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Title: A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group, Safety and Efficacy Study of a Range of Linaclotide Doses Administered Orally to Children, Ages 6 to 17 Years, Who Fulfill Modified Rome III Criteria for Child/Adolescent Functional Constipation (FC)

Protocol Amendment 3 Date: 16 May 2017

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 Linaclotide Doses Administered Orally to
Children, Ages 6 to 17 Years, Who Fulfill Modified Rome III Criteria for
Child/Adolescent Functional Constipation (FC)**

LIN-MD-62

IND #63,290

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Confidentiality Statement

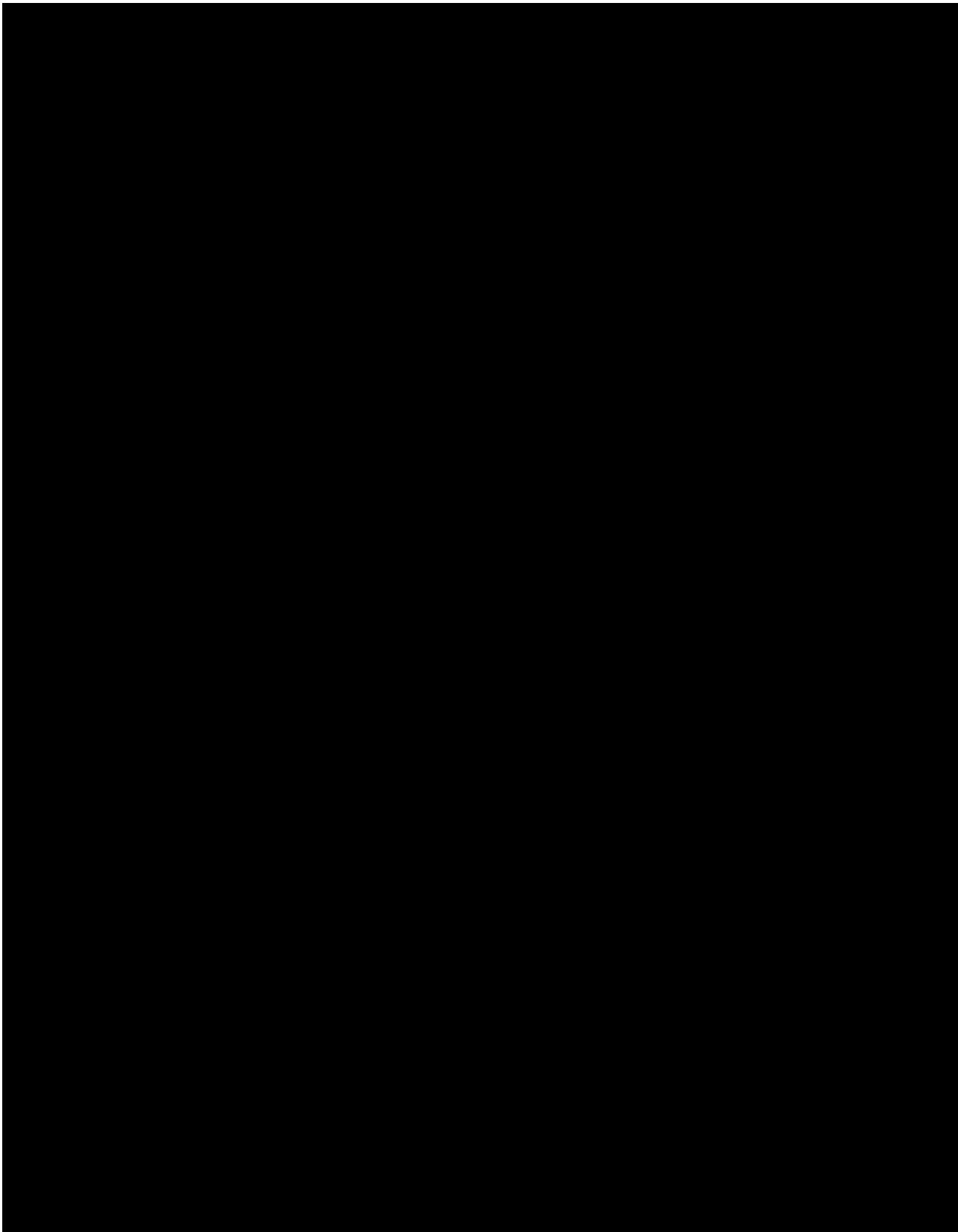
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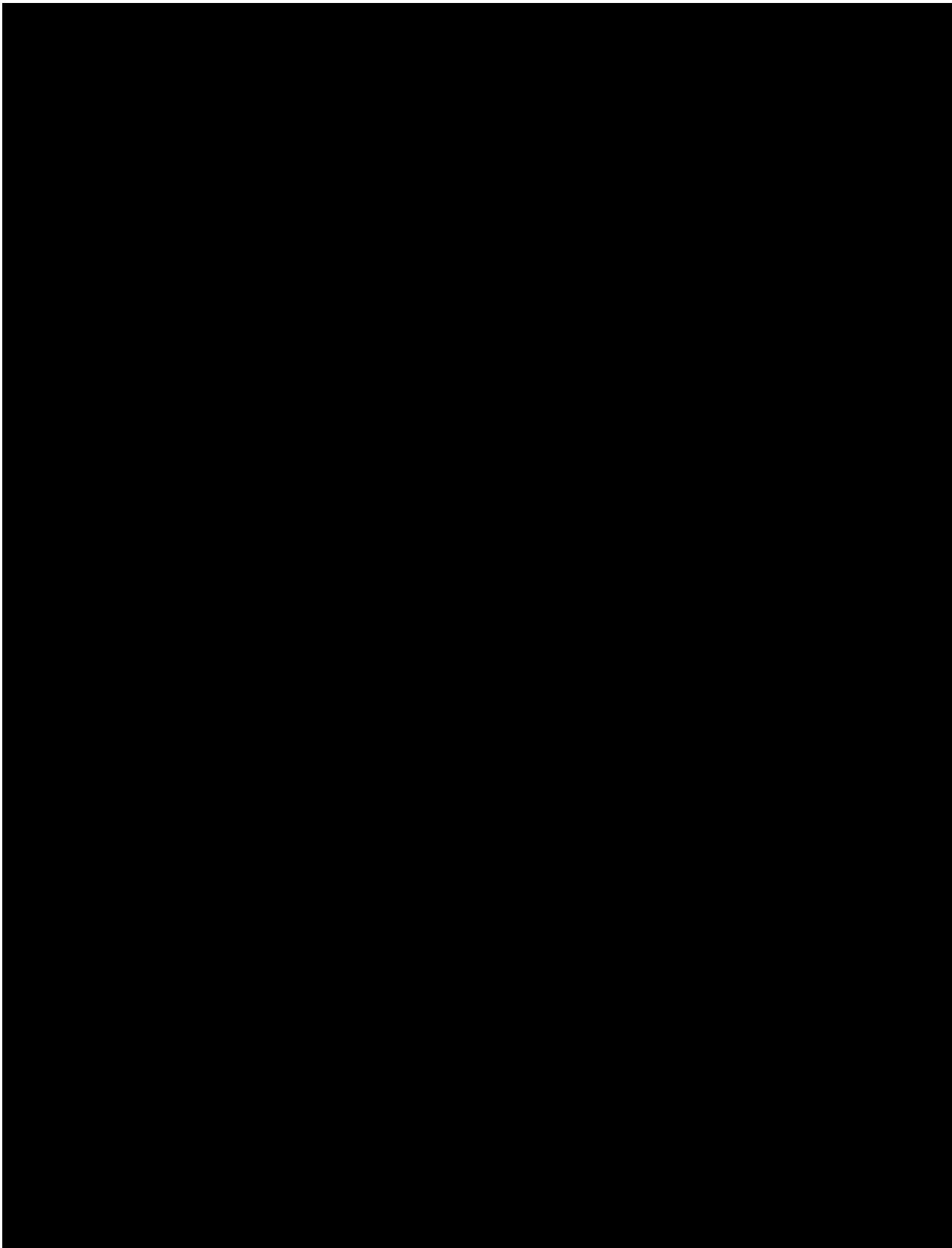
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SYNOPSIS AND SCHEDULE OF EVALUATIONS

CLINICAL STUDY SYNOPSIS: Study LIN-MD-62	
Title of Study	A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group, Safety and Efficacy Study of a Range of Linaclootide Doses Administered Orally to Children, Ages 6 to 17 Years, Who Fulfill Modified Rome III Criteria for Child/Adolescent Functional Constipation (FC)
Study Sites (Country)	Approximately 50 - 100
Development Phase	2
Objective	To evaluate the dose response, safety, and efficacy of 4 weeks of treatment with 1 of 3 linaclootide doses (A, B, or C) or 145 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 6 to 17 years of age who fulfill 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 160 patients are planned. (35 placebo patients, 35 patients per linaclootide dose A, B, or C, and 14-19 patients for the approved adult linaclootide dose, 145 ug [in the 12-17 years of age group only]), with a minimum of 40% of patients per age group (6-11 years and 12-17 years).
Diagnosis and Main Criteria for Inclusion	Male and female pediatric patients 6 to 17 years of age with a diagnosis of FC based on the modified Rome III criteria for child/adolescent FC
Test Product, Dosage, and Mode of Administration	<p>Patients 6 to 11 years of age: linaclootide liquid oral solution taken once daily Patients 12 to 17 years of age: linaclootide solid oral capsule or liquid oral solution taken once daily</p> <p>Dosage is weight-based for the 6 to 11 years of age group: Patients 6 to 11 years of age (weight 18 to < 35 kg)</p> <ul style="list-style-type: none"> • Dose A: 9 ug • Dose B: 18 ug • Dose C: 36 ug <p>Patients 6 to 11 years of age (weight \geq 35 kg)</p> <ul style="list-style-type: none"> • Dose A: 18 ug • Dose B: 36 ug • Dose C: 72 ug <p>Patients 12 to 17 years of age</p> <ul style="list-style-type: none"> • Dose A: 18 ug • Dose B: 36 ug • Dose C: 72 ug • Approved adult dose: 145 ug (for safety and exploratory efficacy only)
Duration of Treatment	<p>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 (\geq 28 days) Double-blind Treatment Period, and finally followed by a 1-week (\geq 7 days) Post-treatment Period.</p> <p>Patients will not receive investigational product during the Pretreatment Period or the Post-treatment Period.</p>

Reference Therapy, Dosage, and Mode of Administration	Patients 6 to 11 years of age: matching placebo liquid oral solution taken once daily Patients 12 to 17 years of age: matching placebo solid oral capsule or liquid oral solution 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)
Safety Measures	Adverse event recording. [REDACTED]
	[REDACTED]
	[REDACTED]
	The primary efficacy parameter is change from baseline in 4-week overall SBM frequency rate (SBMs/week) during the Treatment Period. Comparison between each linaclotide dose (A, B, and C) and placebo will be performed using an analysis-of-covariance (ANCOVA) model (based on the observed data) with treatment and age group (6 - 11 years and 12 - 17 years of age) as factors and baseline value as a covariate. No multiplicity adjustment will be applied in this dose-ranging study. [REDACTED]
	[REDACTED]
	The change-from-baseline secondary efficacy parameters (<i>except fecal incontinence daytime symptoms</i>) defined for the Treatment Period will be analyzed in a similar way as the primary efficacy parameter (with A, B, and C linaclotide dose levels and placebo) using the ANCOVA model. [REDACTED]
	<i>The change from baseline in 4-week fecal incontinence daytime symptoms based on evening diary will be summarized only based on descriptive statistics.</i>
Statistical Methods	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). [REDACTED]
	[REDACTED]
	[REDACTED]
	[REDACTED]





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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 Safety Monitoring Board
██████████	██████████
eCRF	electronic case report form
EDC	electronic data capture
eDiary	electronic diary
FC	functional constipation
FDA	Food and Drug Administration
FGID	functional gastrointestinal disorder
FR	Federal Register
GCP	good clinical practice
GI	gastrointestinal
HIPAA	Health Insurance Portability and Accountability Act
██████████	██████████
IBS	irritable bowel syndrome

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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
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
PID	patient identification
PK	pharmacokinetic
PRO	patient reported outcome
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
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 Good Clinical Practice (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. A unique patient identification (PID) number will be assigned according to Section [9.4.3](#).

5.3.1 Patient Assent Form

To participate in the study, the patient 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 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 their 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, 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.

Functional constipation (FC) is a 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. It often causes significant distress to the child and family, and has a significant impact on healthcare costs. Children who experience painful bowel movements (BMs) may avoid defecation as long as possible, thereby exacerbating the constipation-associated symptoms. At present, the most widely accepted definitions for childhood FC are the Rome III definitions. Abdominal pain is a frequent associated symptom, but its presence is not considered necessary for FC ([Tabbers et al, 2014](#)).

Present guidelines ([Constipation Guideline Committee, 2006](#)) for the treatment of childhood functional constipation recommend a number of agents for disimpaction and relief of constipation, including polyethylene glycol (PEG), other osmotic laxatives (eg, lactulose), lubricants (eg, mineral oil), stimulant laxatives, and enemas. However, some of these agents may be challenging to administer to children ([Hyman et al, 2014](#)), and a meta-analysis revealed that only 61% of treated children fully recovered from constipation by 6 to 12 months after presentation ([Pijpers et al, 2010](#)). In addition, there are no FDA approved products for FC in children. Thus, effective treatment alternatives are needed to provide symptomatic relief in children and adolescents with functional constipation, and the safety and efficacy of such alternatives should be demonstrated in adequate and well controlled studies in children.

7.1 SUMMARY OF LINACLOTIDE PROPERTIES

Linaclotide, 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, 2013) and in the European Union for moderate to severe IBS-C. By activating guanylate cyclase subtype C, orally administered linaclotide has been found to increase both intestinal fluid secretion and intestinal transit and to also decrease visceral pain in animal models. Linaclotide 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 linaclotide, 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

Linaclotide 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 linaclotide that culminated in FDA and European Medicines Agency (EMA) 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 adult 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 linaclotide 290 ug (the adult dose subsequently approved by FDA) administered as a solid oral capsule for 12 or 26 weeks, respectively. In these studies, linaclotide 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 of 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 linaclotide 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 adult studies 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 (\geq 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, 6 to 17 years of age, with FC.

