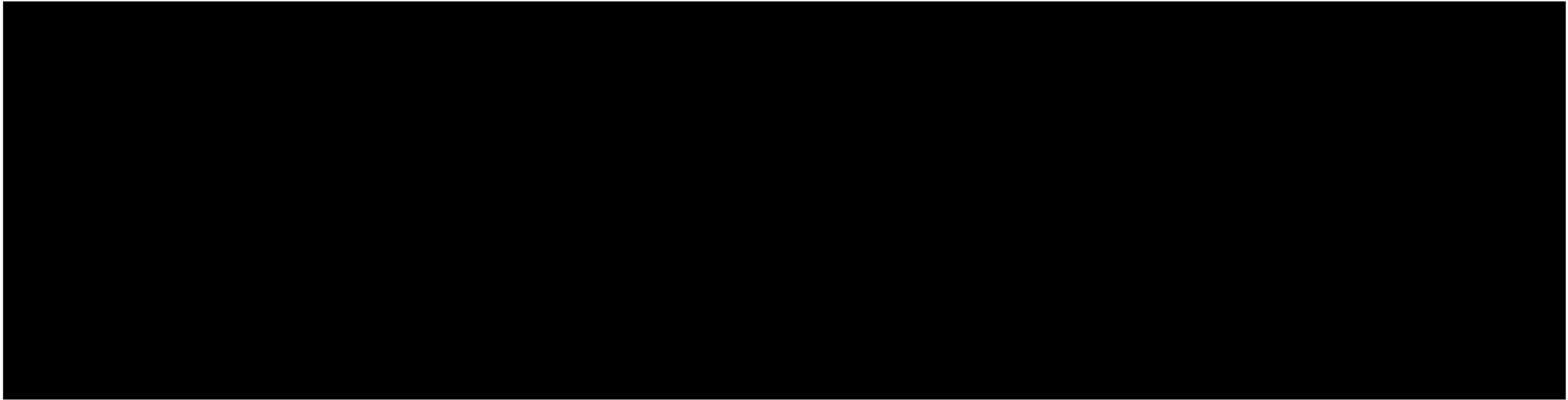
1.7 SCOPE OF PLAN

This statistical analysis plan (SAP) provides a more technical and detailed elaboration of the statistical analyses of the efficacy and safety data as outlined or specified in the final protocol of Study Protocol 652-205 (version dated 19 November 2015) and the most recent amendment (Version 3 dated [14 June 2016]). Specifications of tables, figures, and data listings are contained in a separate document.

This SAP will indicate the methods to be used to analyze the safety and efficacy data collected during the study and will supersede any statistical analyses specified in the protocol. The planned analyses identified in this SAP will be included in regulatory submissions and future manuscripts. Additional exploratory analyses, which are not defined in this SAP, will be labeled as such in any study report or regulatory submission.

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2.0 STUDY POPULATIONS

2.1 DEFINITIONS OF POPULATIONS FOR ANALYSIS

The analysis sets will be defined as specified in Sections 2.1.1 through Section 2.1.3.

2.1.1 Intent-to-Treat Analysis Set

The intent-to-treat (ITT) analysis set will include all enrolled subjects who received at least one dose of study treatment. This analysis set will be used for all baseline characteristics and efficacy analyses.

2.1.2 Per Protocol Analysis Set

Although planned in the protocol, the per protocol analysis will not be conducted as determined by the sponsor.

2.1.3 Safety Analysis Set

The safety analysis set will include all subjects who received at least one dose of study drug. This analysis set will be used for all safety analyses.

As defined in the protocol, the ITT analysis set and safety analysis set are identical. Subjects who only receive one dose of study drug and do not return for any post-baseline visits will be included in the ITT analysis set, although they only provide data for safety assessments and no efficacy measurements.

