NCT03383146

Study ID: RLM-MD-04

Title: A 52-week, Randomized, Double-blind, Placebo-controlled, Phase 3 Study to Evaluate the Safety and Efficacy of Relamorelin in Patients with Diabetic Gastroparesis

Protocol Amendment 3 Date: 12 February 2021

Title Page

Protocol Title: A 52-week, Randomized, Double-blind, Placebo-controlled, Phase 3 Study to Evaluate the Safety and Efficacy of Relamorelin in Patients with Diabetic Gastroparesis

Brief Protocol Title: Diabetic Gastroparesis Study 4
Protocol Number: RLM-MD-04

Amendment Number: 3

Product: Relamorelin

Sponsor Name and Legal Registered Addresses:

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Regulatory Agency Identifying Numbers:

IND: [redacted]
EudraCT: 2017-002144-33

Emergency Telephone Number: Refer to study contacts list
Serious Adverse Event Reporting Email/Fax Number:
[redacted]

Allergan Medical Safety Physician: Refer to study contacts list
Sponsor Signatory: [redacted] Vice President, Clinical Development-GI

Protocol Amendment 3 Summary of Changes

DOCUMENT HISTORY	
Document	**Date**
Amendment 2	29 Mar 2018
Amendment 1	20 Dec 2017
Original Protocol	06 Oct 2017

Amendment 3 (29 Apr 2019)

Overall Rationale for Amendment 3:

This summary includes changes made to Protocol RLM-MD-04 from Protocol Amendment 2 (Dated 29 Mar 2018; details provided in Section 12.19). The purpose of Protocol Amendment 3 is to communicate changes made in response to recommendations from health authorities. These changes will not impact safety assessment of relamorelin or alter the risk-benefit ratio for study subjects.

The following is a summary of content-oriented changes that were made.

Section Number	Description of Change	Rationale
Global change	Replaced "Potential Hy's Law" with "Hy's Law" (ie, deleted "potential throughout"	[redacted]
Section 1 Synopsis and Section 4 Objectives and Endpoints	• Removal of responder endpoints from list of Key Endpoints; • Updates to Key Objectives; [redacted]	
Synopsis Study Schematic and Section 5.1 Overall Design Study Schematic	Schematic updated to show screening starting at Week -6 instead of Week -4	
Synopsis Number of Participants and Section 5.2 Participant and Study Completion	Increased number of screening participants from 4000 to 5000	
Section 1 Synopsis and Section 5.1 Overall Design	Additional requirements for "de novo" participants to have had a history of nausea and/or at most a single episode of vomiting in 2 weeks prior to Screening added at Screening Visit (Visit -2); deleted requirement for BMI.	

Section Number	Description of Change	Rationale
Section 1 Synopsis Number of Sites	Increased number of sites from 400 to 700	[redacted]
Section 1 Synopsis and Section 6.1.2 (Inclusion Criteria) De Novo Participants	Deleted criterion for BMI > 18.5 kg/m^2	
Section 2 SOA	Beginning of Screening Period changed from Day -28 to Day -42 ; changed from "Up to 14 Days" to "Up to 28 Days"	
Section 2 SOA	Footnote "a" – Statement added that results from assessments done at Screening that might result in exclusion from the study are to be obtained prior to the endoscopy if done at the start of the Run-in Period.	
Section 2 SOA	Added ECG assessment at Visit 2	
Section 2 SOA	Footnote referencing urine drug screen (ie, Footnote "j") modified to specify certain prescribed drugs (ie, barbiturates, benzodiazepines, amphetamines, but not opioids and cannabinoids) should not be exclusionary.	
Section 2 SOA	Footnote "k" added for fasting glucose to be serum for all visits except Visits 4 and 6 (plasma).	
Section 4.1 Clinical Hypotheses	Modified hypotheses.	
Section 5.1 Overall Design	Changed requirement for delayed GEBT from occurring at Screening to occurring during the Run-in Period.	
Section 6.1.2 De Novo Participants Inclusion Criteria	Criteria #6 – added option to use upper GI series with contrast to document absence of obstructing lesion; revised time of performance from some time prior to Screening to some time prior to the Run-in Period	
Section 6.2.1 Exclusion Criteria/Both Rollover and De Novo Participants	Section added for 2 new exclusion criteria applicable to both sets of participants including specific ECG results, allergy/ hypersensitivity to study treatment.	

Section Number	Description of Change	Rationale
Section 6.2.3 Exclusion Criteria/De Novo Participants	• Amended Exclusion Criteria #12 to allow a participant with a positive urine drug screen at Screening to continue in the study while confirmatory testing is done on an aliquot of the original sample; added reference to Section 6.4 • Added Exclusion Criteria # 25 (hypersensitivity to study treatments and their excipients) and #26 (ECG results obtained at baseline that would exclude a participant)	[redacted]
Section 6.4 Screen Failures	Added option for the sponsor to permit a participant with a positive urine drug screen at Screening to continue in the Screening Period while confirmatory urine drug screen testing by a more specific method is carried on an aliquot of the original sample.	
Section 7.1 Treatments Administered	Clarified that the first dose of study treatment is to be administered within ***approximately*** 30 minutes ***before*** the morning meal and the second daily dose is to be administered ***approximately*** 30 minutes ***before*** the evening meal. Deleted option for investigator to contact sponsor if the participant could not inject study treatment into abdomen.	
Section 7.4 Blinding/Masking	Unblinding procedures modified; requirement of investigator to notify sponsor prior to unblinding modified to encouraging the investigator to notify the sponsor prior to unblinding, but requiring notification within 24 hours after breaking the blind.	
Section 7.7.1 Prohibited Treatments and Washout Before the Study	SLGT-1 added to same rules for SGLT-2. Addition of details to the requirement of prohibiting SGLT-1 and SGLT-2 inhibitors.	

Section Number	Description of Change	Rationale
Section 7.7.1, Table 7-2 Prohibited Medications and Washout Requirements	• Amended information regarding SGLT-2 inhibitors as noted above and by adding SLGT-1 to same drug class/treatment as SGLT-2, rearranged rows by washout period, added tramadol as an example of opioid. • Pro-motility agents, anticholinergics, anti-emetics, amyline analogue, 5HT4 agonists, and glucagon-like peptide-1 – added washout requirements for de novo participants • Updated description of anti-emetics. • Added row for 5HT4 agonists. • Amended washout period for opioids from "10 days prior to the start of the Run-in Period" to Not applicable since use of opioids is not allowed and referenced exclusion criteria #12 and #13.	[redacted]
Section 7.7.3 Rescue Medicine	• Specified that the day prior to and day of clinic visits are "during the Treatment Period". • Deleted antihistamines as an example of an anti-emetic drug. • Revised to require investigator to contact (ie, "should contact) sponsor if participant requires anti-emetic more than 1 day/week or once weekly repeatedly instead of making it optional for investigator to contact (ie, "should consider contacting).	
Section 8 Discontinuation/Withdrawal Criteria	Deleted "non-compliance with study treatment" as a criterion	
Section 8.1.1 Temporary Discontinuation	Additional criteria added for when the investigator should contact the sponsor.	

Section Number	Description of Change	Rationale
Section 9.1.1 Key Efficacy Assessment -DGSSD	• Added statement detailing when participants would be reporting their symptoms in the DGSSD. • Deleted description on vomiting frequency and how vomiting will be calculated.	[redacted]
[redacted]		
Section 9.2.1 Time Period and Frequency for Collecting AE and SAE Information	Specified that medical occurrences that begin before the start of study treatment but after obtaining IC will be recorded in the AE section of the eCRF and will be considered pretreatment AEs (instead of being recorded on the Medical History/Current Medical Conditions section of the eCRF).	
Section 9.2.7.1 Hy's Law	Clarified reporting procedures for Hy's Law cases	
Section 9.2.7.2 Inadequate Control of Diabetes: Hyperglycemia and Hypoglycemia	Added the phrase "Inadequate Control of Diabetes" to section title	
Section 9.2.8 Medication Errors	Specified 10 µg BID or 20 µg/day as the maximum recommended dose. Deleted statement referencing a dose of greater than 150 µg BID to be considered an overdose.	
Section 10.2 Populations for Analyses/Table 10-1 Analysis Populations	Specified that the mITT Population is a subset of all ***randomized*** participants.	

Section Number	Description of Change	Rationale
Section 10.3.1 Key Statistical Methodology/Table 10-2 Statistical Methodology	Replaced Responder analysis with CFB MMRM methodology and description; deleted CFB ANCOVA methodology and description	[redacted]
Section 10.3.2.1 Key Endpoints/Table 10-3 Key Endpoints	Updated to only include CFB to Week 12 in weekly DGSSS and CFB to Week 52 in weekly average DGSSS	
Section 10.3.2.2 Missing Data	Deleted original text and replaced with reference to SAP	
[redacted]		
Section 10.3.5 Interim Analyses	Replaced the "Non-applicable" statement with a description of a DSMB process that will be used to review interim safety data.	
Section 12.2 Appendix 2 Clinical Laboratory Tests, Table 12-1	Footnote added for fasting blood glucose to be serum at all visits except for Visits 4 & 6	
Section 12.3 Appendix 3: Study Governance Considerations	Headings added for subsections	
Section 12.3.3 Informed Consent Process	Statement added that written documentation must be obtained in accordance with relevant country and local privacy requirements	
Section 12.3.5 Data Quality Assurance	Revised from requirement of investigator retaining records for 15 years after study completion to retaining "as stated in the clinical trial agreement".	
Section 12.3.8 Publication Policy	Added statement that the results of the study may be published or presented at scientific meetings.	

Section Number	Description of Change	Rationale
Section 12.4 Appendix 4 AE Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting	• Updated procedures for reporting AESIs. • Identified specific AESIs (ie, Hy's law cases, inadequate control of diabetes: hyperglycemia and hypoglycemia, and MACE). • Specified that DG symptoms will be captured in the DGSSS and not the CRF	[redacted]
Section 12.5 Appendix 5 Contraceptive Guidance and Collection of Pregnancy Information	• Moved acceptable methods of contraception from text to table. [redacted]	
Section 12.8, Appendix 8 Standard Discontinuation Criteria	Removed criteria for non-compliance	
Section 12.9, Appendix 9 Study Tabular Summary	• Changed trial length from 52 to 54 weeks • Changed number of participants to be screened from 4000 to 5000	

Additional administrative edits were also made, but not specifically noted (eg, corrected spelling, punctuation, grammar, abbreviation, and style errors) including global edits required for consistency.

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1 Synopsis

Protocol Title: A 52-week, Randomized, Double-blind, Placebo-controlled, Phase 3 Study to Evaluate the Safety and Efficacy of Relamorelin in Patients with Diabetic Gastroparesis

Brief Title: Diabetic Gastroparesis Study 4
Study Rationale: Previous non-clinical and Phase 1 studies have shown relamorelin to have a potent prokinetic effect on the stomach, accelerating gastric emptying (GE) in both healthy volunteers and patients with diabetic gastroparesis (DG).

Gastroparesis (GP) is a disorder characterized by signs and symptoms of nausea, abdominal pain, postprandial fullness, bloating, vomiting, and early satiety along with delayed GE, such that movement of food from the stomach to the small intestine takes longer than normal and occurs with unpredictable timing. Diabetes mellitus, either type 1 or 2 (T1DM or T2DM), is considered to be the most common identifiable cause of GP. This complication is a result of chronically elevated blood glucose levels, which are known to damage nerve structure and function. DG complicates management of blood glucose for both T1DM and T2DM patients due to carbohydrates being delivered to and therefore absorbed from the small intestine at variable times after ingestion. As a result, diabetic patients with DG often have poorly controlled diabetes, frequently with alternating hypo- and hyperglycemia, especially if treated with insulin.

In Phase 2 studies, the pharmacodynamic effect of relamorelin was confirmed in larger numbers of participants with DG, and in addition, beneficial effects on the symptoms of DG were observed. Safety and tolerability were shown at therapeutic doses, including the 10 µg twice daily (BID) dose to be studied in Phase 3 studies, supporting the decision to obtain confirmatory evidence of safety and efficacy of relamorelin in Phase 3, and specifically in study RLM-MD-04.

A significant unmet medical need exists for a safe and effective treatment of patients with DG whose quality of life is impacted by their disease and for whom the current standard of care is suboptimal; therefore, the sponsor is performing this study to further the development of relamorelin for the treatment of DG.

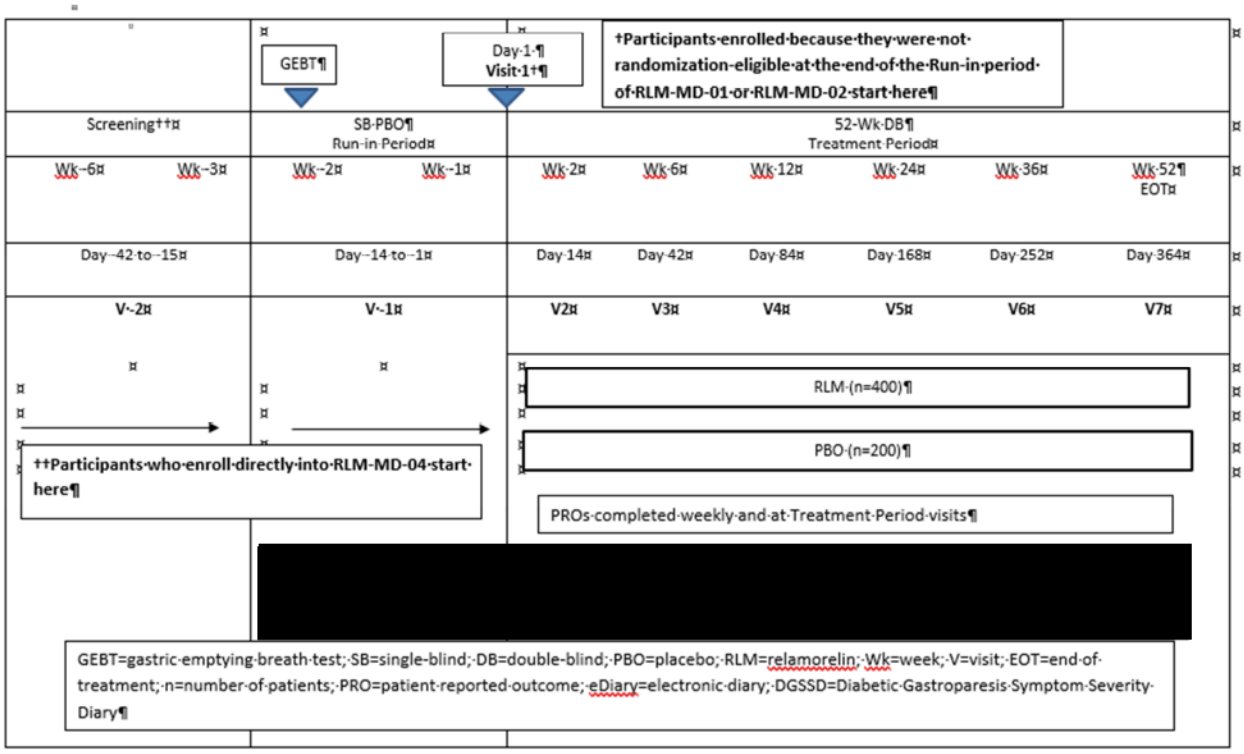
Objectives and Endpoints:

Key Objectives	Key Endpoints
• To compare the efficacy of relamorelin with that of placebo in participants with DG with respect to a composite of the following core signs and symptoms of DG: o Nausea o Abdominal pain o Postprandial fullness o Bloating	• Change from baseline to Week 12 in the weekly DGSSS • Change from baseline to Week 52 in weekly average DGSSS
• To compare the safety of relamorelin with that of placebo in participants with DG	• AEs, clinical laboratory values, vital signs, ECGs, HbA1c, and anti-relamorelin antibodies
[redacted]	

Overall Study Design:

- Global, multicenter, randomized, double-blind, placebo-controlled, parallel-group
- Treatment Group: Relamorelin 10 µg or placebo subcutaneously (SC) twice daily (BID)
- Study Duration: 52-week Treatment Period
- Participants who meet study entry and randomization criteria will be randomized in a 2:1 ratio to blinded treatment with relamorelin 10 µg or placebo, and will use an electronic hand-held device for reporting of their symptoms, [redacted] ompliance, and use of rescue medication.

Study Schematic:



Number of Participants:

Planned enrollment for this study is 600 participants assigned to study treatment (400 to relamorelin and 200 to placebo). A total of 300 participants are expected to complete the study (200 relamorelin- and 100 placebo-treated participants).

Approximately 5000 participants will be screened in lead-in Studies RLM-MD-01 and RLM-MD-02. Participants who do not meet certain randomization criteria may enter this study directly if they meet enrollment criteria defined below.

Study Population:

Two different groups of participants may enter the study:

1. Participants who met all Screening and Run-in Period criteria in lead-in Study RLM-MD-01 or lead-in Study RLM-MD-02 (including compliance with dosing and data entry into the Diabetic Gastroparesis Symptom Severity Diary [DGSSD] during the lead-in study Run-in Period), but were not randomization-eligible at the end of the lead-in study Run-in Period, are eligible for randomization in Study RLM-MD-04 if:

    - They had no vomiting episodes recorded in the DGSSD and had an average daily DGSSS $\geq$ 12 at the end of the lead-in study Run-in Period.

OR

- They had vomiting episodes recorded in the DGSSD but had an average daily DGSSS of ≥ 12 and < 16 at the end of the lead-in study Run-in Period.

In the current study, these "**rollover participants**" will enter the study at Visit 1 (Randomization); they will not undergo Screening (Visit –2) or Run-in Visit (Visit –1) procedures.

2. Patients who undergo screening and run-in procedures in Study RLM-MD-04 are "**de novo participants"**. To be eligible for randomization in the current study, de novo participants must meet all Screening and Run-in Period criteria for Study RLM-MD-04, including:

At the Screening Visit (Visit –2):

- Male or female aged 18 years and older;
- T1DM or T2DM with controlled and stable blood glucose levels and HbA1c ≤ 11%;
- Symptoms suggestive of DG for at least 3 months (one of which must be nausea), with mechanical obstruction of the gastrointestinal (GI) tract as the cause of symptoms having been ruled out;
- History of nausea and/or at most a single episode of vomiting in the 2 weeks prior to Screening (Visit -2), as ascertained by participant history

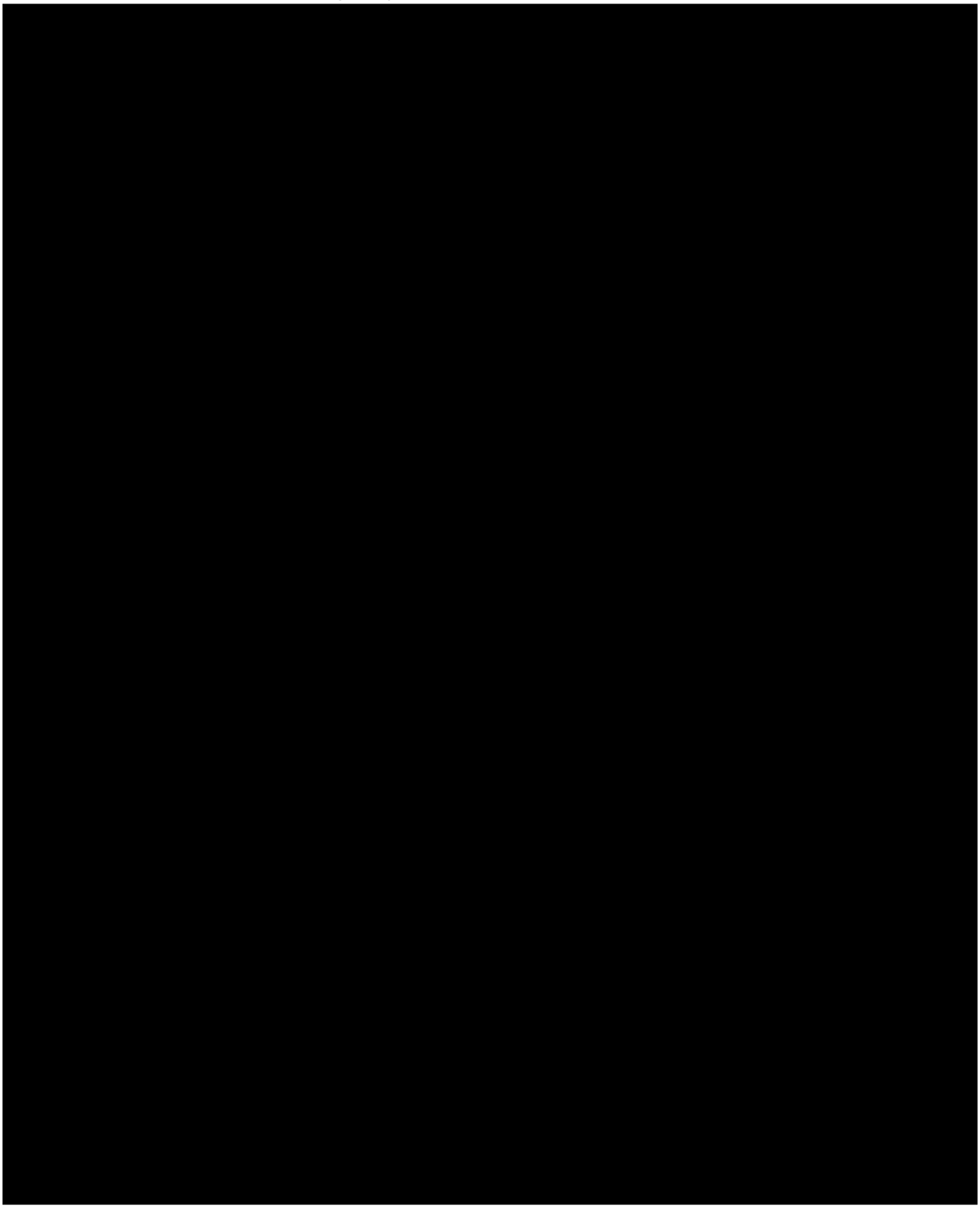
At the End of the Run-in Period:

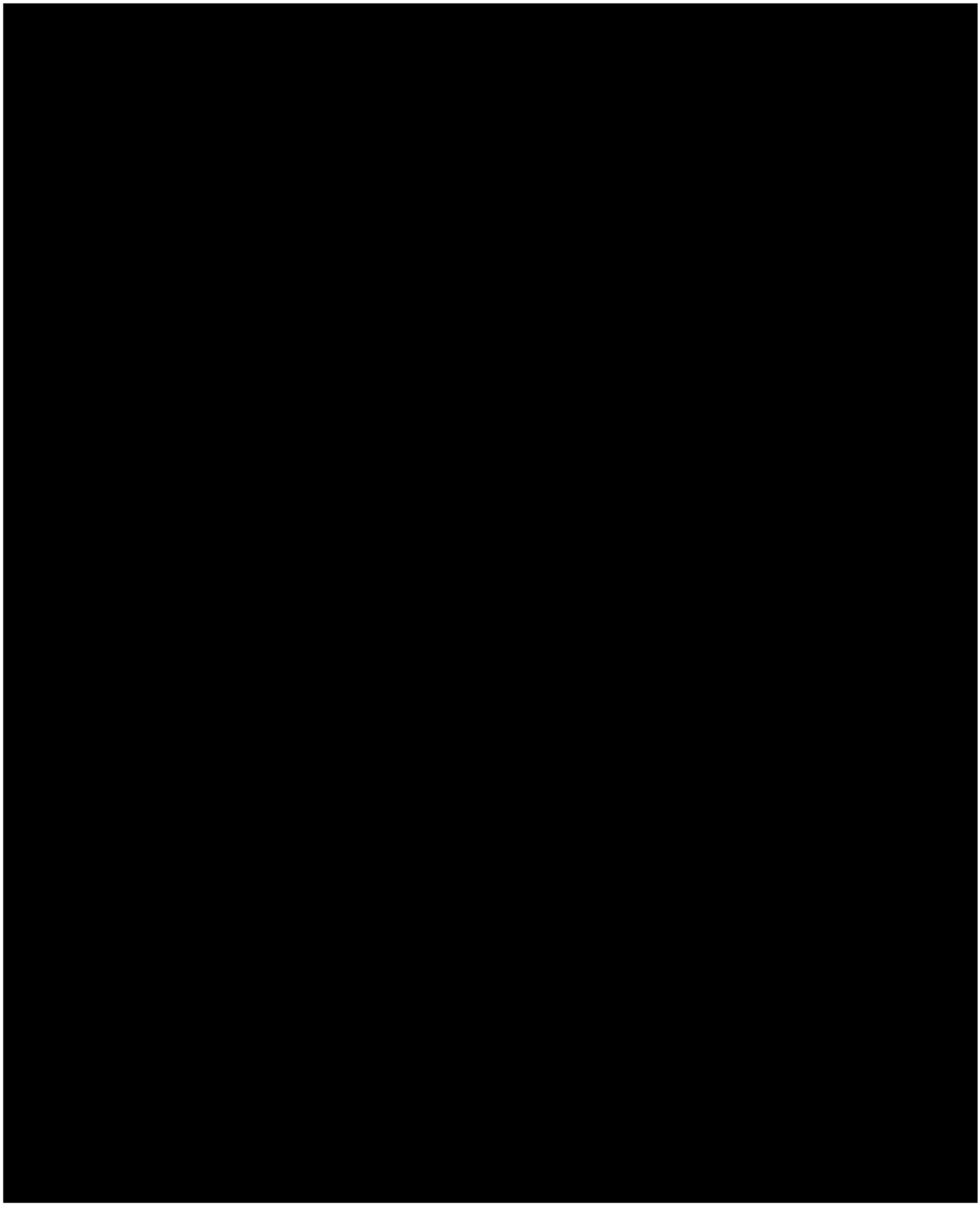
- Evidence of compliance during the Run-in Period with both the use of the electronic hand-held device for entry of data and with twice daily SC injections of the study treatment;
- No treatment with GI promotility agents during the Run-in Period;
- A score of ≥ 12 for the average of the daily DGSSS measured during the Run-in Period.