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 145 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 6 to 17 years of age who fulfill 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 145 ug (only patients 12 - 17 years of age) with placebo in pediatric patients, 6 to 17 years of age, with a diagnosis of FC based on modified Rome III Child/Adolescent Criteria (ie, who 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 160 patients with FC 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, 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. Consented patients will be assigned a unique PID number via interactive Web response system (IWRS) (Section 9.4.3) and will be given a single dose of placebo (liquid oral solution for patients 6 to 11 years of age and solid oral capsule or liquid oral solution for patients 12 to 17 years of age) to swallow to confirm their ability and willingness to swallow the investigational product. Patients 6 - 11 years of age who fail the swallow test for the liquid oral solution will be considered screen failures. Patients 12 - 17 years of age who choose or are assigned to the solid oral capsule formulation will repeat the swallow test for placebo solid oral capsule during the Pretreatment Period. There should be at least a 1-week interval between the swallow tests performed for placebo solid oral capsules during the Screening Period and the Pretreatment 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. Patients 12 to 17 years of age who choose or are assigned to the solid oral capsule formulation during the Screening Period will be provided a single dose of placebo solid oral capsule to repeat the swallow test. There should be at least a 1-week interval between the swallow tests performed for placebo solid oral capsules during the Screening Period and the Pretreatment Period. Baseline symptoms will be assessed and inclusion/exclusion criteria will be reviewed. Patients and caregivers will receive full training on the use and completion of the eDiary, and the decision regarding whether a patient can complete the eDiary on his/her own or if he/she requires assistance will be made at the discretion of the caregiver and carried through to study completion.

Additionally, caregivers of patients 6 to 11 years of age will be trained on completing the observer-completed global items once weekly on the eDiary. Throughout this protocol, eDiary is understood to refer to the patient- or interviewer- administered version of the patient reported outcome (PRO) diary on a handheld electronic device. The eDiary will be completed by all patients (or caregivers) twice daily throughout the Pretreatment Period. During the Pretreatment Period, compliance with the eDiary will be defined as completion of both morning and evening assessments for **10** out of the 14 days immediately preceding the Randomization Visit and must be documented before patients are included in the Double-blind Treatment Period.

IWRS registration during the Pretreatment Period will include protocol-permitted rescue medication assignment (ie, senna [oral] or bisacodyl [oral or rectal])

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).

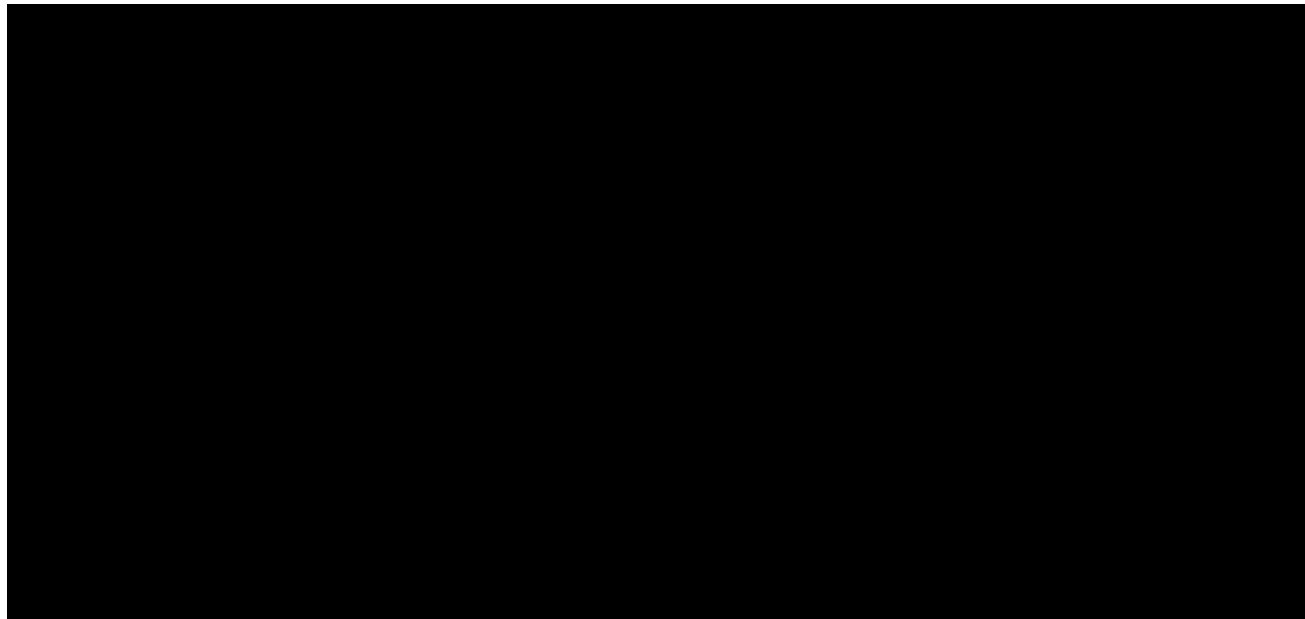
Randomization will be stratified by age group (6 - 11 years of age and 12 - 17 years of age) with a minimum of 40% of patients within each age group. Patients 6 to 11 years of age will be randomized to linaclotide doses (A, B, or C) or placebo in a 1:1:1:1 allocation. Patients 12 to 17 years of age will be randomized to linaclotide doses (A, B, or C, or the approved adult dose, 145 ug) or placebo in a 1:1:1:1:1 allocation ([Table 9.4.5-1](#)).

Patients will complete the eDiary twice daily throughout the Treatment Period and must complete at least 4 weeks of treatment before arriving at the study site for the Week 4 Visit (Visit 5).

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](#).



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 CIC. 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 6 to 17 years of age who fulfill modified Rome III for child/adolescent FC.

The linaclotide doses selected for use in this study were based on prior studies in adult patients with CIC, current product labeling for the treatment of CIC in North America (ie, US, Canada, and Mexico for both indications 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, 6 to 17 years of age (inclusive) at the time the patient provides assent for the study and parent/guardian/LAR has provided signed consent
3. Patient is able to read and/or understand the assessments in the eDiary. If the patient is 6 to 11 years of age and does not meet this criterion, 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

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

6. 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

7. Patient is willing to discontinue any laxatives used before the Pretreatment Visit in favor of the protocol-permitted rescue medicine ([Appendix III](#))

9. 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
10. 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 meets Rome III criteria for Child/Adolescent IBS: At least once per week for at least 2 months before the Screening Visit, the patient has 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

2. 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 (including the morning eDiary assessments reported before administration of first dose of double-blind investigational product on the randomization day)

For more information, contact the Office of the Vice President for Research and the Office of the Vice President for Student Affairs.

The following table summarizes the results of the study.

1000 JOURNAL OF CLIMATE

11. **What is the primary purpose of the *Journal of Clinical Endocrinology and Metabolism*?**

For more information, contact the Office of the Vice President for Research and Economic Development at 319-273-2500 or research@uiowa.edu.

For more information, contact the Office of the Vice President for Research and Economic Development at 319-273-2500 or research@uiowa.edu.

For more information, contact the Office of the Vice President for Research and Economic Development at 319-273-2500 or research@uiowa.edu.

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1. **What is the primary purpose of the study?** The study aims to evaluate the effectiveness of a new treatment for hypertension in a diverse population.

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

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

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 (ie, treatment-related AEs of special interest [Sections 9.5.2.1.1 and 9.5.2.6]). The Investigator should contact the Study Physician if there is any question whether the criteria for an AE of special interest 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
- Non-compliance 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 6 to 11 years of age will be randomized to linaclotide doses (A, B, or C dose) 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 dose or the approved adult dose, 145 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, 30 minutes before their evening meal. Confirmation will be recorded in the source documents that the dosing regimen and dosing instructions were discussed with the patient and caregiver and that written dosing instructions were provided.

Throughout the study, it is recommended that patients take the investigational product at approximately the same time each day (Section 9.4.5).

9.4.1.1 *Rescue Medication*

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

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).

9.4.2 Identity of Investigational Products

All investigational products (linaclotide and placebo) will be supplied to the site by the Sponsor.

[REDACTED]

Immediately before dispensing the investigational product, the Investigator or designee will write the patient's initials (where applicable), PID number, and dispensing date on the label.

[REDACTED] Immediately before dispensing the rescue medication, the Investigator or designee will write the patient's initials (where applicable), PID number, and dispensing date on the label.

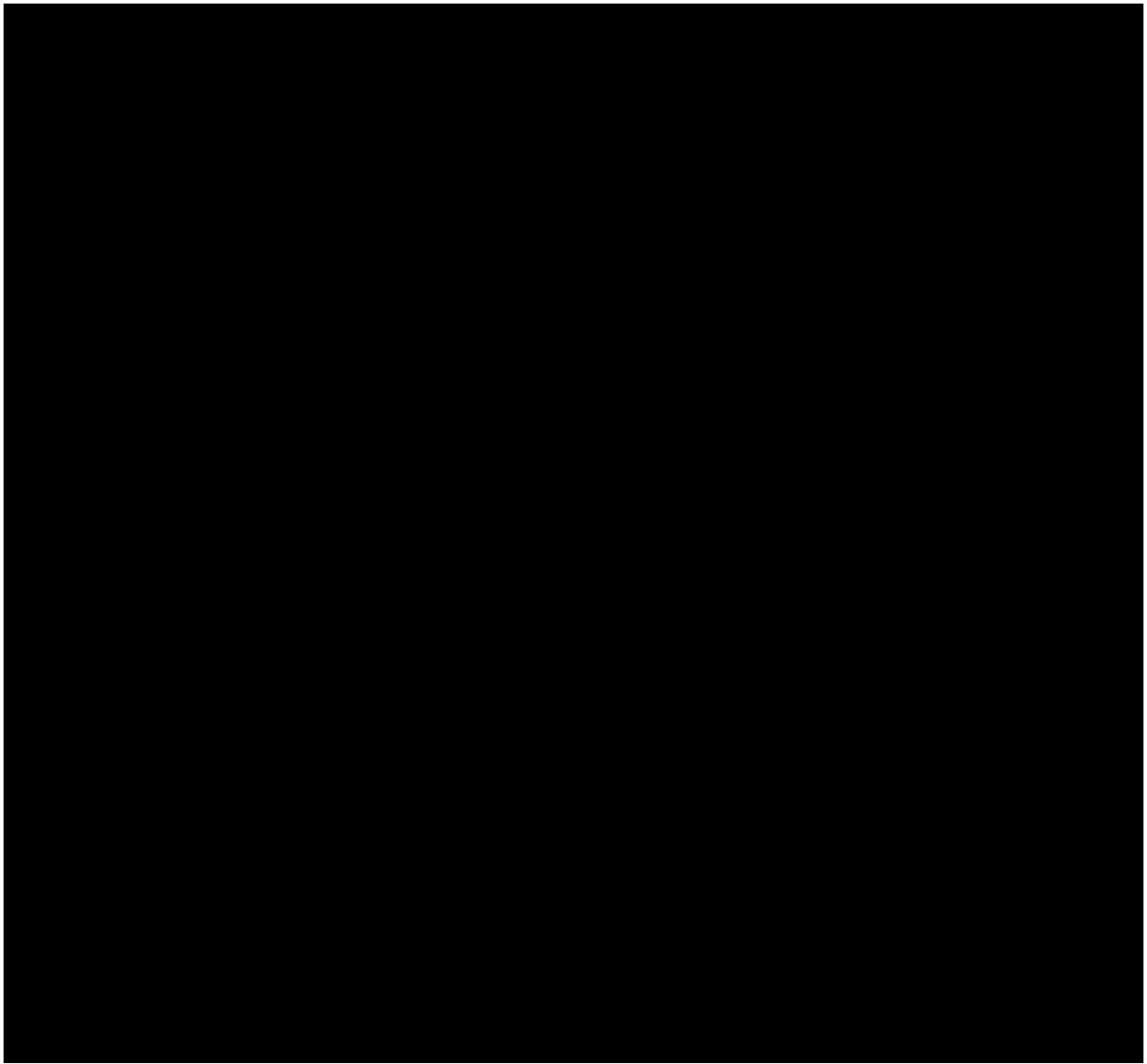
Label requirements listed above will be modified per country-specific requirements.

Investigational products in bottles containing solid oral capsules must be stored at the study site in an appropriate secure area (eg, a locked cabinet in a locked room) at

[REDACTED]

Investigational products in bottles containing liquid oral solution

[REDACTED]



The Investigator or designee is responsible for recording the receipt and use of all investigational products supplied and for ensuring the supervision of the storage and allocation of these supplies. All unused investigational products and dispensed protocol-permitted rescue medications must be returned; and, whenever investigational products and dispensed protocol-permitted rescue medications are returned, unit counts must be performed (Section 9.4.9). All investigational products and dispensed rescue medications must be accounted for. At the end of the study, all unused investigational products, empty investigational product/dispensed rescue medication packages and unused rescue medications should be returned to the Sponsor or the local distributor at the address provided in the Study Reference Binder.

9.4.3 Method of Assigning Patients to Treatment Groups

After a patient and parent/LAR/caregiver sign the assent/permission/consent at the first Screening Visit (Visit 1), study personnel will register the patient in the IWRS, and the system will assign the patient a sequential PID number. The first patient entered in the system at each study site will be assigned the first number in the sequence by the system.

[REDACTED] This PID number will be used to identify the patient throughout the study (ie, at all study phases).

The study site must contact the IWRS at screening in order to obtain the kit number for the investigational product that will be dispensed to the patient throughout the study.

Confirmation of the investigational product number will be faxed or e-mailed (per the study site's preference) to the study site following each assignment. A detailed description of IWRS procedures is contained in the IWRS Manual in the Study Reference Binder.

