

NCT02590432

**Study ID:** LIN-MD-10

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

**Protocol Amendment 2 Date:** 05-Oct-2015

**1.0**

**TITLE PAGE**



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

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

**LIN-MD-10**

**IND #63,290**

**Original Protocol / Date:    Protocol MCP-103-402, 25 Nov 2013**

**Amendment #1                      09 Apr 2015**

**Amendment #2                      05 Oct 2015**

***Confidentiality Statement***

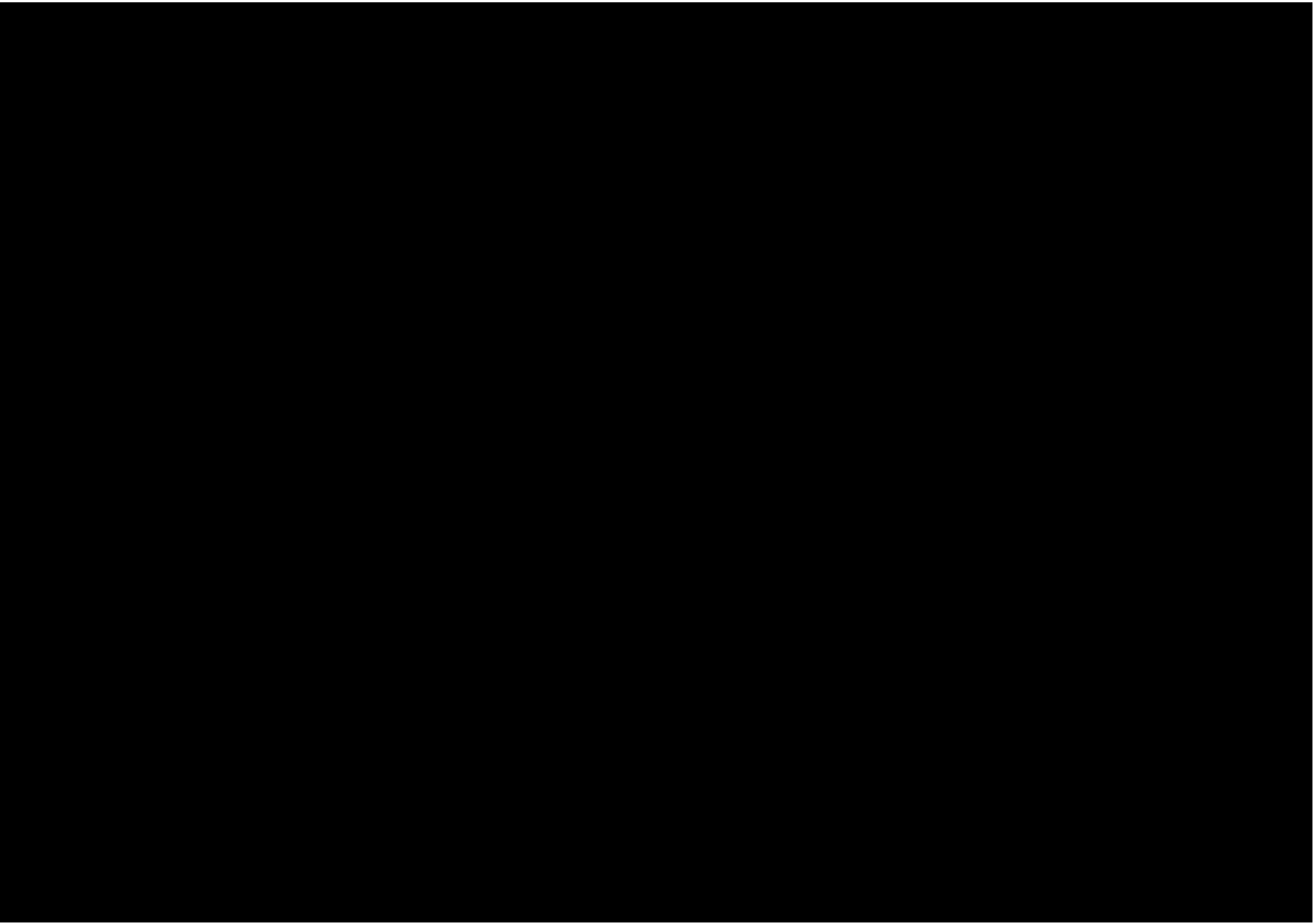
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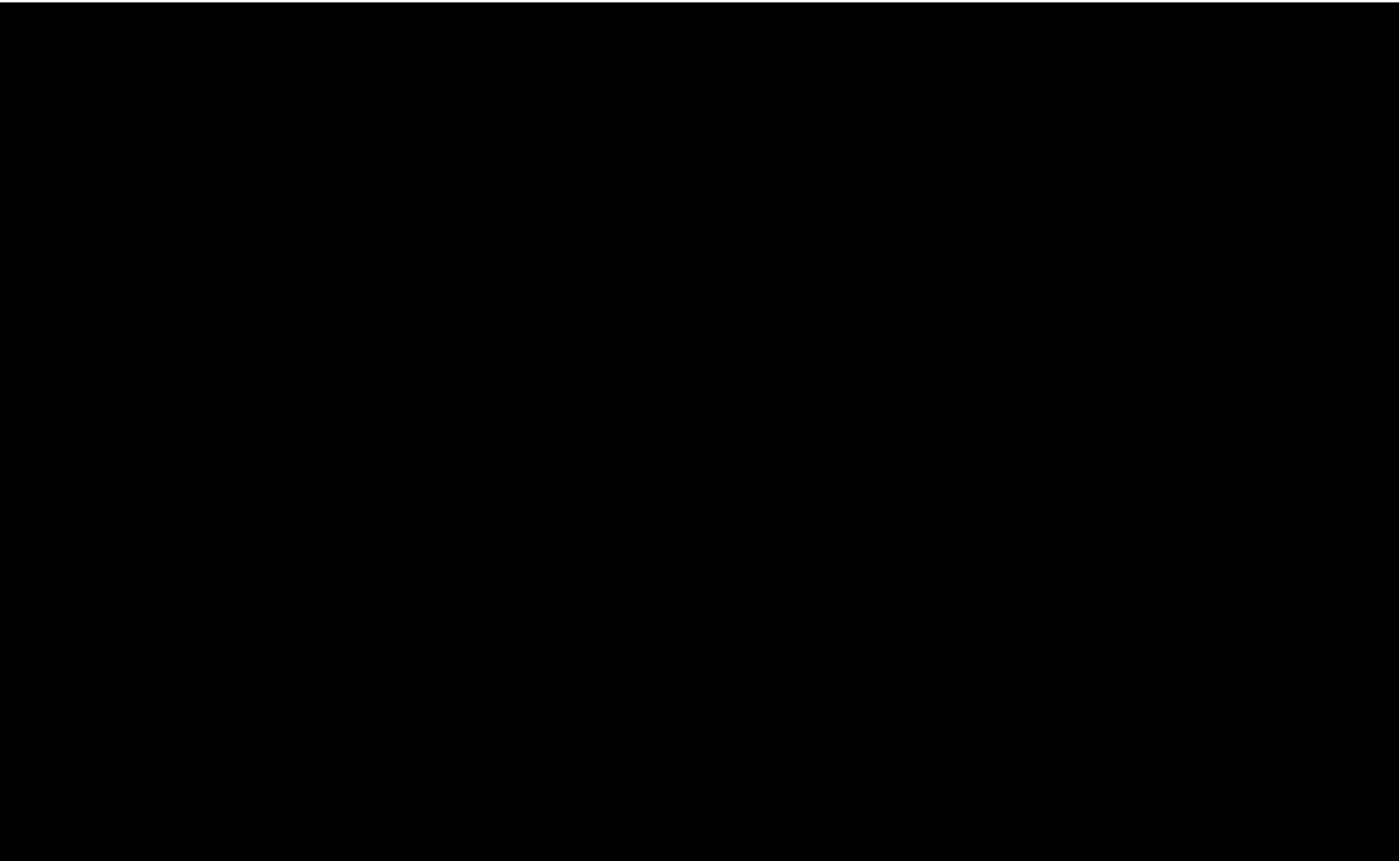
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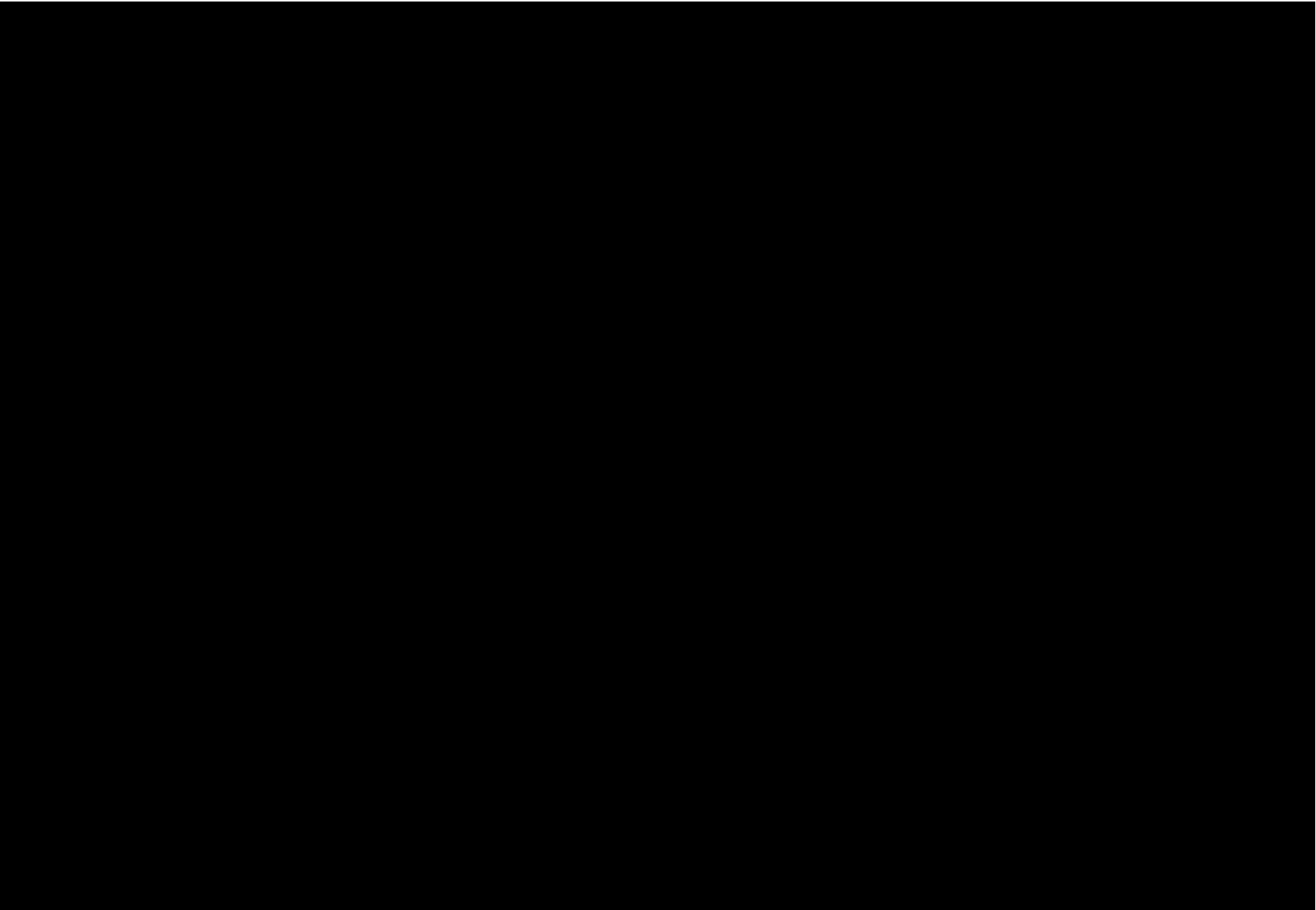
## **SYNOPSIS AND SCHEDULE OF EVALUATIONS**

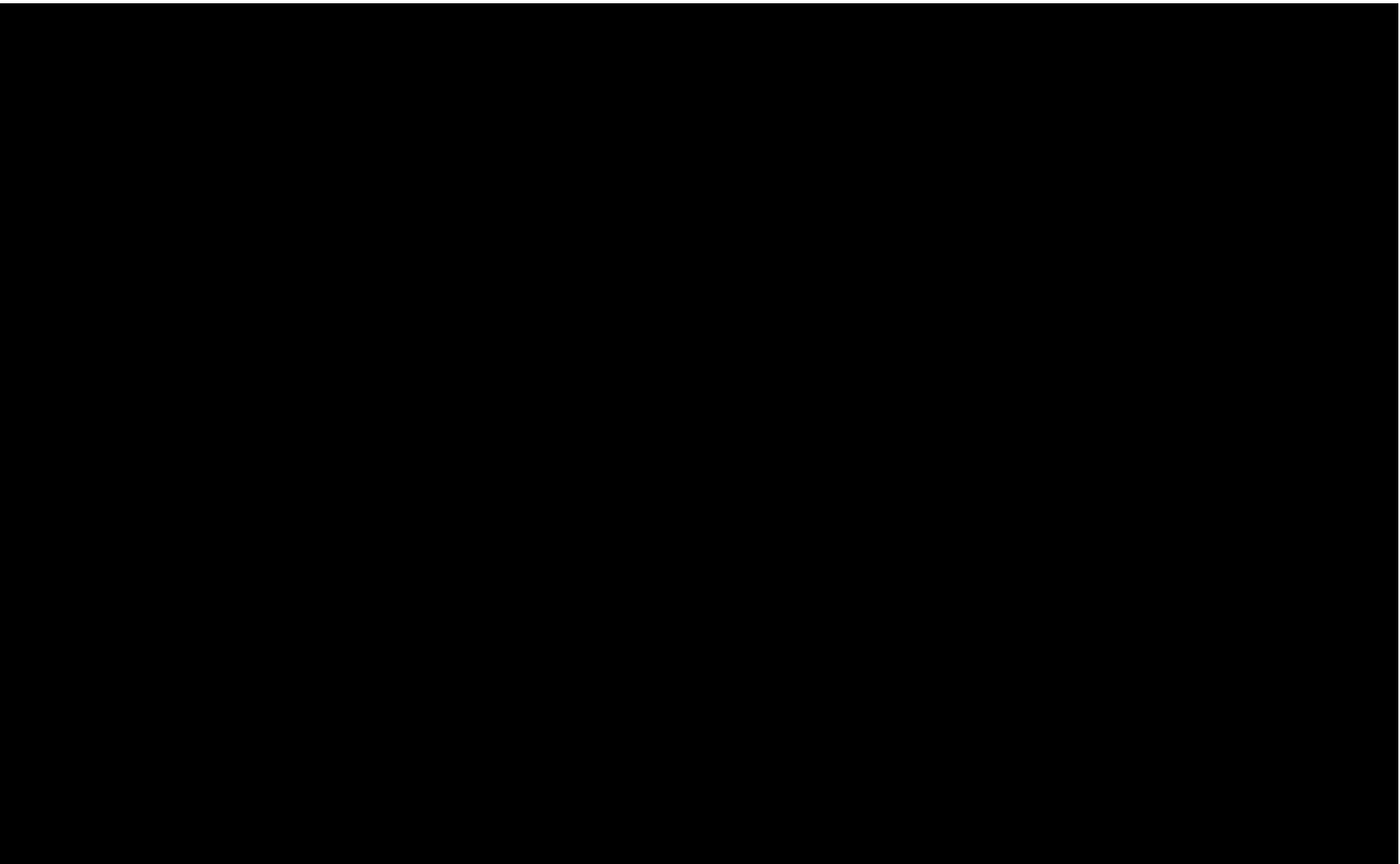
| <b>CLINICAL STUDY SYNOPSIS: Study LIN-MD-10</b>              |  |
|--|--|
| <b>Study Number</b>  | LIN-MD-10  |
| <b>Title of Study</b>  | An Open-label, Long-term Study to Assess the Immunogenicity of Linaclotide Administered Orally to Adult Patients With Irritable Bowel Syndrome With Constipation or Chronic Idiopathic Constipation  |
| <b>Study Centers (Country)</b>                               | Approximately 80 (United States)   |
| <b>Development Phase</b>                                     | 4  |
| <b>Objectives</b>  | The primary objective of this study is to assess the potential of linaclotide treatment to induce the development of anti-drug antibodies (ADAs). The secondary objectives are to provide additional evidence supporting the long-term safety and efficacy of linaclotide in adult irritable bowel syndrome with constipation (IBS-C) and chronic idiopathic constipation (CIC) patients and to evaluate lower doses of linaclotide in patients who consider study withdrawal due to intolerable adverse events (AEs). |
| <b>Methodology</b>   | Multicenter, open-label study. Patients who experience intolerable AEs (defined as AEs that subjectively would cause a patient to consider study withdrawal), may have their dosing suspended and, following resolution of the intolerable AEs, be randomized to receive the same or lower doses of double-blind linaclotide as an optional treatment course. Patients who experience further intolerable AEs after the randomization can be transitioned to open-label 72 ug linaclotide.                             |
| <b>Number of Patients</b>                                    | 1000 (projected number screened); 800 IBS-C or CIC enrolled. For each patient group (IBS-C or CIC), at least 300 patients are expected to be enrolled.   |
| <b>Diagnosis and Main Criteria for Inclusion</b>             | Male and female adult ( $\geq 18$ years of age) outpatients who meet the Rome III criteria for IBS-C or CIC  |
| <b>Test Product, Dosage, and Mode of Administration</b>      | Patients with CIC: linaclotide 145-ug capsules, orally, once daily<br>Patients with IBS-C: linaclotide 290-ug capsules, orally, once daily<br>Patients with intolerable AEs will be randomized to receive 290 ug, 145 ug, or the lower (unapproved) dose of 72 ug linaclotide oral capsules for IBS-C; and 145 ug or 72 ug for CIC. Patients who experience further intolerable AEs after the randomization can be transitioned to open-label 72 ug linaclotide.   |
| <b>Duration of Treatment</b>                                 | Up to a 3-week Screening Period, followed by a 52-week Treatment Period  |
| <b>Reference Therapy, Dosage, and Mode of Administration</b> | None   |
| <b>Criteria for Evaluation</b>                               | Patient-reported assessments   |
| <b>Pharmacokinetic Analysis</b>                              | Immunogenicity assessments   |
| <b>Primary Outcome Measure</b>                               | ADA determinations from blood samples  |
| <b>Secondary Outcome Measures</b>                            | AE reporting of recurrence (including date) of intolerable diarrhea after randomization to double-blind treatment following resolution of initial intolerable diarrhea.<br>Assessments of efficacy [REDACTED] during open-label treatment, and during double-blind treatment.  |
| [REDACTED]   | [REDACTED]   |

