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Study ID: Study ID: 3071-305-020

Title: Open-label Extension Study of Relamorelin for the Treatment of Diabetic Gastroparesis

Protocol Amendment 2 Date: 12 February 2021

Title Page

Protocol Title:	Open-label Extension Study of Relamorelin for the Treatment of Diabetic Gastroparesis
Protocol Number:	3071-305-020
Amendment Number:	2
Product:	Relamorelin
Brief Protocol Title:	Diabetic Gastroparesis Study 05
Development Phase:	Phase 3b
Sponsor Name and Legal Registered Addresses:	Allergan Sales, LLC, 5 Giralda Farms, Madison, NJ 07940, United States Allergan Ltd., Marlow International, Parkway, Marlow SL7 1YL, United Kingdom
Regulatory Agency Identifying Numbers:	
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SAE Reporting Email/Fax Number:	[redacted]
Approval Date:	20 Dec 2019
Sponsor Signatory:	[redacted] MD Vice President, Clinical Development-GI

The signature of the sponsor signatory is collected on the protocol approval page.

Protocol Amendment Summary of Changes

DOCUMENT HISTORY	
Document	**Date**
Original Protocol	17 Oct 2018
Amendment 1	21 May 2019

Amendment 2 (20 Dec 2019)

Overall Rationale for the Amendment

This summary includes changes made to Protocol 3071-305-020 Amendment 1 (dated 21 May 2019). The purpose of this protocol amendment is to communicate changes made in response to recommendations from health authorities. These changes will not impact the safety assessment of relamorelin or alter the risk-benefit ratio for study participants.

Changes were also made to align with the current Allergan protocol template for clarity that do not impact the conduct of the study.

Summary of Changes in Global Protocol Amendment 2

Section No. and Name	*Description of Change*	*Brief Rationale*
Section 1.1, Synopsis; Intervention Groups and Study Duration	Deleted reference to 2024: The study is planned to start enrollment of participants in December 2018 and will end when RLM becomes commercially available or the sponsor terminates development~~. RLM is expected to become commercially available in 2024.~~	[redacted]
Section 1.2, Schema	Revised schema to reflect change of end of study	
Section 1.3, Schedule of Activities	• Added a column heading ***"Study Period: Open-Label Treatment"*** • Added visit in days + visit window • Footnote A revised as follows: Scheduled evaluations and laboratory tests (hematology, clinical chemistry, ~~and~~ urinalysis, ***HbA1c, and pregnancy test*** assessments) will be performed every 3 months (Months 15, 18, 21, 24, etc.) for follow-up per participant until the end of the study. ~~HbA1c and pregnancy assessments will be performed prior to initiation of the study~~	

Section No. and Name	*Description of Change*	*Brief Rationale*
	• Footnote D: ~~Complete~~ Physical examinations ***(as per the investigator's standard of care)*** ~~(excluding pelvic exam in women and genital exam in men, and rectal exam in both genders)~~ are to be performed at baseline, at each annual visit, and at the Early Termination/Final Visit ***(see Section 8.2.1)***.	[redacted]
Section 4.4, End of Study Definition	Deleted date RLM is expected to become available: This study will continue until RLM becomes commercially available ~~(expected in 2024)~~ or the sponsor terminates development.	
Section 6.1, Study Interventions Administered; Table 6-1	Added a supplier: • Baxter (prefilled cartridge) • Allergan (assembled pen) • ***Sharp (assembled pen)***	
Section 7, Discontinuation of Study Intervention and Participant Discontinuation/ Withdrawal; Section 7.1.2 Permanent Discontinuation	Permanent discontinuation of study intervention also requires discontinuation from the study. The following criteria ~~are to~~ ***should be*** evaluated: • ***Special consideration should be paid to the appearance of a***bnormal laboratory test results suggesting severe drug-induced liver injury ***(DILI)***. Discontinuation of study intervention for abnormal liver function ***should be considered*** by the investigator ~~is required~~ when a participant meets criteria for Hy's law ***(see Section 8.3.7.1 and Appendix 9*** or if the investigator believes that it is in best interest of the participant (~~for definition see Section 8.3.7.1 and Appendix 9). Suggested actions and follow-up assessments for liver safety are provided in Appendix 9~~	
Section 8, Study Assessments and Procedures	Scheduled evaluations and laboratory tests (serum chemistries and hematologic assessments, ***including HbA1c and pregnancy testing***) for each participant will be performed as noted in the SoA (refer to Section 1.3~~) for up to 5 years or until RLM becomes commercially available or sponsor terminates development~~.	

Section No. and Name	*Description of Change*	*Brief Rationale*
Section 8.2.1, Physical Examinations	~~Complete~~ Physical ***examinations (as per the investigator's standard of care)*** ~~(excluding pelvic exam in women and genital exam in men, and rectal exam in both genders)~~ are to be performed at baseline, at each annual visit, and at the Final Visit. Symptom-directed (abbreviated) physical examinations, including evaluation of the injection sites for clinically significant reactions, may be conducted as required at other study visits. A clinically significant injection site reaction is to be reported as an AE.	[redacted]
Section 8.3.3, 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 AESIs as defined in Appendix 3 will be followed until resolution, stabilization, the event's ***etiology*** is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). ***Further information of AE/SAE follow-up procedures is given in Appendix 3.***	
Section 8.3.7.1, Potential Hy's Law	~~Study site personnel must record and report every participant who meets the criteria for potential Hy's law as SAEs (see Appendix 9 for detailed description on handling potential Hy's law cases and liver toxicity). Potential Hy's law cases are also considered AESIs and~~ Criteria for potential Hy's law cases are as follows: • ALT or AST ≥ 3 × ULN) AND • Total bilirubin ≥ 2 × ULN AND • Alkaline phosphatase < 2 × ULN ***Study site personnel must record and report every participant who meets the criteria for potential Hy's law as SAEs (see Appendix 9 for detailed description on handling potential Hy's law cases and liver toxicity).*** 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 last dose of study intervention.	