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, 145 ug once daily was approved for CIC. Pediatric patients 6 to 11 years of age will be dosed using a weight-based approach; patients will receive 1 of 3 linaclotide doses. For patients who weigh < 35 kg, the doses administered will correspond to about 0.25 to 0.5, 0.5 to 1, or 1 to 2 ug/kg. For patients who weigh \geq 35 kg, the doses will not exceed 0.5, 1, or 2 ug/kg. Pediatric patients 12 to 17 years of age will receive 1 of 4 linaclotide dose levels. The approved adult dose level of 145 ug for CIC 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 taken 30 minutes before the evening meal on a consistent, ongoing basis.

Patients who continue to meet all eligibility criteria on Visit 3 (Day 1) will be assigned a randomization number, dispensed the corresponding double-blind investigational product, and receive their first dose of investigational product at the study site. Patients 6 to 11 years of age will receive 1 or more bottles containing the liquid oral solution. Patients 12 to 17 years of age will receive 1 or more bottles containing solid oral capsules or liquid oral solution, based on choice or assignment. Patients will be instructed to take their assigned dose orally as a single daily dose at approximately the same time each day, 30 minutes before their evening meal. Any alternate schedule must be approved and documented by the Investigator.

Dosage will be determined by weight for patients 6 to 11 years of age (18 to < 35 kg or ≥ 35 kg) ([Table 9.4.5-1](#)).

Patients will be instructed to return the empty/partially used bottle at the next study visit whether there is any remaining investigational product or if the bottle is empty. Investigational product will be dispensed as per the schedule shown in Section [2.0](#).

Table 9.4.5-1. Double-blind Dosing Regimen

		4-Week Treatment Period			
Age Group	Weight	Linaclotide Dose A	Linaclotide Dose B	Linaclotide Dose C	Approved Adult Dose
Patients 6 -11 years ^a					
18- < 35 kg	18 ug	9 ug	18 ug	36 ug	—
	placebo	placebo	placebo	placebo	—
	≥ 35 kg	18 ug	36 ug	72 ug	—
	placebo	placebo	placebo	placebo	—
Patients 12 -17 years ^b					
		18 ug	36 ug	72 ug	145 ug ^c
		placebo	placebo	placebo	placebo

a Patients 6 to 11 years of age will receive linaclotide or placebo in a liquid oral solution.

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

c Approved 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 for the investigational product to be identified for the medical management of the patient. The Investigator has to notify the study physician immediately ([Appendix II](#)) and a full written explanation must be provided if the blind is broken. Before the investigational product is unblinded, every attempt should be made to discuss the case with the Study Physician. Breaking the code at the study site will immediately disqualify the patient from further participation in the study.

Treatment codes may be broken by Patient Safety for regulatory reporting purposes. In such cases, the study staff will be kept blinded and the patient will not need to be disqualified from the study. Representatives of the bioanalytical team may be unblinded prior to database lock in support of PK sample analysis. The unblinding of the bioanalytical representatives is to be carried out in a secure manner following the Sponsor's standard operating procedures. Extreme care will be taken to ensure no other individuals outside the bioanalytical team will be unblinded.

For IWRS Unblinding

In an emergency, the Investigator can obtain the treatment assignment of any patient at his or her study site through the IWRS. In an emergency, the Investigator will access the IWRS to break the blind and record the unblinding in the eCRF.

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 eDiary and evening eDiary). Patients and caregivers must be able to read and understand the eDiary as a condition for study participation (inclusion criterion 3). If the patient is 6 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 Secondary Efficacy Assessments

In addition to the primary efficacy assessment, 6 secondary efficacy assessments are included in the study regarding abdominal symptoms, BM characteristics, and fecal incontinence that will be determined by the daily assessments recorded in the eDiary.

Abdominal Pain – Daytime

For this parameter, patients will rate their abdominal pain by responding to the following in the evening eDiary:

- 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

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

Abdominal Bloating - Daytime

For this parameter, 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?
 - Yes
 - No
 - I don't know what you mean
 - 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

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

Fecal Incontinence - Daytime

Patients will record their episodes of fecal incontinence by responding to the following evening assessments.

- From when you got up this morning until now, did you have a pooping accident (even a little)?
 - Yes

No

- From when you got up this morning until now, did you have any poop marks or stains on your underwear?

- Yes
- No
- I don't know

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

the *Journal of the American Statistical Association* (1990, 85, 13-21) and the *Journal of the Royal Statistical Society, Series B* (1991, 53, 393-415). The latter paper also contains a detailed description of the *Bayesian* approach to the analysis of the data. The *Bayesian* approach is based on the use of a prior distribution for the parameters of the model, and the posterior distribution is obtained by combining the prior distribution with the information contained in the data. The posterior distribution is then used to obtain estimates of the parameters and to make inferences about the parameters. The *Bayesian* approach is a powerful tool for the analysis of complex data sets, and it has been used in a variety of applications, including the analysis of astronomical data, the analysis of medical data, and the analysis of social data.

1. **What is the primary purpose of the proposed legislation?**

11. **What is the primary purpose of the proposed system?**

— [REDACTED] — [REDACTED]

1

— [REDACTED] — [REDACTED]

10 of 10

1 [REDACTED]

1

11. **What is the primary purpose of the *Journal of Clinical Endocrinology and Metabolism*?**

— [REDACTED]

100% of the time, the system is able to correctly identify the target class.

[REDACTED]

[REDACTED]

10

113. **What is the name of the person who is the subject of the investigation?**

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A black and white image showing a white rectangular area on the right and a black L-shaped block on the left.

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.

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 (e.g., 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 poststudy 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.

9.5.2.6 *Immediate Reporting of Serious Adverse Events*

The Sponsor is required to inform worldwide regulatory authorities of SAEs that meet specific criteria. Therefore, the Sponsor must be notified immediately regarding any SAE that occurs after informed consent is obtained.

Within 24 hours of learning of any AE that meets one of the criteria for an SAE, the study site personnel must report the event to Forest Global Drug Safety on the SAE Form for Clinical Trials. The Sponsor’s Study Physician may also be notified by telephone.

If, during follow-up, any non-serious AE worsens and eventually meets the criteria for an SAE, that AE should be recorded as a new SAE.

The site must transmit the SAE Form for Clinical Trials to the SAE fax number shown below. Even if an initial report is made by telephone, the SAE Form for Clinical Trials completed with all available details must still be faxed within 24 hours of knowledge of the event at the study site.

Supplemental information should be submitted as soon as available and may include laboratory results, radiology reports, progress notes, hospital admission and emergency room notes, holding and observation notes, discharge summaries, autopsy reports, and death certificates.

The Investigator is expected to take all therapeutic measures necessary for resolution of the SAE. Any medications or procedures necessary for treatment of the SAE must be recorded on the appropriate pages of the patient's eCRF. All SAEs are to be followed by the study staff until resolution or until the SAE is deemed stable. The Sponsor may contact the study site to solicit additional information or follow up on the event.

Fax the SAE Form for Clinical Trials to the Sponsor.

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[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

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[REDACTED]

[REDACTED]

Term	Percentage
GMOs	~85%
Organic	~98%
Natural	~95%
Artificial	~75%
Organic	~98%
Natural	~95%
Artificial	~75%
Organic	~98%
Natural	~95%
Artificial	~75%

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- [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. Electronic data capture (EDC) functionality training is provided via computer-based training to train Investigators and authorized designees on recording the data in the eCRFs using the EDC system. After the first patient is enrolled, the Sponsor's representative, a Regional Site Manager or designee, will periodically monitor the progress of the study by conducting on-site visits. This Regional Site Manager or designee will review query statuses remotely, possibly warranting more frequent communication and/or site visits with the Investigator and the study site staff. The Investigator will make available to the Regional Site Manager or designee source documents (written notes and electronic medical records, if used), signed consent forms, and all other study-related documents. The Investigator and the study site staff will be responsible for data entry of patient data into the eCRFs via the EDC system, resolving data queries generated via the EDC system and providing missing or corrected data. The Investigator or designee will be responsible for approving all changes performed on the data, and endorsing the patient data within the EDC system. This approval method will include applying an electronic signature linked to a uniquely assigned username and password that together will represent a traditional handwritten signature used in the past.

The study site staff will be fully trained by a representative of the eDiary vendor on the use of the eDiary and how to train patients and caregivers in the use of the eDiary (ie, how to complete their daily and weekly assessments and download their data). The study site staff will then be responsible for ensuring that all patients and caregivers enrolled in the study are given full training and support materials in relation to the completion of the eDiary.

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. Patient's data are to be entered into the EDC system by the Investigator or designee using their assigned EDC user account. After data entry into the EDC system by the Investigator or designee, a combination of manual and programmatic edit checks will be used to review the data for completeness, logic, and adherence to study protocol. As a result of these edits checks, data monitoring and reviews; queries may be electronically issued to the site and should be answered electronically via the EDC system.

Each query will carry identifying information (assigned username, date and time) to assist the Sponsor and the Investigator on the origin of the data clarification request and the response provided by the Investigator. All data changes made to the patient's data via a data query will be approved by the Investigator prior to final database lock.

After all data have been reviewed and all issues have been resolved, the database will be locked.

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.



9.7 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 on 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 [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 [REDACTED]

9.7.3 Demographics and Other Baseline Characteristics

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

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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] . 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]

Baseline

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

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.

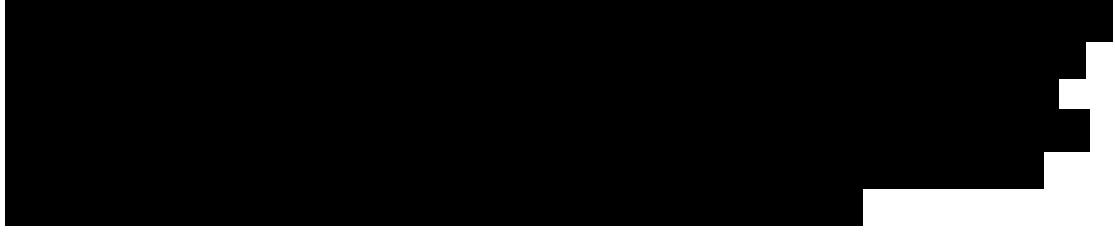
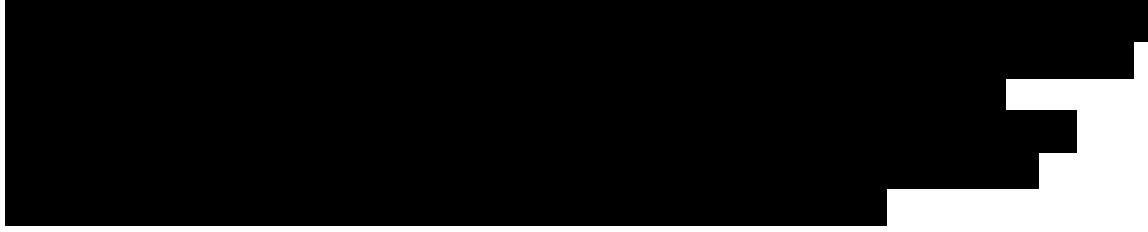
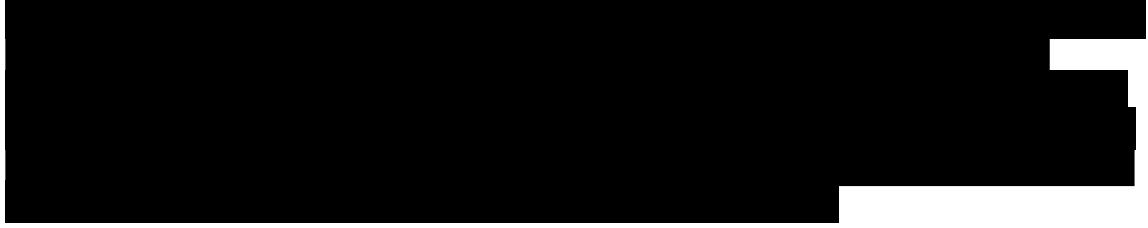
An observed-cases approach to missing postbaseline data will be applied. The overall analysis (incorporating both age groups) including placebo and linaclootide doses (A, B, and C) will be the analysis to evaluate the main objective of this study.

[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 (6 - 11 years of age and 12 - 17 years of age) as factors and baseline value as a covariate. Least squares means (LSMs) for each treatment group, differences in LSMs between each linaclotide treatment group versus placebo, associated 2-sided 95% CIs for these differences in LSMs, and the corresponding statistical test p-values will be reported.



9.7.5.2 Secondary Efficacy Parameters

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

Change From Baseline in 4-Week Abdominal Pain Daytime Symptoms Based on Evening Assessment

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.

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.

Change From Baseline in 4-Week Abdominal Bloating Daytime Symptoms Based on Evening Assessment

Abdominal bloating 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 bloating 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 bloating daytime symptoms during the Treatment Period are defined as the average of the nonmissing daily abdominal bloating daytime symptoms reported in evening assessments in the eDiary during the 4-week Treatment Period.

Change From Baseline in 4-Week Overall CSBM Frequency Rate (CSBMs/week) During the Treatment Period

A patient's 4-week overall CSBM frequency rate will be the CSBM rate (CSBMs/week) calculated over the 4-week Treatment Period. The numerator of the CSBM rate (CSBMs/week) during the 4-week Treatment Period will be derived based on the total number of CSBMs a patient reported during this period in his/her morning and evening eDiary.

Change From Baseline in 4-Week Fecal Incontinence Daytime Symptoms Based on Evening Assessment

Fecal incontinence will be collected daily in the evening eDiary. Patients are asked two questions (as discussed in Section 9.5.1.3) to cover the interval from when the patient wakes up until bedtime as part of the evening assessment. Any "yes" response in either of these questions will be counted as presence of fecal incontinence. The patient's 4-week fecal incontinence daytime symptoms during the Treatment Period are defined as the average of the nonmissing daily fecal incontinence daytime symptoms reported in evening assessments in the eDiary during the 4-week Treatment Period.