|                            |  |
|----------------------------|--|
| <b>Statistical Methods</b> | <p><b>Immunogenicity Assessments</b></p> <p>For each indication separately and combined, the number and percentage of patients meeting treatment-related ADA-positive status will be summarized, along with the 1-sided 95% Clopper-Pearson confidence interval, for Safety Population patients with at least 1 assessable postbaseline sample, ie, patients who are not postbaseline ADA undetermined (sample lost, damaged, or out of specifications). A sensitivity analysis will be performed where baseline ADA undetermined patients are excluded.</p> <p><b>Efficacy</b> [REDACTED]</p> <p>The efficacy [REDACTED] will be analyzed descriptively based on the Intent-to-Treat Population. As this is an open-label study, no inferential statistics will be performed.</p> <p>[REDACTED]</p> <p>[REDACTED]</p> |
|----------------------------|--|











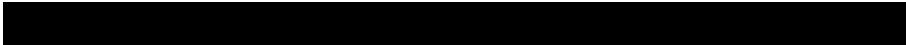


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**4.0**

**LIST OF ABBREVIATIONS**

|       |   |
|-------|---|
| ADA   | anti-drug antibody                                  |
| AE    | adverse event                                       |
| BM    | bowel movement                                      |
| BP    | blood pressure                                      |
| BSFS  | Bristol Stool Form Scale                            |
| CIC   | chronic idiopathic constipation                     |
| CFR   | Code of Federal Regulations                         |
| ECG   | electrocardiogram, electrocardiographic             |
| eCRF  | electronic case report form                         |
| EDC   | electronic data capture                             |
|       |   |
| EOS   | end of study  |
| ET    | early termination                                   |
| FDA   | US Food and Drug Administration                     |
| FR    | Federal Register                                    |
| GCP   | good clinical practice                              |
| GI    | gastrointestinal                                    |
| HIPAA | Health Insurance Portability and Accountability Act |
| IBS   | irritable bowel syndrome                            |
| IBS-C | irritable bowel syndrome with constipation          |
|       |   |
| ICF   | informed consent form                               |
| ICH   | International Conference on Harmonisation           |
| IND   | Investigational New Drug (application)              |

|      |                                      |
|------|--------------------------------------|
| IRB  | Institutional Review Board           |
| ITT  | intent to treat                      |
| IWRS | interactive Web response system      |
| NDA  | New Drug Application                 |
| NEAE | newly emergent adverse event         |
|      |                                      |
| PCS  | potentially clinically significant   |
| QTc  | QT interval corrected for heart rate |
| RSM  | Regional Site Manager                |
| SAE  | serious adverse event                |
| SBM  | spontaneous bowel movement           |
| TEAE | treatment-emergent adverse event     |

## **5.0** **ETHICAL CONSIDERATIONS**

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

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., 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 study center's IRB in conformance with CFR, Title 21, Part 56.

### **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 ICH Guidances on General Considerations for Clinical Trials (ICH-E8; 62 FR 66113, 17 Dec 1997) and GCP (ICH-E6; 62 FR 25692, 09 May 1997), as well as Part 312 of the CFR.

### **5.3** **PATIENT INFORMATION AND INFORMED CONSENT**

Patients, after being given an explanation of the study, will give voluntary and written informed consent and HIPAA authorization (in compliance with 21 CFR, Parts 50 and 312) or other appropriate forms before participating in any study-related procedures.

Each patient will read, assent to an understanding of, and sign an instrument of informed consent or other locally applicable regulation and authorization form, after having had an opportunity to discuss the study and the ICF with the study staff; each patient will be made aware that he or she may withdraw from the study at any time without impact to further treatment.

The informed consent statement contains all the elements of informed consent listed in Appendix I of this protocol. Signed copies of the ICF and the HIPAA or other locally applicable form will be given to the patient, and both documents will be placed in the Investigator's study files.

## **6.0** **INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE**

This study will be performed at approximately 80 study centers in the United States.

The Investigator is responsible for ensuring that the study is conducted according to the signed Investigator statement, the study protocol, 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 used in the study. An Investigator shall obtain the informed consent of each 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 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 staff qualified by education, experience, and licensure (in accordance with local regulations) and that the Investigator oversight is documented and assessment of Investigator capabilities and performance consistent with the study protocol. 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**

### **7.1** **CHRONIC IDIOPATHIC CONSTIPATION**

The symptoms of chronic idiopathic constipation (CIC) are reported in approximately 15% of the general population ([Stewart et al, 1999](#)). The prevalence of CIC is higher in women than men and increases with age ([Johanson et al, 1989](#); [Lembo and Camilleri, 2003](#)). Patients with CIC report multiple bowel and abdominal symptoms including straining, gas, hard stools, abdominal discomfort, infrequent bowel movements (BMs), bloating, a sense of incomplete evacuation, and abdominal pain ([Johanson and Kralstein, 2007](#)).

### **7.2** **IRRITABLE BOWEL SYNDROME WITH CONSTIPATION**

Irritable bowel syndrome (IBS) is a chronic functional gastrointestinal (GI) disorder characterized by recurrent symptoms of abdominal pain and/or discomfort accompanied by altered bowel function ([Longstreth et al, 2006](#)). In moderate to severe cases of IBS, an overall deterioration in quality of life is often present ([Drossman et al, 2002](#)). IBS is one of the most common GI disorders diagnosed in the United States; data suggest the prevalence of IBS is 10% to 15% of the population in North America and Europe ([Muller-Lissner et al, 2001](#)). Based on Rome III guidelines, IBS is subtyped as IBS with diarrhea (IBS-D) or IBS with constipation (IBS-C); patients who do not fit IBS-C or IBS-D subtypes are classified as having mixed IBS (IBS-M) or untyped IBS (IBS-U) ([Longstreth et al, 2006](#)). In addition to abdominal pain or discomfort and reduced stool frequency, IBS-C patients also report a number of other complaints including bloating, hard stools, straining, and a sensation of incomplete evacuation.

### **7.3** **SUMMARY OF LINACLOTIDE PROPERTIES**

Linacotide, a 14-amino acid peptide that acts on the apical surface of epithelial cells in the intestinal lumen to stimulate guanylate cyclase subtype C, is approved and marketed as an orally administered therapeutic for the treatment of CIC and IBS-C. By activating guanylate cyclase subtype C, orally administered linacotide has been found to increase both intestinal fluid secretion and intestinal transit and also to decrease visceral pain in animal models ([Linacotide, 2013](#)). Linacotide has minimal oral bioavailability ( $\leq 0.2\%$ ) in several animal species ([Bryant et al, 2010](#); [Eutamene et al, 2009](#)). Refer to the Investigator's Brochure for a more detailed description of the chemistry, pharmacology, efficacy, and safety of linacotide, based on studies conducted in animals, healthy volunteers, and in patients with IBS-C and CIC ([Linacotide, 2013](#)).

## 7.4 CLINICAL EXPERIENCE

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

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

In addition, a randomized, double-blind, placebo-controlled, parallel-group Phase 3b study (LIN-MD-04) in patients with CIC was recently completed.

The 2 IBS-C studies (LIN-MD-31 and MCP-103-302) evaluated the safety and efficacy of linacotide 290 ug (the adult dose subsequently approved by FDA) administered as an oral capsule for 12 or 26 weeks, respectively. In these studies, linacotide demonstrated statistically significant and clinically meaningful improvements in patients' constipation symptoms and abdominal pain, and met all the pre-specified primary and secondary endpoints. Study MCP-103-302 demonstrated improvement in abdominal and bowel symptoms at 12 weeks that was maintained throughout 26 weeks of treatment. Study LIN-MD-31 included a 4-week double-blind, randomized withdrawal period immediately following the 12-week treatment period to assess the potential for rebound worsening 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 linacotide was discontinued. The most common adverse event (AE) was diarrhea occurring in approximately 20% of IBS-C patients in both studies. Overall, there was no obvious pattern in the types of SAEs experienced in either the placebo or linacotide group. There were no SAEs of diarrhea.

The 2 CIC studies (LIN-MD-01 and MCP-103-303) evaluated the safety and efficacy of linacotide 145 ug (the adult dose subsequently approved by FDA for this indication) and linacotide 290 ug administered as 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 was diarrhea occurring in 13.1% to 17.2% of CIC patients in both studies. 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 linacotide dose groups in the incidence of diarrhea treatment-emergent adverse events (TEAEs), severe diarrhea TEAEs, or diarrhea that resulted in discontinuation from the studies.

The systemic exposure to linaclotide was also evaluated in the Phase 3 IBS-C and CIC studies in adults. Analysis of plasma indicated that linaclotide and its only active metabolite (des tyrosine linaclotide) MM-419447, plasma concentrations are generally not detectable. Linaclotide was detectable at concentrations just above the limit of detection (0.2 ng/mL) in the plasma of only 2 out of the 465 patients whose plasma samples were analyzed (both were IBS-C patients). MM-419447 was not detectable in any patient plasma samples.

Because of linaclotide's limited systemic availability, a thorough QT study was not performed. However, triplicate electrocardiograms (ECGs) were part of the safety data obtained during the Phase 3 studies in adults. There were no clinically meaningful differences between placebo and linaclotide groups in the mean or change from baseline QT interval (corrected by either the Bazett or Fridericia formula). Overall the data indicated that linaclotide does not adversely affect the ECG of adult linaclotide-treated patients.

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. Study MCP-103-305 had a single case of aplastic anemia reported; the clinical presentation of the patient suggested that the disease process culminating in aplastic anemia began prior to linaclotide exposure and was most likely idiopathic. Post-hoc analyses of the linaclotide Phase 3 clinical studies and long-term safety studies were undertaken to determine whether there was any evidence of a linaclotide effect on blood cell counts. There was no evidence of such an effect and based on linaclotide's pharmacologic properties and minimal systemic bioavailability, linaclotide is unlikely to cause aplastic anemia. 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 recently 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 chronic constipation and prominent abdominal bloating at baseline (ie, bloating  $\geq$  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.

Safety data from these studies in adults showed that, except for diarrhea, the proportion of patients reporting a TEAE was similar between placebo and each linaclotide dose group, and the incidence of TEAEs was not dose-related. With the exception of the 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.

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. 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 in young juvenile mice.

## **7.5 RATIONALE FOR THIS STUDY**

The possibility of an immune response to linaclotide, in the form of anti-drug antibody (ADA), was not evaluated in the linaclotide clinical development program. Upon approval of the NDA, the FDA Division of Gastroenterology and Inborn Errors Products required the Sponsors to evaluate this possibility by performing "a clinical trial in adults receiving Linzess (linaclotide) to assess development of ADA responses in patient samples." The Division also prescribed that in this trial "adverse events will be collected."

Evaluation of the immunogenicity of therapeutic proteins and peptides remains an important part of product development. Antibody-related clinical sequelae that can occur in humans range from no apparent or mild side effects to altered efficacy, immune-complex-mediated symptoms, and allergic reactions. Thus, it is necessary to collect appropriate data regarding the possibility of the appearance of and, if they appear, the characteristics of antibodies induced over time and assess how these findings may be associated with clinical outcomes. ([Koren et al, 2008](#); [Parenky et al, 2014](#); [Shankar et al, 2014](#))



This open-label study is designed to fulfill a post-marketing requirement and in doing so determine if ADAs develop in patients treated with linaclotide. Secondly, the study will provide additional evidence to support the long-term safety of linaclotide in adult IBS-C and CIC patients and evaluate lower doses of linaclotide in patients who develop intolerable AEs that prompt consideration of study withdrawal.

## **8.0**                      **STUDY OBJECTIVES**

The primary objective of this study is to assess the potential of linaclotide treatment to induce the development of ADAs. The secondary objectives are to provide additional evidence supporting the long-term safety and efficacy of linaclotide in adult irritable bowel syndrome with constipation (IBS-C) and CIC patients and to evaluate lower doses of linaclotide in patients who consider study withdrawal due to intolerable AEs.

## **9.0** **INVESTIGATIONAL PLAN**

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

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

The study will consist of up to a 3-week Screening Period, followed by a 52-week Treatment Period ([Figure 9.1–1](#)). Patients who meet the entry criteria will receive once daily, open-label doses of 290 ug linaclotide for patients with IBS-C; those with CIC will receive once daily, open-label doses of 145 ug linaclotide.

In order to limit patient withdrawals from the study due to AEs and to gain information about the effect of lowering the dose in patients who experience intolerable AEs (defined as AEs that subjectively would cause a patient to consider study withdrawal), in particular diarrhea and other GI AEs that may be related to the use of linaclotide, the following intervention ([Figure 9.1–2](#)) will be offered as an optional treatment course to such patients, unless deemed clinically inappropriate by the Investigator:

1. A temporary suspension of dosing of up to 7 days. If the dose suspension needs to last longer than 7 days because the intolerable AE has not resolved, then the Investigator should contact the Study Physician to discuss the duration of the dose suspension or withdrawal of the patient from the study. All AEs resulting in the temporary suspension will be recorded on the eCRF.
2. After the intolerable AE has resolved, the patient will be randomized into a Double-blind Treatment Period via an interactive Web response system (IWRS) and will receive dose regimens specific to each indication as follows. If the randomized dose regimen is tolerated, the patient will remain on this dose for the duration of the study (total duration of linaclotide exposure [whether open-label or double-blind] is not to exceed 52 weeks).

