1.0 TITLE PAGE

3152-201-002

Open-label Rollover Study of Cenicriviroc for the Treatment of Liver Fibrosis in Adult Subjects with Nonalcoholic Steatohepatitis (NASH)

STATISTICAL ANALYSIS PLAN - Clinical Study Report

Version 1.0: 30JAN2019

2.0 TABLE OF CONTENTS

3.0 LIST OF ABBREVIATIONS

AE	adverse event
BMI	body mass index
CRF	case report form
CVC	cenicriviroc mesylate
ECG	electrocardiogram, electrocardiographic
IgG	immunoglobulin G
INR	international normalized ratio
ITT	intent to treat
NASH	nonalcoholic steatohepatitis
OC	observed cases
PCS	potentially clinically significant
PID	participant identification
PPI	proton pump inhibitor
SAE	serious adverse event
SAP	statistical analysis plan
SI	*Le Système International d'Unités* (International System of Units)
TEAE	treatment-emergent adverse event

4.0 INTRODUCTION

This statistical analysis plan (SAP) provides a more technical and detailed elaboration of the statistical analyses of the safety data as outlined and/or specified in the final protocol of Study 3152-201-002 (version dated 01 Dec 2016) and the most recent amendment (version 1 dated 14 Apr 2018). Specifications of tables, figures, and data listings are contained in a separate document.

Study 3152-201-002 is a Phase 2, open-label, multi-center, study to provide open-label cenicriviroc mesylate (CVC) to participants with liver fibrosis in the treatment of nonalcoholic steatohepatitis (NASH).

Participants from the following studies will be eligible to receive open-label CVC 150 mg once daily:

- Participants who have completed both Treatment Period 1 and Treatment Period 2 (Year 1 and Year 2) of the CENTAUR study (652-2-203), regardless of their treatment assignment in the CENTAUR study (CVC or placebo).
- Participants who have exited the AURORA study (3152-301-002) as a result of progression to cirrhosis or reaching an adjudicated liver-related clinical outcome in either Part 1 or Part 2 of the study, regardless of their treatment assignment (CVC or placebo).

Participants will be required to rollover to this continued access study within 1 month of completing their final visit assessments in either the CENTAUR or AURORA study. Eligible participants who completed these studies, prior to initiation of this protocol at their study center, will be allowed to enroll in this rollover study.

Participants will undergo study visits for safety assessments at the start of this continued access study (Baseline), then every 3 months for the duration of the study, or at the discretion of the investigator. A central laboratory will be used for laboratory assessments, including any deemed necessary by the investigator; all other study assessments will be conducted locally.

This is a rollover study in which CVC treatment will continue to be provided on an open label basis until it is commercially available or if development is terminated, as applicable.

The study design is illustrated as follows:

