NCT02590432

Study ID: LIN-MD-10

Title: An Open-label, Long-term Study to Assess the Immunogenicity of Linaclotide Administered Orally to Adult Patients With Irritable Bowel Syndrome With Constipation or Chronic Idiopathic Constipation

Statistical Analysis Plan Date: 23-May-2018

1. Title Page

STATISTICAL ANALYSIS PLAN

An Open-label, Long-term Study to Assess the Immunogenicity of Linaclotide Administered Orally to Adult Patients With Irritable Bowel Syndrome With Constipation or Chronic Idiopathic Constipation

Final 2.0: 2018-05-23

Protocol Number:	LIN-MD-10
Development Phase:	4
Product Name:	Linaclotide
Study Statistician:	[redacted]
Sponsor:	Allergan Sales, LLC 5 Giralda Farms Madison, NJ 07940

2. Table of Contents

2.1 List of Tables

[redacted]

2.2 List of Figures

3. List of Abbreviations and Definition of Terms

Table 3–1 Abbreviations and Definitions of Terms

Abbreviation/Term	Definition
ADA	anti-drug antibody
AE	adverse event
ANCOVA	analysis of covariance
ATC	Anatomical Therapeutic Chemical
BM	bowel movement
CIC	chronic idiopathic constipation
CFB	change from baseline
eCRF	electronic case report form
ECG	electrocardiogram, electrocardiographic
eDISH	evaluation of drug-induced serious hepatotoxicity.
[redacted]	[redacted]
GCP	Good Clinical Practice
GI	gastrointestinal
HR	hazard ratio
IBS	irritable bowel syndrome
IBS-C	irritable bowel syndrome with constipation
[redacted]	[redacted]
ICF	informed consent form
ITT	intent-to-treat
LIN	linaclotide
LLN	lower limit of normal
LS	least squares
MedDRA	Medication Dictionary for Regulatory Activities
NEAE	newly emergent adverse event
OR	odds ratio
[redacted]	[redacted]
[redacted]	[redacted]
PID	participant identification
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
SAP	statistical analysis plan
SBM	spontaneous bowel movement
TEAE	treatment-emergent adverse event
[redacted]	[redacted]
WHO	World Health Organization

4. Introduction

This statistical analysis plan (SAP) details comprehensive, technical specifications of the statistical analyses of the efficacy and safety data outlined and/or specified in the final protocol of Study LIN-MD-10 and the most recent amendment (version 2). Specifications of tables, figures, and data listings are contained in a separate document.

4.1 Study Design Summary

This will be a multicenter, open-label, long-term clinical study to assess the immunogenicity and long-term safety of linaclotide administered orally to adult participants with irritable bowel syndrome with constipation (IBS-C) and chronic idiopathic constipation (CIC), and to evaluate lower doses of linaclotide in participants who consider study withdrawal due to intolerable adverse events (AEs) that may be related to the use of linaclotide. Approximately 800 IBS-C or CIC participants (a minimum of 300 each) will be enrolled.

The study will consist of up to a 3-week Screening Period, followed by a 52-week Treatment Period (Figure 4–1). Participants who meet the entry criteria will receive once daily, open-label doses of 290 µg linaclotide for participants with IBS-C; those with CIC will receive once daily, open-label doses of 145 µg linaclotide.

In order to limit participant withdrawals from the study due to AEs and to gain information about the effect of lowering the dose in participants who experience intolerable AEs (defined as AEs that subjectively would cause a participant to consider study withdrawal), in particular diarrhea and other gastrointestinal (GI) AEs that may be related to the use of linaclotide, the following intervention (Figure 4-2) will be offered as an optional treatment course to such participants, unless deemed clinically inappropriate by the Investigator:

1. A temporary suspension of dosing of up to 7 days. If the dose suspension needs to last longer than 7 days because the intolerable AE has not resolved, then the Investigator should contact the Study Physician to discuss the duration of the dose suspension or withdrawal of the participant from the study. All AEs resulting in the temporary suspension will be recorded on the electronic case report form (eCRF).

2. After the intolerable AE has resolved, the participant will be randomized into a Double-blind Treatment Period via an interactive Web response system (IWRS) and will receive dose regimens specific to each indication as follows. If the randomized dose regimen is tolerated, the participant will remain on this dose for the duration of the study (total duration of linaclotide exposure [whether open-label or double-blind] is not to exceed 52 weeks).

   IBS-C participants will be randomized in a 1:1:1 ratio to 1 of the following regimens:

   - Linaclotide 290 µg every day
   - Linaclotide 145 µg every day
   - Linaclotide 72 µg every day

   CIC participants will be randomized in a 1:1 ratio to 1 of the following regimens:

   - Linaclotide 145 µg every day
   - Linaclotide 72 µg every day

3. If, after randomization, participants experience intolerable AEs, in particular diarrhea or other GI AEs, the dosing should be temporarily suspended for up to 7 days. If the dose suspension needs to last longer than 7 days because the intolerable AE has not resolved, then the Investigator should inform the Study Physician about the duration of dose suspensions or withdrawal of the participant from the study.

   After the intolerable AE has resolved, irrespective of the IBS-C or CIC status, participants should be dispensed open-label linaclotide (72 µg) and may continue on this dose in a Dose-reduced Open-label Treatment Period for the duration of the study.

4. If participants experience an intolerable AE while receiving the adjusted dose of 72 µg in the Dose-reduced Open-label Treatment Period, study participation should be terminated.

5. In the event of a planned procedure or an AE during which a participant requires dose suspension longer than 7 days, the Investigator should inform the Study Physician about the duration of dose suspensions. Upon event completion or AE resolution, the participant should be resumed on the assigned dose.

