

1.0

TITLE PAGE



**Forest Research Institute, Inc., an affiliate of Allergan.
Harborside Financial Center, Plaza V
Jersey City, NJ 07311**

**A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group,
Safety and Efficacy Study of a Range of Linacotide Doses Administered Orally to
Children, Ages 7 to 17 Years, With Irritable Bowel Syndrome With Constipation
(IBS-C) (ie, Fulfill Rome III Criteria for Child/Adolescent IBS and Fulfill Modified
Rome III Criteria for Child/Adolescent Functional Constipation)**

LIN-MD-63

IND #63,290

Original Protocol Date: 15 Apr 2015

Amendment #1: 13 Aug 2015

Amendment #2: 20 Jul 2016

Amendment #3: 16 May 2017

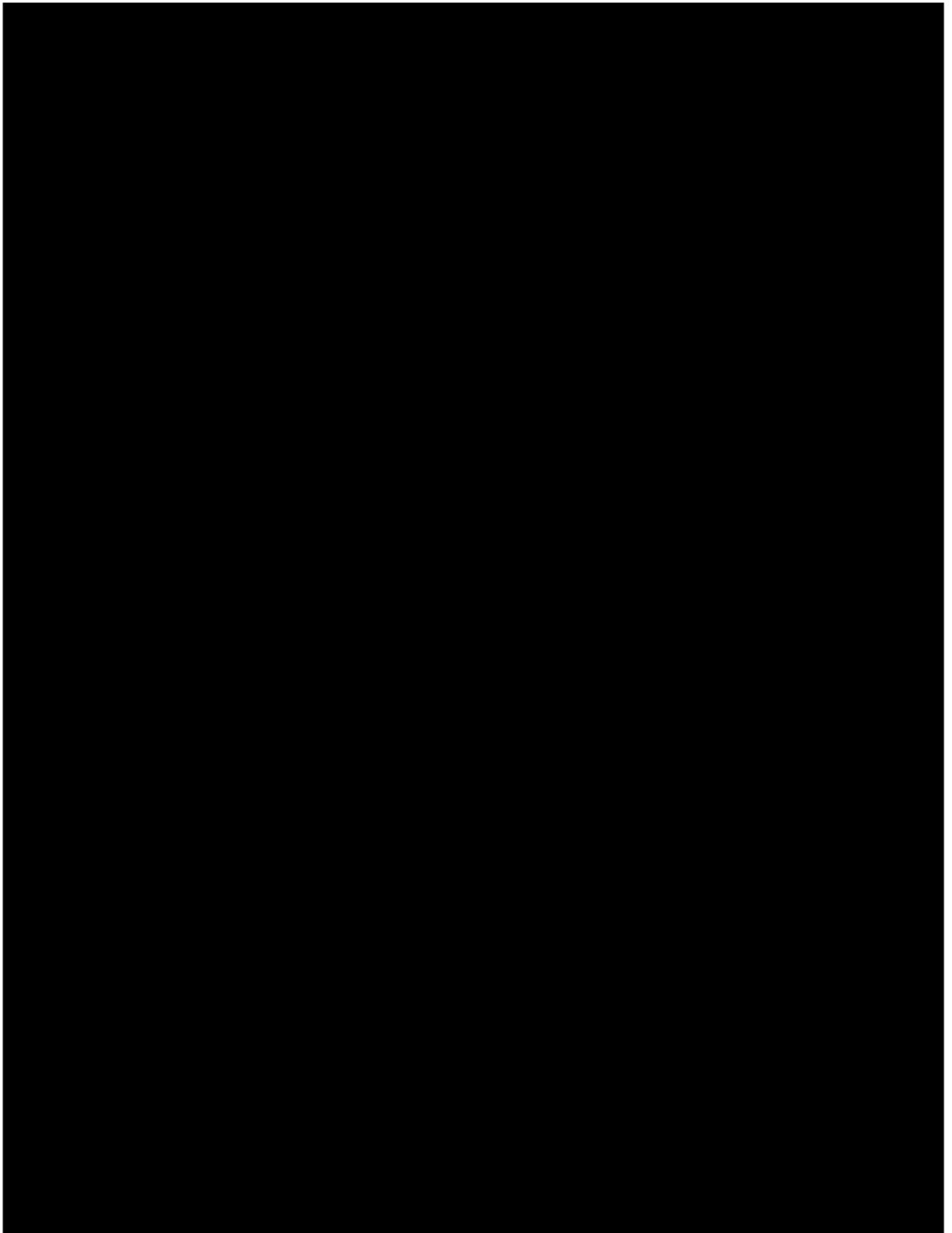
Confidentiality Statement

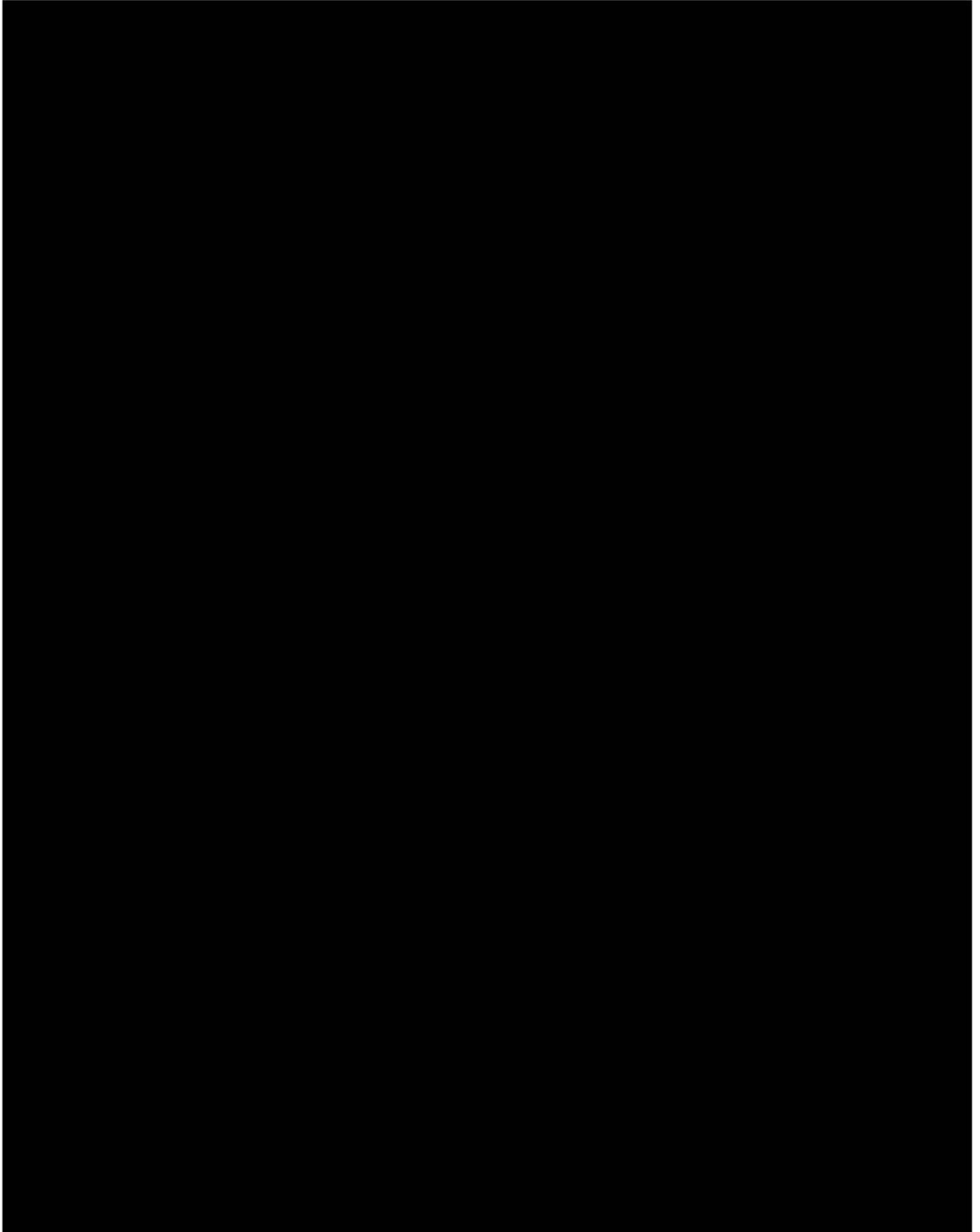
This document is the property of Forest Research Institute, Inc., and may not—in full or part—be passed on, reproduced, published, distributed, or submitted to any regulatory authority without the express written permission of Forest Research Institute, Inc.

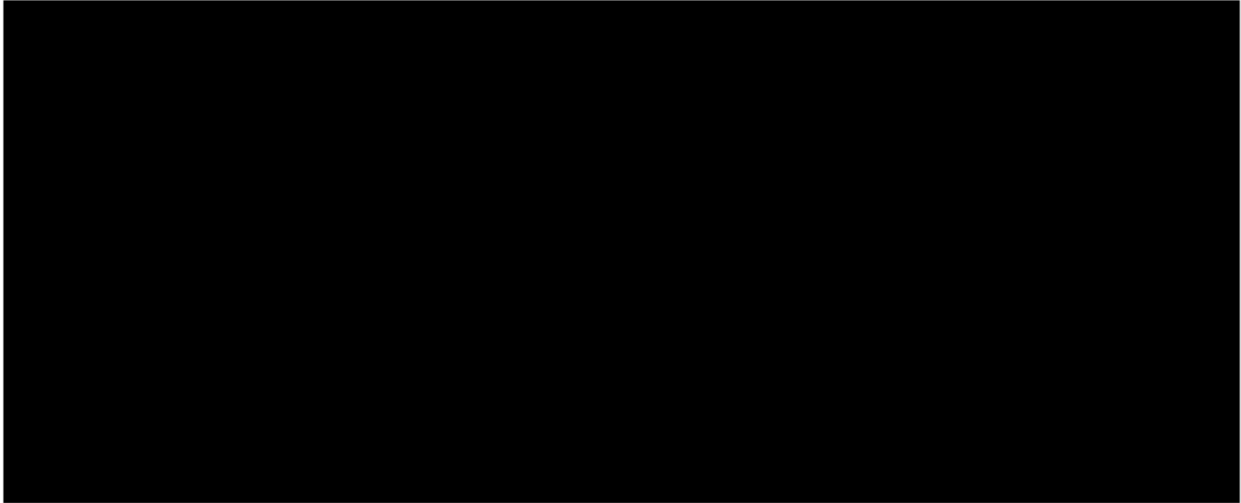
2.0 **SYNOPSIS AND SCHEDULE OF EVALUATIONS**

CLINICAL STUDY SYNOPSIS: Study LIN-MD-63	
Title of Study	A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group, Safety and Efficacy Study of a Range of Linaclotide Doses Administered Orally to Children, Ages 7 to 17 Years, With Irritable Bowel Syndrome With Constipation (IBS-C) (ie, Fulfill Rome III Criteria for Child/Adolescent IBS and Fulfill Modified Rome III Criteria for Child/Adolescent Functional Constipation)
Study Sites	approximately 50 - 100
Development Phase	2
Objective	To evaluate the dose response, safety, and efficacy of 4 weeks of treatment with 1 of 3 linaclotide doses (A, B, or C) or 290 ug [REDACTED] compared with placebo in pediatric patients 7 to 17 years of age who fulfill the Rome III criteria for child/adolescent irritable bowel syndrome (IBS) and modified Rome III criteria for child/adolescent functional constipation (FC)
Methodology	Multicenter, randomized, double-blind, placebo-controlled, parallel-group, safety and efficacy dose-ranging study in pediatric patients
Number of Patients	Approximately 260 patients are planned (58 placebo patients, 58 patients per linaclotide dose [A, B, or C], and 23 - 31 patients for the linaclotide approved adult dose, 290 ug [in the 12 - 17 years of age group only]), with a minimum of 40% of patients per age group (7 - 11 years and 12 - 17 years)
Diagnosis and Main Criteria for Inclusion	Male and female pediatric patients 7 to 17 years of age with a diagnosis of irritable bowel syndrome with constipation (IBS-C) based on the Rome III criteria for child/adolescent IBS and modified Rome III criteria for child/adolescent FC
Test Product, Dosage, and Mode of Administration	<p>Patients 7 to 11 years of age: linaclotide liquid oral solution or solid oral capsule taken once daily</p> <p>Patients 12 to 17 years of age: linaclotide solid oral capsule taken once daily</p> <p>Dosage is weight-based within the 7 to 11 years of age group:</p> <p>Patients 7 to 11 years of age (weight 18 to < 35 kg)</p> <ul style="list-style-type: none"> • Dose A: 18 ug • Dose B: 36 ug • Dose C: 72 ug <p>Patients 7 to 11 years of age (weight ≥ 35 kg)</p> <ul style="list-style-type: none"> • Dose A: 36 ug • Dose B: 72 ug • Dose C: 145 ug <p>Patients 12 to 17 years of age</p> <ul style="list-style-type: none"> • Dose A: 36 ug • Dose B: 72 ug • Dose C: 145 ug • Approved adult dose: 290 ug (for safety [REDACTED])
Duration of Treatment	The study will be approximately 9 to 12 weeks in duration: up to a 4-week (14 - 28 days) Screening Period, a 2- to 3-week (14 to 21 days) Pretreatment Period, followed by a 4-week (≥ 28 days) Double-blind Treatment Period, and finally followed by a 1-week (≥ 7 days) Post-treatment Period. Patients will not receive investigational product during the Pretreatment Period or the Post-treatment Period.

Reference Therapy, Dosage, and Mode of Administration	Patients 7 to 11 years of age: matching placebo liquid oral solution or solid oral capsule taken once daily Patients 12 to 17 years of age: matching placebo solid oral capsule taken once daily
Criteria for Evaluation	
Primary Outcome Measure	Bowel movement (BM) characteristic assessments that determine the occurrences of spontaneous bowel movements (SBMs) (ie, BM frequency and rescue medication use) recorded morning and evening in either the patient- or interviewer-administered version of the handheld electronic diary (eDiary)
Key Secondary Outcome Measure	Evening assessment of abdominal pain daytime symptoms as recorded in the eDiary
Safety Measures	Adverse event recording, clinical laboratory tests, vital sign measurements including weight, electrocardiograms, and physical examinations
Pharmacokinetic Analysis	Individual plasma concentrations of linaclotide and its active metabolite (MM-419447) will be listed by patient.
Statistical Methods	<p>The primary efficacy parameter is change from baseline in 4-week overall SBM frequency rate (SBMs/week) during the Treatment Period.</p> <p>No multiplicity adjustment will be applied in this dose-ranging study. To understand the dose-response relationship, a test for linear trend will be performed for the primary efficacy parameter based on the ordinal dosing.</p> <p>The key secondary efficacy parameter is change from baseline in 4-week abdominal pain daytime symptoms based on evening assessments during the Treatment Period. This key secondary efficacy parameter and other change-from-baseline secondary efficacy parameters defined for the Treatment Period will be analyzed in the similar way as the primary efficacy parameter (with A, B, and C linaclotide doses and placebo).</p> <p>All safety parameters will be analyzed descriptively based on the Safety Population, defined as all randomized patients who receive at least 1 dose of double-blind investigational product. All efficacy analyses will be based on the Intent-to-Treat Population, defined as all patients in the Safety Population who have at least 1 postbaseline entry of BM assessments that determine occurrences of SBMs (ie, BM frequency and rescue medication use).</p> <p>The planned sample size is designed for the overall analysis of placebo and A, B, and C linaclotide dose groups, with 58 patients per treatment group (232 patients in total for the overall analysis). With the inclusion of an additional 23 to 31 patients 12 to 17 years of age for the approved adult linaclotide dose, 290 µg, the planned sample size for the study is approximately 260 patients.</p>







3.0 OVERALL TABLE OF CONTENTS

1.0	TITLE PAGE	1
2.0	SYNOPSIS AND SCHEDULE OF EVALUATIONS	2
3.0	OVERALL TABLE OF CONTENTS	7
3.1	LIST OF IN-TEXT TABLES	9
3.2	LIST OF IN-TEXT FIGURES	9
4.0	LIST OF ABBREVIATIONS	10
5.0	ETHICAL CONSIDERATIONS	12
5.1	Institutional Review Board and Independent Ethics Committee	12
5.2	Ethical Conduct of the Study	12
5.3	Patient Information and Informed Consent	13
5.3.1	Patient Assent Form	13
5.3.2	Parent, Legal Guardian, and Legally Authorized Representative/ <i>Caregiver</i> Informed Consent	13
6.0	INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE	15
7.0	INTRODUCTION	16
7.1	Summary of Linaclotide Properties	17
7.2	Clinical Experience	17
7.2.1	Other Information	20
8.0	STUDY OBJECTIVES	21
9.0	INVESTIGATIONAL PLAN	22
9.1	Overall Study Design and Plan: Description	22
9.1.1	Screening Period	22
9.1.2	Pretreatment Period	23
9.1.3	Double-blind Treatment Period	23
9.1.4	Post-treatment Period	24
9.2	Discussion of Study Design, Including the Choice of Control Groups	25
9.3	Selection of Study Population	25
9.3.1	Inclusion Criteria	25
9.3.2	Exclusion Criteria	27
9.3.3	Removal of Patients from Therapy or Assessment	30
9.3.4	Patient Replacement Procedures	31
9.4	Treatments	31
9.4.1	Treatments Administered	32
9.4.1.1	Rescue Medication	32
9.4.2	Identity of Investigational Products	32
9.4.3	Method of Assigning Patients to Treatment Groups	35
9.4.4	Selection of Dosages in the Study	35
9.4.5	Selection and Timing of Dose for Each Patient	36
9.4.6	Blinding	37
9.4.7	Unblinding	37
9.4.8	Prior and Concomitant Therapy	37

9.4.9	Monitoring Treatment Compliance and Accountability	38
9.5	Efficacy and Safety Variables	38
9.5.1	Efficacy Assessments	38
9.5.1.1	Primary Efficacy Assessment	38
9.5.1.2	Key Secondary Efficacy Assessments	40
9.5.1.3	Other Secondary Efficacy Assessments	40
9.5.1.4	Additional Efficacy Assessments	42
9.5.2	Safety Assessments	47
9.5.2.1	Adverse Events [REDACTED]	47
9.5.2.2	Causality Assessment	48
9.5.2.3	Severity Assessment	49
9.5.2.4	Serious Adverse Events	49
9.5.2.5	Reporting Adverse Events and Serious Adverse Events	50
9.5.2.6	Immediate Reporting of Serious Adverse Events [REDACTED]	51
9.5.2.7	Reporting of Pregnancies Occurring During the Study	52
9.5.2.8	Potential Hy's Law Cases	52
9.5.2.9	Clinical Laboratory Determinations	53
9.5.2.10	Vital Signs Including Weight	55
9.5.2.11	Electrocardiograms	55
9.5.2.12	Other Safety Assessments	56
9.5.3	Investigational Product Concentration Measurements	56
9.5.5	Schedule of Assessments	56
9.5.5.1	Screening Period (Visit 1)	57
9.5.5.2	Pretreatment Period (Visit 2)	59
9.5.5.3	Randomization (Visit 3, Day 1)	60
9.5.5.4	Week 2 (Visit 4)	62
9.5.5.5	Week 4 (Visit 5)	62
9.5.5.6	Post-treatment/End-of-Study Visit (Visit 6)	63
9.6	Data Quality Assurance	64
9.6.1	Data Monitoring	64
9.6.2	Data Recording and Documentation	65
9.6.3	Data and Safety Monitoring Board	65
9.7	Statistical Methods and Determination of Sample Size	65
9.7.1	Patient Populations	65
9.7.1.1	Screened Population	66
9.7.1.2	Randomized Population	66
9.7.1.3	Safety Population	66
9.7.1.4	Intent-to-Treat Population	66
9.7.2	Patient Disposition	66
9.7.3	Demographics and Other Baseline Characteristics	67
9.7.5	Efficacy Analyses	68
9.7.5.1	Primary Efficacy Parameter	70
9.7.5.2	Secondary Efficacy Parameter	71
9.7.5.3	Additional Efficacy Parameters	73
9.7.6	Safety Analyses	77
9.7.6.1	Adverse Events	77

	9.7.8	Interim Analysis80
	9.7.9	Determination of Sample Size80
	9.7.10	Computer Methods81
9.8		Changes in the Conduct of the Study or Planned Analyses81
9.9		Protocol Deviations81
10.0		STUDY SPONSORSHIP82
10.1		Study Termination82
10.2		Reporting and Publication82
11.0		INVESTIGATOR OBLIGATIONS83
11.1		Documentation83
11.2		Performance83
11.3		Use of Investigational Materials84
11.4		Case Report Forms84
11.5		Retention and Review of Records84
11.6		Patient Confidentiality85
12.0		INVESTIGATOR'S STATEMENT86
13.0		APPENDICES87
	Appendix I	Elements of Informed Consent87
	Appendix II	Contact Information89
	Appendix III	Concomitant Medications90
14.0		LITERATURE CITED96

3.1 LIST OF IN-TEXT TABLES

Table 9.4.2–1.	Investigational Product Formulation34
Table 9.4.5–1.	Double-blind Dosing Regimen36

3.2 LIST OF IN-TEXT FIGURES

Figure 9.1.4–1.	Study Design24
-----------------	----------------------

4.0 **LIST OF ABBREVIATIONS**

AE	adverse event
ANCOVA	analysis of covariance
β-hCG	beta human chorionic gonadotropin
BM	bowel movement
BP	blood pressure
CFR	Code of Federal Regulations
CI	confidence interval
CIC	chronic idiopathic constipation
CMH	Cochran-Mantel-Haenszel
CSBM	complete spontaneous bowel movement
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram, electrocardiographic
eCRF	electronic case report form
EDC	electronic data capture
eDiary	electronic diary
FC	functional constipation
FDA	Food and Drug Administration
FGID	functional gastrointestinal disorders
FR	Federal Register
GCP	good clinical practice
GI	gastrointestinal
HIPAA	Health Insurance Portability and Accountability Act
HRQL	health-related quality of life
IBS	irritable bowel syndrome

IBS-C	irritable bowel syndrome with constipation
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug (application)
IRB	Institutional Review Board
ITT	intent to treat (Intent-to-Treat Population)
IWRS	interactive Web response system
LAR	legally authorized representative
LSM	least squares means
NDA	New Drug Application
p-BSFS	Pediatric Bristol Stool Form Scale
PCS	potentially clinically significant
PedsQL™	Pediatric Quality of Life Inventory
PID	patient identification
PK	pharmacokinetic
PRO	patient reported outcome
QTcB	QT interval corrected for heart rate using the Bazett formula ($QTcB = QT/(RR)^{1/2}$)
QTcF	QT interval corrected for heart rate using the Fridericia formula ($QTcF = QT/(RR)^{1/3}$)
SAE	serious adverse event
SAP	statistical analysis plan
SBM	spontaneous bowel movement
SOC	system organ class
TEAE	treatment-emergent adverse event
ULN	upper limit of normal

5.0 **ETHICAL CONSIDERATIONS**

5.1 **INSTITUTIONAL REVIEW BOARD AND INDEPENDENT ETHICS COMMITTEE**

United States

Approval by the Institutional Review Board (IRB) before the start of the study will be the responsibility of the Investigator. A copy of the approval letter will be supplied to Forest Research Institute, Inc. (the Sponsor), along with a roster of IRB members or the US Department of Health and Human Services general assurance number. During the course of the study, the Investigator will provide timely and accurate reports to the IRB on the progress of the study, at intervals not exceeding 1 year (or as appropriate), and will notify the IRB of serious adverse events (SAEs) or other significant safety findings. The study protocol, informed consent form (ICF), information sheet advertisements, and amendments (if any) will be approved by the IRBs at the study sites in conformance with the US CFR, Title 21, Part 56.