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3.0 STATISTICAL ANALYSIS

3.1 GENERAL

Descriptive statistical methods will be used to summarize the data from this study. Unless stated otherwise, the term *descriptive statistics* refers to number of subjects with nonmissing data (n), mean, median, standard deviation, minimum, and maximum (with quartiles, 10th and 90th percentile) for continuous data and frequencies and percentages for categorical data.

Appendix listings of data from this study will also be provided.

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3.3 METHODS FOR HANDLING DROPOUTS AND MISSING DATA

Data will be analyzed as recorded. There will be no imputations conducted for missing data. Data will be analyzed at the visit at which the investigator assigned the data, even if the visit occurred outside of a visit window for that visit. Analyses using longitudinal models will implicitly use available data to inform the analysis of missing data, but no data will be explicitly imputed.

3.4 BASELINE VALUES

The baseline value will be defined as the last nonmissing value on or before the baseline visit (Day 1).

4.0   SUBJECT ENROLLMENT AND DISPOSITION

The following will be summarized with frequencies and percentages of subjects in safety analysis set: subject enrollment (subjects enrolled who signed ICF); inclusion in analysis sets (ITT and safety analysis sets); number of subjects completing the study; number of subjects discontinuing the study before study completion; reasons for premature discontinuation; and the number of days on study. The number of subjects discontinued by visit will also be presented.

Date and time of last dose will also be provided in a listing.

5.0   EVALUATION OF BASELINE MEASUREMENTS

This section describes the analysis of all demographics, baseline characteristics, medical history, and tests performed as part of inclusion and exclusion criteria, evaluated at screening exclusively.

5.1   DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Demographic parameters (e.g., age [based on date of birth and date of signed informed consent form], sex, race, ethnicity, height, weight, body mass index [BMI]) and baseline characteristics (e.g., type of IBD, and Partial Mayo Risk score at baseline) will be summarized descriptively for the ITT analysis set. BMI is calculated as a person's weight in kilograms divided by height in meters squared (kg/m^2). Demographic and baseline characteristic data will be summarized and listed for the safety analysis set.

5.2   MEDICAL HISTORY

Medical history, including pre-treatment AEs, will be collected at the screening visit. Medical history will include all information on a subject until the first dose of study medication. Medical history data (medical history verbatim term, start date, end date or ongoing status at baseline) will be provided in an appendix listing for the safety analysis set.

5.3   SCREENING BLOOD TESTS

At screening, blood will be drawn for infectious disease assessments (hepatitis B surface antigen, hepatitis C virus antibody, human immunodeficiency virus 1 and human immunodeficiency virus 2 antibodies, and anti–smooth muscle antibody. Infectious diseases assessments and anti–smooth muscle antibody data will be provided in a listing for the safety analysis set.

5.4   URINE DRUG SCREEN AND PREGNANCY TESTS

A urine drug result will be collected at screening for amphetamines, barbiturates, cocaine, methadone, and opiates. For females of childbearing potential only, a urine pregnancy test (dipstick) and serum pregnancy test will be performed also at

screening. Urine drug screen data and pregnancy test data for enrolled subjects will be provided in an appendix listing for the safety analysis set.

6.0 EVALUATION OF TREATMENT EXPOSURE AND COMPLIANCE

All eligible subjects will receive 150 mg CVC daily for 24 weeks. CVC should be taken every morning with food. Study medication (i.e., CVC) will be supplied in a bottle containing 37 tablets for each subject, which is sufficient for 28 days of dosing. Study drug bottles are dispensed, and any unused medication and the medication bottles are returned at baseline (dispensed only) and at Week 4, Week 8, Week 12, Week 16, and Week 24 (returned only).

6.1 EXPOSURE TO TREATMENT

The treatment duration is calculated as the number of days from the date of the first dose of study medication taken to the date of last dose taken, inclusively. Descriptive statistics will be presented for the safety analysis set.

6.2 COMPLIANCE TO STUDY TREATMENT

Study medication dosing compliance for a *specified period* is defined as the total number of tablets taken by a subject during that period divided by the number of tablets expected to be taken during the same period multiplied by 100.