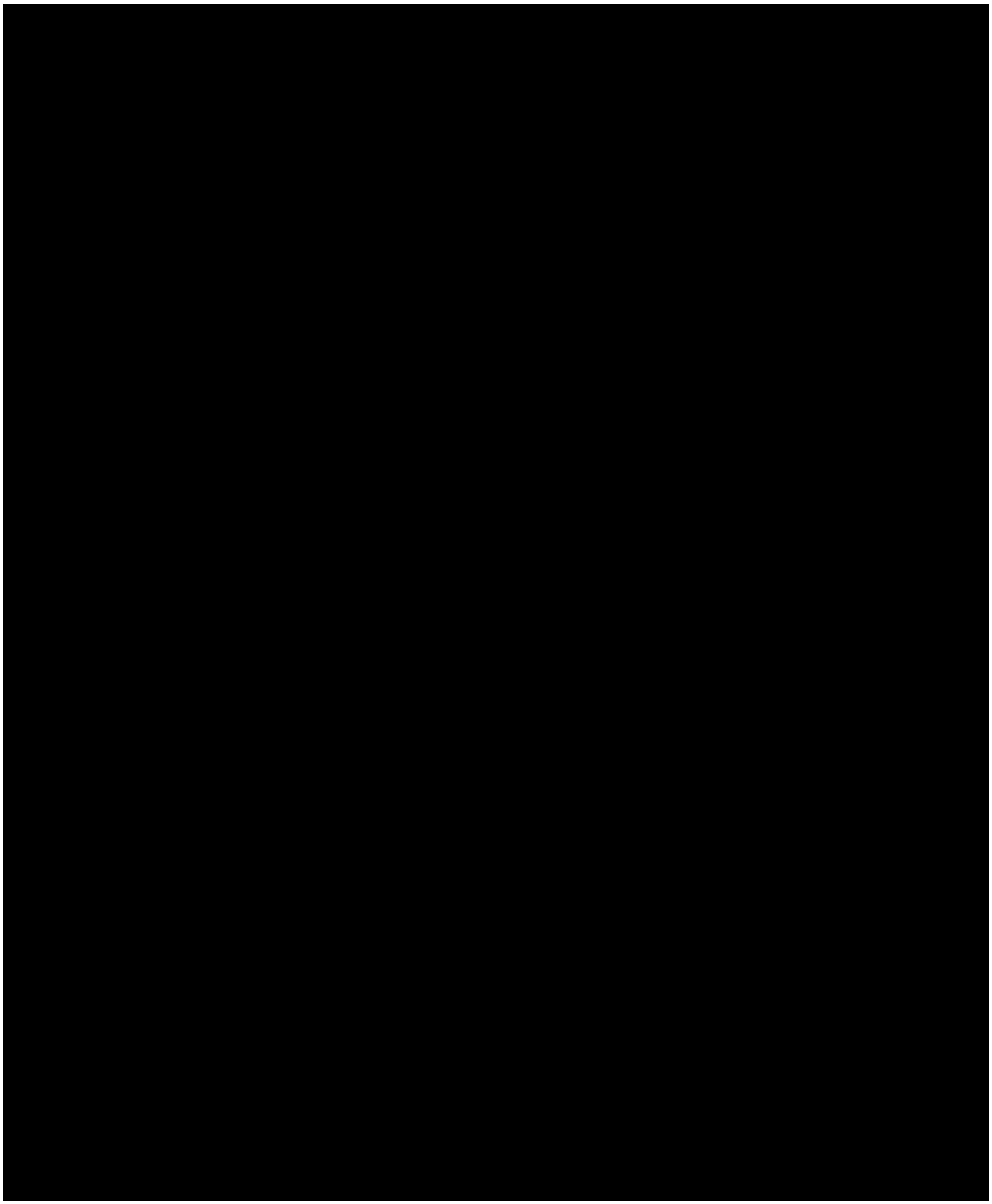
Open-Label Period CVC 150 mg once daily		**Safety Follow-up**
Year 1	**Year 2; and ongoing**	1-month Follow-up
Baseline Day 1[a]	Months 3, 6, 9, 12, 15, 18, 21, 24[b]	

a Participants completing Treatment Periods 1 and 2 of the CENTAUR study or completing the AURORA study as a result of progression to cirrhosis or reaching an adjudicated liver-related clinical outcome in either Part 1 or Part 2 of the study, regardless of their treatment assignment (CVC or placebo), must provide informed consent to Study 3152-201-002 before receiving open label CVC. Participants are required to rollover to Study 3152-201-002 within 1 month of completing their final visit assessments in either the CENTAUR or AURORA study. Participants who completed the CENTAUR or the AURORA study, prior to initiation of this protocol at their study center, will be allowed to participate in this rollover study.

b Participants will continue to be seen every 3 months until CVC becomes commercially available or if development is terminated, as applicable.

The schedule of assessments for Study 3152-201-002 is presented in Table 4-1.

Table 4-1. Schedule of Assessments: Study 3152-201-002



5.0 OBJECTIVES

Primary Objective:

The primary objective of this study is to provide open-label treatment with CVC to participants who have previously been enrolled in CVC studies.

Secondary Objective:

The secondary objective of this study is to assess the long-term safety of continued treatment with CVC for participants who have previously enrolled in CVC studies.