Outside the United States

If performed outside the United States, this study will be carried out in full compliance with the guidelines of the independent ethics committee (IEC) and government agencies of each respective country as well as the European Union Clinical Trial Directive (Directive 2001/20/EC), where applicable. Before the study begins, the study site will require approval from an IEC and government agency. During the course of the study, the Sponsor or authorized representative will provide timely and accurate reports to the IEC on the progress of the study, at intervals not exceeding 1 year (or as appropriate) and will notify the IEC of SAEs or other significant safety findings. The study protocol, ICF, information sheet advertisements, and amendments (if any) will be approved by the IEC at the study site in conformance with CFR, Title 21, Part 56, the European Union Clinical Trial Directive (Directive 2001/20/EC), and local regulations.

5.2 **ETHICAL CONDUCT OF THE STUDY**

This clinical study will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki.

This clinical study will comply with the ICH Guidance on General Considerations for Clinical Trials (ICH-E8; 62 FR 66113, 17 Dec 1997) and GCP (ICH-E6; 62 FR 25692, 09 May 1997), as well as Part 312 of the US CFR.

5.3 PATIENT INFORMATION AND INFORMED CONSENT

After being given an explanation of the study and before participating in any study procedures, each patient must provide assent, and his or her parent(s), legal guardian(s), or legally authorized representative (LAR) (hereafter referred to as parent/guardian/LAR) must provide voluntary and written informed consent in compliance with 21 CFR, Parts 50 and 312 and give HIPAA authorization (or an equivalent of HIPAA authorization in non-US countries).

The signed documents will be placed in the Investigator's study files. The informed consent statement contains all the elements of informed consent listed in [Appendix I](#) of this protocol. [REDACTED]

5.3.1 Patient Assent Form

To participate in the study, patients will read, assent to an understanding of, sign the assent form, and be made aware they can withdraw from the study at any time. Patients who are unable to read the assent form will have the statements read to them. If the patient cannot sign the form, a witness will be allowed to provide written verification of oral assent. A copy of the signed assent will be given to the patient's parent/guardian/LAR.

5.3.2 Parent, Legal Guardian, and Legally Authorized Representative/Caregiver Informed Consent

Written informed consent will be obtained from the patient's parent/guardian/LAR before the patient participates in any study-related procedure. To provide consent for the patient's participation in the study, the patient's parent/guardian/LAR will read, assent to an understanding of, and sign an instrument of informed consent or other locally applicable regulations and authorization form after having had an opportunity to discuss the forms with the Investigator before signing. The parent/guardian/LAR will be made aware that the patient may withdraw from the study at any time and will receive a copy of the signed ICF. Patients who reach the age of majority (ie, 18 years of age in most jurisdictions) during the course of the study are required to re-consent.

A caregiver is a person identified as able and willing to provide safety and efficacy information about the patient and oversee the administration of investigational product and completion of the daily electronic diary (eDiary), and may be a different individual than the parent/guardian/LAR. The caregiver must commit to accompany the patient to each study visit. To be eligible for the study, the caregiver, whether or not he or she is the parent/guardian/LAR, must read and sign the caregiver consent or a combined parent/legal guardian/caregiver permission ICF document. If the parent/guardian/LAR is the caregiver, he or she will be asked to read and sign both the parent/legal guardian

permission (ICF) and the caregiver consent or a combined parent/legal guardian/caregiver permission (ICF). The parent/guardian/LAR or caregiver who supervises the patient in the completion of the eDiary or administers the interviewer-administered version should be the same individual throughout the course of the study. If a caregiver is replaced during the study, each caregiver must provide separate ICF/caregiver consents and be given a signed copy of his or her caregiver consent.

6.0 **INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE**

This study will be performed at approximately 50 – 100 study sites.

The Investigator is responsible for ensuring that an investigation is conducted according to the signed Investigator statement, the investigational plan, GCP guidelines, and applicable regulations; for protecting the rights, safety, and welfare of patients under the Investigator's care; and for the control of investigational products under investigation. An Investigator shall obtain the informed consent of each human patient prior to the patient enrolling in the study and/or prior to participating in any study-related activity.

The Investigator at each site must meet his or her obligations to the patients, ethics committee, Sponsor, and regulatory authorities by maintaining oversight and control of the study's conduct and the study staff. It is the responsibility of the Investigator to ensure that any and all delegated duties be assigned to qualified staff by education, experience, and licensure (in accordance with local regulations) and that the Investigator oversight is documented and assessment of their capabilities and performance consistent with the study investigational plan. The Investigator at each site will be responsible for the management of the study, including maintaining the study file and the patient records, corresponding with the IRB/IEC, and completing the electronic case report forms (eCRFs).

7.0 INTRODUCTION

Functional gastrointestinal disorders (FGIDs) are common conditions of the digestive system in which symptoms cannot be explained by the presence of structural or tissue abnormalities (Hyams, 1999). The Rome criteria were developed to classify the FGIDS in adults and children based on clinical symptoms.

The most common and best researched FGID is irritable bowel syndrome (IBS) (Sandhu and Paul, 2014). IBS is characterized by abdominal pain and altered bowel symptoms (altered bowel frequency and consistency) (Longstreth et al, 2006). It is a prevalent condition that is associated with a significantly impaired health-related quality of life and reduced work productivity. Prevalence estimates range from 1% to more than 20%, and it is one of the most common disorders managed by gastroenterologists and primary care physicians (Brandt et al, 2009). In the pediatric population, a literature review estimated that 10% to 15% of children and adolescents suffer from IBS (Sandhu and Paul, 2014).

In adults, Rome III criteria has classified IBS with constipation (IBS-C), IBS with diarrhea, mixed IBS, and unsubtyped IBS, depending on the stool consistency (Longstreth et al, 2006). In children, although IBS subtypes are encountered in clinical practice, a classification based on stool consistency has not been specified (Sandhu and Paul, 2014). Such classification is important as the management will, in part, depend on the presenting stool pattern.

Functional constipation (FC) is another common FGID in childhood, with an estimated prevalence of 3% worldwide. It is often associated with infrequent and/or painful defecation, fecal incontinence, and abdominal pain. Rome III criteria (for children and adolescents) distinguish FC and IBS by requiring that children with FC have insufficient criteria for a diagnosis of IBS.

Given the overlap of clinical presentation between IBS-C and FC, the Sponsor integrated the diagnostic criteria for IBS with diagnostic criteria for FC to create a pediatric IBS-C subtype classification. Therefore, we defined childhood IBS-C as fulfilling Rome III criteria for child/adolescent IBS and modified Rome III criteria for child/adolescent FC.

IBS no longer remains a condition thought to affect only adults and adolescents and is being increasingly recognized as a common condition in young children. As there is no FDA-approved drug for pediatric IBS, well-planned, randomized, placebo-controlled evaluations of pharmacological therapies in children are needed (Sandhu and Paul, 2014).

7.1 SUMMARY OF LINACLOTIDE PROPERTIES

Linacotide, a 14-amino acid peptide that acts on the apical surface of epithelial cells in the intestinal lumen to stimulate guanylate cyclase subtype C, is approved in the United States for the treatment of adults with IBS-C and with chronic idiopathic constipation (CIC) ([Linzess, 2015](#)) and in the European Union for moderate to severe IBS-C. By activating guanylate cyclase subtype C, orally administered linacotide has been found to increase both intestinal fluid secretion and intestinal transit and to also decrease visceral pain in animal models. Linacotide has minimal oral bioavailability ($\leq 0.2\%$) in several animal species ([Bryant et al, 2010](#); [Eutamene et al, 2010](#)). Refer to the Investigator's Brochure for a more detailed description of the chemistry, pharmacology, efficacy, and safety of linacotide, based on studies conducted in animals, healthy volunteers, and in adult patients with IBS-C and CIC ([Investigator's Brochure, 2016](#)).

7.2 CLINICAL EXPERIENCE

Linacotide has been developed by the Sponsor and Ironwood Pharmaceuticals, Inc. for the treatment of CIC and IBS-C in adults. The clinical development program for linacotide that culminated in FDA and European Medicines Agency approvals included the following North American studies in adult patients:

- 4 large double-blind, placebo-controlled Phase 3 registration studies (2 IBS-C studies [[LIN-MD-31](#) and [MCP-103-302](#)] and 2 CIC studies [[LIN-MD-01](#) and [MCP-103-303](#)])
- 2 long-term safety studies ([LIN-MD-02](#) and [MCP-103-305](#)), each with 78-week treatment periods

In addition, 2 randomized, double-blind, placebo-controlled, parallel-group, North American studies: Phase 3b study ([LIN-MD-04](#)) and Phase 3 study ([MCP-103-309](#)) have been completed.

The 2 IBS-C studies ([LIN-MD-31](#) and [MCP-103-302](#)) evaluated the safety and efficacy of linacotide 290 ug (the adult dose subsequently approved by FDA) administered as a solid oral capsule for 12 or 26 weeks, respectively. In these studies, linacotide demonstrated statistically significant and clinically meaningful improvements in patients' constipation symptoms and abdominal pain, and met all the pre-specified primary and secondary endpoints. Study [MCP-103-302](#) demonstrated improvement in abdominal and bowel symptoms at 12 weeks that was maintained throughout 26 weeks of treatment. Study [LIN-MD-31](#) included a 4-week double-blind, randomized withdrawal period immediately following the 12-week treatment period to assess the potential for rebound worsening bowel or abdominal symptoms. The results from the randomized withdrawal period showed that there was no evidence of development of tolerance, nor was there evidence of rebound worsening of bowel or abdominal symptoms relative to baseline once the linacotide was discontinued. The most common adverse event (AE) was diarrhea occurring in approximately 20% of IBS-C patients in both studies. Overall,

there was no obvious pattern in the types of SAEs experienced in either the placebo or linaclotide group. There were no SAEs of diarrhea.

The 2 CIC studies ([LIN-MD-01](#) and [MCP-103-303](#)) evaluated the safety and efficacy of linaclotide 145 ug (the adult dose subsequently approved by FDA for this indication) and linaclotide 290 ug administered as solid oral capsules. Both the 145-ug and 290-ug doses demonstrated statistically significant and clinically meaningful improvement in constipation and abdominal symptoms, and met all pre-specified primary and secondary endpoints. The most common AE in CIC patients was diarrhea occurring in 16% of patients treated with the 145-ug dose, and 14.2% of patients treated with the 290 ug dose. There were no SAEs of diarrhea although diarrhea was reported in 1 patient along with SAEs of dehydration and orthostatic hypotension. There were no clinically relevant differences between the 2 linaclotide dose groups in the incidence of diarrhea treatment-emergent adverse events (TEAEs), severe diarrhea TEAEs, or diarrhea that resulted in discontinuation from the studies.

[REDACTED]

[REDACTED]

Long-term studies [LIN-MD-02](#) and [MCP-103-305](#) included 78-week treatment periods to evaluate the long-term safety of linaclotide in IBS-C and CIC adult patients. Both studies included patients who completed 1 of the linaclotide Phase 2 or 3 studies, or completed the Pretreatment Period of 1 of the Phase 3 double-blind studies, but failed to meet specific inclusion or exclusion criteria to be randomized.

[REDACTED]

In both Study

MCP-103-305 and Study LIN-MD-02, the most commonly reported AE was diarrhea, which occurred in approximately 30% of CIC patients and IBS-C patients in both studies. Neither study reported SAEs of diarrhea.

The completed Phase 3b study (LIN-MD-04) was a randomized, double-blind, placebo-controlled, parallel-group, study. Linaclotide at doses of 145 ug/day and 290 ug/day was administered orally for 12 weeks to 487 randomized adult patients with CIC and prominent abdominal bloating at baseline (ie, bloating ≥ 5.0 on an 11-point numerical rating scale. No new safety trends or concerns were identified. There were no deaths during the study and no SAEs of diarrhea.

The completed Phase 3 study (MCP-103-309) was a randomized, double-blind, placebo-controlled, parallel-group study in patients with CIC at baseline. Linaclotide at doses of 72 ug/day and 145 ug/day was administered orally for 12 weeks to 1223 randomized adult patients. No new safety trends or concerns were identified. There were no deaths during the study and no SAEs of diarrhea. One patient in the linaclotide 145-ug group experienced an SAE of colitis that was considered by the investigator to be possibly related to study drug.

Safety data from these studies in adults showed that, except for diarrhea, the proportion of patients reporting a TEAE was similar between placebo and, in the CIC studies, each linaclotide dose group, and the incidence of TEAEs was not dose-related. With the exception of the gastrointestinal (GI) system organ class (SOC), the occurrence of TEAEs in the CIC and IBS-C patients was balanced across treatment groups in each SOC for the adult Phase 3 placebo-controlled studies. Diarrhea was the most common TEAE in linaclotide-treated CIC and IBS-C patients, consistent with its pharmacology; however diarrhea was rarely associated with serious sequelae such as dehydration, fecal incontinence, or defecation urgency.

SAEs were infrequent and balanced across treatment arms within each indication. An analysis of the SAEs across the entire clinical development program revealed no pattern to suggest that linaclotide causes any specific serious condition.

Minor abnormalities in laboratory, vital sign, or ECG parameters were observed rarely; overall, there were no clinically meaningful differences between linaclotide and placebo treatment groups for any of these parameters in the Phase 3 placebo-controlled studies in adults.

The following registration studies were conducted outside of North America:

- ICP-103-307: A Phase 3 international, multicenter, randomized, double-blind, placebo-controlled, parallel-group efficacy and safety trial of linaclotide orally administered once daily for 12 weeks to patients with IBS-C in China, Australia, New Zealand, the US, and Canada. A total of 839 patients were randomized into 1 of 2 treatment groups: linaclotide 290 ug (417 patients) or placebo (422 patients)

- 0456-CL-0031: A 2-part study, Part 1 was a multicenter, randomized, double-blind, placebo-controlled, parallel-group Phase 3 trial of linaclotide orally administered once daily for 12 weeks to patients with IBS-C in Japan. [REDACTED]

Both IBS-C studies evaluated the safety and efficacy of double-blind linaclotide administered as a solid oral capsule for 12 weeks. In these studies, linaclotide demonstrated statistically significant and clinically meaningful improvements in patients' constipation symptoms and abdominal pain, and met all the prespecified primary endpoints. Statistically significant improvements were achieved for linaclotide versus placebo in multiple prespecified abdominal and bowel symptom secondary endpoints, including bloating and abdominal pain/discomfort. The most common adverse event (AE) was diarrhea, which occurred in 9-12% of linaclotide patients. Overall, there was no obvious pattern in the types of SAEs experienced in either the placebo or linaclotide groups. There were no SAEs of diarrhea.

7.2.1 Other Information

Linaclotide is contraindicated in pediatric patients up to 6 years of age. This is because in nonclinical studies, administration of a single, clinically relevant adult oral dose of linaclotide caused deaths due to dehydration in young (Day 7 postpartum) juvenile mice. Supplemental subcutaneous fluid administration prevented death after linaclotide administration in neonatal mice, and significantly higher doses (≥ 10 times the clinically relevant adult dose) were tolerated in older juvenile mice without supplemental fluid administration.

In post-marketing experience, severe diarrhea AEs associated with dizziness, syncope, hypotension and electrolyte abnormalities (hypokalemia and hyponatremia) requiring hospitalization or intravenous fluid administration have been reported in patients treated with linaclotide.

This study will be the first to evaluate the safety and efficacy of linaclotide relative to placebo in pediatric patients, 7 to 17 years of age, with IBS-C.

8.0 **STUDY OBJECTIVES**

The objective of this study is to evaluate the dose response, safety, and efficacy of 4 weeks of treatment with 1 of 3 linaclotide doses (A, B, or C) or 290 ug (as an exploratory objective in the adolescent patients 12 - 17 years of age using the approved adult dose) compared with placebo in pediatric patients 7 to 17 years of age who fulfill the Rome III criteria for child/adolescent IBS and modified Rome III criteria for child/adolescent FC.

9.0 **INVESTIGATIONAL PLAN**

9.1 **OVERALL STUDY DESIGN AND PLAN: DESCRIPTION**

This clinical study will be a multicenter, randomized, double-blind, placebo-controlled, parallel-group, safety and efficacy study comparing 1 of 3 linaclotide doses (A, B, and C) or 290 ug (only patients 12 - 17 years of age) with placebo in pediatric patients, 7 to 17 years of age, with a diagnosis of IBS-C based on Rome III child/adolescent criteria (ie, fulfill Rome III criteria for child/adolescent IBS and fulfill modified Rome III criteria for child/adolescent FC). The study will include a total of 6 visits and will be approximately 9 to 12 weeks in duration (Figure 9.1.4–1). Approximately 260 patients with IBS-C will be enrolled in this study.

- Screening Period (14 to 28 days)
- Pretreatment Period (14 to 21 days)
- Double-blind Treatment Period (hereinafter referred to as Treatment Period) (at least 28 days [4 weeks] on treatment)
- Post-treatment Period (at least 7 days [1 week] after the Week 4 End-of-Treatment Visit)



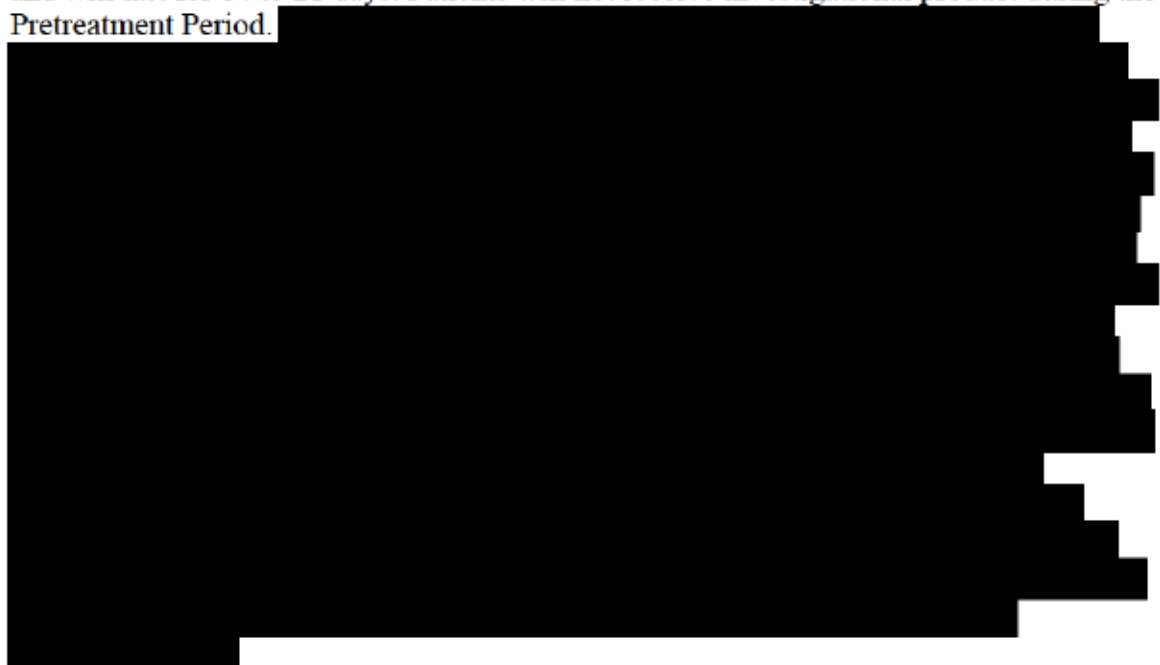
9.1.1 **Screening Period**

After obtaining assent and informed consent (Section 5.3), patient eligibility for entry into the study will be determined (Sections 9.3.1 and 9.3.2). The Screening Period will begin up to 7 weeks before Randomization (Visit 3/Day 1) and will last for 14 to 28 days. Patients will not receive any investigational product during the Screening Period.



9.1.2 Pretreatment Period

The Pretreatment Period will occur up to 3 weeks before Randomization (Visit 3/Day 1) and will last for 14 to 21 days. Patients will not receive investigational product during the Pretreatment Period.



9.1.3 Double-blind Treatment Period

Patients will complete at least 4 weeks of investigational product treatment during the Double-blind Treatment Period (referred to as Treatment Period). Three study visits will occur during the Treatment Period: a Randomization Visit (Visit 3/Day 1), a Week 2 Visit (Visit 4, approximately Day 15) and a Week 4 End-of-Treatment-Period Visit (Visit 5, approximately Day 29). Randomization will occur on the first day of the Treatment Period. Based on randomization, patients will receive placebo or linaclotide. The first dose of investigational product will be administered at the study site following randomization (Visit 3/Day 1).

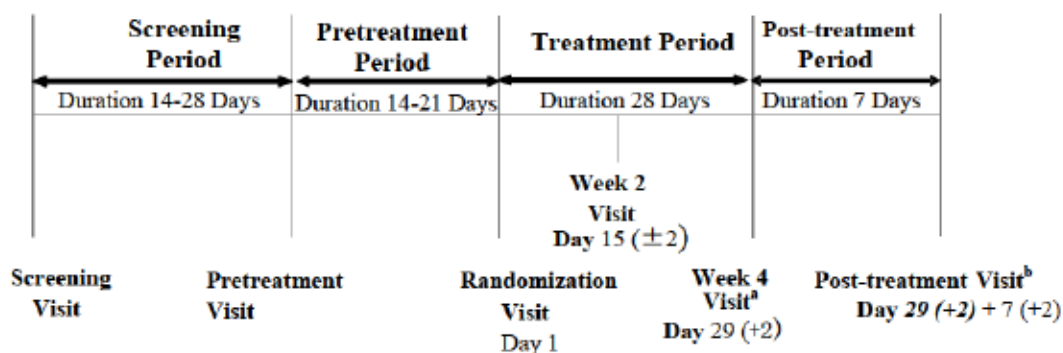


9.1.4 Post-treatment Period

The End-of-Study Visit (Visit 6/Post-treatment Visit) must occur at least 7 days after the Week 4 Visit (Visit 5). Patients will not receive investigational product during the Post-treatment Period, but will continue to complete the eDiary twice daily throughout the Post-treatment Period.