Section No. and Name	*Description of Change*	*Brief Rationale*
Section 9.6, Data Monitoring Committee	Data Monitoring Committee section was added along with the following text: ***A Data Monitoring Committee was not used for this study.***	[redacted]
Section 10.1.10/ Appendix 1, Compliance with Protocol	Compliance with Protocol section added along with the following text: ***The investigator is responsible for compliance with the protocol at the investigational site. A representative of the sponsor will make frequent contact with the investigator and his/her research staff and will conduct regular monitoring visits at the site to review participant and study intervention accountability records for compliance with the protocol. Protocol deviations will be discussed with the investigator upon identification. Significant protocol deviations will be reported to the IRB/IEC according to the IRB/IEC's reporting requirements.***	
Section 10.2/ Appendix 2, Clinical Laboratory Tests/ Table 10-1, Protocol-Required Safety Laboratory Assessments	Other Screening Tests was amended to read: Urine human chorionic gonadotropin (hCG) pregnancy test ~~(at Baseline as noted in the SoA) as needed~~ for women of childbearing potential ***will be performed every 3 months as specified in the SoA***.	
Section 10.3.1/ Appendix 3, Definition of AE; AE of Special Interest (AESI)	Serious AESIs ~~should~~ ***must*** be reported to the sponsor within 24 hours via the SAE form. Nonserious AESIs do not require submission on an SAE form; should be recorded on the appropriate page of the eCRF.	

[redacted]

Section No. and Name	*Description of Change*	*Brief Rationale*
Section 10.3.4/Appendix 3, Reporting of SAEs	Revise subsection tabular information to read: SAE Reporting ***to Sponsor or Designee Within 24 Hours***	[redacted]
Section 10.7/ Appendix 7, Contraceptive Guidance and Collection of Pregnancy Information; Pregnancy Testing	• WOCBP ~~are~~ ***should*** only ~~to~~ be included in the study after a confirmed menstrual period and a negative urine pregnancy test. [redacted]	
Section 19.9/ Appendix 9, Liver Safety: Suggested Actions and Follow-up Assessments	Entire appendix has been revised.	
Section 10.10/ Appendix 10, Protocol Amendment History	Moved Summary of Changes text in Amendment 1 to appendices	

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1. Protocol Summary

1.1. Synopsis

Protocol Title: Open-label Extension Study of Relamorelin for the Treatment of Diabetic Gastroparesis

Protocol Number: 3071-305-020

Brief Title: Diabetic Gastroparesis Study 05

Study Phase: Phase 3b

Study Rationale:
Previous Phase 2 studies have provided evidence that RLM may be a safe and effective treatment for participants with DG.

GP is 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 duodenum and small intestine takes longer than normal and occurs with unpredictable timing. DM, either Type 1 or Type 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.

The pharmacodynamic effect of RLM on gastric emptying was confirmed, and the beneficial effects on the symptoms of DG were observed in the Phase 2b study, RM-131-009. Efficacy, safety, and tolerability of RLM are under investigation in Phase 3 studies, including long-term efficacy and safety studies conducted for up to 12 months' duration.

A significant unmet medical need exists for a safe and effective treatment of patients with DG whose quality of life is negatively impacted by their disease and for whom the current standard of care is suboptimal. While waiting for regulatory assessment of the results in the Phase 3 studies,

the sponsor is planning to provide access to RLM to participants with DG who have completed double-blind treatment in the Phase 3 program (Studies RLM-MD-03 and RLM-MD-04).

The objective of Study 3071-305-020 is to assess the safety of RLM in participants with DG who have previously completed the Phase 3 studies, RLM-MD-03 or RLM-MD-04. Safety assessments include AEs, clinical laboratory values, vital signs, and ECGs (reported as clinically significant AEs). No endpoints were specified for this study.

Overall Study Design:
Study 3071-305-020 is an open-label, multicenter, multinational safety study in participants with DG who completed the Phase 3 studies, RLM-MD-03 or RLM-MD-04. Participants who discontinued Studies RLM-MD-03 or RLM-MD-04 for any reason are not to be enrolled into this study. Participants who roll over to this continued-access study within 30 days (ie, ≤ 30 days) of completing their final visit assessments in either Study RLM-MD-03 or Study RLM-MD-04 do not need to complete baseline assessments; information from the final visit of Studies RLM-MD-03 or RLM-MD-04 will be used as the information for Visit 1 of this study. Visit 1 should occur in ≤ 30 days of the last visit of the lead-in study. If a participant enters this continued-access study > 30 days after last visit in either lead-in study, Visit 1 baseline assessments will be completed as shown in Section 1.3.

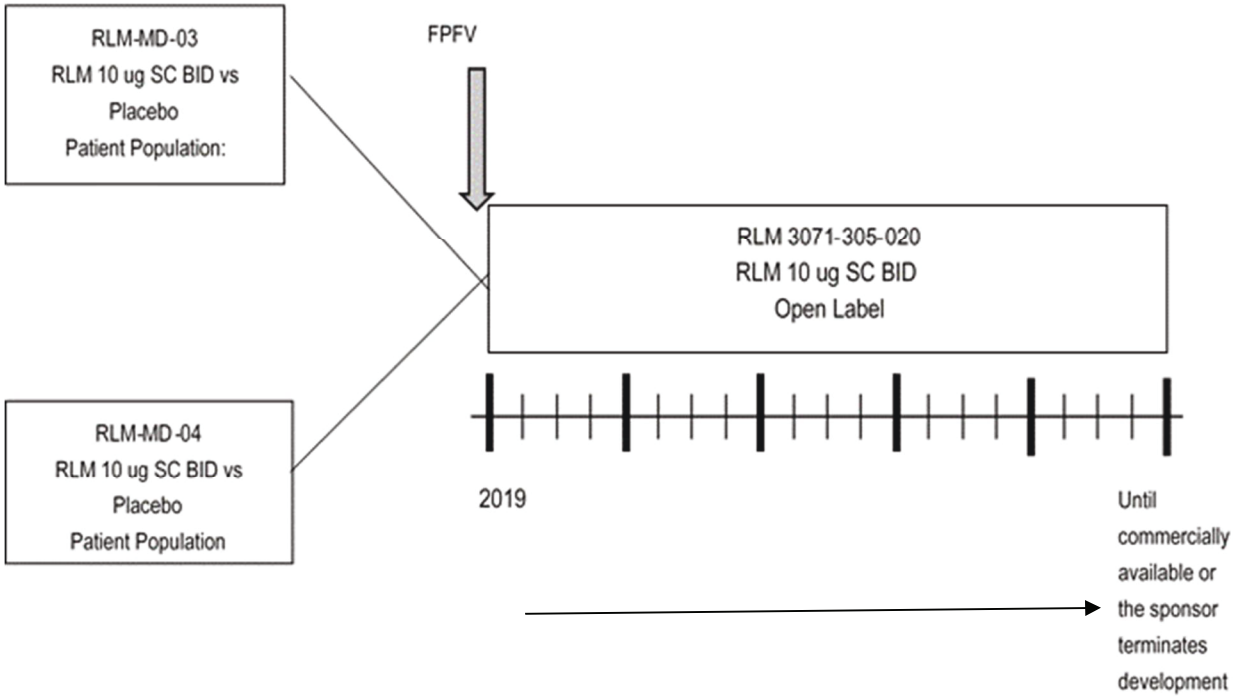
Approximately 1000 participants may roll over from Studies RLM-MD-03 or RLM-MD-04 at approximately 700 sites with an anticipated attrition rate of approximately 20% per year. No participant replacement is planned in this continued-access, open-label study.