The number of tablets actually taken will be calculated by subtracting the tablets returned from the total number of tablets dispensed. The number of tablets expected to be taken for a specified period is the number of days in that period.

Descriptive statistics for the study medication compliance will be presented for each period between two consecutive visits, and over the 24 weeks (overall) for the safety analysis set.

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7.0   EVALUATION OF EFFICACY PARAMETERS

This study will evaluate the effects of CVC in adult subjects with PSC. ██████

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7.1   PRIMARY EFFICACY ENDPOINT

The primary endpoint for this study is the percent change from baseline through Week 24 in ALP.

The percent change from baseline will be calculated as follows:

$$ALP\ (\%) = \frac{(value\ at\ each\ visit - baseline\ value)}{baseline\ value} \times 100$$

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If the normality and homogeneity of variance assumptions are significantly violated, then the baseline and percentage change from baseline parameters are first ranked separately, using the combined data from all visits. Tied values will receive the mean value (midranks) of the corresponding ranks. Then, the same mixed-

effect repeated measure model with ranked data will be used for the primary efficacy analyses.

7.1.1 Pre-treatment Change per Week with On-treatment Change per Week

Also a comparison of *pre-treatment change per week with on-treatment change per week* will be made through an estimate specification and the corresponding 95% confidence interval will be reported. To this end, a similar linear mixed-effect repeated measure model will be fit with change from baseline at the visit as the dependent variable, visits (baseline, Weeks 4, 8, 12, 16, and 24) as fixed factors, baseline score and baseline score-by-visit interaction as covariates, the visit nested within subject and subject as a random effect to model correlations among the within-subject repeated measures. A compound symmetry structure will be used initially in the model for the correlation pattern among the repeated measures. If this does not converge, then other covariance structure, for example, the spatial power covariance structure for unequally spaced time intervals will be used to model the repeated assessment over time. Denominator degrees of freedom will be estimated using the Kenward-Roger method.

Pre-treatment change from baseline is defined as follows:

$$screening\ value - baseline\ value$$

For multiple t-test, pairwise comparisons based on the Bonferroni adjusted t-test would produce comparisons of the group means for *on-treatment change* from baseline at the visit *back to pre-treatment change*. Through this model, two-sided 95% confidence intervals will be produced for comparisons of the group means at the visit (*on-treatment change*) back to the first time point (*pre-treatment change*).

Percent changes in ALP from baseline will be summarized using descriptive statistics for the respective pre-treatment and on-treatment visits.

The ALP raw values and the percent change from baseline in ALP at each visit will be summarized descriptively by visit: before treatment (screening, baseline) and during treatment (Weeks 2, 4, 8, 12, 16, and 24).

Descriptive comparisons will be made for the following:

- Subjects with a history of IBD vs. no history of no IBD at screening

- Subjects who received UDCA for at least 3 months before screening vs. who have not received UDCA for at least 3 months before screening

Figures for the percent changes in ALP from baseline by visit will also be presented.

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7.2   SECONDARY EFFICACY ENDPOINTS

Secondary efficacy endpoints include the following:

- The proportion of patients who achieve ALP normalization (ALP values outside of the central laboratory reference range at baseline, but within the central laboratory reference range at each visit according to the central laboratory reference ranges) at each visit, with secondary endpoint defined at Week 24

- The proportion of patients who achieve a decrease in ALP of $<1.5 \times$ ULN at each visit with secondary endpoint defined at Week 24

- The proportion of patients who achieve a 50% decrease in ALP from baseline at each visit, with secondary endpoint defined at Week 24

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7.4 PATIENT PROFILE

Subject profiles will be used to further explore the biological activity of CVC. The subject profiles will contain stick plots of ALP over time, plotted simultaneously with ALT over time. Demographic and baseline factors that will appear in the figure will include the following: age, sex, race, type of IBD, Partial Mayo Risk score at the screening visit, and treatment-emergent serious adverse events (SAEs).

