NCT03441581

Study ID: 3030-401-002

Title: An Open-Label Pilot Study of Eluxadoline in Participants with Irritable Bowel Syndrome with Diarrhea (IBS-D) Who Have Evidence of Bile Acid Malabsorption (BAM)

Statistical Analysis Plan Date: March 20, 2020

1.0 TITLE PAGE

3030-401-002

An Open-Label Pilot Study of Eluxadoline in Participants with Irritable Bowel Syndrome with Diarrhea (IBS-D) Who Have Evidence of Bile Acid Malabsorption (BAM)

STATISTICAL ANALYSIS PLAN

Final 1.0: 26 Feb 2018
Amendment 1: 20 March 2020

2.0 TABLE OF CONTENTS

3.0 LIST OF ABBREVIATIONS

7αC4	7a-hydroxy-4-cholesten-3-one
AE	adverse event
BAM	bile acid malabsorption
BP	blood pressure
BSFS	Bristol Stool Form Scale
eCRF	electronic case report form
eDiary	electronic diary
ETO	end of treatment
ET	early termination
mITT	modified intent to treat
IBS	irritable bowel syndrome
IBS-D	irritable bowel syndrome with diarrhea
IBS-Quality of Life	IBS-Quality of Life
PCS	potentially clinically significant
PK	pharmacokinetic
SAE	serious adverse event
SAP	statistical analysis plan
SI	*Le Système International d'Unités* (International System of Units)
TEAE	treatment-emergent adverse event

Summary of Changes from the Final SAP:

Date	Section	Description
03/16/2020	16.2 Derived Variables	IBS-QOL conversion

4.0 INTRODUCTION

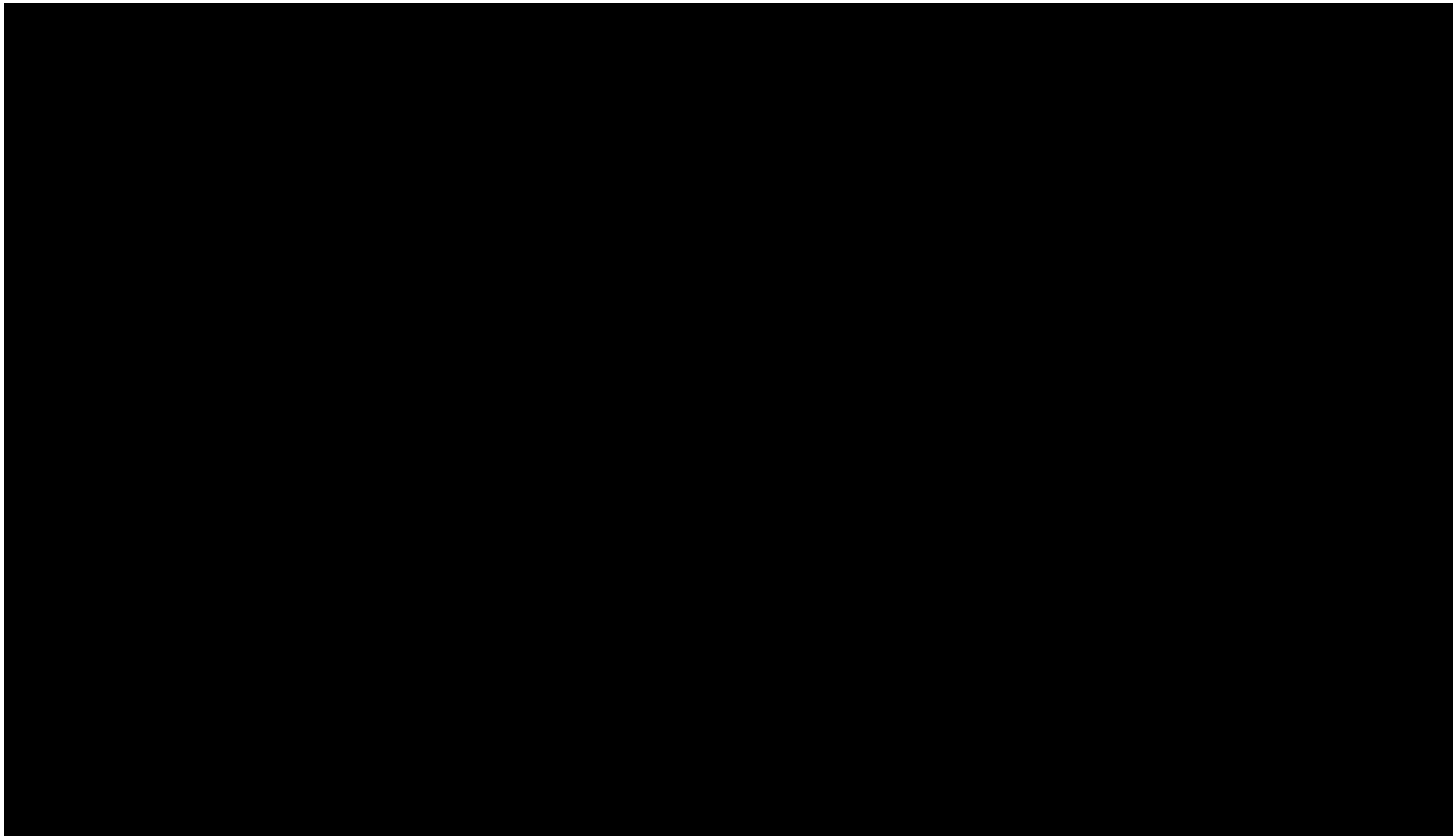
This statistical analysis plan (SAP) provides a more technical and detailed elaboration of the statistical analyses of the efficacy and safety data as outlined and/or specified in the final protocol of Study 3030-401-002 dated 19 Oct 2017 and the most recent amendment dated 17 Apr 2019. Specifications of tables, figures, and data listings are contained in a separate document. The SAP for pharmacokinetic will be prepared separately.