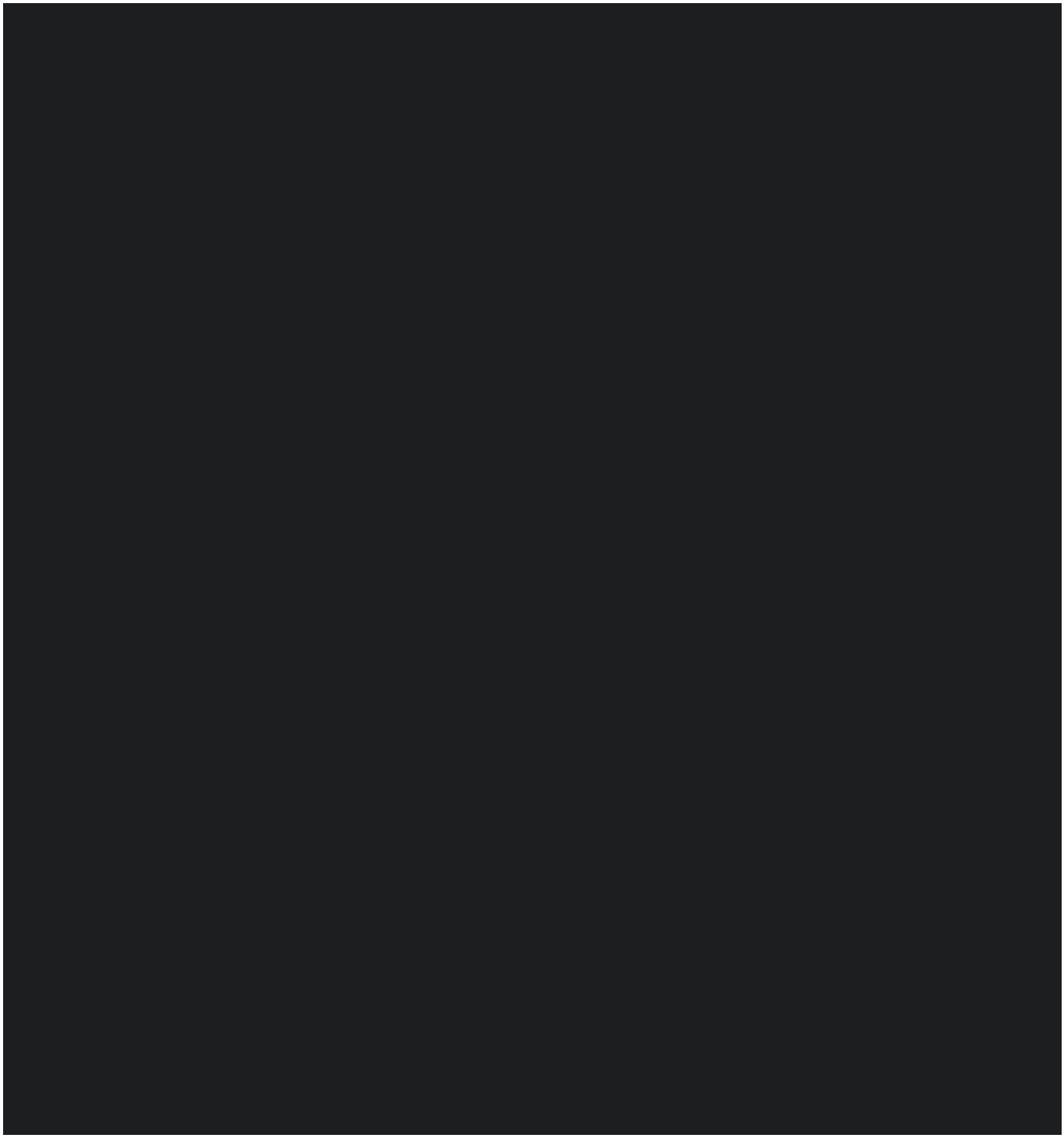
Number of Sites:
Approximately 700 study sites that participated in Studies RLM-MD-03 or RLM-MD-04 will have the option to participate in the continued-access, open-label study.