The figure below provides a schematic of the study design. The Schedule of Evaluations is presented in Section 2.0. Detailed descriptions of each study visit can be found in Section 9.5.1.

Figure 9.1.4–1. Study Design



Note: There is no Day 0.

a The patient must complete at least 4 weeks (28 days) of treatment before arriving at the study site for the Week 4 Visit.

b The Post-treatment Visit has to be at least 7 days after the Week 4 Visit.

9.2 DISCUSSION OF STUDY DESIGN, INCLUDING THE CHOICE OF CONTROL GROUPS

A multicenter, randomized, double-blind, placebo-controlled, parallel-group, safety and efficacy dose-ranging study design was chosen based on prior studies that established linaclotide efficacy and safety in adult patients with IBS-C. Additionally, this study was designed with reference to the FDA Guidance for Industry E11 Clinical Investigation of Medicinal Products in the Pediatric Population. In this pediatric study, Investigators will enroll patients 7 to 17 years of age with a diagnosis of IBS-C based on Rome III criteria for child/adolescent IBS and modified Rome III criteria for child/adolescent FC.

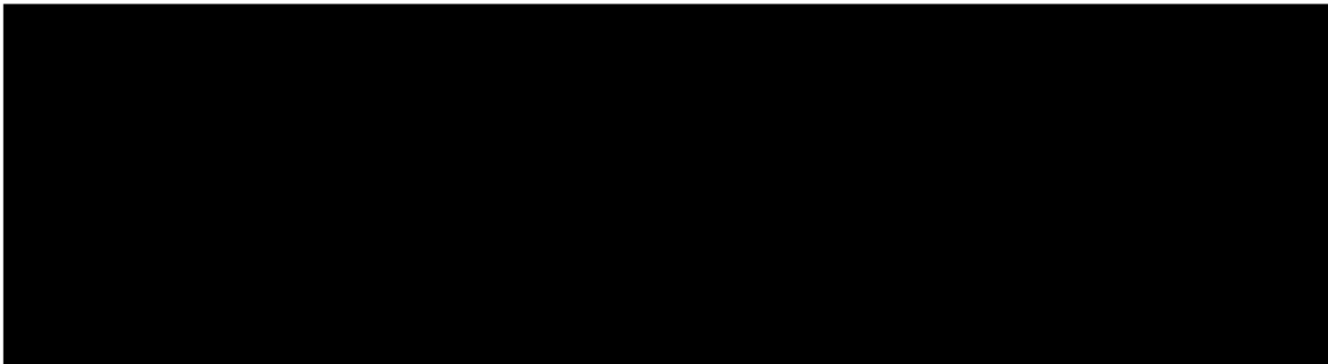
The linaclotide doses selected for use in this study were based on prior studies in adult patients with IBS-C, current product labeling for the treatment of IBS-C and/or CIC in North America (ie, US, Canada, and Mexico for both indications in adult patients) and the European Union (IBS-C only in adult patients), and communications with the FDA.

9.3 SELECTION OF STUDY POPULATION

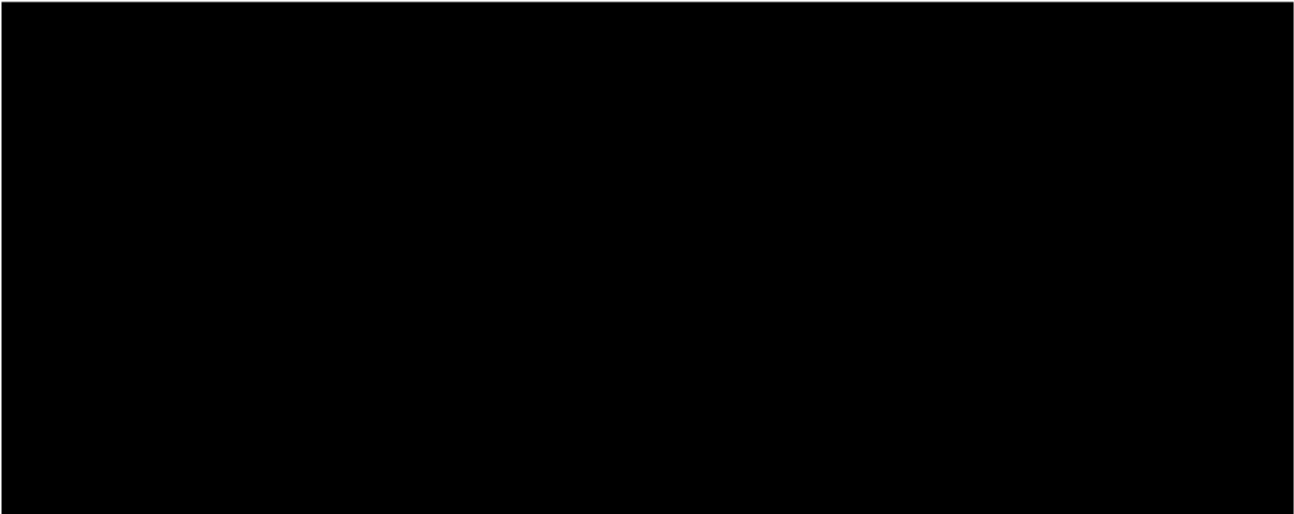
9.3.1 Inclusion Criteria

To be eligible to participate in the study, patients must meet the following criteria:

1. Patient must provide written or verbal informed assent and the parent/guardian/LAR and caregiver must provide written informed consent before the initiation of any study-specific procedures (Section 5.3)
2. Patient is a male or female outpatient, weighing ≥ 18 kg, 7 to 17 years of age (inclusive) at the time the patient provides assent for the study and parent/guardian/LAR has provided signed consent



- 
6. Patient meets Rome III criteria for child/adolescent IBS: at least once per week for at least 2 months before the Screening Visit, the patient experienced abdominal discomfort (an uncomfortable sensation not described as pain) or pain associated with 2 or more of the following at least 25% of the time:
 - a. Improvement with defecation
 - b. Onset associated with a change in frequency of stool
 - c. Onset associated with a change in form (appearance) of stool
 7. Patient meets modified Rome III criteria for child/adolescent FC: For at least 2 months before the Screening Visit, the patient has had 2 or fewer defecations (with each defecation occurring in the absence of any laxative, suppository, or enema use during the preceding 24 hours) in the toilet per week

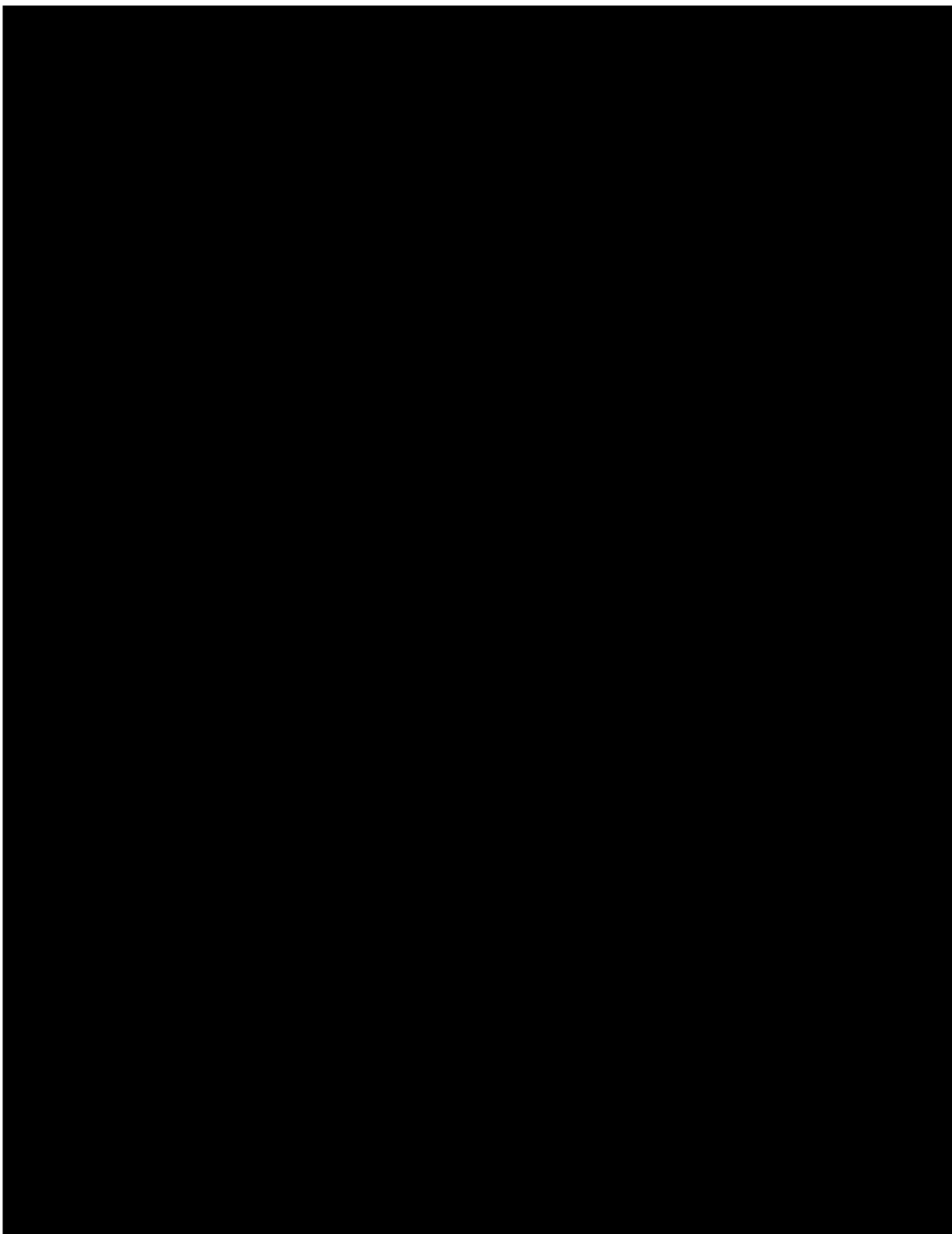
In addition, at least once per week, patient meets 1 or more of the following:
 - a. History of retentive posturing or excessive volitional stool retention
 - b. History of painful or hard bowel movements (BMs)
 - c. Presence of a large fecal mass in the rectum
 - d. History of large diameter stools that may obstruct the toilet
 - e. *At least one episode of fecal incontinence per week*
 8. Patient is willing to discontinue any laxatives used before the Pretreatment Visit in favor of the protocol-permitted rescue medicine ([Appendix III](#))

- 
11. Patient has an average of fewer than 3 spontaneous BMs (SBMs) per week during the 14 days before the randomization day and up to the randomization (including the morning eDiary assessments reported before administration of first dose of double-blind investigational product on the randomization day). An SBM is defined as a BM that occurs in the absence of laxative, enema, or suppository use on the calendar day of the BM or the calendar day before the BM
 12. Patient or parent/guardian/LAR or caregiver is compliant with eDiary by completing both the morning and evening assessments for **10** out of the 14 days immediately preceding the Randomization Visit (Section 9.1.2)

9.3.2 Exclusion Criteria

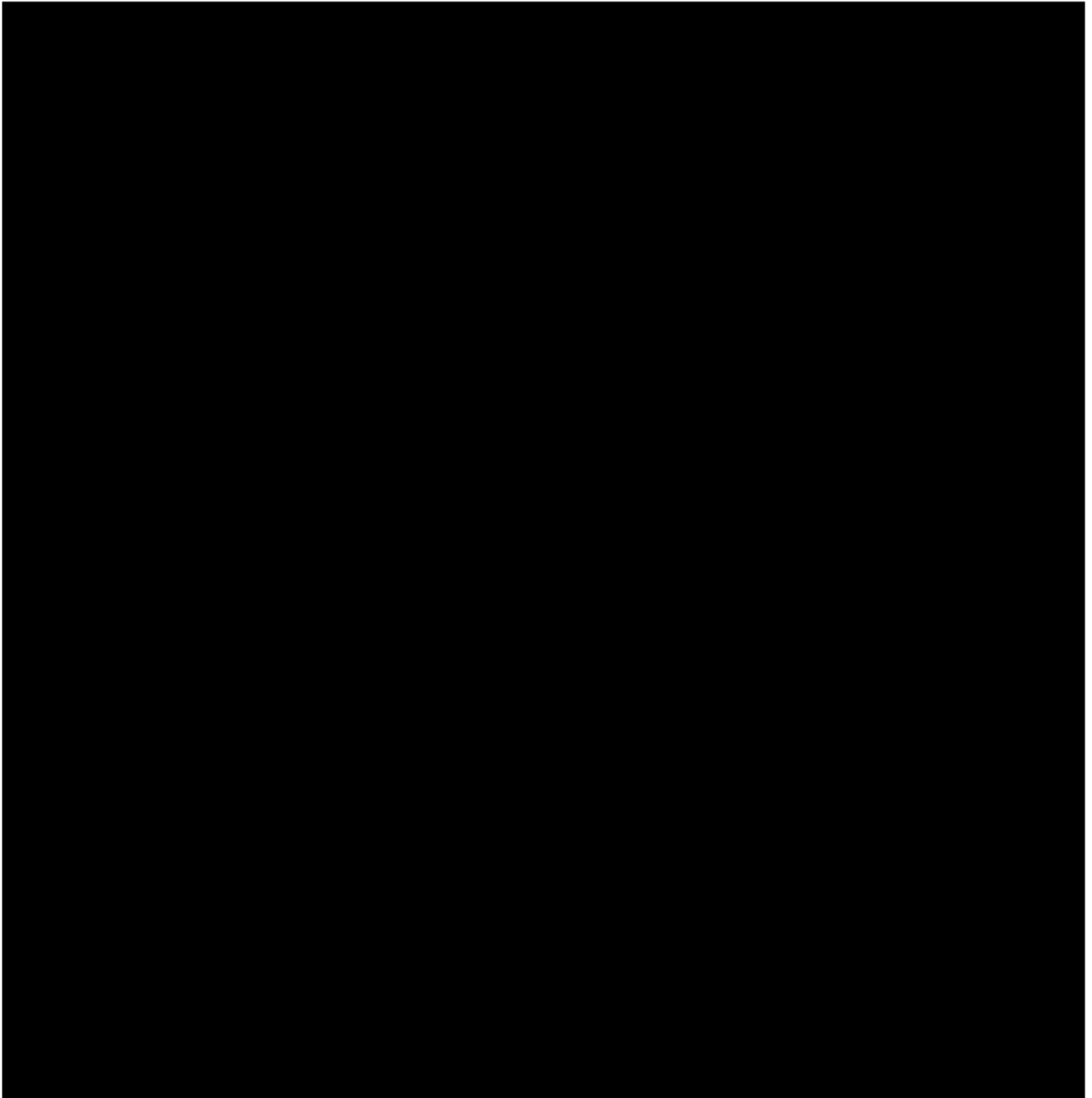
Patients who meet any of the following criteria will not be eligible to participate in the study:

1. Patient reports having more than 1 loose, mushy stool (eDiary-recorded stool consistency of 6 on the Pediatric Bristol Stool Form Scale [p-BSFS]) or any watery stool (eDiary-recorded stool consistency of 7 on the p-BSFS) with any SBM that occurred in the absence of laxative use on the calendar day of the BM or the calendar day before the BM during the 14 days before the randomization day and up to the randomization
- 
- 





6. Patient has required manual disimpaction anytime prior to randomization or disimpaction during in-patient hospitalization within 1 year prior to randomization



[REDACTED]

16. Patient is unable to tolerate the placebo prior to randomization

[REDACTED]

9.3.3 Removal of Patients from Therapy or Assessment

A premature discontinuation will occur when a patient who gave voluntary assent and whose parent/guardian/LAR and caregiver gave consent ceases participation in the study, regardless of circumstances, before the completion of the study visits and procedures. Patients will be prematurely discontinued from the study for reasons of safety including those who experience an SAE considered by the Investigator or the Sponsor to be related to investigational product. Patients will also be prematurely discontinued from the study for evidence of significant volume depletion and/or significant electrolyte and/or ECG abnormalities that are considered by the Investigator or Sponsor to be related to diarrhea related to the investigational product [REDACTED].

[REDACTED]. The Investigator should contact the Study Physician if there is any question whether the criteria for an AE [REDACTED] have been met and the patient should be discontinued from the study.

Patients can also be prematurely discontinued from the study after careful consideration for one of the following reasons:

- Screen failure (failure to meet inclusion/exclusion criteria)
- Withdrawal of consent
- AE
- Lack of efficacy
- Protocol violation
- Noncompliance with investigational product
- Lost to follow-up

- Study terminated by Sponsor
- Site terminated by Sponsor
- Other

All randomized patients who prematurely discontinue from the study, regardless of cause, should be seen for the assessments to be completed at the End-of-Treatment Visit (Week 4/Visit 5). The end-of-treatment assessments are defined as completion of the evaluations scheduled for all patients at Week 4 (Visit 5). In addition to the end-of-treatment assessments, all patients discontinuing the study prematurely should enter the Post-treatment Period and complete a Post-treatment Visit (Visit 6).

Patients who discontinue from the study and do not return to the study site for Visit 5 and/or Visit 6 must be requested in writing to return to the study site for procedures in Visit 5 or Visit 6 and return any unused investigational product and the handheld eDiary. A copy of the letter, together with the source documentation, will be kept in the Investigator's files. The reason for premature discontinuation from the study will be recorded on the Study Termination Page of the eCRF. Study site staff will be contacted by the Sponsor after each premature discontinuation to ensure proper characterization of the reason for discontinuation is captured.

9.3.4 Patient Replacement Procedures

Patients in this study who prematurely discontinue treatment will not be replaced.

9.4 TREATMENTS

Patients meeting the eligibility criteria during Visit 3 (Day 1) will be randomized in a double-blind fashion to linaclotide or placebo ([Table 9.4.5–1](#)).

Randomization will be stratified by age group:

- Patients 7 to 11 years of age will be randomized to linaclotide doses (A, B, or C) or placebo in a 1:1:1:1 allocation
- Patients 12 to 17 years of age will be randomized to linaclotide doses (A, B, or C, or the approved adult dose, 290 ug) or placebo in a 1:1:1:1:1 allocation

9.4.1 Treatments Administered

Investigational product in the form of liquid oral solution or solid oral capsules will be packaged in bottles and provided by the Sponsor. Patients will be supplied with blinded investigational product and will be instructed to take their assigned dose orally, once daily as a single dose. [REDACTED]

9.4.1.1 Rescue Medication

During the Pretreatment and Treatment Periods, a patient may use dispensed, protocol-permitted laxatives as rescue medication [REDACTED]

Protocol-permitted rescue medication will be a choice of senna (oral) or bisacodyl (oral or rectal) that will be dispensed according to the [Schedule of Evaluations](#) (Section 2.0). [REDACTED]

9.4.2 Identity of Investigational Products

All investigational product (linaclotide and placebo) will be supplied to the site by the Sponsor. [REDACTED]