Number of Sites:

Approximately 700 sites globally (the combined number of sites from Studies RLM-MD-01 and RLM-MD-02).

2 Schedule of Activities (SoA)





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3 Introduction

Relamorelin (also known as RM-131) is a novel, potent, and selective synthetic penta-peptide ghrelin analogue, which is being developed for treatment of diabetic gastroparesis (DG).

Ghrelin, a 28 amino-acid peptide, is produced predominantly by specialized cells of the stomach and pancreas, and has been demonstrated to be a central modulator of energy homeostasis. It is the natural ligand for the Growth Hormone Secretagogue 1 α (GHS1α) receptor, a potential target for treatment of clinical conditions associated with impaired gastric motility and energy balance. Administration of ghrelin has been shown to promote gastric motility in mice, rats, dogs and humans (Dornonville et al, 2004; Trudel et al, 2003; and Murray et al, 2005). It can increase body weight, attributed to a combination of enhanced food intake, increased gastric emptying (GE), and increased food assimilation, coupled with a transient increase in growth hormone (GH), which promotes nutrient incorporation into tissues.

Relamorelin has similar characteristics to native ghrelin but with enhanced efficacy, plasma stability, and circulating half-life. As a ghrelin mimetic, it acts as a potent prokinetic agent, as evidenced by significant effects on GE as well as effects on overall colonic transit (Acosta et al, 2015, Acosta et al, 2016).

Gastroparesis (GP) is a disorder characterized by delayed GE, such that movement of food from the stomach to the small intestine is delayed. The pathophysiology of GP has not been fully elucidated but seems to involve abnormalities in the autonomic nervous system (vagus nerve), smooth muscle cells, enteric neurons, and interstitial cells of Cajal; in DG, change in the type of macrophages in the gastric musculature suggest a role for inflammation as a cause of delayed GE.

Diabetes mellitus, either type 1 or 2 (T1DM or T2DM, respectively), is considered to be the most common, specifically identifiable cause of GP. This complication is a result of chronically elevated blood glucose levels, which are known to damage nerve structure in general, and the vagus nerve in particular, and negatively affect function (Parkman et al, 2004).

DG is a chronic condition that requires prolonged treatment. Core signs and symptoms of DG are nausea, abdominal pain, postprandial fullness, bloating, vomiting, and early satiety (a feeling of fullness after eating just a few bites) (Camilleri et al, 2013). These symptoms can be debilitating and, when uncontrolled, have a significant negative impact on patient quality of life and functioning, including work productivity (Camilleri et al, 2011, Parkman et al, 2011). Serious adverse sequelae of DG include: potentially life-threatening dehydration due to persistent vomiting, gastroesophageal reflux disease (GERD) that can advance to esophagitis, formation of

bezoars, difficulty managing blood glucose levels, and malnutrition due to poor absorption of nutrients or a low-calorie intake (U.S. Department of Health and Human Services, 2012). Aside from the impact on patients, these events often lead to hospitalization (Koch et al, 2016), resulting in a high economic burden for health care systems.

DG complicates management of blood glucose for both T1DM and T2DM patients due to carbohydrates being delivered to and therefore absorbed from the small intestine at unpredictable times (Rayner et al, 2001). As a result, diabetic patients with DG often have poorly controlled diabetes, frequently with alternating hypo- and hyperglycemia, especially if treated with insulin.

Little data on the incidence and prevalence of GP are available; however, an older epidemiology study of diagnosed GP (defined as typical symptoms plus confirmed delayed GE by scintigraphy) showed prevalence of 24.3 per 100,000 inhabitants and incidence of 6.3 per 100,000 persons per year in Olmstead County, MN from 1996 to 2006 (Jung et al, 2008). This study reported that age-adjusted prevalence of GP was approximately 4 times greater for women than men (37.8 versus 9.6 cases per 100,000 persons). It has been reported that 30 to 50% of diabetic patients have delayed GE, while the prevalence of the specific symptoms of GP (nausea and vomiting) is lower, with approximately 10% of patients with diabetes being affected (HopkinsMedicine.org, 2013). According to Bharucha (2015), in a restricted community-based study of GP in diabetes mellitus, the average cumulative incidence of symptoms and delayed GE over 10 years was higher in T1DM (5%) than in T2DM (1%) and controls (1%). It is expected that the incidence of DG will increase worldwide in proportion to the increase in T2DM due to increasing obesity.

3.1 Study Rationale

Previous non-clinical and Phase 1 studies have shown relamorelin to have a potent prokinetic effect on the stomach, accelerating GE in both healthy volunteers and patients with DG.

GP is a disorder characterized by signs and symptoms of nausea, abdominal pain, postprandial fullness, bloating, vomiting, and early satiety along with delayed gastric emptying (GE), such that movement of food from the stomach to the small intestine takes longer than normal and occurs with unpredictable timing. T1DM or T2DM is considered to be the most common identifiable cause of GP. This complication is a result of chronically elevated blood glucose levels, which are known to damage nerve structure and function. DG complicates management of blood glucose for both T1DM and T2DM patients due to carbohydrates being delivered to and therefore absorbed from the small intestine at variable times after ingestion. As a result, diabetic patients with DG often have poorly controlled diabetes, frequently with alternating hypo- and hyperglycemia, especially if treated with insulin.

In Phase 2 studies, the pharmacodynamic effect of relamorelin was confirmed in larger numbers of participants with DG, and in addition, beneficial effects on the symptoms of DG were observed. Safety and tolerability were shown at therapeutic doses, including the 10 µg twice daily (BID) dose to be studied in Phase 3 studies, supporting the decision to obtain confirmatory evidence of safety and efficacy of relamorelin in Phase 3, including supportive evidence from Study RLM-MD-04.

A significant unmet medical need exists for a safe and effective treatment of patients with DG whose quality of life is impacted by their disease and for whom the current standard of care is suboptimal; therefore, the sponsor is performing this study to further the development of relamorelin for the treatment of DG, specifically to assess the effect of long-term treatment in a population with less vomiting and/or lower baseline Diabetic Gastroparesis Symptom Severity Score (DGSSS) than the population enrolled in the pivotal efficacy studies, RLM-MD-01 and RLM-MD-02.

3.2 Background

Relamorelin is being developed for the treatment of patients with DG to address the existing unmet need for an effective and safe/tolerable treatment, attested to by the FDA's granting of fast-track designation to relamorelin for the treatment of DG in adults. It is a member of an established class of compounds, ghrelin agonists, but if granted regulatory approval, will be the first member of this class to attain marketing approval.

In clinical studies to date, 466 participants with T1DM or T2DM with DG have been exposed to relamorelin at doses up to 100 µg administered twice daily by subcutaneous (SC) injection for 12-weeks.
In a randomized, placebo-controlled, multiple-dose Phase 2a study (RM-131-004), participants with T1DM and T2DM and DG received 28 days of double-blind treatment with relamorelin. GE was accelerated and compared to placebo, relamorelin 10 µg BID significantly decreased the vomiting severity score and mean number of weekly vomiting episodes in participants with vomiting at baseline and produced improvement in the 4 individual DG symptoms of nausea, abdominal pain, bloating and early satiety as well as significant improvement in the composite endpoint of the 4 symptoms ($p = 0.043$). The safety and tolerability profile of relamorelin in Study RM-131-004 was generally good.

The results in Study RM-131-004 helped the sponsor select the target patient population for enrollment in the Phase 2b Study RM-131-009, DG patients with vomiting at baseline, and encouraged assessment of a wider range of relamorelin doses.

Study RM-131-009 was a randomized, double-blind, placebo-controlled, stratified, multiple dose, multi-national study with 10 µg BID, 30 µg BID, and 100 µg BID doses of relamorelin. A total of 393 participants with T1DM or T2DM, who had both delayed GE and moderate to severe symptoms of GP were enrolled and treated. The Phase 2b study confirmed a statistically significant effect of relamorelin over placebo on GE for the 10 µg and 30 µg doses. Vomiting episodes were reduced from baseline to Week 12 by approximately 75% in all relamorelin dose groups; however, there was also a strong, previously unobserved placebo effect on vomiting frequency (reduction of approximately 70%) that precluded statistical significance of the relamorelin effect that was observed. Results for the key secondary endpoint, a composite score of 4 DG symptoms (nausea, abdominal pain, bloating, and early satiety) showed benefit of treatment with relamorelin compared to placebo although the difference was not statistically significant; the same was true for an exploratory endpoint, a composite score of 4 DG symptoms that included postprandial fullness instead of early satiety.

Relamorelin was generally safe and well tolerated among patients with T1DM or T2DM and DG. There were more reports of diarrhea and hyperglycemia-related events on relamorelin compared to placebo; hypoglycemia was infrequently reported (1.2% incidence in the placebo and relamorelin 100 µg groups only). Twenty-three serious adverse events (SAEs) were reported in the 289 participants treated with the 3 doses of relamorelin and 8 in the 104 participants treated with placebo. The number and characteristics of the reported SAEs reflected the advanced underlying disease state of this DG population with long-standing T1DM or T2DM and other common co-morbidities and only 2 of the SAEs (cardiac failure congestive and diabetes mellitus inadequate control) were assessed by the investigator as possibly related to study treatment, both in the 100-µg treatment group. Three adverse events (AEs) of diabetic ketoacidosis were reported, one event on each relamorelin dose. A total of 20 relamorelin-treated participants and 3 placebo-treated participants discontinued study treatment because of a treatment-emergent AE; only 3 in the relamorelin 10 µg BID group.

With respect to laboratory findings, in some participants, glycemic control may have been negatively affected by the introduction of relamorelin. There were trends in increasing hemoglobin A1c (HbA1c) values after the initiation of relamorelin, which increased slightly after approximately 8 weeks, and dose-related trends in fasting hyperglycemia. Otherwise, no clinically relevant abnormalities were seen for other laboratory tests, including liver function tests, electrocardiograms (ECGs), physical examination findings, and injection site reactions; anti-drug antibodies (ADAs) were not found.

A detailed description of the chemistry, pharmacology, efficacy, and safety of relamorelin is provided in the investigator's brochure (Relamorelin Investigator's Brochure).

3.3 Benefit/Risk Assessment

Based on information about relamorelin obtained to date, the benefits of study participation are expected to include accelerated GE and clinically meaningful improvement in the symptoms of DG, including nausea, abdominal pain, postprandial fullness, bloating, vomiting frequency, early satiety, and vomiting severity. A potential risk of treatment is worsening of glycemic control, including the possibility of diabetic ketoacidosis occurring. However, preventive measures, including special laboratory assessments to allow early recognition by investigators and participants of rising glucose levels, are being included in this protocol so that early remedial action (eg, adjustment of medication and diet) may be taken to minimize increase in glucose levels; this might increase the incidence of hypoglycemic reactions, especially in participants with T1DM. See Section 5, Study Design for details of study procedures, dose, and study design justification.

More detailed information about the known and expected benefits and risks and reasonably expected AEs associated with relamorelin treatment may be found in the investigator's brochure (Relamorelin Investigator's Brochure); information about the investigational directions for use for the pen injector, the device that will be used to administer study treatment are also provided.

4 Objectives and Endpoints

Key Objectives	Key Endpoints
• To compare the efficacy of relamorelin with that of placebo in participants with DG with respect to a composite of the following core signs and symptoms of DG: o Nausea o Abdominal pain o Postprandial fullness o Bloating	• Change from baseline to Week 12 in the weekly DGSSS • Change from baseline to Week 52 in weekly average DGSSS
• To compare the safety of relamorelin with that of placebo in participants with DG	• AEs, clinical laboratory values, vital signs, ECGs, HbA1c, and anti-relamorelin antibodies
[redacted]	

4.1 Clinical Hypotheses

The clinical hypotheses are:

DG participants receiving relamorelin compared to DG participants receiving placebo will experience greater improvement in DGSSS as measured by:

- The change from baseline to Week 12 weekly DGSSS, and
- The change from baseline to Week 52 weekly average DGSSS (defined as the average of the 4 weekly DGSSS from the 4 weeks prior to the Week 52 visit).

Baseline is defined as the average of the 2 average DGSSS from the 2-week placebo Run-in Period.

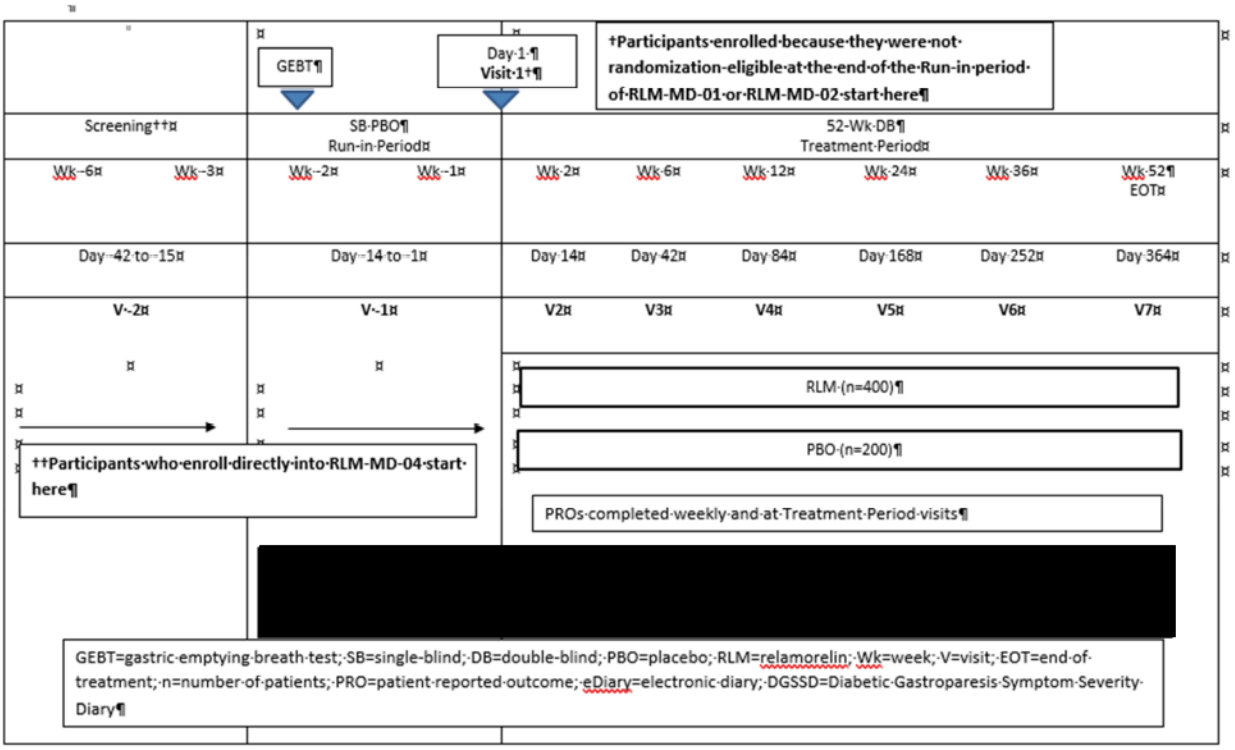
5 Study Design

5.1 Overall Design

- Global, multicenter, randomized, double-blind, placebo-controlled, parallel-group
- Treatment Groups: Relamorelin 10 µg and placebo; BID, SC
- Study Duration: 52-week Treatment Period.

See Figure 5-1 for a Study Schematic.

Figure 5-1 RLM-MD-04 Study Schematic



Study Population:

Two different groups of participants may enter into the study:

1. Participants who met all Screening and Run-in Period criteria in lead-in Study RLM-MD-01 or lead-in Study RLM-MD-02 (including compliance with dosing and data entry into the DGSSD during the lead-in study Run-in Period), but were not randomization-eligible at the end of the lead-in study Run-in Period, are eligible for randomization in Study RLM-MD-04 if:

    - They had no vomiting episodes recorded in the DGSSD and had an average daily DGSSS ≥ 12 at the end of the lead-in study Run-in Period.

    OR

    - They had vomiting episodes recorded in the DGSSD but had an average daily DGSSS of ≥ 12 and < 16 at the end of the lead-in study Run-in Period.

In the current study, these "**rollover participants**" will enter the study at Visit 1 (Randomization); they will not undergo Screening (Visit –2) or the Run-in Visit (Visit –1) procedures

2. Patients who undergo screening and run-in procedures in Study RLM-MD-04 are "**de novo participants"**. To be eligible for randomization in the current study, de novo participants must meet all Screening and Run-in Period criteria for Study RLM-MD-04, including:

    a. At Screening, be male or female age 18 years and older; T1DM or T2DM with controlled and stable blood glucose levels and HbA1c ≤ 11%; symptoms suggestive of DG for at least 3 months (one of which must be nausea), with mechanical obstruction of the GI tract as the cause of symptoms having been ruled out.

    b. History of nausea and/or at most a single episode of vomiting in the 2 weeks prior to Screening (Visit -2), as ascertained by participant history

    c. During the Run-in Period, delayed GE by gastric emptying breath test (GEBT)

    d. After Run-in Period: Evidence of compliance during the Run-in Period with the use of the electronic hand-held device for entry of data, with twice daily SC injections of the study treatment, and no treatment with GI promotility agents; a score of ≥ 12 for the average of the daily DGSSS measured during the Run-in Period.

For studies conducted at US (IND) sites and non-US (non-IND) sites, data from IND and non-IND study sites will be pooled together for analysis.

5.2 Participant and Study Completion

Approximately 5000 participants will be screened in lead-in Studies RLM-MD-01 and RLM-MD-02. Certain participants who were not eligible for randomization at the end of the lead-in study Run-in Period (rollover participants) may enter this study (see Section 5.1 for rollover participant eligibility criteria).

In addition, participants who undergo Screening and Run-in Visit procedures will be eligible for randomization if they meet all inclusion/exclusion criteria for the current study (see Sections 6.1.2 and 6.2.3 for de novo participant eligibility criteria).

The goal is to achieve 600 participants assigned to study treatment (400 to relamorelin and 200 to placebo). A total of 300 participants are expected to complete the study (200 treated with relamorelin and 100 with placebo). See Section 10.1 for details on sample size determination.

5.3 End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study.

A participant is considered to have completed the study if he/she has completed at least 364 days of treatment, and the last visit (Visit 7). Independent of the end of study definition, all laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical safety physician (MSP).

5.4 Scientific Rationale for Study Design

The sponsor has designed this randomized, double-blind, placebo-controlled, parallel-group study to follow regulatory recommendations for conduct of Phase 3 therapeutic confirmatory studies, specifically the ICH Harmonized Tripartite Guideline E8 (General Considerations for Clinical Trials, Current Step 4 version dated 20 July 2000) and Guideline E10 (Choice of Control Group and Related Issues in Clinical Trials, Current Step 4 version dated 17 July 1997). The study also has been designed to comply with recommendations made by the US FDA, Center for Drug Evaluation and Research (CDER) in the Draft Guidance for Industry, Gastroparesis: Clinical Evaluation of Drugs for Treatment, July 2015, including those for the minimum duration of studies to show efficacy (at least 12 weeks) and for inclusion of a long-term placebo-controlled safety study (12 months, with appropriate pre-specified provisions for rescue medications) as part of the development plan.

Several design features have been incorporated in the current study in an effort to minimize bias, including double-blind design and random assignment of participants, helping to ensure that both known and unknown risk factors are distributed evenly between treatment groups. The use of a placebo control permits prospective comparison between the relamorelin group and the control group.

5.5 Justification for Dose

Study RM-131-009 was a 12-week Phase 2b, randomized, double-blind, placebo-controlled, parallel group study to evaluate the safety and efficacy of relamorelin in diabetic participants with moderate to severe DG. The doses included within the study were 10 µg BID, 30 µg BID, and 100 µg BID. In general, all doses tested within RM-131-009 appeared to demonstrate meaningful reductions in overall DG symptom scores including vomiting episodes, with acceptable safety and tolerability. The frequency of vomiting episodes was reduced from baseline over the 12-week treatment period to a similar extent for participants who received the 3 doses of relamorelin tested and placebo. Based upon the observed dose response of change-from-baseline symptom scores collected daily over the course of 12 weeks using the DGSSD, the 30 µg BID,

and 100 µg BID doses demonstrated apparent maximal symptom score improvements, while the 10 µg BID dose achieved near maximal improvements. Of note, the twice-a-day regimen of relamorelin appears to be necessary for effective symptom relief; the 10 µg once daily (QD) relamorelin did not demonstrate significant improvement in symptom relief compared to placebo after 28 days of dosing in Study RM-131-004.

Review of the safety laboratory data collected in RM-131-009 revealed an apparent dose-related increase in HbA1c values. Although the variability in HbA1c response was high across all treatments, the 30 µg BID and 100 µg BID doses demonstrated apparent maximal changes in HbA1c values, while the 10 µg BID dose resulted in an approximately half-maximal increase after 12 weeks of study. Shorter durations of treatment (4 weeks) with 10 µg BID of relamorelin, as observed in Study RM-131-004, did not demonstrate this apparent increase in HbA1c in diabetic participants.

Based on the efficacy and safety data, the relamorelin dose selected for this study is 10 µg BID.

6 Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1 Inclusion Criteria

6.1.1 Rollover Participants

Participants who were not randomization-eligible at the end of the Run-in Period of lead-in Studies RLM-MD-01 or RLM-MD-02 are eligible to be randomized in the study if all of the following criteria apply:

In the lead-in studies, participants must have met all Screening Visit and Run-in Period criteria for randomization into the Treatment Period (including compliance with dosing, entry of diary data into the DGSSD) except that:

1. They had zero vomiting episodes and an average daily DGSSS of ≥ 12 at the end of the lead-in study Run-in Period, as reported using the electronic hand-held device;

OR

2. They had vomiting episodes and an average daily DGSSS of ≥ 12 but < 16 at the end of the lead-in study Run-in Period, as reported using the electronic hand-held device.