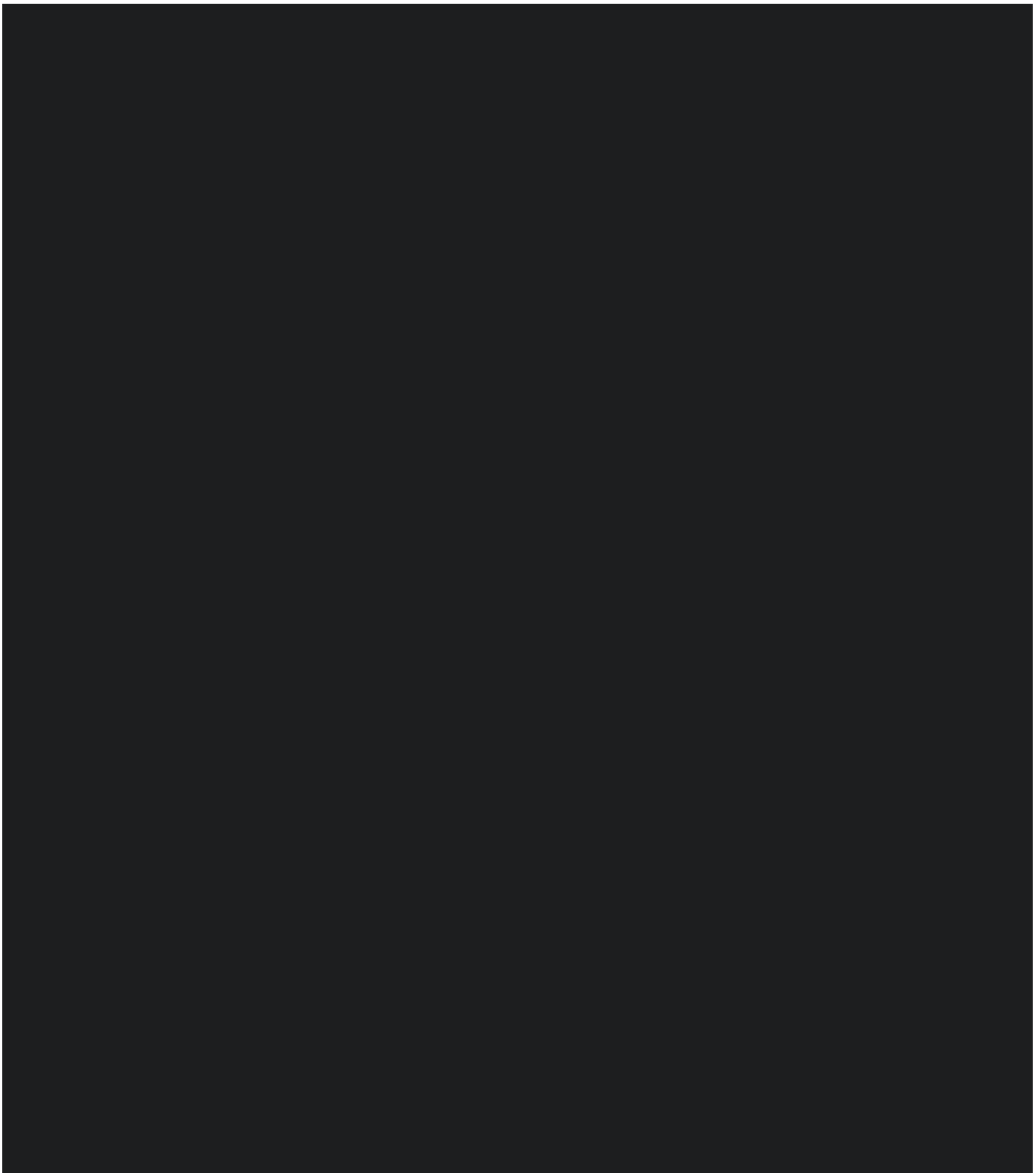
Intervention Groups and Study Duration:
The study is planned to start enrollment of participants in December 2018 and will end when RLM becomes commercially available or the sponsor terminates development.

Data Monitoring Committee: No

1.2. Schema







2. 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 DG.

Ghrelin, a 28 amino-acid peptide, is produced predominantly by specialized cells of the stomach and pancreas. Ghrelin has been demonstrated to be a central modulator of energy homeostasis. It is the natural ligand for the 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 2004; Trudel 2003; and Murray 2005). It can increase body weight, attributed to a combination of enhanced food intake, increased GE, and increased food assimilation, coupled with a transient increase in growth hormone, which promotes nutrient incorporation into tissues.

RLM 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 2015; Acosta 2016).

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.

DM, either Type 1 or Type 2 (T1DM/T2DM), 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, and negatively affect function (Parkman 2004).

DG is a chronic condition that requires prolonged treatment. Core signs and symptoms of DG are nausea, abdominal pain, post-prandial fullness, bloating, vomiting, and early satiety (a feeling of fullness after eating just a few bites) (Camilleri 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 2011; Parkman 2011). Serious adverse sequelae of DG

include: potentially life-threatening dehydration due to persistent vomiting, 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 (US Department of Health and Human Services 2012). Aside from the impact on patients, these events often lead to hospitalization (Koch 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 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 2009). This study reported that age-adjusted prevalence of GP was approximately 4 times greater for women than men (37.8 vs 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 (Hopkins Medicine 2013). According to Bharucha (2015), in a restricted community-based study of GP in DM, 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 prevalence of obesity.

2.1. Study Rationale

Previous Phase 2 studies have provided evidence that RLM may be a safe and effective treatment for patients with DG.

GP is 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 duodenum and small intestine takes longer than normal and occurs with unpredictable timing. DM, either Type 1 or Type 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.

The PD effect of RLM on gastric emptying was confirmed, and the beneficial effects on the symptoms of DG were observed in the Phase 2b study, RM-131-009. Efficacy, safety, and tolerability of RLM are under investigation in Phase 3 studies, including long-term efficacy and safety studies conducted for up to 12 months' duration.

A significant unmet medical need exists for a safe and effective treatment of patients with DG whose quality of life is negatively impacted by their disease and for whom the current standard of care is suboptimal. While waiting for regulatory assessment of the results in the Phase 3 studies, the sponsor is planning to provide access to RLM to participants with DG who have completed double-blind treatment in the Phase 3 program (Studies RLM-MD-03 and RLM-MD-04).

The objective of Study 3071-305-020 is to assess the safety of RLM in participants with DG who have previously completed the Phase 3 studies, RLM-MD-03 or RLM-MD-04. Safety assessments include AEs, clinical laboratory values, vital signs, and ECGs (reported as clinically significant AEs). No endpoints were specified for this study.

2.2. Background

RLM 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 RLM for the treatment of DG in adults. RLM is a member of an established class of compounds, ghrelin agonists, but if granted regulatory approval, it will be the first member of this class to attain marketing approval for DG.

In completed clinical studies to date, 466 participants with T1DM or T2DM with DG have been exposed to RLM at doses up to 100 µg administered BID by SC injection for up to 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 RLM. GE was accelerated and RLM 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 ($p = 0.043$) compared with placebo. The safety and tolerability profile of RLM in Study RM-131-004 was generally good.

Study RM-131-009 was a randomized, double-blind, placebo-controlled, stratified, multiple-dose, multinational study with 10 µg BID, 30 µg BID, and 100 µg BID doses of RLM. 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 target participant population for enrollment in the Phase 2b Study RM-131-009 (DG participants with vomiting at baseline) and encouraged assessment of a wider range of RLM doses was based on results from Study RM-131-004.