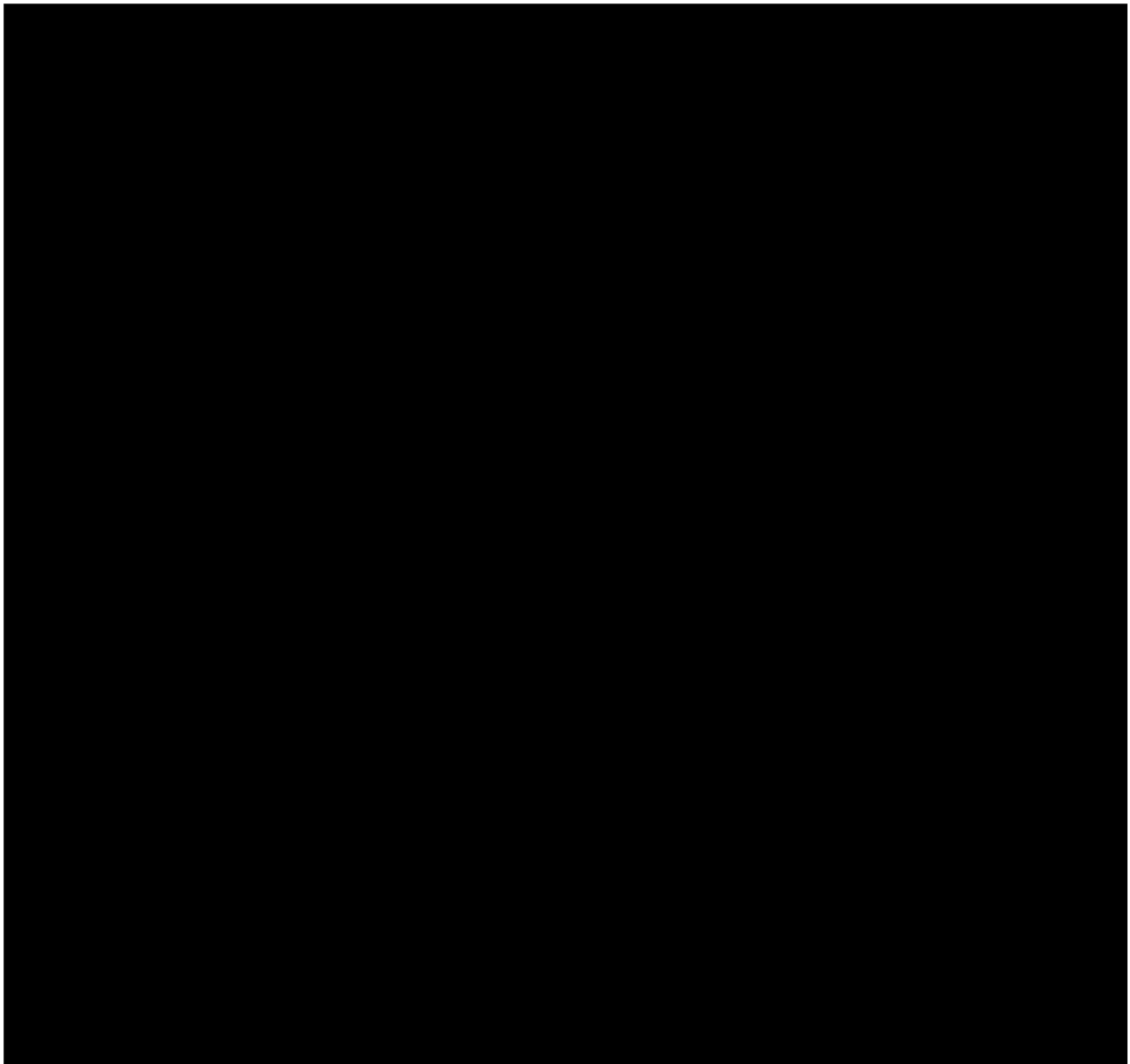
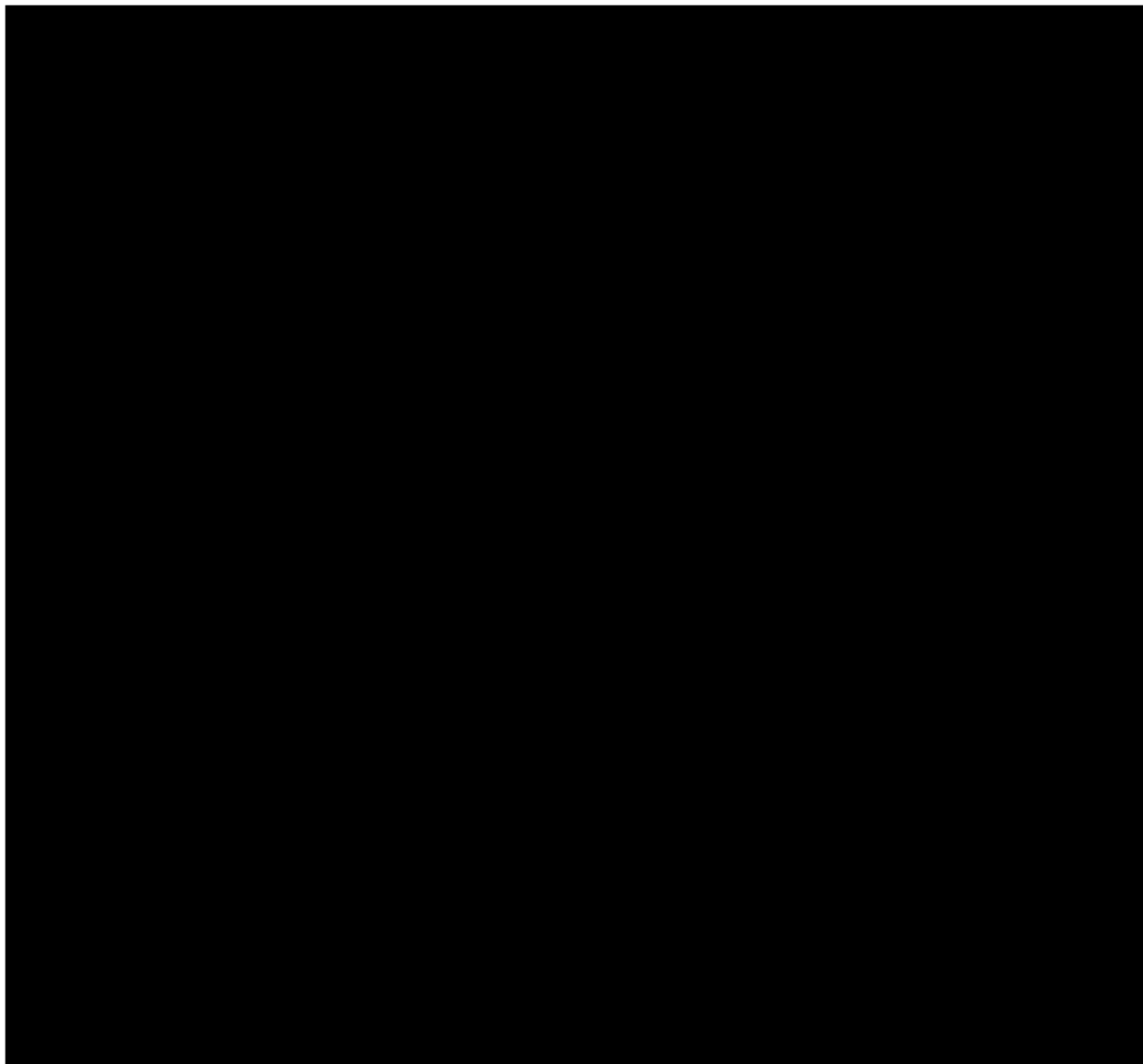
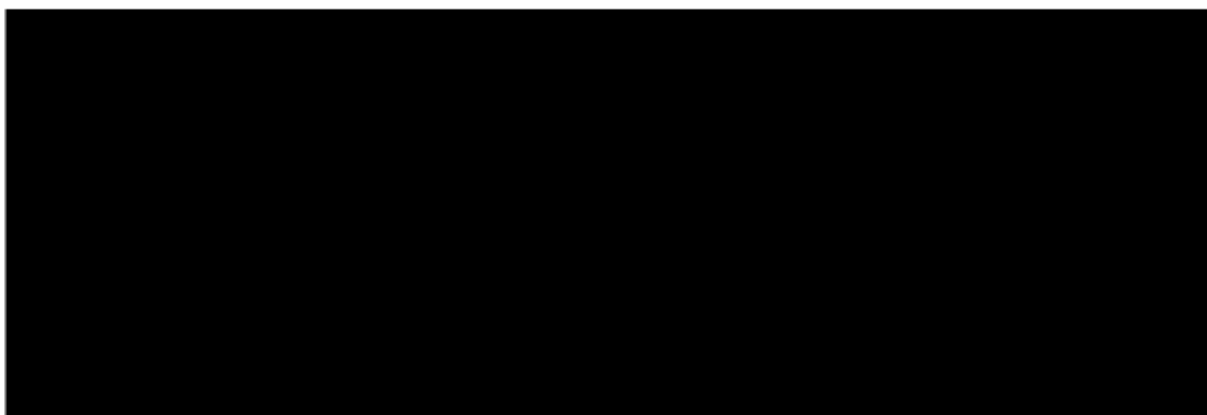


Table 9.4.2-1. Investigational Product Formulation





9.4.3 Method of Assigning Patients to Treatment Groups

After a patient and parent/LAR/caregiver signs the assent/permission/consent at the first Screening Visit (Visit 1), study personnel will register the patient



9.4.4 Selection of Dosages in the Study

The doses chosen for this dose-ranging pediatric study are based on results obtained in the adult linaclotide clinical development program. In the adult program, 290 ug once daily was approved for IBS-C. Pediatric patients 7 to 11 years of age will be dosed using a weight-based approach; patients will receive 1 of 3 linaclotide doses. For patients weighing < 35 kg, the doses administered will correspond to about 0.5 to 1, 1 to 2, or 2 to 4 ug/kg. For patients weighing \geq 35 kg, the doses will not exceed 1, 2, or 4 ug/kg. Pediatric patients 12 to 17 years of age will receive 1 of 4 linaclotide doses. The approved adult dose, 290 ug for IBS-C, will be evaluated to obtain safety data in older pediatric patients ([Table 9.4.5–1](#)).

9.4.5 Selection and Timing of Dose for Each Patient

All investigational products will be administered orally as a single daily dose, [REDACTED]

Dosage will be determined by weight for patients 7 to 11 years of age (18 to < 35 kg or ≥ 35 kg) (Table 9.4.5–1).

Table 9.4.5–1. Double-blind Dosing Regimen

Age Group	Weight	4-Week Treatment Period			
		Linacotide Dose A	Linacotide Dose B	Linacotide Dose C	Approved Adult Dose
Patients 7 - 11 years ^a					
	18 - < 35 kg	18 ug	36 ug	72 ug	—
		placebo	placebo	placebo	—
	≥ 35 kg	36 ug	72 ug	145 ug	—
		placebo	placebo	placebo	—
Patients 12 - 17 years ^b					
		36 ug	72 ug	145 ug	290 ug ^c
		placebo	placebo	placebo	placebo

a Patients 7 to 11 years of age will receive linacotide or placebo in a liquid oral solution or solid oral capsules.

b Patients 12 to 17 years of age will receive linacotide or placebo in a solid oral capsule.

c Approved adult dose is for safety and exploratory efficacy only.

The Investigator may allow a patient to stop taking investigational product for up to 3 days because of an intolerable AE. If the Investigator believes that the patient is unable to resume dosing after 3 days, or requires a suspension of dosing on more than 1 occasion, the Investigator is required to contact the Study Physician to discuss the patient's continued participation in the study.

9.4.6 Blinding

A list of patient randomization codes will be generated by Statistical Programming and implemented by the IWRS vendor (an electronic version will be stored on a secure server). This list will identify each patient by randomization number and include the patient's corresponding treatment assignment.

9.4.7 Unblinding

Any unblinding at the study site level should be done only in an emergency that requires the investigational product to be identified for the medical management of the patient.

[REDACTED]

[REDACTED]

[REDACTED]

9.4.8 Prior and Concomitant Therapy

A list of example medications that are allowed and not allowed as concomitant medications for either episodic or chronic use is provided in [Appendix III](#). Medication history during the previous 3 months will be recorded at Screening (Visit 1) in the eCRF. Thereafter, any changes in concomitant medications or any new medications (other than dispensed, protocol-permitted rescue medications) will be recorded in the eCRF.

9.4.9 Monitoring Treatment Compliance and Accountability

Investigational product accountability and compliance during any period will be closely monitored.

[REDACTED]

Treatment compliance will be assessed through patient/caregiver and study site staff discussion at study visits and recorded on the eCRF. Every effort will be made to collect all unused investigational product at the final visit. .

9.5 EFFICACY AND SAFETY VARIABLES

9.5.1 Efficacy Assessments

All efficacy assessments will be determined by responses entered in the eDiary twice daily (morning and evening). Patients and caregivers must be able to read and/or understand the eDiary as a condition for study participation (inclusion criterion 3). If the patient is 7 to 11 years of age and has difficulty reading and understanding the eDiary without help, the interviewer-administered version of the eDiary must be used and the parent/guardian/LAR or caregiver who will be administering the interviewer-administered version of the eDiary must undergo training. At the start of the Pretreatment Period, patients and caregivers will receive full training in the use and completion of the eDiary at the study visit in which they are given the eDiary. The parent/guardian/LAR or caregiver who supervises the patient in the completion of the eDiary or administers the interviewer-administered version should be the same individual throughout the course of the study (Section 5.3.2).

9.5.1.1 Primary Efficacy Assessment

The primary efficacy assessments used to determine the change from baseline in 4-week overall SBM frequency rate during the Treatment Period (primary efficacy parameter) are the occurrences of SBMs (ie, BM frequency and rescue medication use) determined by the overall assessment of BM frequency as recorded in the eDiary. A SBM is a BM that occurs in the absence of laxative, suppository, or enema use on the calendar day of the BM or the calendar day before the BM. Patients will report their BM frequency (the number of BMs each day) and report their use of rescue medication by responding to the following:

Bowel Movement Frequency

- Morning eDiary

From bedtime last night until now, how many times did you poop (and poop came out)?

- Enter number of times

- Evening eDiary

From when you got up this morning until now, how many times did you poop (and poop came out)?

- Enter number of times

If response is > 0 BMs, then the patient answers the following question for each BM reported:

When did you poop today?

- In the morning (from when you woke up until lunch)
- In the afternoon (from lunch until dinner)
- In the evening (from dinner until bedtime)
- I don't know

Rescue Medication Use

- Morning eDiary

From bedtime last night until now, did you take any medicine to help you poop, other than the study medicine?

- Yes
- No

- Evening eDiary

From when you got up this morning until now, did you take any medicine to help you poop, other than the study medicine?

- Yes
- No

If the response is 'yes', then the patient answers the following question:

When did you take the medicine (NOT your study medicine) to help you poop?

- In the morning (from when you woke up until lunch)
- In the afternoon (from lunch until dinner)
- In the evening (from dinner until bedtime)
- I don't know

9.5.1.2 *Key Secondary Efficacy Assessments*

In addition to the primary efficacy assessment, the key secondary efficacy parameter (the change from baseline in 4-week abdominal pain daytime symptoms) will be determined by the evening assessment of abdominal pain as recorded in the eDiary. For this parameter, patients will rate their abdominal pain by responding to the following:

Abdominal Pain - Daytime

- From when you got up this morning until now, did your tummy hurt at all?
 - Yes
 - No

If “yes”, then patient answers the following question:

- How much did your tummy hurt?
 - 1 = a tiny bit
 - 2 = a little
 - 3 = some
 - 4 = a lot

9.5.1.3 *Other Secondary Efficacy Assessments*

Other secondary efficacy assessments are included in the study regarding BM characteristics and abdominal symptoms that will be determined by the twice daily assessments recorded in the eDiary.

The following BM characteristics will be assessed for each BM reported in the morning and evening eDiaries:

Stool Consistency (Pediatric Bristol Stool Form Scale)

Stool consistency of each BM will be based on the p-BSFS ([Appendix V](#)). The BSFS is a well-accepted and widely used measurement of stool consistency ([Lewis and Heaton, 1997](#)). The p-BSFS was developed by the Sponsor and Ironwood Pharmaceuticals based on the original BSFS and was refined based on qualitative research with pediatric patients with FC and IBS-C. Patients will use the p-BSFS 7-point ordinal scale to rate their stool consistency:

"Use the card provided to choose the poop that is most like the poop you had."

Type 1 = looks like small hard lumps or balls, like pebbles

Type 2 = looks like fat sausage shape but lumpy and hard

Type 3 = looks like a sausage but with cracks on it

Type 4 = looks like a sausage or snake, smooth and soft

Type 5 = looks like chicken nuggets, soft smooth blobs

Type 6 = looks like oatmeal, fluffy mushy pieces

Type 7 = looks like a milkshake, watery

99 - I don't know

Straining With Bowel Movement

Patients will assess the degree of straining by responding to the following:

- When you pooped, how hard did you push?
 - 0 = not hard at all
 - 1 = I pushed a tiny bit hard
 - 2 = I pushed a little hard
 - 3 = I pushed hard
 - 4 = I pushed very hard

Complete Spontaneous Bowel Movement/Incomplete Evacuation

A complete spontaneous bowel movement (CSBM) is an SBM that is associated with a sense of complete evacuation. Patients will record their assessment of the sensation of incomplete evacuation by responding to the following:

- When you pooped, did it feel like there was more poop left inside that didn't come out?
 - Yes
 - No

The following abdominal symptoms will be assessed:

Abdominal Bloating - Daytime

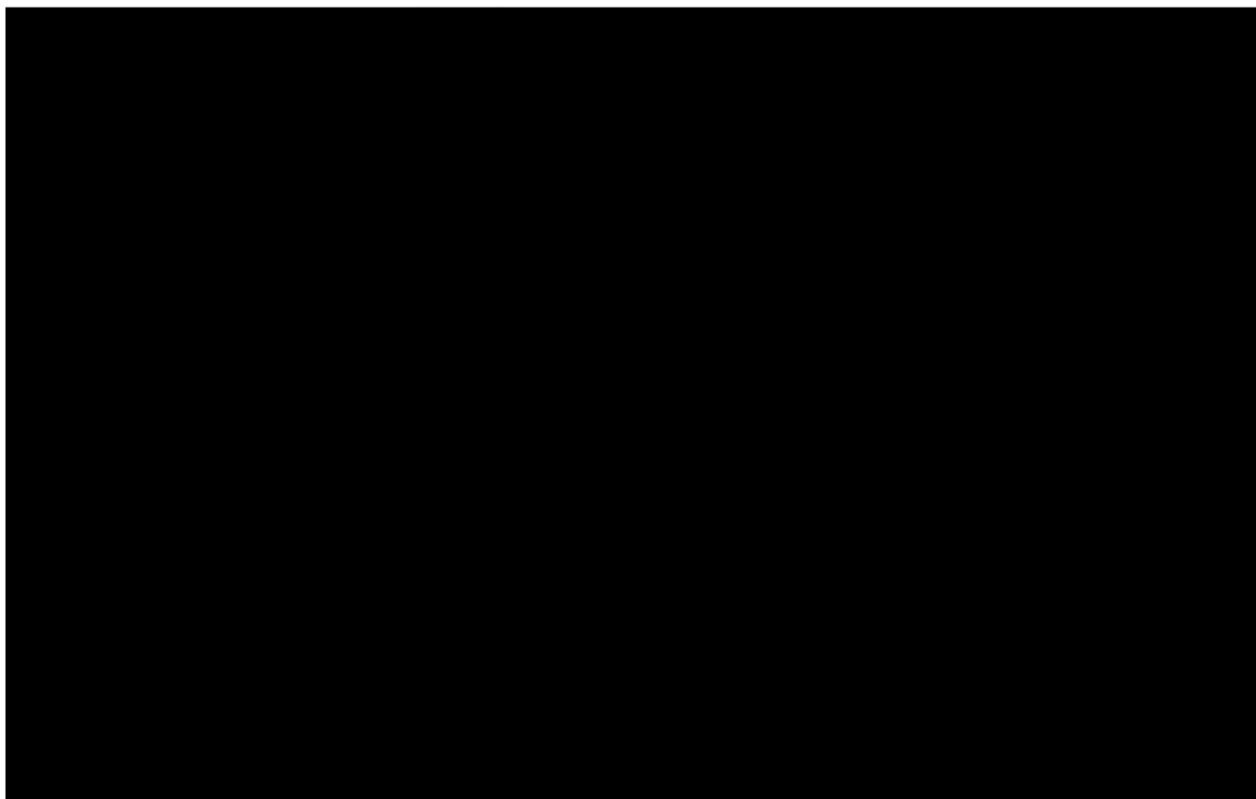
Patients will record their assessment of abdominal bloating by responding to the following in the evening eDiary:

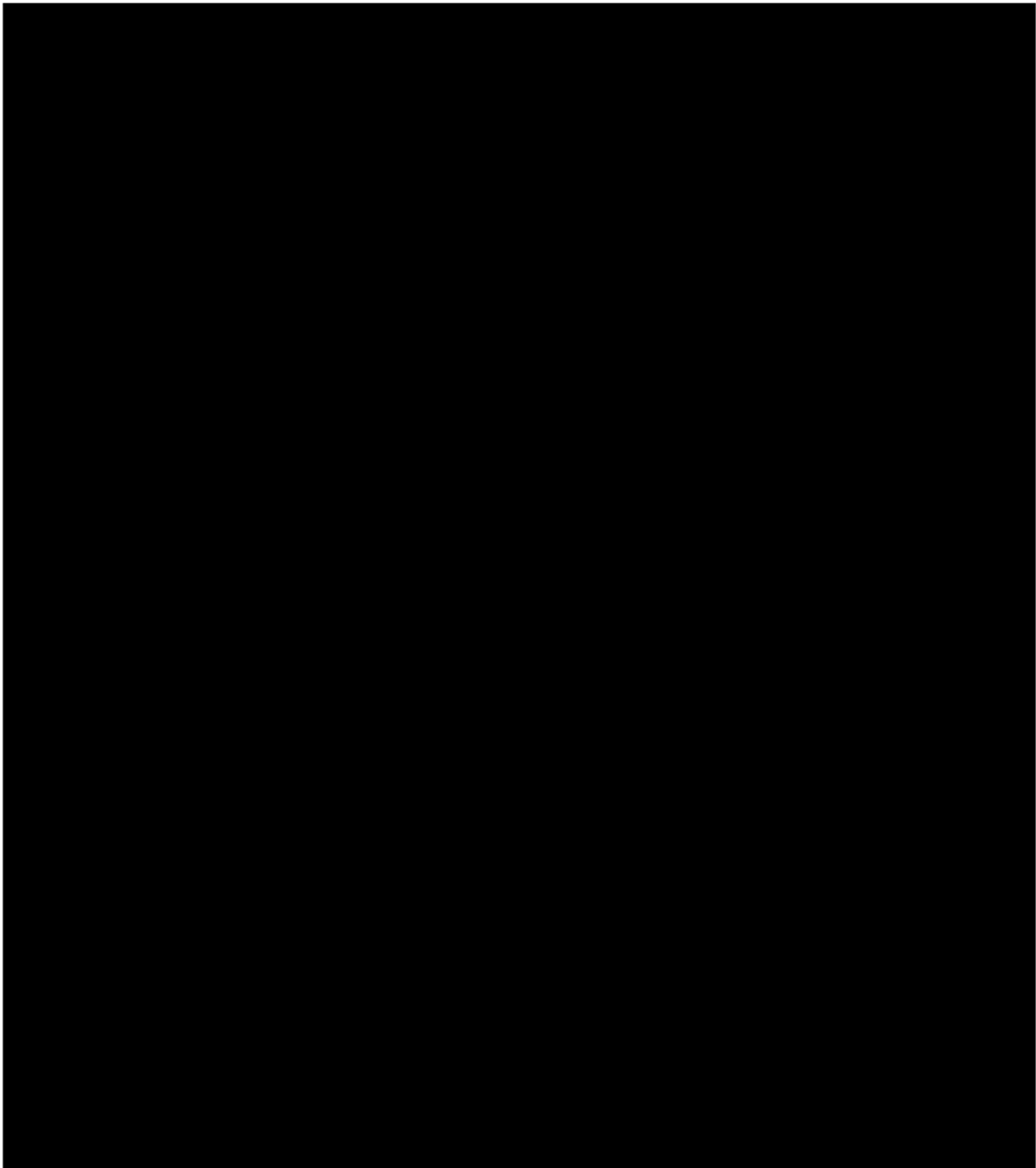
- From when you got up this morning until now, did your tummy FEEL big and full?
1 = yes
0 = no
98 = I don't know what you mean
99 = I don't remember