6.1.2 De Novo Participants

Participants who undergo screening and run-in procedures for Study RLM-MD-04 are eligible to be included in the study if all of the following criteria apply:

1. Male or female participants aged 18 years or older at Screening (Visit –2)
2. T1DM or T2DM of at least 5 years' duration, with controlled and stable blood glucose levels (ie, no episodes of diabetic ketoacidosis, Hyperosmolar Hyperglycemic Nonketotic Diabetic Syndrome, or severe hypoglycemia within the 6 months preceding Screening [Visit –2])
3. HbA1c ≤ 11.0% at Screening (Visit –2) in participants being treated with oral and/or parenteral medications for T1DM or T2DM with the goal of achieving controlled and stable glucose levels
4. DG defined as at least a 3-month history prior to Screening (Visit –2) of symptoms (one of which must be nausea) on an ongoing basis that are suggestive of GP (eg, nausea, abdominal pain, postprandial fullness, bloating, vomiting, and early satiety)
5. Female participants willing to minimize the risk of inducing pregnancy for the duration of the clinical study and Follow-up Period

   A female participant is eligible to participate if she is not pregnant (has a negative urine pregnancy result prior to randomization; see Appendix 5), not breastfeeding, and at least one of the following conditions applies:

   a. Not a woman of childbearing potential (WOCBP) as defined in Appendix 5

   OR

   b. A WOCBP who agrees to follow the contraceptive guidance in Appendix 5 during the Treatment Period and for at least 7 days after the last dose of study treatment

6. Documentation of absence of an obstructing lesion on upper GI series with contrast or upper endoscopy, performed at some time before the Run-in period (Visit 2) but after the appearance of symptoms that led to the diagnosis of DG
7. Nausea and/or at most a single episode of vomiting during the 2 weeks prior to Screening (Visit –2), as ascertained by participant history
8. Delayed GE confirmed by abnormal GEBT, defined as GE half-time ($t_{½}$) ≥ 79 minutes at the start of the placebo-controlled Run-in Period (Visit 2 of RLM-MD-01, RLM-MD-02, or this study). In countries where the GEBT is not available, delayed GE may be confirmed by abnormal scintigraphy result (> 60% retention at 2 hours or > 10% at 4 hours). Refer to the Study Reference Manual
9. The BMI criterion has been removed.
10. Able to provide written informed consent (IC) prior to any study procedures and willing and able to comply with study procedures

    Additional inclusion criteria for randomization after the 2-week, placebo Run-in Period:

11. Compliance with the entry of data into the hand-held electronic device on at least 10 of 14 days during the Run-in Period

12. Compliance with administration of SC twice daily injections, as evidenced by entries made by the participant using the electronic, hand-held device on at least 10 of 14 days during the Run-in Period
13. The average of the daily DGSSS from the 2-week, Run-in Period must be ≥ 12

6.2 Exclusion Criteria

6.2.1 Both Rollover and De Novo Participants

1. Corrected QT Interval (QTc) > 470 msec in the absence of right or left bundle branch block, other intraventricular conduction delay (IVCD) with QRS duration > 120 msec, or paced beat on the ECG obtained at Screening (Visit 1).

2. Participants with a known allergy or hypersensitivity to the study treatments and their excipients (ie, mannitol or phenol)

6.2.2 Rollover Participants

Participants will be excluded from this study if any of the lead-in study exclusion criteria apply at Screening (Visit 1) and at the end of the Run-in Period (Visit 3) for randomization into the Treatment Period of Studies RLM-MD-01 and RLM-MD-02, except as specified in the inclusion criteria (Section 6.1).

6.2.3 De Novo Participants

1. Symptomatic Irritable Bowel Syndrome at Screening (Visit –2)

2. Small intestinal bacterial overgrowth (SIBO) at Screening (Visit –2)

3. History of anorexia nervosa, binge-eating, bulimia, or other eating disorder within 5 years of Screening (Visit –2)

4. History of intestinal malabsorption (including celiac disease even if well-controlled on a gluten-free diet) or pancreatic exocrine insufficiency; also, history of non-celiac gluten sensitivity

5. History of belching disorders, other nausea and vomiting disorders (eg, chronic nausea and vomiting syndrome, cyclic vomiting syndrome, cannabinoid hyperemesis syndrome), or rumination syndrome
6. History of chronic obstructive pulmonary disease or other causes of pulmonary dysfunction that have resulted in CO2 retention
7. Gastric or duodenal ulcer within 3 months of Screening (Visit 1)

8. Evidence of hepatic disease defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 3 x ULN, and/or direct bilirubin ≥ 2 x ULN at Screening (Visit -2)

9. History of malignancy in the 3 years prior to Visit 1, except for adequately treated basal cell or squamous cell skin cancer, or in situ cervical cancer

10. Currently receiving parenteral feeding or presence of a nasogastric or other enteral tube for feeding or decompression

11. Use of metoclopramide, domperidone, prucalopride, macrolide antibiotics (eg, erythromycin, clarithromycin, azithromycin), or other drugs considered to be GI pro-motility agents (Table 7–2) for at least 10 days prior to the start of the Run-in Period (Visit –1)

12. Positive results on the urine drug screen at Screening (Visit -2). The sponsor may permit a participant with a positive urine drug screen (UDS) by immunoassay at Screening to continue in screening while confirmatory testing by a more specific method is carried out on an aliquot of the original urine sample. If the confirmatory test is negative, the initial positive UDS will be considered to have been a false-positive urine drug screen and the participant can continue in screening. Confirmatory testing will be done at the discretion of the sponsor and must be approved by the sponsor prior to analysis. The significance of a positive screen result for drugs prescribed for the participant (eg, barbiturates, benzodiazepines, amphetamines, but not opioids or cannabinoids) should be assessed by the Investigator as to whether their stable-dose usage is clinically appropriate, and, therefore, should not be exclusionary; use of these drugs on an as-needed basis is not allowed. See Section 6.4 for additional details regarding positive urine drug screen.

13. Currently taking opiates, or expecting to use opiates during the course of the clinical study. (see Section 7.7.1 for an exception to this prohibition)

14. Treatment with glucagon-like peptide-1 (GLP-1) agonist for at least 6 weeks prior to the start of the Run-in Period (Visit –1)

15. History of pyloric injection of botulinum toxin within 6 months of screening

16. History of gastric surgery such as fundoplication, gastrectomy, gastric pacemaker placement, vagotomy, or bariatric procedure (a history of diagnostic endoscopy is not exclusionary)

17. Randomization in any previous study in which relamorelin was a treatment

18. Estimated glomerular filtration rate (eGFR) of < 30 mL/min

19. Current enrollment in an investigational drug or device study or participation in such a study within 30 days of entry into this study

20. Allergic to, or intolerant of egg, wheat, milk, or algae, as these are components of the GEBT study meal

21. Females who are pregnant, nursing, or planning a pregnancy during the study. For females who are of childbearing potential, see Appendix 5
22. The participant has a condition or is in a situation which, in the investigator's opinion, may put the participant at significant risk, may confound the study results, or may interfere significantly with the participant's participation in the study
23. Participant is directly or indirectly involved in the conduct and administration of this study as an investigator, subinvestigator, study coordinator, other study staff member, or employee of Allergan, Inc.; or the participant is a first-degree family member, significant other, or relative residing with one of the above persons involved directly or indirectly in the study; or the participant is enrolled in this study at another clinical study site
24. Functional dyspepsia diagnosed before the diagnosis of diabetes mellitus
25. Hypersensitivity to the study treatments and their excipients (ie, mannitol or phenol)
26. Corrected QC Interval (QTc) > 470 msec in the absence of right or left bundle branch block, other intraventricular conduction delay (IVCD) with QRS duration > 120 msec, or paced beat on the ECG obtained at Screening (Visit 1)

6.3 Lifestyle Restrictions

There are no specific dietary restrictions in the study. It is expected that participants are aware of the importance of maintaining reasonable consistency in timing and size of meals (and specifically carbohydrate intake) for achieving adequate control of hyperglycemia but appreciate that the presence of GP may make this difficult.

For timing of meals around the GEBT, refer to the Study Reference Manual.

6.4 Screen Failures

For de novo participants, screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study treatment. Screen failures can fail to meet criteria for random assignment to study treatment in the study either before or after participation in the Run-in Period.

De novo participants who do not meet the criteria for participation in this study (screen failure) before entering the Run-in Period may be rescreened once if the reason for screen failure is only because of Inclusion Criterion 3 "HbA1c ≤11.0% at Screening (Visit -2)." In this specific situation, the participant may be rescreened after at least one month and no more than 6 months of further effort to achieve improved glycemic control, as indicated by HbA1c being ≤11.0%.

The sponsor may permit a participant with a positive urine drug screen by immunoassay, at Screening (Visit -2) to continue in the Screening Period while confirmatory urine drug screen

testing by a more specific method is carried out on an aliquot of the original urine sample. If the confirmatory test is negative, the initial positive urine drug screen will be considered to have been a false-positive urine drug screen and the participant can continue in screening. Confirmatory testing will be done at the discretion of the sponsor and must be approved by the sponsor prior to analysis. The significance of a positive urine drug screen result for drugs prescribed for the participant (ie, barbiturates, benzodiazepines, amphetamines, but not opioid or cannabinoids) should be assessed by the Investigator as to whether their stable-dose usage is clinically appropriate, and if so, should not be exclusionary; use of the prescribed drugs on an as-needed basis is not allowed.

Rescreening of a participant for any other reason is up to the discretion of the Sponsor and must be approved by the Sponsor prior to any rescreening procedures. The timeframe for rescreening is up to 6 months from the time of screen failure. Participants who enter the Run-in Period will not be allowed to be rescreened. Rescreening requires that a participant be assigned a new participant number and after repeating the Informed Consent Process, undergo all original screening assessments.

A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

7 Treatments

Study treatment is defined as any investigational treatments, marketed product, or medical device intended to be administered to a study participant according to the study protocol.

7.1 Treatments Administered

Participants who meet study entry criteria will be randomized in a 2:1 ratio to blinded treatment with relamorelin 10 µg or placebo. At Visit 1, participants will self-administer study treatment in the presence of study center personnel.

After Visit 1, participants are to self-administer study treatment twice daily SC, with the first daily dose being administered within approximately 30 minutes before the morning meal (ie, breakfast, at approximately 08:00) and the second daily dose within approximately 30 minutes before the evening meal (ie, dinner, at approximately 18:00). If a participant does not eat morning or evening meals, study treatment should be administered during typical meal times (eg, 06:00 to 09:00 and 17:00 to 20:00).

Should a participant miss a dose prior to either the morning or evening meal, he/she should adjust his/her study treatment administration as follows:

- If within 6 hours of the normal dosing time relative to the morning or evening dose, the participant should self-administer the dose at that time
- If later than 6 hours after the normal dosing time relative to the morning or evening dose, the participant should not self-administer the dose. Resume normal dosing at the next scheduled time (ie, that evening if the morning dose was missed, or the next morning if the evening dose was missed)

Participants should rotate injection sites in the abdomen.

Study treatment will be dispensed as pen injectors with pre-filled cartridges of either relamorelin or placebo. Study treatment details are provided in Table 7–1.

Table 7–1 Study Treatment Details

Study Treatment	Relamorelin	Placebo
Dosage Formulation	Pre-Filled Cartridge in Multi-dose Pen Injector	Pre-Filled Cartridge in Multi-dose Pen Injector
Unit Dose Strength	10 µg dose	N/A
Route of Administration	Subcutaneous	Subcutaneous
Dosing Instructions	Administer twice daily	Administer twice daily
Packaging and Labeling	Study treatment will be provided in a single unit carton. Each carton will be labeled as required per country requirement.	Study treatment will be provided in a single unit carton. Each carton will be labeled as required per country requirement.
Manufacturer	Baxter (Prefilled Cartridge) Allergan (Assembled Pen)	Baxter (Prefilled Cartridge) Allergan (Assembled Pen)
Injection Device	Utilize Multi-dose Pen Injector for the administration of the study treatment or placebo. Refer to the Relamorelin Pen Investigational Directions for Use for detailed instructions on use of the injection device. Each pen injector is to be used for 28 days.	Utilize Multi-dose Pen Injector for the administration of the study treatment or placebo. Refer to the Relamorelin Pen Investigational Directions for Use for detailed instructions on use of the injection device. Each pen injector is to be used for 28 days.

7.1.1 Study Supplies

1. The Allergan-manufactured medical devices (or devices manufactured for Allergan by a third party) provided for use in this study are: (1) Prefilled Cartridge, and (2) Multi-dose Pen Injector.

2. Instructions for medical device use are provided in Relamorelin Pen Investigational Directions for Use.

3. Medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the investigator throughout the study (see Appendix 7).

7.2 Dose Modification

Not applicable

7.3 Method of Treatment Assignment

All participants will be centrally assigned to randomized study treatment using an interactive web response system (IWRS). Before the study is initiated, the log-in information and directions for the IWRS will be provided to each site.

At the beginning of the 52-week Treatment Period, participants will be randomized in a 2:1 ratio to blinded treatment with relamorelin 10 µg or placebo.

Study treatment will be dispensed at the study visits indicated in the SoA (Section 2).

Returned study treatment should not be re-dispensed to the participants.

7.4 Blinding/Masking

The investigator, investigational staff, and participant will be fully blinded to study treatment during the 52-week Treatment Period. All study treatment will be provided in identical pen injectors and cartons to maintain blinding of the study.

The IWRS will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator is encouraged to contact the sponsor prior to unblinding a participant's treatment assignment unless this could delay emergency treatment of the participant. If a participant's treatment assignment is

unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form, as applicable.

7.5 Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
2. Only participants enrolled in the study may receive study treatment, and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study treatment are provided in the Study Reference Manual.

7.6 Treatment Compliance

Study treatment compliance will be closely monitored by assessing the participant's daily reporting of self-administered study treatment on the electronic hand-held device. Before dispensing new study treatment, study site personnel will make every effort to collect all used and unused study treatment.

In the event of early termination, compliance will be assessed using the available daily reports on the hand-held device and/or by the coordinator depending on when the termination occurs. In the event of AE or intercurrent illness, dosing of study treatment can be stopped temporarily, for a maximum duration of 3 days. Should longer cessation of dosing be necessary, the investigator should contact the sponsor (Section 8.1.1).

The study centers will keep an accurate drug disposition record that specifies study treatment dispensed to each participant and the date of dispensing.

7.7 Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded on the electronic case report form (eCRF) along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

As much as possible, the dose and frequency of all concomitant medications taken for chronic conditions with the exception of diabetes mellitus (see Section 7.7.2—Permitted Treatments) should be held stable during the study. The sponsor should be contacted if there are any questions regarding concomitant or prior therapy.

7.7.1 Prohibited Treatments and Washout Before the Study

The classes of drugs prohibited in the study are, with the exception SLGT-1 and SGLT-2 inhibitors, those that affect GI motility, either positively or negatively, and therefore could confound the assessment of the efficacy of study treatment on the signs and symptoms of DG. The SGLT-1 and SGLT-2 inhibitors are prohibited Their mechanism of action is through causing increased glycosuria, which may affect interpretation of the GEBT results.

Table 7–2 provides a list of drug classes and treatments that are prohibited during this study and require washout during the Run-in Periods of the current study and the lead-in Studies (RLM-MD-01 or RLM-MD-02).

Table 7–2 Prohibited Medications and Washout Requirements

Drug Class/Treatment	*Washout Required Prior to Baseline*
Sodium-glucose co-transporter-2 (SGLT-1 or SGLT-2) inhibitors: Empagliflozin, canagliflozin, dapagliflozin, etc.	Prohibited only 3 days prior to the GEBT done in a subset of participants at a subset of sites at Visit 4 or the Early Termination Visit
Pro-motility agents: Metoclopramide, macrolide antibiotics (eg, erythromycin, clarithromycin, azithromycin), domperidone, prucalopride, or other drugs considered to be GI pro-motility agents	**Rollover Participants**: 10 days prior to the start of the Run-in Period of the Lead-in study **De novo Participants:** 10 days prior to the start of the Run-in Period of this study, RLM MD-04
Anticholinergics: Drugs with an anti-cholinergic mechanism of action as the basis of their therapeutic benefit, not those that have anti-cholinergic activity as a side effect	
Anti-emetics (Used for more than 1 day a week, or participant requires an anti-emetic drug once weekly repeatedly (ie, for 3 consecutive weeks or more), the investigator should contact the sponsor to discuss the safety of the participant continuing study treatment.)	
Amylin analogue: pramlintide	
5HT4 agonists (cisapride, tegaserod, and prucalopride)	
Opioids[a] (eg, tramadol)	Washout period is not applicable as the use of opioids is not allowed. See Exclusion Criteria #12 and #13.
Glucagon-like peptide-1 (GLP-1) agonists: Exenatide, liraglutide, etc.	**Rollover Participants:** 6 weeks prior to the start of the Run-in Period of the Lead-in study **De novo Participants:** 6 weeks prior to the start of the Run-in Period of this study, RLM MD-04
Botulinum toxin injections (eg, Botox®) by pyloric injection only; injection of Botox in other parts of the body is allowed	6 months prior to screening (Visit –2)

[a] Exception to prohibition: An opioid prescribed for severe pain following a surgical operation, dental procedure, or injury may be taken as directed for up to 72 hours a maximum of two times during the study.

7.7.2 Permitted Treatments

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded in the eCRF along with:

- Indication
- Dates of administration including start and end dates
- Dosage information including dose and frequency

DG participants enrolled in this study will likely consist mostly of patients receiving one or more prescription medications for blood-glucose control. Good clinical practice allows for frequent adjustment of medication by patients and their health care providers to minimize large fluctuations in glycemia, and this practice is encouraged in this study. It should be remembered that certain diabetic drugs (see Table 7–2) delay GE and are prohibited during this study. Other therapy considered necessary for the participant's welfare may be given at the discretion of the investigator. If the permissibility of a specific medication/treatment is in question, please contact the sponsor.

The sponsor or designee should be contacted if there are any questions regarding concomitant or prior therapy.

7.7.3 Rescue Medicine

Use of medications that may impact efficacy evaluations is strongly discouraged at any time after Visit 1 in the study. However, participants who experience severe symptoms of GP may receive a single day of treatment per week with an anti-emetic drug, but should avoid such treatment, if possible, during the 2-week Run-in Period, and on the day prior to and day of clinic visits during the Treatment Period. If a participant requires an anti-emetic drug (eg, 5-HT3 receptor antagonists, NK1 receptor antagonists) for more than one day a week, or requires an anti-emetic drug once weekly repeatedly (ie, for 3 consecutive weeks or more), the investigator should contact the sponsor to discuss the safety of the participant continuing study treatment.

The date of rescue-medication administration as well as the name and dosage regimen of the rescue medication should be recorded in the concomitant medications page of the eCRF.

7.8 Treatment after the End of the Study

Participants who complete the study should follow up with the investigator regarding treatment at the end of the study.

8 Discontinuation/Withdrawal Criteria

Reasons for discontinuation from study treatment and/or the study may include the following:

- Adverse event
- Completed
- Death

- Failure to meet entry criteria
- Lack of efficacy
- Lost to follow-up
- Other
- Investigator decision
- Pregnancy
- Protocol deviation
- Site terminated by sponsor
- Study terminated by sponsor
- Withdrawal by participant

The reason for discontinuation should be clearly documented on the appropriate eCRF. Discontinuation of study treatment also requires discontinuation from the study. (See Appendix 8 for Standard Discontinuation Criteria/Definitions.)

8.1 Discontinuation of Study Treatment

Discontinuation of study treatment also requires discontinuation from the study. The following criteria should be evaluated:

- Special attention should be paid to the appearance of abnormal laboratory test results suggesting severe, drug-induced liver injury (DILI). Discontinuation of study treatment for abnormal liver function should be considered by the investigator when a participant meets criteria for Hy's law (see Section 9.2.7.1 and Appendix 6) or if the investigator believes that it is in best interest of the participant.

- ECGs should be carefully analyzed for findings pointing to potentially important cardiac events. If a clinically significant finding is identified (including, but not limited to changes from baseline in QT interval corrected using QTcB or QTcF after enrollment, the investigator or qualified designee should determine if the participant can continue in the study and if any change in participant management is needed. Generally, a QTc value of > 500 msec or an increase from baseline of > 60 msec after start of study treatment should prompt discontinuation of the participant from the study. Review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

- Female participants who become pregnant during the study must be discontinued from treatment immediately and withdrawn from the study. See Section 9.2.5 and Appendix 5 for further details regarding follow-up of the participant through the pregnancy.

See the SoA (Section 2) for data to be collected at the time of treatment discontinuation.

8.1.1 Temporary Discontinuation

In the event of AE or intercurrent illness, dosing of study treatment can be stopped temporarily, for a maximum duration of 3 days. Should longer cessation of dosing be necessary, the investigator should contact the sponsor. The investigator should also contact the sponsor should either recurrence of the AE that prompted discontinuation or the appearance of a new AE that requires discontinuation be experienced after reintroduction of treatment to discuss the safety of this participant continuing study.

8.2 Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, compliance, or administrative reasons. An early termination visit must be performed as soon as possible after the decision to withdraw has been made by the participant or the decision to withdraw the participant has been made by the investigator.

- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

- See the SoA for data to be collected at the time of study discontinuation.

8.3 Lost to Follow Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

9 Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA (Section 2).
- Protocol waivers or exemptions are not allowed.

- Safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

- Adherence to the study design requirements, including those specified in the schedule of activities, is essential and required for study conduct.

- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 66.5 mL for rollover participants or 74.5 mL for de novo participants. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

9.1 Efficacy Assessments

9.1.1 Key Efficacy Assessment - DGSSD

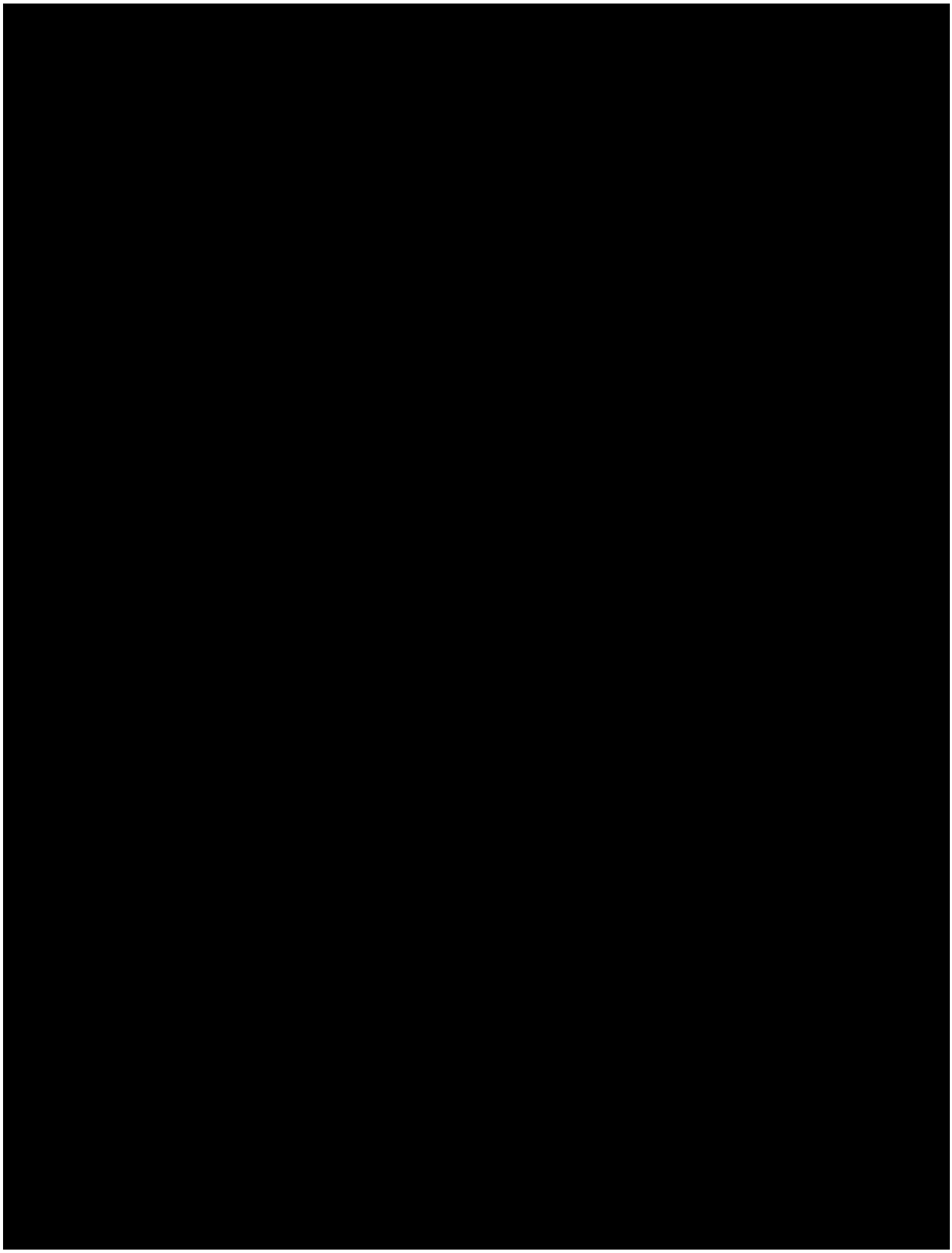
The main efficacy assessment is the DGSSD, a 7-item, patient-reported diary designed to assess the severity of 6 core signs and symptoms of DG —nausea, abdominal pain, postprandial fullness, bloating, vomiting, and early satiety—and the frequency of vomiting episodes (Appendix 13). Participants will report their symptoms daily from Visit 1 to Visit 4 (Day 84) in the DGSSD. Thereafter, participants will report their symptoms daily for each of the 4 weeks preceding Visits 5, 6, and 7. DGSSD entries are to be made daily at the same time every evening on the electronic hand-held device throughout the Treatment Period. Planned periods for DGSSD entries are provided in the SoA (Section 2).