Results from Study RM-131-009 showed a statistically significant effect of RLM 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 RLM 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 RLM advantage. 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 RLM compared with 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 (Camilleri 2017).

RLM was generally safe and well tolerated among participants with T1DM or T2DM and DG. There were more reports of diarrhea and hyperglycemia-related events on RLM compared with placebo; hypoglycemia was infrequently reported (only 1.0% incidence in the placebo group and 1.2% in the RLM 100 µg group). Twenty-three SAEs were reported in the 289 participants treated with the 3 doses of RLM 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 comorbidities. Only 2 of the SAEs (cardiac failure congestive and DM inadequate control) were assessed by the investigator as possibly related to study treatment, both in the 100-µg treatment group. Three AEs of diabetic ketoacidosis were reported, 1 event on each RLM dose. A total of 20 RLM-treated participants and 3 placebo-treated participants discontinued study treatment due to an AE, only 3 of which were in the RLM 10 µg BID group.

With respect to laboratory findings, in some participants, glycemic control appeared to be negatively affected by treatment with RLM. There were trends in increasing HbA1c values after the initiation of RLM, which changed little 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, ECGs, physical examination findings, and injection site reactions; anti-drug antibodies were not found.

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

2.3. Benefit/Risk Assessment

Based on RLM information 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 are in place, including special laboratory assessments to allow early recognition by investigators and participants of a change of glycemic control. Thus, blood glucose and HbA1c assessments are included in this protocol so that action (eg, adjustment of medication and diet) may be taken, if necessary, to maintain stable glucose levels while participants are self-administering RLM. This, however, might increase the incidence of hypoglycemic reactions, especially in participants with T1DM. Participants' self-monitoring of glucose levels using glucometers is expected to alert participants and investigators to the possibility of hypoglycemic events as well. See Section 4, 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 RLM treatment may be found in the investigator's brochure (Relamorelin Investigator's Brochure); the Investigational Directions for Use for the pen injector, the device that will be used to administer study intervention, is also provided.

3. Objectives and Endpoints

Objectives	Endpoints/Assessments
Primary	
• To assess the safety of continued treatment with RLM for participants who previously completed the RLM-MD-03 or RLM-MD-04 study	• No endpoints were specified for this study. Safety assessments include: AEs, clinical laboratory values, vital signs, ECGs (reported as clinically significant AEs)

4. Study Design

4.1. Overall Design

Study 3071-305-020 is an open-label, multicenter, multinational safety study in participants with DG who completed the Phase 3 studies, RLM-MD-03 or RLM-MD-04, and have no ongoing AEs from either lead-in study that, in the investigator's opinion, would preclude participation. Participants who discontinued Studies RLM-MD-03 or RLM-MD-04 for any reason are not to be enrolled into this study. Participants who roll over to this continued access study within 30 days (ie, ≤ 30 days) of completing their final visit assessments in either Study RLM-MD-03 or Study RLM-MD-04 do not need to complete baseline assessments; information from the final visit of Studies RLM-MD-03 or RLM-MD-04 will be used as the information for Visit 1 of this study (see Section 8). Visit 1 should occur in ≤ 30 days of the last visit of the lead-in study. If a participant enters this continued-access study > 30 days after last visit in either lead-in study, Visit 1 baseline assessments will be completed as shown in Section 1.3

Approximately 1000 participants may roll over from Studies RLM-MD-03 or RLM-MD-04 at approximately 700 sites with an anticipated attrition rate of approximately 20% per year. No participant replacement is planned in this continued-access, open-label study.

4.1.1. Clinical Hypotheses

There is no specific clinical hypothesis related to the efficacy of treatment.

4.2. Scientific Rationale for Study Design

The Phase 3 studies will provide placebo-controlled information on the safety and efficacy of RLM in the treatment of DG. This open-label continuation of treatment will provide additional information on the long-term safety of RLM. The current study , will provide sufficient long-term safety information to support the safe use of RLM as a chronic treatment of DG.

4.3. Justification for Dose

A RLM dose of 10 µg SC BID will be used, which is the same as the dose in the Phase 3 program.

This dose was selected based on clinical safety and efficacy data from Study RLM-131-009, which also provided PK and PD information for the 10 µg 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 RLM 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 Study 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 RLM 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 effects, while the 10 µg BID dose achieved near maximal reductions. Of note, the twice-a-day regimen of RLM appears to be necessary for effective symptom relief; the 10 µg once daily study treatment did not demonstrate significant improvement in symptom relief compared with placebo after 28 days of dosing in Study RM-131-004.

Review of the safety laboratory data collected in RM-131-009 revealed a 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 an increase in HbA1c values that was approximately twice as much as observed for the 10 µg BID dose after 12 weeks of study. Shorter durations of treatment (4 weeks) with 10 µg BID of RLM, as observed in Study RM-131-004, did not demonstrate this increase in HbA1c in diabetic participants.

4.4. End of Study Definition

This study will continue until RLM becomes commercially available or the sponsor terminates development.

A participant is considered to have completed the study if he/she has completed a final visit assessment.

5. Study Population

The target population is adult participants with DG who have successfully completed Study RLM-MD-03 or RLM-MD-04. Prospective approval of protocol deviations to enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all the following criteria apply:

1. Successful completion of either Study RLM-MD-03 or Study RLM-MD-04 (completed final study visit), and rolling over into Study 3071-305-020 in ≤ 30 days; eligible participants who completed these studies prior to administrative initiation of this protocol at their study center, will also be allowed to participate in this continued-access study
2. Ability to provide written IC prior to any study procedures and willingness and ability to comply with study procedures
3. Demonstration of adequate compliance with the study procedures in Study RLM-MD-03 or RLM-MD-04, in the opinion of the investigator

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Participant is planning to receive an investigational drug (other than study intervention) or investigational device at any time during Study 3071-305-020.
2. Participant has an unresolved AE from a lead-in study that, in the investigator's opinion, would limit the participant's ability to participate in the study (see also Section 8).
3. Any other reason that, in the investigator's opinion, would confound proper interpretation of the study or expose a participant to unacceptable risk, including renal, hepatic, or cardiopulmonary disease
4. Females who are pregnant, nursing, or planning a pregnancy during the study

5. Participant is directly or indirectly involved in the conduct and administration of this study as an investigator, sub-investigator, study coordinator, other study staff member, or employee of Allergan; 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.