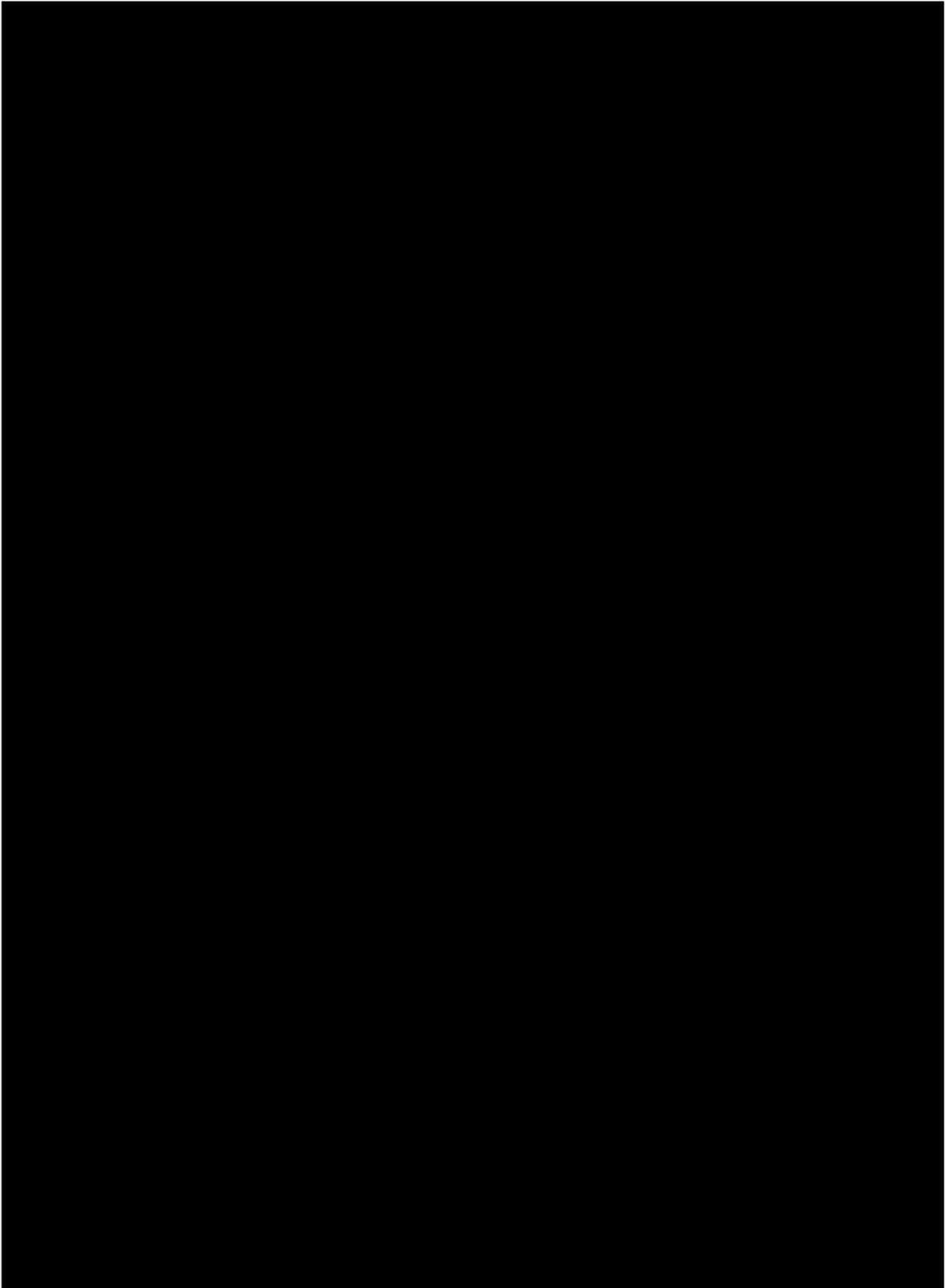
If "yes" then patient answers the following question:

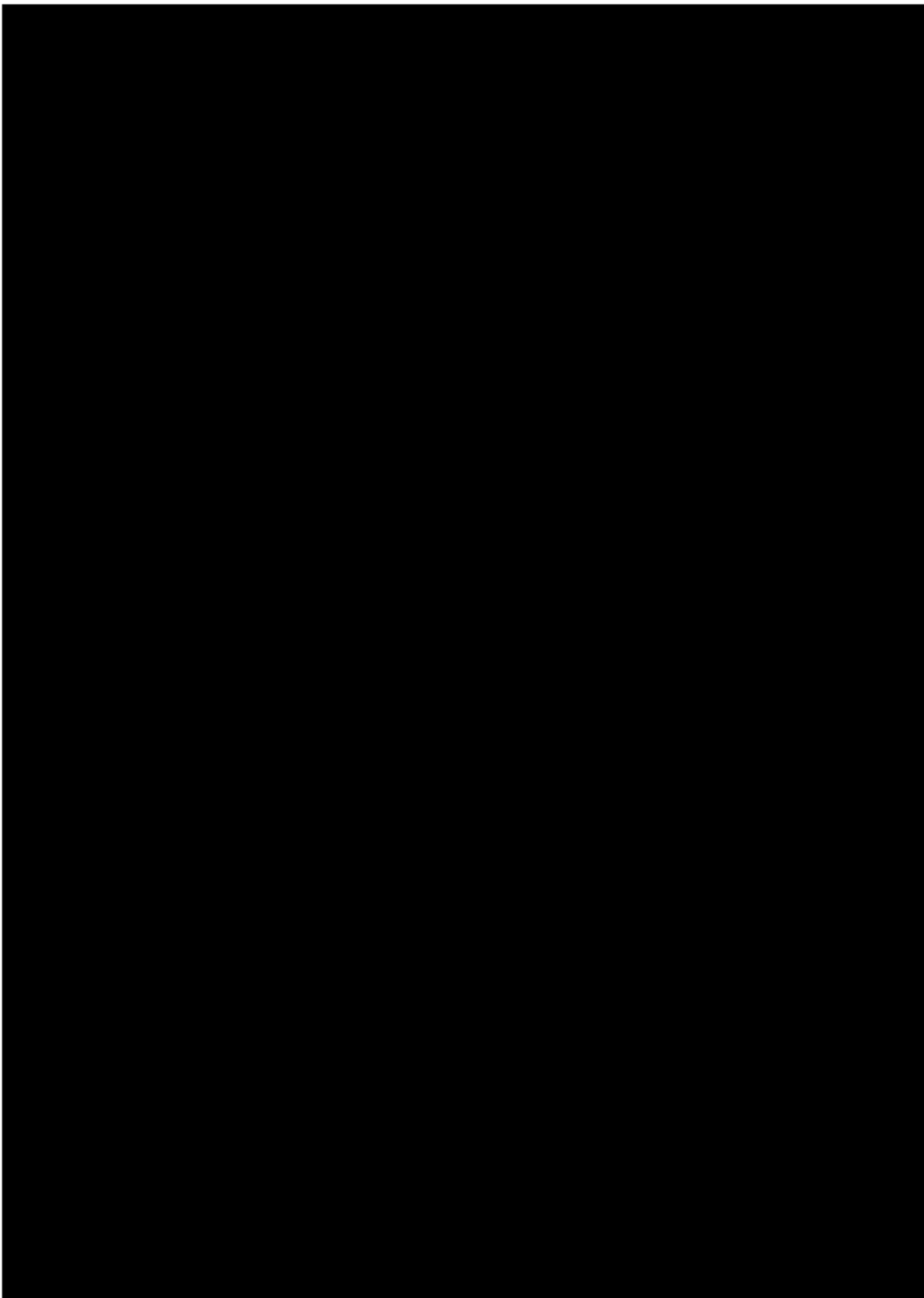
- How big and full did your tummy FEEL?
1 = a tiny bit
2 = a little
3 = medium
4 = very

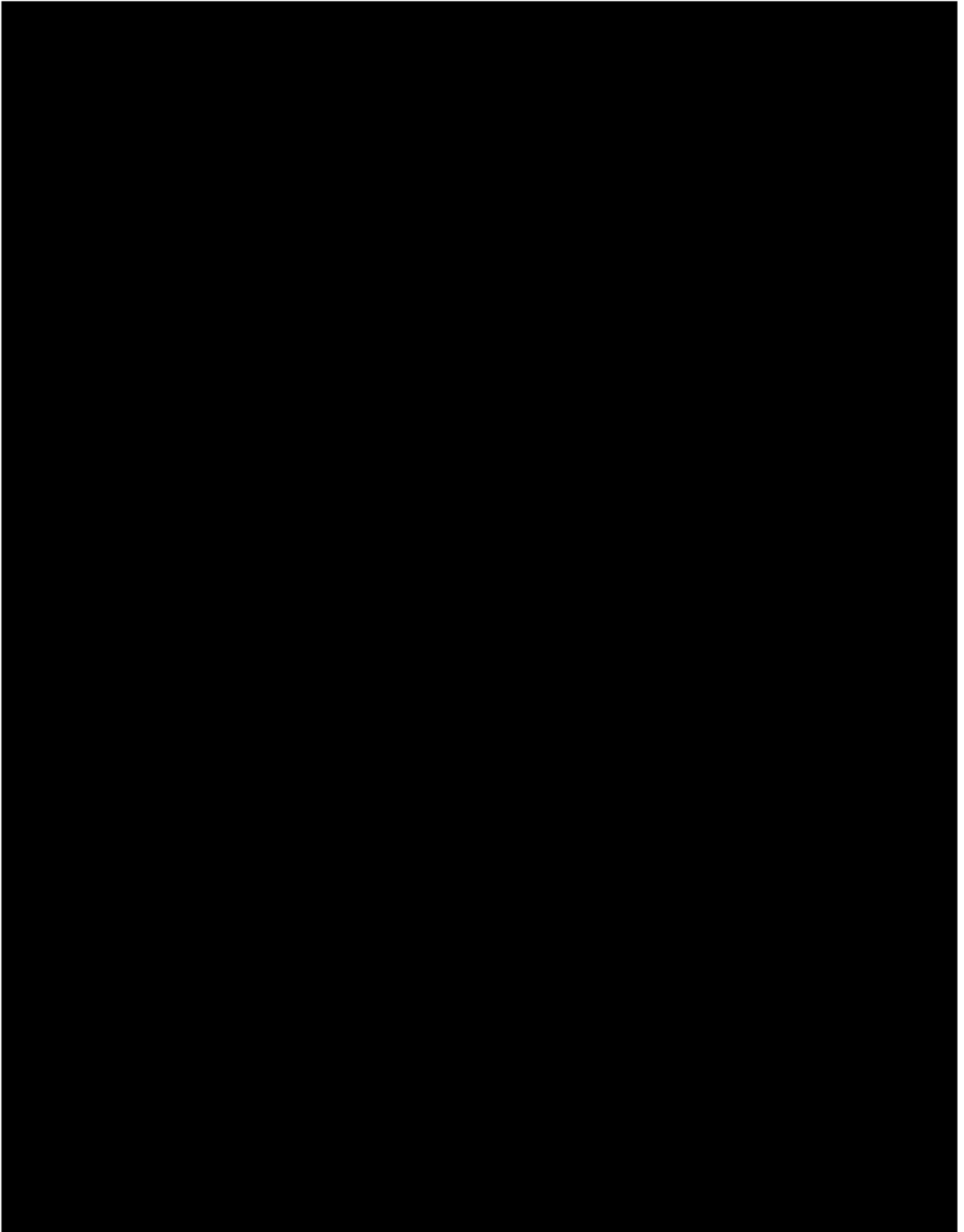
9.5.1.4 *Additional Efficacy Assessments*











9.5.2 Safety Assessments

Patients must be evaluated by a physician or an appropriately trained health care professional at every visit and the evaluation must be documented. The procedures discussed below will be completed at the designated visits. Safety assessments should not be administered to the patient unless the patient is accompanied by his or her consented caregiver.

9.5.2.1 Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product (ICH-E2A).

For the purpose of the site's data collection responsibilities, any untoward event that was reported from the time written consent was obtained until 30 days after the final protocol-defined study visit (or the last known dose of investigational product if the final visit does not occur) is to be considered an AE.

Examples of AEs are as follows:

- Changes in the general condition of the patient
- Subjective symptoms offered by or elicited from the patient
- Objective signs observed by the Investigator or other study site personnel
- All diseases that occur after signing the informed consent, including any change in severity or frequency of preexisting disease
- All clinically relevant abnormalities in laboratory values or clinically relevant physical findings that occur during the study schedule

Please note medical procedures scheduled prior to consenting, but occurring during the study should not be captured as AEs, but should be listed in the medical history if related to a pre-existing condition.

[REDACTED]

9.5.2.2 Causality Assessment

For each AE, the Investigator must provide an assessment of causal relationship to the investigational product. The causality assessment must be recorded on the appropriate AE reporting page of the patient's eCRF. Causal relationship must be assessed by answering the following question:

Is there a reasonable possibility the investigational product caused the event?

Yes: There is evidence to suggest a causal relationship between the investigational product and AE, ie:

- There is a reasonable temporal relationship between the investigational product and the event, and/or
- The event is unlikely to be attributed to underlying/concurrent disease, other investigational products, or other factors, and/or
- Positive dechallenge and/or rechallenge exist

No: There is no evidence to suggest a causal relationship between the investigational product and AE, ie:

- There is no reasonable temporal relationship between the investigational product and the event, or
- The patient did not take the investigational product, or

- The event is likely to be attributed to underlying/concurrent disease, other investigational products, or other factors, or
- The event is commonly occurring in the (study) population independent of investigational product exposure

9.5.2.3 *Severity Assessment*

The Investigator will provide an assessment of the severity of each AE by recording a severity rating on the appropriate AE reporting page of the patient's eCRF. *Severity*, which is a description of the intensity of manifestation of the AE, is distinct from *seriousness*, which implies a patient outcome or AE-required treatment measure associated with a threat to life or functionality (Section 9.5.2.4). Severity will be assessed according to the following scale:

- Mild:** The AE was an annoyance to the patient but did not further hinder baseline functioning; the AE may have been intermittent or continuous.
- Moderate:** The AE caused the patient to experience some discomfort or some interference with normal activities but was not hazardous to health; prescription drug therapy may have been employed to treat the AE.
- Severe:** The AE caused the patient to experience severe discomfort or severely limited or prevented normal activities and represented a definite hazard to health; prescription drug therapy and/or hospitalization may have been employed to treat the AE.

9.5.2.4 *Serious Adverse Events*

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- Is a congenital anomaly/birth defect

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based on appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in patient hospitalization, or the development of investigational product dependency or drug abuse.

Emergency room visits that do not result in hospitalization should be evaluated for one of the other serious outcomes to determine whether they qualify as SAEs.

Preplanned hospitalizations (eg, elective procedures for preexisting conditions that did not worsen, such as cosmetic surgery and hysterectomy) are excluded from SAE reporting.

9.5.2.5 *Reporting Adverse Events and Serious Adverse Events*

At each visit, patients are to be queried regarding any AEs or SAEs that have occurred since the previous visit. Patients will be asked to volunteer information with a nonleading question such as, “How do you feel since your last visit?” Study site personnel will record all pertinent information in the patient’s eCRF. Any AEs reported in diaries will also be reported on the relevant eCRF page.

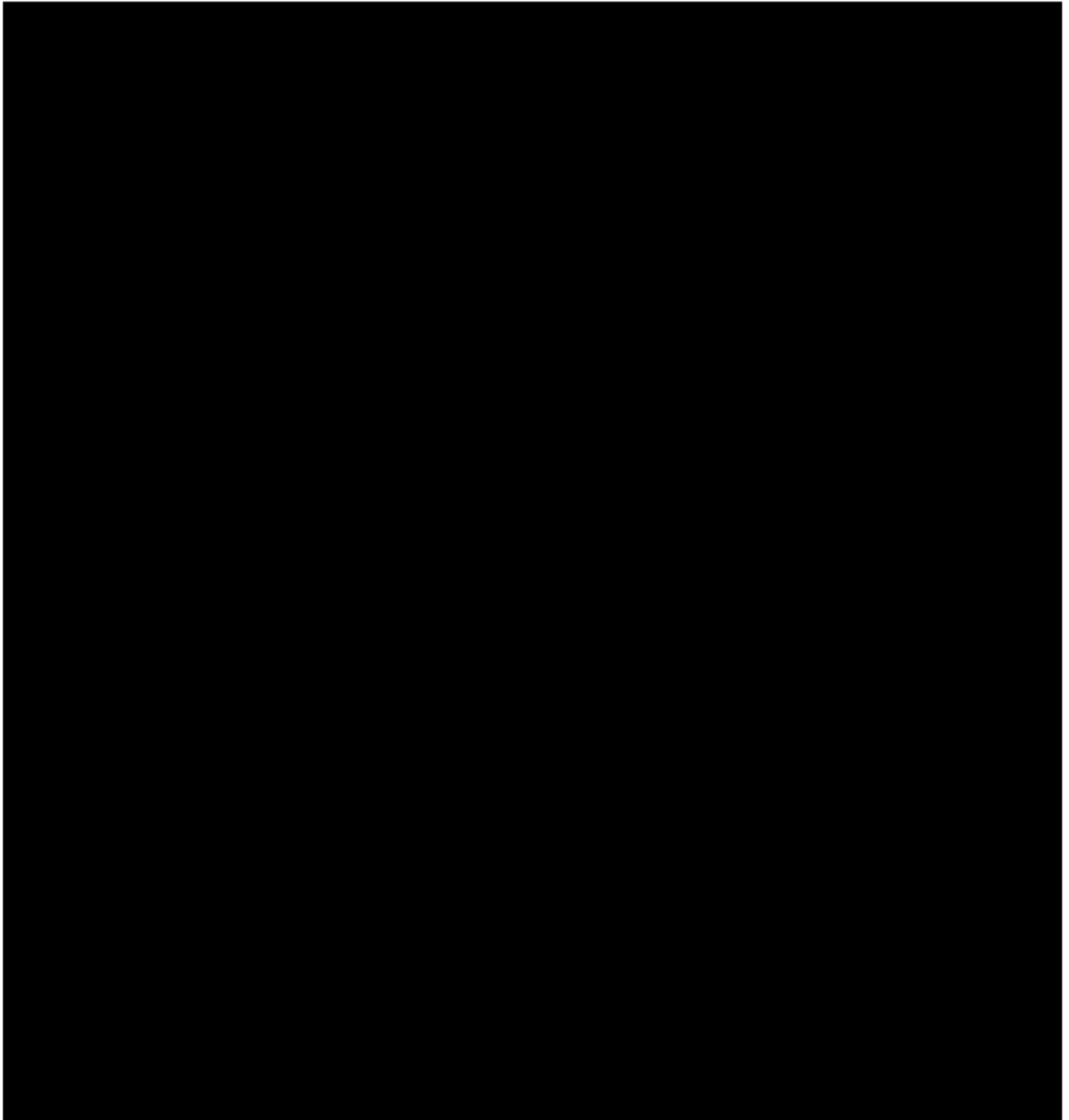
All AEs must be recorded on the appropriate AE reporting page of the patient’s eCRF whether or not they are considered causally related to the investigational product.

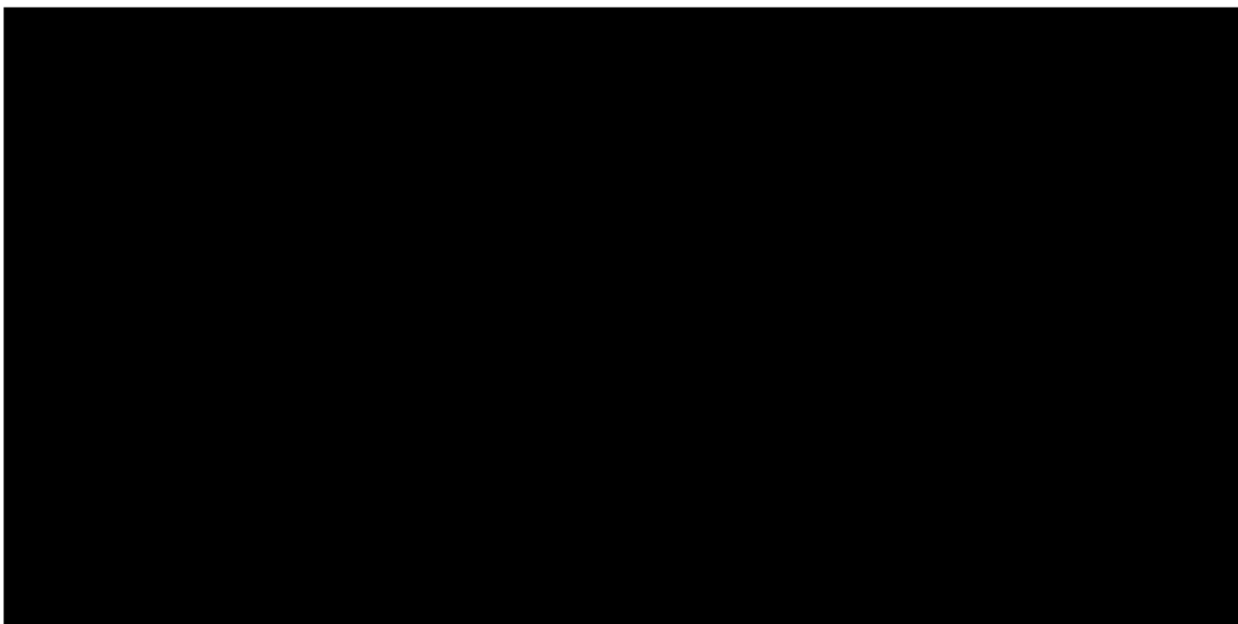
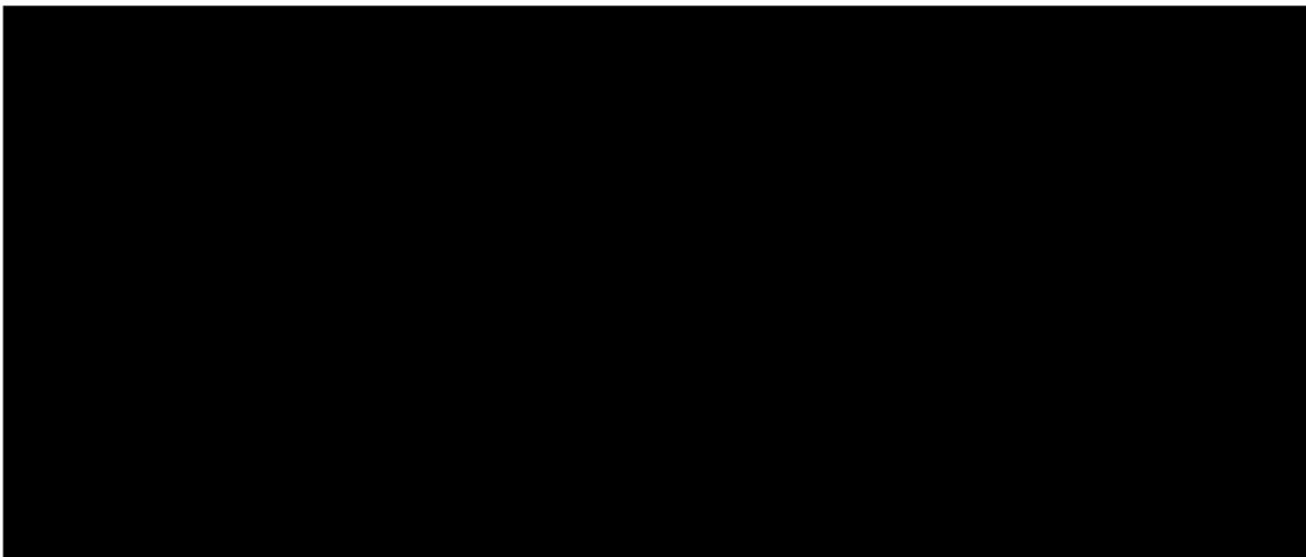
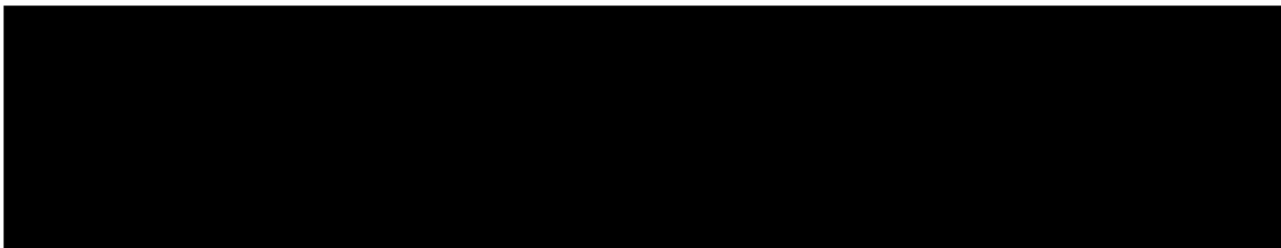
For every AE, the Investigator must:

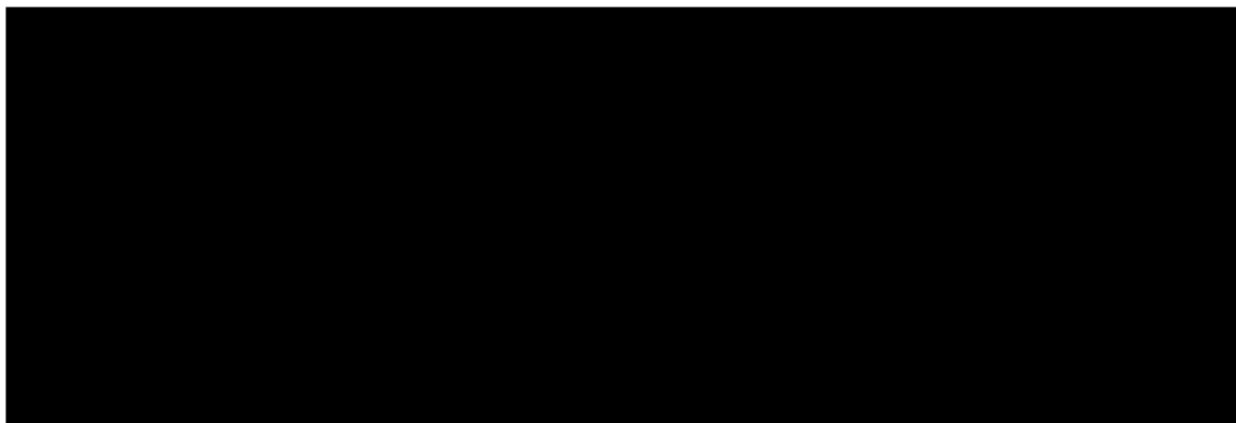
- Provide an assessment of the seriousness of the event (ie, is it an SAE?), as well as the severity and causal relationship
- Document all actions taken with regard to the investigational product
- Detail any other treatment measures taken for the AE
- Document the outcome of the AE

In addition, patients are to be reminded, as described in the ICF and in accordance with Section 9.5.2.1, to notify site personnel of any AEs occurring during the 30-day post-study period. Any AEs reported by the patient (or patient representative) during this period are to be recorded in the eCRF.