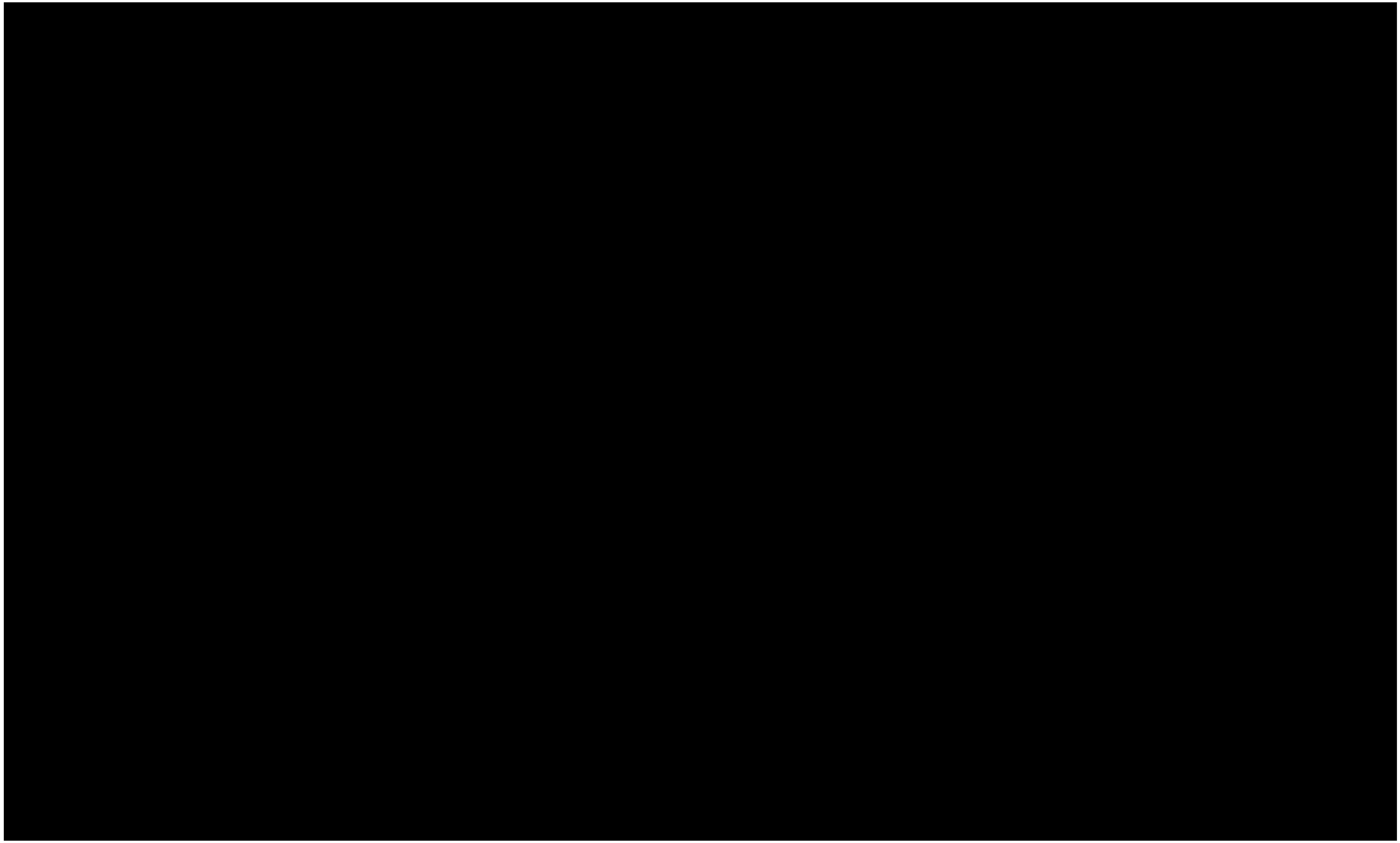
Study 3030-401-002 is a Phase 4, non-randomized, open-label, parallel-group, cohort controlled trial to evaluate the efficacy, safety, tolerability and pharmacokinetics of eluxadoline in participants meeting the Rome IV criteria for IBS-D with and without evidence of BAM. This study will be comprised of a 0 to 2-week screening period, a 2 to 3-week pretreatment period, a 4-week open-label treatment period during which time participants will receive eluxadoline 100 mg BID, and a 2-week post-treatment safety follow-up.