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

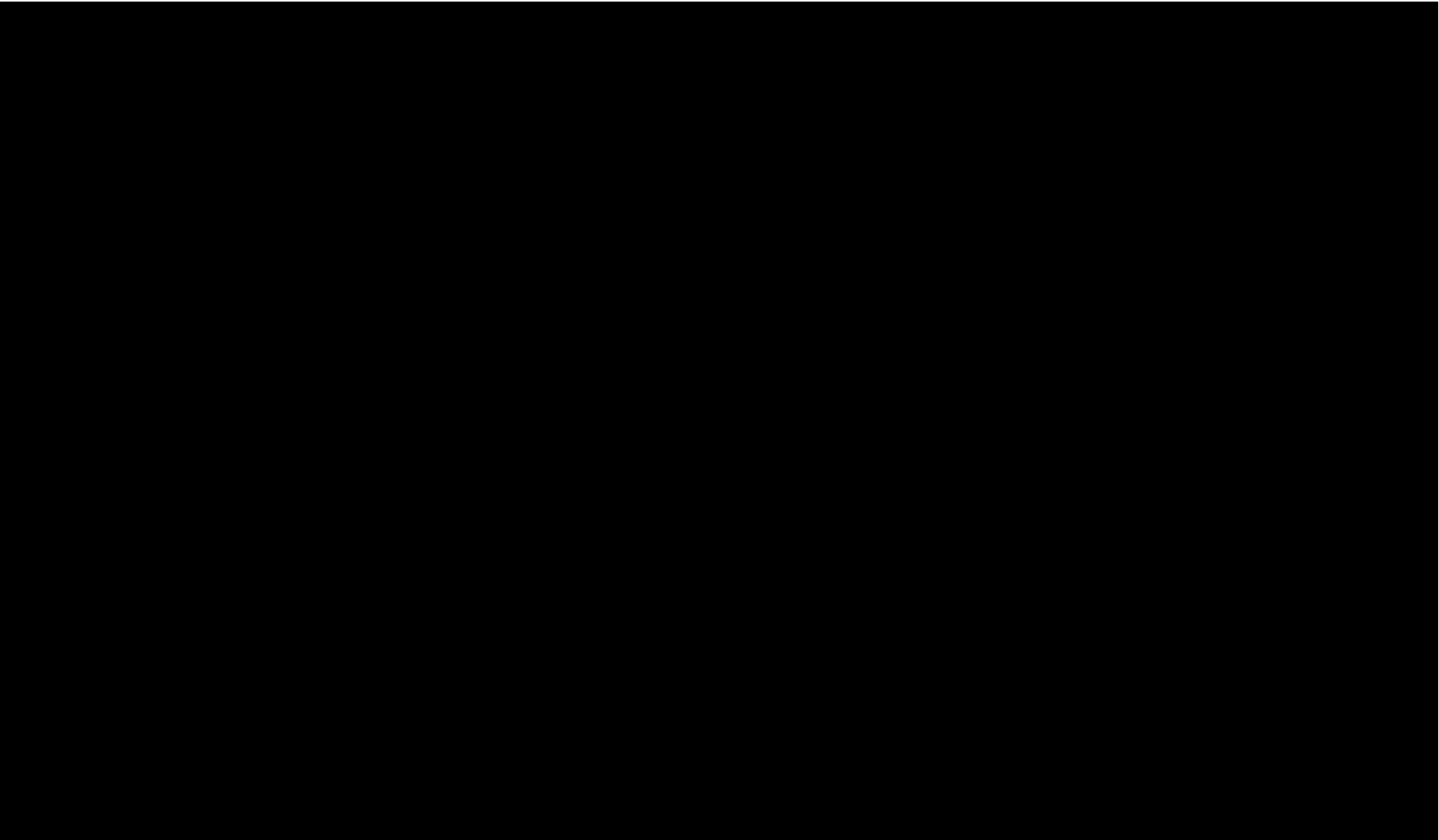
- Linaclotide 290 ug every day
- Linaclotide 145 ug every day
- Linaclotide 72 ug every day

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

- Linaclotide 145 ug every day
  - Linaclotide 72 ug every day
3. If, after randomization, patients experience intolerable AEs, in particular diarrhea or other GI AEs, the dosing should be temporarily suspended for up to 7 days. If the dose suspension needs to last longer than 7 days because the intolerable AE has not resolved, then the Investigator should inform the Study Physician about the duration of dose suspensions or withdrawal of the patient from the study.

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

4. If patients experience an intolerable AE while receiving the adjusted dose of 72 ug in the Dose-Reduced Open-label Treatment Period, study participation should be terminated.
5. In the event of a planned procedure or an AE during which a patient requires dose suspension longer than 7 days, the Investigator should inform the Study Physician about the duration of dose suspensions. Upon event completion or AE resolution, the patient should be resumed on the assigned dose.





### ***Screening Period***

The Screening Period starts with signing of the ICF and lasts for up to 21 calendar days. During this period, patient eligibility for entry into the Treatment Period will be determined, based on results of physical examination, medication history, medical/surgical history, all laboratory tests, ECG, and colonoscopy (if applicable). The end of the Screening Period coincides with the start of the Treatment Period.

### ***Treatment Period***

The Treatment Period lasts for 52 weeks, including open-label treatment (all patients) and double-blind treatment (patients with intolerable AEs). Patients will attend study visits to complete all assessments. A list of assessments to be completed for all patients, for IBS-C patients, and for CIC patients, as well as the visits at which they are performed is provided in the Schedule of Evaluations ([Section 2.0](#)).

### ***Follow-up Period***

***The follow-up period consists of a 1-month telephone visit for all patients (Visit 9). A 4-Month Follow-Up Visit (Visit 10) is required only for patients with treatment-related ADAs at the time of study completion (52 weeks, Visit 8) or early termination [ET]. If treatment-related ADAs are still present in the patient's serum at the 4-Month Follow-up Visit, an 8-Month Follow-up Visit will be required for ADA testing. Patients completing the 4-Month Follow-up Visit will also have a subsequent 1-month telephone call to review ADA status and determine if continuation to an 8-Month Follow-up Visit (Visit 11) is necessary.***

***If an ADA-positive patient becomes ADA negative or a baseline ADA-positive patient's titer returns to less than 4-fold the baseline titer at the end the treatment period (52 weeks or early termination) or 4-Month Follow-up Visit (Visit 10), no further follow-up or visits are required. A list of assessments and the visits at which they are performed is provided in the Schedule of Evaluations (Section 2.0).***

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

An open-label study design with up to 52 weeks (12 months) of investigational-product exposure was chosen in accordance with the concepts in the ICH-E1 guideline for the safety evaluation of drugs intended for the long-term treatment (chronic or repeated intermittent use for longer than 6 months) of non-life-threatening diseases. The 12-month duration of the study will allow for assessment of the potential for ADAs to develop in response to long-term linaclotide treatment.

Two of the linaclotide doses selected for use in this study for CIC and IBS-C patients (145- and 290-ug, respectively) have been approved, and are currently marketed, in North America (ie, United States, Canada, and Mexico for both indications) and the European Union (IBS-C only). Patients with intolerable AEs that occur during open-label dosing will be randomized to receive double-blind treatments of 290 ug, 145 ug, or the lower (unapproved) dose of 72 ug linaclotide oral capsules for IBS-C; and 145 ug or 72 ug for CIC. Patients who experience further intolerable AEs after the randomization can be transitioned to open-label 72 ug linaclotide.

## **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. Provide written informed consent obtained from the patient before the initiation of any study-specific procedures

2. Be an ambulatory, community-dwelling male or non-pregnant female 18 years or older at the Screening Visit

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

6. Patient meets the colonoscopy requirements defined in [Appendix V](#), which are modified from the Summary of the US-Multi-Society Task Force on Colorectal Cancer and other Colonoscopy Requirements
7. Patient has no clinically significant findings on a physical examination, 12-lead ECG, and clinical laboratory tests (clinical chemistry panel, complete blood count, urine drug screen, urinalysis) after signing the ICF but before receiving the first dose of investigational product. (Note: The Investigator will determine if a particular finding is clinically significant. In making this determination, the Investigator will consider whether the particular finding could prevent the patient from performing any of the protocol-specified assessments, could represent a condition that would exclude the patient from the study, could represent a safety concern if the patient participates in the study, or could confound the study-specified assessments of safety or efficacy)
8. Patient meets the Rome III criteria for IBS-C or CIC as described below:

**IBS-C Criteria:** the patient must meet the following 2 criteria (A and B):

- A. *IBS Criteria:* The patient must have abdominal pain or discomfort at least 3 days per month in the 3 months before diagnosis (with symptom onset at least 6 months before diagnosis) associated with 2 or more of the following:



1. Improvement with defecation
  2. Onset associated with a change in frequency of stool
  3. Onset associated with a change in form (appearance) of stool
- B *Stool Consistency Requirement:* During the 3 months before diagnosis in the absence of laxative or enema use, the patient has hard or lumpy stools (Bristol Stool Form Scale [BSFS] score 1 or 2) with at least 25% of BMs and has loose or mushy stools (BSFS 5 or 6) with < 25% of BMs

**CIC Criteria:** the patient must meet the following 3 criteria (A, B, and C):

- A. Patient meets 2 or more of the following criteria for 3 months before the diagnosis with symptom onset at least 6 months before diagnosis:
  1. Straining during at least 25% of defecations
  2. Lumpy or hard stools in at least 25% of defecations
  3. Sensation of incomplete evacuation for at least 25% of defecations
  4. Sensation of anorectal obstruction/blockage for at least 25% of defecations
  5. Manual maneuvers to facilitate at least 25% of defecations (eg, digital evacuation, support of the pelvic floor)
  6. Fewer than 3 defecations per week
- B. Loose stools are rarely present without the use of laxatives
- C. Insufficient criteria for irritable bowel syndrome. (The criteria for IBS are provided in Point A under IBS Criteria, above)



### 9.3.2 Exclusion Criteria

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

1. At the Day 1 Visit, the patient reports having 6 or more spontaneous bowel movements (SBMs) when asked about the number of SBMs that they had during the week before the visit. (Note: An SBM is a bowel movement that occurred in the absence of laxative, enema, or suppository use on either the day of the BM or the day before the BM)
2. At the Day 1 Visit, patient reports having any SBMs that were watery (BSFS = 7) or more than 1 SBM that was mushy (BSFS = 6) when asked about the number of SBMs that were watery or mushy during the week before the visit

3. Patients who have any of the following:

[REDACTED]

[REDACTED]

[REDACTED]

- Structural abnormality of the GI tract or a disease or history of a condition that can affect GI motility (eg, gastroparesis, celiac disease)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[illegible]

- 05 Oct 2015

[REDACTED]

[REDACTED]

[REDACTED]

### **9.3.3 Removal of Patients from Therapy or Assessment**

A premature discontinuation will occur when a patient who signed the ICF ceases participation in the study, regardless of circumstances, before the completion of the study. Patients can be prematurely discontinued from the study for one of the following reasons:

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

All enrolled patients who prematurely discontinue from the study, unless the cause is screen failure, must be seen for a final assessment at ET, and follow-up blood samples as described in the Schedule of Evaluations ([Section 2.0](#)) should be obtained for patients who are ADA positive at the last visit. A *final assessment* will be defined as completion of the evaluations scheduled for the Final Visit at the end of Week 52 End of Study (EOS)/ET Visit (Visit 8).

Any patient who withdraws because of an AE will be followed until the AE resolves, stabilizes, or can be explained as being unrelated to investigational product. The study centers must make a reasonable effort to follow pregnant patients until delivery or end of the pregnancy.

Patients who do not complete all required scheduled visits/procedures must be requested in writing to come in for an ET Visit and to return any unused investigational product. A clear description of premature discontinuation must be documented. A copy of the letter, together with the source documentation, will be kept by the Investigator. The reasons for premature discontinuation from the study will be reflected on the eCRF.

#### **9.3.4 Patient Replacement Procedures**

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

### **9.4 TREATMENTS**

#### **9.4.1 Treatments Administered**

Investigational product in the form of capsules will be provided by the Sponsor. Patients will be supplied capsules with identical appearance containing either 72 ug linaclotide, 145 ug linaclotide, or 290 ug linaclotide.

Rescue medication will not be provided; however, patients may use any laxative, suppository, or enema that they choose when at least 72 hours have passed since their previous BM or when their symptoms become intolerable. Laxative, suppository or enema use must be documented with all other concomitant medication use in the eCRF.

#### **9.4.2 Identity of Investigational Products**

All investigational product will be supplied in bottles containing 35 capsules and will be labeled with the following content: protocol number, storage information, warning language (“Caution: New Drug-Limited by Federal Law to Investigational Use. Keep Out of Reach of Children”), and instructions to take as directed. The label will also include the kit number. All 3 strengths of linaclotide (72 ug, 145 ug, and 290 ug) will be listed on the bottle label. IWRS will be used to dispense kits in Open-label and Double-blind treatment periods.

Immediately before dispensing investigational product, the Investigator or designee will write the patient’s initials, patient identification number, and dispensing date on the label.

Investigational product must be stored at the study center in an appropriate secure area (eg, a locked cabinet in a locked room) [REDACTED] excursions permitted between [REDACTED]. Keep product in the original container. Do not subdivide or repackage. Protect from moisture. Do not remove desiccant from the container. Keep bottles tightly closed in a dry place.

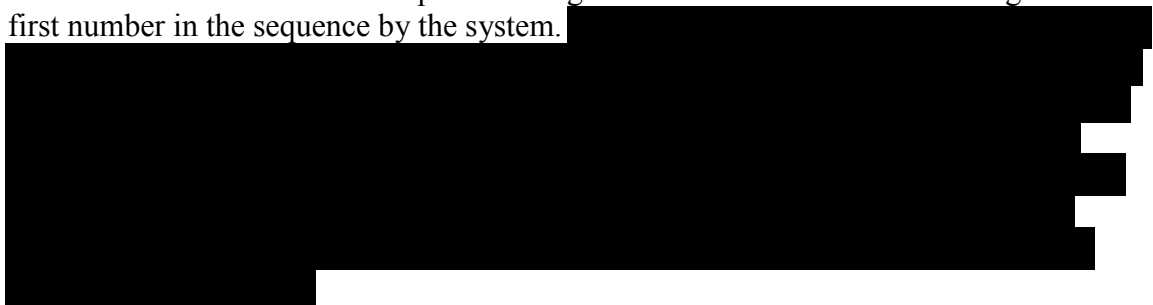
Formulation information for the investigational products is provided below.

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

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 must be returned, and whenever investigational products are returned, unit counts must be performed. All investigational products must be accounted for. At the end of the study, all unused investigational products and empty investigational product bottles 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 signs the ICF at the first screening visit, study personnel will register the patient in the IWRS, and the system will assign the patient a sequential patient identification number. The first patient to sign the ICF at each site will be assigned the first number in the sequence by the system.



The study center must contact the IWRS at the Screening Visit and at investigational product dispensing visits; the IWRS will assign the kit number for the investigational product to be dispensed to the patient at the first Treatment Period visit (Visit 2) and at other visits as designated on the Schedule of Evaluations ([Section 2.0](#)).

This is an open-label (unblinded) study, with IBS-C patients initially assigned to receive 290 ug linaclotide and CIC patients assigned to receive 145 ug. Patients who experience intolerable AEs during open-label phase will be randomized into a Double-blind Treatment Period via the IWRS and will receive dose regimens specific to each indication as described in [Section 9.4.4](#).

### **9.4.4 Selection of Dosages in the Study**

The linaclotide dosages chosen for the open-label phase of this study (145 ug and 290 ug) have been shown to be safe and effective in adults for treatment of IBS-C (290 ug) and CIC (145 ug) and are approved in North America at those doses for those indications. Data from the pivotal clinical studies showed that for patients in both patient populations treated with linaclotide, diarrhea was the most frequent AE, reported in 20% for IBS-C patients treated with 290 ug linaclotide and in 16% for CIC patients treated with 145 ug linaclotide, and was the most common reason for discontinuation (5%). In the majority of cases, onset of the diarrhea occurred within the first 2 weeks of treatment, and the diarrhea was generally mild to moderate (being assessed as severe in only 2% of linaclotide-treated patients in each patient population).

Patients with intolerable AEs that may be related to the use of linaclotide will be randomized to receive double-blind 290 ug, 145 ug, or 72 ug linaclotide oral capsules for IBS-C; and 145 ug or 72 ug for CIC. Patients who experience further intolerable AEs after the randomization can be transitioned to open-label 72 ug linaclotide.

The 72 ug dose was selected as part of the dose regimen during the double-blind phase for patients with intolerable AEs as it demonstrated efficacy in Phase 2b IBS-C and CIC studies, particularly related to improvement of bowel symptoms, with an improved safety profile compared to higher doses.

#### **9.4.5 Selection and Timing of Dose for Each Patient**

All investigational product will be administered orally as a single daily dose in the morning at least 30 minutes before the first meal of the day.

Patients who meet all eligibility criteria at Day 1 (Visit 2) will be dispensed 1 bottle (assigned by IWRS) containing 35 capsules of investigational product. Additional bottles of investigational product will be dispensed at subsequent visits per the Schedule of Evaluations ([Section 2.0](#)). Patients will be instructed to return any unused investigational product at the next study visit.

Patients must have fasted for at least 2 hours before arriving at the site for Day 1 (Visit 2). Patients will take their initial dose of investigational product (1 capsule) at the study center during Day 1 (Visit 2) after all study eligibility criteria have been confirmed. On all subsequent days, the patient will take 1 capsule of investigational product in the morning at least 30 minutes before breakfast. If, for any reason, it is inconvenient for a patient to take linaclotide in the morning, the dose may be taken at another time during the day with the Investigator's prior approval and documentation, as long as linaclotide is taken on an empty stomach or at least 2 hours after a meal.