Any AEs that are ongoing at the time of the final protocol-defined study visit will be followed until the condition returns to prestudy status, has resolved, or *has* stabilized. If a follow-up visit is deemed necessary for appropriate safety surveillance, it will take place within 30 days of the final protocol-defined study visit.







9.5.2.9 Clinical Laboratory Determinations

Blood and urine samples for clinical laboratory tests will be collected as detailed in the [Schedule of Evaluations](#) (Section 2.0). During the Screening Period, the Investigator will assess the clinical significance of any values that are outside the reference ranges provided by the central laboratory. Patients with abnormalities judged to be clinically significant will be excluded from the study.

[Redacted text block]

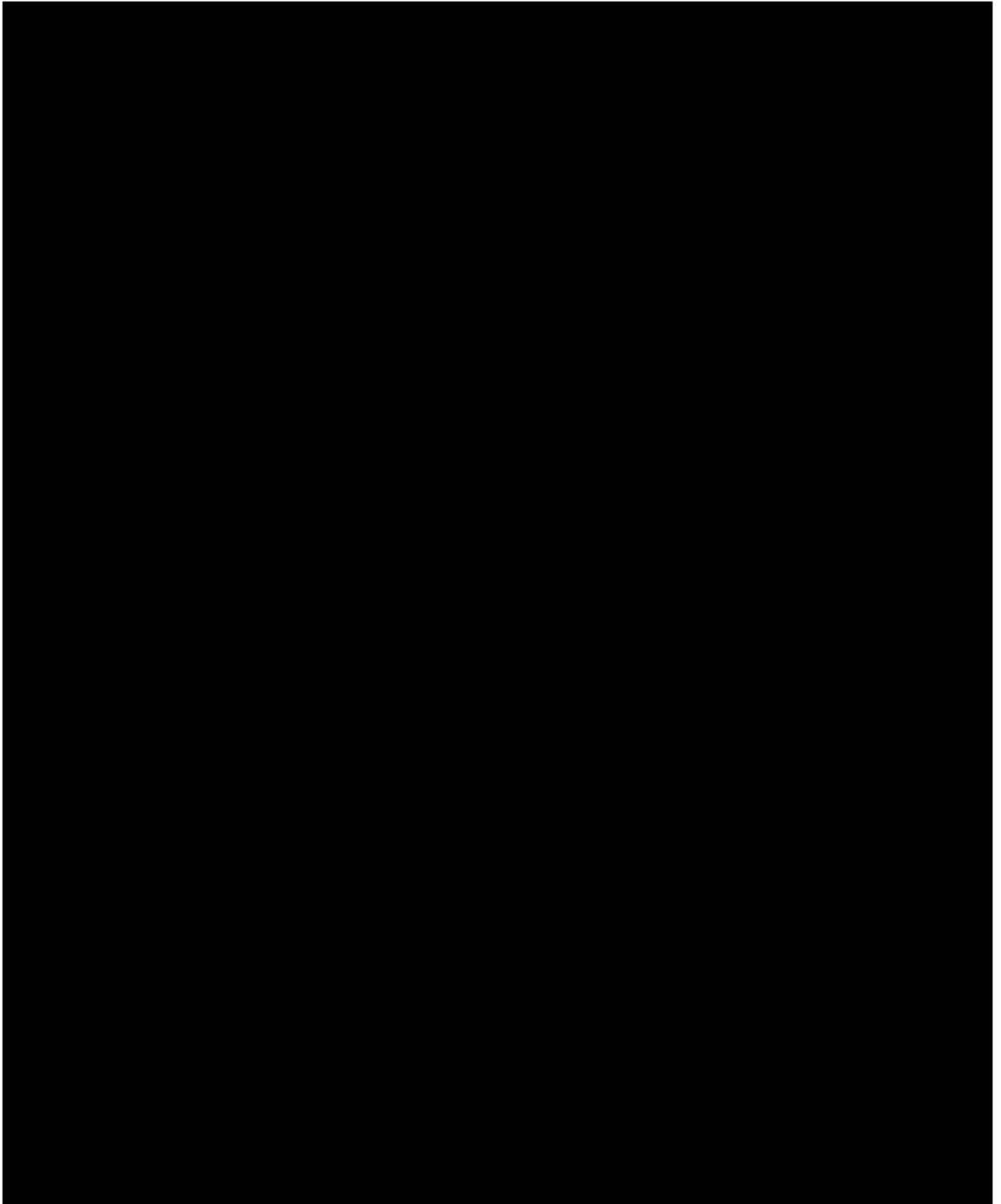
[Redacted text block]

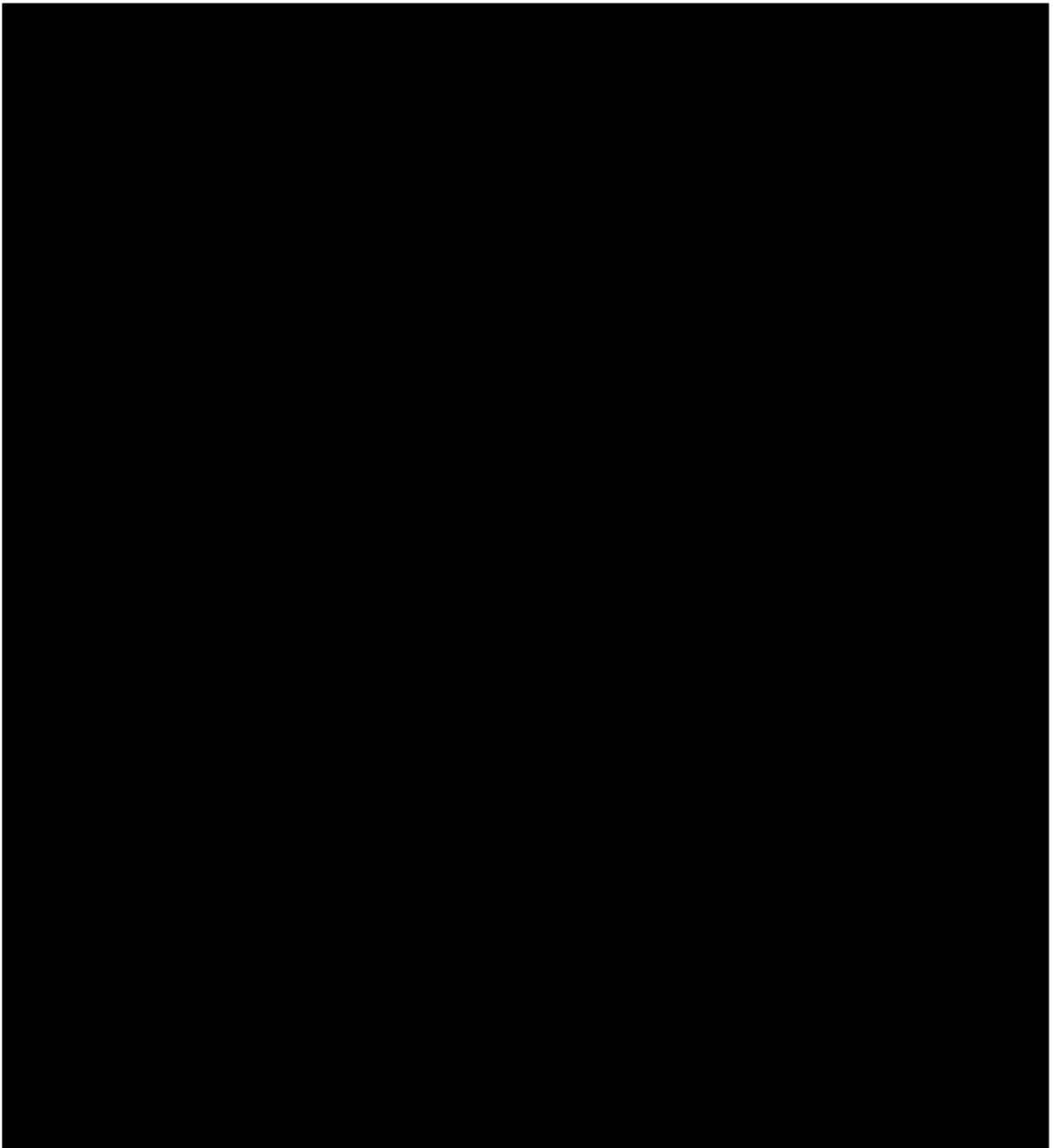
[Redacted text block]

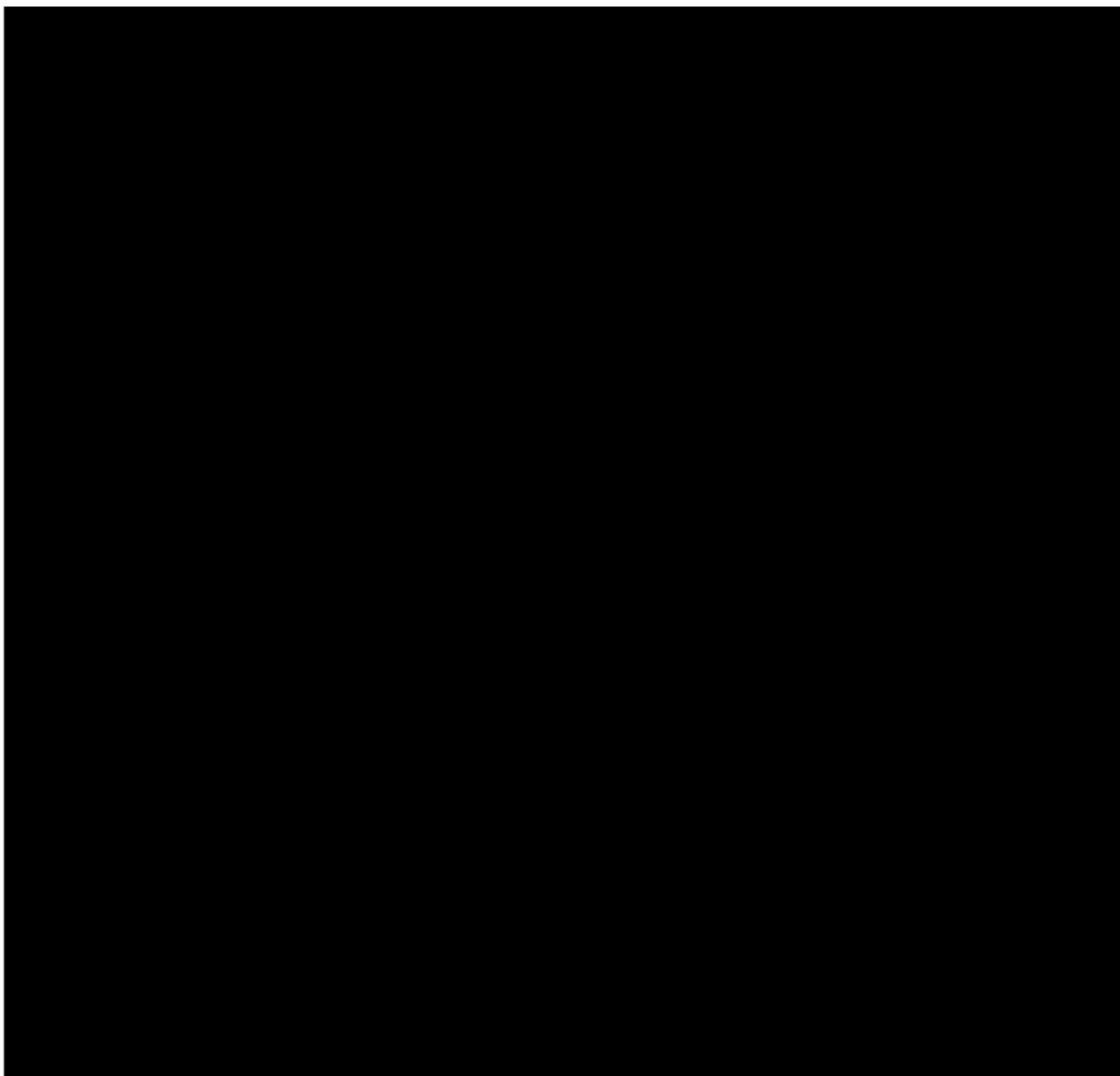
[Redacted text block]

[Redacted text block]

[Redacted text block]







[Redacted]

[Redacted]

[Redacted]

9.5.5 Schedule of Assessments

The schedule of study procedures and assessments is tabulated by visit in the [Schedule of Evaluations](#) in Section 2.0. The descriptions of the procedures to be performed at each visit are provided below.

9.5.5.1 *Screening Period (Visit 1)*

The Screening Period will occur up to 7 weeks before Randomization (Visit 3/Day 1) and last for 14 to 28 days during which time study procedures will be reviewed with the patient, parent/guardian/LAR, and caregiver; and informed assent (from patient), and parent/guardian/LAR and caregiver consent will be obtained and documented (Section 5.3).

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

9.5.5.2 *Pretreatment Period (Visit 2)*

The Pretreatment Period will occur up to 3 weeks before Randomization (Visit 3/Day 1) for 14 to 21 days duration. Patients will not receive investigational product during the Pretreatment Period.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

- I [REDACTED]
- I [REDACTED]
- I [REDACTED]
- I [REDACTED]
- I [REDACTED]
- I [REDACTED]
- I [REDACTED]
- I [REDACTED]
- I [REDACTED]

9.5.5.3 Randomization (Visit 3, Day 1)

Patients' eligibility to enter the Treatment period must be confirmed prior to randomization

- [REDACTED]
- [REDACTED]
- [REDACTED]
- I [REDACTED]

- I [REDACTED]
- I [REDACTED]
- I [REDACTED]
- I [REDACTED]
- I [REDACTED]
- I [REDACTED]
- I [REDACTED]
- I [REDACTED]
- I [REDACTED]
- I [REDACTED]
- I [REDACTED]
- I [REDACTED]
- I [REDACTED]
- I [REDACTED]
- I [REDACTED]

[REDACTED]

9.5.5.4 Week 2 (Visit 4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

9.5.5.5 Week 4 (Visit 5)

[REDACTED]

[REDACTED]

[REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

9.5.5.6 Post-treatment/End-of-Study Visit (Visit 6)

The Post-treatment Visit (End-of-Study Visit) must occur at least 7 days after the Week 4 Visit (Visit 5). Patients will not receive investigational product during the Post-treatment Period.

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

█ [REDACTED]

█ [REDACTED]

9.6 DATA QUALITY ASSURANCE

9.6.1 Data Monitoring

Before any patient enters the study, a representative of the Sponsor will meet with the Investigator and the study site staff to review the procedures to be followed during the study.

[REDACTED]

[REDACTED]

9.6.2 Data Recording and Documentation

Data collection will involve the use of the Sponsor's EDC system, to which only authorized personnel will have access. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

All data collected in the context of this study will be stored and evaluated per regulatory requirements and applicable guidance for electronic records. Also, data will be stored and evaluated in such a way as to guarantee patient confidentiality in accordance with the legal stipulations applying to confidentiality of data. Study records (eg, copies of eCRFs, laboratory reports, patient diaries, regulatory documents) will be retained at the site, along with adequate source documentation, according to FDA and ICH requirements. All study records must be available for inspection by the Sponsor, its authorized representatives, and the FDA or other health authorities.

9.6.3 Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) will review interim safety data at defined intervals throughout the study. The DSMB will communicate their recommendations to the Sponsor after each meeting but will serve in an advisory capacity only; the Board will not be empowered to stop the study or require changes in the protocol. Further details of the DSMB (composition, policy, and procedures) are specified in a separate DSMB Charter.

9.7 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

9.7.1 Patient Populations

The following populations will be considered in the statistical analysis of the study.

9.7.1.1 *Screened Population*

The Screened Population will consist of all patients who undergo the Screening Visit (Visit 1) and receive a PID number.

9.7.1.2 *Randomized Population*

The Randomized Population will consist of all patients in the Screened Population who are randomized to a treatment group in the study.

9.7.1.3 *Safety Population*

The Safety Population will consist of all patients in the Randomized Population who took at least 1 dose of double-blind investigational product.

9.7.1.4 *Intent-to-Treat Population*

The Intent-to-Treat (ITT) Population will consist of all patients in the Safety Population who had at least 1 postbaseline entry of BM characteristic assessments that determine occurrences of SBMs (ie, BM frequency and rescue medication use).

9.7.2 *Patient Disposition*

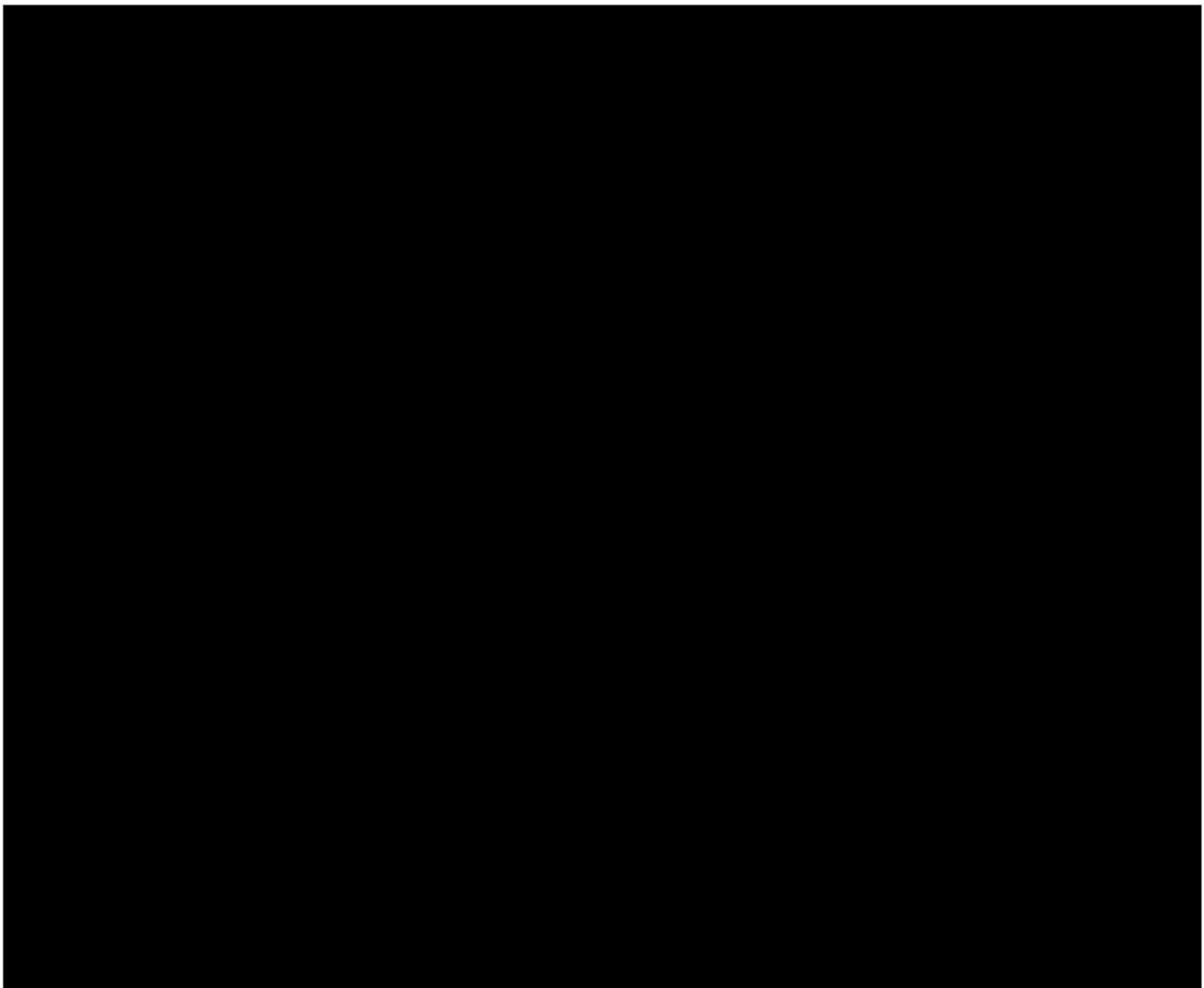
The number of patients in each of the study populations described in Section 9.7.1 will be summarized overall, by treatment group, [REDACTED]

The number of screen failures (ie, patients who enter the Screening Period but not the Pretreatment Period) and patients ineligible for randomization (ie, patients who enter the Pretreatment Period but are not randomized at Visit 3), along with the associated reasons for failure, will be tabulated overall and by age group. [REDACTED]

The number and percentage of patients who complete the Double-blind Treatment Period (ie, the Treatment Period) and the number and percentage of patients who prematurely discontinue during the Treatment Period will be presented by treatment group and overall for Randomized Population [REDACTED]. The reasons for premature discontinuation from the Treatment Period as recorded on the study termination page of the eCRFs will be summarized (number and percentage) by treatment group and overall for the Randomized Population. Patients who complete the Treatment Period and patients who prematurely discontinue during the Treatment Period for their corresponding reasons will also be summarized by treatment group and overall for each age group within Randomized Population. [REDACTED]

9.7.3 Demographics and Other Baseline Characteristics

Demographic parameters (eg, age, race, ethnicity, sex, weight) and other baseline characteristics will be summarized by treatment group for the Safety and ITT Populations. [REDACTED]



9.7.5 Efficacy Analyses

Efficacy analyses will be based on the ITT Population.