8.0 EVALUATION OF SAFETY PARAMETERS

The safety analysis will be performed using the safety analysis set. The safety parameters will include AEs, clinical laboratory parameters, vital signs, and ECG parameters.

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The safety endpoints to be summarized are as follows:

- Evaluation of the safety and tolerability of CVC through 24 weeks of treatment in adult subjects with PSC

- Evaluation of the proportion of subjects with a treatment-emergent adverse event (TEAE) or a clinically significant laboratory abnormality (overall and of any given type)

- Evaluation of the proportion of subjects who discontinue due to an AE

- Evaluation of AEs, clinical laboratory tests, physical examination, and 12-lead ECG

Unless otherwise specified, safety will be evaluated using the safety analysis set and will be presented in appropriate listings and frequency tables.

8.1   ADVERSE EVENTS

An *adverse event* is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, regardless of whether related to the medicinal (investigational) product.

Verbatim descriptions of AEs will be coded by using Medical Dictionary for Regulatory Activities (MedDRA), Version 18.1 or later. The investigator will assess the grade for each AE and SAE reported during the study.

The AE severity will be graded according to the scale below, in addition to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03, Table for Grading the Severity of Adult Adverse Events. The clinical significance of the AE is determined by the investigator.

- Grade 1 (mild): asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

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- Grade 2 (moderate): minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)

- Grade 3 (severe): medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL

- Grade 4 (life-threatening): life-threatening consequences; urgent intervention indicated

- Grade 5 (death): death related to AE

8.1.1 Serious Adverse Events

An AE or suspected adverse reaction is considered serious if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death

- Life-threatening AE (An AE or suspected AE is considered life-threatening if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.)

- Inpatient hospitalization (i.e., admission, overnight stay) or prolongation of existing hospitalization

- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

- Congenital anomaly/birth defect

- Important medical events (An important medical event is one that, when based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above in the definition of an SAE. Examples of such events include allergic bronchospasm requiring intensive treatment at an emergency room or at home, blood dyscrasias, convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.)

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A *treatment-emergent adverse event* is defined as any AE (classified by preferred term [PT]) not present before the first dose of the study medication or any adverse event already present that worsens in severity grade after the first dose of the study drug. If more than one AE is reported before the first dose of the study medication and coded to the same PT, then the AE with the greatest severity will be used as the benchmark for comparison to the AEs occurring during the study that were also coded to that PT. Dates and times for AEs will not be imputed. AEs with a missing start date or time that leads to ambiguity about whether the AE is treatment emergent will be considered treatment emergent.

The incidence of TEAEs will be summarized overall by system organ class (SOC) and PT. For each level of SOC and PT, a subject will be counted only once for the purpose of summarization.

The incidence of treatment-emergent SAEs, TEAEs leading to study drug discontinuation, and TEAEs related to study drug will summarized by SOC and PT.

A summary of TEAEs occurring in 5% or more of subjects will be reported by SOC and PT, and information can be extracted from the main TEAE incidence table.

Separate summaries will be presented for Grade 3 toxicities resulting in study drug interruption by SOC and PT and for Grade 4 toxicities resulting in study drug discontinuation by SOC and PT.

In the summary tables (except the summaries of the TEAEs reported by maximum severity) the number and percentage of subjects reporting at least one TEAE will be presented, followed by the number of events. For each SOC, the number and percentage of subjects reporting one or more TEAEs within that SOC will be reported. Then, each PT within that SOC will be reported, showing number and percentage of subjects reporting at least one TEAE classified as that particular PT. The summary will be produced at the SOC level according to the MedDRA internationally agreed sorting order, and then within the SOC by descending frequency at the PT level.

For the summary of TEAE by maximum severity grade, if a subject has more than one event with different severities within a given PT, then the most severe event will be included in the table. Within each SOC, each TEAE listed by PT will have up to five associated rows, one for each observed severity grade. The number and

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percentage of subjects who have at least one TEAE with that PT at that greatest severity will be shown. If a subject had more than one TEAE mapped to the same PT, then that TEAE will be represented according to the corresponding maximal level of severity.