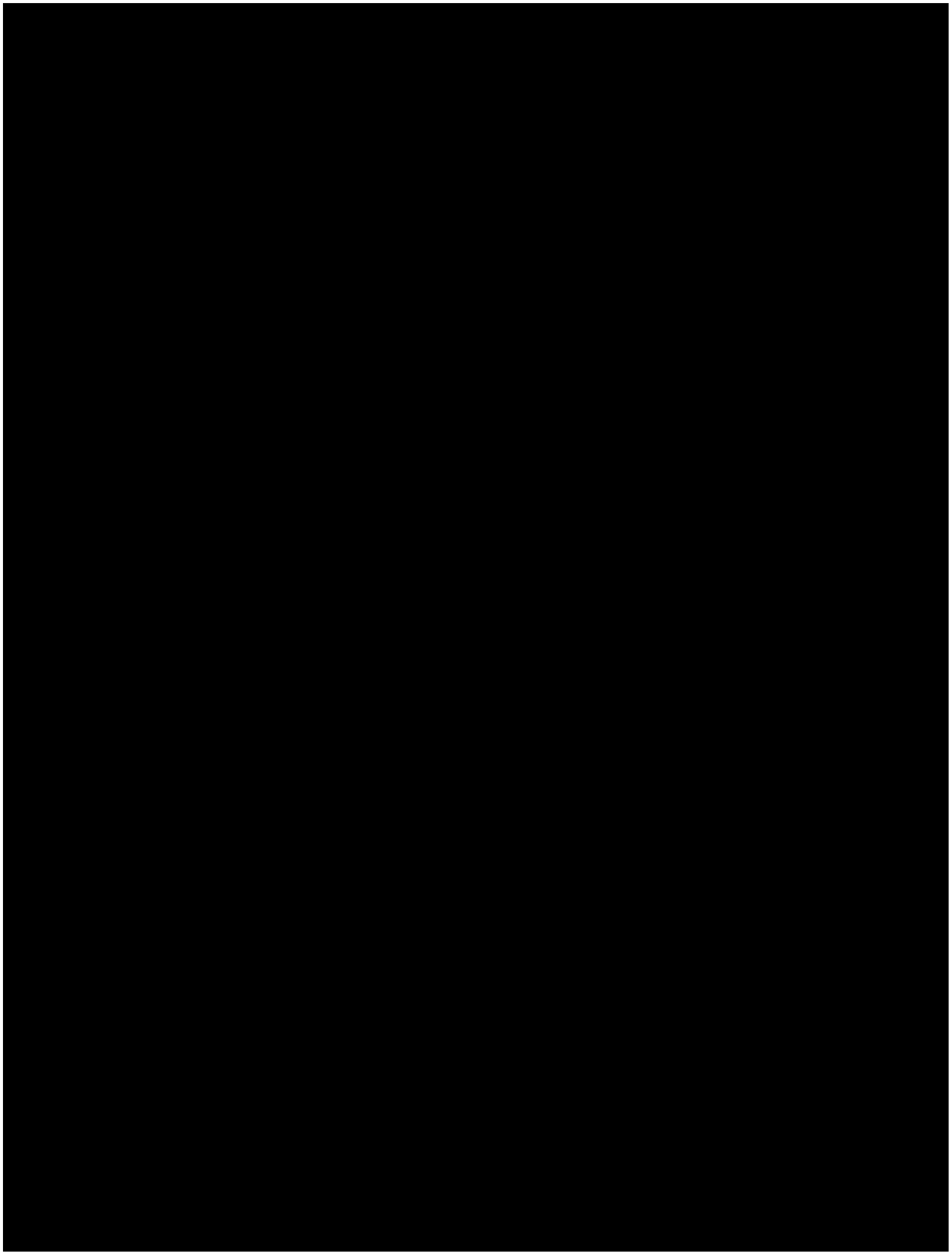
The severity of DG symptoms are assessed using a 0 to 10 numerical rating scale (NRS), on which 0 = "no" or "not at all uncomfortable" (ie, absence of the DG symptom) and 10 = "worst possible" or "most uncomfortable" (ie, worst experience of the DG symptom).

The overall assessment of the severity of non-vomiting symptoms is derived from the weekly DGSSS, as the sum of the weekly averages of the DGSSD items of nausea, abdominal pain, postprandial fullness, and bloating, calculated from a participant's daily DGSSD responses.

The range of DGSSS is 0-40 with the worst possible DGSSS for the 4 DG symptoms being 40, and the best possible DGSSS being 0. Psychometric analyses have shown that a decrease in the DGSSS by ≥ 8 points and a decrease in individual symptom scores by ≥ 2 points is recognized as a clinically meaningful improvement in DG symptoms by affected patients (Psychometric Evaluation, RTI Health, 2017). Further psychometric analyses will be conducted to confirm the clinically meaningful thresholds for improvement.

[redacted]





9.2 Adverse Events

The definitions of an AE or SAE can be found in Appendix 4.

AEs will be reported by the participant or noted by the investigator.

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or study procedures, or that caused the participant to discontinue the study treatment (see Section 8).

9.2.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the signing of the informed consent form (ICF) until 30 days after the final visit in the study (Visit 7) or Early Termination Visit at the time points specified in the SoA (Section 2). For rollover participants, ongoing AEs from lead-in Studies RLM-MD-01 and RLM-MD-02, and new AEs that occur after the signing of the ICF for RLM-MD-04 are considered to be AEs in RLM-MD-04.

Medical occurrences that begin before the start of study treatment but after obtaining IC (informed consent) will be recorded in the AE section of the eCRF and will be considered pretreatment AEs.

All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix 4. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

9.2.2 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

9.2.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs/SAEs and non-serious AEs of special interest ([AESI] as defined in Appendix 4) will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3). Further information on AE/SAE follow-up procedures is given in Appendix 4.

9.2.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, institutional review boards (IRBs)/independent ethics committees (IECs), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the investigator's brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.2.5 Pregnancy

- Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study treatment and until 7 days after the last dose.

- If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 5.

- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

9.2.6 Medical Device Incidents (Including Malfunctions)

Medical devices are being provided for use in this study for the purposes of study treatment self-administration. In order to fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of incident or malfunction that occur during the study with such devices.

The definition of a medical device incident can be found in Appendix 7.

NOTE: Incidents fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 9.2 and Appendix 4 of the protocol.

9.2.6.1 Time Period for Detecting Medical Device Incidents

- Medical device incidents or malfunctions of the device that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.

- If the investigator learns of any incident at any time after a participant has been discharged from the study, and such incident is considered reasonably related to a medical device provided for the study, the investigator will promptly notify the sponsor.

The method of documenting medical device incidents is provided in Appendix 7.

9.2.6.2 Follow-up of Medical Device Incidents

- All medical device incidents involving an AE will be followed and reported in the same manner as other AEs (see Section 9.2). This applies to all participants, including those who discontinue study treatment or the study.

- The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the incident.

- New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

9.2.6.3 Prompt Reporting of Medical Device Incidents to Sponsor

- Medical device incidents will be reported to the sponsor within 24 hours after the investigator determines that the event meets the protocol definition of a medical device incident.

9.2.6.4 Regulatory Reporting Requirements for Medical Device Incidents

- The investigator will promptly report all incidents occurring with any medical device provided for use in the study in order for the sponsor to fulfill the legal responsibility, if needed, to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

- The investigator, or responsible person according to local requirements (eg, the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of incidents to the IRB/IEC.

9.2.7 Adverse Events of Special Interest

9.2.7.1 Hy's Law

Study site personnel must report every participant who meets Hy's Law criteria, which are as follows:

- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $\geq 3 \times$ upper limits of normal (ULN) AND

- Total bilirubin $\geq 2 \times$ ULN AND

- Alkaline phosphatase $< 2 \times$ ULN

Typically, all analytes will be obtained from the same sample, but they may come from multiple samples taken within a 24-hour period. This requirement applies from the time the participant signs the ICF for the study until 30 days after the final protocol-defined study visit or the last known dose of study treatment (if the final visit does not occur).

A laboratory alert for Hy's laws cases will be in place. Investigators and the sponsor must be immediately notified when the above criteria have been met. [redacted] Every effort to determine the cause of the liver enzyme abnormalities must be made, and close monitoring should be initiated in conjunction with the MSP and in accordance with the FDA Guidance for Industry, Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009.

Additional details regarding liver safety assessments and follow up are provided in Appendix 6.

9.2.7.2 Inadequate Control of Diabetes: Hyperglycemia and Hypoglycemia

The irregular and delayed emptying of the stomach in DG has a major effect on the presentation of ingested carbohydrate to the small intestine for absorption, complicating the dosing of hypoglycemic agents (including insulin) used to manage glycemia. Participants should be closely monitored for changes to their diabetes control while in the study, and events related to hyperglycemia or hypoglycemia that are considered to be clinically significant should be reported as AEs (Section 9.2.1).

9.2.7.3 Major Adverse Cardiovascular Events

Patients with DG typically have long-standing diabetes mellitus, which predisposes them to develop macrovascular (and microvascular) complications. These include Major Adverse Cardiovascular Events (MACE) commonly defined as death from cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke, and often also including revascularization (coronary or peripheral) procedures, and hospitalization for unstable angina pectoris.

In this study, occurrence of any of these events should be reported to the MSP within 24 hours of being made aware on the SAE form, followed by a complete report including narrative description of the event, test results, and copies of hospital records, if applicable. All reports of possible MACE will be adjudicated internally in a blinded fashion by a committee of qualified physicians on a periodic basis depending on the frequency of reported events. The functioning of the committee will be governed by charter.

9.2.8 Medication Errors

Medication error refers to any unintended error in the dosing and/or administration of the study treatment as per instructions in the protocol. Medication errors generally fall into 4 categories as follows:

- Wrong study drug/device
- Wrong dose (including dosing regimen, strength, form, concentration, amount)
- Wrong route of administration
- Wrong participant (ie, not administered to the intended participant)

Medication errors include occurrences of overdose and underdose of the study treatment.

Overdose: Unintentional administration of a quantity of the study treatment given per administration or per day that is above the maximum recommended dose (10 µg BID or 20 µg/day) according to the reference safety information or protocol for the study treatment or comparator as applicable. This also takes into account cumulative effects due to overdose.

Underdose: Unintentional administration of a quantity of the study treatment given per administration or per day that is under the minimum recommended dose according to the reference safety information or protocol. Since there is no clinical information on the efficacy of relamorelin at a dose less than 10 µg BID, a dose of 10 µg once daily should be considered an underdose.

9.3 Treatment of Overdose

The sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the MSP immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities until study treatment can no longer be detected systemically.
3. Document the quantity of the excess dose as well as the duration of the overdose in the site's source documents for the participant.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the MSP based on the clinical evaluation of the participant.

9.4 Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA (Section 2).

9.4.1 Physical Examinations

Complete physical examinations (excluding pelvic exam in women and genital exam in men, and rectal exam in both genders) are to be performed. Symptom-directed (abbreviated) physical examinations, including evaluation of the injection sites for clinically significant reactions, may be conducted as required at other study visits.

Participants should be weighed with no shoes, in light clothing, without any outerwear. Height should be measured only at the first study visit (at Visit 1 of lead-in Studies RLM-MD-01 or RLM-MD-02 for rollover participants; at Visit –2 of RLM-MD-04 for de novo participants).

Any abnormality noted on the physical examination done at Visit 7 or the early termination visit that was not present on the physical examination at screening should be reported as an AE if considered by the investigator to be clinically significant.

9.4.2 Vital Signs

- Heart rate (HR), respiratory rate, systolic and diastolic blood pressure (BP), and temperature will be assessed; the method for measuring temperature will be per the site's preference
- BP and HR measurements will be assessed in the sitting position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- BP and HR measurements should be preceded by at least 3 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).
- Vital signs are to be taken before blood collection for laboratory tests.

9.4.3 Electrocardiograms

- Single12-lead ECG will be obtained as outlined in the SoA (see Section 2) using an ECG machine that automatically calculates the HR and measures PR, QRS, QT, and QTc intervals. Refer to Section 8.1 for QTc withdrawal criteria.

9.4.4 Clinical Safety Laboratory Assessments

- See Appendix 2 for the list of clinical laboratory tests to be performed and refer to the SoA for the timing and frequency.

- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study treatment should be repeated until the values return to normal or baseline, or are no longer considered clinically significant by the investigator or MSP.

    - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

    - All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the schedule of activities.

    - If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the eCRF.

9.4.5 Self-monitoring of Blood Glucose

Participants will be strongly encouraged to carry out self-monitoring of blood glucose (SMBG) at home in order to achieve and maintain optimum glucose control during the study. This is almost always required by patients with T1DM and is good clinical practice in patients with T2DM. At the start of the Run-in Period, the Sponsor will provide each roll-over and de novo participant with a glucose monitor, test strips, and all supplies necessary for testing finger-stick capillary blood glucose throughout the study. It is recommended that this be done twice daily, pre-breakfast (fasting) and approximately 2 hours post-lunch or dinner (whichever is the larger meal).

Information from SMBG, in addition to that provided by values of HbA1c and fasting blood glucose, will be available to investigators for decision-making regarding adjustment of diabetic medications, diet, and exercise (or, alternatively, for decision-making regarding referral of the participant to his/her health care provider for the same purpose).

9.5 Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

9.6 Pharmacodynamics

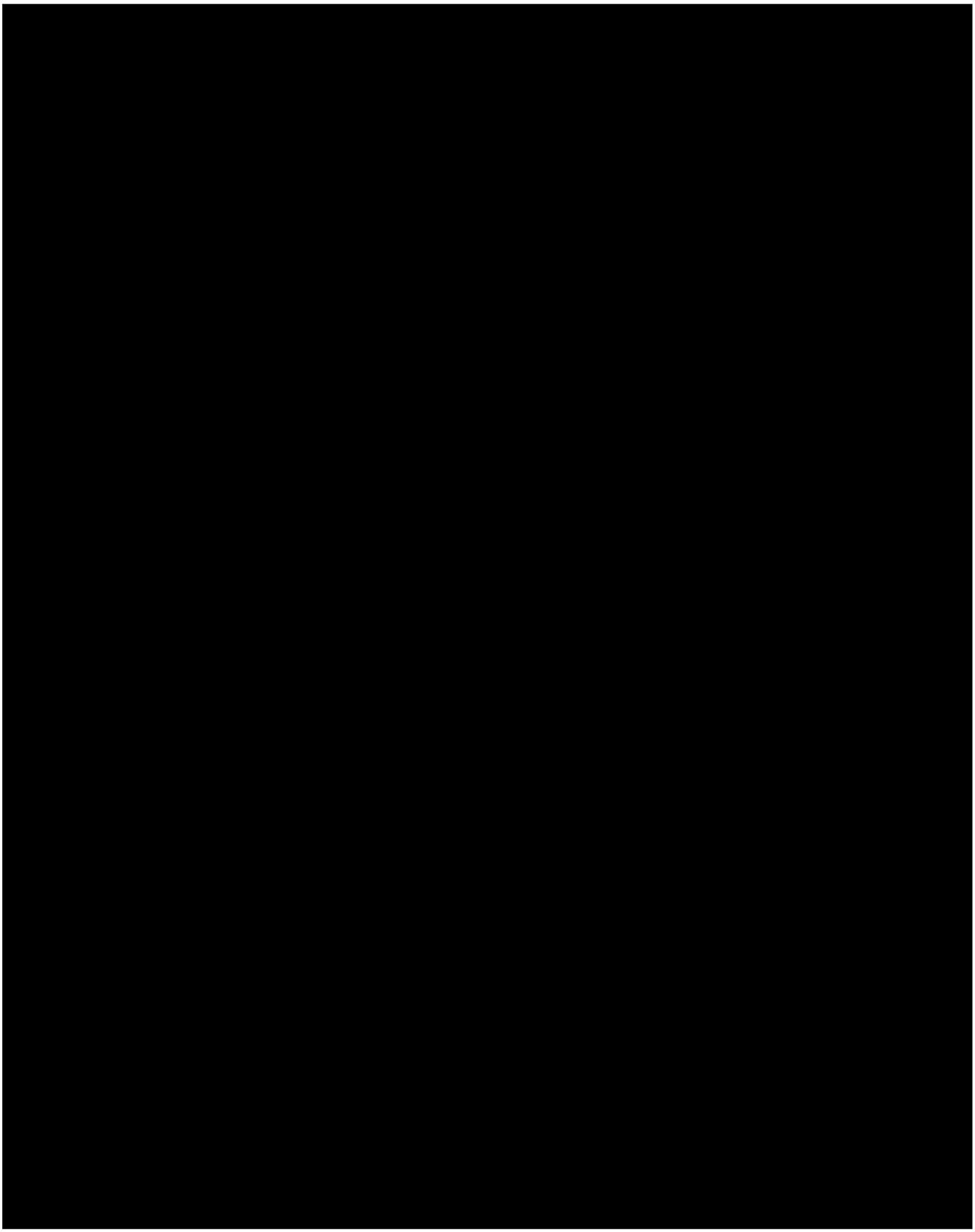
Pharmacodynamic parameters are not evaluated in this study.

9.7 Genetics

Genetics are not evaluated in this study.

9.8 Biomarkers

Biomarkers are used in the study only to help characterize the diabetes mellitus of individual participants as either type 1 or type 2.



10 Statistical Considerations

10.1 Sample Size Determination

There were no extensive sample size calculations performed formally for this study. A sample size of approximately 600 participants (with randomization ratio treatment to placebo of 2:1) will provide 90% power to detect a statistically significant difference in response rate from placebo in both the 4-symptom composite DGSSS endpoint (assuming a placebo rate of 14% and a treatment rate of 35%) and in the vomiting response endpoint (assuming a placebo rate of 11% and a treatment rate of 26%). Assumed response rates were those calculated from Study RM-131-009.

10.2 Populations for Analyses

The analysis populations will consist of participants as defined in Table 10–1.

Table 10–1 Analysis Populations

Population	Definition
Screened	All participants who sign informed consent
Intent-to-treat (ITT)	All randomized participants
Modified intent-to-treat (mITT)	All randomized participants with ≥ 1 postbaseline assessment of DGSSD
Safety	All participants who received ≥ 1 administration of study treatment

10.3 Statistical Analyses

The statistical analysis plan (SAP) will be developed and finalized before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing data. This section is a summary of the planned statistical analyses of the key endpoints.

10.3.1 Key Statistical Methodology

The methodologies defined in Table 10–2 apply as specified to individual endpoints defined in the SAP. All statistical tests will be 2-sided hypothesis tests performed at the 5% level of significance for main effects. All CIs will be 2-sided 95% CIs, unless stated otherwise.

Table 10–2 Statistical Methodology

Methodology	Description
Categorical counts	• Number of participants in individual categories o Participants with ≥ 1 qualifying event counted once per individual category
Categorical descriptives	• Number and percentage of participants in individual categories o Participants with ≥ 1 qualifying event counted once per individual category • N1 if percentage denominator ≠ number of participants in the population (standard percentage denominator) o N1 = participants with nonmissing baseline value
Continuous descriptives	• N1, mean, SD, median, minimum, maximum • N1 = participants with nonmissing value
CFB descriptives	• Continuous descriptives for baseline, postbaseline, and change from baseline (CFB) values • N1 = participants with nonmissing values at both baseline and the specified postbaseline analysis visit
CFB MMRM	• Continuous descriptives and standard error (SE) for baseline, postbaseline, and CFB values o Estimates derived from mixed model for repeated measures (MMRM) for CFB value controlling for factors (treatment group, site) and covariates (baseline value) ▪ Least squares (LS) means and standard errors ▪ LS mean differences, standard errors, and CIs vs placebo ▪ P-values from contrast t-test comparing treatment group vs placebo • N1 = participants with nonmissing values at both baseline and the specified postbaseline analysis visit

10.3.2 Efficacy Analyses

10.3.2.1 Key Endpoints

Table 10–3 displays the key efficacy endpoints that will be analyzed for the mITT population. All other efficacy endpoints and analyses will be defined in the SAP.

Table 10–3 Key Endpoints

Key Endpoints	Description	Timing	Methodology
Key Endpoints			
CFB to Week 12 in weekly DGSSS	Change from baseline to Week 12 in weekly DGSSS	Week 12	CFB MMRM
CFB to Week 52 in weekly average DGSSS	Change from baseline in average of the weekly average DGSSS from Weeks 49 to 52	Week 49-Week 52	CFB MMRM

10.3.2.2 Missing Data

Handling of missing data will be provided in the SAP.

10.3.3 Safety Analyses

All safety analyses will be performed on the Safety Population.

The following safety categories will be summarized as appropriate (eg, categorical or continuous descriptives, shift tables) for the safety population and will be fully defined in the SAP.

- AEs
    - Clinically significant hyperglycemia- and hypoglycemia-related events
- Clinical laboratory assessments
    - Hy's law cases
- Vital signs
- ECGs
- Study-specific assessments
    - HbA1c

[redacted]

10.3.5 Interim Analyses

In addition to the above, monitoring of participant safety data will be performed by an independent Data and Safety Monitoring Board (DSMB). The DSMB will review interim safety data at defined intervals throughout the study. The DSMB will communicate their recommendations to the Sponsor after each meeting, but will serve in an advisory capacity only; the Board will not be empowered to stop the study or require changes to the protocol. Study conduct may be interrupted or terminated by the Sponsor based on DSMB recommendations if safety data become available that appear to represent an undue risk to the study participants' health or well being. Further details of the DSMB (composition, policy, and procedures) are specified in a separate DSMB charter.

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All references are available upon request.

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12 Appendices

12.1 Appendix 1: Abbreviations and Trademarks

ADA	anti-drug antibodies
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BID	twice daily
BMI	body mass index
BP	blood pressure
[redacted]	
CDER	Center for Drug Evaluation and Research
CFB	change from baseline
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting
CSR	clinical study report
DG	diabetic gastroparesis
DGSSD	Diabetic Gastroparesis Symptom Severity Diary
DGSSS	Diabetic Gastroparesis Symptom Severity Score
DILI	drug-induced liver injury
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram

eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
FDA	US Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
[redacted]	
GE	gastric emptying
GEBT	gastric emptying breath test
GERD	gastroesophageal reflux disease
GHS1α	Growth Hormone Secretagogue 1 α
GI	gastrointestinal
GLP-1	glucagon-like peptide-1
GP	gastroparesis
HbA1c	glycosylated hemoglobin A1c
HEOR	health economic outcomes research
HIPAA	Health Insurance Portability and Accountability Act
HR	heart rate
HRT	hormonal replacement therapy
ICF	informed consent form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IGF-1	insulin-like growth factor-1

IND	Investigational New Drug Application
INR	international normalized ratio
IRB	Institutional Review Board
IWRS	interactive web response system
MACE	Major Adverse Cardiovascular Events
MAR	missing at random
mITT	modified intent-to-treat
MMRM	mixed model for repeated measures
MSP	medical safety physician
NRS	numerical rating scale
[redacted]	
QTcB	QT interval corrected for heart rate using the Bazett formula
QTcF	QT interval corrected for heart rate using Fridericia formula
RLM	relamorelin
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous(ly)
SF-12v2	12-item Short Form Survey (version 2)
SGLT-2	Sodium glucose co-transporter 2
SMBG	self-monitoring of blood glucose
SoA	Schedule of Activities

SUSAR	suspected unexpected serious adverse reaction
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
ULN	upper limits of normal
US	United States of America
WOCBP	women of childbearing potential

12.2 Appendix 2: Clinical Laboratory Tests

- All clinical laboratory tests should be done after participants have fasted for at least 8 hours
- The tests detailed in Section 9.4.4 will be performed by the central laboratory
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Sections 6.1 and 6.2 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Investigators must document their review of each laboratory safety report.

Table 12–1 Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet count RBC count Hemoglobin Hematocrit	RBC indices: MCV MCH MCHC % Reticulocytes	WBC count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry	BUN Creatinine eGFR Fasting blood glucose[a] Hemoglobin A1c	Potassium Chloride Bicarbonate Sodium Calcium Phosphorus Uric acid	Aspartate aminotransferase (AST)[b] Alanine aminotransferase (ALT)[b] Alkaline phosphatase[b]	Total and direct bilirubin[b] Total protein Albumin Lipid profile (cholesterol, triglycerides, HDL cholesterol, LDL cholesterol (calculated)
Other Laboratory Assessments	C-peptide Anti-relamorelin antibodies	GADA (GAD 65) IA-2A ZnT8		
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• Serum and urine human chorionic gonadotropin (hCG) pregnancy test ([at Visit -2 and Visit 1, respectively, and as noted in the SoA] as needed for women of childbearing potential) • Urine drug screen (to include at a minimum: amphetamines, barbiturates, benzodiazepines, cocaine, cannabinoids, phencyclidine, and opiates[c]) at Screening Visit,			

BUN = blood urea nitrogen, eGFR = estimated glomerular filtration rate, GADA = glutamic acid decarboxylase autoantibodies, IA-2A = islet antigen–2 antibodies, MCV = mean corpuscular volume, MCH = mean corpuscular hemoglobin, MCHC = mean corpuscular hemoglobin concentration, RBC = red blood cell, WBC = white blood cell, ZnT8 = zinc transporter 8.