Rationale for Inclusion and Exclusion Criteria
The inclusion and exclusion criteria are meant to create a population of participants that is well characterized as having DG with symptoms that require chronic treatment.

5.3. Lifestyle Considerations

There are no specific dietary restrictions in the study. It is expected that participants are aware of the importance of maintaining reasonable consistency in treating DM and maintaining healthy lifestyle and dietary restrictions for achieving adequate control of hyperglycemia.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study.

Individuals who do not meet the criteria for participation in this study (screen failures) may not be rescreened.

6. Study Intervention

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

The only study intervention planned is the daily administration of RLM 10 µg SC BID.

6.1. Study Interventions Administered

Participants are to self-administer open-label study intervention SC BID 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 intervention is to be administered during typical meal times (eg, 06:00 to 09:00 and 17:00 to 20:00).

If a participant misses a dose before either the morning or evening meal, he/she is to adjust his/her study intervention administration as follows:

- If within 6 hours of the normal dosing time relative to the morning or evening dose, the participant is to self-administer the dose at that time.
- If more than 6 hours after the normal dosing time relative to the morning or evening dose, the participant is not to self-administer the dose, and should 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 are to rotate injection sites in the abdomen.

Study intervention will be dispensed as pen injectors with prefilled cartridges of RLM. Study intervention details are provided in Table 6-1.

Table 6-1 Study Intervention Details

Study Intervention	RLM
Dosage Formulation	Prefilled cartridge in multi-dose pen injector
Unit Dose Strength	10 µg dose
Route of Administration	SC
Dosing Instructions	Administer twice daily
Packaging and Labeling	Study intervention 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) Sharp (assembled pen)
Injection Device	Utilize multi-dose pen injector for the administration of the study intervention. 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.

6.1.1. 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 the 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 Section 8.3.6).
4. Other medical devices (not manufactured by or for Allergan) provided for use in this study may include a glucometer.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled 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 intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study interventions are provided in the Study Reference Manual.
5. Devices that are damaged during shipment or at the site or that malfunction during use must be accounted for and returned. The investigator will promptly notify the sponsor's Clinical Research department of any device malfunction. The Clinical Research or Product Support representative will provide instruction for the return of any faulty device for evaluation.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is an open-label study. No blinding of assigned study intervention will occur.

6.4. Study Intervention Compliance

Study intervention compliance will be assessed using participant recall during each study visit.

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

6.5. 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 eCRF along with:

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

Prior medications that were ongoing at the end of Studies RLM-MD-03 and RLM-MD-04 will be automatically transferred into the Study 3071-305-020 database.

As much as possible, the dose and frequency of all concomitant medications taken for chronic conditions with the exception of DM are to be held stable during the study. The sponsor is to be contacted if there are any questions regarding concomitant or prior therapy. Diabetic medications will be adjusted as needed to keep glycemic control at a steady level (Section 6.5.2).

6.5.1. Prohibited Interventions

There are no prohibited drug classes in this study. However, some drugs, eg, GLP-1 agonists, pramlintide or opioid drugs, may slow GE and may be undesirable in participants with DG.

6.5.2. Permitted Interventions

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving during the study must be recorded on 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 consist mostly of participants receiving 1 or more prescription medications for blood-glucose control, as needed. Good clinical practice allows for frequent adjustment of medication by participants and their health care providers to minimize large fluctuations in glycemia, and this practice is encouraged in this study. Certain diabetic drugs delay GE and are not expected to benefit participants with DG. Other therapy considered necessary for the participant's welfare may be given at the discretion of the investigator or participant's health care provider.

The sponsor or designee is to be contacted if there are any questions regarding concomitant therapy.

6.5.3. Rescue Medicine

There is no restriction on the use of medications to alleviate symptoms of DG such as nausea and vomiting. The use of such treatment and its frequency are to be recorded on the concomitant medications eCRF.

6.6. Dose Modification

No dose modifications are planned.

6.7. Intervention after the End of the Study

No interventions are planned after closure of the study.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

A premature discontinuation will occur if a participant who signs the ICF and is dosed with study intervention ceases participation in the study, regardless of circumstances, before the completion of the protocol-defined study procedures.

Definitions of the standard terms that may lead to discontinuations are provided in Appendix 5.

Reasons for discontinuation from the study intervention and/or the study may include the following commonly used or other acceptable terms:

Commonly Used Terms	Other Acceptable Terms
Adverse event	Death
Completed	Disease relapse
Lack of efficacy	Failure to meet entry criteria
Lost to follow-up	Progressive disease
Other	Technical problems
Physician decision	
Pregnancy	
Protocol deviation	
Site terminated by sponsor	
Study terminated by sponsor	
Withdrawal by subject	

7.1. Discontinuation of Study Intervention

7.1.1. Temporary Discontinuation

In the event of AE or intercurrent illness, dosing of study intervention can be stopped temporarily for a maximum duration of 14 days. If longer cessation of dosing is necessary, the investigator must contact the sponsor.

7.1.2. Permanent Discontinuation

Permanent discontinuation of study intervention also requires discontinuation from the study. The following criteria should be evaluated:

- Special consideration should be paid to the appearance of abnormal laboratory test results suggesting severe drug-induced liver injury (DILI). Discontinuation of study intervention for abnormal liver function should be considered by the investigator when a participant meets criteria for Hy's law (see Section 8.3.7.1 and Appendix 9) or if the investigator believes that it is in the best interest of the participant.
- Documented episode of diabetic ketoacidosis, hyperosmolar non-ketotic diabetic syndrome, or severe hypoglycemia (defined as glucose levels < 3mmol/L, or < 54 mg/dl) that are assessed as study treatment-related.
- Female participants who become pregnant during the study must be discontinued from study intervention immediately and withdrawn from the study. See Appendix 7 for further details regarding follow-up of the participant through the pregnancy.

See the SoA (Section 1.3) for data to be collected at the time of study intervention discontinuation.

7.2. Participant Discontinuation/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, behavioral, compliance, or administrative reasons.
- 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 and follow-up and for any further evaluations that need to be completed.