Should an intolerable AE occur and, in the Investigator's judgment, the patient is unable to resume investigational product dosing after 7 days, the Investigator must contact the Study Physician to discuss the patient's continued participation in the study

#### **9.4.6 Blinding**

Randomization only occurs for those patients who experience intolerable AEs that may be related to the use of linaclotide and undergo intervention ([Section 9.1](#)). For those patients, a list of patient randomization codes will be generated by Statistical Programming at the Sponsor or designee, 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**

In the open-label and double-blind treatment phases, bottles of linaclotide will be dispensed that include on the label: contains either 72 ug linaclotide, 145 ug linaclotide, or 290 ug linaclotide. During the open-label treatment phase both the Investigator and patient will be made aware of the dose contained in the IWRS-assigned bottle.

Unblinding procedures are applicable to the double-blind treatment phase only.

Any unblinding (performed only via IWRS) at a study center should be done only in an emergency that requires the investigational product to be identified for the medical management of the patient. The Investigator must notify the Study Physician immediately (see [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 center will immediately disqualify the patient from further participation in the study.

Treatment codes may be broken by the Patient Safety Department at Forest Research Institute, Inc., 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.

In an emergency, the Investigator can obtain the treatment assignment of any patient at his or her study site through the IWRS.

#### **9.4.8 Prior and Concomitant Therapy**

All ongoing medicines taken by the patient at the time of screening and prior to first dose of investigational product will be recorded as prior medications. Any changes in concomitant medicines or new medicines added will be recorded in the eCRF. Concomitant medicines will be recorded at study visits throughout the entire study (beginning at Visit 1) including the Follow-up Period (Visits 9 - 11).

The concomitant medicines listed below are prohibited from the Screening Visit until the end of the Treatment Period ([Appendix III](#)):

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

During the Follow-up Period there are no concomitant medication restrictions.

#### **9.4.9 Monitoring Treatment Compliance**

Investigational-product compliance during the Treatment Period will be monitored by counting the number of capsules dispensed and returned. Patients will be instructed to return all investigational product and bottles at specified visits defined in the Schedule of Evaluations ([Section 2.0](#)). Before new investigational product is dispensed at the specified visits, every effort will be made to collect all unused investigational product.

### **9.5 EFFICACY AND SAFETY VARIABLES**

#### **9.5.1 Primary Outcome Assessment**

Assessments of total anti-linacotide antibodies will be used to determine the primary outcome parameter, the presence of ADAs. The presence of anti-linacotide antibodies will be determined by a validated assay.

##### **9.5.1.1 Immunogenicity Assessments**

Blood will be collected for determination of ADAs to linacotide at the Day 1 Visit (Visit 2) prior to the patient receiving investigational product (to acquire a baseline), and at all scheduled study visits during the Treatment Period. For patients who prematurely discontinue, blood samples should be obtained within 7 days of the last dose of linacotide, and follow-up blood samples as described in the Schedule of Evaluations ([Section 2.0](#)) should be obtained for patients who are ADA positive at the last visit.

Blood samples collected for ADA determinations will be analyzed in batches; therefore real-time reports of ADA results will not be available.

Investigators and patients will remain blinded throughout the study as to ADA status. Patients who develop positive or increased ADA titers will not be withdrawn from treatment; investigators will continue such patients on therapy as they would any patient in the study. Clinical symptoms of hypersensitivity such as anaphylactic shock, angioedema, skin rash, and urticaria require treatment withdrawal even without ADA results available at the time of occurrence.

Each individual sample will be assayed and categorized as one of the following:

- ADA positive
- ADA negative
- ADA undetermined (sample lost, damaged, or out of specifications)

A sample is only considered ADA positive if the screening and confirmatory assay both indicate the presence of ADAs. A sample indicating the presence of ADAs by the screening assay that cannot be confirmed (eg, insufficient sample, laboratory error) will be considered ADA undetermined.

***ADA-positive patients will be split into two groups at the end of the study; treatment-related ADA and non-treatment-related ADA. A treatment-related ADA is any patient who is ADA negative at baseline and becomes ADA positive at one or more time points in the study (treatment induced ADA), or who is ADA positive at baseline and has a titer increase greater than or equal to 4-times the baseline titer at one or more time points in the study (treatment boosted ADA). A non-treatment-related ADA positive patient is any patient who is ADA positive at baseline and is either ADA negative or has a titer less than 4-fold the baseline titer at any time point in the study.***

***Patients with treatment-related ADAs detected at the end of the Treatment Period (52 weeks visit or early termination visit) will be followed at 4 months (Visit 10) and, if needed, up to a maximum of 8 months (Visit 11), or until they are ADA negative or their titers revert to baseline. Any patient who is ADA negative or has non-treatment-related ADA at the end of the treatment period (52 weeks or ET) does not require follow up regardless of ADA status at any other time during the study. In order to minimize the number of ADA-undetermined results, patients whose serum samples from the Week 52 EOS/ET Visit (Visit 8) are lost, damaged, or out of specification may be called for an unscheduled visit to obtain another sample.***

***In order to show reversion to baseline for treatment-related ADA-positive patients who require follow up, 1 negative sample or 1 sample showing a return to an ADA titer less than 4-fold the baseline titer is required. Patients with treatment-related ADAs who complete the study or terminate early will be requested to return for additional follow-up visits to provide blood samples for ADA assessments at 4 and 8 months to document persistence of positivity or reversion to baseline. No further visits will be required after the 8-Month Follow-up Visit (Visit 11). Patients previously ADA positive who have become ADA negative or have reverted back to within 4-fold their baseline titer at the 4-Month Follow-up Visit will not be required to complete the 8-Month Follow-up Visit. Investigators will be notified of the ADA status following patient completion or ET and before the 1-month follow-up phone call to the patient.***

Samples will be banked for ***up to*** 10 years in case further testing for isoform, subform, and/or linaclotide concentration is requested. Consent for storage and further testing will be obtained from patients.

In cases of SAEs, ADA status can be reported to both patients and investigators if requested and felt to be necessary for the medical care of the patient. If the blind is broken, the patient must be withdrawn from treatment.

The study Sponsor will contract with ***Q-Squared Solutions BioSciences LLC*** for ADA testing.

The testing methods will be the following:

- Screening assay for ***the presence of*** anti-linaclotide antibodies: custom bridging ELISA with electrochemiluminescence detection. Positive results in the screening assay will be confirmed by competitive displacement of the anti-linaclotide antibodies with free linaclotide using the same assay. ***A sample is considered ADA negative if it is negative in either the screening or confirmatory assays. A sample is considered ADA positive if it is positive in the confirmatory assay***
- ADA positive serum will be titrated and assayed for neutralizing antibodies and cross reactivity with the endogenous hormones, guanylin and uroguanylin

### **9.5.2 Efficacy Assessments**

The following information will be captured at the specified study visits ([Section 2.0](#)). All assessments required on Day 1 Visit (Visit 2) should be performed before first dose of linaclotide.

*For all patients:*

- Patient Assessment of Constipation Severity (captured at all study visits except the Screening Visit [Visit 1]):
  - Rating of the constipation severity during the previous 7 days on a 5-point ordinal scale will be provided by the patient answering the following question:  
“On average, how would you rate your constipation during the past 7 days?”
    - 1=None
    - 2=Mild
    - 3=Moderate
    - 4=Severe
    - 5=Very Severe

*For IBS-C patients:*

- Patient Assessment of IBS Symptom Severity (captured at all study visits except the Screening Visit [Visit 1]):
  - Rating of IBS symptoms severity during the previous 7 days on a 5-point ordinal scale will be provided by the patient answering the following question:  
“On average, how would you rate your IBS symptoms during the past 7 days?”
    - 1=None
    - 2=Mild
    - 3=Moderate

- 4=Severe
  - 5=Very severe
- Degree of Relief of IBS Symptoms (captured at all study visits except the Screening Visit [Visit 1]):
  - Rating of degree of relief of IBS symptoms during previous 7 days on a 7-point balanced ordinal scale will be provided by the patient answering the following question:

“Compared to before you started this study, how would you rate your IBS symptoms during the past 7 days?”

    - 1 = completely relieved,
    - 2 = considerably relieved
    - 3 = somewhat relieved
    - 4 = unchanged
    - 5 = somewhat worse
    - 6 = considerably worse
    - 7 = as bad as I can imagine
- IBS Treatment Satisfaction Assessment (captured at all study visits except the Screening [Visit 1] and Day 1 Visits [Visit 2]):
  - Rating of degree of satisfaction with the investigational product’s ability to relieve IBS symptoms on a 5-point ordinal scale will be provided by the patient answering the following question:

“Overall, how satisfied are you with the study medication’s ability to relieve your IBS symptoms?”

    - 1=Not at all satisfied
    - 2=A little satisfied
    - 3=Moderately satisfied
    - 4=Quite satisfied
    - 5=Very satisfied

*For CIC patients:*

- Constipation Treatment Satisfaction Assessment (captured at all study visits except the Screening [Visit 1] and Day 1 Visits [Visit 2]):
  - Rating of degree of satisfaction with the investigational product’s ability to relieve constipation symptoms on a 5-point ordinal scale will be provided by the patient answering the following question:

“Overall, how satisfied are you with the study medication’s ability to relieve your constipation symptoms?”

    - 1=Not at all satisfied
    - 2=A little satisfied

- [illegible]

#### 9.5.4.1 Adverse Events

APPROVED

For the purpose of the site's data collection responsibilities, any untoward event that was reported from the time the patient signed the ICF until 30 days after the last known dose of investigational product, until ADA positive status for antibody positive patients has reverted to ADA negative, or until the end of the Follow-up Period (whichever is later), 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 informed consent, including any change in severity or frequency of pre-existing disease
- All clinically relevant abnormalities in laboratory values or clinically relevant physical findings that occur during the study schedule

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

[REDACTED]

[illegible]



### **9.5.4.3                      Severity Assessment**

The Investigator will provide an assessment of the severity of each AE by recording a severity rating on the appropriate AE reporting page of the patient's eCRF. *Severity*, which is a description of the intensity of manifestation of the AE, is distinct from *seriousness*, which implies a patient outcome or AE-required treatment measure associated with a threat to life or functionality (Section 9.5.4.4). Severity will be assessed according to the following scale:

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

### **9.5.4.4                      Serious Adverse Events**

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

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

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

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

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

#### **9.5.4.5 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 9.5.4.1, to notify site personnel of any AEs occurring up to 30 days after the last known dose of linaclotide, or for ADA positive patients, until the end of the 8-month Follow-up Period. Any AEs reported by the patient (or patient representative) during this period are to be recorded in original source documents. AEs are also to be recorded in the eCRF if at least 1 of the following conditions is met: 1) the event meets the criteria for an SAE (see Sections 9.5.4.4 and 9.5.4.6), and/or 2) the event is considered by the Investigator to be potentially causally related to investigational product.

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 stabilized, or can be explained as being unrelated to the investigational product. 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.

#### **9.5.4.6 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 Patient Safety on the SAE Form for Clinical Studies. The Sponsor's Study Physician may also be notified by telephone.

If, during follow-up, any nonserious 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 Studies to the SAE fax number shown below. Even if an initial report is made by telephone, the SAE Form for Clinical Studies 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 Studies to Forest Research Institute, Inc.

SAE fax number: [REDACTED]

Sponsor's Study Physician Medical Emergency phone number: [REDACTED]

#### **9.5.4.7 Reporting of Pregnancies That Occur During the Study**

Study site personnel must report a pregnancy from the time the patient signs the ICF until 30 days after the last dose of investigational product. Within 24 hours of learning of the pregnancy, the study site personnel must report the event to Forest Patient Safety on the Clinical Study Pregnancy Form and fax it to the SAE/Pregnancy fax number stated in Section 9.5.4.6, even if no AE has occurred. Pregnancies in female partners of male patients occurring during the time frame described above must also be reported.

The pregnancy must be followed to term and the outcome reported by completing a follow-up Clinical Study Pregnancy Form. If the pregnancy is associated with an SAE (eg, if the mother is hospitalized for hemorrhage), a separate SAE Form for Clinical Studies must be filed as described in Section 9.5.4.6 with the appropriate serious criterion (eg, hospitalization) indicated in addition to the Pregnancy Form.

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## **9.6 DATA QUALITY ASSURANCE**

### **9.6.1 Data Monitoring**

Before any patient enters the study, a representative of Forest Research Institute, Inc., 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 electronic data capture EDC system. After the first patient is enrolled, the Forest representative, a Regional Site Manager (RSM) or designee, will periodically monitor the progress of the study by conducting on-site visits. This RSM 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 RSM 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.

### **9.6.2 Data Recording and Documentation**

Data collection will involve the use of the Forest 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 Forest 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, etc.) 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 Forest Research Institute, Inc., 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 sign an ICF for the study and receive a patient identification number.

#### **9.7.1.2 *Safety Population***

The Safety Population will consist of all patients in the Screened Population who receive at least 1 dose of investigational product during the Treatment Period.

**9.7.1.3                      *Intent-to-Treat Population***

The Intent-to-Treat (ITT) Population will consist of all patients in the Safety Population who have at least 1 postbaseline assessment for any efficacy or health outcomes parameter.

**9.7.1.4                      *Randomized Population***

The Randomized Population will consist of all patients in the Safety Population who are randomized to double-blind investigational product following resolution of an intolerable AE.

**9.7.1.5                      *Double-blind Safety Population***

The Double-blind Safety Population will consist of all patients in the Randomized Population who receive at least 1 dose of investigational product during the Double-blind Treatment Period.

**9.7.1.6                      *Double-blind ITT Population***

The Double-blind ITT Population will consist of all patients in the Double-blind Safety Population who have at least 1 post-randomization assessment for any parameter during the Double-blind Treatment Period.

**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 indication (IBS-C or CIC), and study center.

The number of screen failures (ie, patients who enter the Screening Period but not the Treatment Period) along with the associated reasons for failure will be tabulated overall.

The number and percentage of patients in the categories described in Table 9.7.2–1 will be summarized overall and by treatment group, if specified, for each indication in the Safety Population.

**Table 9.7.2–1. Summarization of Patient Disposition**

| <i>Category</i>  | <i>By Treatment Group</i> |
|--|---------------------------|
| Patients who complete the Open-label Treatment Period  | No                        |
| Patients who prematurely discontinue during the Open-label Treatment Period  | No                        |
| Reasons for premature discontinuation of open-label treatment as recorded on the eCRF  | No                        |
| Patients who prematurely discontinue open-label treatment due to AE who do not randomize to double-blind treatment                     | No                        |
| Patients who prematurely discontinue open-label treatment due to AE who do randomize to double-blind treatment (Randomized Population) | Yes                       |
| Patients who complete the Double-blind Treatment Period  | Yes                       |
| Patients who prematurely discontinue during the Double-blind Treatment Period  | Yes                       |
| Reasons for premature discontinuation of double-blind treatment as recorded on the eCRF  | Yes                       |
| Patients who prematurely discontinue double-blind treatment due to AE who do not reduce dose to open-label 72 ug dose                  | Yes                       |
| Patients who prematurely discontinue double-blind treatment due to AE who do reduce dose to open-label 72 ug dose                      | Yes                       |
| Patients who complete the Dose-Reduced Open-label Treatment Period   | Yes                       |
| Patients who prematurely discontinue during the Dose-Reduced Open-label Treatment Period   | Yes                       |
| Reasons for premature discontinuation of dose-reduced open-label treatment as recorded on the eCRF                                     | Yes                       |

### **9.7.3 Demographics and Other Baseline Characteristics**

Demographic parameters (ie, age, race, ethnicity, sex, weight, height, and body mass index) and other baseline characteristics will be summarized by indication for the Safety Population, and for each indication by randomized treatment group for the Double-blind ITT Population.

*Prior medicines* are defined as any medicines taken prior to date of first dose of investigational product. Concomitant medicines are defined as any medicines taken during the Treatment Period (ie, between the date of the first dose of investigational product in the Treatment Period and the date of the last dose of investigational product in the Treatment Period, inclusive). Any medicines started after the date of last dose of investigational product will not be considered concomitant medicines for summary purposes, but will be included in the patient data listings.

Both prior and concomitant medicine use will be summarized by the number and proportion of patients in each patient group receiving each medicine within each therapeutic class. Concomitant medicine use will be presented for the Treatment Period as a whole by indication (IBS-C and CIC) for the Safety Population. Multiple medicines used by a patient in the same category (based on Anatomical-Therapeutic-Chemical classification) will only be counted once.

The *WHO Drug Dictionary*, Version September 2013 or newer, will be used to classify prior and concomitant medications by therapeutic class and drug name.

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### **9.7.5 Efficacy Analyses**

The efficacy analyses will be based on the ITT Population. As this is an open-label study, no inferential statistics will be performed on these endpoints.

Descriptive statistics (n, mean, standard deviation, median, minimum, and maximum) will be presented for continuous variables, and frequency distributions will be presented for categorical variables. These summaries will be presented by indication (IBS-C and CIC) and, where the endpoint is measured for both IBS-C and CIC, pooled across both indications at each scheduled visit the parameter is assessed.