[a] Serum for all visits except for Visits 4 and 6

[b] Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Appendix 6.

[c] Screening for drugs of abuse will be conducted using a urine drug screen at Visit -2.

Investigators must document their review of each laboratory safety report.

12.3 Appendix 3: Study Governance Considerations

12.3.1 Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
    - Applicable ICH Good Clinical Practice (GCP) guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, investigator's brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
    - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
    - Providing oversight of the overall conduct of the study at the site and adherence to requirements of applicable local regulations, for example 21 CFR, ICH guidelines, the IRB/IEC, and European regulation 536/2014 for clinical studies (if applicable)

12.3.2 Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are

responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

12.3.3 Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Written documentation must be obtained in accordance with the relevant country and local privacy requirements, where applicable (eg, Written Authorization for Use and Release of Health and Research Study Information [US sites] and written Data protection Consent [European sites]).
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant.

Additionally, in accordance with relevant country requirements, written informed consent is to be obtained from each participant prior to enrollment into the study. The informed consent form includes explanation of the following:

1. That the study involves research
2. The objectives of the study
3. The study procedures
4. The expected duration of the participant's participation in the study
5. The approximate number of participants involved in the study

6. The reasonably foreseeable risks or inconveniences to the participant

7. The alternative procedures or courses of treatments that may be available to the participant, and their important potential benefits and risks

8. The compensation and/or treatment available to the participant in the event of study-related injury

9. That the participant's participation in the study is voluntary and that the participant may refuse to participate or withdraw from the study at any time, without penalty or loss of benefits to which the participant is otherwise entitled

10. That the participant will be informed in a timely manner if information becomes available that may be relevant to the participant's willingness to continue participation in the study

11. The foreseeable circumstances and/or reason under which the participant's participation in the study may be terminated

12. That the monitors, auditors, the IRB, and the regulatory authorities may provide direct access to the participant's original medical records. In such cases, the confidentiality of the participant should be protected, and by signing and sealing an informed consent form, the participant is authorizing such access.

13. If the results of the study are published, the participant's identity will remain confidential.

14. The anticipated expenses, if any, to the participant for participating in the study

15. The anticipated prorated payment, if any, to the participant for participating in the study

16. The name, title, and address of the investigator to contact

17. The person(s) to contact for further information regarding the clinical study and the rights of participants, and whom to contact in the event of study-related injury

18. The type of the IRB engaged in the assessment and deliberation about the acceptability of the study, items subject to the assessment of each IRB, and other IRB-related items relating to the study

19. The participant's responsibilities

12.3.4 Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

12.3.5 Data Quality Assurance

- All participant data relating to the study will be recorded on electronic CRFs unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator as stated in the clinical trial agreement. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. Source Documents

12.3.6 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

12.3.7 Study and Site Closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines

- Inadequate recruitment of participants by the investigator

- Discontinuation of further study treatment development

12.3.8 Publication Policy

- Allergan as the sponsor has proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between the investigator or multiple investigators and sites and Allergan personnel. Authorship will be established prior to the writing of the

manuscript. As this study involves multiple centers, no individual publications will be allowed prior to completion of the final report of the multicenter study except as agreed with Allergan.

- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In the case of a multicenter study, a coordinating investigator will be designated by mutual agreement.

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

12.4 Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.

AE of Special Interest (AESI)

An adverse event of special interest (AESI) (serious or nonserious) is one of scientific and medical concern specific to the sponsor's study drug/device or program, which warrants ongoing monitoring and rapid communication by the investigator to the sponsor. Such an event might warrant further investigation in order to characterize and understand it.

The following AESIs have been identified for the study interventions in this protocol (see also Section 9.2.7):

1. Hy's law cases
2. Inadequate control of diabetes: hyperglycemia and hypoglycemia
3. MACE

Serious AESIs should be reported to the sponsor within 24 hours via the SAE form.

[redacted]

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease) • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition • New condition detected or diagnosed after study treatment administration even though it may have been present before the start of the study • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition • The disease/disorder being studied or expected progression, signs, or symptoms (clearly defined) of the disease/disorder being studied, unless more severe than expected for the participant's condition • The following events are considered to be manifestations of diabetic gastroparesis and will be captured in the DGSSS, but will not be reported as AEs or SAEs: nausea,

abdominal pain, upper abdominal pain, vomiting, postprandial fullness, bloating, early satiety. If the investigator considers these manifestations to have a reasonable possibility of relationship to the study drug/device(s) then they should be reported as AEs or SAEs

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen

Definition of SAE
If an event is not an AE per the definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life threatening

The term *life threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.

- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording an AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

- The investigator will then record all relevant AE/SAE information in the eCRF.

- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE/SAE CRF page.

- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

MILD	A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
MODERATE	A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
SEVERE	A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

An event is defined as *serious* when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the investigator's brochure (IB) and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal

information to include in the initial report to the Sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.**

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the Sponsor with a copy of any post-mortem findings including histopathology
- New or updated information will be recorded in the originally completed eCRF
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information

Reporting of SAEs

SAE Reporting to the Sponsor via e-mail, fax, or telephone

- Email is the preferred method for transmission of SAE information to the Sponsor.

[redacted]

- Facsimile transmission of SAE information is also acceptable.

[redacted]

- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable, with a copy of the SAE form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to

complete and sign the SAE form within the designated reporting time frames.

- Contacts for SAE reporting can be found in the Study Reference Manual.

12.5 Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).
Women in the following categories are not considered WOCBP:

1. Premenarchal
2. Premenopausal female with 1 of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

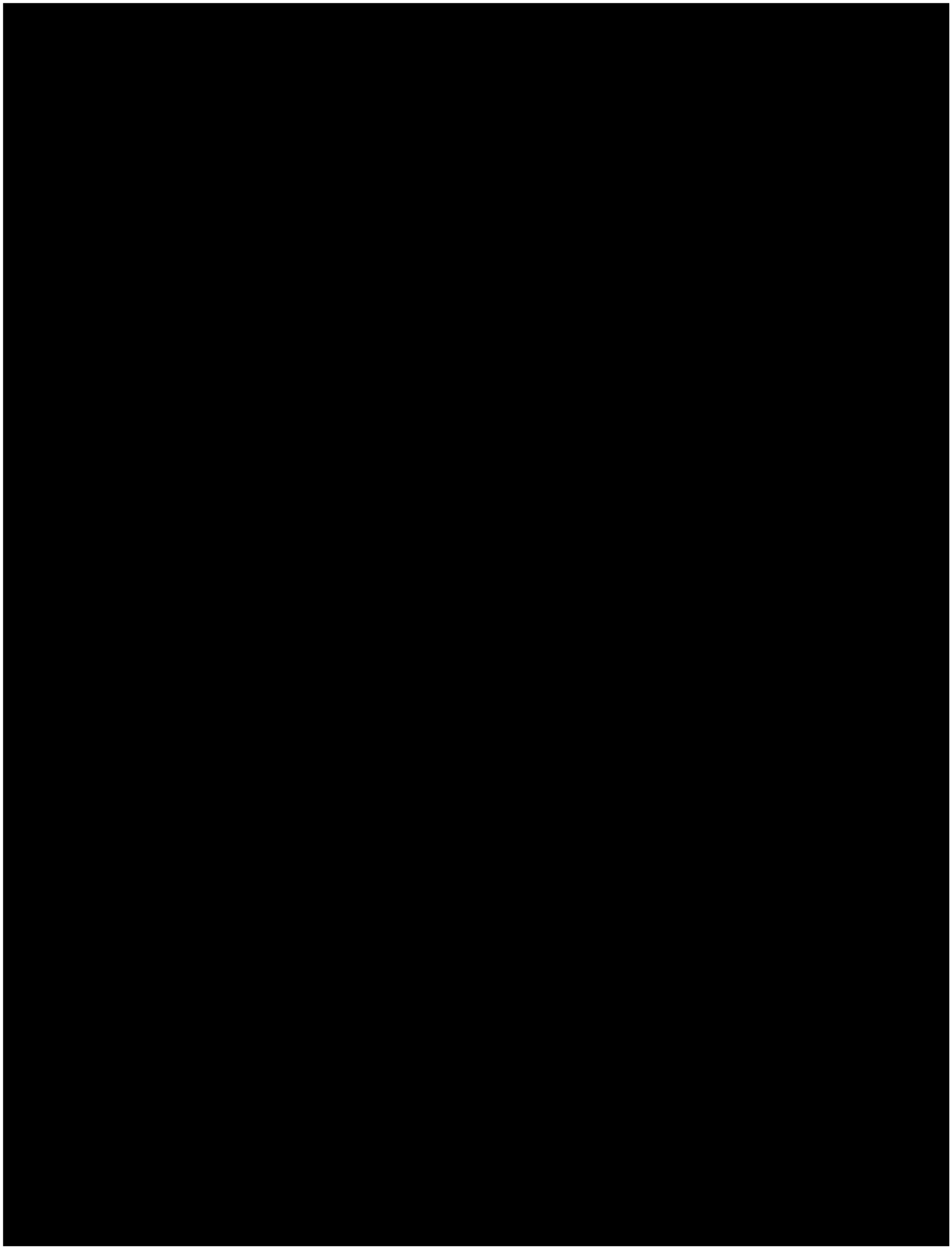
Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

[redacted]



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12.6 Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments

Hy's law cases are considered AESIs. Hy's Law criteria are as follows:

- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 3 × upper limits of normal (ULN)
- AND Total bilirubin ≥ 2 × ULN
- AND Alkaline phosphatase < 2 × ULN

[redacted]

Investigational product must be discontinued if any of the following criteria are met:

- ALT or AST ≥ 3 × ULN and the participant is symptomatic with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia (> 5%)
- ALT or AST ≥ 3 × ULN and total bilirubin > 2 × ULN or INR > 1.5 x ULN
- ALT or AST ≥ 5 × ULN for more than 2 weeks
- ALT or AST ≥ 8 × ULN

The participant may be re-challenged with study treatment only after consultation with the Allergan MSP. For participants who are not re-challenged with study treatment, the participant should be discontinued from the study and complete the Early Termination Visit. Participants should receive appropriate follow-up as per standard of care.

Hy's Law Cases

Sites must report every subject who meets the following Hy's law criteria if this occurs within the time the subject signs the ICF until 30 days after the last dose of study treatment.

A laboratory alert for Hy's laws cases will be in place, and the investigators and Allergan will be notified immediately when the above criteria have been met. Any Hy's laws case should be considered an SAE and also reported as an AE of Special Interest.

[redacted] Every effort to determine the cause of the liver abnormalities must be made, and close monitoring should be initiated in conjunction with the Allergan medical monitor and in accordance with the FDA "Guidance for Industry: Drug Induced Liver Injury - Pre-Marketing Clinical Evaluation" July 2009.

12.7 Appendix 7: Medical Device Incidents: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definitions of a Medical Device Incident

The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study (see Section 7.1 for the list of sponsor medical devices).

Medical Device Incident Definition
• A medical device incident is any malfunction or deterioration in the characteristics and/or performance of a device as well as any inadequacy in the labelling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a participant/user/other person or to a serious deterioration in his/her state of health. • Not all incidents lead to death or serious deterioration in health. The non-occurrence of such a result might have been due to other fortunate circumstances or to the intervention of health care personnel.

It is sufficient that:

- An **incident** associated with a device happened

  AND

- The **incident** was such that, if it occurred again, might lead to death or a serious deterioration in health.

A serious deterioration in state of health can include any of the following:

- Life-threatening illness
- Permanent impairment of body function or permanent damage to body structure
- Condition necessitating medical or surgical intervention to prevent one of the above
- Fetal distress, fetal death, or any congenital abnormality or birth defects

Examples of Incidents

- A participant, user, caregiver, or healthcare professional is injured as a result of a medical device failure or its misuse.
- A participant's study treatment is interrupted or compromised by a medical device failure.
- A misdiagnosis due to medical device failure leads to inappropriate treatment.
- A participant's health deteriorates due to medical device failure.

Documenting Medical Device Incidents

[redacted]

12.8 Appendix 8: Standard Discontinuation Criteria

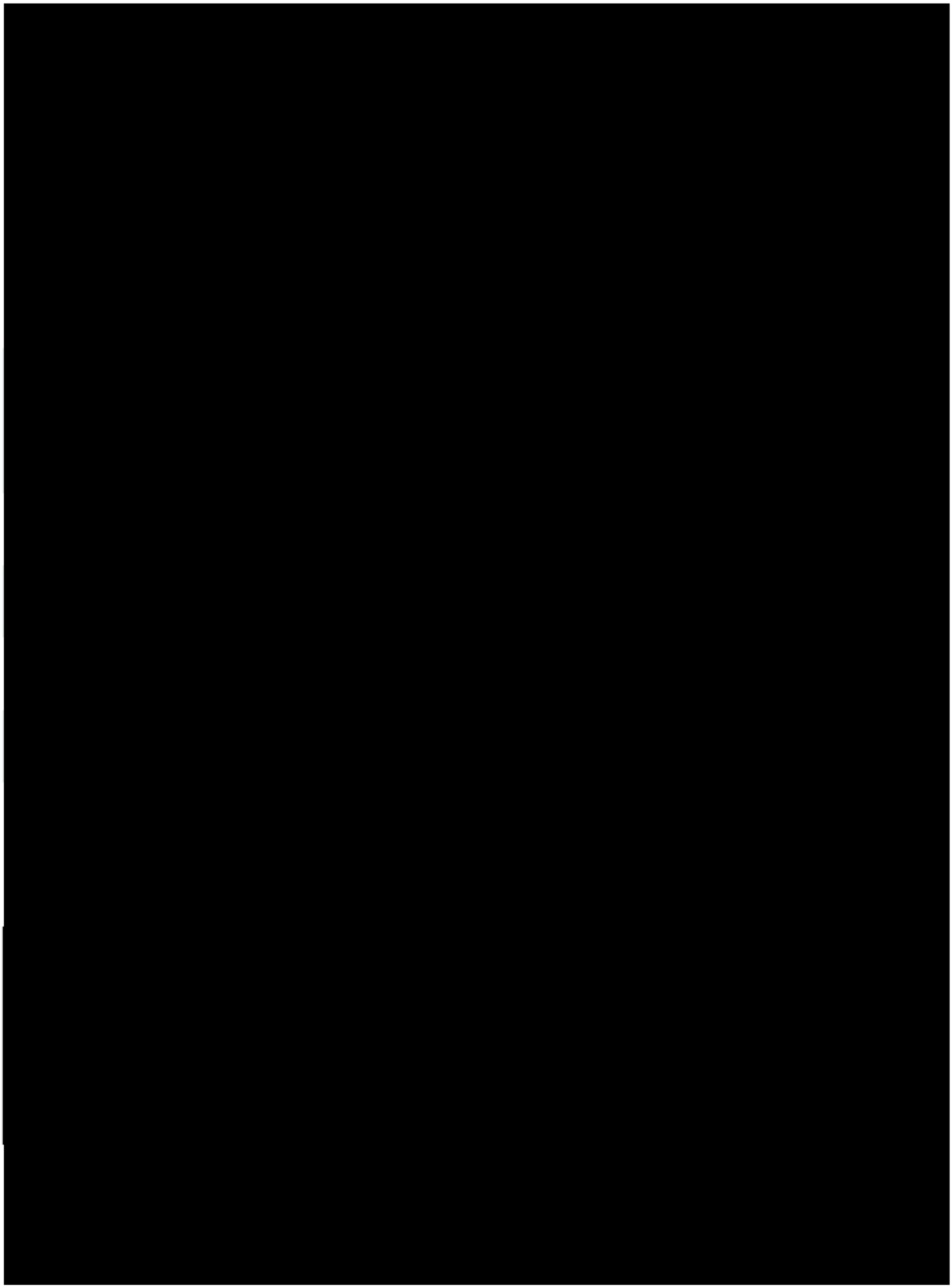
CDISC Submission Value	CDISC Definition
Adverse event	Any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. For further information, see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting. [Modified from ICH E2A] Synonyms: side effect, adverse experience. See also serious adverse event, serious adverse experience. (CDISC glossary)
Completed	To possess every necessary or normal part or component or step; having come or been brought to a conclusion (NCI)
Death	The absence of life or state of being dead (NCI)
Failure to meet randomization criteria	An indication that the subject has been unable to fulfill/satisfy the criteria required for assignment into a randomized group
Lack of efficacy	The lack of expected or desired effect related to a therapy (NCI)
Lost to follow-up	The loss or lack of continuation of a subject to follow-up
Other	Different than the one(s) previously specified or mentioned (NCI)
Investigator decision	A position, opinion or judgment reached after consideration by a physician with reference to subject (NCI)
Pregnancy	Pregnancy is the state or condition of having a developing embryo or fetus in the body (uterus), after union of an ovum and spermatozoon, during the period from conception to birth. (NCI)
Protocol deviation	An event or decision that stands in contrast to the guidelines set out by the protocol (NCI)
Screen failure	The potential subject who does not meet one or more criteria required for participation in a study
Site terminated by sponsor	An indication that a clinical study was stopped at a particular site by its sponsor (NCI)
Study terminated by sponsor	An indication that a clinical study was stopped by its sponsor (NCI)
Withdrawal by participant	An indication that a study participant has removed itself from the study (NCI)

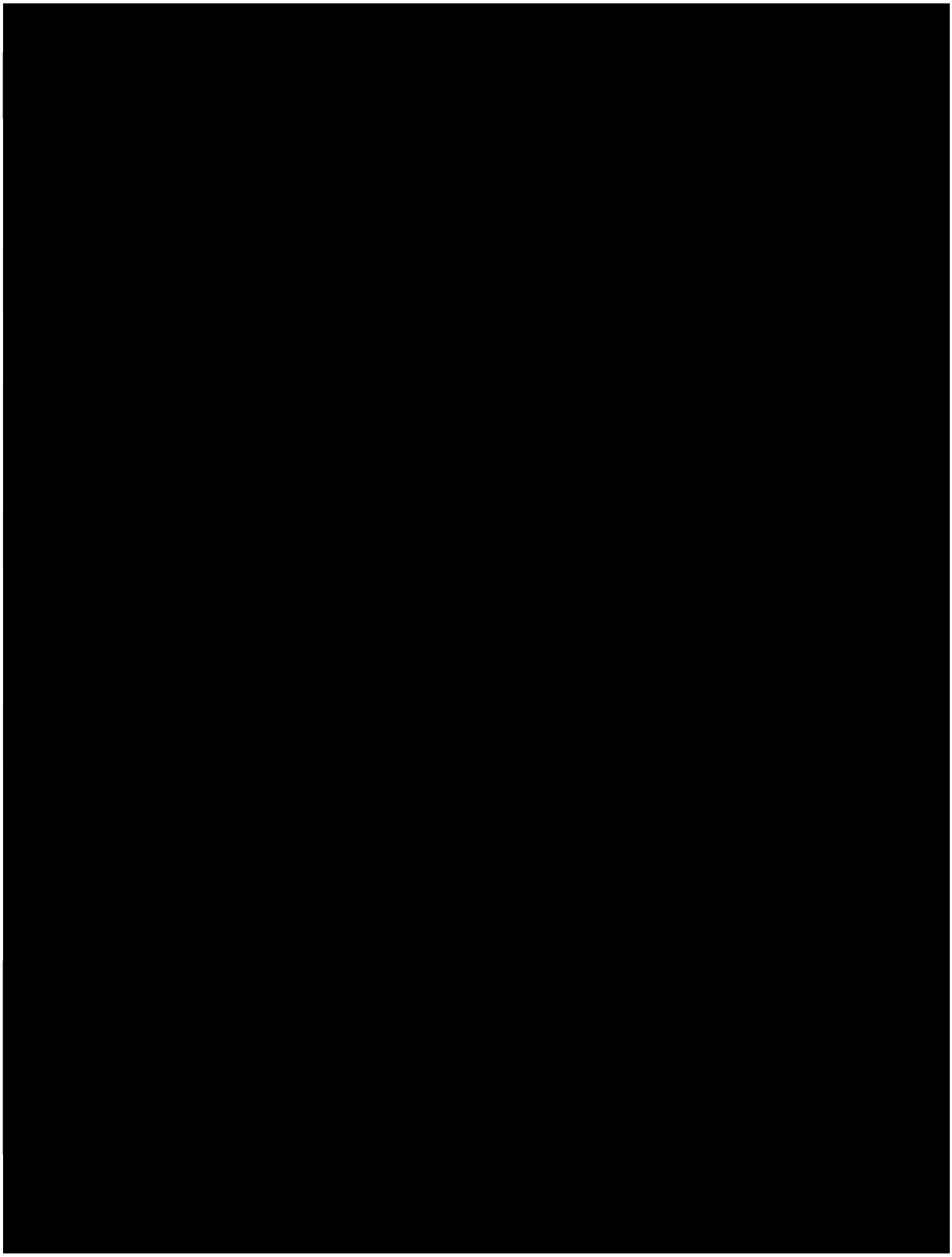
12.9 Appendix 9: Study Tabular Summary

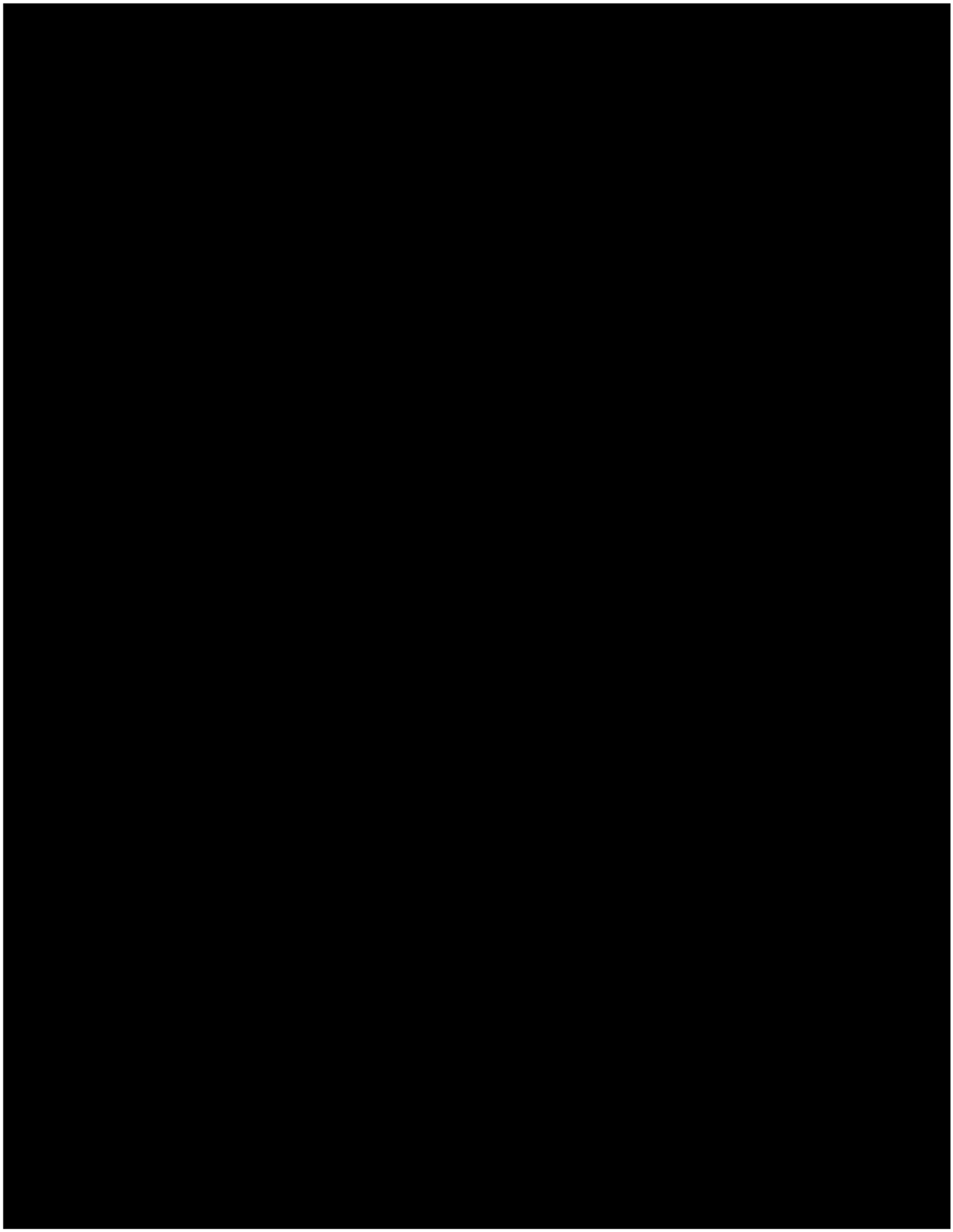
Parameter Group	Parameter	Value
Study information	Study Title	A 52-week, Randomized, Double-blind, Placebo-controlled, Phase 3 Study to Evaluate the Safety and Efficacy of Relamorelin in Patients with Gastroparesis
	Clinical Study Sponsor	Allergan Sales
	Study Phase Classification	Phase 3 Study
	Study Indication	Diabetic gastroparesis
	Study Indication Type	Treatment
	Study Type	Efficacy Safety
	Study Length	Up to 58 weeks, consisting of a 4-week Screening Period, 2-week Run-in Period, and a 52-week Treatment Period
	Planned Country of Investigational Sites	Global
	Planned Number of Subjects	Approximately 5000 participants will be screened in studies RLM-MD-01 and RLM-MD-02. Participants who screen fail those studies for certain reasons (see below) may enter this study to achieve 600 participants assigned to study treatment (400 to relamorelin and 200 to placebo). A total of 300 participants are expected to complete the study (200 relamorelin- and 100 placebo-treated participants).
	FDA-Regulated Device Study Indicator	No
	FDA-Regulated Drug Study Indicator	No
	Pediatric Study Indicator	No
Subject information	Diagnosis Group	Diabetes mellitus
	Healthy Subject Indicator	No
	Planned Minimum Age of Subjects	18
	Planned Maximum Age of Subjects	none
	Sex of Participants	Both
	Stable Disease Minimum Duration	3 months