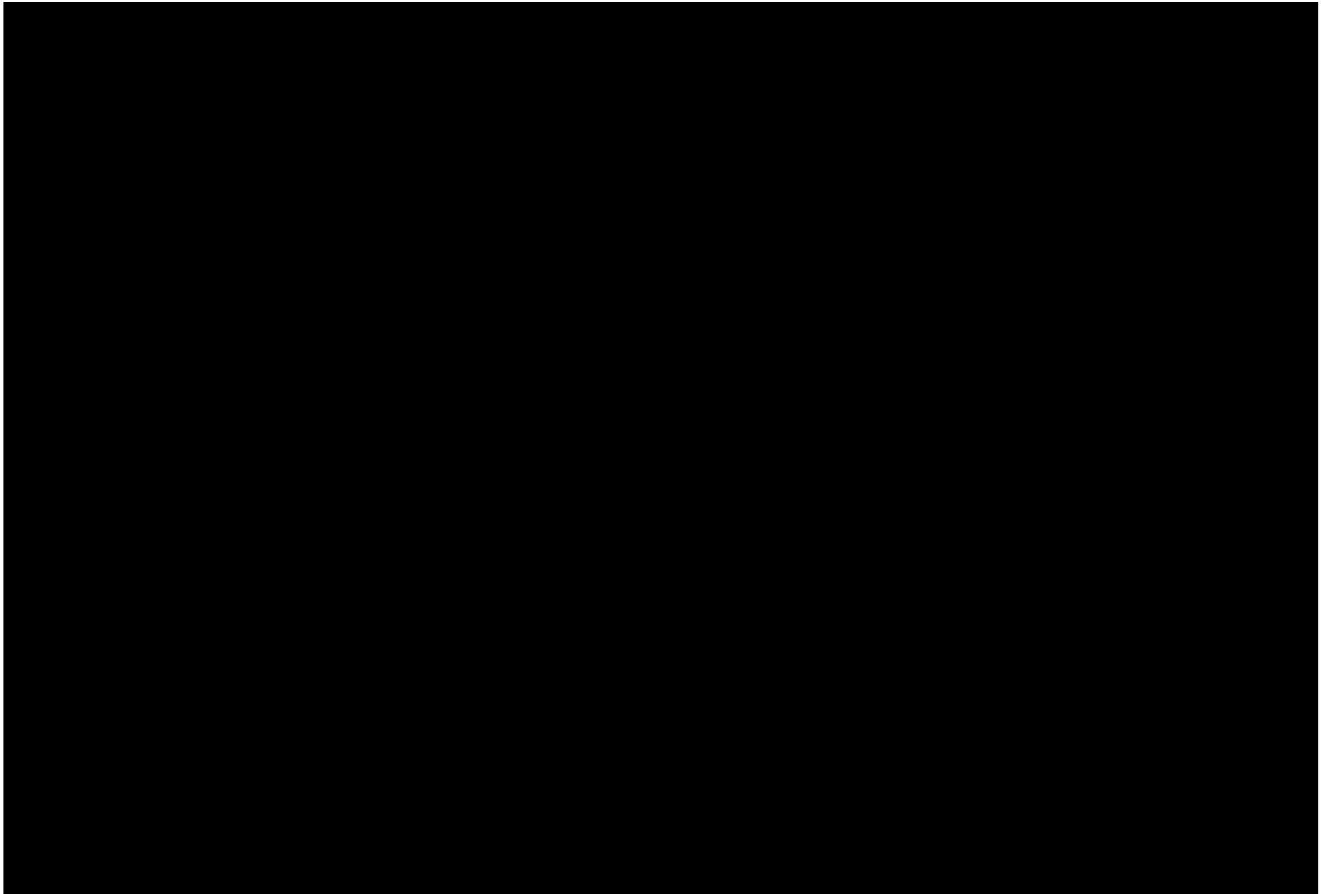
[redacted]