Analysis Method for Change-From-Baseline Parameters

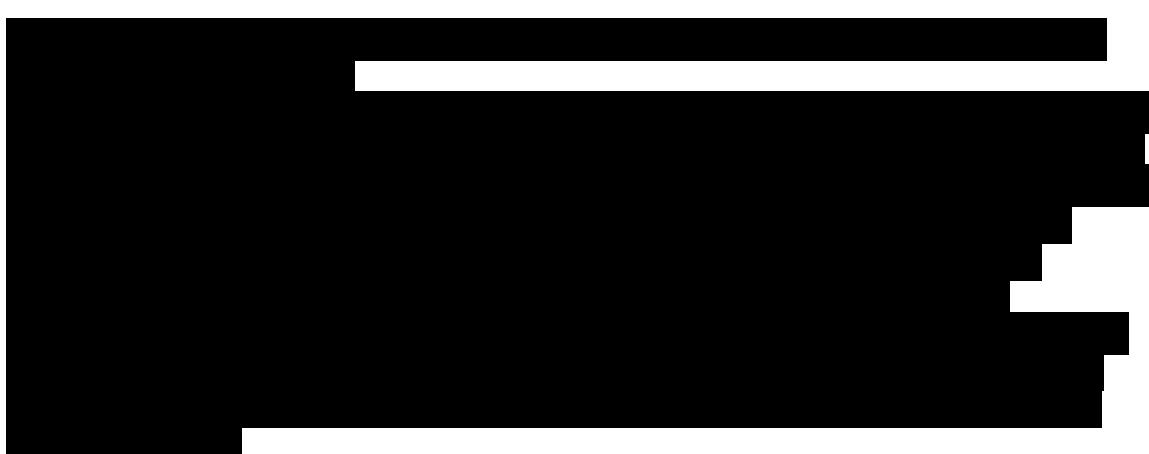
For each change-from-baseline parameter (*except change from baseline in 4-week fecal incontinence daytime symptoms based on evening assessment*), each linaclotide dose group (A, B, and C) will be compared with the placebo group using an ANCOVA model with treatment (linaclotide doses A, B, and C, and placebo) and age group (6 - 11 years of age and 12 - 17 years of age) as factors and baseline value as a covariate. LSMs for each treatment group, differences in LSMs between each linaclotide treatment group versus placebo, associated 2-sided 95% CIs for these differences in LSMs, and the corresponding statistical test p-values will be reported.



Change from baseline in 4-week fecal incontinence daytime symptoms based on evening assessment will be summarized based on descriptive statistics by treatment group.



In addition, stool consistency and straining during the analysis period (based on morning and evening assessments) will also be derived as the mean of the patient's non-missing, SBM-associated scores during the analysis period (similar to LIN-MD-31 and MCP-103-302 adult studies).



[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[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]

[REDACTED] 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]

[REDACTED]

[REDACTED] [REDACTED]

[REDACTED]

9.7.8 Interim Analysis

No interim analysis is planned for this study.

[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. An integrated clinical and statistical report will be prepared at the completion of the study.

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/EC 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/EC, as stated in Section [5.1](#)
- A copy of the IRB/EC-approved ICF
- A copy of the HIPAA authorization form, or other local privacy applicable forms
- A list of the IRB/EC 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. At study initiation, a representative from the Sponsor will inventory the investigational products at the site. The Investigator must maintain adequate records documenting the receipt and disposition of all study supplies. The Sponsor will supply forms on which to record the date the investigational products were received and a dispensing record in which to record each patient's use. All unused investigational products must be returned to the Sponsor. It is the Investigator's responsibility to ensure that patients return their investigational product.

11.4 CASE REPORT FORMS

All patient data relating to the study will be recorded on eCRFs to be provided by the Sponsor through the EDC system. The investigator is responsible for verifying that all data entries in the eCRFs are accurate and correct by electronically signing the completed eCRF casebook submitted to the Sponsor. The investigator must maintain and retain accurate documentation that supports the information entered into the EDC system for source document verification and possible regulatory inspection.

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

All patient records will only be identified by initials (where applicable) and PID number. Patients' names are not to be transmitted to the Sponsor. The Investigator will keep a master patient list on which the PID number and the full name, address, and telephone number of each patient are listed.

12.0 **INVESTIGATOR'S STATEMENT**

I agree to conduct the study in accordance with this protocol amendment (LIN-MD-62, 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; 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/EC 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

Contact information for the Sponsor's personnel is maintained in the Study Reference Binder.

APPENDIX III. CONCOMITANT MEDICATIONS

Rescue Medication

Rescue medication will be provided [REDACTED]

[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]

[REDACTED]

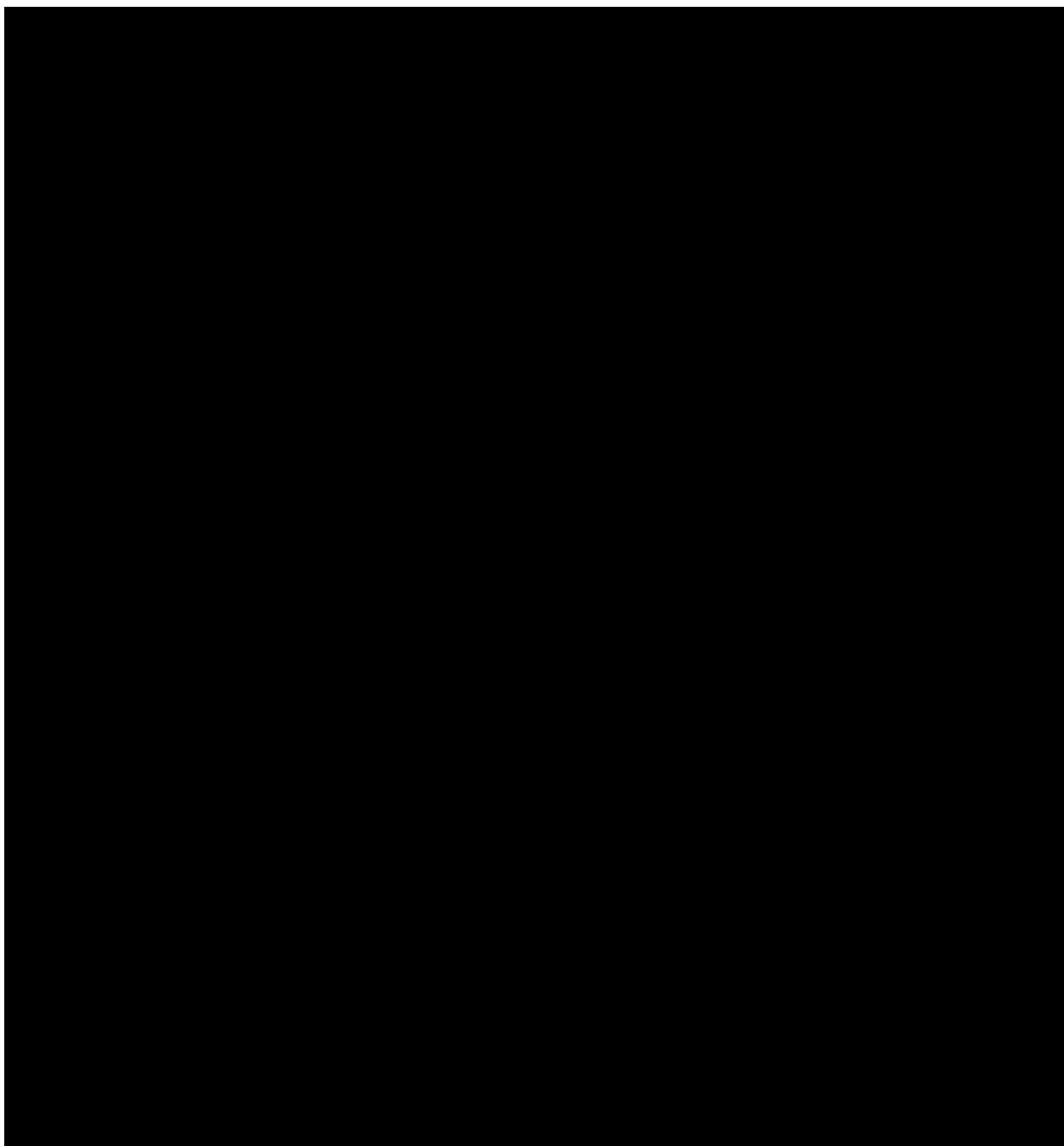
APPENDIX IV. BLOOD SAMPLING AND SHIPPING INSTRUCTIONS

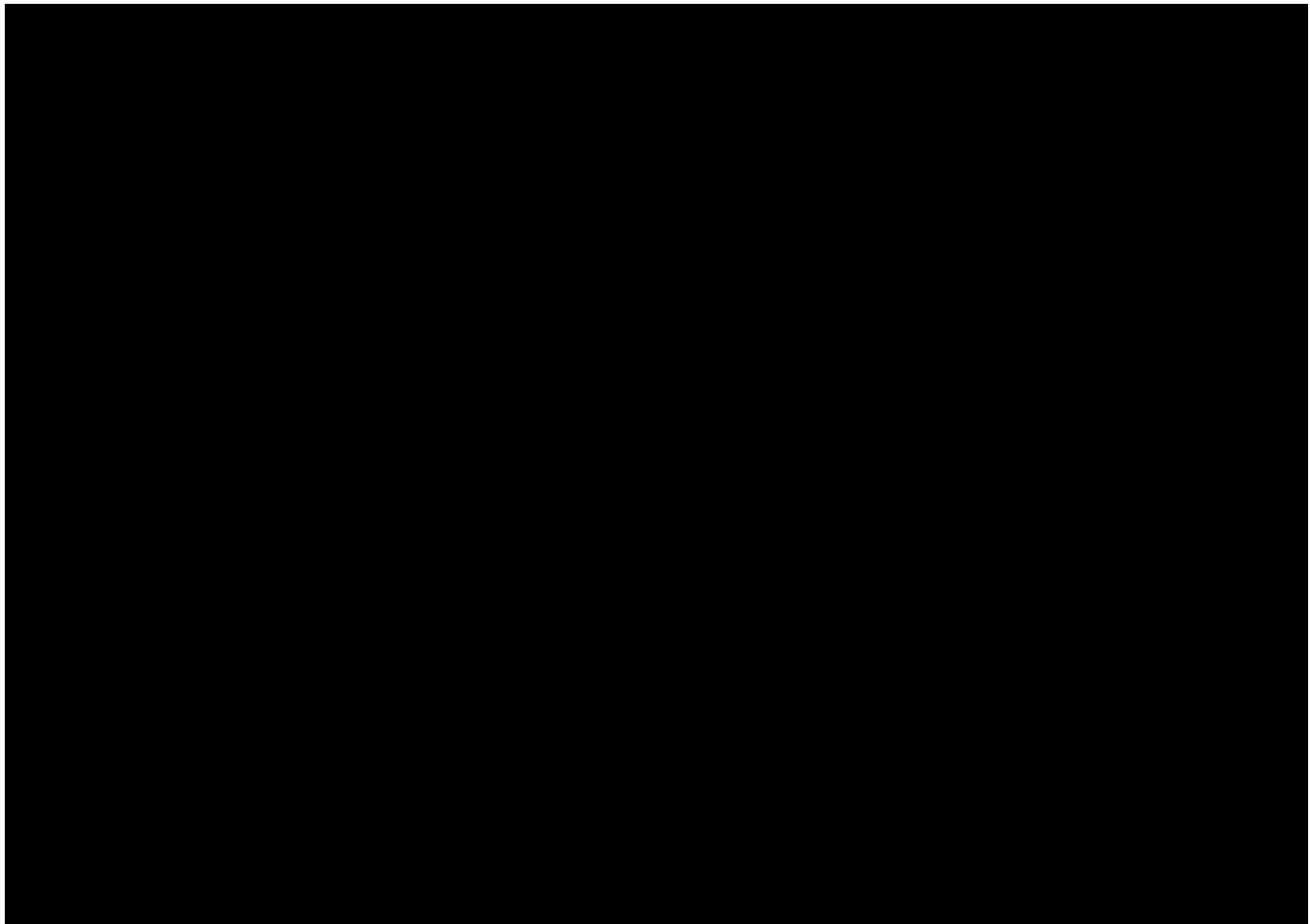
Blood collection procedure

Blood and urine samples will be collected, handled, and processed according to the instructions provided in the Central Laboratory Manual.

Sample shipping guide from the study center to the central laboratory

Samples will be shipped from the study site to the central laboratory on the day of collection or as specified in the Central Laboratory Manual. The central laboratory will provide packaging, labeling, and shipping instructions.





14.0 LITERATURE CITED

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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.

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Study MCP-103-201: a randomized, multicenter, double-blind, placebo-controlled, dose-range-finding, parallel-group, phase 2 trial of oral linaclotide acetate administered to patients with chronic constipation. Cambridge, MA: Ironwood Pharmaceuticals, Inc: 2009 Aug 07.

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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.

Study MCP-103-309: a Phase 3, Randomized, Double-blind, Placebo controlled, Parallel-group Trial of Linaclotide (72 ug or 145 ug) Administered Orally for 12 Weeks to Patients with Chronic Idiopathic Constipation. Cambridge, MA: Ironwood Pharmaceuticals, Inc; 2010 Feb 10.

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

SUMMARY OF CHANGES TO PROTOCOL

**A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group,
Safety and Efficacy Study of a Range of Linaclotide Doses Administered Orally to
Children, Ages 6 to 17 Years, Who Fulfill Modified Rome III Criteria for
Child/Adolescent Functional Constipation (FC)**

LIN-MD-62

IND #63,290

Original Protocol Date: 15 Apr 2015

Amendment #1: 13 Aug 2015

Amendment #2: 11 Sep 2016

Amendment #3: 16 May 2017

Confidentiality Statement

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1.0 INTRODUCTION

In response to protocol comments provided by the FDA on 12 Jun 2015, Amendment #1 to the original protocol was completed 13 Aug 2015. In a subsequent effort to stimulate enrollment into the study and to respond to European regulatory advice, Amendment #2 was completed on 11 Sep 2016. In order to comply fully with FDA instructions relating to follow-up to adverse events, and to incorporate additional FDA feedback, Amendment #3 was developed.