The following parameters will be summarized:

- Constipation severity
- IBS symptom severity (IBS-C only)
- Degree of relief of IBS symptoms (IBS-C only)
- IBS treatment satisfaction (IBS-C only)
- Constipation treatment satisfaction (CIC only)



For recurrence of diarrhea parameters, tables based on the Double-blind ITT Population will specifically refer to recurrence of diarrhea. Listings based on the Randomized Population will identify the patient-specific AEs.

| <i>Parameter</i>                                   | <i>Description</i>   |
|--|--|
|  |  |
| Recurrence of (intolerable) diarrhea               | Frequency summary; Fisher exact test, comparing treatment groups.  |
| Time to first recurrence of (intolerable) diarrhea | Parameter = First recurrence of (intolerable) diarrhea date – first randomized dose date + 1; censored at date of last randomized dose for patients who do not have recurrence of (intolerable) diarrhea.<br>Summary statistics for patients who have recurrence of (intolerable) diarrhea; Kaplan-Meier summary statistics, log-rank test, and figure, and hazard ratio per Cox proportional hazards regression model, for all patients, comparing treatment groups, controlling for geographic region. |
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#### 9.7.8.2.1 Immunogenicity Assessments

A patient's baseline ADA status (ADA positive, ADA negative, or ADA undetermined) will be the assay result of the Treatment Period Day 1 (Visit 2) sample. A patient's overall postbaseline ADA status will be derived from all postbaseline samples during the Treatment Period and within **7 days** after the last dose of investigational product. The possible categories, dependent on baseline ADA status, are described in [Table 9.7.8.2.1-1](#).

**Table 9.7.8.2.1-1. Patient Postbaseline ADA Categorization**

| <b><i>Baseline ADA Negative and ADA Undetermined Patients</i></b> | <b><i>Baseline ADA Positive Patients</i></b> |
|---|--|
| Treatment-induced ADA positive                                    | Treatment-boosted ADA positive               |
|   | Non-treatment-boosted ADA positive           |
| ADA negative  | ADA negative                                 |
| ADA undetermined  | ADA undetermined                             |

Postbaseline ADA category derived for each patient based all postbaseline samples after Visit 2 through **7 days** after last dose of investigational product.

Treatment-induced ADA positive: Baseline ADA negative or ADA undetermined patient with  $\geq 1$  ADA positive sample

Treatment-boosted ADA positive: Baseline ADA positive patient with  $\geq 1$  ADA positive sample and with **titer  $\geq 4$ -fold the baseline titer**

Non-treatment-boosted ADA positive: Baseline ADA positive patient with **subsequent** ADA positive samples **that have titer values  $< 4$ -fold increase from the baseline**

ADA negative: Patient with  $\geq 1$  ADA negative sample with no ADA positive samples

ADA undetermined: Patient with no assessable samples (sample lost, damaged, or out of specifications)

A patient will meet treatment-related ADA positive status if the patient meets either of the following criteria:

- Treatment-induced ADA positive for baseline ADA negative or ADA undetermined patients
- Treatment-boosted ADA positive for baseline ADA positive patients

A sensitivity analysis will be performed where baseline ADA undetermined patients are excluded.

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#### *9.7.8.5.2 Interim Analysis*

No interim analysis is planned for this study.

### **9.7.9 Determination of Sample Size**

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

### **9.7.10 Computer Methods**

Statistical analyses will be performed using version 9.3 (or newer) of SAS on a Linux operating system.

## **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 Forest Research Institute, Inc. No protocol amendment may be implemented (with the exceptions noted below) before it has been approved by the IRB and the signature page, signed by the Investigator, has been received by Forest Research Institute, Inc. If the protocol is amended to eliminate or reduce the risk to patients, the amendment may be implemented before IRB review and approval. However, the IRB 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 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 Forest Research Institute, Inc. Protocol deviations should be reported to the Sponsor (either verbally or electronically) in a timely manner from the date 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 must be notified according to the criteria and time period dictated by the IRB associated with this study.



**10.0**                      **STUDY SPONSORSHIP**

This study is sponsored Forest Research Institute, Inc.

**10.1**                      **STUDY TERMINATION**

Forest Research Institute, Inc., reserves the right to terminate the study in its entirety or at a specific study center before study completion.

**10.2**                      **REPORTING AND PUBLICATION**

All data generated in this study are the property of Forest Research Institute, Inc. and Ironwood Pharmaceuticals, Inc. 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, Forest Research Institute Inc., and Ironwood Pharmaceuticals Inc.

## **11.0** **INVESTIGATOR OBLIGATIONS**

### **11.1** **DOCUMENTATION**

The Investigator must provide the following to Forest Research Institute, Inc., 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 Forest Research Institute, Inc., for submission to the FDA
- A fully executed contract
- The curricula vitae for the Investigator and all Sub-Investigators listed on Form FDA 1572, including a copy of each physician's license
- A copy of the original IRB 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, as stated in Section [5.1](#)
- A copy of the IRB-approved ICF
- A copy of the HIPAA authorization form, or other local privacy applicable forms
- A list of the IRB members or the 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 Sub Investigators listed on Form FDA 1572. The Investigator and all Sub Investigators 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 Sub-Investigators 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 Forest Research Institute, Inc., will inventory the investigational products at the site. The Investigator must maintain adequate records documenting the receipt and disposition of all study supplies. Forest Research Institute, Inc., 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 and empty investigational product bottles should be returned to the Sponsor or the local distributor at the address provided in the Study Reference Binder. 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 Forest Research Institute, Inc., 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 Forest. 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 case report forms, 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 Principal Investigator must permit access to any documentation relating to the study upon request of the Sponsor or applicable regulatory authorities. If the Principal 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.

#### **11.6 PATIENT CONFIDENTIALITY**

All patient records will only be identified by initials and patient identification number. Patients' names are not to be transmitted to Forest Research Institute, Inc. The Investigator will keep a master patient list on which the patient identification 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 (LIN-MD-10, dated 05 Oct 2015), and with all applicable government regulations and good clinical practice guidance.

\_\_\_\_\_  
Principal Investigator's Signature                    Date \_\_\_\_/\_\_\_\_/\_\_\_\_

\_\_\_\_\_  
Principal 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 legally authorized representative. 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; Forest Research Institute, Inc.; 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 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 participate . . .")
- A place for the patient's 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](http://www.ClinicalTrials.gov).

A copy of the signed consent form should be given to the patient.

## **APPENDIX II. CONTACT INFORMATION**

Contact information for Forest Research Institute, Inc., personnel is as follows:

[REDACTED]

[REDACTED]

[REDACTED]

Medical Emergency contact number: [REDACTED]



[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[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 center to the central laboratory on the day of collection or as specified in the laboratory manual. The central laboratory will provide packaging, labeling, and shipping instructions.

## **APPENDIX V. SUMMARY ADAPTED FROM GUIDELINES OF THE US MULTI-SOCIETY TASK FORCE ON COLORECTAL CANCER AND OTHER COLONOSCOPY REQUIREMENTS**

**Note:** Patient may be enrolled if no follow-up colonoscopy after polyp removal is due while participating in the study.

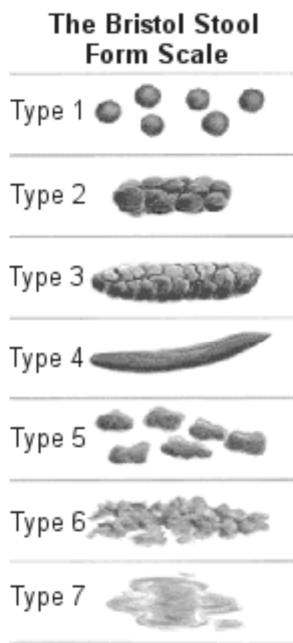
1. Patients age 50 years (40 years if African American) and older must have had a colonoscopy with negative findings within the 10 years prior to the Screening Visit (Visit 1).
2. If the most recent colonoscopy revealed hyperplastic polyps that were entirely removed, the patient may be enrolled, provided the colonoscopy was performed within 10 years prior to the Screening Visit (Visit 1).
3. If the most recent colonoscopy revealed 2 or fewer small ( $\leq 1$  cm) adenomatous polyps with tubular structure with low grade dysplasia and without appreciable villous tissue, the patient may be enrolled, provided the colonoscopy was performed within 5 years prior to the Screening Visit (Visit 1).
4. Patients who have 1 first-degree relative with colorectal cancer or adenomatous polyps diagnosed *before age 60* or 2 first-degree relatives with colorectal cancer diagnosed at any age must have had a colonoscopy with negative findings 5 years before the Screening Visit (Visit 1). This applies to patients who are 40 years or older and to patients younger than 40 years, who are 10 or fewer years from the age at which their youngest relative was found to have 1 of the aforementioned conditions.
5. Patients who have 1 first-degree relative with colorectal cancer or adenomatous polyps diagnosed at *age 60 or older* or 2 second-degree relatives with colorectal cancer diagnosed at any age must have had a colonoscopy with negative findings within 10 years prior to the Screening Visit (Visit 1). This applies to patients who are 40 years or older and to patients younger than 40 years, who are 10 years or fewer years from the age at which their youngest relative was found to have 1 of the aforementioned conditions.

### **Other Colonoscopy Requirements:**

Patients of any age who have alarm symptoms must have had a colonoscopy with negative findings after the onset of the alarm symptoms and within 5 years prior to the Screening Visit (Visit 1). Alarm symptoms include lower GI bleeding (rectal bleeding or heme-positive stool), iron-deficiency anemia, and weight loss. (Note: Current unexplained or clinically significant alarm symptoms are exclusionary.)

These requirements are adapted based on recent Guidance on Colorectal Cancer Screening ([Levin et al, 2008](#); [Lieberman et al, 2012](#); [Quaseem et al, 2012](#)).

## APPENDIX VI. BRISTOL STOOL FORM SCALE



Type 1 - Separate hard lumps like nuts (difficult to pass)

Type 2 - Sausage shaped but lumpy

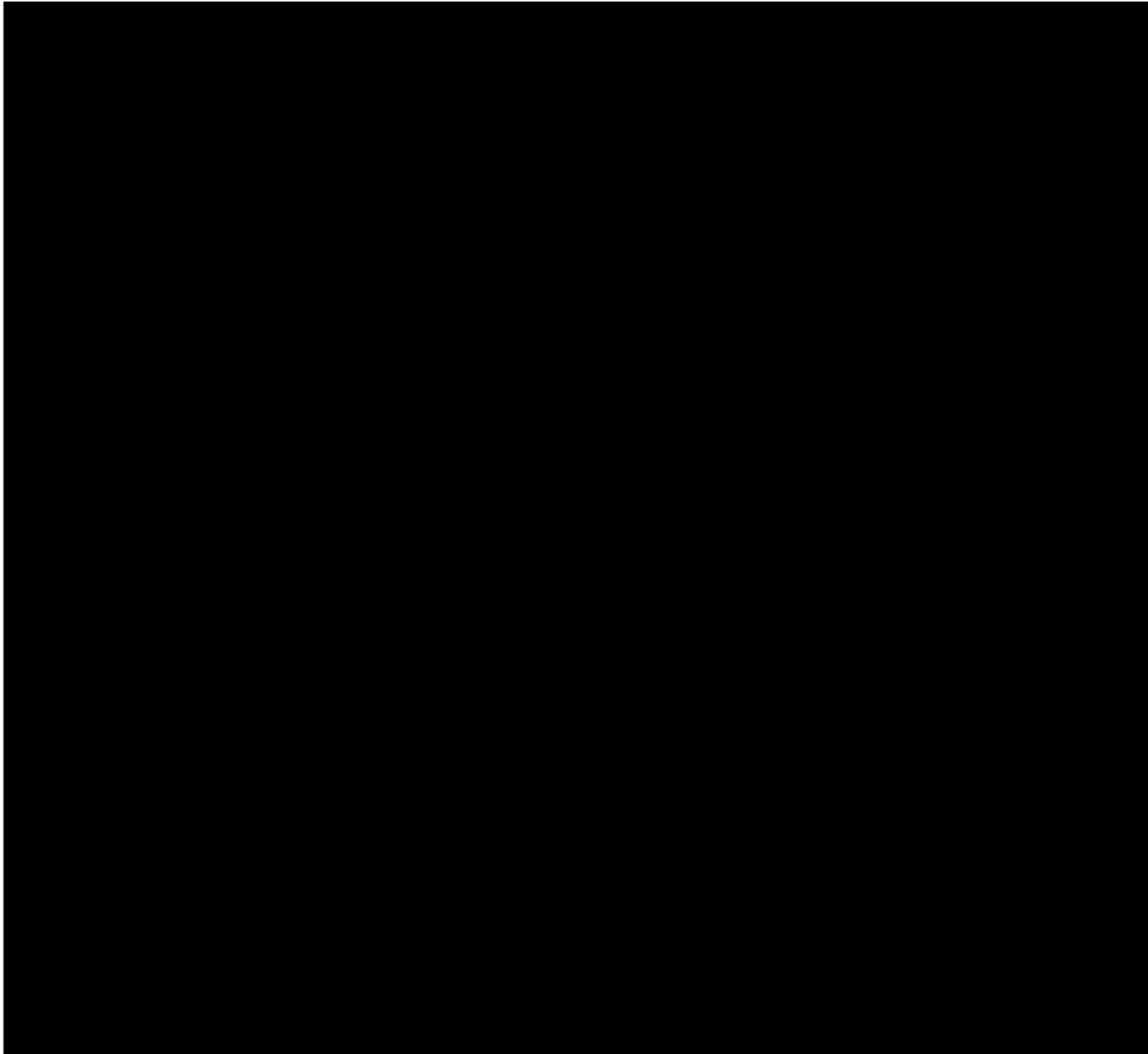
Type 3 - Like a sausage but with cracks on surface

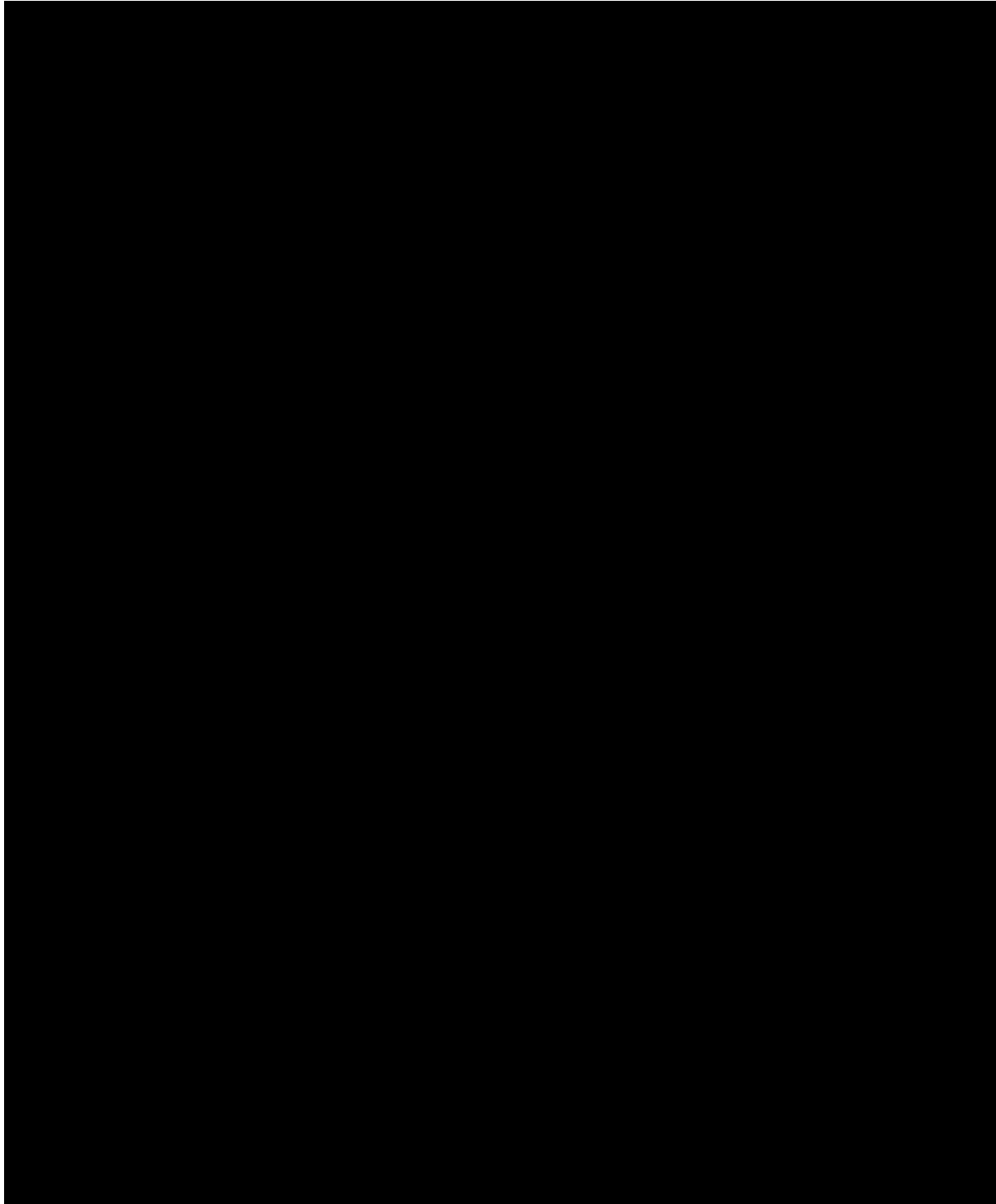
Type 4 - Like a sausage or snake, smooth and soft