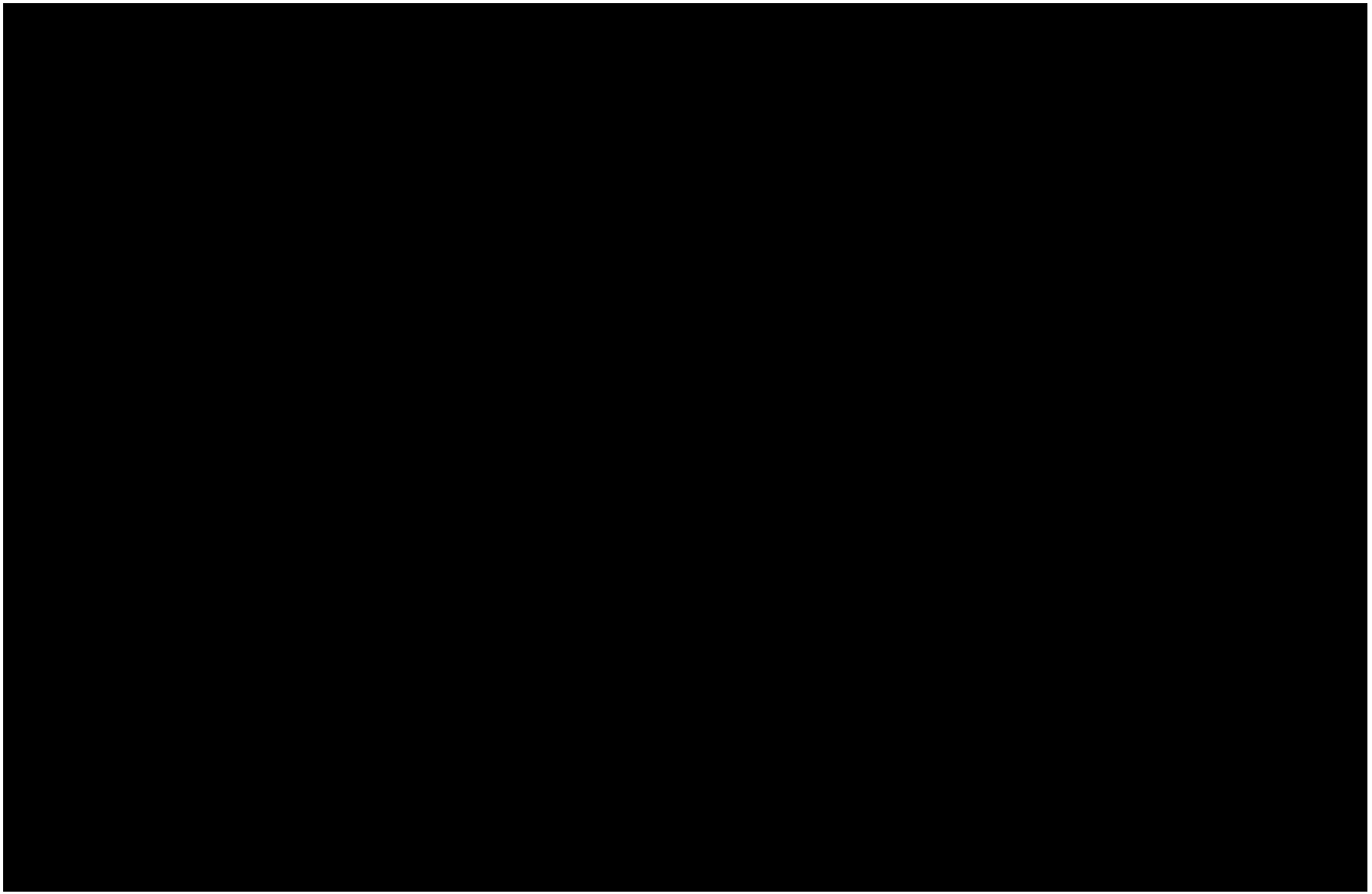
There will be 24 participants enrolled in the study, 12 with evidence of BAM and 12 without evidence of BAM. Cohort 1consists of IBS-D participants with evidence of BAM treated with eluxadoline 100 mg oral tablets BID with food. Cohort 2 consists of IBS-D participants without evidence of BAM treated with eluxadoline 100 mg oral tablets BID with food. The 100 mg BID dose selected for this trial is consistent with US and global labeling for eluxadoline in IBS-D. This non-randomized design is considered most appropriate since the cohort assignment will be based on the determination of BAM status. As far as possible, the 2 cohorts will be matched by age, gender and severity of historic symptoms based on the investigator's discretion.

The total duration of the study is up to 11 weeks, which includes: screening period (1-2 weeks), pretreatment period (2-3 weeks), 4-week open-label treatment period, and 2-week post-treatment follow-up period. A total of 6 study visits are planned for each participant: Screening, Week -3 to -4 (Visit 1); Pretreatment, Week -3 to -2 (Visit 2); Day 1 (Visit 3; first administration of study drug); Week 2 (Visit 4; Week 2 of treatment), may be done by telephone; Week 4 (Visit 5; end of treatment/early termination); Week 6 (Visit 6; post-treatment follow-up), may be done by telephone The end of the study is defined as the date of Visit 6. The schedule of evaluations for Study 3030-401-002 is presented in Table 4-1.