6.0 PARTICIPANT POPULATIONS

6.1 SAFETY POPULATION

The Safety Population will consist of all participants who received at least 1 dose of study treatment (in study 3152-201-002 or in study 3152-301-002).

7.0 PARTICIPANT DISPOSITION

Participant disposition encompasses the distribution of participants who were enrolled, started study drug, completed the study, discontinued study drug early, and discontinued from the study early, along with eCRF-reported discontinuation reasons.

8.0 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Continuous variables will be summarized by number of patients and mean, standard deviation (SD), median, minimum, and maximum values. Categorical variables will be summarized by number and percentage of patients.

Baseline

For this study, baseline is defined as Day 1, the first visit, in the Rollover study, regardless of treatment received in the lead-in studies. The first dose of CVC should be administered during this visit.

Demographics

Demographic parameters including age, age group, race, race group, ethnicity and sex; and baseline characteristics including weight (kg), height (cm), BMI (kg/m^2), waist circumference (cm), hip circumference (cm), and waist-to-hip ratio will be summarized descriptively. Participant's age (years) will be classified into categories of less than 65 years, and greater than or equal to 65 years. In addition, race will be further grouped as white versus non-white.

Disease Characteristics

Other disease characteristics, including fibrosis stage at baseline, NAFLD Activity Score (NAS) at baseline, ballooning at baseline, steatosis at baseline, lobular inflammation at baseline, NASH Clinical Research Network (CRN) Stage, and Ishak stage at baseline will be summarized descriptively.

Medical History

Medical history, encompassing abnormalities and surgeries reported as occurring before the Screening Visit, will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 21.0 or newer. Adverse events (AEs) occurring in either of the two lead-in studies but were resolved before enrollment in this study will be considered medical history in this study. AEs with start dates prior to baseline in this study are considered as medical history, even if the events are ongoing at time of study enrollment. Unique participants who report medical history events will be summarized by MedDRA system organ class (SOC) and preferred term (PT) for the Safety Population.

Prior and Concomitant Medications

A prior medication is defined as a (nonstudy) medication taken at any time during 30 days before first study drug intake and stopped before the date of first dose of study drug. All medications other than study drug taken or received by the participant at any time during the study from first intake of study drug through the 1-Month Follow-up Visit after last study drug intake (or final visit, for participants who do not complete a Follow-up Visit) will be considered concomitant medications. This includes medications ongoing at the time of first study drug intake and medications started after first study drug intake. A new concomitant medication will be a (nonstudy) medication started or for which the

dose increased between first study drug intake through the 1-Month Follow-up Visit after last study drug intake (or final visit, for participants who do not complete a Follow-up Visit).

Medications will be coded using the World Health Organization (WHO) Drug Dictionary, Version B2 Enhanced 201703. Unique participants who reported medications will be summarized by Anatomical Therapeutic Chemical (ATC) 4 class and PT for the Safety Population.

9.0 EXTENT OF EXPOSURE AND TREATMENT COMPLIANCE

9.1 EXTENT OF EXPOSURE

Study treatment exposure and compliance will be summarized for the Safety Population for exposure in the Rollover study. Study treatment exposure in days (ie, last date study drug received – first date study drug received + 1) will be summarized descriptively. The number of days of treatment interruption will be subtracted from the study treatment exposure calculation.

9.2 MEASUREMENT OF TREATMENT COMPLIANCE

Study treatment compliance will be calculated as the number of tablets actually taken divided by the number of tablets expected to be taken at the prescribed rate of 1 tablet per day (i.e., treatment end date – treatment start date + 1), multiplied by 100 and expressed as a percentage. Study treatment compliance will also be tabulated categorically as follows: $< 80\%$, $\geq 80\%$ and $\leq 100\%$, $> 100\%$ and $\leq 120\%$, and $> 120\%$.

10.0 SAFETY ANALYSES

The safety analysis will be performed using the Safety Population. The safety parameters will include AEs and clinical laboratory, and vital sign parameters. For each safety parameter of the clinical laboratory and vital sign parameters, the last nonmissing safety assessment before the first dose of study treatment will be used as the baseline for all analyses of that safety parameter. Continuous variables will be summarized by number of patients and mean, SD, median, minimum, and maximum values. Categorical variables will be summarized by number and percentage of patients.