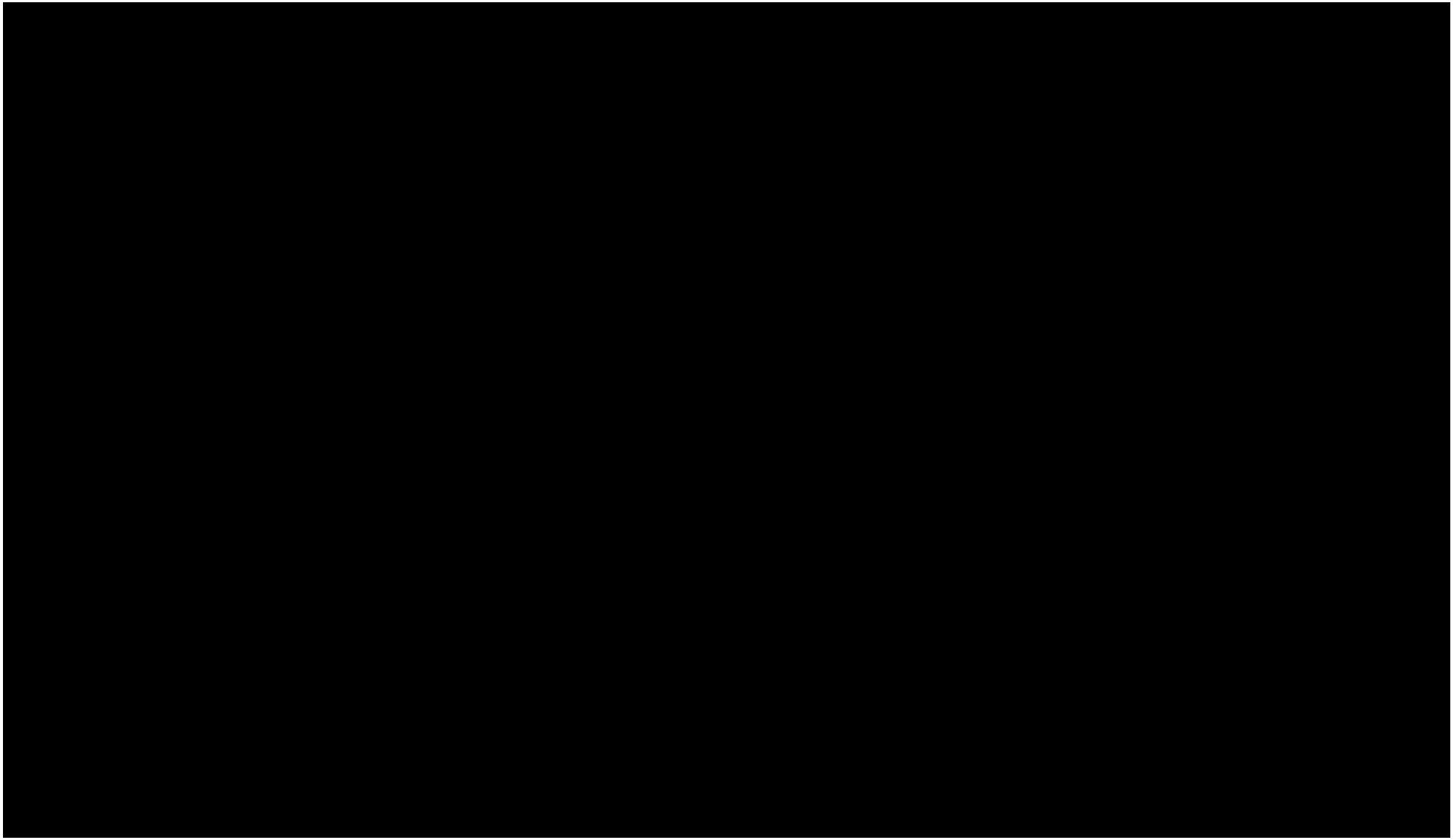
4.2 Study Objectives and Endpoints

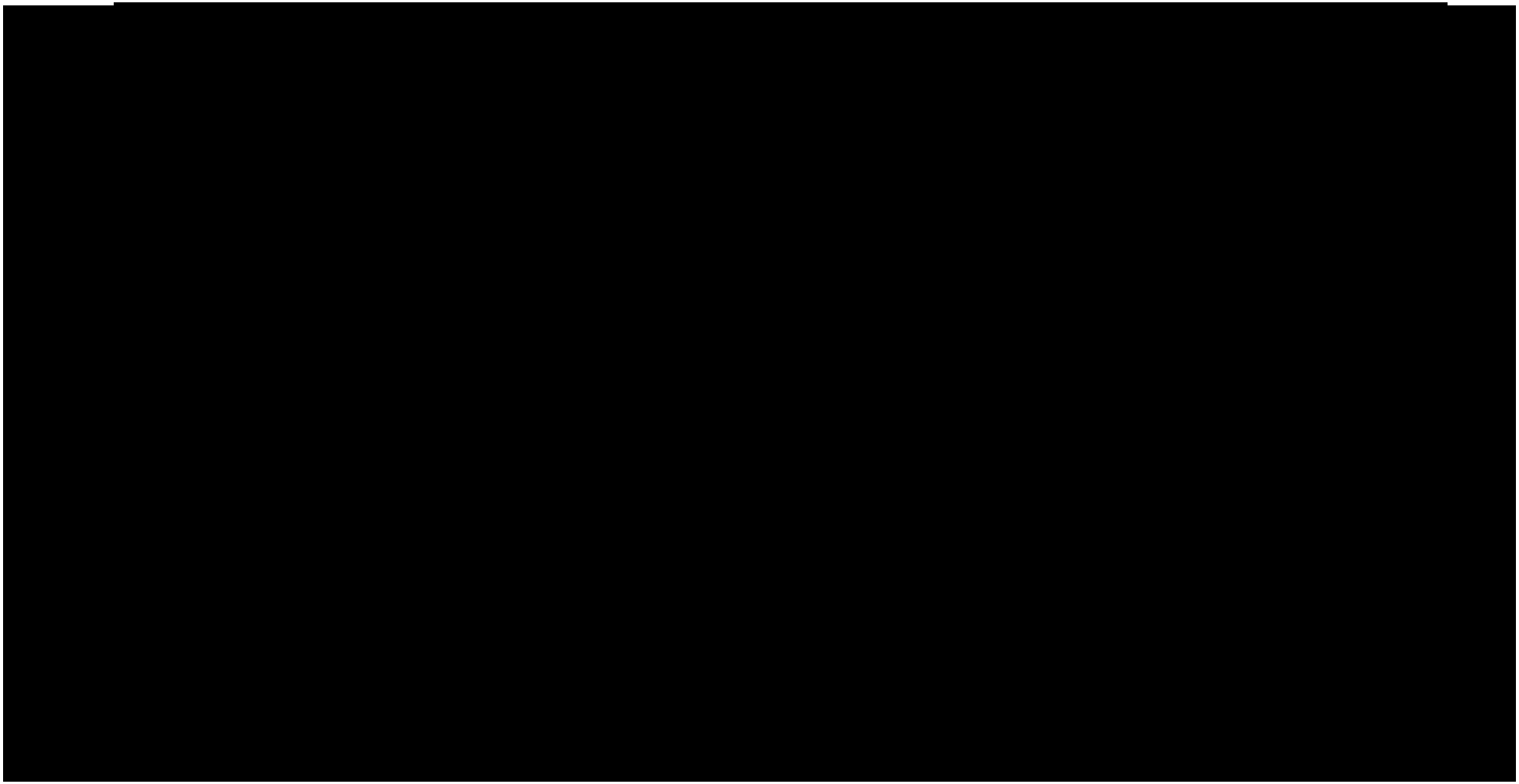
Each study objective is presented with corresponding endpoint(s) below:

Table 4–1 Study Objectives

Objectives	Endpoints
Primary	
• To assess the potential of linaclotide treatment to induce the development of anti-drug antibodies (ADAs)	• Treatment-related ADA positive responder
Secondary	
• To provide additional evidence supporting the long-term safety of linaclotide in adult IBS-C and CIC participants	• Adverse Events • Clinical Laboratory Assessments • Vital Signs • Electrocardiograms • Immunogenicity
• To provide additional evidence supporting the long-term efficacy of linaclotide in adult IBS-C and CIC participants	• Patient assessment of constipation severity • Patient assessment of IBS symptom severity (IBS-C only) • Degree of relief of IBS symptoms (IBS-C only) • IBS treatment satisfaction assessment (IBS-C only) • Constipation treatment satisfaction assessment (CIC only)
• To evaluate lower doses of linaclotide in participants who consider study withdrawal due to intolerable AEs	• Recurrence of diarrhea • Recurrence of intolerable diarrhea • Time to first recurrence of diarrhea • Time to first recurrence of intolerable diarrhea







5. Statistical Methodology and Study Endpoints

5.1 Statistical Methods Planned in the Protocol and Determination of Sample Size

This statistical analysis plan (SAP) expands the statistical section of the protocol and contains a detailed description of methods to analyze data collected in the study. The text portion of the SAP will be included in the CSR report as Appendix 16.1.9.