Table 4-1: Schedule of Activities (SoA)







5.0 OBJECTIVES

The primary objectives of this study are to evaluate the efficacy of eluxadoline 100 mg BID in IBS-D participants with evidence of BAM compared to IBS-D participants without evidence of BAM and to evaluate the safety and tolerability of eluxadoline 100 mg BID in IBS-D participants with evidence of BAM and in IBS-D participants without evidence of BAM. The secondary objectives of this study are to further evaluate the efficacy of eluxadoline 100 mg BID in IBS-D participants with evidence of BAM compared to IBS-D participants without evidence of BAM and to evaluate the population PK of eluxadoline in IBS-D participants with and without evidence of BAM.

6.0 PARTICIPANT POPULATIONS

The analysis populations will consist of participants as defined below.

6.1 SCREENED POPULATION

All screened participants who sign informed consent.

6.2 ENROLLED POPULATION

All participants in Screened Population who meet the eligibility criteria and enter the open-label treatment period (on Day 1, Visit 3).

6.3 MODIFIED INTENT-TO-TREAT POPULATION

All participants in Enrolled Population with ≥ 1 postbaseline assessment for Bristol Stool Form Scale (BSFS).

6.4 SAFETY POPULATION

All participants who received ≥ 1 dose of study treatment.

7.0 PARTICIPANT DISPOSITION

The number of participants in 3 study populations (Enrolled, mITT, and Safety) will be summarized overall, by participant group (BAM or Non-BAM) and overall for the Screened Population.

The number of screen failures (ie, participants who enter the Screening Period and the Pretreatment but not enter the open-label treatment period (on Day 1, Visit 3)) and participants ineligible for enrollment, along with the associated reasons for failure, will be tabulated overall. Screened participants who are not enrolled will also be listed with the reasons for exclusion.

The number and percentage of participants who complete the open-label Treatment Period and Post-treatment Period and of participants who prematurely discontinue during the same period will be presented by participant group and overall for Enrolled Population. The reasons for premature discontinuation from the open-label study period or Post-treatment Period as recorded in the eCRF will be summarized (number and percentage) by participant group for the Enrolled Population. All participants who prematurely discontinue during the open-label Treatment Period or Post-treatment Period will be listed by discontinuation reason for the Enrolled Population.

8.0 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Demographic parameters (age; sex; race; ethnicity), baseline characteristics (weight; height) will be summarized descriptively by participant group (BAM or Non-BAM) for the Safety population. Continuous variables will be summarized by number of participants and mean, SD, median, minimum, and maximum values. Categorical variables will be summarized by number and percentage of participants.

Abnormalities in participants' medical and surgical histories will be coded using the *MedDRA (Medical Dictionary for Regulatory Activities,* version 20 or newer). The number and percentage of participants with abnormalities in medical and surgical histories in each system organ class and preferred term will be summarized by participant group for the Safety Population.

All prescription drugs, herbal products, vitamins, minerals, and over-the-counter medications taken within 30 days prior to the open-label treatment period will be recorded as prior medications. All medications taken after beginning open-label treatment and through the early termination or follow-up visit will be recorded as concomitant therapy. The use of all prior and concomitant medications is to be recorded on the participant's electronic case report form (eCRF) at each visit along with the reason the medication was taken.

Prior and concomitant medications will be listed by participant group with the drug names and Anatomical Therapeutic Chemical classification codes based on the data collected in the eCRF.

The World Health Organization (WHO) Drug Dictionary, version March 2017 or newer, will be used to classify prior and concomitant medications by therapeutic class and drug name.

9.0 EXTENT OF EXPOSURE AND TREATMENT COMPLIANCE

9.1 EXTENT OF EXPOSURE

Exposure to the study treatment for the Safety Population during the treatment period will be summarized for treatment duration, calculated as the number of days from the date of the first dose of study treatment to the date of the last dose of study treatment, inclusive. Descriptive statistics (number of participants, mean, SD, median, minimum, and maximum) will be presented by participant group (BAM or Non-BAM).

Patient-years, defined as exposure to the study treatment in years, will be summarized by participant group for the Safety Population.

9.2 MEASUREMENT OF TREATMENT COMPLIANCE

Dosing compliance for a specified period is defined as the number of tablets taken by a participant during that period divided by the number of tablets prescribed for the same period multiplied by 100. This information will be obtained from Study Treatment Record of the participant's electronic case report form.

Descriptive statistics for study drug compliance will be presented by participant group for each period between 2 consecutive visits, as well as for the whole treatment period (Visit 4 to Visit 5), for the Safety Population.

10.0 EFFICACY ANALYSES

The efficacy of eluxadoline will be based on eDiary measures related to improvements in IBS-D signs and symptoms. Participants will be required to access the eDiary each evening, preferably at the same time each day, to record daily IBS symptoms.

The efficacy analyses will be based on the mITT Population. Baseline for efficacy based on eDiary measures will be determined for the respective scores average over 14 days prior to the first dose of study treatment. Baseline for efficacy based on study visit measures (IBS-QoL and 7αC4) will be the last assessment before the first dose of study treatment. Continuous variables will be summarized by number of participants and mean, SD, median, minimum, and maximum values. Categorical variables will be summarized by number and percentage of participants. All efficacy endpoints will be summarized by participant group (BAM or Non-BAM).