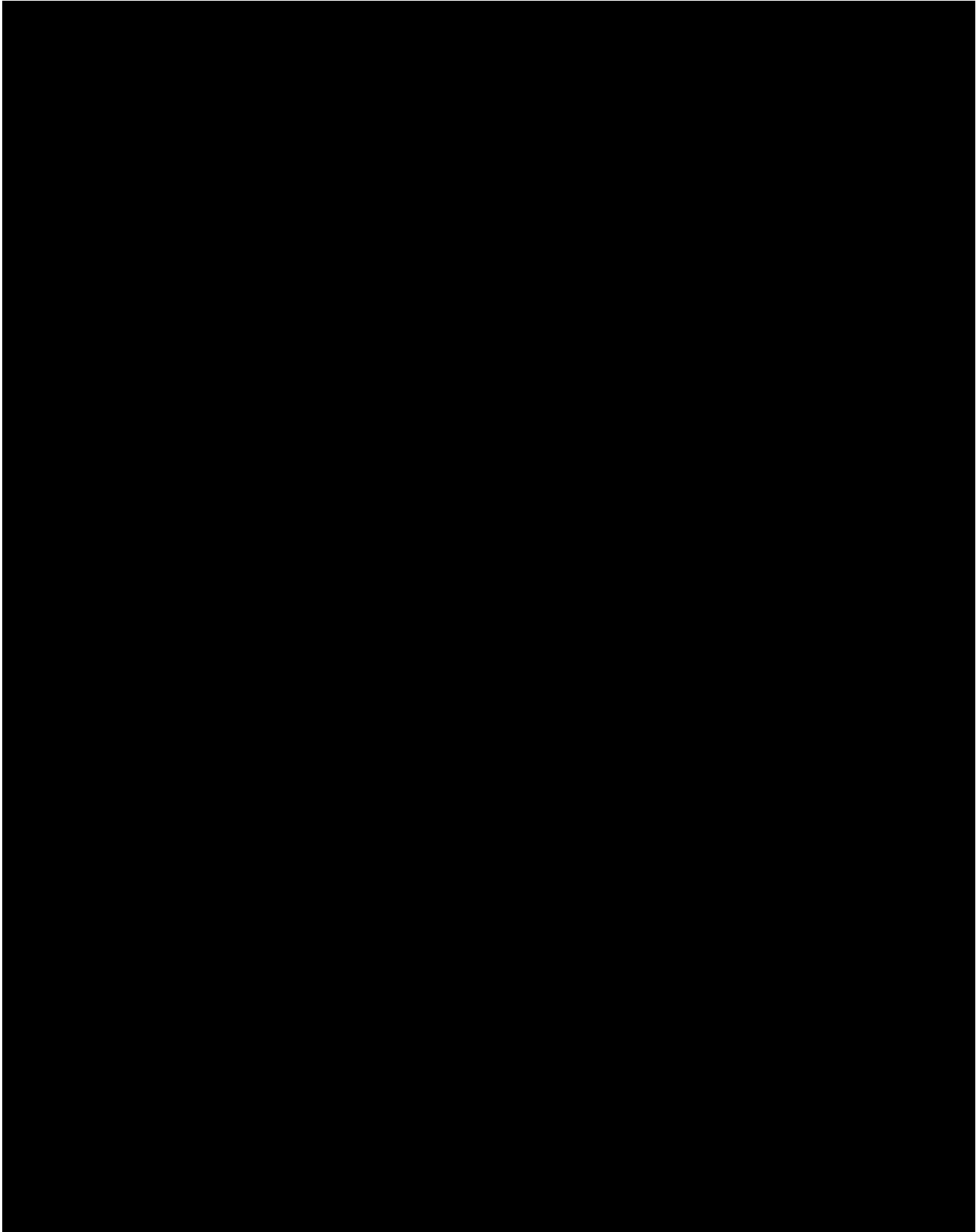
Type 5 - Soft blobs with clear-cut edges (passed easily)

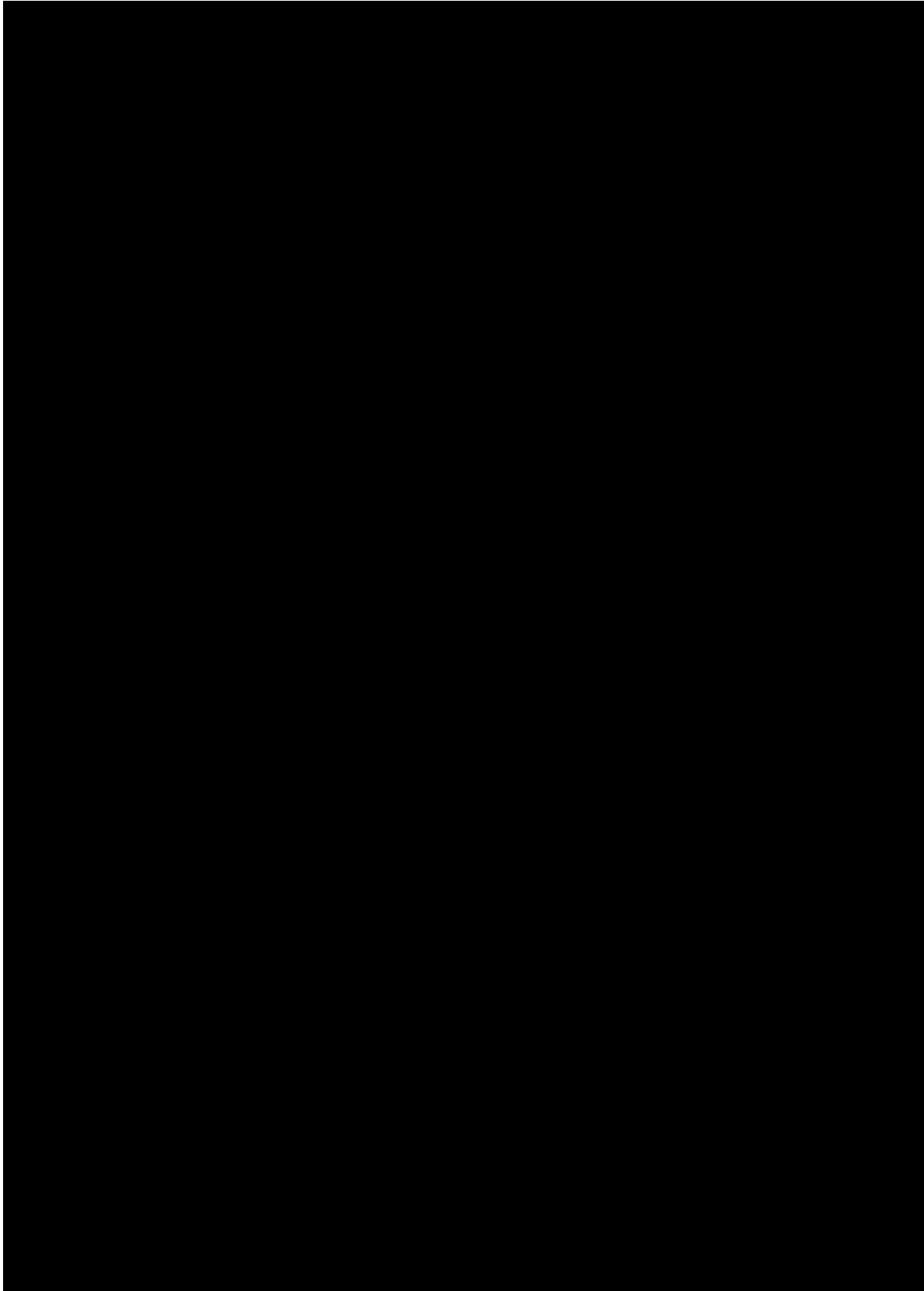
Type 6 - Fluffy pieces with ragged edges, a mushy stool

Type 7 - Watery, no solid pieces (entirely liquid)