10.1 ADVERSE EVENTS

Adverse events will be coded by system organ class and preferred term using the *Medical Dictionary for Regulatory Activities,* version 21.0 or newer.

An event will be considered a treatment-emergent adverse event (TEAE) if:

- The event began on or after the date of the first dose of study drug; or
- An exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency and/or intensity of the condition on or after the date of the first dose of study drug

An AE that occurs more than 30 days after the last dose of study drug will not be counted as a TEAE.

Examples:

- The worsening of a chronic condition (eg, hypertension, diabetes) during the study would be considered as a TEAE if it was present before the date of the first dose of study treatment but increased in severity and/or seriousness after the first dose of study treatment.

- The recurrence of an intermittent condition (eg, seizures) after the first dose of study treatment would be considered a TEAE.

If more than 1 AE was reported before the first dose of study treatment and coded to the same preferred term, the AE with the greatest severity will be used for comparison with the AEs occurring during the study. An AE that occurs more than 30 days after the date of the last dose of study treatment will not be considered as a TEAE.

However, AEs starting in one of the two lead-in studies but were not resolved before enrollment in this study will be considered as medical history in this study, not as TEAEs.

Overall summary of AEs will be provided on a per-participant basis for categories of all TEAEs, treatment-related TEAEs, serious TEAEs (STEAEs), deaths, and AEs leading to study discontinuation.

The number and percentage of participants reporting TEAEs will be tabulated by descending percentage in any group, by system organ class and preferred term, and further categorized by severity. If more than 1 AE is coded to the same preferred term for the same patient, the patient will be counted only once for that preferred term using the greatest severity for the summarization by severity. In addition, All AEs will be listed for individual participants showing both verbatim and MedDRA preferred terms.

The number and percentage of participants who have SAEs will be summarized by preferred term. In addition, the incidence of on-therapy SAEs that led to death will be summarized separately by preferred term.

The number and percentage of participants in the Safety Population who have AEs leading to premature discontinuation of the study treatment will be summarized by preferred term and treatment.

10.2 CLINICAL LABORATORY PARAMETERS

Descriptive statistics for clinical laboratory values (in SI units) and changes from the baseline values at each assessment time point will be presented for the following laboratory parameters:

Hematology:	Hemoglobin, hematocrit, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), red blood cell count, red blood cell distribution width, white blood cell count, white blood cell count differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils), and platelet count
Coagulation Profile:	International normalized ratio (INR)
Serum Chemistry:	Alkaline phosphatase (ALP), Alanine aminotransferase (ALT), albumin, aspartate aminotransferase (AST), direct bilirubin, γ-glutamyl transferase (GGT), total bilirubin, amylase, bicarbonate, blood urea nitrogen, calcium, chloride, cholesterol (total), creatinine phosphokinase, creatinine, glucose, lactate dehydrogenase, magnesium, phosphorus, potassium, sodium, total protein, triglycerides, and uric acid

Other tests: Follicle-stimulating hormone (FSH) for postmenopausal women only (baseline only) and urine pregnancy test for females of childbearing potential only

Clinical laboratory test values will be considered potentially clinically significant (PCS) if they meet either the lower-limit or higher-limit PCS criteria listed in Table 10.2–**1**. The number and percentage of patients who have PCS postbaseline clinical laboratory values will be tabulated. The percentages will be calculated relative to the number of patients with available non-PCS baseline values and at least 1 postbaseline assessment for the study period. The numerator will be the total number of patients with available non-PCS baseline values and at least 1 PCS postbaseline value for the study period. A supportive tabular display of patients with PCS postbaseline values will be provided, including the PID number, baseline and all postbaseline (including non-PCS) values.

In addition, a tabular display showing all AEs that occurred in patients who had PCS postbaseline clinical laboratory values will be provided.