10.1 PRIMARY EFFICACY PARAMETER

The primary efficacy parameter will be the change from baseline in average BSFS score over 4 weeks of treatment period. The participant-reported BSFS is a 1 to 7 scale where 1 corresponds to a hard stool and 7 corresponds to watery stool. For each participant, all available (non-missing) postbaseline BSFS score of the treatment period will be used to calculate the average BSFS score.

10.2 SECONDARY EFFICACY PARAMETERS

The secondary efficacy parameter will be:

- Change from baseline in the 4-week average of daily bowel movement frequency during the treatment period;
- Change from baseline in the 4-week average of daily worst abdominal pain scores during the treatment period;
- Change from baseline in the 4-week average of daily bloating during the treatment period;
- Change from baseline in the 4-week average of number of daily urgent bowel movements during the treatment period;
- The proportion of participants with any fecal incontinence during the treatment period;
- Change from baseline in IBS-QoL total score at the end of the treatment period;

Change from baseline in serum 7αC4 levels at the end of the treatment period..

11.0 SAFETY ANALYSES

The safety analysis will be performed using the Safety Population. The safety parameters will include adverse events (AEs), clinical laboratory and vital signs. For each safety parameter of the clinical laboratory and vital sign parameters, the last non-missing 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 participants and mean, SD, median, minimum, and maximum values. Categorical variables will be summarized by number and percentage of participants.

11.1 ADVERSE EVENTS

Adverse events will be coded by system organ class and preferred term using the *Medical Dictionary for Regulatory Activities (MedDRA),* version 20 or newer.

An AE will be considered a treatment-emergent adverse event (TEAE) if it was present after the first dose of study treatment or was present before the date of the first dose of study treatment and increased in severity after the first dose of study treatment. 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 as the benchmark for comparison with the AEs occurring during the study. An AE that occurs after the date of the last protocol-defined study visit (or last contact date if last study visit is missing) will not be counted as a TEAE.

The incidence of participants reporting TEAEs in each participant group will be tabulated by system organ class (SOC) and preferred term; by SOC, preferred term, and severity; and by SOC, preferred term, and relationship to the study drug. If more than 1 event occurs with the same preferred term for the same participant, the participant will be counted only once for that preferred term using the most severe and most related occurrence for the summarizations by severity and by relationship to the study drug.

The distribution of TEAEs by SOC and preferred term, severity, and relationship to study drug will be summarized by participant group.

In addition, the incidence of serious adverse events and events that caused death, if any, will be summarized by participant group, SOC, and preferred term.

A listing of participants who discontinued because of an AE(s) and a listing of participants with serious AEs and participants who died (if any) will be presented.

AEs during the Post-treatment Period will also be included in the listings.

11.2 CLINICAL LABORATORY PARAMETERS

Descriptive statistics for clinical laboratory values (in SI units) at baseline, at end-of-treatment, changes from the baseline to end-of-treatment will be presented by participant group for the following laboratory parameters:

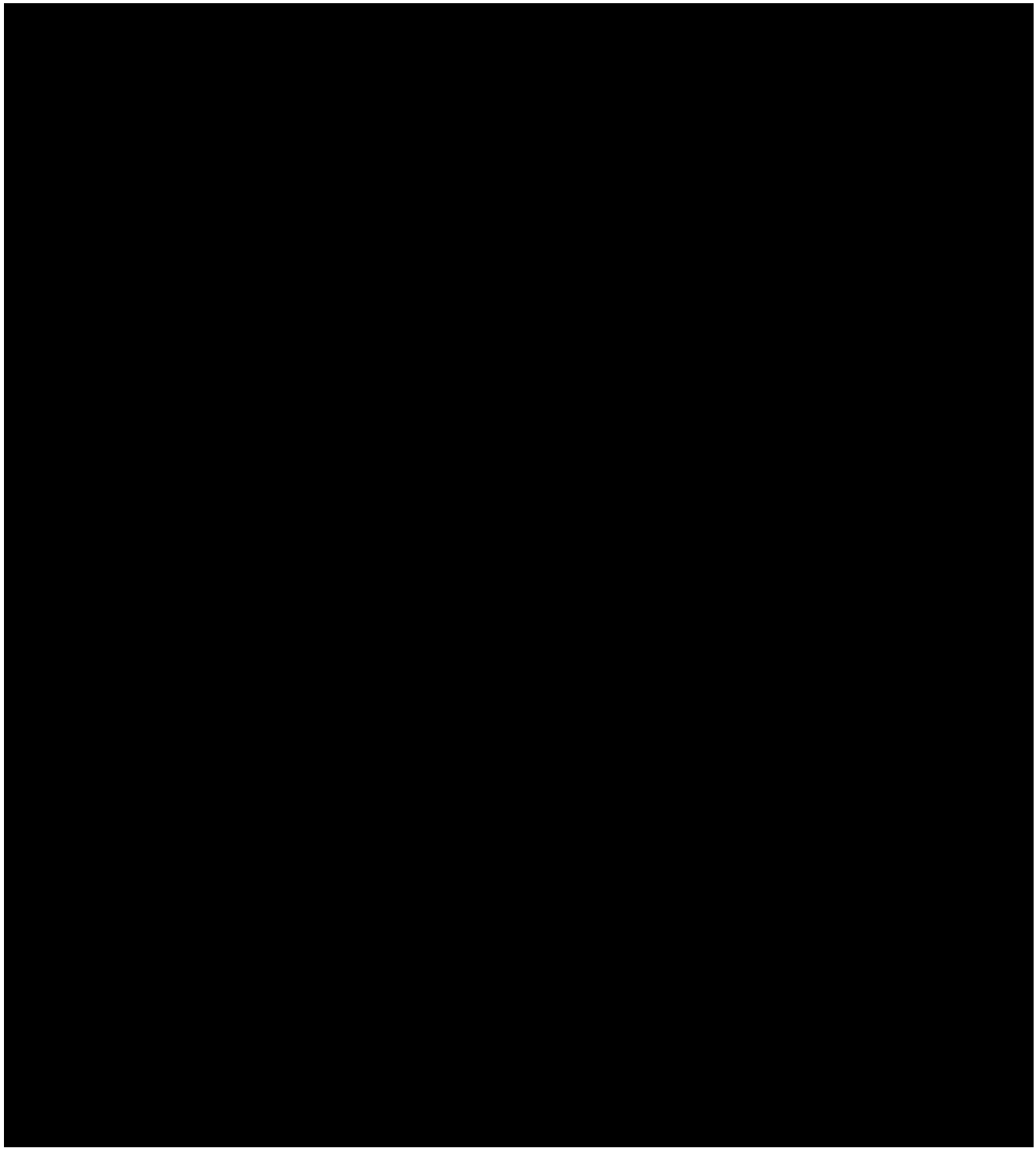
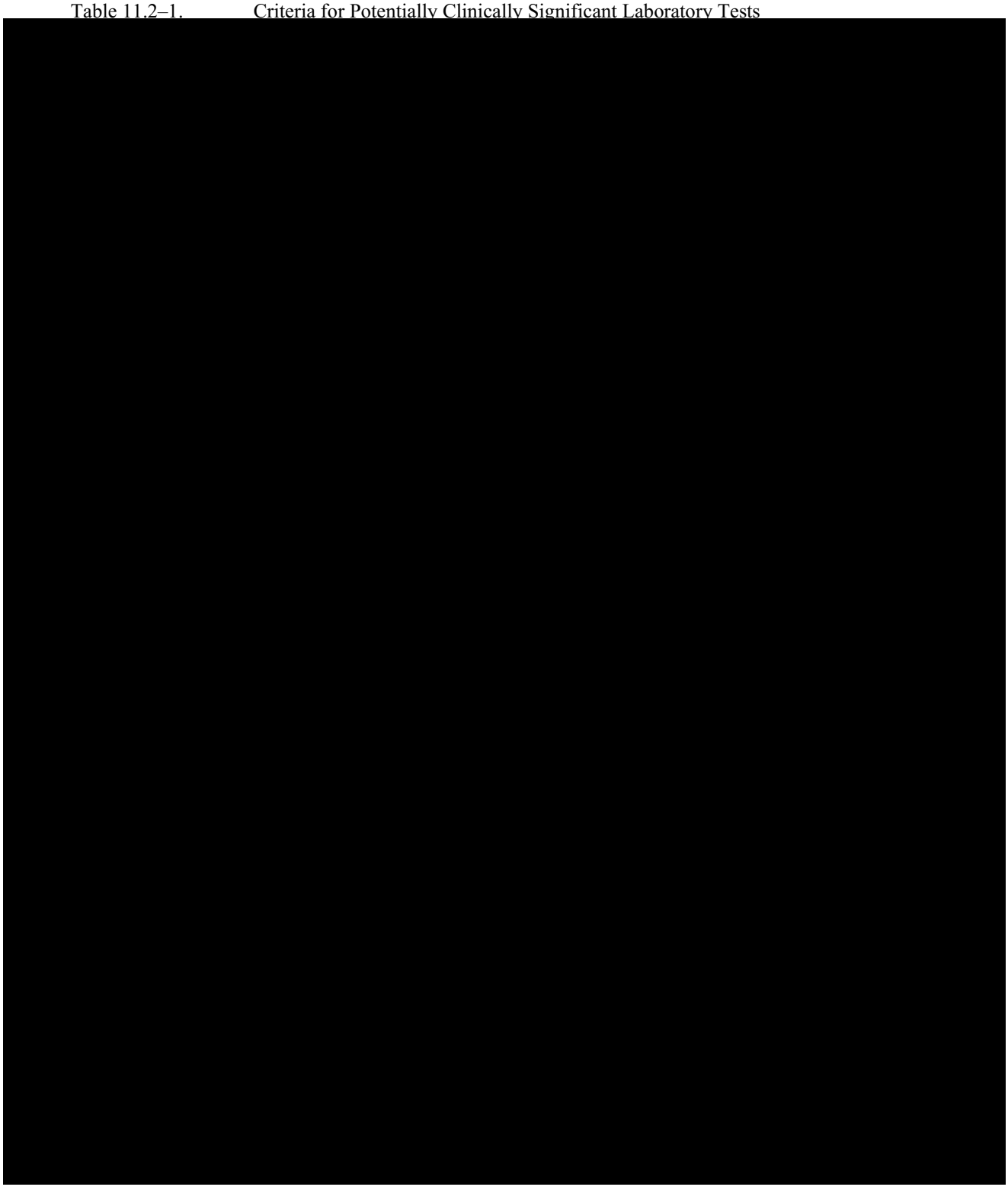


Table 11.2–1. Criteria for Potentially Clinically Significant Laboratory Tests



11.3 VITAL SIGNS

Vital signs to be assessed include systolic and diastolic blood pressure (BP), pulse rate, respiration rate and weight.