Amendment #1 specified the following changes to the original protocol LIN-MD-62, dated 15 Apr 2015:

- to allow patients 12-17 years of age to select liquid oral solution as an alternative to the previously specified solid oral capsules
[REDACTED]
- to include a repeat swallow test for patients who receive capsules to assess those patients' ability to swallow capsules on 2 occasions a minimum of 1 week apart
[REDACTED]
[REDACTED]
[REDACTED].

Amendment #2 specified the following changes to protocol LIN-MD-62 as previously amended, dated 13 Aug 2015:

- to change the name of the sponsor
- to increase the number of study sites
- to correct the duration of treatment
- to update Sections 9.1.2, 9.3.1, 9.5.5.2, and 9.5.5.3 to require compliance with eDiary on 8 out of 14 days
- to supplement clinical experience information with details of recently completed studies
[REDACTED]
- to clarify inclusion criterion #5 and to allow fecal incontinence as part of Rome III criteria in #6

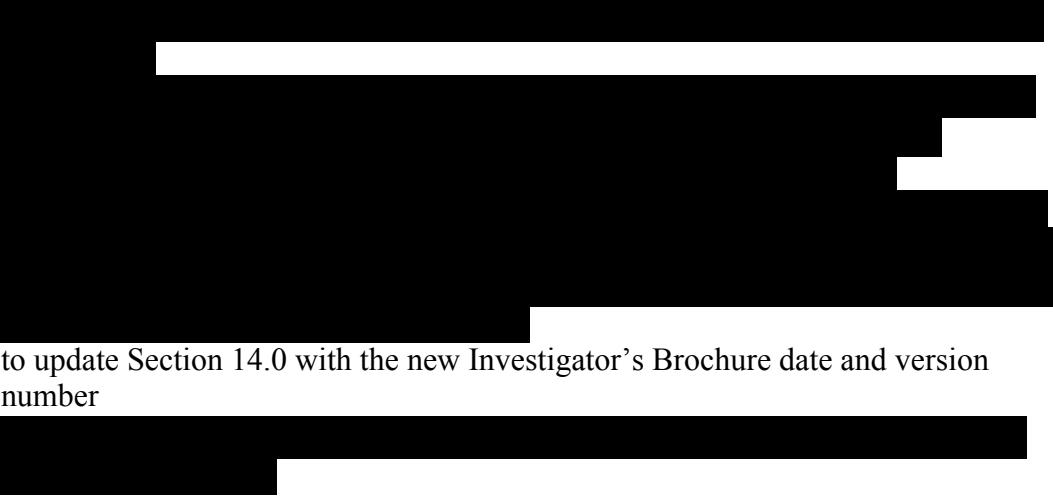
- to clarify exclusion criteria # 7
- to broaden the text describing rescue medications and use of IWRS
- to remove the use of patient's initials (where applicable)
- to clarify monitoring of treatment compliance and accountability
- to reorder the secondary efficacy assessments, to add fecal incontinence as a secondary efficacy assessment, and to move abdominal pain-daytime from the additional efficacy assessments to the secondary efficacy assessments

- to clarify the AE time window definition and to update SAE reporting contact information

In addition, minor clarifications of previous text were made in several sections of the document.

Amendment #3 specifies the following changes to protocol LIN-MD-62 as previously amended, dated 11 Sep 2016:

- to update the Synopsis (Statistical Methods) regarding fecal incontinence data summarization
- to update Section 7.1 with the new Investigator's Brochure date
- to update Section 7.2.1 to supplement clinical experience information with details of recent post-marketing experience
- to update Sections 9.1.2, 9.3.1, 9.5.5.2, and 9.5.5.3 to require compliance with eDiary on at least 10 of 14 days
- to update the footnote to Table 9.4.2-1 with correct abbreviation description for NF (National Formulary)



- to update Section 14.0 with the new Investigator's Brochure date and version number

Not summarized here, minor clarifications of previous text were made in several sections of the document.

2.0 **GLOBAL CHANGES**

None.

3.0 SECTIONS DELETED

None.

4.0 **SECTIONS ADDED**

None.

5.0 **REVISIONS**

5.1 SECTION 2.0 SYNOPSIS AND SCHEDULE OF EVALUATIONS (STATISTICAL METHODS)

Rationale: The synopsis (Statistical Methods) has been revised to indicate that fecal incontinence daytime symptoms based on evening diary will be only summarized based on descriptive statistics.

The second paragraph of statistical methods has been updated and now reads as follows:

The change-from-baseline secondary efficacy parameters (except fecal incontinence daytime symptoms) defined for the Treatment Period will be analyzed in a similar way as the primary efficacy parameter (with A, B, and C linaclotide dose levels and placebo) using the ANCOVA model. An exploratory analysis with the approved adult linaclotide dose, 145 ug, within the 12 to 17 year age group will be provided. The change from baseline in 4-week fecal incontinence daytime symptoms based on evening diary will be summarized only based on descriptive statistics.

5.2 SECTION 7.1, SUMMARY OF LINACLOTIDE PROPERTIES

Rationale: The Investigator's Brochure has been updated.

The last sentence of the section now reads as follows:

Refer to the Investigator's Brochure for a more detailed description of the chemistry, pharmacology, efficacy, and safety of linaclotide, based on studies conducted in animals, healthy volunteers, and in adult patients with IBS-C and CIC (Investigator's Brochure, 2015-2016).

5.3 SECTION 7.2.1, OTHER INFORMATION

Rationale: Updated post-marketing experience has become available.

A second paragraph that reads as follows has been added to this section:

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.

5.4 SECTION 9.1.2 PRETREATMENT PERIOD

Rationale: Compliance with the eDiary has been made more stringent at FDA request.

The last sentence of the first paragraph now reads as follows:

During the Pretreatment Period, compliance with the eDiary will be defined as completion of both morning and evening assessments for 8-10 out of the 14 days immediately preceding the Randomization Visit and must be documented before patients are included in the Double-blind Treatment Period.

5.5 SECTION 9.3.1 INCLUSION CRITERIA

Rationale: Compliance with the eDiary has been made more stringent at FDA request.

Inclusion criterion #10 now reads as follows:

Patient or parent/guardian/LAR or caregiver is compliant with eDiary by completing both the morning and evening assessments for 8-10 out of the 14 days immediately preceding the Randomization Visit (Section 9.1.2)

5.6 TABLE 9.4.2-1 INVESTIGATIONAL PRODUCT FORMULATION

Rationale: Previous erroneous footnote text has been corrected.

The footnote text now reads as follows:

NF = National Formulary; nonformulary

Treatment Type	Radiotherapy (%)	Chemotherapy (%)	Surgery (%)	Immunotherapy (%)
1	10	10	10	70
2	10	10	10	70
3	10	10	10	70
4	10	10	10	70
5	10	10	10	70
6	10	10	10	70
7	10	10	10	70
8	10	10	10	70
9	10	10	10	70
10	10	10	10	70
11	10	10	10	70
12	10	10	10	70
13	10	10	10	70
14	10	10	10	70
15	10	10	10	70
16	10	10	10	70
17	10	10	10	70
18	10	10	10	70
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22	10	10	10	70
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93	10	10	10	70
94	10	10	10	70
95	10	10	10	70
96	10	10	10	70
97	10	10	10	70
98	10	10	10	70
99	10	10	10	70
100	10	10	10	70

The figure consists of a 10x10 grid of black bars on a white background. The bars are arranged in a pattern where they are longer in the center and shorter at the edges of each row and column. The bars in the 5th row and 5th column are the longest, spanning almost the full width and height of the grid respectively. The bars in the 10th row and 10th column are the shortest, appearing as small black squares.

5.11 SECTION 9.7.5.1 , PRIMARY EFFICACY PARAMETER

Rationale: Additional sensitivity analysis has been added for primary efficacy parameter

Summary of Changes for Protocol Amendment #3

16 May 2017

A new sentence in the second paragraph that reads as follows has been added to this section:

[REDACTED]

**5.12 SECTION 9.7.5.2 , SECONDARY EFFICACY PARAMETERS
(ANALYSIS METHOD FOR CHANGE-FROM-BASELINE
PARAMETERS)**

Rationale: Clarified analysis for change from baseline in 4-week fecal incontinence daytime symptoms based on evening assessment. [REDACTED]

[REDACTED]

New sentences in the first and second paragraphs, and a new third paragraph, that read as follows have been added to this section:

For each change-from-baseline parameter (except change from baseline in 4-week fecal incontinence daytime symptoms based on evening assessment), each linaclotide dose group (A, B, and C) will be compared with the placebo group using an ANCOVA model with treatment (linaclotide doses A, B, and C, and placebo) and age group (6 - 11 years of age and 12 - 17 years of age) as factors and baseline value as a covariate.

Change from baseline in 4-week fecal incontinence daytime symptoms based on evening assessment will be summarized based on descriptive statistics by treatment group. [REDACTED]

[REDACTED]

[REDACTED]

5.13 SECTION 14.0 LITERATURE CITED

Rationale: The Investigator's Brochure has been updated.

The reference notation now reads as follows:

Linaclotide: Investigator's brochure. Edition ~~10~~11. Cambridge, MA: Ironwood
Pharmaceuticals, Inc; ~~2015 May 15~~2016 Nov 22.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

6.0 INVESTIGATOR'S STATEMENT

I agree to conduct the study in accordance with this protocol amendment (LIN-MD-62, Amendment #3, dated 16 May 2017) and with all applicable government regulations and good clinical practice guidance.

_____ / _____ / _____

Investigator's Signature

Date

Investigator's Name



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

SUMMARY OF CHANGES TO PROTOCOL

**A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group,
Safety and Efficacy Study of a Range of Linaclotide Doses Administered Orally to
Children, Ages 6 to 17 Years, Who Fulfill Modified Rome III Criteria for
Child/Adolescent Functional Constipation (FC)**

LIN-MD-62

IND #63,290

Original Protocol Date: 15 Apr 2015

Amendment #1: 13 Aug 2015

Amendment #2: 11 Sep 2016

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1.0 INTRODUCTION

In response to protocol comments provided by the FDA on 12 Jun 2015, Amendment #1 to the original protocol was completed 13 Aug 2015. In a subsequent effort to stimulate enrollment into the study and to respond to European regulatory advice, Amendment #2 was planned.

Amendment #1 specified the following changes to the original protocol LIN-MD-62, dated 15 Apr 2015:

- to allow patients 12-17 years of age to select liquid oral solution as an alternative to the previously specified solid oral capsules
[REDACTED]
- to include a repeat swallow test for patients who receive capsules to assess those patients' ability to swallow capsules on 2 occasions a minimum of 1 week apart
[REDACTED]

[REDACTED] and minor clarifications of previous text were made in several sections.

Amendment #2 specifies the following changes to protocol LIN-MD-62 as previously amended, dated 13 Aug 2015:

- to change the name of the sponsor
- to increase the number of study sites
- to correct the duration of treatment
- to supplement clinical experience information with details of recently completed studies
[REDACTED]
- to merge the Parent, Legal Guardian, and Legally Authorized Representative informed consent text with the Caregiver Informed Consent
- to clarify inclusion criterion #5 and to allow fecal incontinence as part of Rome III criteria in #6
[REDACTED]
- to clarify exclusion criteria # 7
- to broaden the text describing rescue medications and use of IWRS
- to remove the use of patient's initials (where applicable)

- to reorder the secondary efficacy assessments, to add fecal incontinence as a secondary efficacy assessment, and to move abdominal pain-daytime from the additional efficacy assessments to the secondary efficacy assessments
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]
- to update Sections 9.7.5, 9.7.5.2, 9.7.5.3, 9.7.6.1, and 9.7.6.4 to clarify various definitions and analysis methods, to add assessment of the secondary efficacy parameter related to fecal incontinence, and to move abdominal pain daytime symptoms from the additional efficacy parameters to the secondary efficacy parameters
- to update Section 11.5 adding document retention details for countries covered by ICH

In addition, minor clarifications of previous text were made in several sections of the document. The protocol section numbers in the headings of this amendment are those of the previous version of the protocol.

2.0 GLOBAL CHANGES

2.1 EDIARY COMPLIANCE

Inclusion criterion #10 which addresses required compliance with use of the eDiary has been relaxed to allow more flexibility in use of the eDiary.

Inclusion criterion #10 now reads as follows, and all mentions of the requirement for eDiary compliance throughout the protocol have been altered accordingly:

Patient or parent/guardian/LAR or caregiver is compliant with eDiary by completing both the morning and evening assessments for ~~10~~8 out of the 14 days immediately preceding the Randomization Visit (Section 9.1.2)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

2.3 USE OF IWRS AND PATIENT INITIALS

The text around use of patient initials and use of the IWRS has been made more generic to allow for study execution in differing jurisdictions.

Text in Sections 2.0, 9.4.1.1, 9.4.2, 9.5.5.2, 9.5.5.3, 9.5.5.4, 9.5.5.5, and 11.6 that refers to patient initials or use of the IWRS has been adjusted using the words “where applicable”.

3.0 SECTIONS DELETED

The heading and text for Section 5.3.3, Caregiver Consent has been deleted. The text from this section has been merged into the previous section: 5.3.2 Parent, Legal Guardian, and Legally Authorized Representative/Caregiver Informed Consent.

Caregiver 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 accompanying 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 and meet the relevant inclusion/exclusion criteria. If the parent/guardian/LAR is the caregiver, he or she will be asked to sign both the parent/legal guardian permission (ICF) and the caregiver consent. 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.~~

4.0 SECTIONS ADDED

A new section heading: “Section 7.2.1. Other Information” was added to the Introduction in order to aid organization.

5.0 REVISIONS

5.1 SECTION 1.0, TITLE PAGE

Rationale: The name of the sponsor has changed from Actavis to Allergan.

The sponsor line on this page now reads as follows:

Forest Research Institute, Inc., an affiliate of ~~Aetavis, Inc.~~ Allergan.

5.2 SECTION 2.0, SYNOPSIS AND SCHEDULE OF EVALUATION, Study Sites

Rationale: The number of estimated study sites has been increased.