5.1.1 Statistical and Analytical Plans

Statistical analyses will be conducted using SAS Version 9.3 or newer.

5.1.1.1 Common Conventions

5.1.1.1.1 Analysis Populations

The analysis populations will consist of participants as defined below:

Table 5–1 Analysis Populations

Population	Definition	Study Treatment
Screened	All screened participants who sign an ICF for the study and receive a participant identification number (PID) • Rescreened participants considered separately for each unique PID	—
All enrolled participants	All Screened Population participants who continue into the Open-label Treatment Period per the screening disposition eCRF • This population will be used for selected listings only and is not considered a formal analysis population	Indication
Safety	All Screened Population participants who receive ≥ 1 administration of study treatment	Indication
Intent-to-Treat (ITT)	All Safety Population participants with ≥ 1 postbaseline assessment for any efficacy or health outcomes parameter during the Treatment Period, fully described in Section 5.1.1.3 • Patient assessment of constipation severity • Patient assessment of IBS symptom severity (IBS-C only) • Degree of relief of IBS symptoms (IBS-C only) • IBS treatment satisfaction assessment (IBS-C only) • Constipation treatment satisfaction assessment (CIC only) [redacted]	Indication
Randomized	All Safety Population participants who are randomized to double-blind study treatment following resolution of an intolerable AE	Randomized assignment
Double-blind Safety	All Randomized Population participants who receive ≥ 1 administration of study treatment during the Double-blind Treatment Period	Randomized assignment

Population	Definition	Study Treatment
Double-blind ITT	All Double-blind Safety Population participants with ≥ 1 post-randomization assessment for any efficacy or health outcomes parameter during the Double-blind Treatment Period, fully described in Section 5.1.1.3 • Patient assessment of constipation severity • Patient assessment of IBS symptom severity (IBS-C only) • Degree of relief of IBS symptoms (IBS-C only) • IBS treatment satisfaction assessment (IBS-C only) • Constipation treatment satisfaction assessment (CIC only) [redacted]	Randomized assignment

5.1.1.1.2 Study Treatments

The following linaclotide (LIN) treatment groups are defined for this study:

Table 5–2 Treatment Groups by Indication and Treatment Period

	Indication	
Treatment Period	**IBS-C**	**CIC**
Open-label	LIN 290 µg	LIN 145 µg
Double-blind	LIN 290 µg LIN 145 µg LIN 72 µg	 LIN 145 µg LIN 72 µg
Dose-reduced Open-label	LIN 72 µg	LIN 72 µg

5.1.1.1.3 Statistical Methodology

The methodologies defined below apply as specified to individual endpoints defined in this SAP. When indicated, 95% 2-sided confidence intervals (CIs) and 2-sided p-values will be presented unless otherwise specified.

Table 5–3 Statistical Methodology

Methodology	Description
Categorical counts	• Number of participants in individual categories ○ Participants with ≥ 1 qualifying event counted once per individual category

Categorical descriptives	• Number and percentage of participants in individual categories
	  ○ Participants with ≥ 1 qualifying event counted once per individual category
	• (Optional if specified) N1 if percentage denominator ≠ number of participants in the population (standard percentage denominator)
	  ○ N1 = participants with non-missing baseline value

[redacted]	[redacted]

Methodology	Description
	○ Unevaluable assessments considered missing ○ If specified, participants with baseline PCS values will be excluded
[redacted]	[redacted]
Continuous descriptives	• N1, mean, SD, median, minimum, maximum • N1 = participants with non-missing value
CFB descriptives	• Continuous descriptives for baseline, postbaseline, and change from baseline (CFB) values • N1 = participants with non-missing values at both baseline and the specified postbaseline analysis visit
[redacted]	[redacted]
CFB ANCOVA	• Continuous descriptives and SE for baseline, postbaseline, and CFB values • Estimates derived from ANCOVA model for CFB value controlling for fixed factors (treatment group) and fixed covariates (baseline value) ○ Least squares (LS) means and standard errors ○ LS mean differences, standard errors, and CIs vs highest LIN dose[1] ○ P-values from contrast t-test comparing lower LIN doses[2] vs highest LIN dose[1] • N1 = participants with non-missing values at both baseline and the specified postbaseline analysis visit
Responder	• Categorical descriptives for responders and nonresponders ○ Nonresponders include: ▪ Participants who do not meet responder criteria ▪ Participants with no postbaseline values • Risk differences and Wald CIs vs highest LIN dose[1] • Unadjusted risk ratios (RRs), odds ratios (ORs), and CIs vs highest LIN dose[1] • P-values from Fisher's exact test comparing lower LIN doses[2] vs highest LIN dose[1]
Immunogenicity responder	• Categorical descriptives for responders and nonresponders ○ Nonresponders include: ▪ Participants who do not meet responder criteria ▪ Participants with no postbaseline values • Responder rate 1-sided 95% Clopper-Pearson CIs • N1 = all participants unless otherwise specified
Time-to-event	• Categorical descriptives for participants with events and censoring ○ Censoring includes: ▪ Participants who do not meet event criteria ▪ Participants with no postbaseline values • Quartiles and CIs derived from Kaplan-Meier (KM) nonparametric model using log-log transformation of survivor function • Estimates derived from Cox proportional hazards model controlling for factor (treatment group) ○ Hazard ratios (HRs) and CIs vs highest LIN dose[1] • Estimates derived from log-rank model controlling for factor (treatment group) ○ P-values comparing lower LIN doses[2] vs highest LIN dose[1] • N1 = all participants unless otherwise specified
KM figure	• Step-function figure of cumulative distribution function (1 – survivor function) estimates with censoring indicators, derived from KM nonparametric model

CFB = change from baseline; ANCOVA = analysis of covariance; TTE = time-to-event.

Methodology	Description

[1] Highest LIN dose by indication: IBS-C: LIN 290 µg; CIC: LIN 145 µg.
[2] Lower LIN doses by indication: IBS-C: LIN 72 µg, LIN 145 µg; CIC: LIN 72 µg.

Raw and derived data listings will be provided, and will be fully defined in the table, figure, and data listing specification document.