Table 10.2–1. Criteria for Potentially Clinically Significant Laboratory Results

Parameter	***SI Unit***	***Lower Limit***	***Higher Limit***
CHEMISTRY			
Albumin	g/L	< 0.9 × LLN	> 1.1 × ULN
Alanine aminotransferase	U/L	—	≥ 3 × ULN
Alkaline phosphatase	U/L	—	≥ 3 × ULN
Aspartate aminotransferase	U/L	—	≥ 3 × ULN
Bilirubin, total	µmol/L	—	> 1.5 × ULN
Calcium	mmol/L	< 0.9 × LLN	> 1.1 × ULN
Chloride	mmol/L	< 0.9 × LLN	> 1.1 × ULN
Cholesterol	mmol/L	—	> 1.3 × ULN
Creatinine	µmol/L	—	> 1.3 × ULN
Glucose, fasting	mmol/L	< 0.8 × LLN	> 1.2 × ULN
Glucose, nonfasting	mmol/L	< 0.8 × LLN	> 1.4 × ULN
Potassium	mmol/L	< 0.9 × LLN	> 1.1 × ULN
Protein, total	g/L	< 0.9 × LLN	> 1.1 × ULN
Sodium	mmol/L	< 0.9 × LLN	> 1.1 × ULN
Triglycerides	mmol/L	—	> 2 × ULN
Urea nitrogen	mmol/L	—	> 1.2 × ULN

Table 10.2–1. Criteria for Potentially Clinically Significant Laboratory Results

Parameter	***SI Unit***	***Lower Limit***	***Higher Limit***
Uric acid	µmol/L	—	> 1.2 × ULN
HEMATOLOGY			
Basophils, absolute cell count	10^9/L	—	> 3 × ULN
Neutrophils, absolute cell count	10^9/L	< 0.8 × LLN	> 1.5 × ULN
Hematocrit	Ratio	< 0.9 × LLN	> 1.1 × ULN
Hemoglobin	g/L	< 0.9 × LLN	> 1.1 × ULN
Platelet count	10^9/L	≤ 0.5 × LLN	≥ 1.5 × ULN
Red blood cell count	10^{12}/L	< 0.9 × LLN	> 1.1 × ULN
White blood cell count	10^9/L	≤ 0.7 × LLN	≥ 1.5 × ULN

LLN = lower limit of normal value provided by the laboratory; SI = *Le Système International d'Unités* (International System of Units); ULN = upper limit of normal value provided by the laboratory.

10.3 VITAL SIGNS

No vital signs data will be presented or analyzed.

10.4 OTHER SAFETY PARAMETERS

Descriptive statistics will be provided for subjects who have confirmed ALP, ALT, AST, or total bilirubin elevations with or without liver-related clinical symptoms based on the baseline and treatment-emergent categories in the protocol (Table 11-1). In addition, a shift table for the same hepatic function parameters will be provided for baseline and the worst value postbaseline.

ALT, AST, ALP, and total bilirubin values will be summarized for subjects meeting any of the following criteria:

- Any postbaseline ALT, AST, or ALP>3x ULN and normal baseline value
- Any postbaseline ALT, AST, or ALP>2x BL and baseline > ULN
- Any postbaseline total bilirubin >2x ULN and normal baseline value
- Any postbaseline total bilirubin >1.5x BL value and baseline > ULN

11.0 HEALTH OUTCOMES ANALYSES

Not applicable.

12.0 INTERIM ANALYSIS

No interim analysis is planned for this study.

13.0 DETERMINATION OF SAMPLE SIZE

Approximately 560 participants are expected to enroll from both the CENTAUR study (652-2-203) and the AURORA study (3152-301-002) to receive open-label CVC.

14.0 STATISTICAL SOFTWARE

Statistical analyses will be performed using SAS version 9.3 or newer.

15.0 DATA HANDLING CONVENTIONS

15.1 VISIT TIME WINDOWS

Except for Baseline and Discontinuation Visits, the participant visit window is ± 2 weeks. However, for analyses, analysis windows will be used for the nominal visits.