The Study Sites row now reads as follows:

Approximately 50 - 100

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

**5.4 SECTION 5.3.2 PARENT, LEGAL GUARDIAN, AND
LEGALLY AUTHORIZED REPRESENTATIVE/CAREGIVER
INFORMED CONSENT**

Rationale: The text for parent and caregiver consent (formerly in 2 separate sections) has been merged into a single section.

The last paragraph of the section now reads as follows:

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 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.

**5.5 SECTION 6.0 INVESTIGATORS AND STUDY
ADMINISTRATIVE STRUCTURE**

Rationale: The number of estimated study sites has been increased.

The first sentence of the section now reads as follows:

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

5.6 SECTION 7.1 SUMMARY OF LINACLOTIDE PROPERTIES

Rationale: The Investigator Brochure has been updated.

The last sentence of the section now reads as follows:

Refer to the Investigator's Brochure for a more detailed description of the chemistry, pharmacology, efficacy, and safety of linaclotide, based on studies conducted in animals, healthy volunteers, and in adult patients with IBS-C and CIC ([Investigator's Brochure, 2014](#)2015).

5.7 SECTION 7.2 CLINICAL EXPERIENCE

Rationale: New information about recently completed studies has become available.

The first, second, ninth, thirteenth, and fourteenth paragraphs of the section now read as follows:

Linaclotide 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 linaclotide that culminated in FDA and European Medicines Agency (EMA) 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 adult 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 ~~in patients with CIC~~ ([LIN-MD-04](#)) and Phase 3 study ([MCP-103-309](#)) ~~was recently~~have been completed.

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.

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.

5.8 SECTION 9.1.1 SCREENING PERIOD (PAGE 23)

Rationale: The order of paragraph 1 has been adjusted for clarity.

The first paragraph of this section now reads as follows:

After obtaining assent and informed consent, 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. ~~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).~~ Consented patients will be assigned a unique PID via interactive Web response system (IWRS) (Section 9.4.3) and will be given a single dose of placebo (liquid oral solution or solid oral capsule for patients 7 to 11 years of age, and solid oral capsule for patients 12 to 17 years of age) to swallow to confirm their ability and willingness to swallow the investigational product. Patients who choose or are assigned to the solid oral capsule formulation will repeat the swallow test for solid oral capsule during the Pretreatment Period. There should be at least a 1-week interval between the swallow tests performed for placebo solid oral capsules during the Screening Period and the Pretreatment Period.

5.9 SECTION 9.1.2 PRETREATMENT PERIOD

Rationale: The text around rescue medications and use of the IWRS has been made more generic.

The second paragraph of this section now reads as follows:

IWRS registration during the Pretreatment Period will include protocol-permitted rescue medication assignment (ie, senna [oral] syrup [~~known as Senokot syrup in Canada~~, ~~bisacodyl tablets~~, or bisacodyl -[oral or rectal]suppositories) and random assignment to 1 of 4 pharmacokinetic (PK) sampling schedules in a 1:1:1:1 allocation.

5.10 SECTION 9.3.1, INCLUSION CRITERIA



5.11 SECTION 9.3.1, INCLUSION CRITERIA

Rationale: Assessment of fecal incontinence has been added to inclusion criterion #6.

Inclusion criterion #6 now reads as follows:

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

5.12 SECTION 9.3.2, EXCLUSION CRITERIA

Rationale: Exclusion criterion #7 has been made more stringent to exclude patients who have required disimpaction.

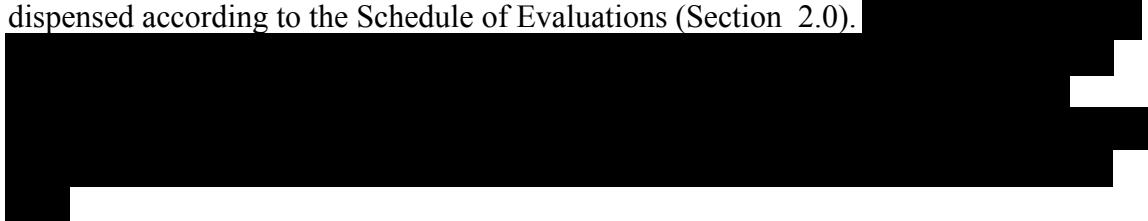
Exclusion criterion #7 now reads as follows:

Patient has required manual disimpaction anytime prior to randomization or hospital-based disimpaction during in-patient hospitalization ~~any time within 1 year~~ prior to randomization

5.13 SECTION 9.4.1.1, RESCUE MEDICATION (PAGE 31)

Rationale: The text around rescue medications and use of the IWRS has been made more generic.

The second and third paragraphs of this section now read as follows:

Protocol-permitted rescue medication will be a choice of senna (oral) syrup (known as Senokot syrup in Canada), ~~bisacodyl 5 mg tablets~~, or bisacodyl (oral or rectal) 10 mg suppositories (~~5 mg and 10 mg suppositories are available in Canada~~) that will be dispensed according to the Schedule of Evaluations (Section 2.0). 


5.14 SECTION 9.4.9, MONITORING TREATMENT COMPLIANCE AND ACCOUNTABILITY

Rationale: The method of assessing treatment compliance has been upgraded.

The first and second paragraphs of this section now read as follows:

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

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.

~~Investigational product accountability will be monitored by counting the number of solid oral capsules/weighing the bottle of liquid oral solution returned. Study sites will be provided a scale for weighing the bottles of liquid oral solution and instructed how to properly obtain and record the weight.~~

5.15 SECTION 9.5.1.2 SECONDARY EFFICACY ASSESSMENTS

Rationale: The secondary efficacy assessments have been reordered to match Section 9.7.5.2, to move assessment of Abdominal Pain-Daytime from the section on Additional Efficacy Assessments, and to include assessment of Fecal Incontinence-Daytime.

The first, fourth, and last paragraphs of the section now read as follows:

In addition to the primary efficacy assessment, 6 secondary efficacy assessments are included in the study regarding abdominal symptoms, BM characteristics, and BM characteristics, and fecal incontinence abdominal symptoms that will be determined by the ~~twice~~ daily assessments recorded in the eDiary.

Abdominal Pain – Daytime

For this parameter, patients will rate their abdominal pain by responding to the following in the evening eDiary:

- 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

Abdominal Bloating - Daytime

For this parameter, 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

Fecal Incontinence - Daytime

Patients will record their episodes of fecal incontinence by responding to the following evening assessments.

- From when you got up this morning until now, did you have a pooping accident (even a little)?

- Yes
- No

- From when you got up this morning until now, did you have any poop marks or stains on your underwear?

- Yes
- No
- I don't know

The following abdominal symptoms will be assessed:

The image consists of several horizontal bars of varying lengths, primarily black on a white background. There are also a few small, distinct vertical bar structures in the center. The overall pattern is abstract and geometric.

[REDACTED]

5.17

SECTION 9.5.2.1. ADVERSE EVENTS AND [REDACTED]

Rationale: The AE time window description has been adjusted (lengthened) to align with previous linaclotide studies.

Paragraph 2 of this section now reads as follows:

For the purpose of the site's data collection responsibilities, any untoward event that was reported from the time written consent was obtained until ~~1 day~~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. Particular attention must be given to the AE of diarrhea, which was the most frequently reported AE in the adult linaclotide program. Please refer to Section 9.5.2.5 for details about AE reporting.

5.18

SECTION 9.5.2.6. IMMEDIATE REPORTING OF SERIOUS ADVERSE EVENTS AND EVENTS OF SPECIAL INTEREST

[REDACTED]

5.25 SECTION 9.7.2, PATIENT DISPOSITION

Rationale: Use of Fisher's exact test to compare rates of premature discontinuations has been removed.

The third sentence of the third paragraph of this section has been deleted:

The percentage of premature discontinuations will be compared overall and for each discontinuation reason between treatment groups using the Fisher exact test.

A series of horizontal black bars of varying lengths, likely representing data points or categories in a visualization. The bars are arranged vertically and have white gaps between them. The lengths of the bars vary significantly, with some being very short and others being very long, suggesting a wide range of values or categories.

5.28

SECTION 9.7.5, EFFICACY PARAMETERS

Rationale: The baseline fecal incontinence daytime symptoms, based on evening assessment, have been added.

The last sentence of the second paragraph of this section now reads as follows:

Baseline fecal incontinence daytime symptoms, based on evening assessment, will be calculated as the average of nonmissing patient scores reported in the evening diary.

5.29

SECTION 9.7.5.2, SECONDARY EFFICACY PARAMETERS

Rationale: Two secondary efficacy assessments have been added to this section. Change from Baseline in 4-Week Abdominal Pain Daytime Symptoms Based on Evening Assessment has been moved from additional efficacy parameters to the secondary section, and a new paragraph on Fecal Incontinence-Daytime has been added. The fourth secondary efficacy parameter (Change from Baseline in 4-Week Abdominal Bloating Daytime Symptoms Based on Evening Assessment) has been clarified, and the additional derivation for stool consistency and straining parameters has been clarified.

The first and second paragraphs of this section now read as follows:

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

Change From Baseline in 4-Week Abdominal Pain Daytime Symptoms Based on Evening Assessment

~~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 using a 4-point ordinal scale 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 at bedtime. 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.~~

The fifth and seventh paragraphs of this section now read as follows:

Change From Baseline in 4-Week Abdominal Bloating Daytime Symptoms Based on Evening Assessment

~~Abdominal bloating 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 bloating using a 4-point scale 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 at bedtime. The patient's 4-week abdominal bloating daytime symptoms during the Treatment Period are defined as the average of the nonmissing daily abdominal bloating daytime symptoms reported in evening assessments in the eDiary during the 4-week Treatment Period.~~

Change From Baseline in 4-Week Fecal Incontinence Daytime Symptoms Based on Evening Assessment

~~Fecal incontinence will be collected daily in the evening eDiary. Patients are asked two questions (as discussed in Section 9.5.1.3) to cover the interval from when the patient wakes up until bedtime as part of the evening assessment. Any "yes" response in either of these questions will be counted as presence of fecal incontinence. The patient's 4-week fecal incontinence daytime symptoms during the Treatment Period are defined as the average of the nonmissing daily fecal incontinence daytime symptoms reported in evening assessments in the eDiary during the 4-week Treatment Period.~~

The last paragraph of this section now reads as follows:

~~In addition, stool consistency and straining during the analysis period (based on morning and evening assessments) will also be derived as the mean of the patient's non-missing, SBM-associated scores during the analysis period (similar to LIN-MD-31 and MCP-103-302 adult studies).~~

A high-contrast, black and white image showing a series of horizontal bars. The bars are mostly black, with white rectangular highlights appearing at regular intervals. The bars are set against a white background. The image has a grainy, high-contrast texture, suggesting it is a scan of a physical object or a specific type of signal visualization.

A large black rectangular redaction box covers the majority of the page content, from approximately y=111 to y=250 and x=113 to x=886. It is positioned above a white horizontal bar.

11. **What is the primary purpose of the following statement?**

A thick black horizontal bar with a white rectangular cutout in the center, positioned above a thick black horizontal bar.

[REDACTED]

[REDACTED]

5.31 SECTION 9.7.6.1, ADVERSE EVENTS

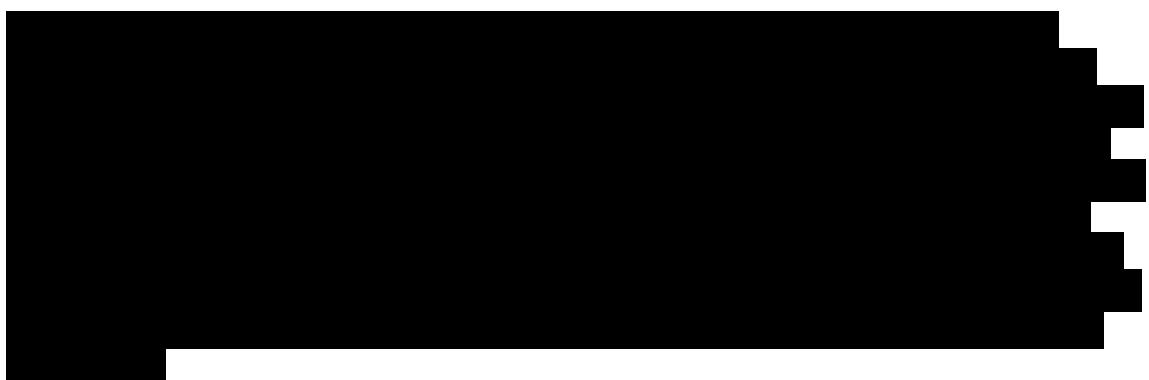
Rationale: Information about the dictionary used has been updated. The method of summarization for TEAEs has been clarified.

The first paragraph of this section now reads as follows:

AEs will be coded using the *Medical Dictionary for Regulatory Activities* (MedDRA), Version ~~17~~18.0 or newer.

The third paragraph of this section now reads as follows:

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



5.33

**SECTION 11.5, RETENTION AND REVIEW OF RECORDS
(PAGE 85)**

Rationale: Information has been added about document retention details for countries covered by ICH.

The fourth and fifth paragraphs of this section now read as follows:

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.

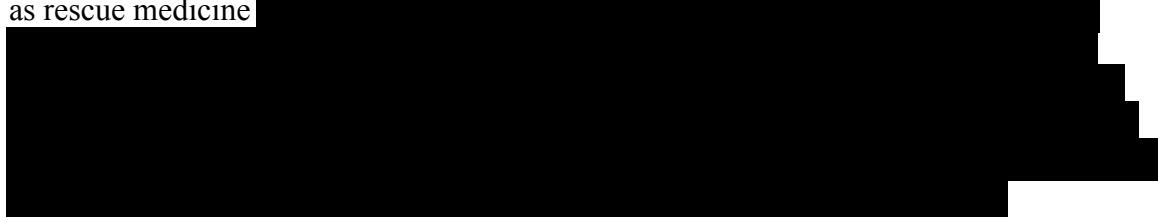
In addition, for countries not falling within the scope of the ICH guidelines, local regulatory requirements should be followed regarding the retention of clinical study documentation.

5.34 APPENDIX III. CONCOMITANT MEDICATIONS, (PAGE 88)

Rationale: The text around rescue medications has been made more generic.