5.1.1.1.4 Missing Data

General missing data handling conventions are specified for methodologies in Section 5.1.1.1.3 and summarized as follows:

Table 5–4 Missing Data Handling by Endpoint Type

Parameter type	Timing	Missing Data Handling
Responder	Double-blind Treatment Period	• All participants included unless otherwise specified • Participants with no postbaseline values = nonresponders
Immunogenicity responder	Treatment Period	• Participants with no postbaseline assessable values excluded
Time-to-event	Double-blind Treatment Period	• Participants not reporting specified event (intolerable diarrhea) during the Open-label Treatment Period excluded • Participants with no postbaseline values = censored

CFB ANCOVA	Treatment Period	• If missing covariates (including baseline if applicable)
		  ○ Participant excluded
		• If missing derived value at the specified postbaseline analysis visit:
		  ○ Participant excluded

5.1.1.1.5 Treatment Periods

The non-overlapping Open-label, Double-blind, and Dose-reduced Open-label treatment periods are defined by their respective treatment start and end dates. These 3 treatment periods are subsets of the overall Treatment Period. The start and end dates for each period are defined as follows:

Table 5–5 Treatment Period Definitions

Parameter	Start	End
Treatment Period	Treatment start date = first dose date of any LIN treatment	Treatment end date = last dose date of any LIN treatment
Open-label Treatment Period	Open-label start date = first dose date of open-label LIN treatment • Identical to treatment start date	Open-label end date = last dose date of open-label LIN treatment • Identical to treatment end date for participants who do not enter the Double-blind Treatment Period
Double-blind Treatment Period	Double-blind start date = first dose date of double-blind LIN treatment	Double-blind end date = last dose date of double-blind LIN treatment • Identical to treatment end date for participants who do not enter the Dose-reduced Open-label Treatment Period

Dose-reduced Open-label Treatment Period	Dose-reduced open-label start date = first dose date of dose-reduced open-label LIN treatment	Dose-reduced open-label end date = last dose date of open-label LIN treatment • Identical to treatment end date

5.1.1.2 Demographics

5.1.1.2.1 Analysis Populations

The distribution of participants within the analysis populations will be summarized as follows:

Table 5–6 Analysis Population Summaries

Parameter	Description	Timing	Methodology
Screened, Safety, and Intent-to-Treat (ITT) populations	Distribution overall and within sites in total and by indication	—	Categorical counts
Randomized, Double-blind Safety, and Double-blind ITT populations	Distribution overall and within sites in total and by treatment group within each indication	—	Categorical counts

5.1.1.2.2 Participant Disposition

Participant disposition encompasses the distribution of participants who enter, complete, and discontinue each specified period (epoch) as defined by study design, along with eCRF-reported discontinuation reasons from each respective period. Participant disposition will be summarized as follows:

Table 5–7 Participant Disposition Summaries

Parameter	Description	Timing	Methodology
Screening Period Disposition	Distribution in total for the Screened Population	Screening Period	Categorical descriptives
Treatment Period Disposition	Distribution in total and by indication for the Safety Population • Participants categorized based on latest available eCRF from the Open-label, Double-blind, and Dose-reduced Open-label treatment periods	Treatment Period	Categorical descriptives
Open-label Treatment Period Disposition	Distribution in total and by indication for the Safety Population Include distribution of participants who discontinue who: • do continue to Double-blind Treatment Period • do not continue to Double-blind Treatment Period	Open-label Treatment Period	Categorical descriptives
Double-blind Treatment Period Disposition	Distribution in total and by treatment group within each indication for the Randomized Population Include distribution of participants who	Double-blind Treatment Period	Categorical descriptives

Parameter	Description	Timing	Methodology
	discontinue who: • do continue to Dose-Reduced Open-label Treatment Period • do not continue to Dose-Reduced Open-label Treatment Period		
Dose-reduced Open-label Treatment Period Disposition	Distribution in total and by treatment group within each indication for the Randomized Population	Dose-reduced Open-label Treatment Period	Categorical descriptives

5.1.1.2.3 Significant Protocol Deviations

Protocol deviations and significance classification will be defined in the protocol deviation requirements specification document. Unique participants reporting significant protocol deviations will be summarized in total and by indication as follows:

Table 5–8 Protocol Deviation Summary

Parameter	Description	Timing	Methodology
Significant protocol deviations	Overall summary and by protocol deviation term	—	Categorical descriptives

5.1.1.2.4 Demographics

Demographics will be summarized in treated and non-treated groups for the Screened Population, in total and by indication for the Safety and ITT populations, and in total and by treatment group within each indication for the Double-blind ITT Population as follows:

Table 5–9 Demographic Summaries

Parameter	Description	Timing	Methodology
Age	Age (years) relative to informed consent date	Informed consent	Continuous descriptives
Age group	• < 40 years • ≥ 40 – < 65 years • ≥ 65 years	Informed consent	Categorical descriptives

Sex, race, race group, and ethnicity	• eCRF categories
	• Race group
	  ○ White
	  ○ Non-white
		Screening Period	Categorical descriptives

5.1.1.2.5 Baseline Characteristics

Baseline characteristics will be summarized in total and by indication for the Safety and ITT populations, and in total and by treatment group within each indication for the Double-blind ITT Population as follows:

Table 5–10 Baseline Characteristics Summaries

Parameter	Description	Timing	Methodology
Baseline characteristics	• Height (cm) • Weight (kg) • Body mass index (BMI) ○ Weight (kg) / height (m)^2	Latest assessment on or before Treatment Day 1	Continuous descriptives
Baseline efficacy	Endpoints fully described in Section 5.1.1.3 • Patient assessment of constipation severity • Patient assessment of IBS symptom severity (IBS-C only) • Degree of relief of IBS symptoms (IBS-C only) [redacted] Summarize only for the ITT population	Latest assessment on or before Treatment Day 1	Continuous descriptives

5.1.1.2.6 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 19.0 or newer. Unique participants who report medical history events will be summarized by MedDRA system organ class and preferred term in total and by indication for the Safety Population as follows:

Table 5–11 Medical History Summary

Parameter	Description	Timing	Methodology
Medical history	Abnormalities and surgeries occurring before the Screening Visit	Screening Period	Categorical descriptives