Table 15.1–**1** presents the analysis visit windows for safety analyses.

Table 15.1–1. Analysis Visit Time Windows

Derived Visit	***Scheduled Visit Day***[a]	***Analysis Window***
Baseline	Day 1	Days ≤ 1
Month 3	Day 90	Days [2, 135]
Month 6	Day 180	Days [136, 225]
Month 9	Day 270	Days [226, 315]
Month 12	Day 360	Days [316, 405]
Month 15	Day 450	Days [406, 495]
Month 18	Day 540	Days [496, 585]
Month 21	Day 630	Days [586, 675]
Month 24	Day 720	Days [676, 765]
Month X (every 3 months)	Day X*30	Days (X*30-44, X*30+45)
30-Day Follow-Up	Day X*30 +30	Days (X*30-44+30, X*30+45+30)
End of study[b]	Final or Termination Visit during the study period	

a Relative to the date of the first dose of study treatment. Day 1 = the date of the first dose of study treatment. There is no Day 0.

b Presented in analysis tables for safety parameters, including but not limited to clinical laboratory values and vital signs.

If the assessment date (if the assessment date is unavailable, use visit date instead) is on or after the date of the first dose of study treatment, the study day is calculated by assessment date – date of the first dose of study treatment + 1. If the assessment date is before the date of the first dose of study treatment, the study day is calculated by assessment date – date of the first dose of study treatment. Therefore, a negative day indicates a day before the start of the study treatment.

If a participant has 2 or more visits within the same window, the last visit with a nonmissing value will be used for analysis.

15.2 DERIVED VARIABLES

Not applicable.

15.3 REPEATED OR UNSCHEDULED ASSESSMENTS OF SAFETY PARAMETERS

If a patient has repeated assessments before the start of the first treatment, the results from the final nonmissing assessment made prior to the start of the study treatment will be used as baseline. If end-of-study assessments are repeated or if unscheduled visits occur, the last nonmissing postbaseline assessment will be used as the end-of-study assessment for generating summary statistics.

15.4 MISSING DATE OF THE LAST DOSE OF STUDY TREATMENT

When the date of the last dose of study treatment is missing for a patient in the Safety Population, all efforts should be made to obtain the date from the Investigator. If after all efforts are made it is still missing, the last available dosing record date will be used as the last dose date.

15.5 MISSING SEVERITY ASSESSMENT FOR ADVERSE EVENTS

If severity is missing for an AE that started before the date of the first dose of study treatment, an intensity of mild will be assigned. If severity is missing for an AE that started on or after the date of the first dose of study treatment, an intensity of severe will be assigned. The imputed values for severity assessment will be used for the incidence summary; the values will be shown as missing in the data listings.

15.6 MISSING CAUSAL RELATIONSHIP TO STUDY DRUG FOR ADVERSE EVENTS

If the causal relationship to the study treatment is missing for an AE that started on or after the date of the first dose of study treatment, a causality of yes will be assigned. The imputed values for causal relationship to study treatment will be used for the incidence summary; the values will be shown as missing in the data listings.

15.7 MISSING DATE INFORMATION FOR ADVERSE EVENTS

The following imputation rules only apply to cases in which the start date for AEs is incomplete (ie, partly missing).

Missing month and day

- If the year of the incomplete start date is the same as the year of the first dose of study treatment, the month and day of the first dose of study treatment will be assigned to the missing fields

- If the year of the incomplete start date is before the year of the first dose of study treatment, *December 31* will be assigned to the missing fields

- If the year of the incomplete start date is after the year of the first dose of study treatment, *January 1* will be assigned to the missing fields

Missing month only

- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure

Missing day only

- If the month and year of the incomplete start date are the same as the month and year of the first dose of study treatment, the day of the first dose of study treatment will be assigned to the missing day

- If either the year of the incomplete start date is before the year of the date of the first dose of study treatment or if both years are the same but the month of the incomplete start date is before the month of the date of the first dose of study treatment, the last day of the month will be assigned to the missing day

- If either the year of the incomplete start date is after the year of the date of the first dose of study treatment or if both years are the same but the month of the incomplete start date is after the month of the date of the first dose of study treatment, the first day of the month will be assigned to the missing day

If the stop date is complete and the imputed start date as above is after the stop date, the start date will be imputed by the stop date.