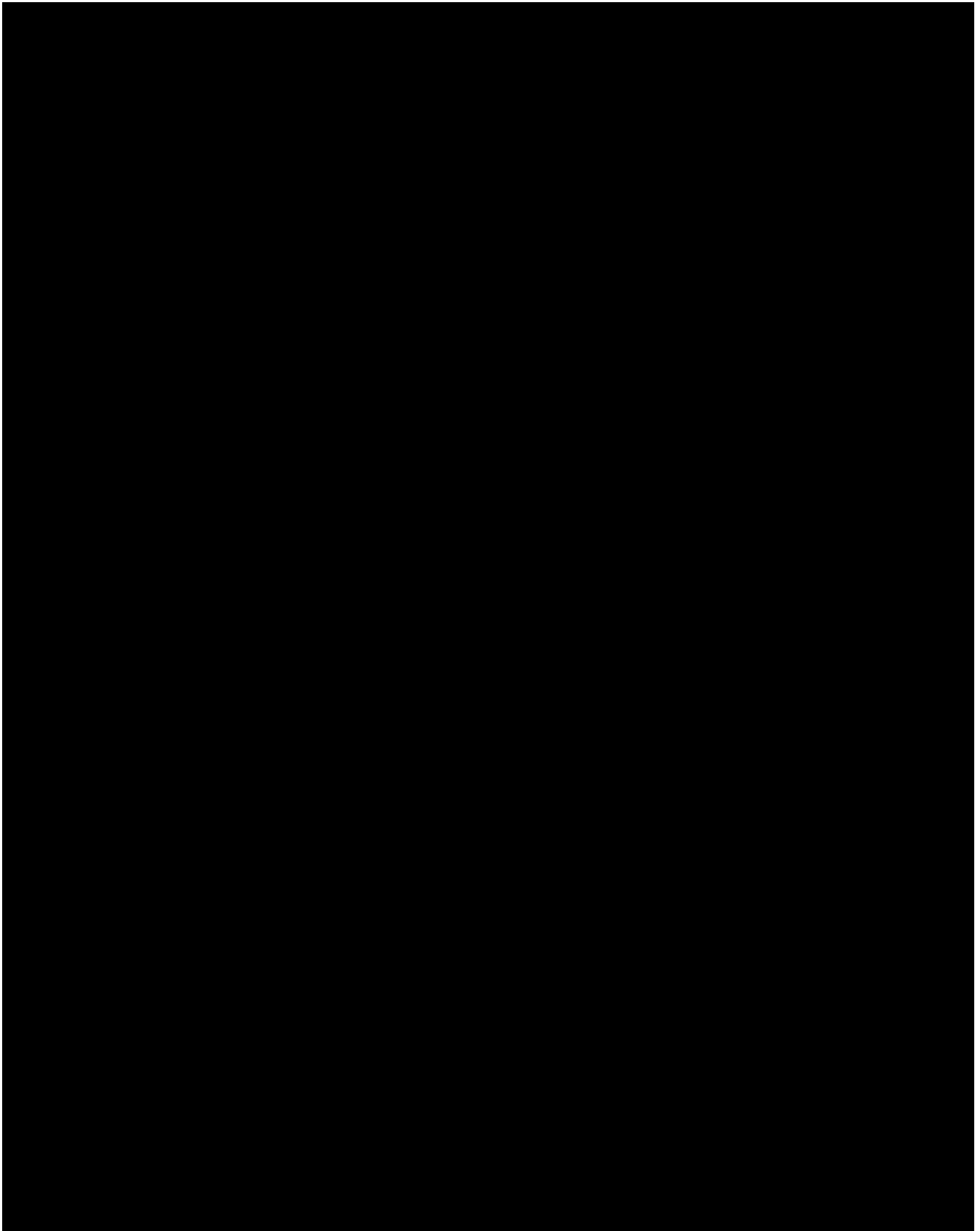


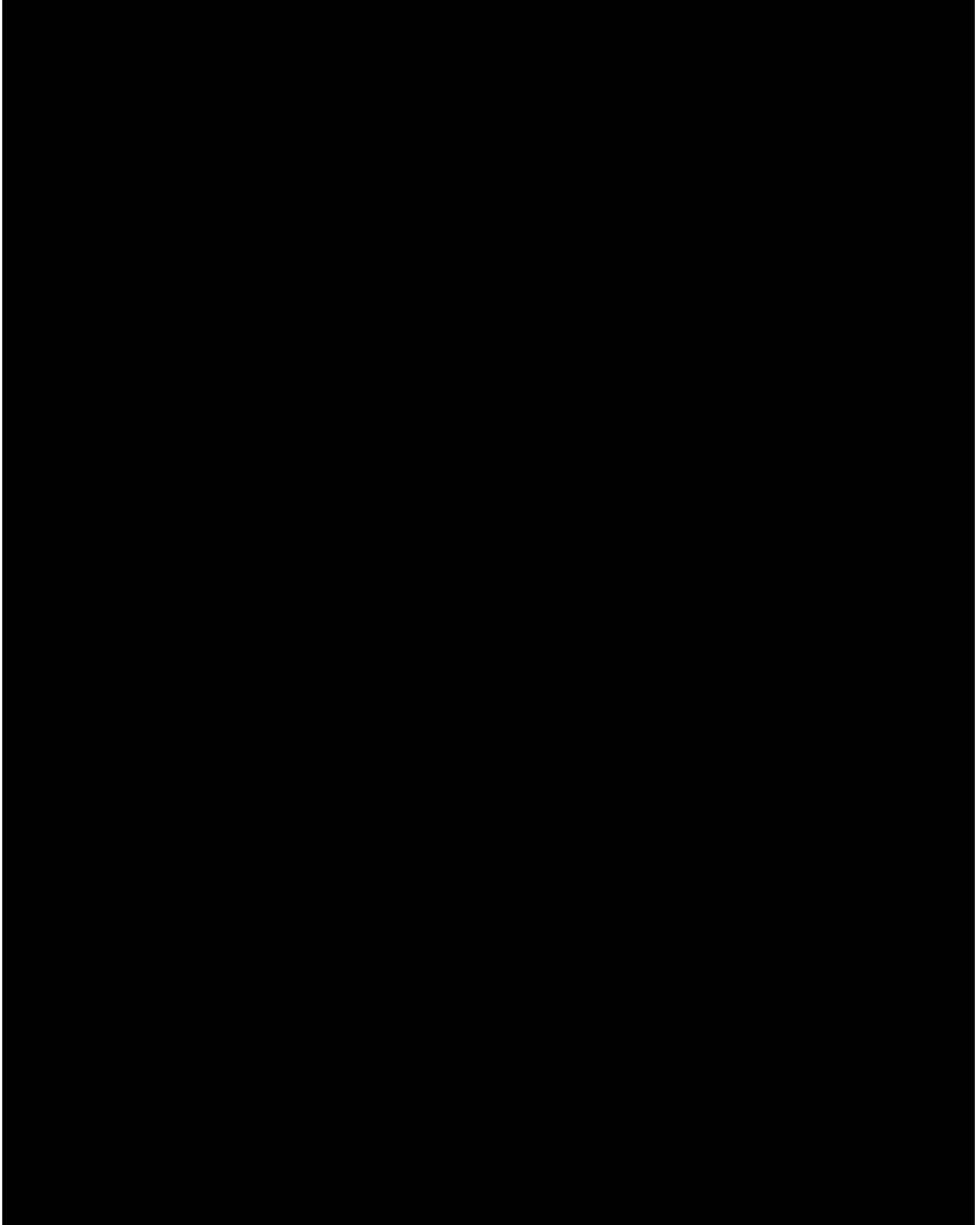


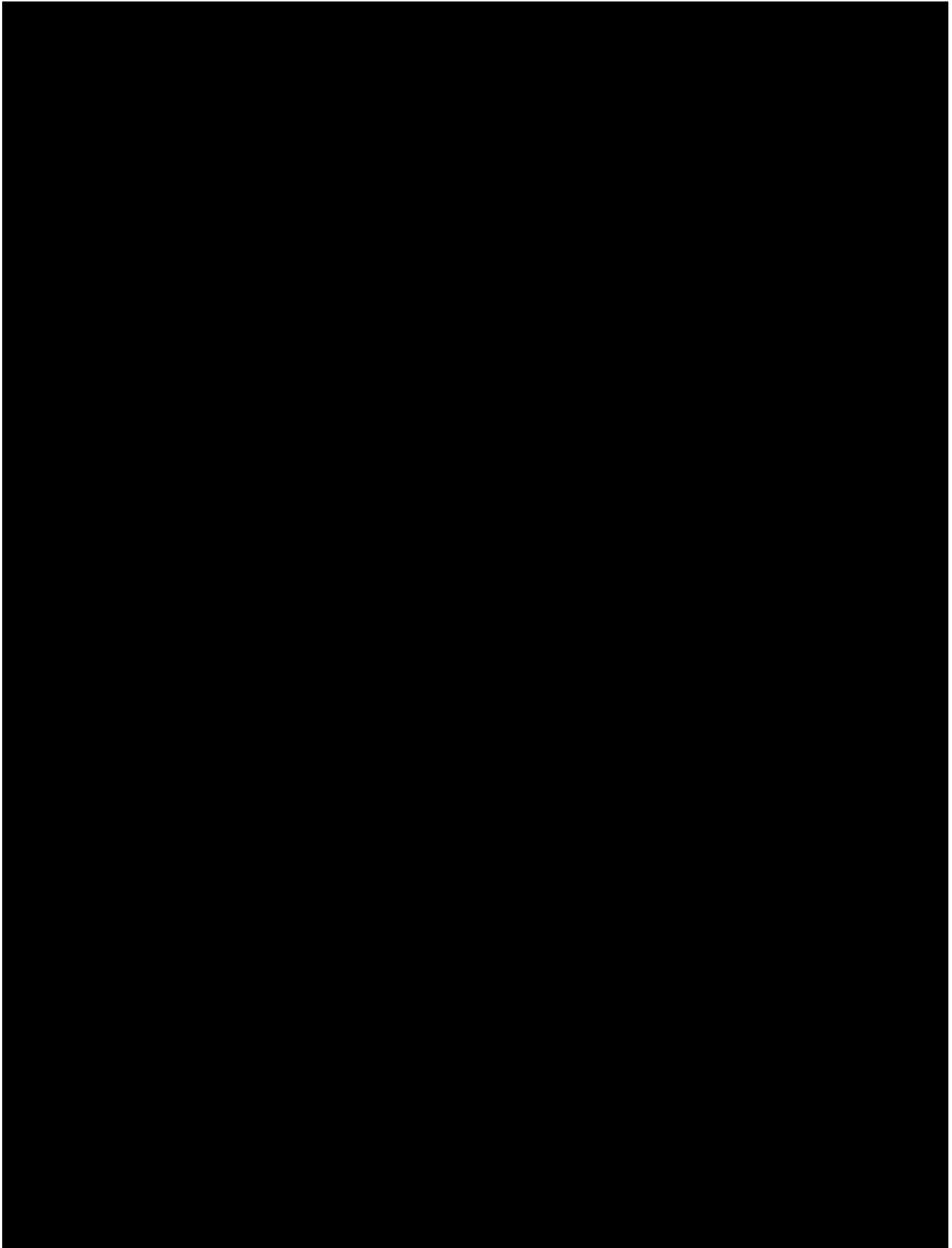


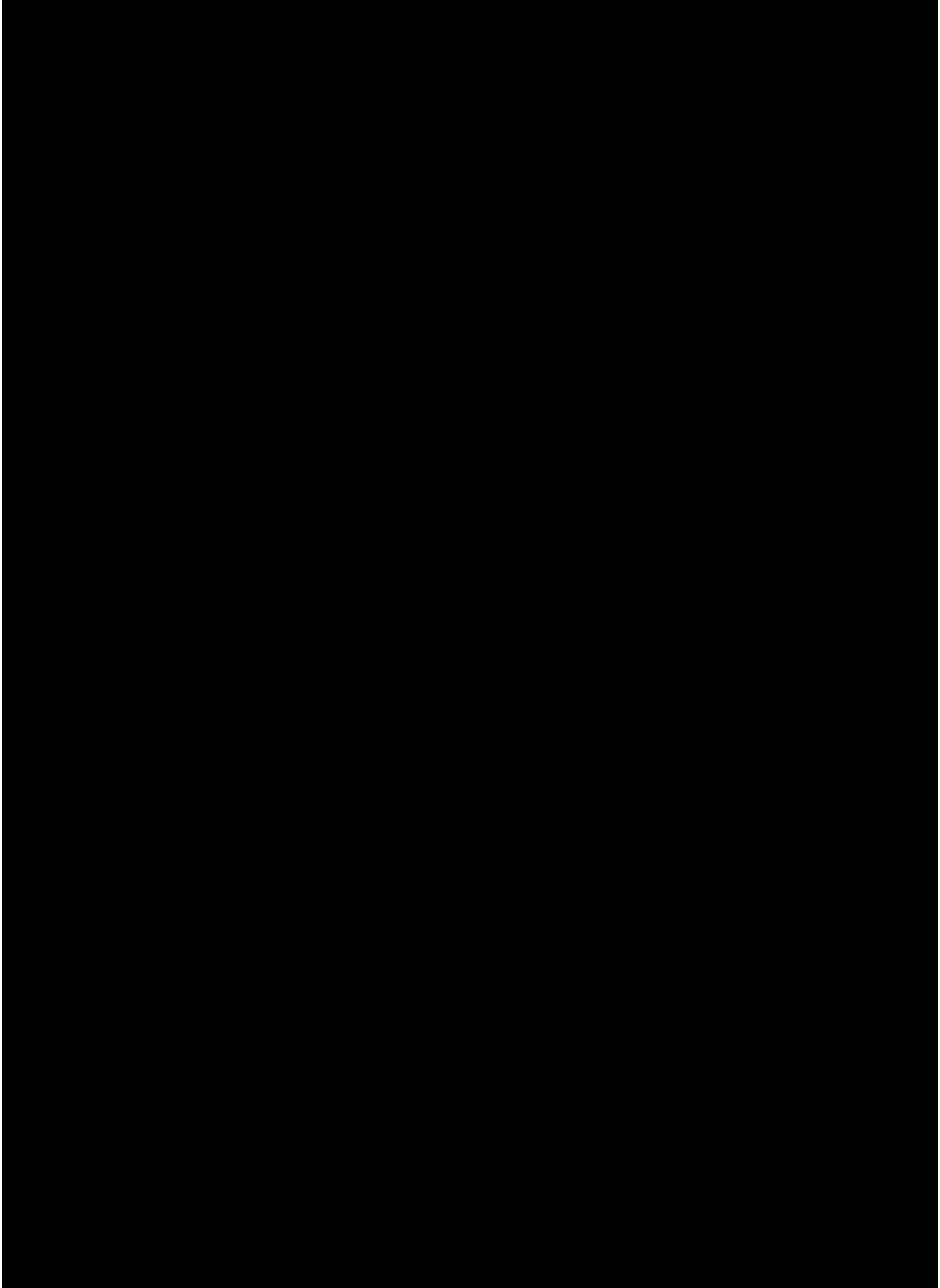


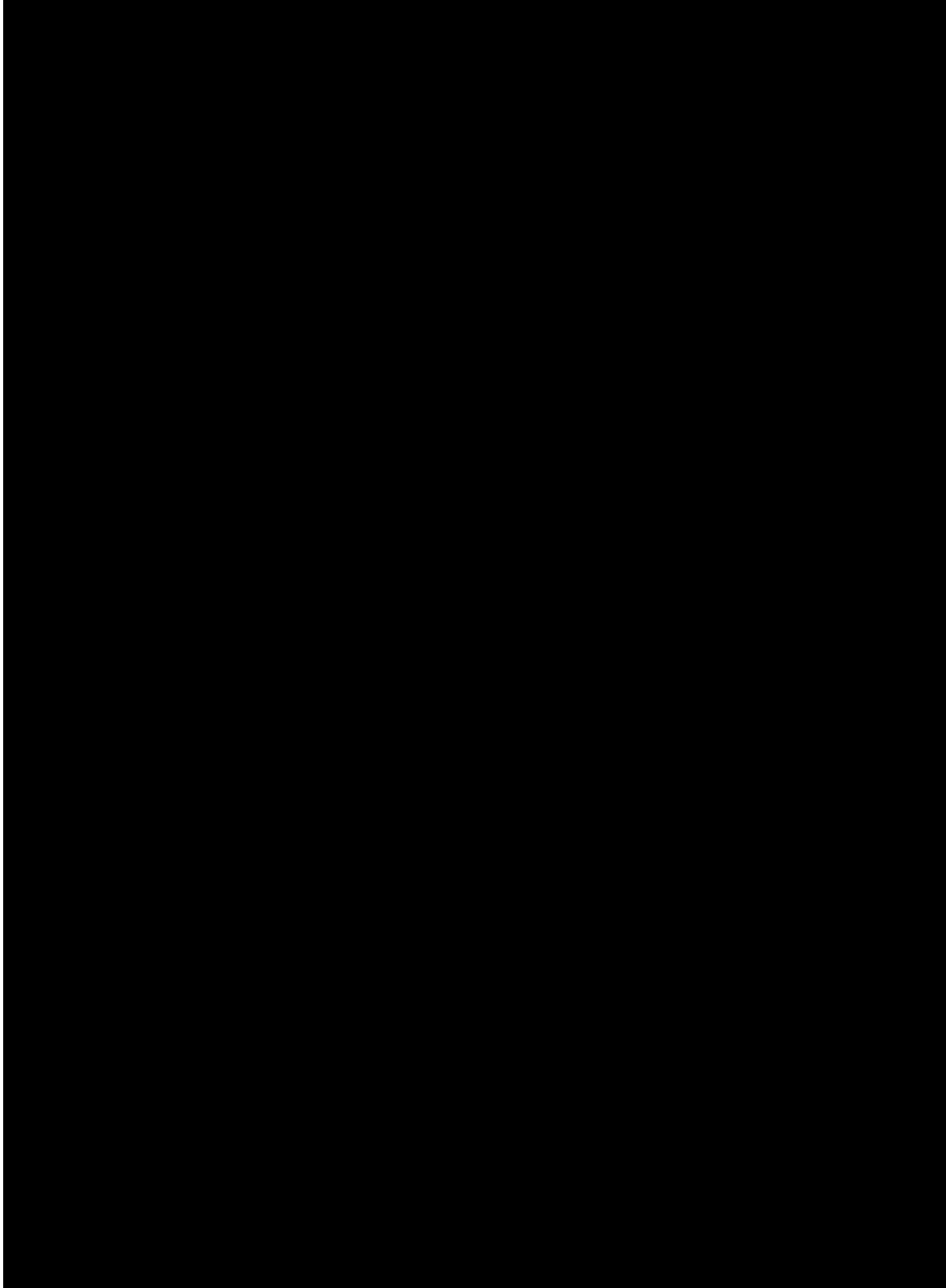


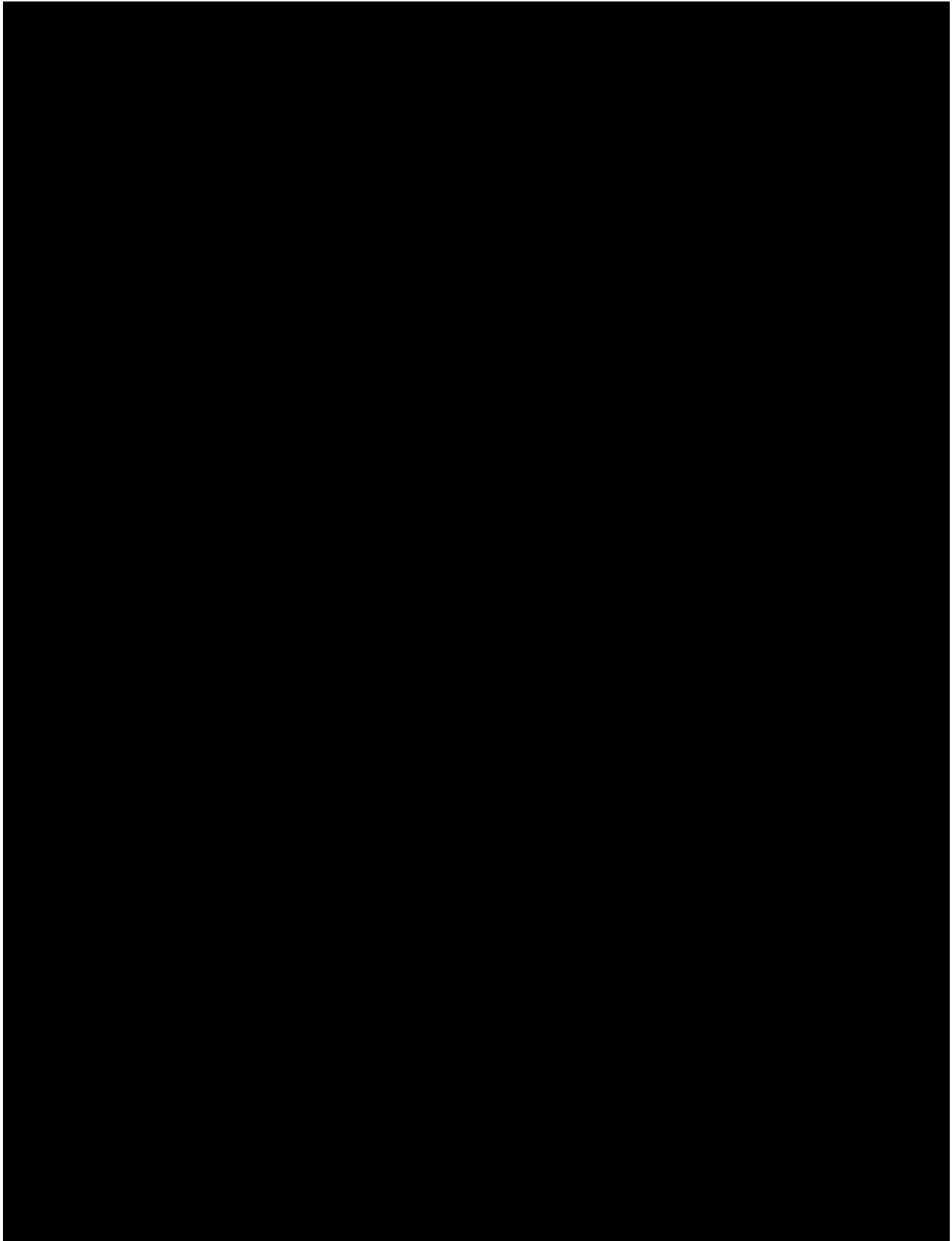


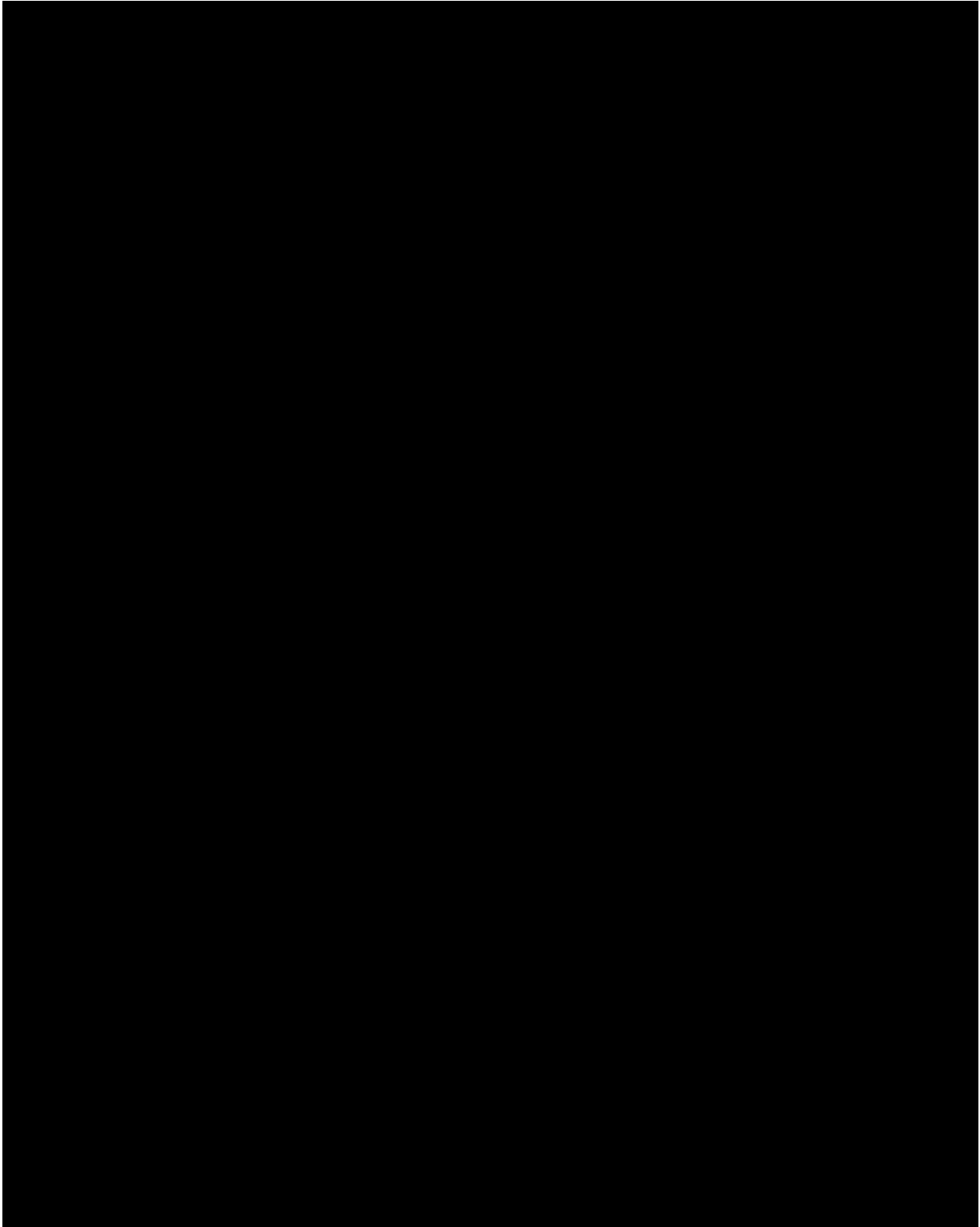


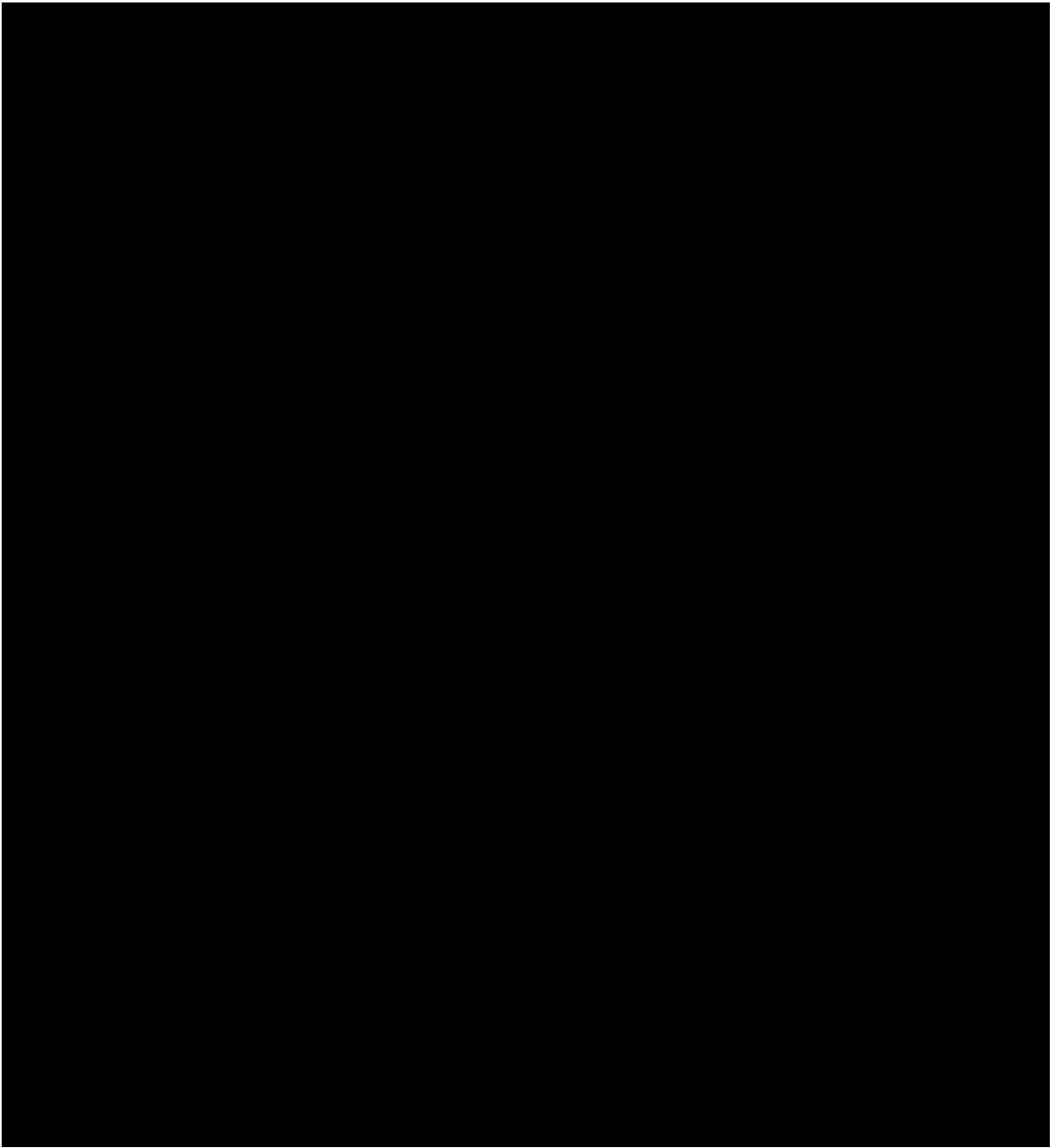




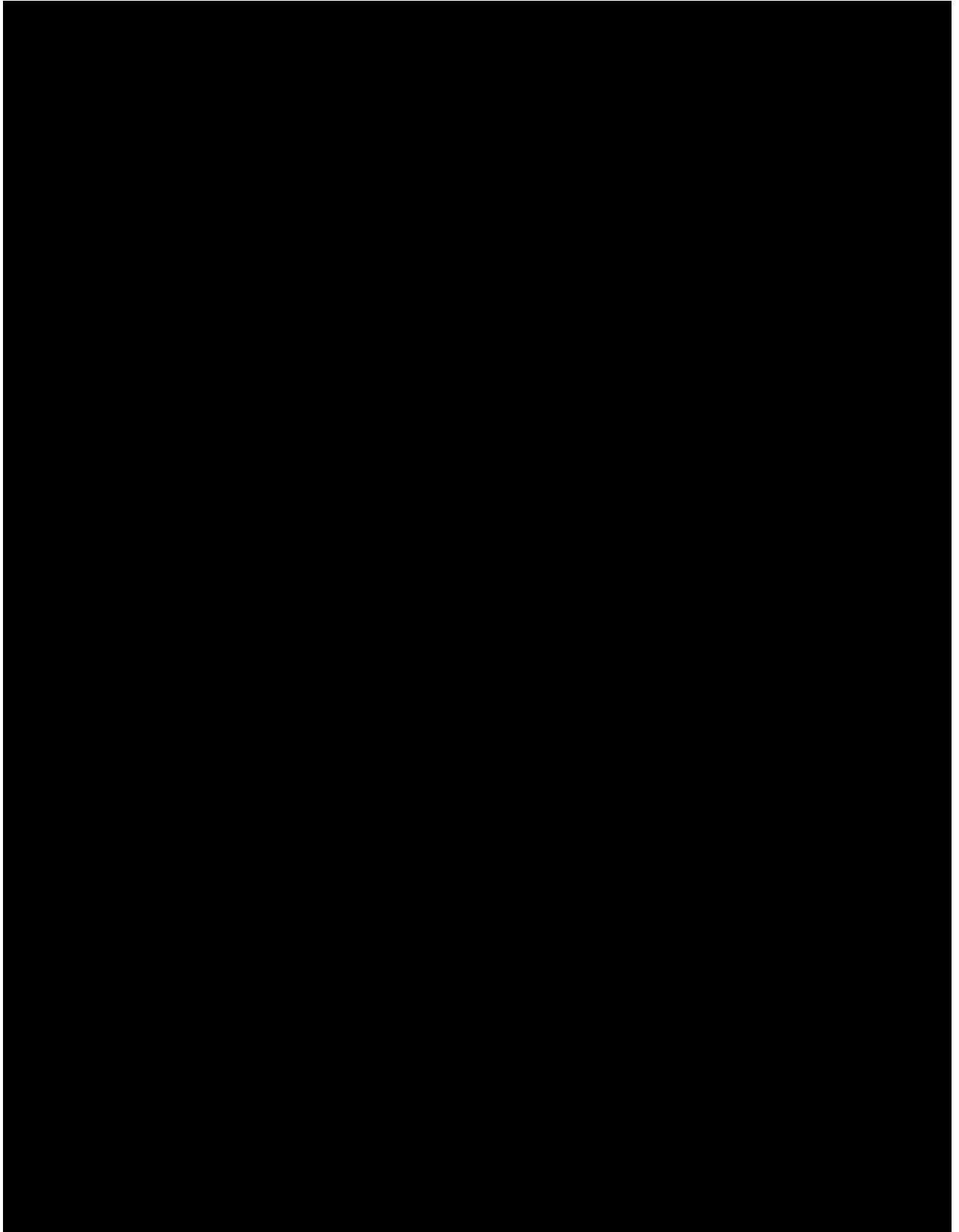


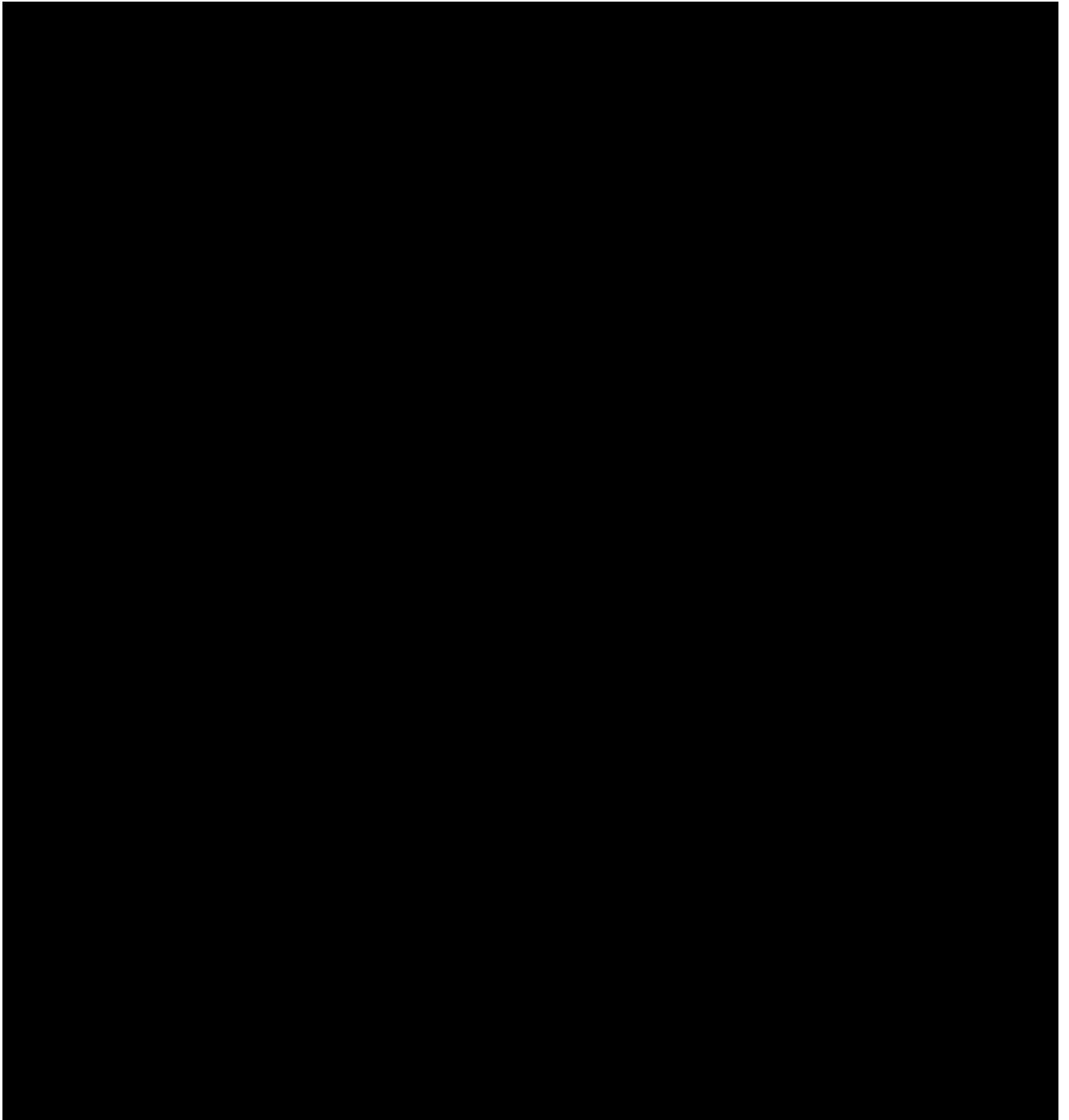














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**Forest Research Institute, Inc., an affiliate of Actavis Inc.  
Harborside Financial Center, Plaza V  
Jersey City, NJ 07311**

**SUMMARY OF CHANGES TO PROTOCOL**

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

**LIN-MD-10**

**IND #63,290**

**Original Protocol / Date:     Ironwood Protocol MCP-103-402, 25 Nov 2013**

**Amendment #1:                 09 Apr 2015**

**Amendment #2:                 05 Oct 2015**

***Confidentiality Statement***

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## **1.0**                      **INTRODUCTION**

Amendment #2 specifies the following changes to the original, FDA-approved protocol Ironwood Pharmaceuticals, Inc., Protocol MCP-103-402, dated 25 Nov 2013 and previously amended 09 Apr 2015:

[REDACTED]

[REDACTED]

3. Updating of contact information
4. Correction of minor typographic errors

This summary of changes presents all new content as green underlined text. Deleted material is shown as strikeout text. The page numbers shown in the headings of this document are those of the last published version of the protocol (Amendment #1).



## **2.0**                      **GLOBAL CHANGES**

The following changes have been made globally to the protocol:

- [REDACTED]

**3.0**                      **SECTIONS DELETED**

The following sections have been removed from the protocol, and subsequent sections and appendices have been renumbered:

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

**4.0**                      **SECTIONS ADDED**

***Rationale:*** A new section has been added to introduce the possibility that some patients' ADAs may not have reverted to baseline at the 4-Month Follow-up Visit; an additional visit (Visit 11) will be required for those patients.

***The new section will read as follows:***

[REDACTED]