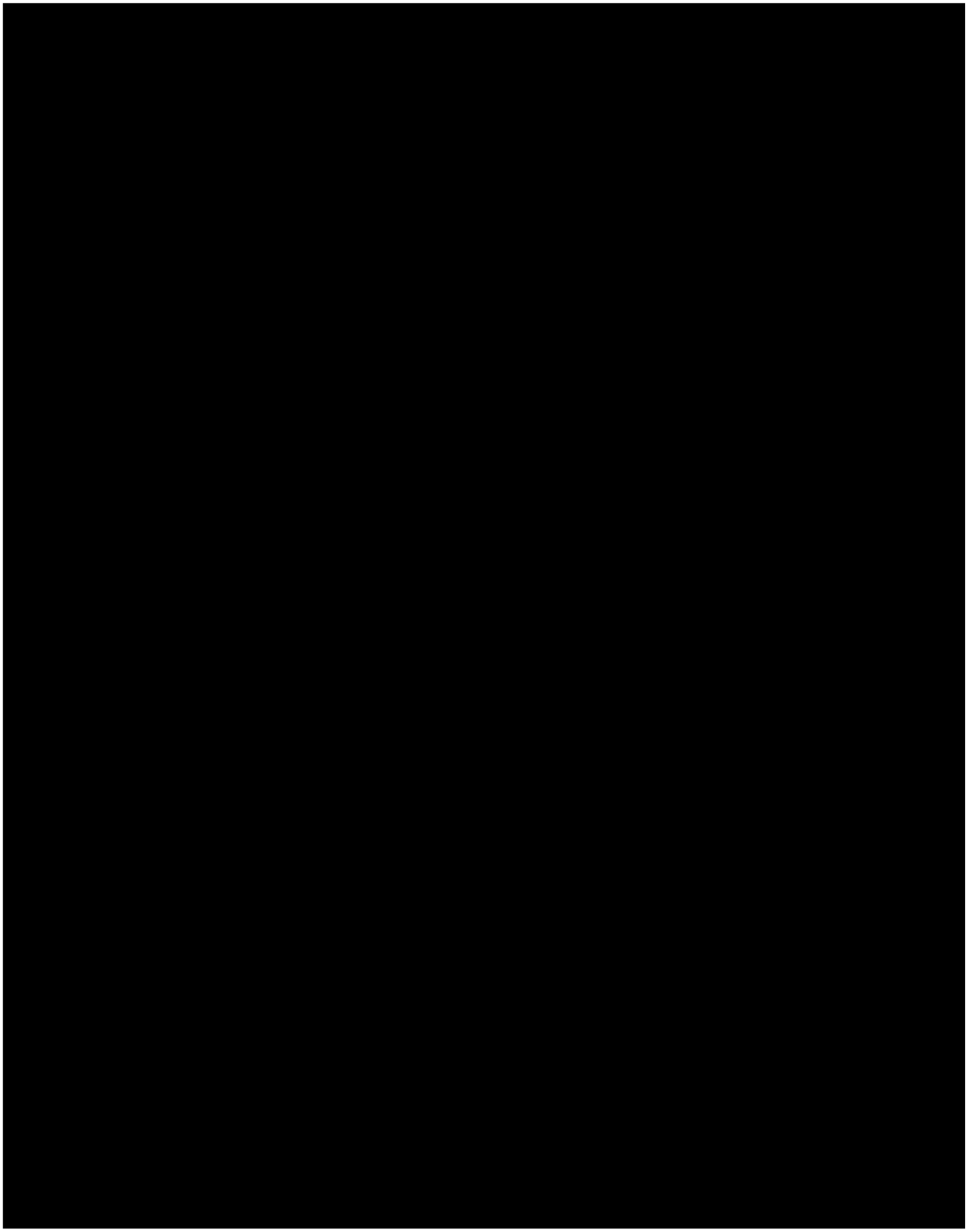
Parameter Group	Parameter	Value
Treatments	Investigational Therapy or Treatment	relamorelin
	Intervention Type	drug
	Pharmacological Class of Invest. Therapy	synthetic ghrelin analogue
	Dose per Administration	10 µg
	Dose Units	Pre-Filled Cartridge in Multi-dose Pen Injector
	Dosing Frequency	twice daily
	Route of Administration	subcutaneous injection
	Current Therapy or Treatment	treatment
	Added on to Existing Treatments	No
	Control Type	Placebo
	Comparative Treatment Name	none
Study design	Study Type	Interventional
	Intervention Model	Parallel
	Planned Number of Arms	2
	Study is Randomized	yes
	Randomization Quotient	2 : 1
	Study Blinding Schema	Double-blind
	Stratification Factor	Not applicable
	Adaptive Design	No
	Study Stop Rules	Not stated

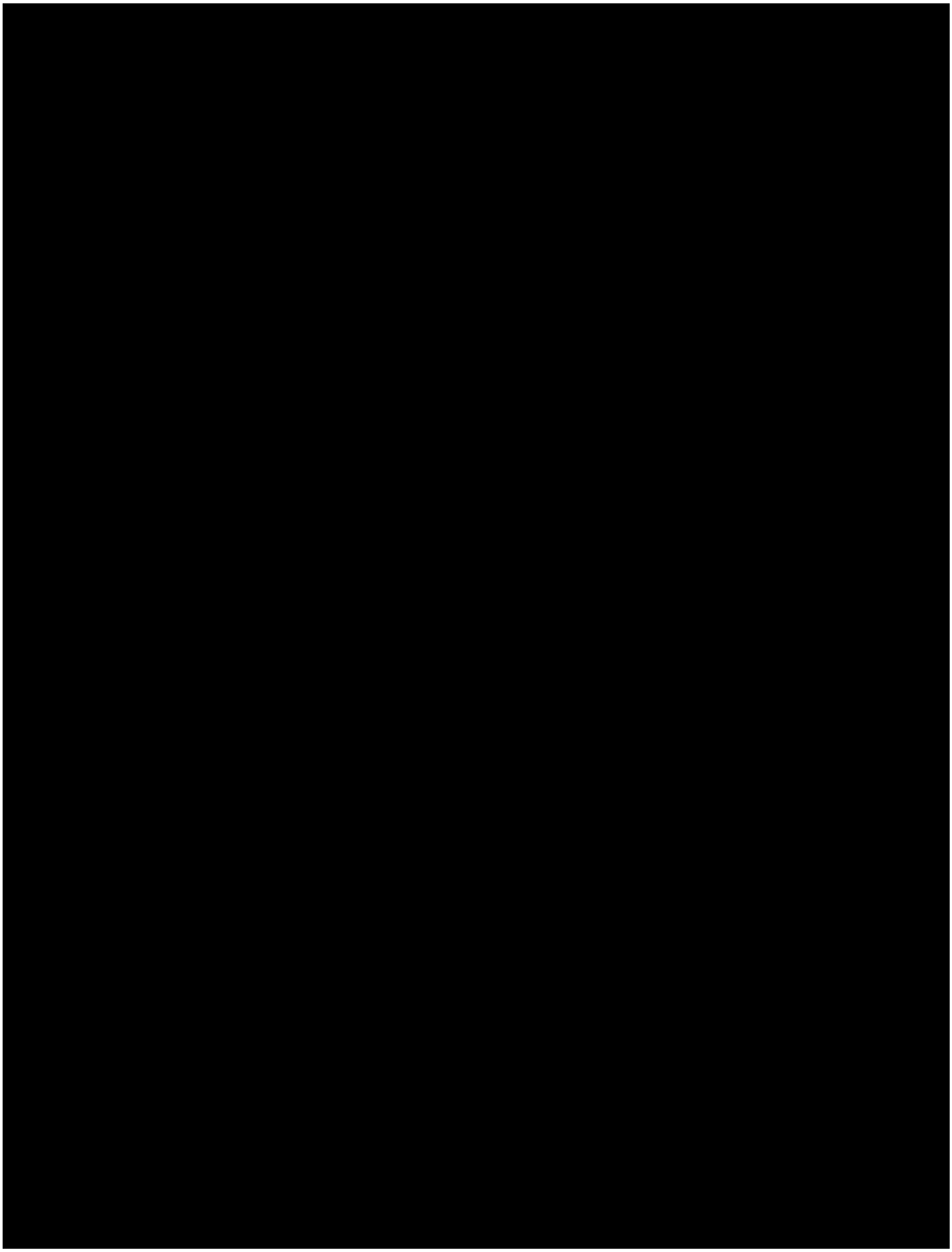
[redacted]