If the start date is completely missing and the stop date is complete, the following algorithm will be used to impute the start date:

- If the stop date is after the date of the first dose of study treatment, the date of the first dose of study treatment will be assigned to the missing start date

- If the stop date is before the date of the first dose of study treatment, the stop date will be assigned to the missing start date

15.8 MISSING DATE INFORMATION FOR PRIOR OR CONCOMITANT MEDICATIONS

For prior or concomitant medications, incomplete (ie, partly missing) start dates and/or stop dates will be imputed. When the start date and the stop date are both incomplete for a patient, the start date will be imputed first.

15.8.1 Incomplete Start Date

The following rules will be applied to impute the missing numeric fields for an incomplete prior or concomitant medication start date. If the stop date is complete (or imputed) and the imputed start date is after the stop date, the start date will be imputed using the stop date.

Missing month and day

- If the year of the incomplete start date is the same as the year of the first dose of study treatment, the month and day of the first dose of study treatment will be assigned to the missing fields

- If the year of the incomplete start date is before the year of the first dose of study treatment, *December 31* will be assigned to the missing fields

- If the year of the incomplete start date is after the year of the first dose of study treatment, *January 1* will be assigned to the missing fields

Missing month only

- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure

Missing day only

- If the month and year of the incomplete start date are the same as the month and year of the first dose of study treatment, the day of the first dose of study treatment will be assigned to the missing day

- If either the year of the incomplete start date is before the year of the date of the first dose of study treatment or if both years are the same but the month of the incomplete start date is before the month of the date of the first dose of study treatment, the last day of the month will be assigned to the missing day.

- If either the year of the incomplete start date is after the year of the date of the first dose of study treatment or if both years are the same but the month of the incomplete start date is after the month of the date of the first dose of study treatment, the first day of the month will be assigned to the missing day

15.8.2 Incomplete Stop Date

The following rules will be applied to impute the missing numeric fields for an incomplete prior or concomitant medication stop date. If the date of the last dose of study treatment is missing, impute it as descripted in Section 15.4. If the imputed stop date is before the start date (imputed or nonimputed start date), the imputed stop date will be equal to the start date.

Missing month and day

- If the year of the incomplete stop date is the same as the year of the last dose of study treatment, the month and day of the last dose of study treatment will be assigned to the missing fields

- If the year of the incomplete stop date is before the year of the last dose of study treatment, *December 31* will be assigned to the missing fields

- If the year of the incomplete stop date is after the year of the last dose of study treatment, *January 1* will be assigned to the missing fields