5.1.1.2.7 Prior and Concomitant Medications

Medications will be coded using the World Health Organization (WHO) Drug Dictionary, version March 2016 or newer. Unique participants who reported medications will be summarized by Anatomical Therapeutic Chemical (ATC) 4 class and preferred term in total and by indication for the Safety Population as follows:

Table 5–12 Medication Summaries

Parameter	Description	Timing	Methodology
Prior medications	Medications taken ≥ 1 time before the treatment start date, regardless of	Screening Period	Categorical descriptives

Parameter	Description	Timing	Methodology
	medication end date		
Concomitant medications	Medications taken ≥ 1 time on or after the treatment start date, regardless of medication start date • Medications starting 1 day after treatment end date will be listed but excluded from analysis	Treatment Period	Categorical descriptives

5.1.1.3 Efficacy [redacted]

Efficacy [redacted] will be based on the ITT Population unless otherwise specified.

Baseline values for efficacy [redacted] endpoints are defined as the latest assessment on or before Treatment Day 1. There are no baseline values for treatment satisfaction endpoints.

5.1.1.3.1 Efficacy Analyses

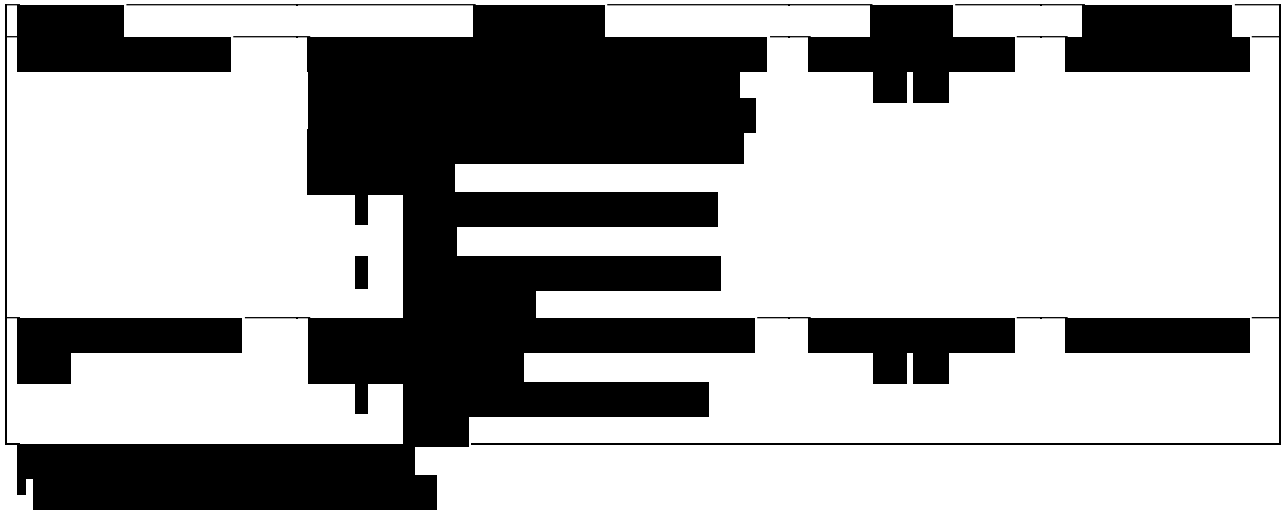
Efficacy endpoints will be summarized in total and by indication (if applicable) as follows:

Table 5–13 Efficacy Endpoints

Endpoint	Description	Timing	Methodology
Patient assessment of constipation severity	Rating of constipation severity during the previous 7 days on a 5-point ordinal scale • Higher scores indicate greater severity	Weeks 2, 4, 12, 26, 40, 52[1]	CFB descriptives
Patient assessment of IBS symptom severity (IBS-C only)	Rating of IBS symptoms severity during the previous 7 days on a 5-point ordinal scale • Higher scores indicate greater severity	Weeks 2, 4, 12, 26, 40, 52[1]	CFB descriptives
Degree of relief of IBS symptoms (IBS-C only)	Rating of degree of relief of IBS symptoms during previous 7 days on a 7-point balanced ordinal scale • Lower scores indicate greater relief	Weeks 2, 4, 12, 26, 40, 52[1]	CFB descriptives
IBS treatment satisfaction assessment (IBS-C only)	Rating of degree of satisfaction with the study treatment's ability to relieve IBS symptoms on a 5-point ordinal scale • Higher scores indicate greater satisfaction	Weeks 2, 4, 12, 26, 40, 52[1]	Continuous descriptives
Constipation treatment satisfaction assessment (CIC only)	Rating of degree of satisfaction with the study treatment's ability to relieve constipation symptoms on a 5-point ordinal scale • Higher scores indicate greater satisfaction	Weeks 2, 4, 12, 26, 40, 52[1]	Continuous descriptives

[1] Analysis visits defined in Section 6.2.

[redacted]