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8.2   PRIOR AND CONCOMITANT MEDICATIONS

Any prior medication received within 28 days of the first dose of study drug will be recorded in the case report form (CRF). All medications (or treatments) other than study drug taken or received by the subject at any time during the study from

screening through the 4-week follow-up visit will be considered concomitant medications (or treatments).

If a medication has an end date that occurs before first dose date, that medication will be considered a prior medication. If a medication has a start date that occurs before first dose date and an end date that occurs after first dose date, that medication will be considered both prior and concomitant. If a medication has a start date that occurs after first dose date, that medication will be considered concomitant. If a missing start date, start time, end date, or end time leads to ambiguity in whether a medication is prior or concomitant, the medication will be considered concomitant.

Prior and concomitant medications will be mapped to a World Health Organization Drug Dictionary Enhanced (WHO DDE), September 2015. The number and percent of subjects taking concomitant medications will be summarized by Anatomical Therapeutic Classification Level 1 code, by descending frequency at the PT level. Prior and concomitant medication will be listed.

8.3   CLINICAL LABORATORY PARAMETERS

Hematology, clinical chemistry, and urinalysis data will be collected at screening, the baseline/Day 1 visit, and at the Week 2, Week 4, Week 8, Week 12, Week 16, and Week 24 visits.

Coagulation profile will be performed only at screening, baseline, and Week 24 and will include INR.

Hematologic profile will report the following parameters: hematocrit, hemoglobin, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, platelet count, red blood cell distribution width, red blood cell count, white blood cell count, and white blood cell differential (absolute counts only): basophils, eosinophils, lymphocytes, monocytes, and neutrophils.

Clinical chemistry profile will include: cholesterol (total), high-density lipoprotein, low-density lipoprotein, triglyceride, amylase (reflex lipase if amylase $\geq 1.5 \times$ ULN), bicarbonate, blood urea nitrogen, calcium, chloride, creatine phosphokinase, creatinine, glucose, lactate dehydrogenase, magnesium, phosphorus, potassium, sodium, total protein, and uric acid.

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Urinalysis profile will report color and appearance, pH and specific gravity, bilirubin, glucose, ketones, leukocytes, nitrite, occult blood, protein, and urobilinogen.

All hematology, coagulation, clinical chemistry, and nominal urinalysis data will be summarized at each time point for the actual values and for changes from baseline. Descriptive summaries of quantitative changes in urinalysis will be presented by study visit in a separate table.

Laboratory abnormalities will be graded according to NCI CTCAE, Version 4.03, and recorded as AEs.

The number and percentage of subjects experiencing with Grade 3 or 4 Treatment-emergent abnormal clinical chemistry values will be presented.

8.4 ELECTROCARDIOGRAMS

A 12-lead ECG will be taken at the baseline/Day 1 visit, and at Week 24. ECGs will be performed with the subject in the supine position after 5 minutes of rest and before any blood draws. ECG parameters include ventricular heart rate (beats/min), RR interval (msec), PR interval (msec), QRS interval (msec), QT interval (msec), QTcF interval (msec). Results will be classified as follows: normal; abnormal, not clinically significant; and abnormal, clinically significant.

Descriptive statistics for ECG parameters (heart rate, RR interval, PR interval, QRS duration, QT interval, and QTc) at each visit (Baseline and Week 24) and changes from baseline values at Week 24 will be presented. The QTc will be calculated using the Fridericia correction.

A shift table from baseline to Week 24 in the clinical significance as per investigator's overall interpretation of the ECG will be presented for the following categories: normal; abnormal, not clinically significant; and abnormal, clinically significant. The tabular display will also show total number of subjects with post baseline, clinically significant ECG abnormalities according to the investigator's overall interpretation.

ECG data will be listed.