The second paragraph of this section now reads as follows:

Protocol-permitted rescue medicine, which will be selected by and dispensed to patients, will be a choice of senna (oral)~~syrup (known as Senokot syrup in Canada), bisacodyl 5 mg tablets, or bisacodyl (oral or rectal) 10 mg suppositories (5 mg and 10 mg suppositories are available in Canada)~~. During the Pretreatment, Treatment, and Post-treatment Periods, patients may use dispensed, protocol-permitted laxatives (ie, senna syrup [known as Senokot syrup in Canada], bisacodyl tablets, or bisacodyl suppositories) as rescue medicine



5.35 SECTION 14.0, LITERATURE CITED (PAGE 94)

Rationale: The Investigator's brochure has been updated.

The seventh reference of this section now reads as follows:

Linaclotide: Investigator's brochure. Edition 8~~10~~. Cambridge, MA: Ironwood Pharmaceuticals, Inc; 2014~~2015~~ Mar 29~~May 15~~.

6.0 INVESTIGATOR'S STATEMENT

I agree to conduct the study in accordance with this protocol amendment (LIN-MD-62, Amendment #2, dated 11 Sep 2016) and with all applicable government regulations and good clinical practice guidance.

_____ / _____ / _____

Investigator's Signature

Date

Investigator's Name



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

SUMMARY OF CHANGES TO PROTOCOL

**A Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group,
Safety and Efficacy Study of a Range of Linaclotide Doses Administered Orally to
Children, Ages 6 to 17 Years, Who Fulfill Modified Rome III Criteria for
Child/Adolescent Functional Constipation (FC)**

LIN-MD-62

IND #63,290

Original Protocol Date: 15 Apr 2015

Amendment #1: 13 Aug 2015

Confidentiality Statement

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1.0 INTRODUCTION

In response to protocol comments provided by the FDA on 12 Jun 2015, Amendment #1 to the original protocol was planned. Amendment #1 specifies the following changes to the original protocol LIN-MD-62, dated 15 Apr 2015: (1) to allow patients 12-17 years of age to select liquid oral solution as an alternative to the previously specified solid oral capsules; [REDACTED]

[REDACTED]) to include a repeat swallow test for patients who receive capsules to assess those patients' ability to swallow capsules on 2 occasions a minimum of 1 week apart; and [REDACTED]

[REDACTED] and minor clarifications of previous text have been made in several sections.

The page and protocol section numbers in the headings of this amendment are those of the previous version of the protocol.

2.0 GLOBAL CHANGES

The following changes have been made globally to the protocol:

- Linaclotide capsules are referred to as solid oral capsules
- Linaclotide oral solution is referred to as liquid oral solution

3.0 **SECTIONS DELETED**

None

4.0

SECTIONS ADDED

[REDACTED]

[REDACTED]

[REDACTED]:

[REDACTED] [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] [REDACTED]

[REDACTED]

[REDACTED]).

5.0 **REVISIONS**

5.1 SECTION 2.0, SYNOPSIS AND SCHEDULE OF EVALUATIONS (PAGE 2)

Rationale: The synopsis has been amended to reflect the addition of liquid oral solution as an alternate formulation for older patients, to clarify the text of the pharmacokinetic analysis, to clarify the statistical methods. The schedule of evaluations has been amended for clarity, to add a second swallow test for capsules, and to add an additional possible timepoint for the PK draw.

The beginning of the row Test Product, Dosage, and Mode of Administration now reads as follows:

Patients 6 to 11 years of age: linaclotide liquid oral solution taken once daily

Patients 12 to 17 years of age: linaclotide solid oral capsule or liquid oral solution taken once daily

The row Reference Therapy, Dosage, and Mode of Administration now reads as follows:

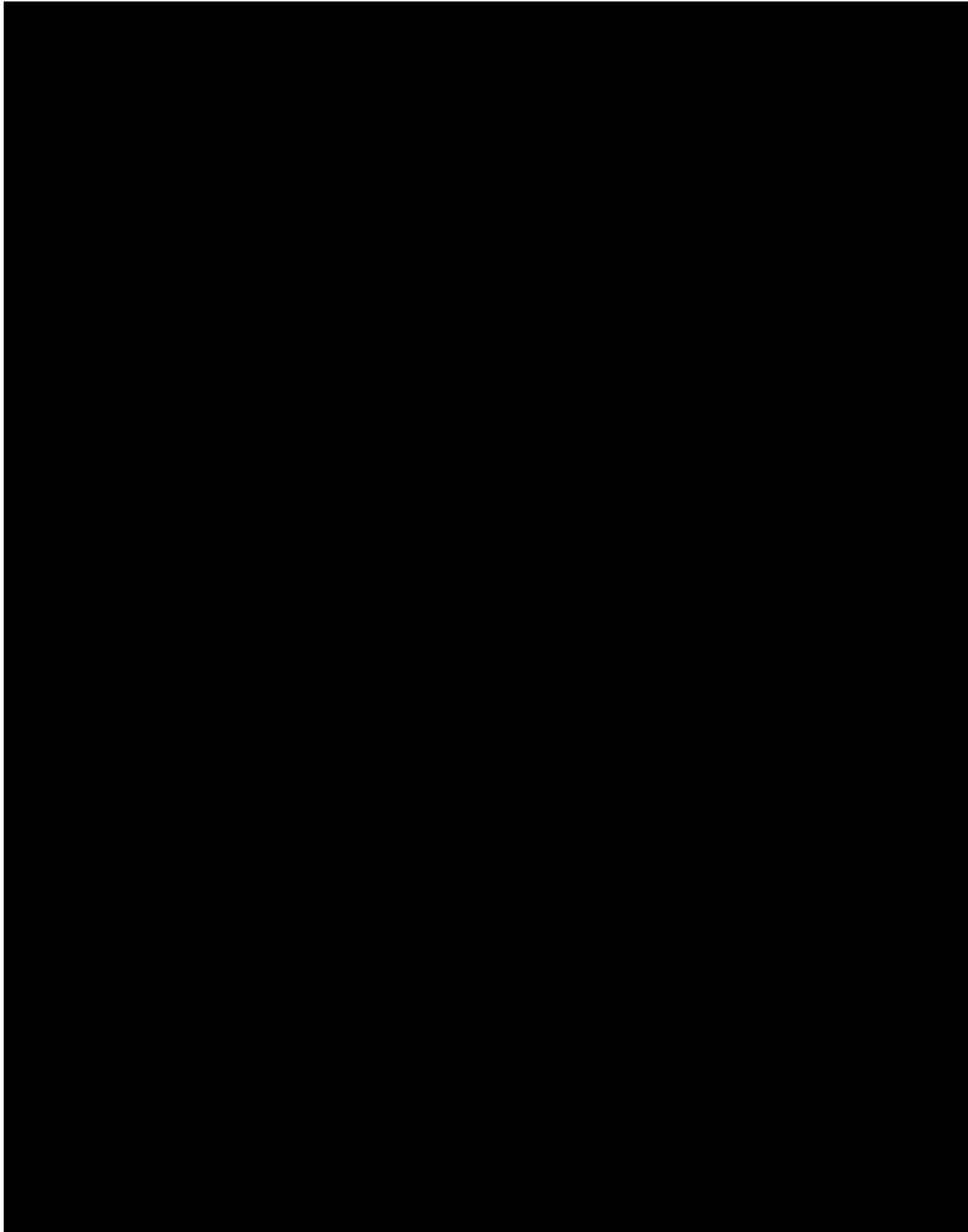
Patients 6 to 11 years of age: matching placebo liquid oral solution taken once daily

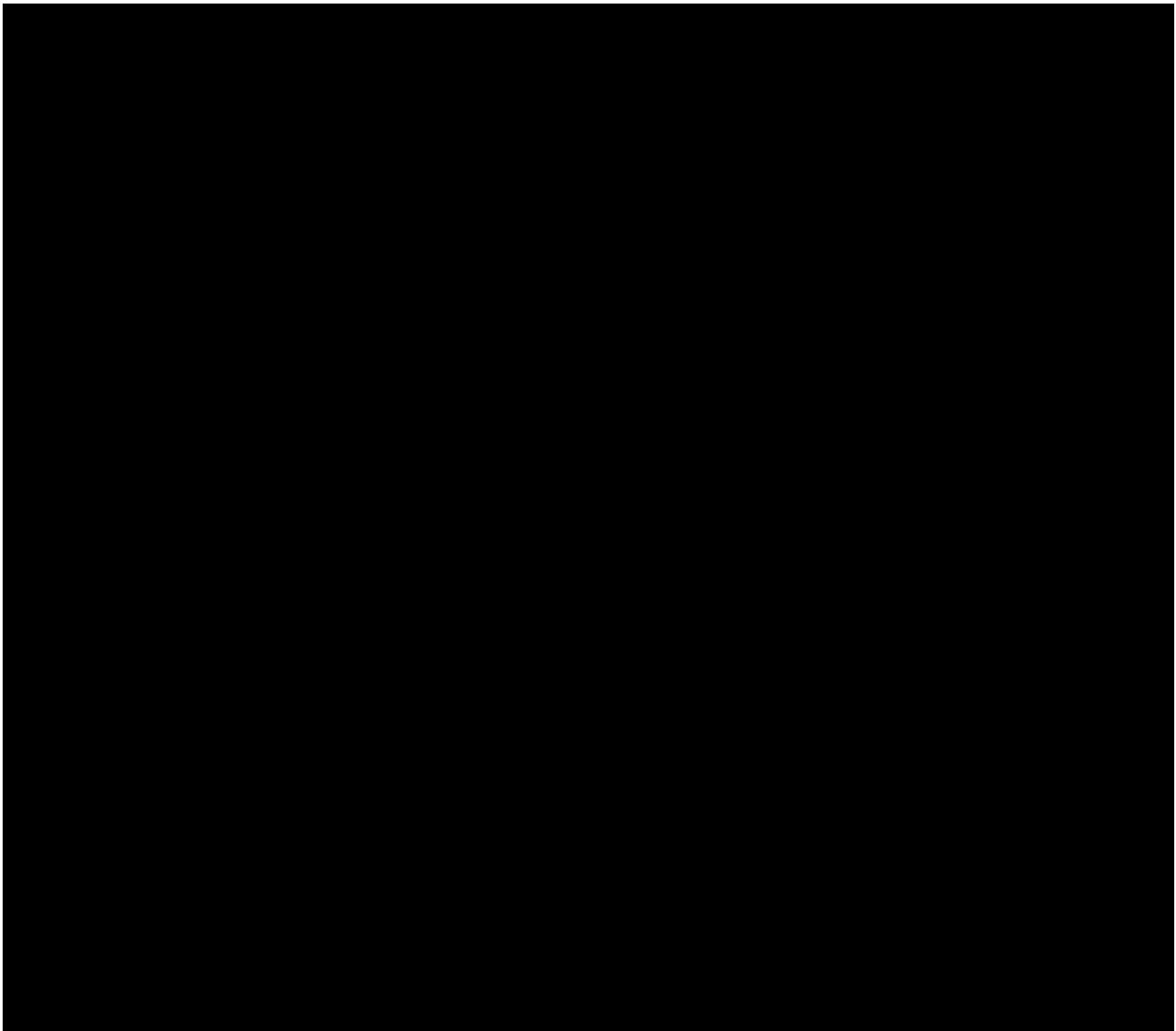
Patients 12 to 17 years of age: matching placebo solid oral capsule or liquid oral solution taken once daily

[REDACTED]

The last paragraph of the row Statistical Methods now reads as follows:

[REDACTED]





5.2 SECTION 7.0, INTRODUCTION (PAGE 20)

Rationale: This section has been amended to clarify the wording.

The first paragraph of this section now reads as follows:

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

5.3 SECTION 9.1.1, SCREENING PERIOD (PAGE 25)

Rationale: This section has been amended to reflect addition of liquid oral solution as an alternate formulation for older patients and to clarify details of the swallow test.

The first paragraph of this section now reads as follows:

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. After obtaining assent and informed consent, patient eligibility for entry into the study will be determined (Sections 9.3.1 and 9.3.2). Consented patients will be assigned a unique PID number via interactive Web response system (IWRS) (Section 9.4.3) and will be given a single dose of placebo (liquid ~~formulation~~ oral solution for patients 6 to 11 years of age and solid oral capsule or liquid oral solution for patients 12 to 17 years of age) to swallow to confirm their ability and willingness to swallow the investigational product. Patients 6 to 11 years of age who fail the swallow test for the liquid oral solution will be considered screen failures. Patients 12 to 17 years of age who choose or are assigned to the solid oral capsule formulation will repeat the swallow test for placebo solid oral capsule during the Pretreatment Period. There should be at least a 1-week interval between the swallow tests performed for placebo solid oral capsules during the Screening Period and the Pretreatment Period.

5.4 SECTION 9.1.2, PRETREATMENT PERIOD (PAGE 26)

Rationale: This section has been amended to reflect addition of liquid oral solution as an alternate formulation for older patients, to clarify details of the swallow test, to clarify training on use of the eDiary, to clarify the definition of eDiary compliance, to clarify the name of one of the rescue medications [REDACTED].