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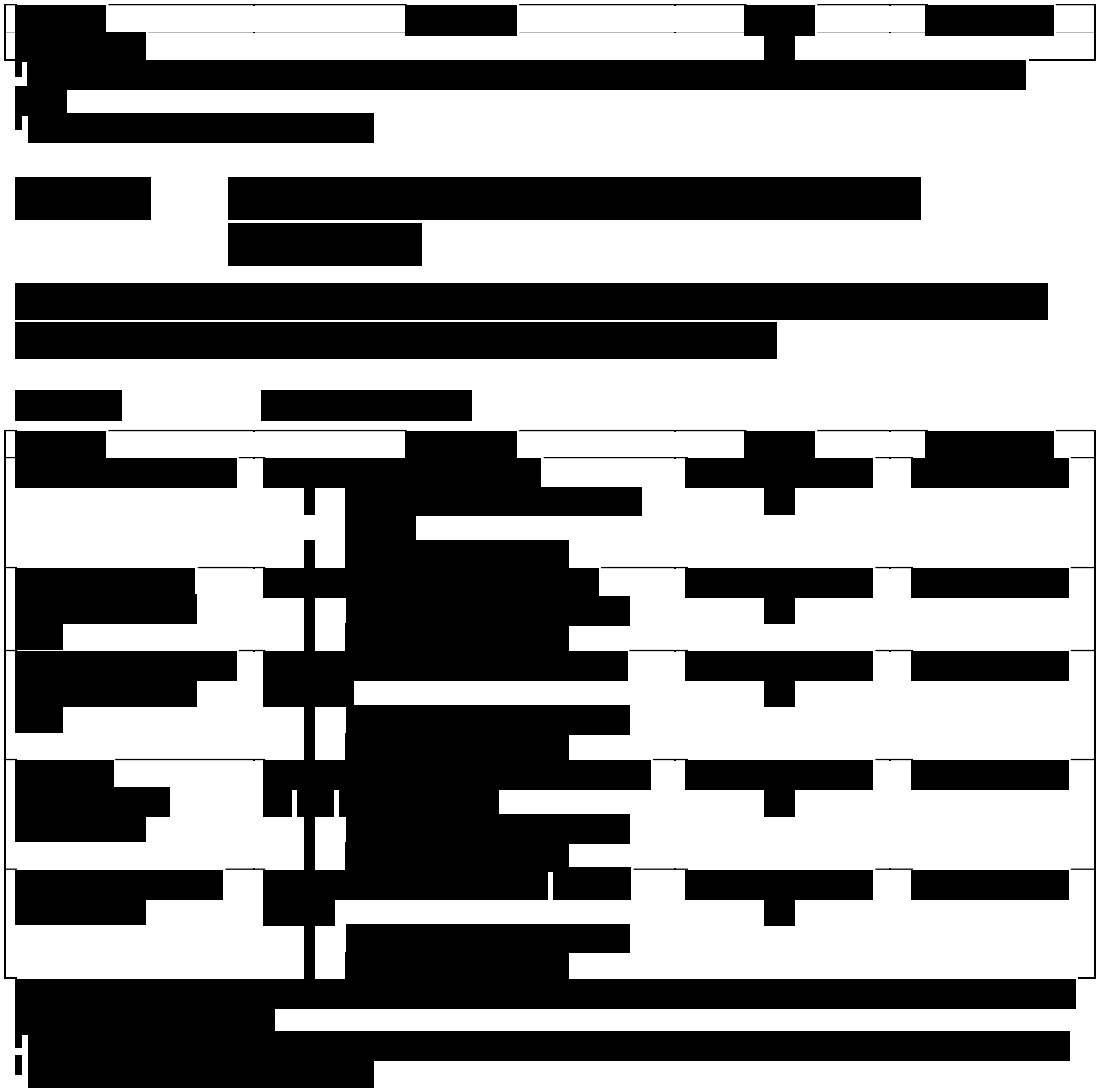


5.1.1.3.3 Double-blind Treatment Period Analyses

A set of exploratory analyses will be conducted for Double-blind Safety Population participants, unless otherwise specified, for the subset of participants who experience an intolerable AE during the initial Open-label Treatment Period. Data from the Dose-reduced Open-label Treatment Period following discontinuation of double-blind treatment will be excluded from these analyses.

Pre-randomization (Double-blind Treatment Period baseline) values for efficacy [redacted] endpoints are defined as the latest available assessment during the Treatment Period on or before the Double-blind start date.

[redacted]

[redacted]

5.1.1.4 Safety Analyses

Safety analyses will be based on the Safety Population unless otherwise specified.

Baseline values for applicable safety endpoints are defined as the latest non-missing assessment on or before the treatment start date.

[redacted]

[redacted]