8.5   VITAL SIGNS

Vital sign measurements (sitting systolic and diastolic blood pressure, temperature, heart rate, and respiration rate) will be taken at screening, the baseline/Day 1 visit, and at the Week 2, Week 4, Week 8, Week 12, Week 16, and Week 24 visits.

Descriptive summaries of raw values of vital signs (systolic blood pressure, diastolic blood pressure, heart rate) will be presented at study visit. Descriptive summaries of changes from baseline in vital signs will also be presented by study visit.

Vital signs will be listed.

8.6   PHYSICAL EXAMINATION

A complete physical examination will be performed at the Screening 1 visit and the baseline/Day 1 visit. A symptom-directed physical examination will be performed, as needed, at the Screening 2 visit, at all on-treatment visits, at the early discontinuation visit within 48 hours of stopping study medication, and at the 4-week follow-up visit. The complete physical examination will include (but will not be limited to) the following organ or body system assessments: skin; head, eyes, ears, nose, and throat; thyroid; lungs; cardiovascular; abdomen (liver and spleen); extremities; lymph nodes; and a brief neurological examination. Abbreviated symptom-directed physical examinations will target signs and symptoms.

Any abnormal findings that are considered clinically significant in the opinion of the investigator will be recorded as AEs or be captured as medical history, if already present at screening.

Physical examination data will be listed.

8.7   PROCEDURES AND THERAPIES

Any procedures and non-drug therapies administered during the study that are recorded in the (CRF) will be listed.

9.0   SPECIFICATIONS FOR ANALYSIS DISPLAYS

9.1   ANALYSIS DISPLAY FORMAT

All analysis displays will be created by using statistical and summarization procedures in ███████████   Displays will be produced by using the Courier New 8-point font. Headers will also be in Courier New 8-point font.

All displays are intended to be printed as landscape on 8.5- × 11-in paper. The top and bottom margins will be 0.50 in, and the left and right margins will be 0.75 in.

9.2   CONVENTIONS FOR PRESENTATION

The conventions for presentation in the analysis displays are shown in Table 2.

Table 2   Conventions for Presentation in the analysis displays

Convention	Description
Decimals for summary statistics	General rule: Relative to number of decimals in original data, use 1 more decimal for mean, median, and percentiles, 2 more decimals for standard deviation/error, and same number for minimum, maximum, and range. Do not exceed 4 decimals. Some laboratory parameters or other data may require judicious deviation from this rule.
Format for percentages	Display percentages with 1 decimal.
Sort order in listings	Subject identification is sorted sequentially.

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9.3 CONVENTIONS FOR CALCULATIONS AND TABULATIONS

The conventions for calculations and tabulations are shown in Table 3.

Table 3.   Conventions for Calculations and Tabulations

Convention	Description
Age calculation	Age is calculated as an integer in years as the difference between the subject's date of informed consent and the date of birth.
AE counting: general summary	In summary displays, AEs are counted only once per subject within MedDRA category (e.g., overall, system organ class, and preferred term).
AE counting: summary by assessment	When AEs are summarized within levels of another AE assessment (e.g., causality or severity), AEs are counted once per subject at the worst level of the assessment (e.g., strongest relationship to study drug or greatest severity). A missing or unknown value for the assessment will be considered Unknown.
"Other" category counting	For purposes of summarization, conditions recorded in the case report form as an "Other" category condition will be counted only once per subject. Hence, the count becomes the number of subjects reporting at least one "Other" condition vs. subjects reporting none. All conditions will be listed in the appendix.

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities.

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10.0 REFERENCES

1   Vickers AJ. The use of percentage change from baseline as an outcome in a controlled trial is statistically inefficient: a simulation study. 2001:1-6.

2   Keene ON. The log transformation is special. Stat Med 1995;14(8):811-819.

3   Törnqvist L, Vartia P, Vartia Y. How Should Relative Changes be Measured? The American Statistician 1985;39(1):43-46.