Missing month only

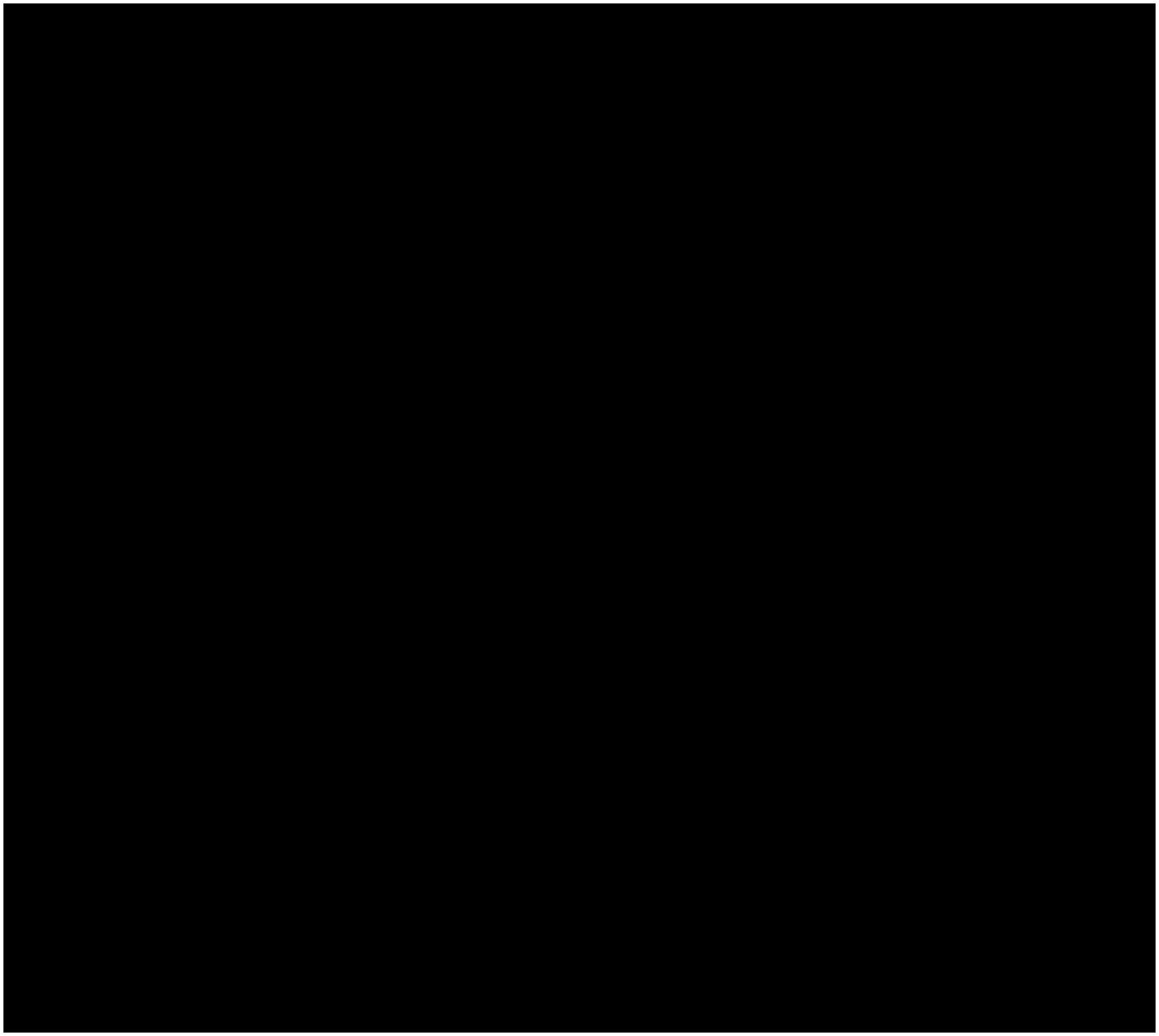
- If only the month is missing, the day will be treated as missing and both the month and the day will be replaced according to the above procedure

Missing day only

- If the month and year of the incomplete stop date are the same as the month and year of the last dose of study treatment, the day of the last dose of study treatment will be assigned to the missing day

- If either the year of the incomplete stop date is before the year of the date of the last dose of study treatment or if both years are the same but the month of the incomplete stop date is before the month of the date of the last dose of study treatment, the last day of the month will be assigned to the missing day

- If either the year of the incomplete stop date is after the year of the date of the last dose of study treatment or if both years are the same but the month of the incomplete stop date is after the month of the date of the last dose of study treatment, the first day of the month will be assigned to the missing day



16.0 CHANGES TO ANALYSES SPECIFIED IN PROTOCOL

Not applicable.

17.0 REFERENCES

Not applicable.

DOCUMENT HISTORY PAGE

Effect Date	Revision Number	Primary Author	Description of Change
01 July 2015	0.1	[redacted]	Initial Release

ALLERGAN

16.1.9._Analysis_Plan_Prior_to_Database_Lock_for_Study_3152-201-002_v1

Date (DD/MMM/YYYY)/Time (PT)	Signed by:	Justification
30-Jan-2019 14:16 GMT-080	[redacted]	Biostatistics Approval
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31-Jan-2019 06:39 GMT-080		Medical Safety Physician Approval
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