Descriptive statistics for BP (systolic and diastolic), pulse rate, respiration rate and weight will be presented by participant group and for all participants at baseline, end-of-treatment, and for changes from baseline to end-of-treatment.

Blood pressure and pulse rate values will be regarded as PCS if they meet both the observed value criteria and the change from baseline value criteria. Weight values will be regarded as PCS if they meet either high or low change from baseline value criterion. The number and percentage of participants who have PCS post-baseline vital sign values will be tabulated by participant group. The percentages will be calculated relative to the number of participants who have available baseline values and at least 1 post-baseline assessment. The numerator will be the total number of participants with available non-PCS baseline values and at least 1 PCS postbaseline value.

A supportive listing of participants with PCS end-of-study vital sign values will be provided, including the participant number and baseline and end-of-treatment values, for the Safety Population. In this listing, any participant with PCS value (if any) during the Post-treatment Period will also be included. Criteria for PCS vital sign parameters is provided below in Table 10.3-1.

Table 11.3–1. Criteria for Potentially Clinically Significant Vital Signs

Parameter	***Flag***	***Criteria***	
		Observed Value	***Change From Baseline***
Sitting systolic blood pressure, mm Hg	High	≥ 180	Increase of ≥ 20
	Low	≤ 90	Decrease of ≥ 20
Sitting diastolic blood pressure, mm Hg	High	≥ 105	Increase of ≥ 15
	Low	≤ 50	Decrease of ≥ 15
Sitting pulse rate, bpm	High	≥ 120	Increase of ≥ 15
	Low	≤ 50	Decrease of ≥ 15
Weight, kg	High	—	Increase of ≥ 7%
	Low	—	Decrease of ≥ 7%

a A postbaseline value is considered potentially clinically significant if it meets both the observed-value and the change-from-baseline criteria.
bpm = beats per minute.

11.4 ELECTROCARDIOGRAM (ECG)

ECG assessment is unavailable in this study.

12.0 HEALTH OUTCOMES ANALYSES

The health outcome data are unavailable in this study.

13.0 INTERIM ANALYSIS

No interim analysis will be conducted

14.0 DETERMINATION OF SAMPLE SIZE

The total sample size for this study is 24 participants (12 participants with BAM and 12 participants without BAM). No formal sample size estimation will be calculated because the sample size for this study is not based on statistical consideration.

15.0 STATISTICAL SOFTWARE

Statistical analyses will be performed using version 9.4 (or newer) of SAS on a Linux operating system.

16.0 DATA HANDLING CONVENTIONS

16.1 VISIT TIME WINDOWS

Table 16.1–1 presents the visits assigned for efficacy and safety analyses and the corresponding range of treatment days (window) during which an actual visit may occur.

Table 16.1–1. Visit Time Windows

Derived Visit	***Scheduled Visit Day[a]***	***Window***
Visit 1 (Screening)		
Visit 2 (Pre-treatment)		
Visit 3 (Baseline)	Day 1	Days ≤ 1
Visit 4	Day 15	Days [2, 21]
Visit 5 (End of Treatment[b])	Day 29	Days >=22 and last dose day +1
Visit 6	Day 33	Days>=last dose day + 2

a Relative to the date of the first dose of treatment period. 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 non-missing value will be used for analysis.

16.2 DERIVED VARIABLES

During the open-label treatment period, participants will record via the eDiary their daily IBS-D symptoms. The average values of non-missing postbaseline will be derived for the following variables:

The primary endpoint: BSFS score;

The secondary endpoints: the worst abdominal pain score, the worst abdominal bloating score, the number of bowel movements and the number of urgent bowel movements.

Only non-missing postbaseline values will be used to calculate the average values. Imputation will not be applied to missing records. The denominator should be adjusted accordingly when average values are calculated.

The IBS-QOL is composed of 34 items scored on a 1-5 scale, where lower item scores indicate greater quality of life. All items are reversed prior to derivation of composite scores; thus, higher IBS-QOL total scores indicate greater quality of life. The transformation formula used for the IBS-QOL total score is

$$\text{Score} = 100 \times \frac{\text{sum of all items} - \text{lowest possible derived score}}{\text{possible sum range}}$$

	Items	Lowest/Highest Possible Derived Score	Possible Sum Range
IBS-QOL total score	All items	34, 170	136

If 7 or more items are missing, the total score will be set to missing; otherwise, the total score will be calculated using the mean score of the non-missing items to replace the missing item.
All items reversed prior to derivation of overall and subscale scores: reversed score = 6 – original score.