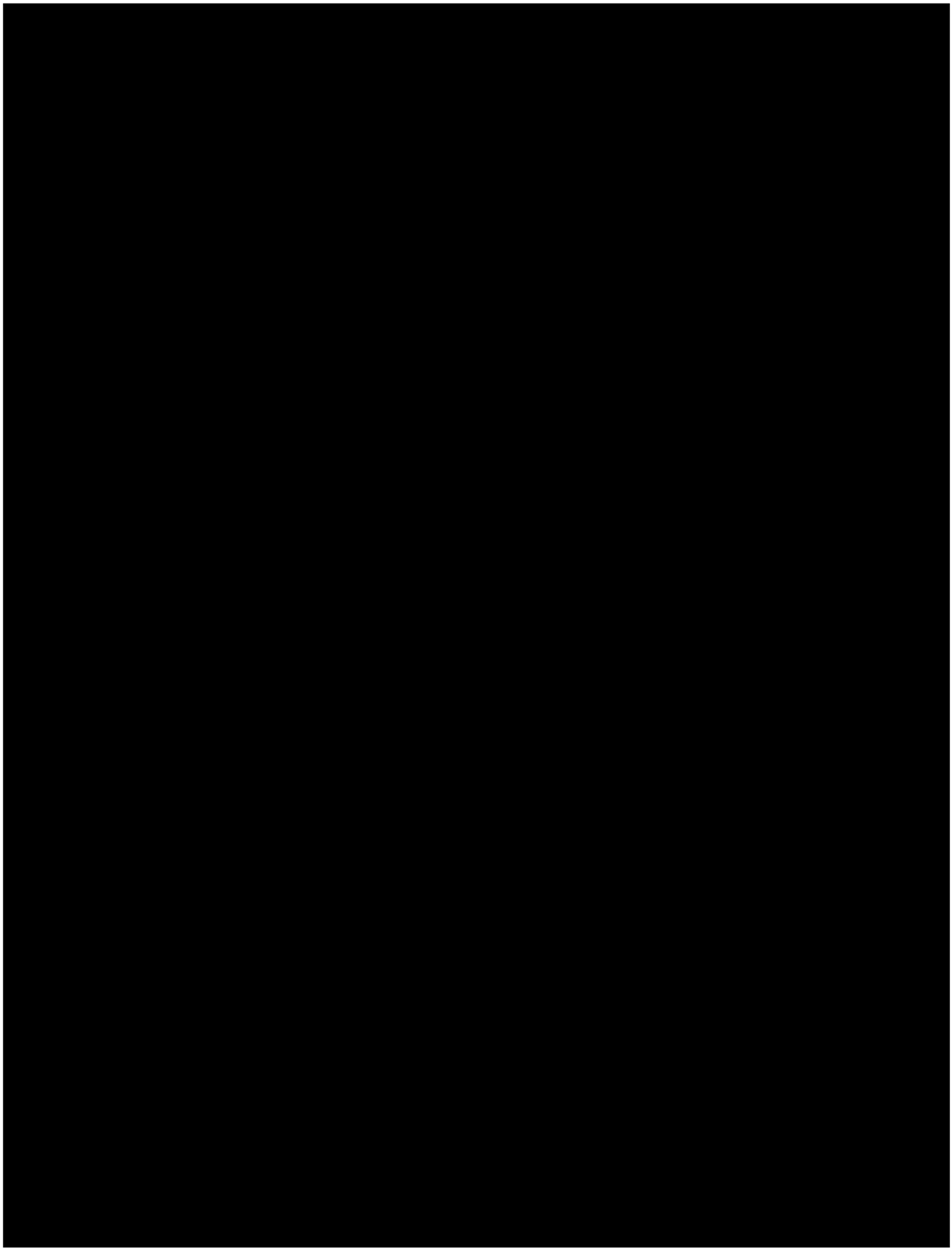


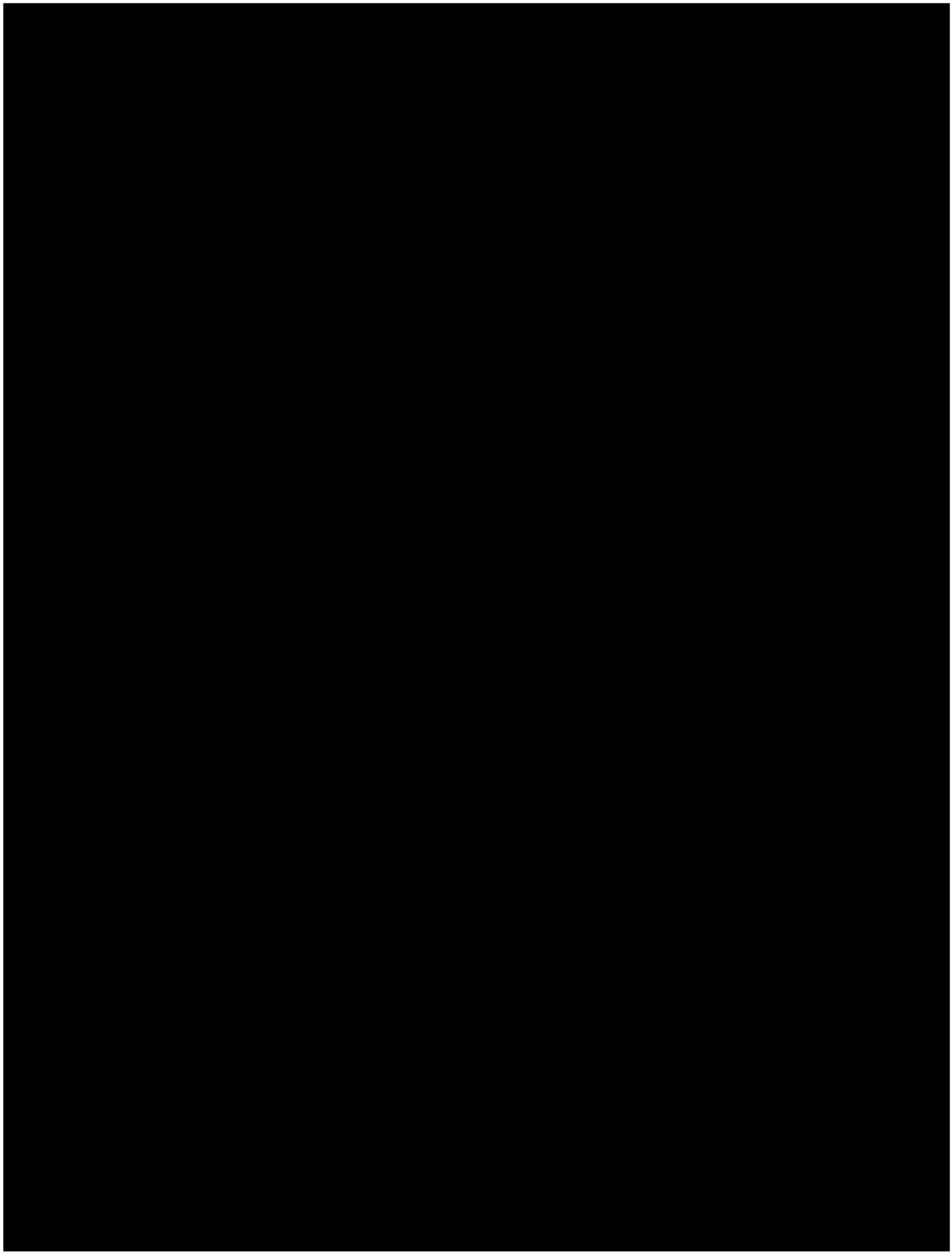


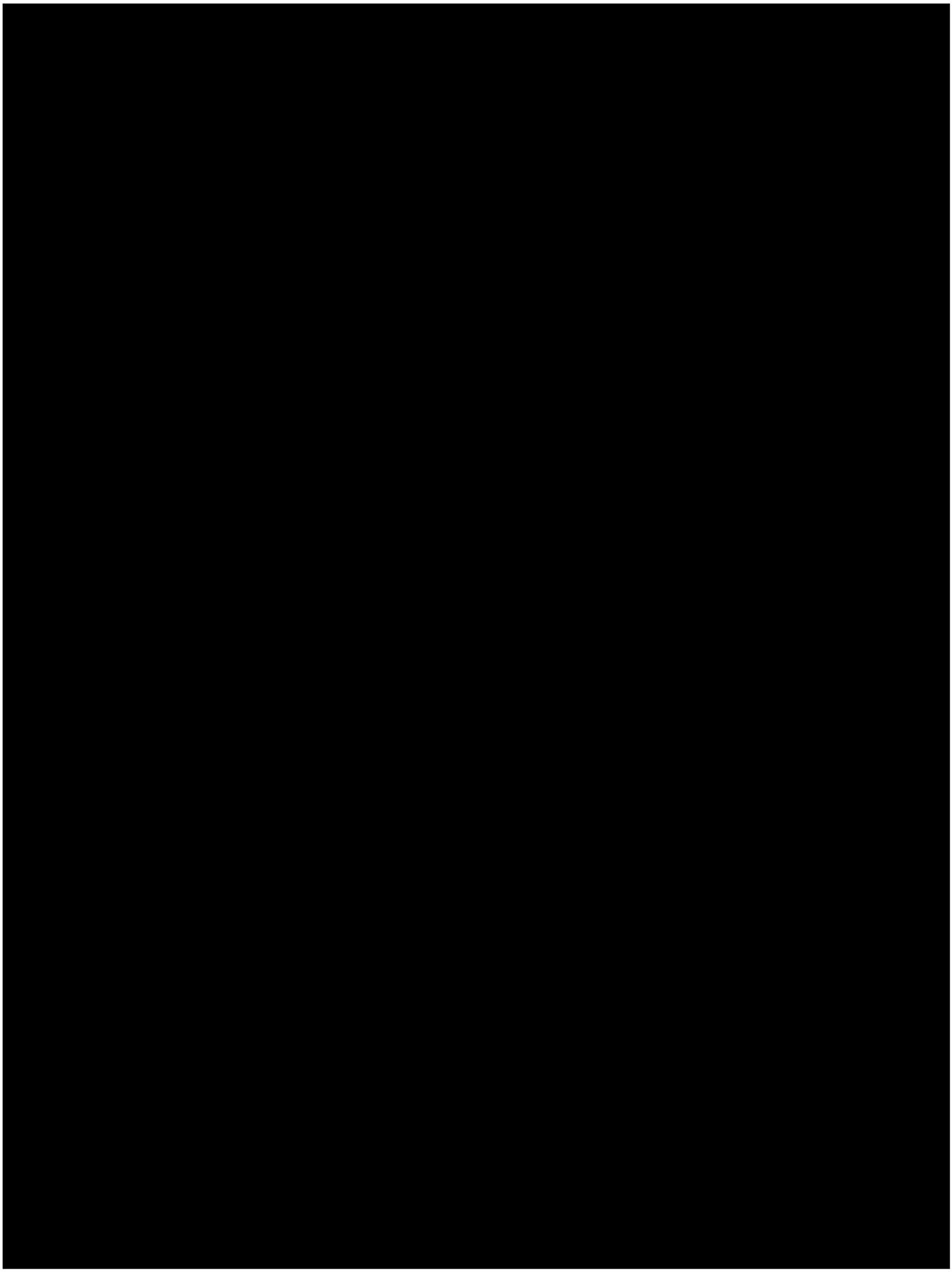


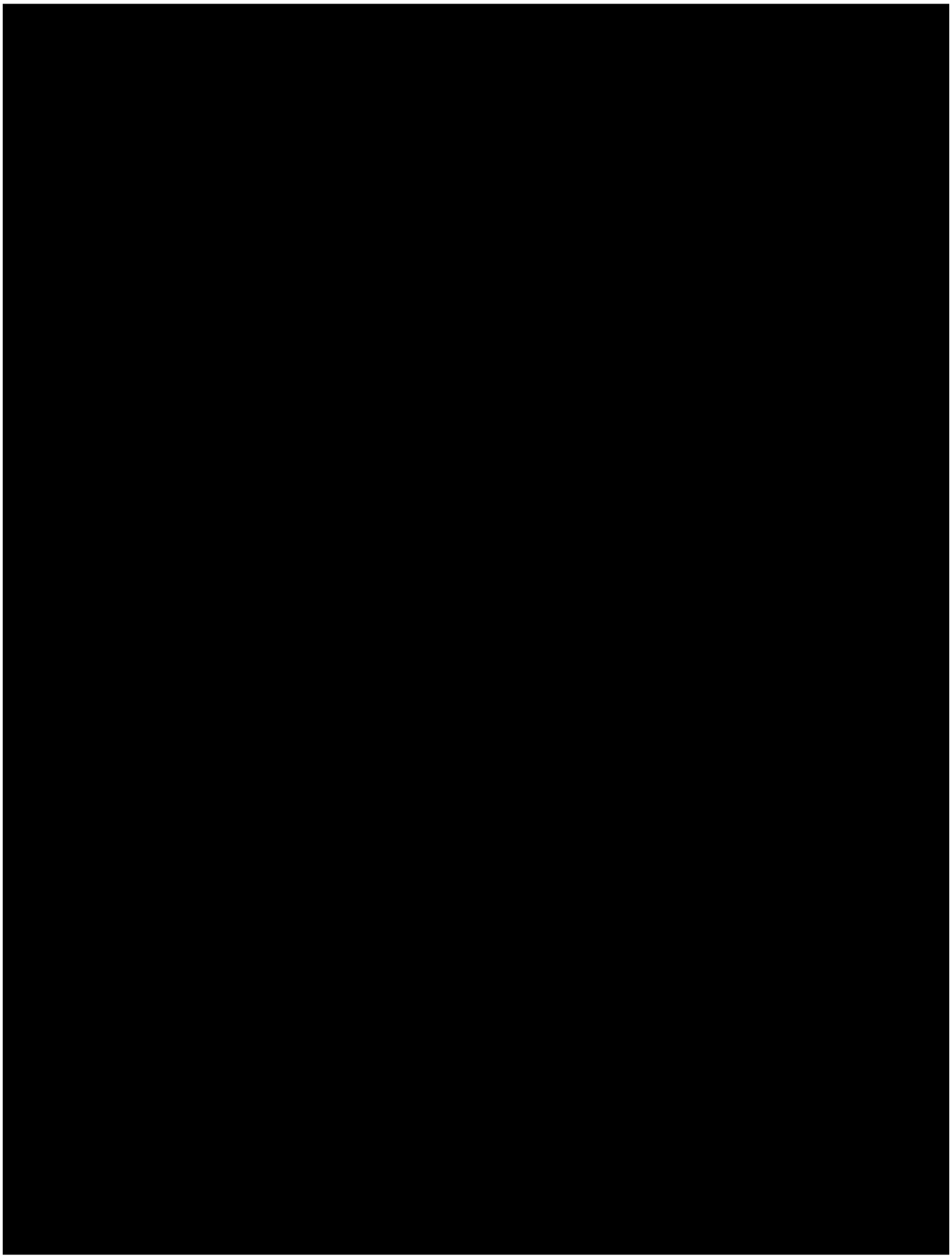


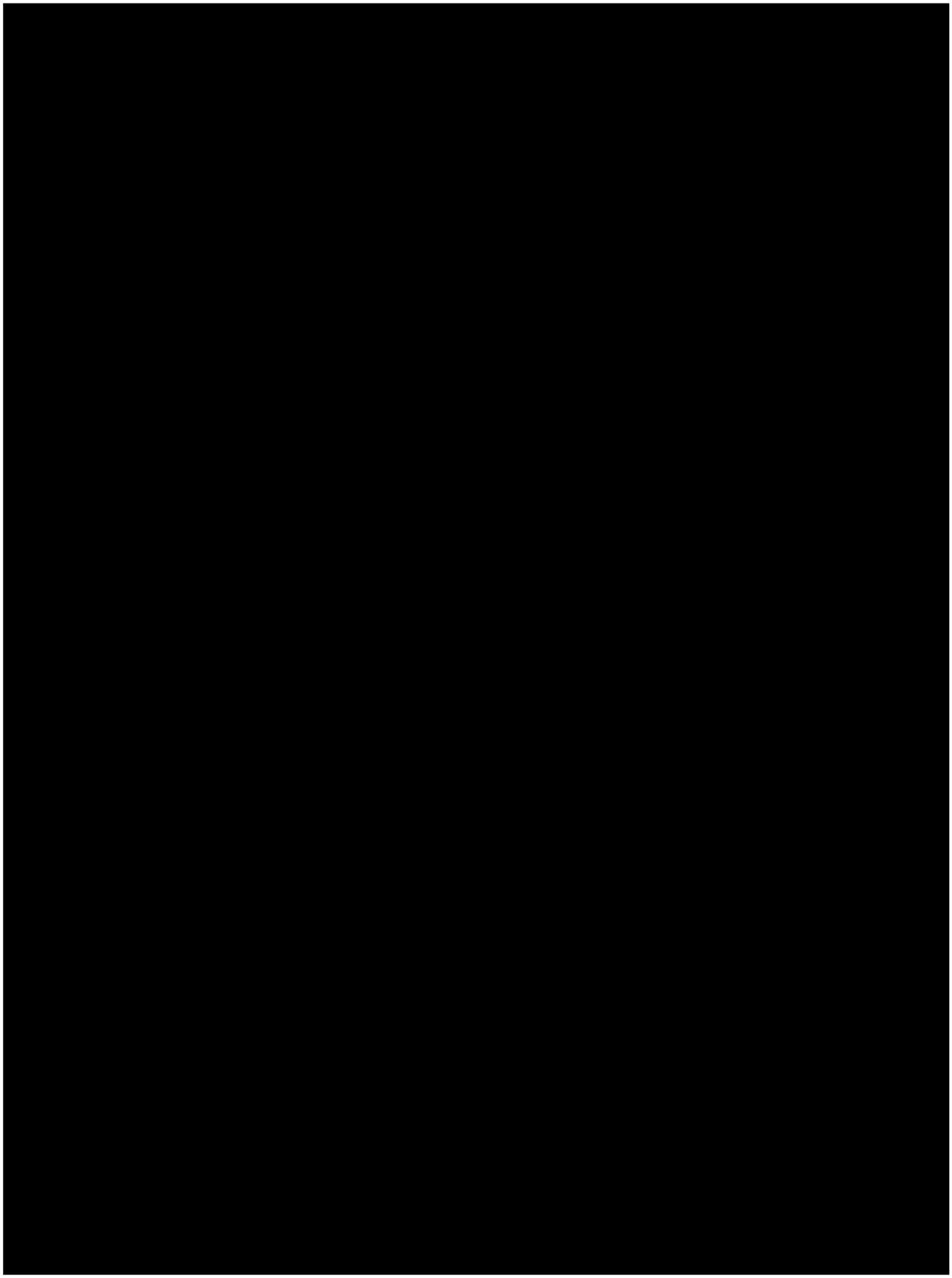


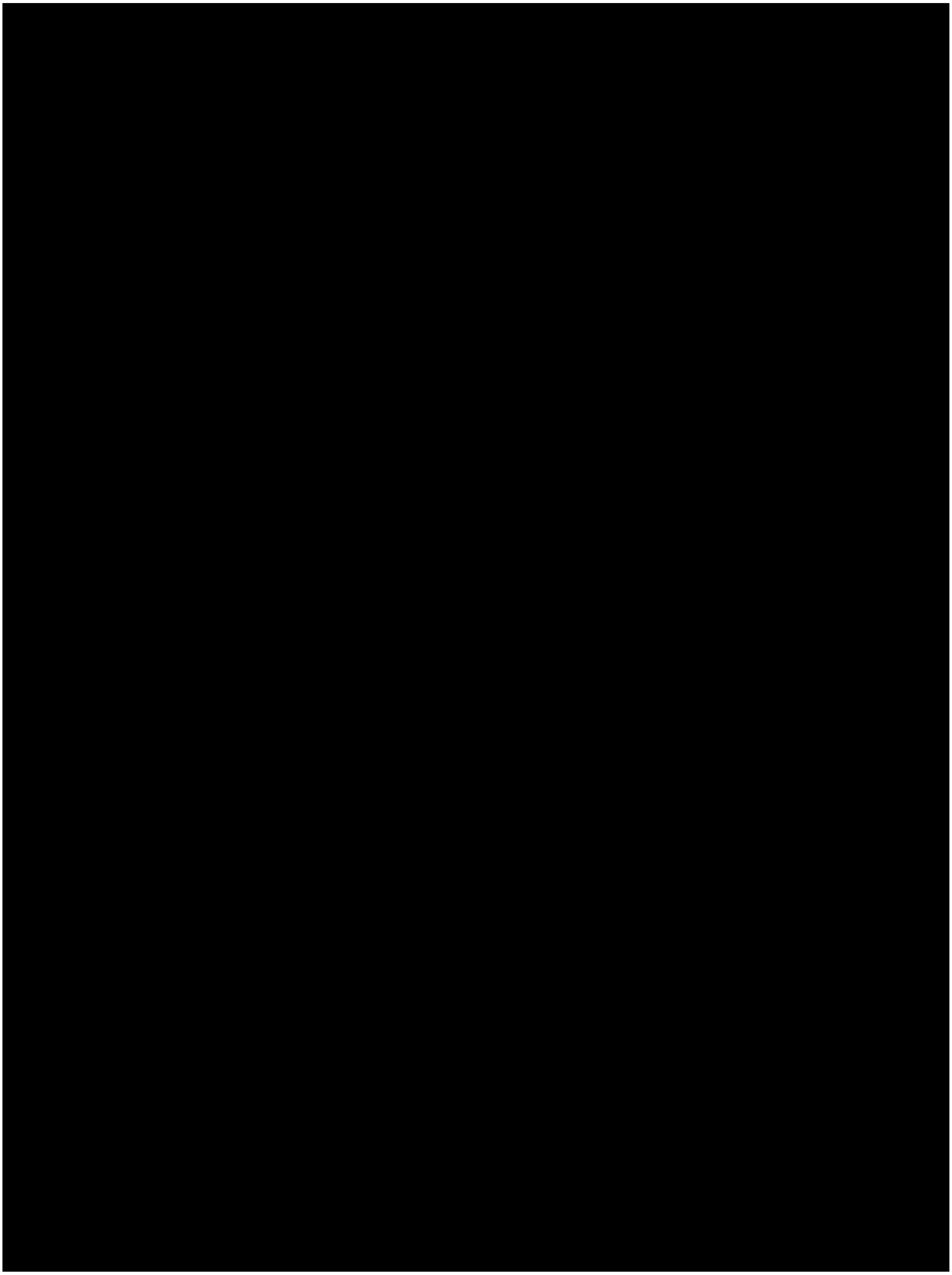


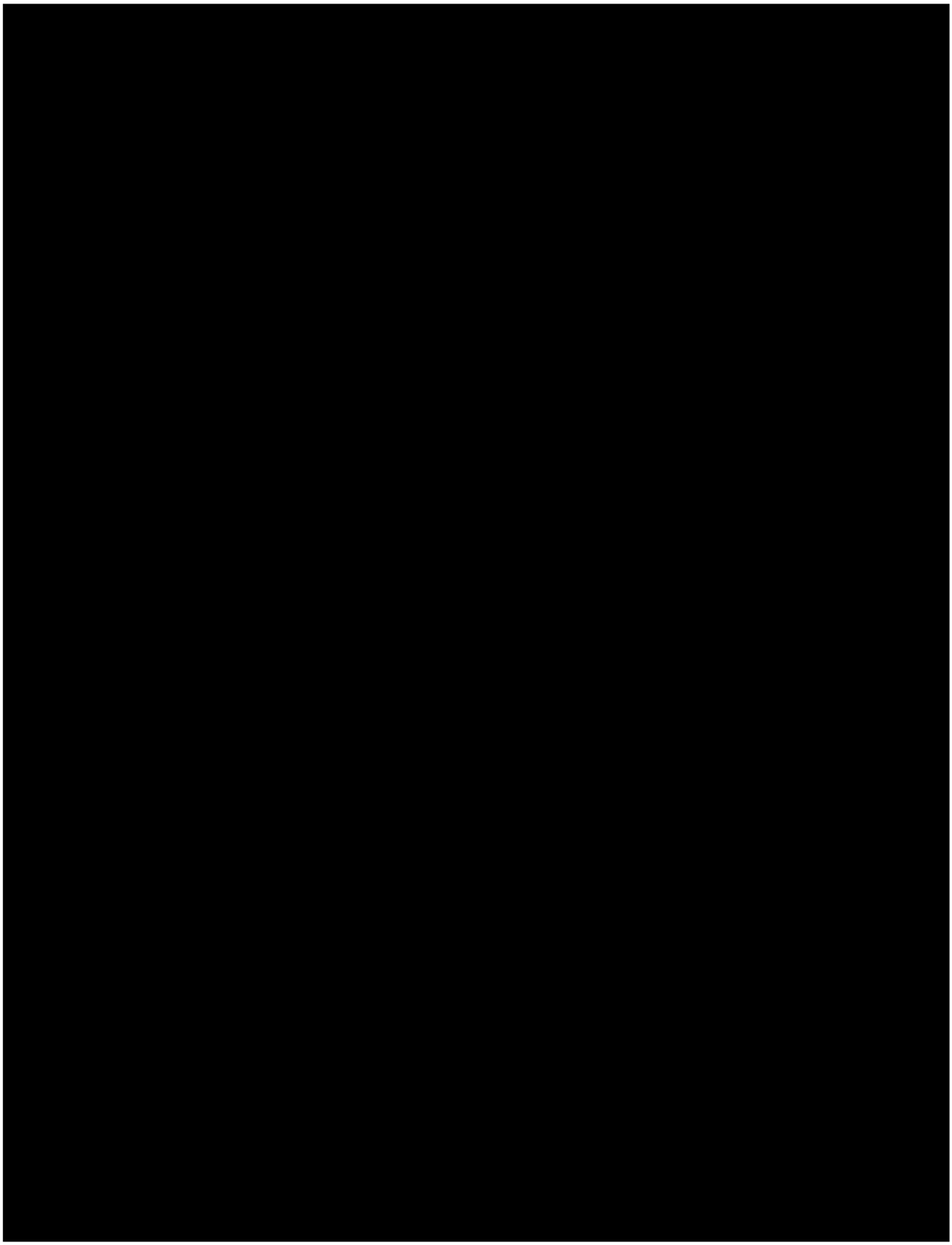


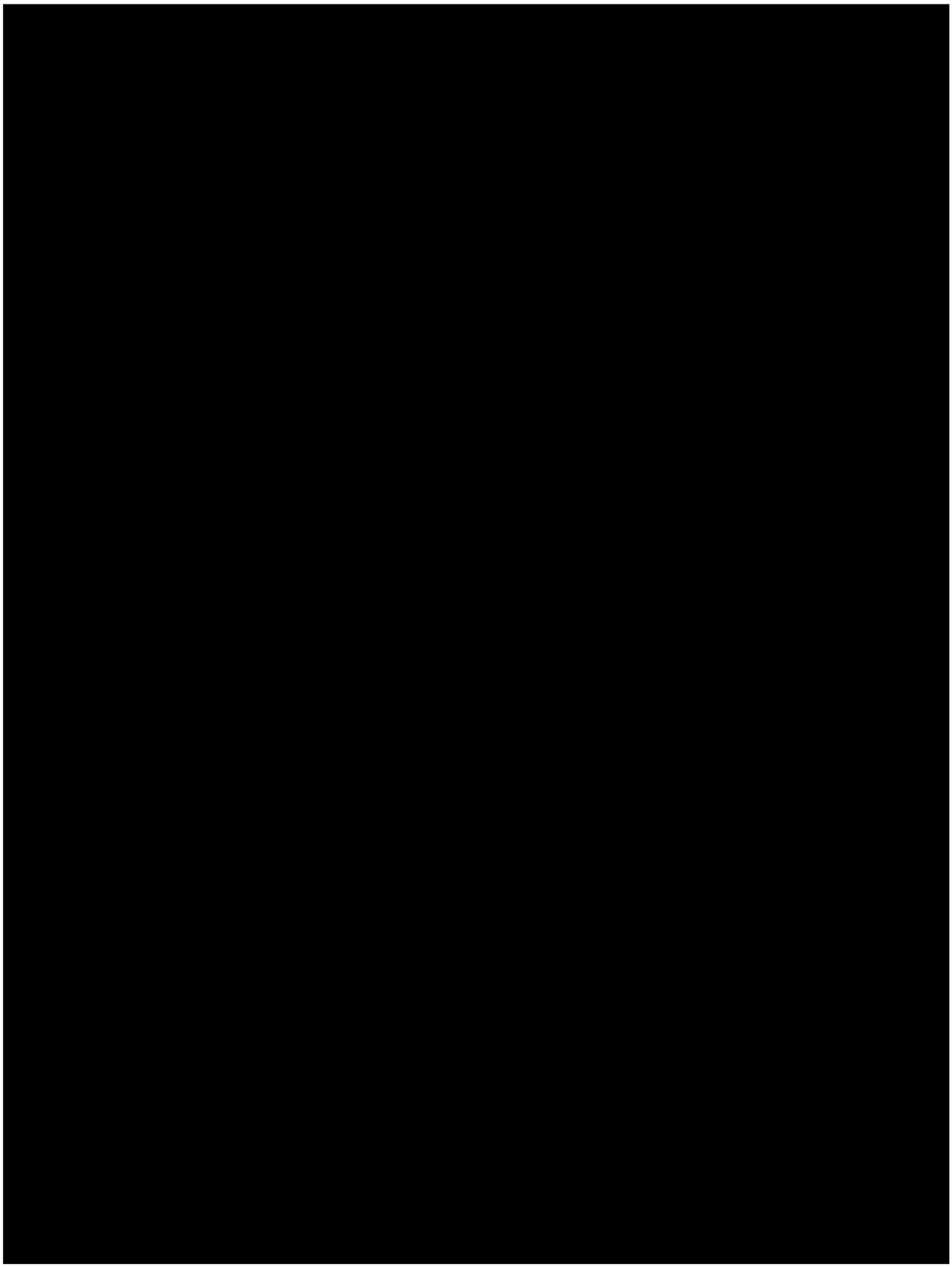


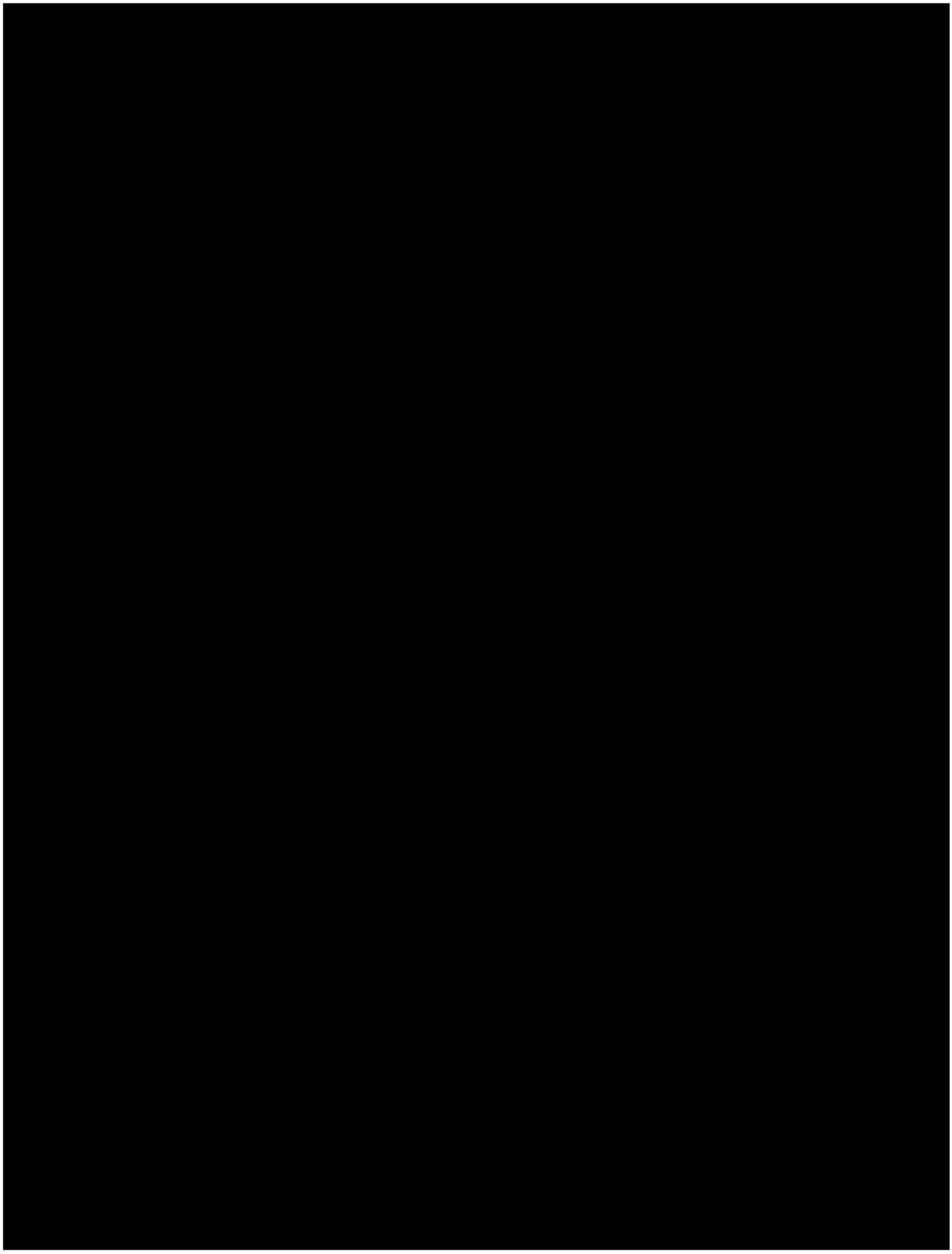


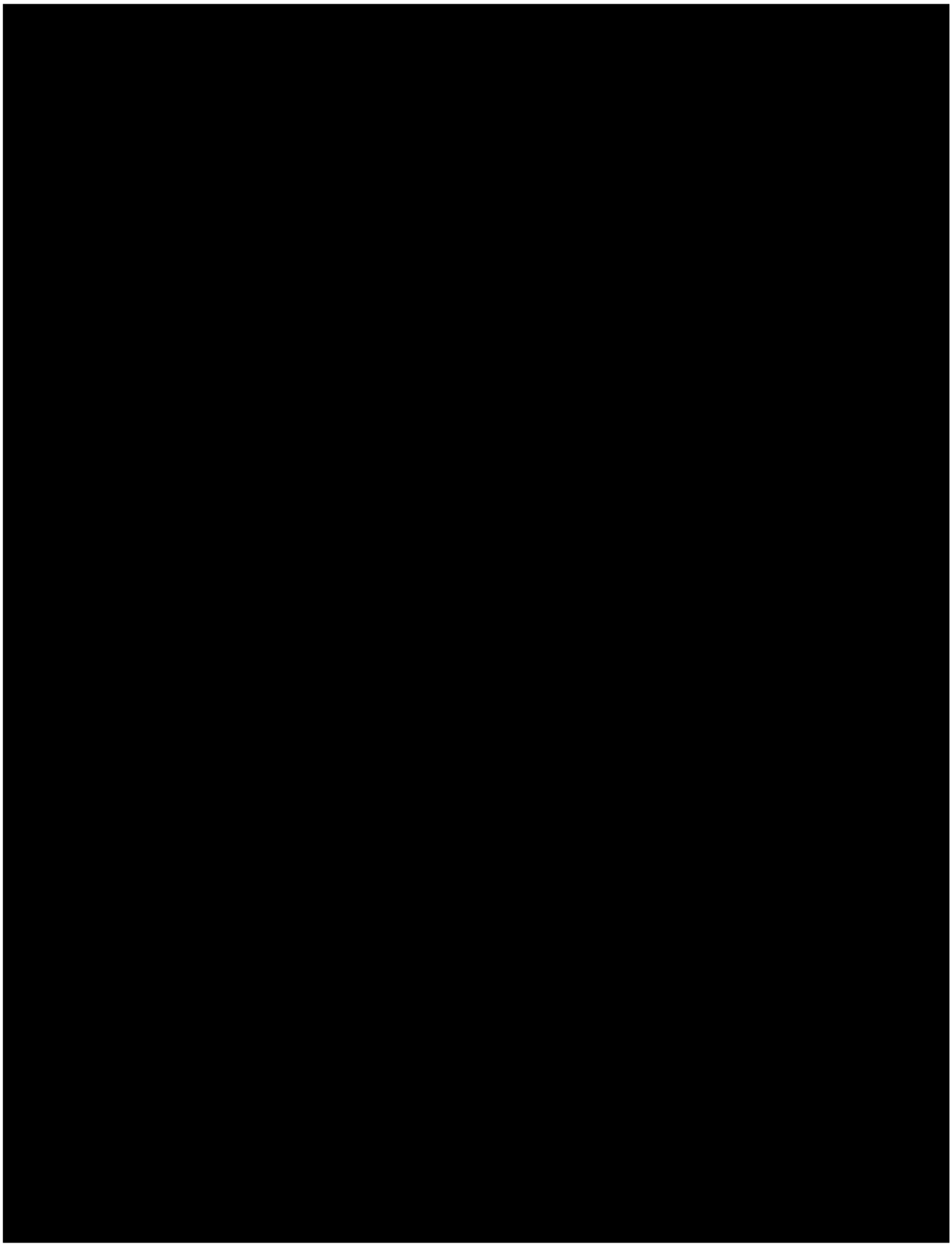