7.3. 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 ought to 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 will be documented in the participant's medical record.
- If the participant continues to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8. Study Assessments and Procedures

Scheduled evaluations and laboratory tests (serum chemistries and hematologic assessments, including HbA1c and pregnancy testing) for each participant will be performed as noted in the SoA (refer to Section 1.3).

A central laboratory will be used for safety laboratory assessments. Safety data as well as central laboratory results will be collected as noted in the SoA.

- Study procedures and their timing are summarized in the SoA (Section 1.3).
- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns are to be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant will continue or discontinue study intervention.

- Adherence to the study design requirements, including those specified in the SoA, 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 be approximately 170 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

All participants who roll over to this continued-access study (Study 3071-305-020) after completing their final visit assessments in either Study RLM-MD-03 or Study RLM-MD-04 are required to sign a new IC. Additionally, eligible participants who completed these studies prior to administrative initiation of this protocol at their study center, will be allowed to participate in this continued-access study, but are required to sign a new IC. Information from the final visit of Study RLM-MD-03 or Study RLM-MD-04 will be used as the information for Visit 1 (Baseline) of this study for these participants; if a participant enters this continued-access study > 30 days after last visit in lead-in study, Visit 1 baseline assessments will be completed (See SoA, Section 1.3). Demography and ongoing medical history will also be rolled over from Studies RLM-MD-03 or RLM-MD-04.

8.1. Efficacy Assessments

No efficacy assessments are planned for this continued-access study.

8.2. Safety Assessments

Safety assessments will include vital signs, clinical laboratory tests (hematology, clinical chemistry including HbA1c, urinalysis), and ECG values reported as clinically significant AEs.

AEs, including SAEs, SUSARs, and study-intervention discontinuation due to AEs will be assessed.

Planned timepoints for all safety assessments are provided in the SoA (Section 1.3).

8.2.1. Physical Examinations

- Physical examinations (as per the investigator's standard of care) are to be performed at baseline, at each annual visit, and at the Final Visit. Symptom-directed (abbreviated) physical examinations, including evaluation of the injection sites for clinically significant reactions, may be conducted as required at other study visits. A clinically significant injection site reaction is to be reported as an AE.
- Any abnormality noted on the physical examination done at Final Study Visit or the Early Termination Visit that was not present on the physical examination at baseline is to be reported as an AE if considered by the investigator to be clinically significant.
- Investigators are to pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

Vital signs will be assessed as follows:

- Systolic and diastolic BP, HR, temperature, and respiratory rate will be assessed at baseline, at each annual visit, and at the Final/Early Termination Visit; BP and HR will be assessed at all other visits; 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 are to 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.

8.2.3. Electrocardiograms

- Single 12-lead ECG will be obtained at baseline from a lead-in study, at Week 2 (Visit 1a), yearly starting at Visit 5 (Month 12), and at the Final Visit. If a participant enters the continued-access study > 30 days after last visit in lead-in study, an ECG will be obtained at Visit 1 as part of the baseline assessments for the continued-access study. All participants will have an ECG at Week 2 (Visit 1a). If a participant continues in the study for longer than 1 year, ECGs are to be performed annually starting at Visit 5. Any clinically significant changes in ECG results should be reported as AEs.

8.2.4. Clinical Safety Laboratory Assessments

- See Appendix 2 for the list of laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study in the AE 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 abnormal values considered clinically significant during participation in the study or within 30 days after the last dose of study intervention must 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 is to 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 SoA (Section 1.3).
    - 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, then the results must be recorded in the eCRF as AEs/SAEs.
    - Urine dipstick kits are to be used to conduct pregnancy tests.

8.2.5. Self-monitoring of Blood Glucose

Participants will be strongly encouraged to perform self-monitoring of blood glucose at home in order to achieve and maintain optimum glucose control during the study. This is almost always required for participants with T1DM and is good clinical practice in participants with T2DM. It is recommended that this be done at least once weekly.

Information from blood glucose self-monitoring, 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).

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Appendix 3.

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

The investigator and any qualified 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 intervention or study procedures, or that caused the participant to discontinue the study intervention (see Section 7.1).

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be collected from the signing of the ICF until 30 days after the final visit in the study, or early termination visit, at the timepoints specified in the SoA (Section 1.3), and as observed or reported spontaneously by study participants.

Medical occurrences that begin before the start of study intervention, but after obtaining IC will be recorded on the AE eCRF.

All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix 3. 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 information after conclusion of the study participation. However, if the investigator learns of any SAEs, 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 intervention or study participation, the investigator must promptly notify the sponsor.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

8.3.2. Method of Detecting AEs and SAEs

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

8.3.3. 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 AESIs as defined in Appendix 3 will be followed until resolution, stabilization, the event's etiology is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on AE/SAE follow-up procedures is given in Appendix 3.

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by MSP 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 MSP with a copy of any postmortem findings including histopathology.

New or updated information will be recorded on the originally completed eCRF.

The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

8.3.4. 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 intervention 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 intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.
- Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAE) 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.

8.3.5. Pregnancy

- Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study intervention and until 7 days after the last dose.
- If a pregnancy is reported, the investigator must inform the sponsor within 24 hours of learning of the pregnancy and must follow the procedures outlined in Appendix 7.
- Abnormal pregnancy outcomes (eg, spontaneous or elective abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6. Medical Device Incidents (Including Malfunctions)

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

The definition of a medical device incident and a device deficiency can be found in Appendix 8.

Incidents fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 8.3.3 and Appendix 3 of the protocol.

8.3.6.1. Time Period for Detecting Medical Device Incidents

- Medical device incidents, deficiencies, 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 8.

8.3.6.2. Follow-up of Medical Device Incidents

- All medical device incidents involving an AE/SAE will be followed and reported in the same manner as other AEs (see Section 8.3.3). This applies to all participants, including those who discontinue study intervention 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.

8.3.6.3. 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.

8.3.6.4. Regulatory Reporting Requirements for Medical Device Incidents and Deficiencies

- 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 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.