Baseline values for efficacy parameters will be derived from the eDiary in the Pretreatment Period, specifically the period of time from 14 days before randomization up to the time of randomization. The baseline weekly SBM or CSBM rate will be derived based on the total number of SBMs or CSBMs a patient had during this period. Baseline stool consistency and straining based on combined morning and evening assessments will be calculated as the observed weighted average of the nonmissing daily values during this period; the nonmissing daily value will be the average of nonmissing morning and/or evening assessments associated with the corresponding (ie, morning and/or evening) SBMs by the patient on that specific day. [REDACTED]

[REDACTED] The sum of the weights during this period will be used in the denominator to calculate the observed weighted average of the nonmissing daily values. [REDACTED]

[REDACTED] Baseline abdominal pain or bloating daytime symptoms based on evening assessment will be calculated as the average of the nonmissing patient scores reported in the evening [REDACTED] assessment.

Since the BM-related assessments and abdominal-symptom assessments in this study will be assessed twice daily via eDiary entries for efficacy parameters that will be derived based on the combined morning and evening assessments; a patient's daily score (based on combined morning and evening assessments) will be defined as the daily average (of the morning score and the evening score), except SBM and CSBM frequency. In case only the morning assessment score or only the evening assessment score is available, the available morning (or the available evening) assessment score will be taken as the patient's daily score.


An observed-cases approach to missing postbaseline data will be applied. The overall analysis (incorporating both age groups) including placebo and linaclotide doses (A, B, and C) will be the analysis to evaluate the main objective of this study. [REDACTED]

[REDACTED] All statistical tests will be 2-sided hypothesis tests performed at the 5% level of significance. All confidence intervals (CIs) will be 2-sided 95% CI, unless stated otherwise. No multiplicity adjustment will be applied in this dose-ranging study. Nominal p-values will be provided for the efficacy parameters as a measure of strength of association between the endpoint and the treatment effect.

9.7.5.1 Primary Efficacy Parameter

The primary efficacy parameter is the change from baseline in 4-week overall SBM frequency rate (SBMs/week) during the Treatment Period. The numerator of the SBM rate (SBMs/week) during the Treatment Period will be derived based on the total number of SBMs a patient reported during this period in the morning and evening eDiaries.

For the primary efficacy parameter, comparison between each linaclotide dose (A, B, and C) and placebo will be performed using an analysis of covariance (ANCOVA) model with treatment and age group (7 - 11 years of age and 12 - 17 years of age) as factors and baseline value as a covariate.



9.7.5.2 *Secondary Efficacy Parameters*

Key Secondary Efficacy Parameter

The key secondary efficacy parameter is change from baseline in 4-week abdominal pain daytime symptoms based on evening assessment of abdominal pain symptoms.

Abdominal pain scores will be collected twice daily in the eDiary: in the morning when a patient wakes up and in the evening at bedtime. Patients are asked to rate their abdominal pain from the time the patient wakes up until bedtime as part of the evening assessment, and a 5-point rating scale is derived from the patient's responses. The patient's 4-week abdominal pain daytime symptoms during the Treatment Period are defined as the average of the nonmissing daily abdominal pain daytime symptoms reported in evening assessments in the eDiary during the 4-week Treatment Period.

Other Secondary Efficacy Parameters

Four change from baseline parameters are additional secondary efficacy parameters in this study. Their description and analyses are provided below.

Change From Baseline in 4-Week Stool Consistency

Stool consistency will be collected twice daily in the eDiary, in the morning when a patient wakes up and in the evening at bedtime, and measured using the 7-point p-BSFS. The patient's p-BSFS score in the 4-week Treatment Period will be the observed weighted average of the daily p-BSFS scores (using weight of 1 for full day and 0.5 for half day) and the denominator in the observed weighted average will be the sum of the weights during this period. The daily p-BSFS score will be the average of nonmissing morning and/or evening assessments of the p-BSFS score from the SBMs reported by the patient on that specific day during the Treatment Period.

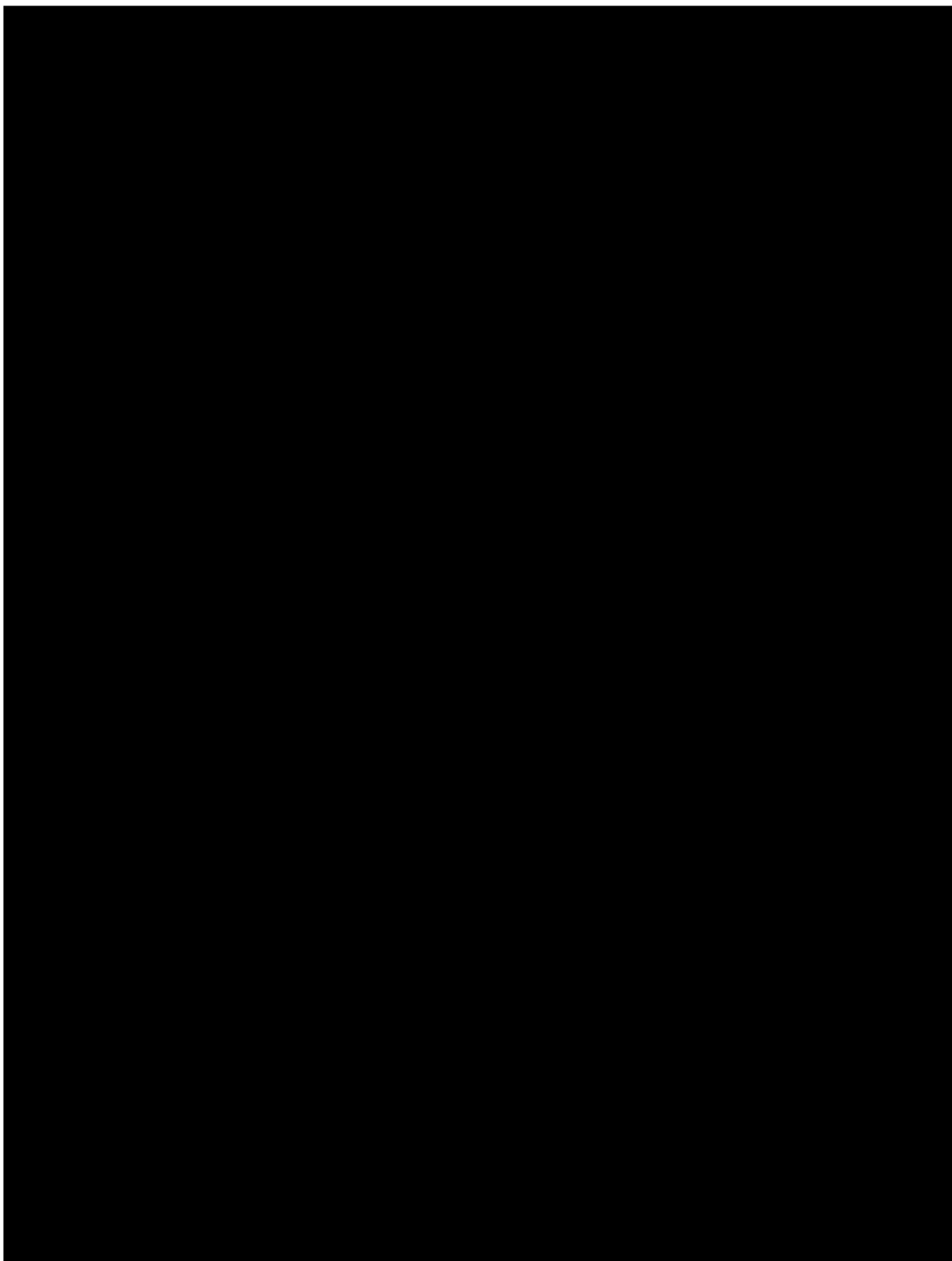
Change From Baseline in 4-Week of Severity of Straining

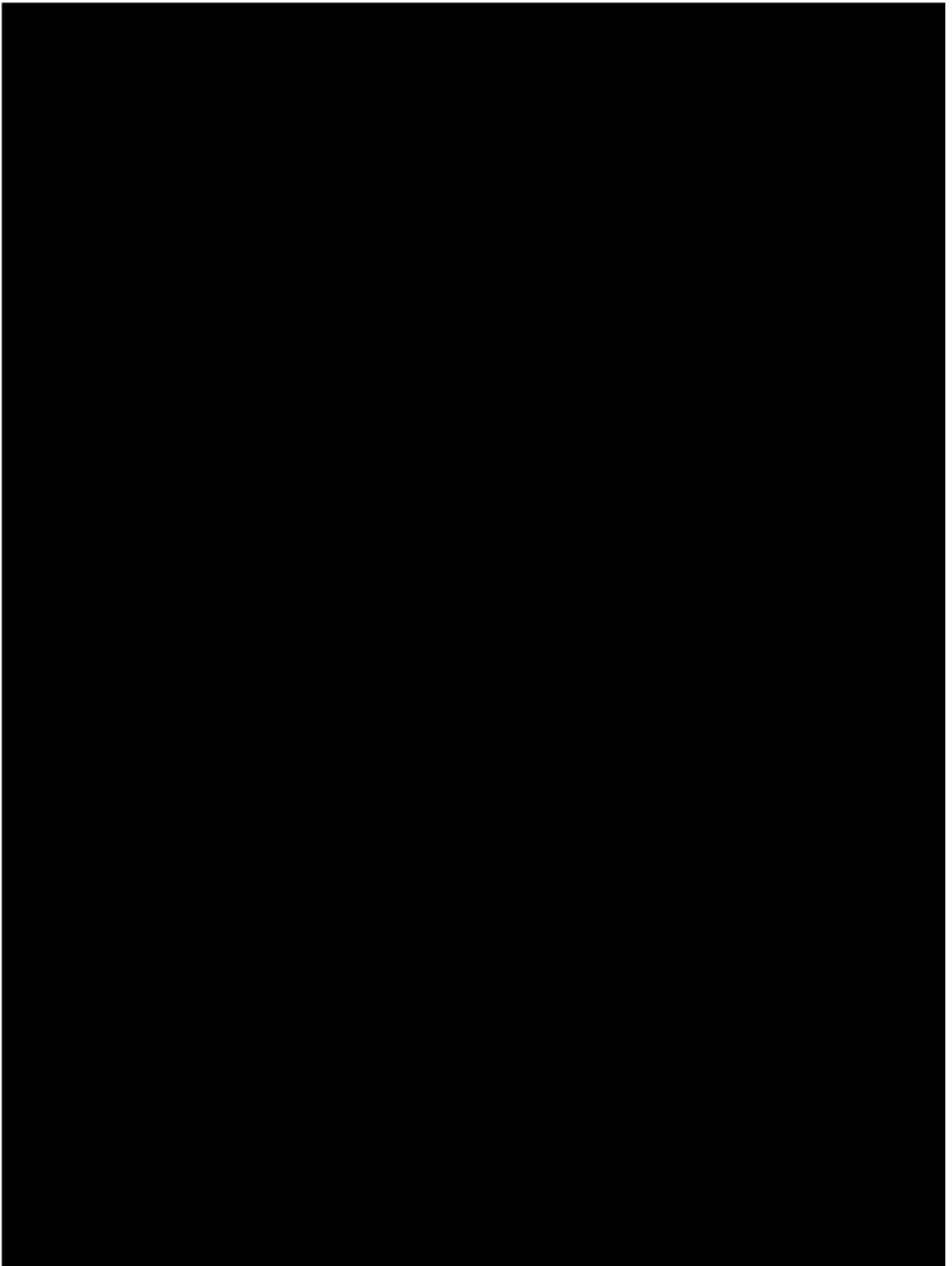
Straining with each BM will be collected twice daily in the eDiary, in the morning when a patient wakes up and in the evening at bedtime, and measured using a 5-point scale. The patient's straining score in the 4-week Treatment Period will be the observed weighted average of daily straining score (using weight of 1 for full day and 0.5 for half day) and the denominator in the observed weighted average will be the sum of the weights during this period. The daily score for the Treatment Period will be the average of the nonmissing morning and/or evening assessments of the straining score from the SBMs reported by the patient on that specific day during the Treatment Period.

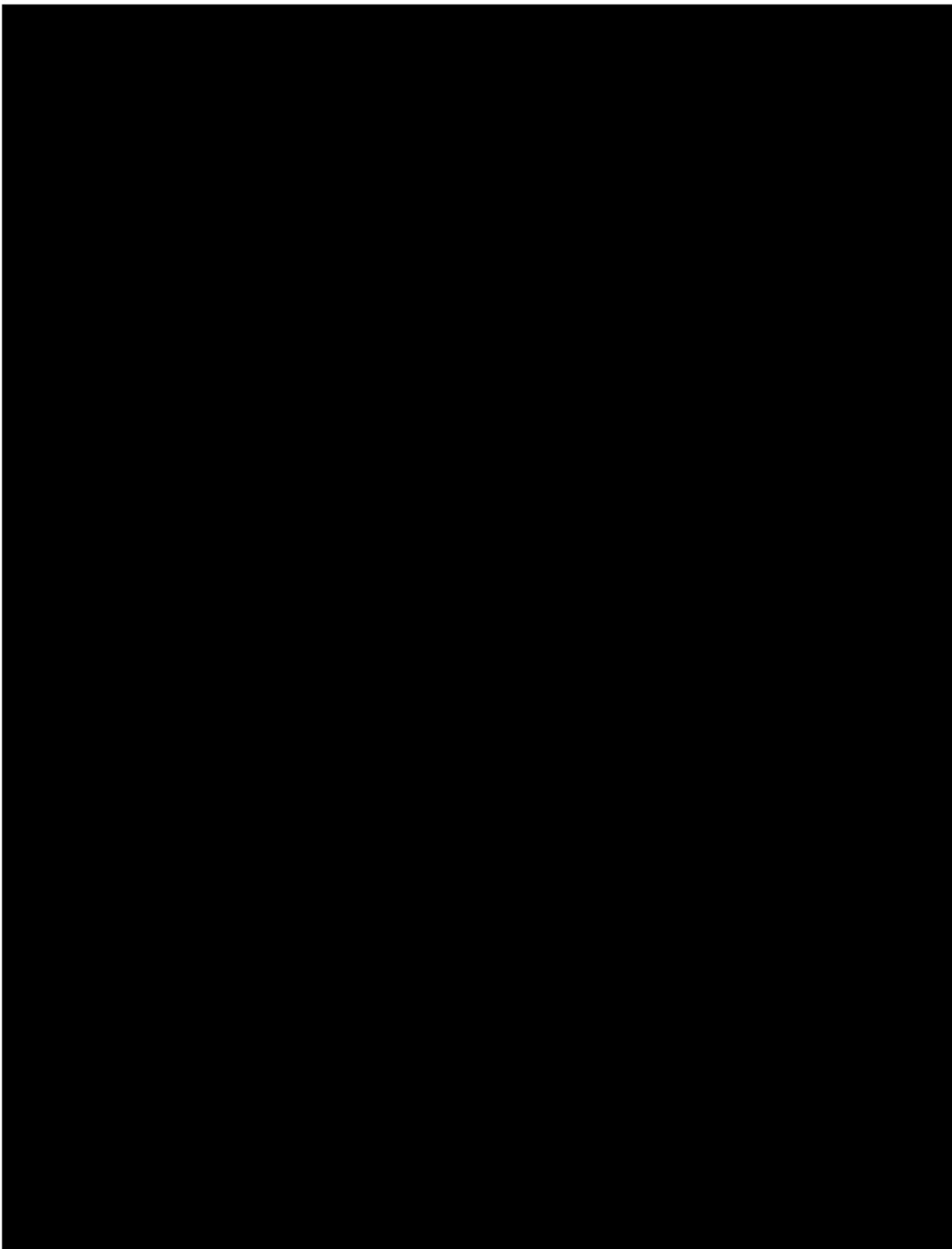
[REDACTED]

[REDACTED]

[REDACTED]







9.7.6 Safety Analyses

The safety analysis will be performed using the Safety Population. The safety summaries will be provided by treatment group overall [REDACTED]. The summaries of the linaclotide approved adult dose, 290 ug, will be included in the age group 12 to 17 years of age. The safety parameters will include AEs, [REDACTED]

9.7.6.1 Adverse Events

AEs will be coded using the *Medical Dictionary for Regulatory Activities* (MedDRA), Version 18.0 or newer.

An AE (classified by preferred term) that occurs during the Treatment Period will be considered a TEAE if it was not present before the date of the first dose of double-blind investigational product or was present before the date of the first dose of double-blind investigational product and increased in severity during the Treatment Period. If more than 1 AE is reported before the date of the first dose of double-blind investigational product 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 Treatment Period that were also coded to that preferred term. An AE that occurs more than 1 day after the date of the last dose of double-blind investigational product will not be counted as a TEAE.

The number and percentage of patients reporting TEAEs in each treatment group will be tabulated by SOC and preferred term; [REDACTED]

The incidence of common ($\geq 5\%$ of patients in any treatment group) TEAEs, on-therapy SAEs, [REDACTED]

[REDACTED] In addition, the incidence of fatal on-therapy SAEs (ie, events that caused death) will be summarized separately by treatment group and preferred term. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

9.7.8 Interim Analysis

No interim analysis is planned for this study.

9.7.9 Determination of Sample Size

The planned sample size is designed for the overall analysis of placebo and linaclotide dose groups (A, B, and C), with 58 patients per treatment group (232 patients in total for the overall analysis). With the inclusion of additional 23 to 31 patients 12 to 17 years of age for the linaclotide approved adult dose, 290 ug, the planned sample size for the study is approximately 260 patients.

[REDACTED]

9.7.10 Computer Methods

Statistical analyses will be performed using [REDACTED]
[REDACTED]

9.8 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

Any amendment to this protocol will be provided to the Investigator in writing by the Sponsor. No protocol amendment may be implemented (with the exceptions noted below) before it has been approved by the IRB/IEC and the signature page, signed by the Investigator, has been received by the Sponsor. If the protocol is amended to eliminate or reduce the risk to patients, the amendment may be implemented before IRB/IEC review and approval. However, the IRB/IEC must be informed in writing of such an amendment, and approval must be obtained within reasonable time limits.

9.9 PROTOCOL DEVIATIONS

A protocol deviation is any change, divergence, or departure from the study design or procedures that is under the Investigator's responsibility and oversight (as defined by regulations) without prior written IRB/IEC approval or favorable opinion of an appropriate amendment and that does not have a major impact on the patient's rights, safety, or well-being, or on the integrity and authenticity of the study data. Deviations may include, but are not limited to, departure from inclusion/exclusion criteria, allowed concomitant medications, dosing or duration of treatment, failure to follow withdrawal criteria or perform the required assessments at specified time points, scheduling of visits not in accordance with specifications.

Deviating from the protocol is permitted only if absolutely necessary for the safety or clinical management of the patients and must immediately be reported to the Sponsor. Protocol deviations should be reported to the Sponsor (either verbally or electronically) in a timely manner from the day of discovery.

Protocol deviations that may impact patient's rights (eg, failure to obtain informed consent prior to initiating study procedures), safety, or well-being (eg, deviations that resulted in an SAE, exposure during pregnancy), or the integrity and authenticity of the study data should be reported to the Sponsor within 24 hours, if possible.

The IRB/IEC must be notified according to the criteria and time period dictated by the IRB/IEC associated with this study.

10.0 **STUDY SPONSORSHIP**

This study is sponsored by Forest Research Institute, Inc. in partnership with Ironwood Pharmaceuticals, Inc.

10.1 **STUDY TERMINATION**

The Sponsor reserves the right to terminate the study in its entirety or at a specific study site before study completion.

10.2 **REPORTING AND PUBLICATION**

All data generated in this study are the property of the Sponsor. [REDACTED]
[REDACTED]

Publication of the results by the Investigator will be subject to mutual agreement between the Investigator and the Sponsor and will follow the Sponsor's standard operating procedures on publications.

11.0 **INVESTIGATOR OBLIGATIONS**

11.1 **DOCUMENTATION**

The Investigator must provide the following to the Sponsor before the start of the study:

- A completed and signed Form FDA 1572. If, during the course of the study, any changes are made that are not reflected on Form FDA 1572, a new Form FDA 1572 must be completed and returned to the Sponsor for submission to the FDA
- A fully executed contract
- The curricula vitae for the Investigator and all Subinvestigators listed on Form FDA 1572, including a copy of each physician's license
- A copy of the original IRB/IEC approval for conducting the study. If the study is ongoing, renewals must be submitted at yearly intervals. All subsequent modifications must be submitted and approved by the IRB/IEC, as stated in Section 5.1
- A copy of the IRB/IEC-approved ICF
- A copy of the HIPAA authorization form, or other local privacy applicable forms
- A list of the IRB/IEC members or the US Department of Health and Human Services general assurance number
- A copy of the laboratory certifications and reference ranges
- The Investigator's Statement page in this protocol signed and dated by the Investigator
- Financial disclosure agreement completed and signed by the Investigator and all Subinvestigators listed on Form FDA 1572. The Investigator and all Subinvestigators will provide an updated financial disclosure agreement to the Sponsor 1 year after the completion of the study

11.2 **PERFORMANCE**

The Investigator must demonstrate reasonable efforts to obtain qualified patients for the study.

11.3 USE OF INVESTIGATIONAL MATERIALS

The Investigator will acknowledge that the investigational product supplies are investigational and as such must be used strictly in accordance with the protocol and only under the supervision of the Investigator or Subinvestigators listed on Form FDA 1572. The investigational products must be stored in a secured place and must be locked. [REDACTED]

[REDACTED]

[REDACTED] CASE REPORT FORMS

All patient data relating to the study will be recorded on eCRFs to be provided by the Sponsor [REDACTED]

[REDACTED]

11.5 RETENTION AND REVIEW OF RECORDS

Records and documents pertaining to the conduct of this study, including eCRFs, source documents, consent forms, regulatory documents, clinical laboratory results, calibration logs, or reports (including, but not limited to, all local and central laboratory results, and ECG reports), and medication inventory records in all formats (including, but not limited to, written, electronic, magnetic, and optical records, and scans, x-rays, and ECGs) must be retained by the Investigator for a period of at least 15 years after study completion unless local regulations or institutional policies require a longer retention period or otherwise notified in writing by the Sponsor.