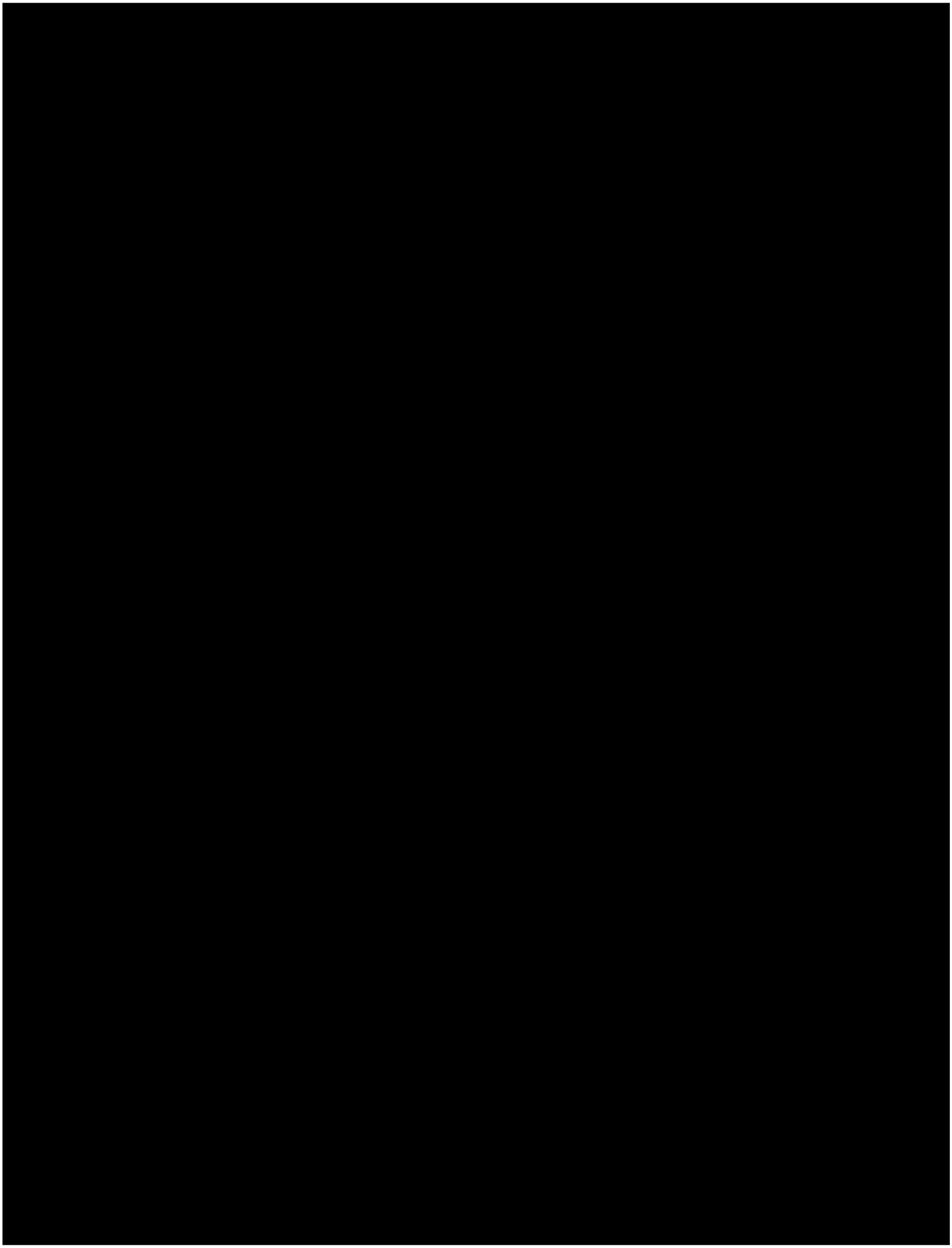


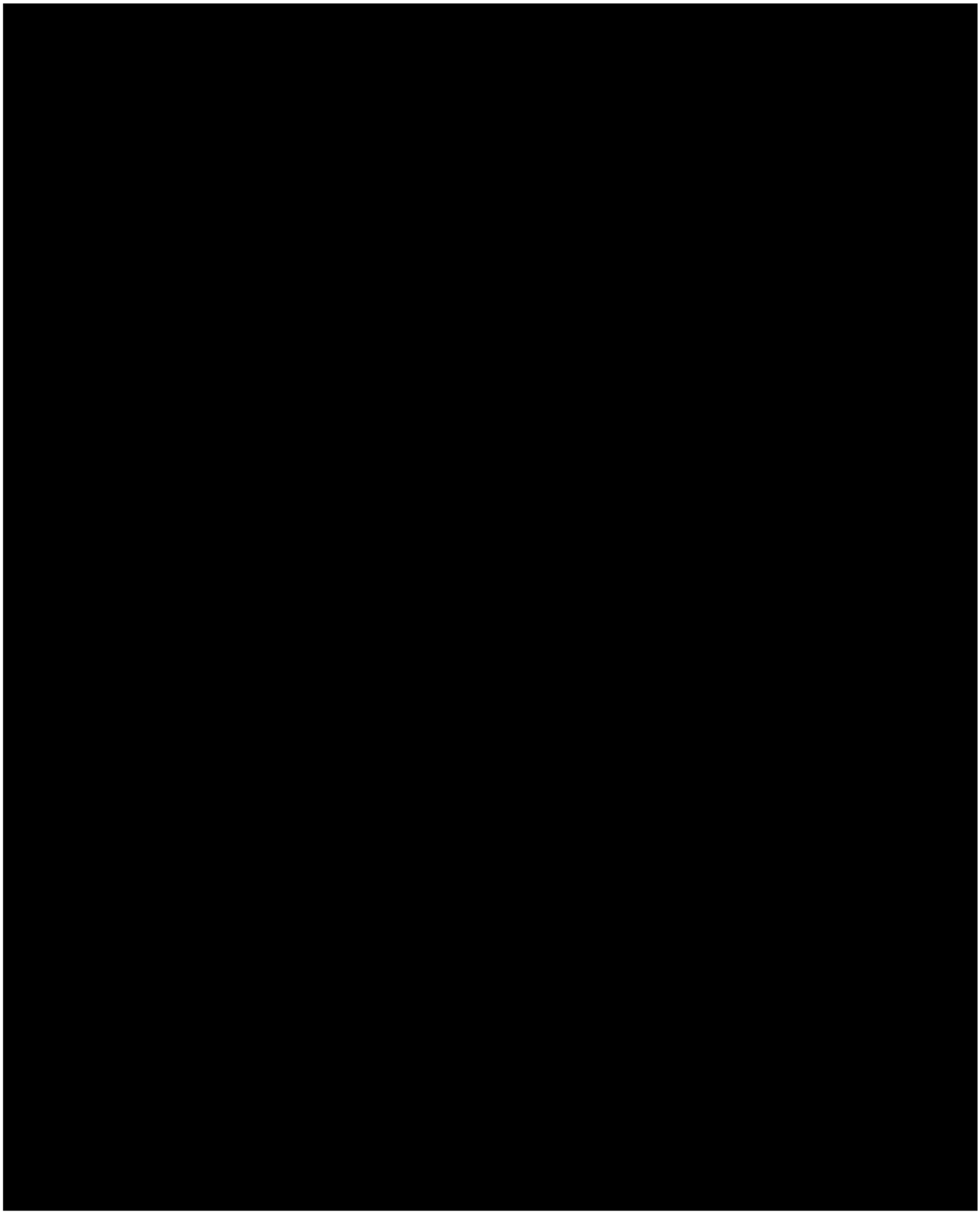


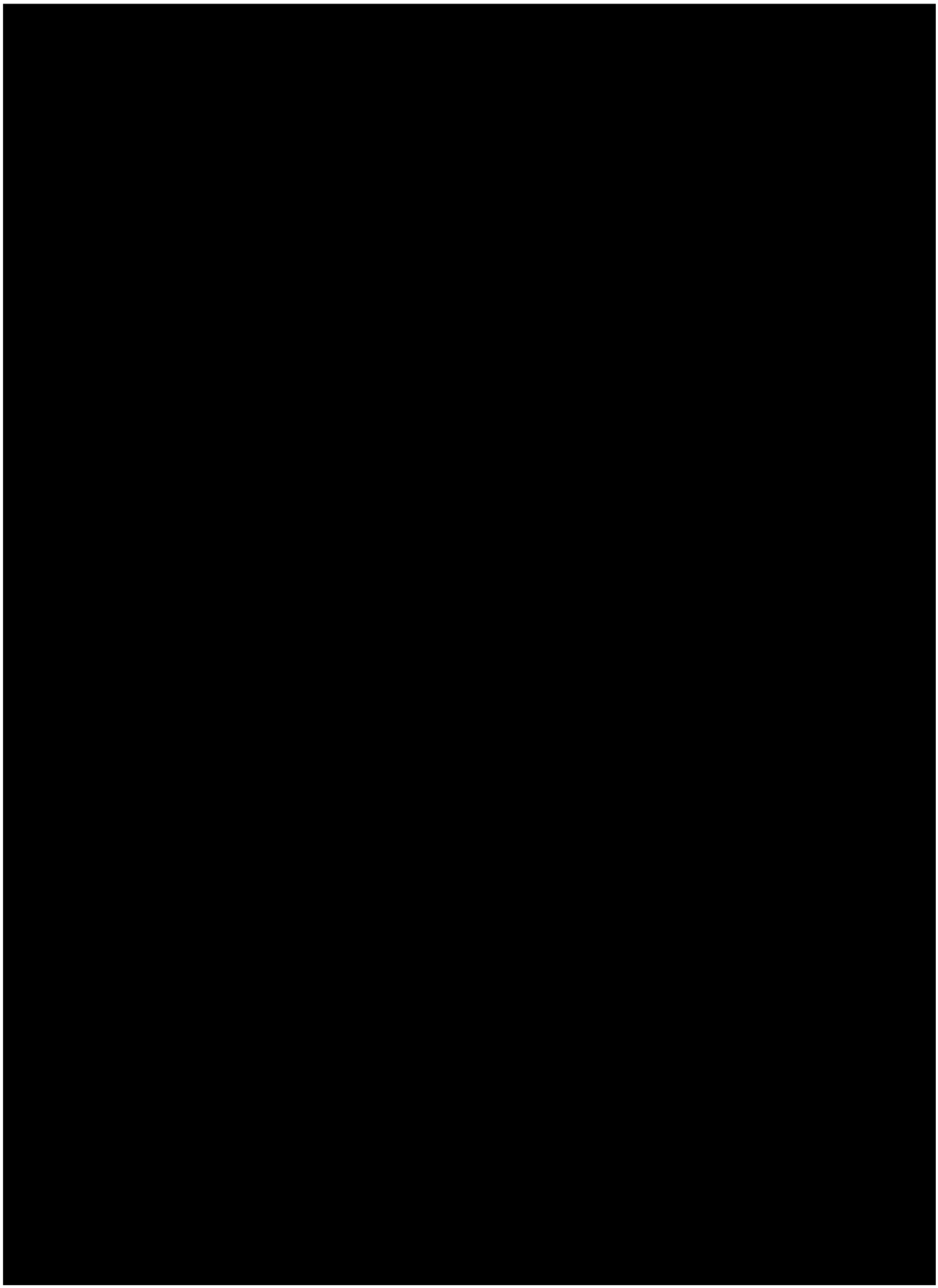


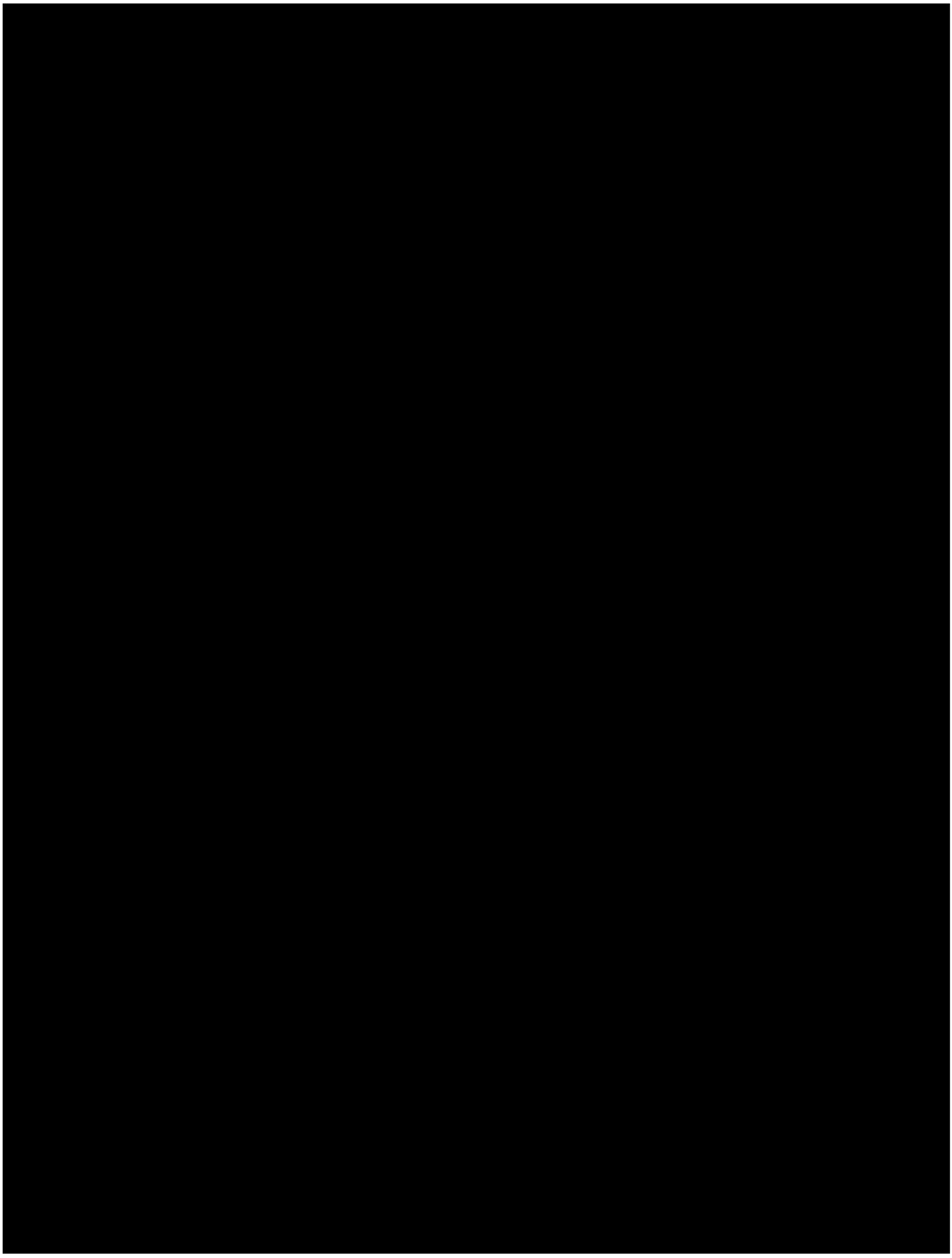












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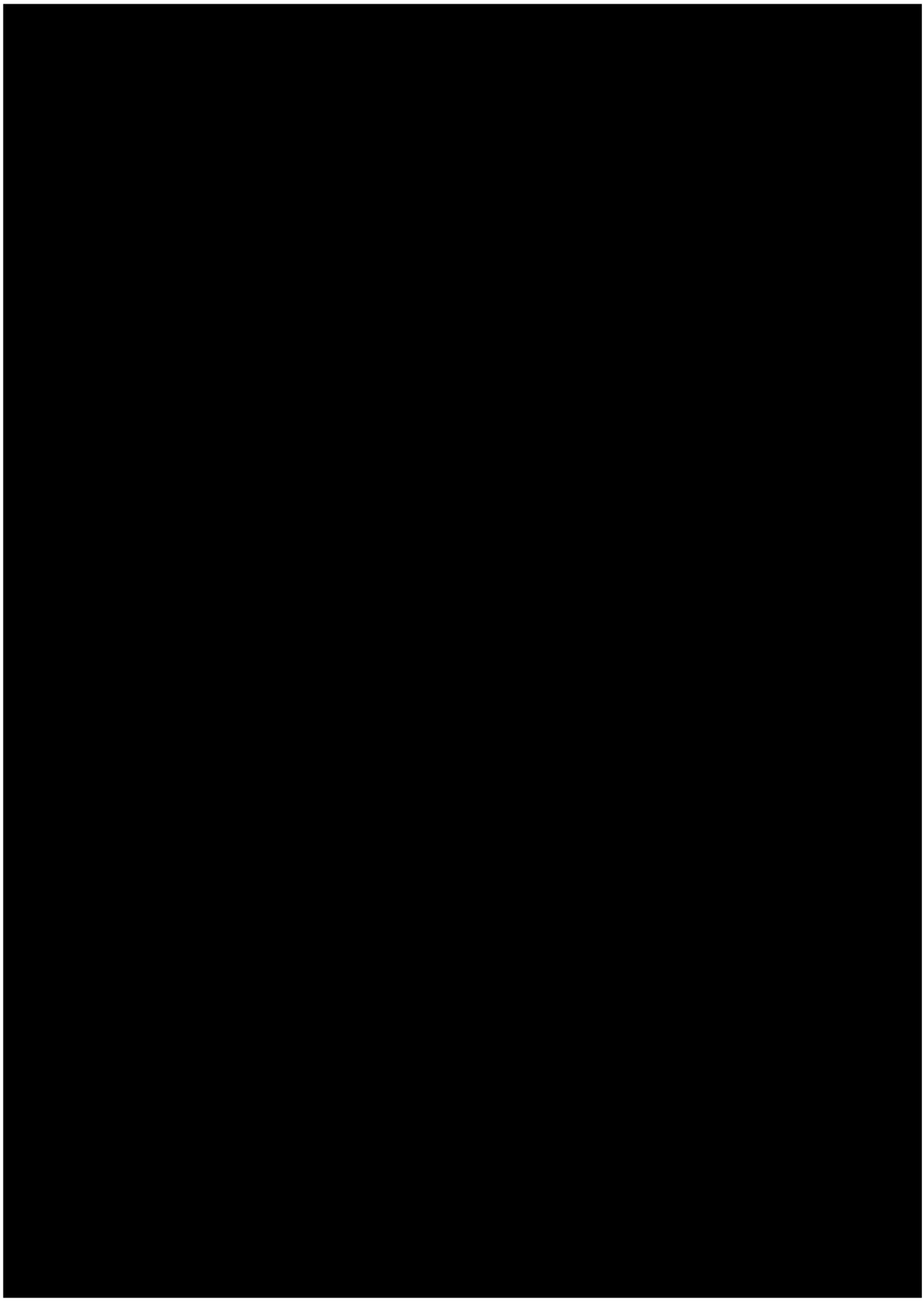

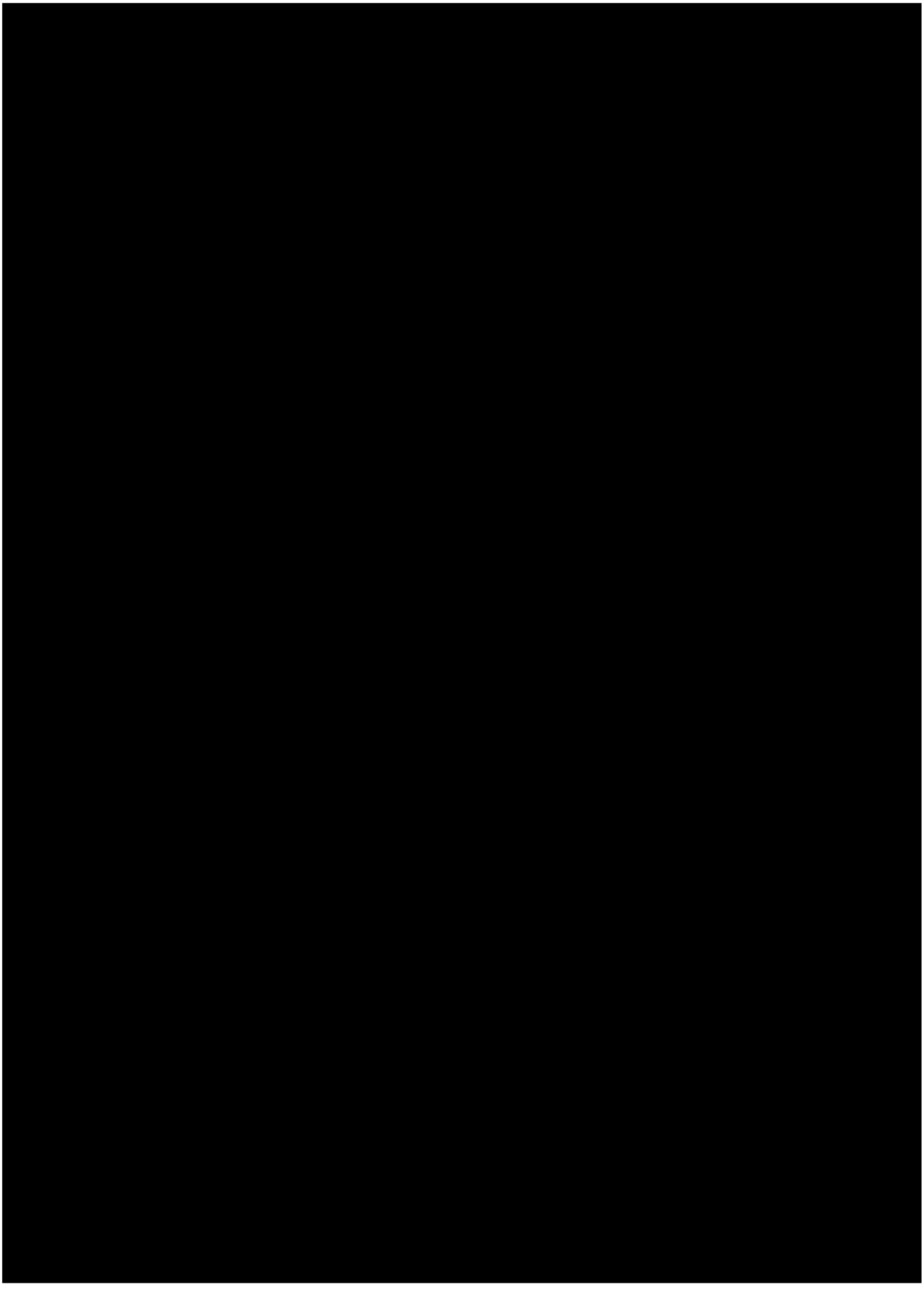

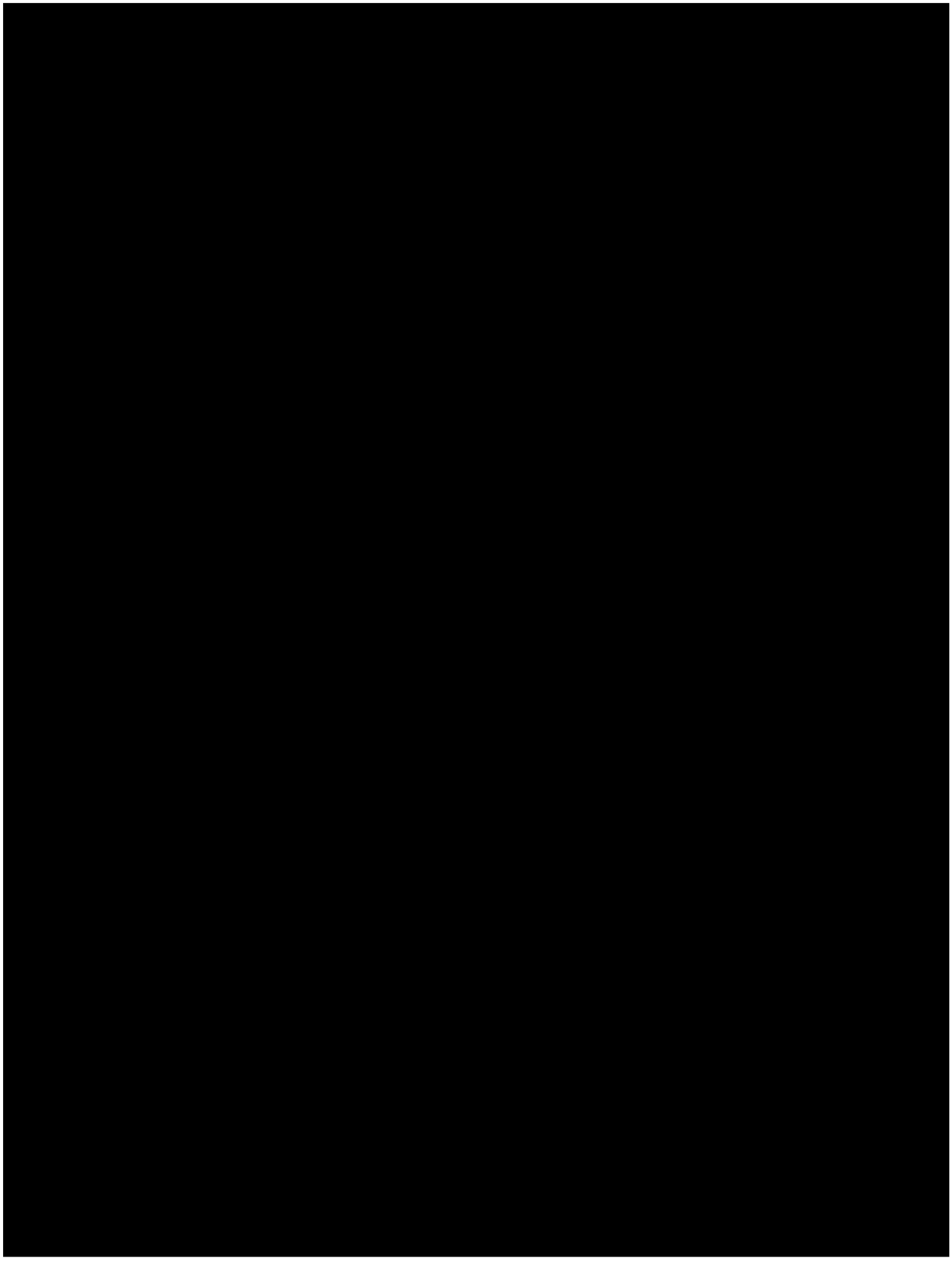

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