16.3 REPEATED OR UNSCHEDULED ASSESSMENTS OF SAFETY PARAMETERS

If a participant has repeated assessments before the start of the first treatment, the results from the final non-missing assessment made prior to the start of the study treatment will be used as baseline. If end-of-treatment assessments are repeated or if unscheduled visits occur, the last non-missing postbaseline assessment will be used as the end-of-treatment assessment for generating summary statistics. However, all postbaseline assessments will be used for PCS value determinations, and all assessments will be presented in the data listings.

16.4 MISSING DATE OF THE LAST DOSE OF STUDY TREATMENT

When the date of the last dose of study treatment is missing for a participant 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.

16.5 MISSING SEVERITY ASSESSMENT FOR ADVERSE EVENTS

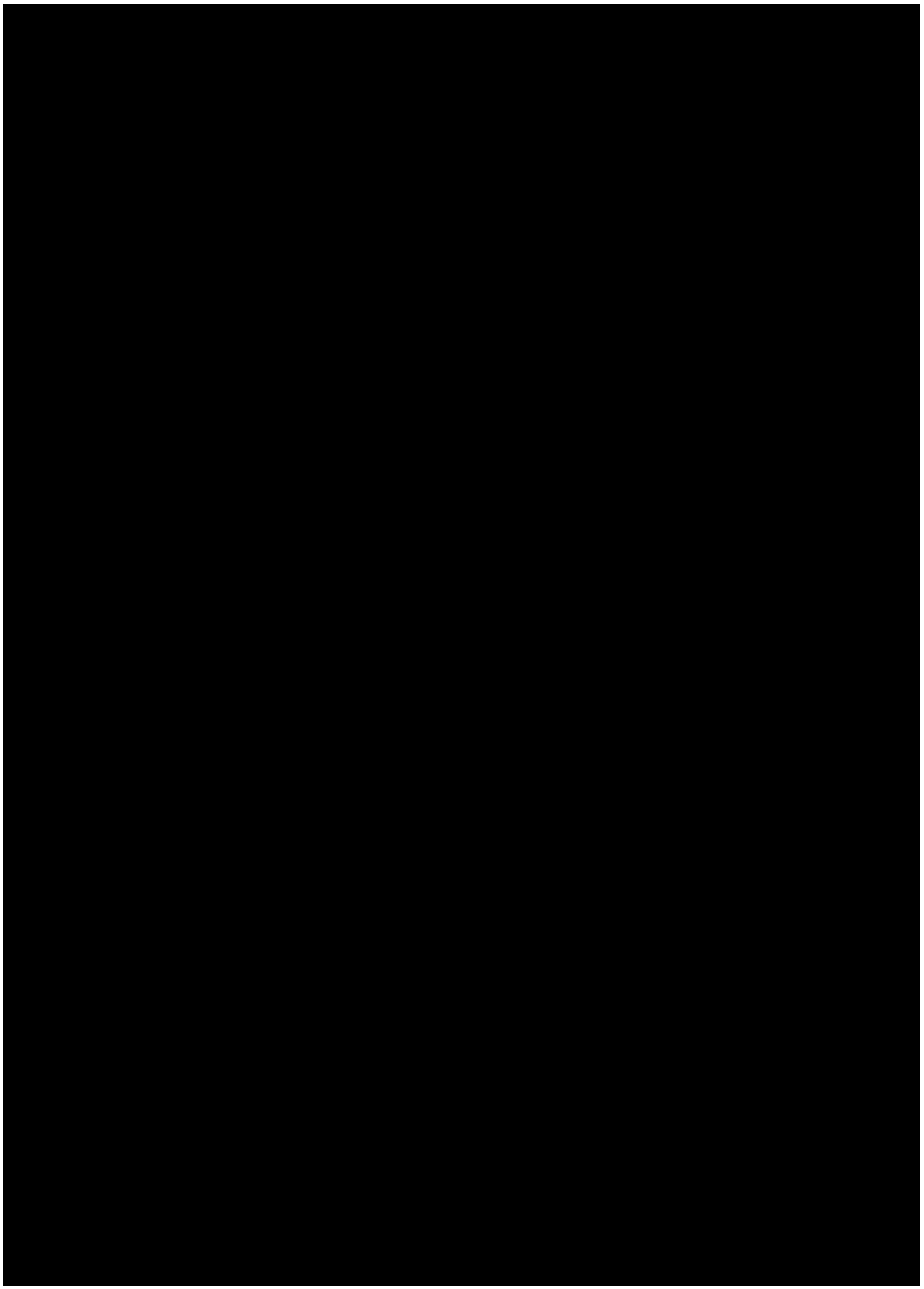
If severity is missing for an AE that started before the date of the first dose of study treatment, an intensity of mild will be assigned. If severity is missing for an AE that started on or after the date of the first dose of study treatment, an intensity of severe will be assigned. The imputed values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

16.6 MISSING CAUSAL RELATIONSHIP TO STUYD 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.

16.7 MISSING DATE INFORMATION FOR ADVERSE EVENTS

16.8 MISSING DATE INFORMATION FOR PRIOR OR CONCOMITANT MEDICATIONS



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17.0 CHANGES TO ANALYSES SPECIFIED IN PROTOCOL

There are no changes to the analyses specified in the latest protocol (dated 19 Oct 2017).

18.0 REFERENCES

N/A