No study records shall be destroyed without notifying the Sponsor and providing the Sponsor the opportunity to arrange long-term storage for such study records or authorizing in writing the destruction of records after the required retention period.

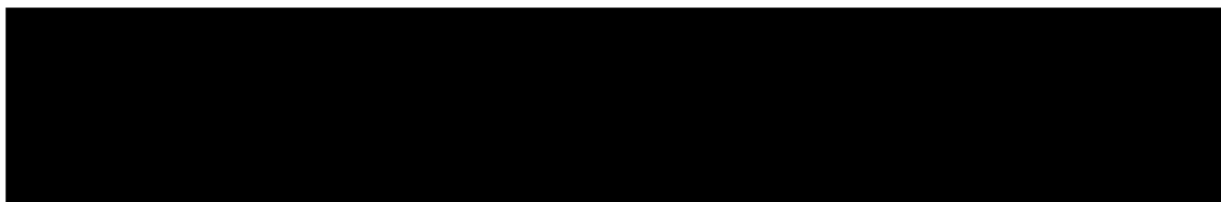
The Investigator must permit access to any documentation relating to the study upon request of the Sponsor or applicable regulatory authorities. If the Investigator for the study retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a suitable alternate custodian employee of the institution or to a suitably qualified and responsible third party. The Sponsor must be notified in writing of the name and address of the new custodian in advance of the transfer.

For countries falling within the scope of the ICH guidelines, the sponsor-specific essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by the sponsor.

In addition, for countries not falling within the scope of the ICH guidelines, local regulatory requirements should be followed regarding the retention of clinical study documentation.

For Canadian study sites only: All records and documents pertaining to the conduct of the study must be retained for a 25-year period in accordance with the Canadian Food and Drugs Act and Regulations.

11.6 PATIENT CONFIDENTIALITY



12.0 **INVESTIGATOR'S STATEMENT**

I agree to conduct the study in accordance with this protocol (LIN-MD-63, Amendment #3, dated 16 May 2017) and with all applicable government regulations and good clinical practice guidance.

_____/_____/_____
Investigator's Signature Date

Investigator's Name

13.0 **APPENDICES**

APPENDIX I ELEMENTS OF INFORMED CONSENT

Procedures will comply with 21 CFR, Parts 50 and 312. Signed informed consent will be obtained from each patient participating in a clinical research study or from the patient's parent/guardian/LAR. This consent must include the following items:

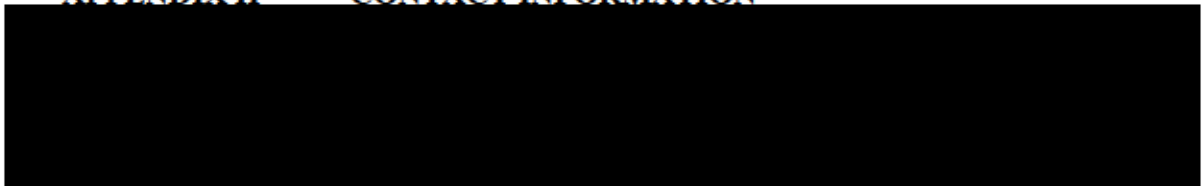
- A statement that the study involves research and an explanation of the purposes of the research; a description of the procedures to be followed and the identification of any procedures that are experimental; and the expected duration of the patient's participation
- A description of any reasonably foreseeable risks or discomforts to the patient
- A description of any benefits to the patient or to others that may reasonably be expected from the research. If the patient is to be paid for participating in the study, the consent form must state the amount that he/she will receive and the schedule of payment (to ensure neither coercion nor undue influence)
- A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the patient
- A statement describing the extent, if any, to which confidentiality of records identifying the patient will be maintained and noting the possibility that the FDA; the Sponsor; the IRB/IEC; or an authorized contract research organization may inspect the records
- For research involving more than minimal risk, an explanation of whether any medical treatment is available if injury occurs and, if so, what it consists of or where further information may be obtained
- An explanation of whom to contact, including the relevant telephone number, for answers to pertinent questions about the research and the research patient's rights and whom to contact in the event of a research-related injury to the patient. (Note: In some cases, it may be necessary to identify a person other than the Investigator as the contact. The guidance of the IRB/IEC may be required)
- A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the patient is otherwise entitled, and that the patient may discontinue participation at any time without penalty or loss of benefits to which the patient is otherwise entitled

- A statement that the particular treatment or procedures may involve risks to the patient (or to the embryo or fetus if the patient is, or may become, pregnant) that are at present unforeseeable
- The expected circumstances for which the patient's participation may be terminated by the Investigator without regard to the patient's consent
- Any additional costs to the patient that may result from participation in the research
- The consequences of a patient's decision to withdraw from the research and procedures for an orderly termination of the patient's participation
- A statement that significant new findings developed during the course of the research that may relate to the patient's willingness to continue participation will be provided to the patient
- The approximate number of patients involved in the study
- A statement of consent (eg, "I agree to allow (my child) to participate . . .")
- A place for the patient's parent/guardian/LAR signature and date of signing
- A statement indicating that information about this study has been, or will be, entered into a databank that is publicly accessible at www.ClinicalTrials.gov.

A copy of the signed consent form must be given to the patient's parent/guardian/LAR.

In addition, the patient will be asked to provide assent that will include a statement agreeing to participate in the study.

APPENDIX II CONTACT INFORMATION



APPENDIX III CONCOMITANT MEDICATIONS

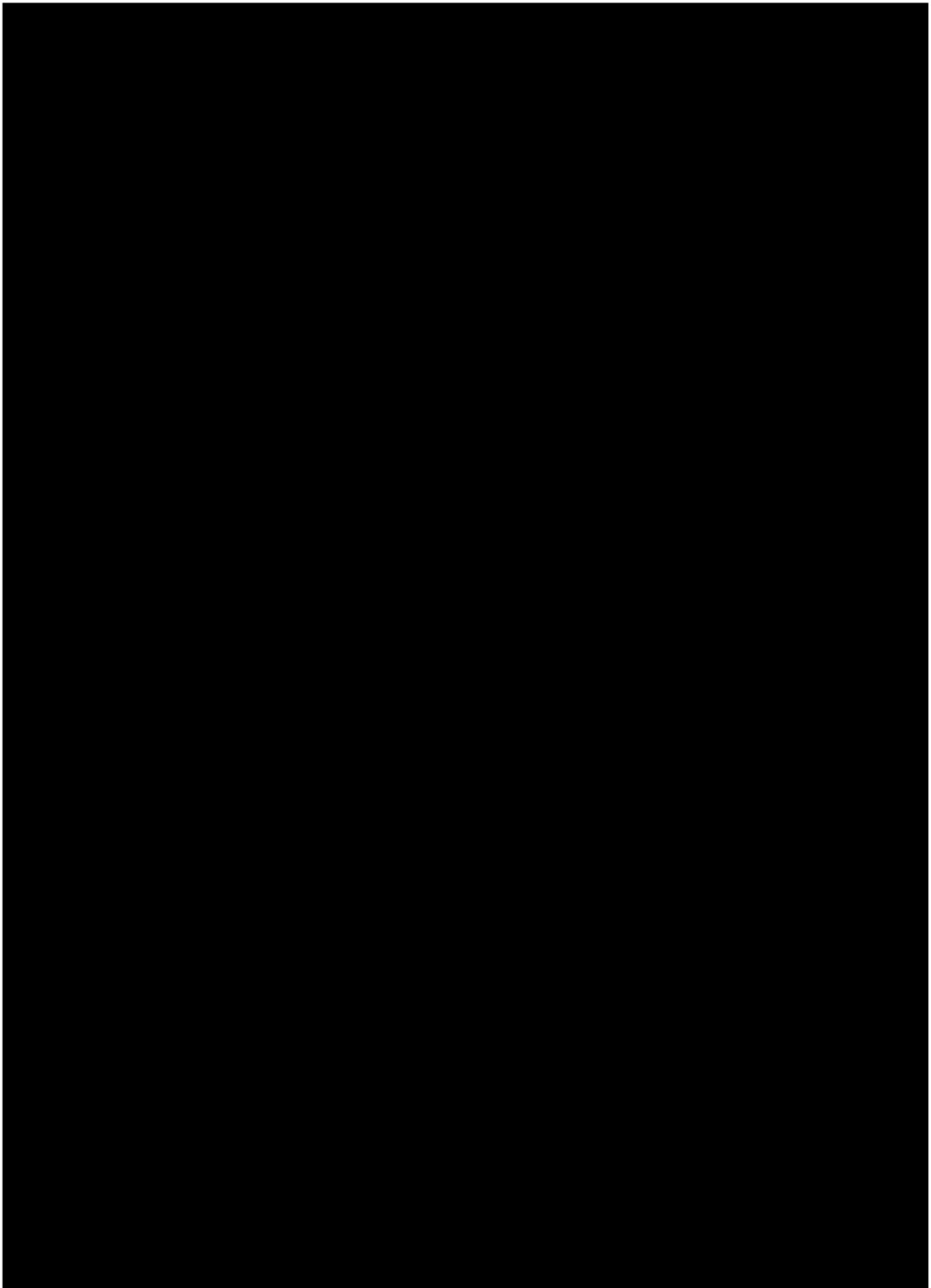
Rescue Medication

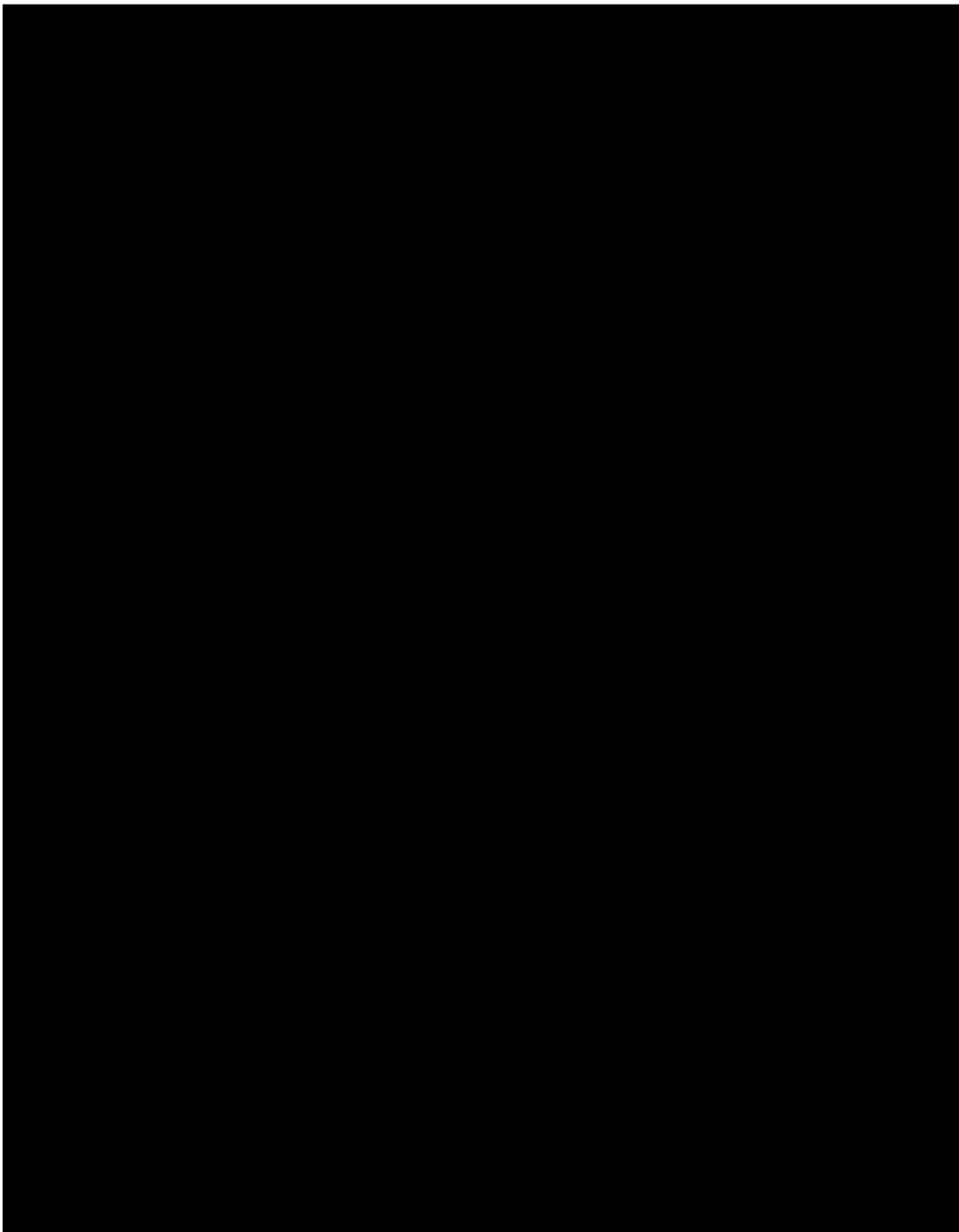
Rescue medication will be provided [REDACTED] Laxative, suppository, or enema use must be documented with all other concomitant medication use in the eDiary.

Protocol-permitted rescue medicine, which will be selected by and dispensed to patients, will be a choice of senna (oral) or bisacodyl (oral or rectal). During the Pretreatment, Treatment, and Post-treatment Periods, patients may use dispensed, protocol-permitted laxatives (ie, senna or bisacodyl) as rescue medicine [REDACTED]

Prohibited Medications

All medicines listed in the sections below [REDACTED] will be excluded during the Pretreatment, Treatment, and Post-treatment Periods. [REDACTED]



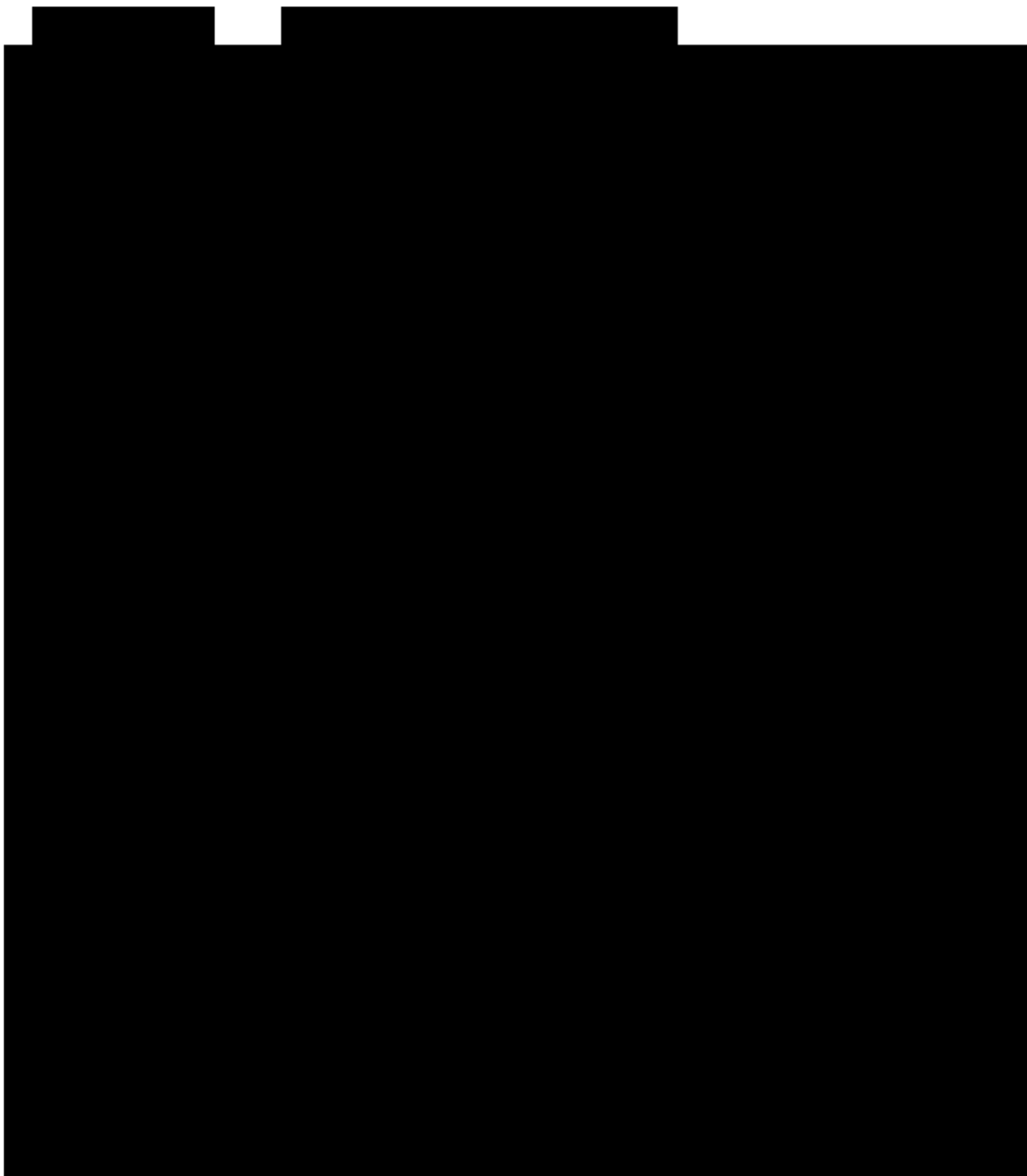




[REDACTED]

[REDACTED]

[REDACTED]



14.0 LITERATURE CITED

Brandt LJ, Chey WD, Foxx-Orenstein AE, et al. An evidence-based systematic review on the management of irritable bowel syndrome. *Am J Gastroenterol* 2009;104 Suppl 1:S8-S35.

Bryant AP, Busby RW, Bartolini WP, et al. Linaclotide is a potent and selective guanylate cyclase C agonist that elicits pharmacological effects locally in the gastrointestinal tract. *Life Sci* 2010;86:760-5.

Eutamene H, Bradesi S, Larauche M, et al. Guanylate cyclase C-mediated antinociceptive effects of linaclotide in rodent models of visceral pain. *Neurogastroenterol Motil* 2010;22:312-e84.

Hyams JS. Functional gastrointestinal disorders. *Curr Opin Pediatr* 1999;11:375-378.

Lewis SJ and Heaton KW. Stool form scale as a useful guide to intestinal transit time. *Scand J Gastroenterol* 1997;32:920-4.

Linaclotide: Investigator's brochure. Edition 11. Cambridge, MA: Ironwood Pharmaceuticals, Inc; 2016 Nov 22.

Linzess [package insert]. 2015 Nov. Available from http://pi.actavis.com/data_stream.asp?product_group=1904&p=pi&language=E. Accessed 2016 Jul 11.

Longstreth GF, Thompson WG, Chey WD, et al. Functional bowel disorders. *Gastroenterology* 2006;130:1480-91.

Sandhu BK and Paul SP. Irritable bowel syndrome in children: pathogenesis, diagnosis and evidence-based treatment. *World J of Gastroenterol* 2014 May;20(20):6013-6023.

Study LIN-MD-01: a phase III, randomized, double-blind, placebo-controlled, parallel-group trial of linaclotide administered orally for 12 weeks in patients with chronic constipation. Jersey City, NJ: Forest Research Institute, Inc; 2010 Jun 2.

Study LIN-MD-02: an open-label, long-term safety study of oral linaclotide administered to patients with chronic constipation or irritable bowel syndrome with constipation. Jersey City, NJ: Forest Research Institute, Inc; 2012 Nov 5.

Study LIN-MD-04: a phase 3b, randomized, double-blind, placebo-controlled, parallel-group trial of linaclotide administered orally for 12 weeks to patients with chronic constipation and prominent abdominal bloating at baseline. Jersey City, NJ: Forest Research Institute, Inc; 2014 March 14.

Study LIN-MD-31: a phase III, randomized, double-blind, placebo-controlled, parallel-group trial of linaclotide administered orally for 12 weeks followed by a 4-week randomized withdrawal period in patients with irritable bowel syndrome with constipation. Jersey City, NJ: Forest Research Institute, Inc; 2011 May 10.

Study MCP-103-302: a phase 3, randomized, double-blind, placebo-controlled, parallel-group trial of linaclotide administered orally for 26 weeks in patients with irritable bowel syndrome with constipation. Cambridge, MA: Ironwood Pharmaceuticals, Inc; 2011 May 24.

Study MCP-103-303: a phase 3, randomized, double-blind, placebo-controlled, parallel-group, trial of linaclotide administered orally for 12 weeks followed by a 4-week randomized withdrawal period in patients with chronic constipation. Cambridge, MA: Ironwood Pharmaceuticals, Inc; 2010 May 7.

Study MCP-103-305: an open-label, long-term safety study of oral linaclotide administered to patients with chronic constipation or irritable bowel syndrome with constipation. Cambridge, MA: Ironwood Pharmaceuticals, Inc; 2012 Oct 18.

Varni JW, Burwinkle TM, Berrin SJ, et al. The PedsQL in pediatric cerebral palsy: reliability, validity, and sensitivity of the Generic Core Scales and Cerebral Palsy Module. *Dev Med Child Neurol* Jun 2006;48(6):442-49.

Varni JW, Burwinkle TM, Jacobs JR, et al. The PedsQL in type 1 and type 2 diabetes: reliability and validity of the Pediatric Quality of Life Inventory Generic Core Scales and type 1 Diabetes Module. *Diabetes Care* Mar 2003;26(3):631-7.

Varni JW, Burwinkle TM, Katz ER, et al. The PedsQL in pediatric cancer: reliability and validity of the Pediatric Quality of Life Inventory Generic Core Scales, Multidimensional Fatigue Scale, and Cancer Module. *Cancer* Apr 1 2002;94(7):2090-106.

Varni JW, Burwinkle TM, Rapoff MA, et al. The PedsQL in pediatric asthma: reliability and validity of the Pediatric Quality of Life Inventory generic core scales and asthma module. *J Behav Med* Jun 2004;27(3):297-318.

Varni JW, Burwinkle TM, Seid M. The PedsQL 4.0 as a school population health measure: feasibility, reliability, and validity. *Qual Life Res*. Mar 2006;15(2):203-15.

Varni JW, Seid M, Kurtin PS. PedsQL 4.0: reliability and validity of the Pediatric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations. *Med Care* Aug 2001;39(8):800-12.

Varni JW, Seid M, Smith Knight T, et al. The PedsQL in pediatric rheumatology: reliability, validity, and responsiveness of the Pediatric Quality of Life Inventory Generic Core Scales and Rheumatology Module. *Arthritis Rheum* Mar 2002;46(3):714-25.