[REDACTED]

1 [REDACTED]

2 [REDACTED]

3 [REDACTED]

4 [REDACTED]

**5.0**                    **REVISIONS**

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

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]







[illegible]



[REDACTED]

[REDACTED]

[REDACTED]

**5.3 SECTION 9.3.1, INCLUSION CRITERIA (PAGE 25)**

***Rationale:*** Inclusion criterion 9 that addresses language fluency had previously been attached in error to the end of inclusion criterion 8.

***The last sentence of inclusion criterion 8 becomes inclusion criterion 9 as follow:***

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

[REDACTED]

**5.6 SECTION 9.5.4.6, IMMEDIATE REPORTING OF SERIOUS  
ADVERSE EVENTS (PAGE 44)**

***Rational:*** This section has been amended to update the Sponsor's Study Physician Medical Emergency phone number.

***The last paragraph of this section now reads as follow:***

Sponsor's Study Physician Medical Emergency phone number: [REDACTED]  
[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

***Bullet 3 of this section now reads as follows:***

- Review and record AEs
  - ~~Patients who report an AE of diarrhea or who report a symptom that could be considered diarrhea (eg, loose stools or BMs, soft stools, watery stools, liquid stools, mushy stools) will also complete the diarrhea questionnaire during the study visit (Appendix VII)~~

[illegible]

[illegible]

[REDACTED]

**5.12 APPENDIX II, CONTACT INFORMATION (PAGE 79)**

***Rationale:*** This appendix was updated to reflect changes of staff for the study team.

***The revised appendix will read as follows:***

Contact information for Forest Research Institute, Inc., personnel is as follows:

[REDACTED]

Medical Emergency contact number: [REDACTED]



**6.0**                      **INVESTIGATOR'S STATEMENT**

I agree to conduct the study in accordance with this protocol (LIN-MD-10, Amendment #2, dated 05 Oct 2015) and with all applicable government regulations and good clinical practice guidance.

\_\_\_\_\_/\_\_\_\_\_/\_\_\_\_\_  
Principal Investigator's Signature                      Date

\_\_\_\_\_  
Principal Investigator's Name