This section now reads as follows:

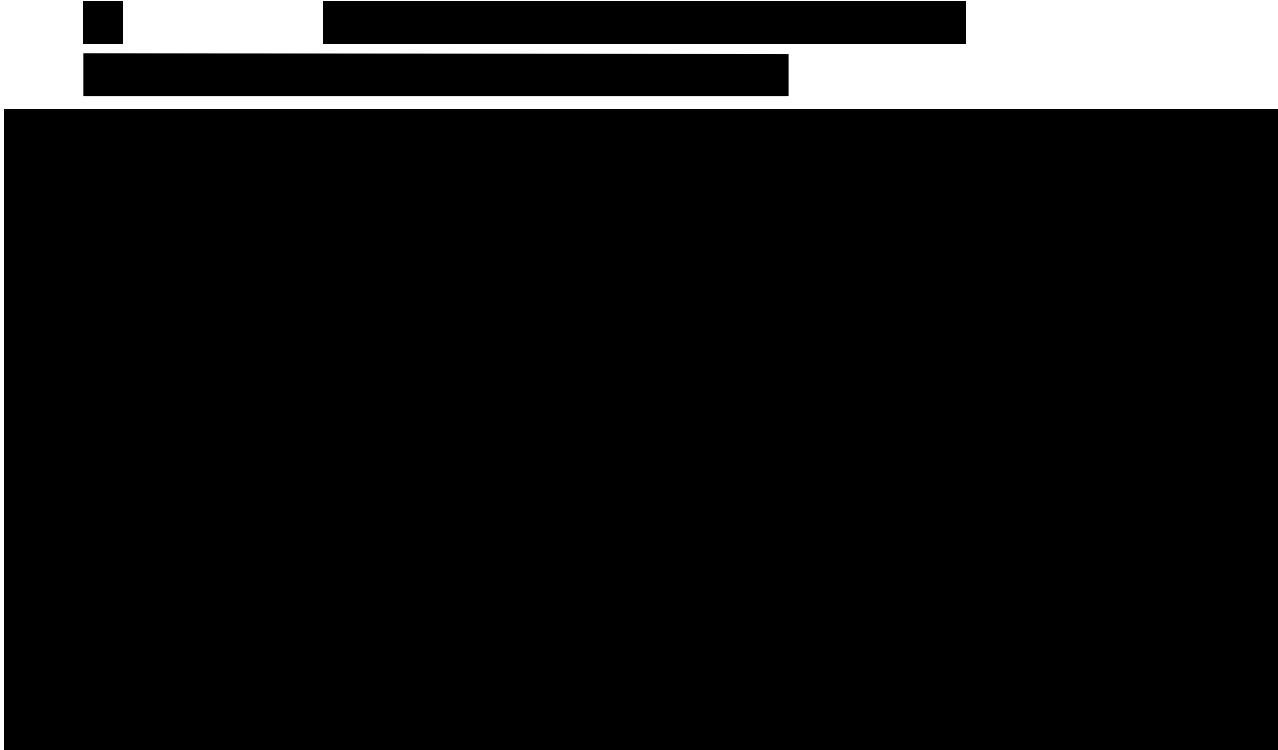
The Pretreatment Period will occur up to 3 weeks before Randomization (Visit 3/Day 1) and will last for 14 to 21 days. Patients will not receive investigational product during the Pretreatment Period. Patients 12 to 17 years of age who choose or are assigned to the solid oral capsule formulation during the Screening Period will be provided a single dose of placebo solid oral capsule to repeat the swallow test. There should be at least a 1-week interval between the swallow tests performed for placebo solid oral capsules during the Screening Period and the Pretreatment Period. Baseline symptoms will be assessed and inclusion/exclusion criteria will be reviewed. Patients and caregivers will ~~become familiar with~~ receive full training on the use and completion of the eDiary, and the decision regarding whether a patient can complete the eDiary on his/her own or if he/she requires assistance will be made at the discretion of the caregiver and carried through to study completion. Additionally, caregivers of patients 6 to 11 years of age will be trained on completing the observer-completed global items once weekly on the eDiary. Throughout this protocol, eDiary is understood to refer to the patient- or interviewer-administered version of the patient reported outcome (PRO) diary on a handheld electronic device. The eDiary will be completed by all patients (or caregivers) twice daily throughout the Pretreatment Period. During the Pretreatment Period, compliance with the eDiary will be defined as completion of both morning and evening assessments for 10 out of the 14 days immediately preceding the Randomization Visit and must be documented before patients are included in the Double-blind Treatment Period.

IWRS registration during the Pretreatment Period will include protocol-permitted rescue medication assignment (ie, senna syrup [known as Senokot syrup in Canada], bisacodyl tablets, or bisacodyl suppositories)

[REDACTED]

[REDACTED]

[REDACTED]



5.6 SECTION 9.3.1, INCLUSION CRITERIA (PAGE 28)

Rationale: Inclusion criterion 6 has been amended to clarify the requirements for meeting modified Rome III criteria. Inclusion criterion 9 has been amended to clarify details of the timing of the assessments of SBMs. Inclusion criterion 10 has been amended to clarify the definition of eDiary compliance.

Inclusion criterion 6 now reads as follows:

6. Patient meets modified Rome III criteria for child/adolescent FC: ~~at least once per week for 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 ~~and in~~

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

Inclusion criterion 9 now reads as follows:

9. Patient has an average of fewer than 3 spontaneous BMs (~~SBM SBMs~~) per week during the 14 days before ~~the start of the Treatment Period 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

Inclusion criterion 10 now reads as follows:

10. 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 Randomization Visit ~~during the Pretreatment Period~~ (Sections 9.1.2 and 9.7.4.2)

5.7 SECTION 9.3.2, EXCLUSION CRITERIA (PAGE 29)

Rationale: Exclusion criterion 2 has been amended to clarify details of the timing of the assessments for stool consistency and frequency. Exclusion criterion 10 has been amended to insert details from Appendix III. Exclusion criterion 17 has been amended to clarify that failing the swallow test at any point is exclusionary.

Exclusion criterion 2 now reads as follows:

2. 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 start of the Treatment Period 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)~~

Exclusion criterion 10 now reads as follows:



Exclusion criterion 17 now reads as follows:

17. Patient is unable to tolerate the placebo ~~during the Screening Period~~ prior to randomization

5.8 SECTION 9.3.3, REMOVAL OF PATIENTS FROM THERAPY OR ASSESSMENT (PAGE 32)

Rationale: This section has been amended to make reference to Section 9.5.2.1.1.

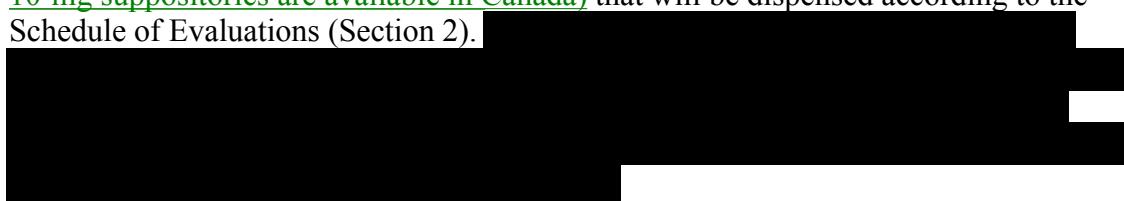
The first paragraph of this section now reads as follows:

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 (ie, treatment-related AEs of special interest [Section Sections 9.5.2.1.1 and 9.5.2.6]). The Investigator should contact the Study Physician if there is any question whether the criteria for an AE of special interest have been met and the patient should be discontinued from the study.

5.9 SECTION 9.4.1.1, RESCUE MEDICATION (PAGE 34)

Rationale: This section has been amended to clarify the name of one of the rescue medications and to include availability of a second bisacodyl presentation for sites in Canada.

The second paragraph of this section now reads as follows:

Protocol-permitted rescue medication will be a choice of senna syrup (known as Senokot syrup in Canada), bisacodyl 5-mg tablets, or bisacodyl 10-mg suppositories (5-mg and 10-mg suppositories are available in Canada) that will be dispensed according to the Schedule of Evaluations (Section 2). 

5.11 SECTION 9.4.5, SELECTION AND TIMING OF DOSE FOR EACH PATIENT (PAGE 37)

Rationale: This section has been amended to reflect addition of liquid oral solution as an alternate formulation for older patients.

The second paragraph of this section now reads as follows:

Patients who continue to meet all eligibility criteria on Visit 3 (Day 1) will be assigned a randomization number, dispensed the corresponding double-blind investigational product, and receive their first dose of investigational product at the study site. ~~Patients will receive a bottle(s) containing the liquid oral solution (for patients 6 to 11 years of age) or solid oral capsules (for patients 12 to 17 years of age). Patients 6 to 11 years of age will receive 1 or more bottles containing the liquid oral solution. Patients 12 to 17 years of age will 1 or more bottles containing solid oral capsules or liquid oral solution, based on choice or assignment.~~ Patients will be instructed to take their assigned dose orally as a single daily dose at approximately the same time each day, 30 minutes before their evening meal. Any alternate schedule must be approved and documented by the Investigator.

Footnote b of Table 9.4.5-1 now reads as follows:

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

**5.12 SECTION 9.5.1.2, SECONDARY EFFICACY ASSESSMENTS
(PAGE 42)**

Rationale: This section has been amended to more accurately describe use of the Pediatric-BSFS tool.

The fourth paragraph in this section now reads as follows:

"Use the card ~~to your left~~ 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

[REDACTED]

5.14 SECTION 9.5.2.1, ADVERSE EVENTS (PAGE 48)

Rationale: This section has been amended to accommodate the newly added section on AE of special interest.

The heading of this section now reads as follows:

9.5.2.1 Adverse Events [REDACTED]

This second paragraph of this section now reads as follows:

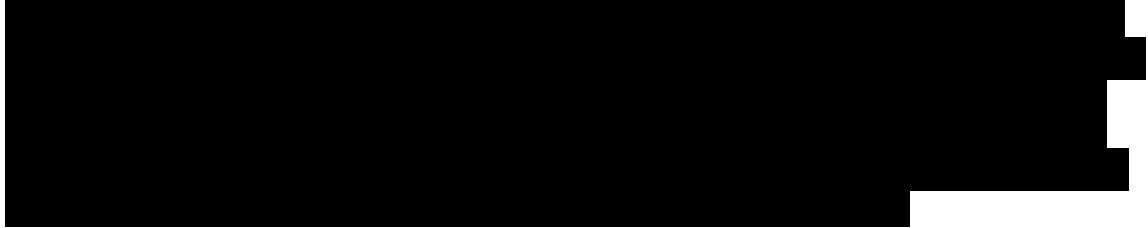
For the purpose of the site's data collection responsibilities, any untoward event that was reported from the time written consent was obtained until 1 day after the last known dose of investigational product (if the final visit does not occur) is to be considered an AE.



The next to last paragraph of this section has been omitted:

~~Particular attention must be given to AEs of diarrhea, which was the most frequently reported AE in the adult linaclotide program, and AEs of special interest (volume depletion and/or significant electrolyte and/or ECG abnormalities considered related to diarrhea) (Sections 9.3.3 and 9.5.2.6).~~

5.15 SECTION 9.5.2.6, IMMEDIATE REPORTING OF SERIOUS ADVERSE EVENTS



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Term	Percentage
GMOs	85%
Organic	92%
Natural	88%
Artificial	65%
Organic	85%
Natural	82%
Artificial	68%
Organic	80%
Natural	78%
Artificial	62%
Organic	75%
Natural	72%
Artificial	58%
Organic	70%
Natural	68%
Artificial	55%
Organic	65%
Natural	62%
Artificial	52%
Organic	60%
Natural	58%
Artificial	48%

5.22 SECTION 9.7.5.1, PRIMARY EFFICACY PARAMETER (PAGE 69)

Rationale: This section has been amended to refer the reader to the Statistical Analysis Plan for information about the sensitivity analysis.

The second paragraph now reads as follows:

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 (6 - 11 years of age and 12 - 17 years of age) as factors and baseline value as a covariate. Least squares means (LSMs) for each treatment group, differences in LSMs between each linaclotide treatment group versus placebo, associated 2-sided 95% CIs for these differences in LSMs, and the corresponding statistical test p-values will be reported [REDACTED]

1. **What is the primary purpose of the proposed legislation?**

A horizontal bar consisting of a thin black line at the top and a thick black bar at the bottom. A small black square is positioned at the top-left corner of the thin line.

[REDACTED]

[REDACTED]

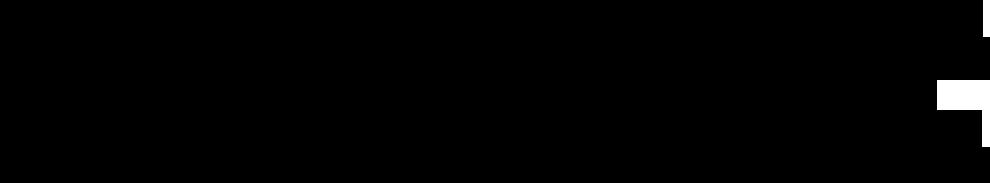
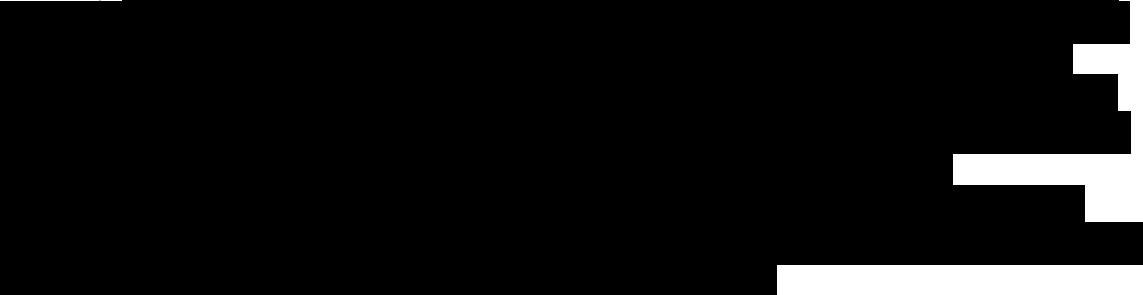
[REDACTED]

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APPENDIX III, CONCOMITANT MEDICATIONS (PAGE 89)

Rationale: This appendix has been amended to correct the name of one of the rescue medications and to include availability of a second bisacodyl presentation for sites in Canada.

The second paragraph now reads follows:

Protocol-permitted rescue medicine, which will be selected by and dispensed to patients, will be a choice of senna syrup (known as Senokot syrup in Canada), bisacodyl 5-mg tablets, or bisacodyl 10-mg suppositories (5-mg and 10-mg suppositories are available in Canada). 


6.0 **INVESTIGATOR'S STATEMENT**

I agree to conduct the study in accordance with this protocol amendment (LIN-MD-62, Amendment #1, dated XX Aug 2015) and with all applicable government regulations and good clinical practice guidance.

_____ / _____ / _____

Investigator's Signature

Date

Investigator's Name