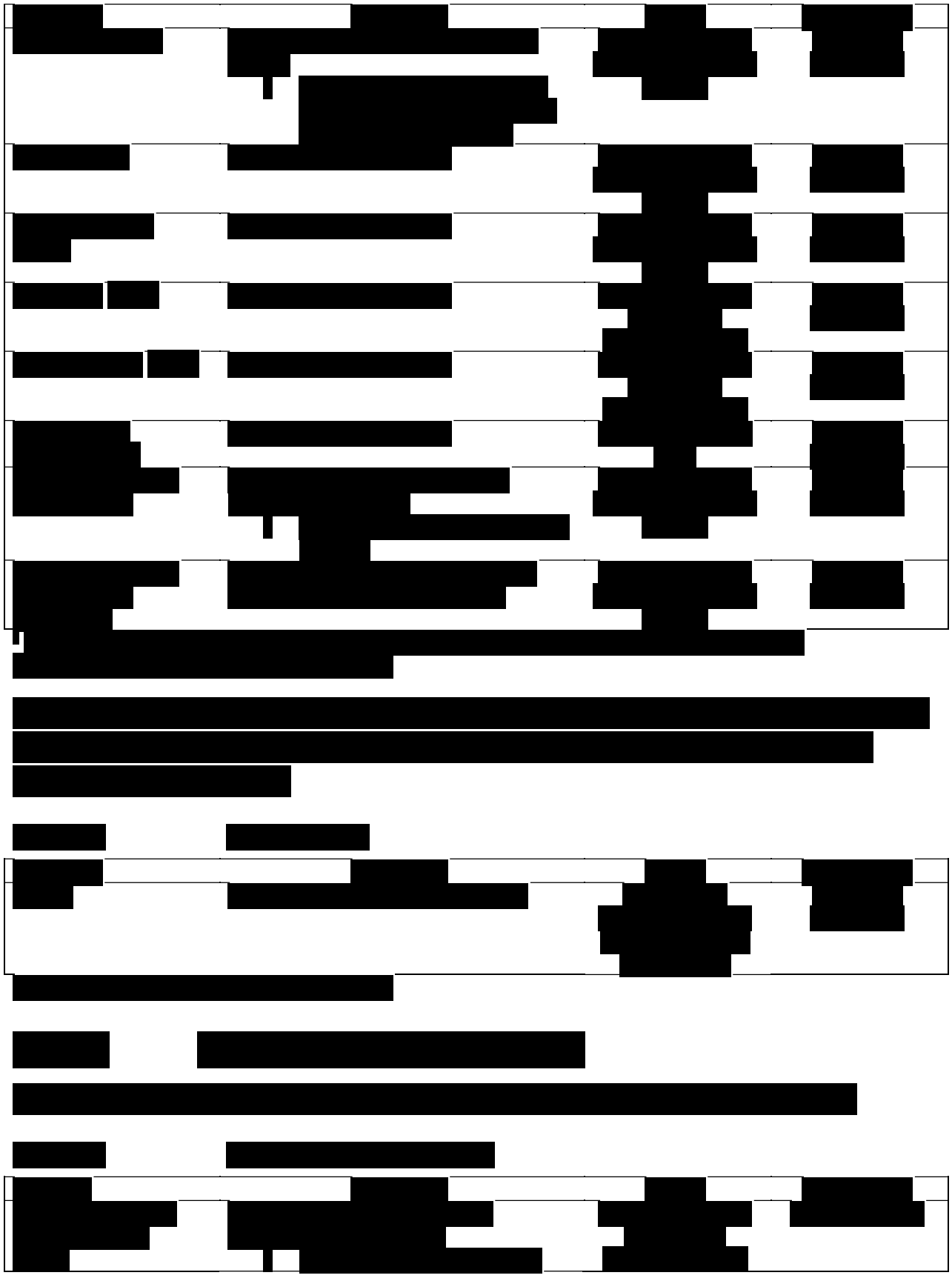
5.1.1.4.2 Adverse Events

The following adverse event (AE) terms are defined:

Table 5–20 AE Terms

Term	Description
Treatment-emergent	An event that meets the following condition: • Treatment start date ≤ event start date ≤ treatment end date + 1 and meets either of the following conditions: • The same term is never reported before the treatment start date • The same term is reported before the treatment start date and the term increases in severity on or after the treatment start date o Event severity > maximum severity of same term reported before the treatment start date
[redacted]	
On-therapy	An event where: • Treatment start date ≤ event start date ≤ treatment end date + 30

[redacted]



Endpoint	[redacted]	[redacted]	[redacted]
	[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

5.1.1.4.6 Immunogenicity

Individual immunogenicity samples will be assayed and categorized as 1 of the following:

- ADA positive
  - Screening result = positive AND confirmatory result for anti-linaclotide antibodies = positive
- ADA negative
  - Any of the following:
    - Screening result = negative
    - Screening result = positive AND confirmatory result for anti-linaclotide antibodies = negative

- ADA undetermined (sample lost, damaged, out of specifications, insufficient volume)
    - Any of the following:
        - Screening result = missing
        - Screening result = positive AND confirmatory result for anti-linaclotide antibodies = missing

Baseline ADA status is defined as the assay result of the Treatment Day 1 (Visit 2) pre-treatment sample.

Overall postbaseline ADA status will be derived using all postbaseline samples during the Treatment Period and within 7 days after the treatment end date, and are defined as follows:

Table 5-27 Overall Postbaseline ADA Status Categories

Assessment/Term	Description
Treatment-induced ADA positive[1]	≥ 1 postbaseline ADA positive sample
Treatment-boosted ADA positive[2]	≥ 1 postbaseline ADA positive sample with titer values ≥ 4 × baseline titer value
Non-treatment-boosted ADA positive[2]	All postbaseline ADA positive samples with titer values < 4 × baseline titer value and not qualifying as ADA negative
ADA negative	≥ 1 postbaseline ADA negative sample and no postbaseline ADA positive samples
ADA undetermined	Participant with no assessable samples (sample lost, damaged, out of specifications, insufficient volume) • Missing data considered ADA undetermined

[1] Only applicable to baseline ADA negative or ADA undetermined participants
[2] Only applicable to baseline ADA positive participants

Immunogenicity endpoints will be summarized in total and by indication as follows:

Table 5–28 Immunogenicity Endpoints

Endpoint	Description	Timing	Methodology
Treatment-related ADA positive responder	Meets either of the following criteria: • Treatment-induced ADA positive for baseline ADA negative or ADA undetermined participants • Treatment-boosted ADA positive for baseline ADA positive participants Non-responder otherwise Only includes participants with ≥ 1 assessable postbaseline sample (ADA undetermined excluded)	Treatment Period + 7 days after treatment end date	Immunogenicity responder
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

5.1.1.5 Subgroup Analyses

Not applicable.

5.1.1.6 Interim Analyses

Not applicable.

5.1.2 Determination of Sample Size

The objective of this study is to assess the long-term safety of linaclotide administered to participants with IBS-C or CIC and to determine the potential of linaclotide to induce ADAs. If 0 of 800 participants develop ADAs, the 1-sided 95% upper CI for this rate (0/800 [0%]) is 0.374%.

[redacted]

[redacted]

[redacted]

Complete

6.4 Efficacy Endpoint Conventions

[redacted]

[redacted]

[redacted]


Bicarbonate
Glucose

[redacted]

[redacted]

[redacted]

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8. History of Change

Amendment 1: 2018-05-23

Section(s)	Description	Rationale
Global	Corrected case for selected hyphenated words: • Dose-reduced • Double-blind	Alignment with MW style guidelines
1	Changed sponsor from Forest to Allergan on cover page and headers, and changed sponsor address	Updated NDA holder
3 Global	Removed selected abbreviations and expansion of [redacted]; Removed instances of removed abbreviations from SAP body; inclusion of selected references in table footnotes	Alignment with MW style guidelines; abbreviations not required
5.1.1.1.1	Added All enrolled participants population	Handling of participants who entered OL with exposure records not indicating treatment was actually taken
5.1.1.2.2	Specified participant disposition based on study design epochs, not analysis periods	Clarification
5.1.1.2.2	For participants who continued to next period, removed "due to AE" clause	Simplification/elimination of confusion
5.1.1.2.3	Specified "significant" protocol deviations	Accuracy
5.1.1.2.5	Changed height unit to cm	Accuracy
5.1.1.3.1 5.1.1.3.2	Changed continuous descriptives to CFB descriptives for endpoints with baseline values	Incorrect analysis references
5.1.1.3.3	Changed population to DB Safety for selected analyses	Incorrectly specified in protocol
5.1.1.3.3	Changed assignment of values on same date as DB start date from post-rand to pre-rand	Value from DB start date assumed to be before first DB administration
[redacted]	[redacted]	Clarification
5.1.1.4.6	Revised details of ADA classification rules; Revised listing specification	Clarification
[redacted]	[redacted]	Correction