8.3.7. Adverse Events of Special Interest

8.3.7.1. Potential Hy's Law

Criteria for potential Hy's law cases are as follows:

- ALT or AST ≥ 3 × ULN) AND
- Total bilirubin ≥ 2 × ULN AND
- Alkaline phosphatase < 2 × ULN

Study site personnel must record and report every participant who meets the criteria for potential Hy's law as SAEs (see Appendix 9 for detailed description on handling potential Hy's law cases and liver toxicity). 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 last dose of study intervention.

Additional details regarding liver safety assessments and follow-up are provided in Appendix 9.

8.3.7.2. 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 must 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 are to be reported as AEs (Section 8.3.3).

Documented episode of diabetic ketoacidosis, hyperosmolar non-ketotic diabetic syndrome, or severe hypoglycemia (defined as glucose levels < 3mm/L, or < 54 mg/dl) that are assessed as study treatment-related will lead to permanent discontinuation of study intervention.

8.3.8. Medication Errors

Medication error refers to any unintended error in the dosing and/or administration of the study intervention 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 intervention.

Overdose: Unintentional administration of a quantity of the study intervention 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 intervention or comparator as applicable. This also takes into account cumulative effects due to overdose.

Underdose: Unintentional administration of a quantity of the study intervention 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 RLM at a dose less than 10 µg BID, a dose of 10 µg once daily will be considered an underdose.

8.4. Treatment of Overdose

The sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator must:

1. Contact the MSP immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities until study intervention 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.

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

PD parameters are not evaluated in this study.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

Biomarkers or other assessments are not used in the study.

8.9. Health Economics

Health economics outcomes will not be captured in this study.

9. Statistical Considerations

9.1. Statistical Hypothesis

There is no specific statistical hypothesis in this study.

9.2. Sample Size Determination

There were no sample size calculations performed for this study.

9.3. Population for Analyses

The analysis populations will consist of participants as defined in Table 9-1.

Table 9-1 Analysis Populations

Population	Definition
Enrolled	All enrolled participants who sign informed consent
Safety	All participants who received ≥ 1 administration of study intervention

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock and will describe the participant populations to be included in the analyses. This section is a summary of the planned statistical analyses:

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

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

Continuous descriptives	• N1, mean, SD, median, minimum, maximum • N1 = participants with nonmissing value
Event descriptives	• Number and percentage of events in individual categories ○ Events counted individually for each instance • Percentage denominator = total number of events
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
Shift analyses	• Number and percentage of participants in individual baseline and postbaseline categories • Percentage denominator = number of participants in individual baseline categories • N1 = participants with nonmissing values at both baseline and the specified postbaseline analysis visit

9.4.1. Safety Analyses

The safety analysis will be performed using the safety population and will be fully defined in the SAP. No endpoints were specified for this study. The safety parameters will include AEs, vital signs, clinical laboratory tests (hematology, clinical chemistry including HbA1c, urinalysis), and ECG values reported as clinically significant AEs.

9.4.1.1. Adverse Events

An AE will be considered a TEAE if:

- The AE began on or after the date of the first dose of study intervention; or
- The AE was present before the date of the first dose of study intervention, but increased in severity or became serious on or after the date of the first dose of study intervention

An AE that occurs more than 30 days after the last dose of study intervention will not be counted as a TEAE.

An AE will be considered a TESAE if it is a TEAE that additionally meets any SAE criteria.

The number and percentage of participants reporting TEAEs will be tabulated by the MedDRA SOC and preferred term, and by SOC, preferred term, and severity (MedDRA version 21.0 or newer).

The number and percentage of participants reporting treatment-related TEAEs will be tabulated by SOC and preferred term.

If more than 1 AE is coded to the same preferred term for the same participant, the participant will be counted only once for that preferred term using the most severe occurrence for the summarizations by severity.

Summary tables will be provided for participants with TESAEs and participants with TEAEs leading to discontinuation. Listings of all AEs, SAEs, and AEs leading to discontinuation by participant will be presented.

The definitions of an AE and SAE can be found in Appendix 3.

9.4.1.2. Clinical Laboratory Assessments

Descriptive statistics for clinical laboratory values (in SI units) at baseline and changes from baseline at each assessment will be presented for each clinical laboratory assessment.

The criteria for PCS laboratory values will be detailed in the SAP. The number and percentage of participants who have PCS postbaseline clinical laboratory values will be tabulated at each assessment. The percentages will be calculated relative to the number of participants who have available non-PCS baseline values and at least 1 postbaseline assessment. The numerator will be

the total number of participants with at least 1 PCS postbaseline value. A supportive listing of participants with PCS postbaseline values will be provided for the safety population.

Shift tables from baseline to end of study for clinical laboratory parameters will be presented.

Study-specific assessments (eg, HbA1c) will be summarized as part of the overall clinical laboratory assessments.

9.4.1.3. Vital Signs

Descriptive statistics for vital signs (systolic and diastolic BP, pulse rate, weight, respiration rate, and temperature) at baseline (screening) and changes from baseline at each assessment will be presented.

Vital sign values will be considered to be PCS if they meet both the observed-value criteria and the change-from-baseline-value criteria that will be detailed in the SAP. The number and percentage of participants who have PCS postbaseline vital sign values will be tabulated for each assessment. The percentages will be calculated relative to the number of participants who have available non-PCS baseline values and at least 1 postbaseline assessment. The numerator will be the total number of participants with at least 1 PCS postbaseline value. A supportive listing of participants with PCS postbaseline values will be provided for the safety population.

Shift tables from baseline to end of study for vital signs will be presented.

9.4.1.4. Electrocardiogram

No specific analyses for ECGs are planned. Clinically significant findings related to ECG results will be recorded as AEs and will be included as part of the AE analyses.

9.5. Interim Analyses

No interim analysis is planned.

9.6. Data Monitoring Committee

A Data Monitoring Committee was not used for this study.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. 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 International Ethical Guidelines
  - Applicable ICH/ISO 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)

10.1.2. Financial Disclosure

Investigators and sub-investigators 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 study and for 1 year after completion of the study.

10.1.3. 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, 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

10.1.4. Data Protection

- Participants will be assigned a unique identifier. 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.

10.1.5. Posting Clinical Study Data

All data generated in this study are the property of the sponsor. An integrated clinical and statistical report will be prepared at the completion of the study.

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on eCRFs 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 physically or 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 eCRF 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.

10.1.7. 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.

10.1.8. Study and Site Closure

The sponsor or 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 intervention development

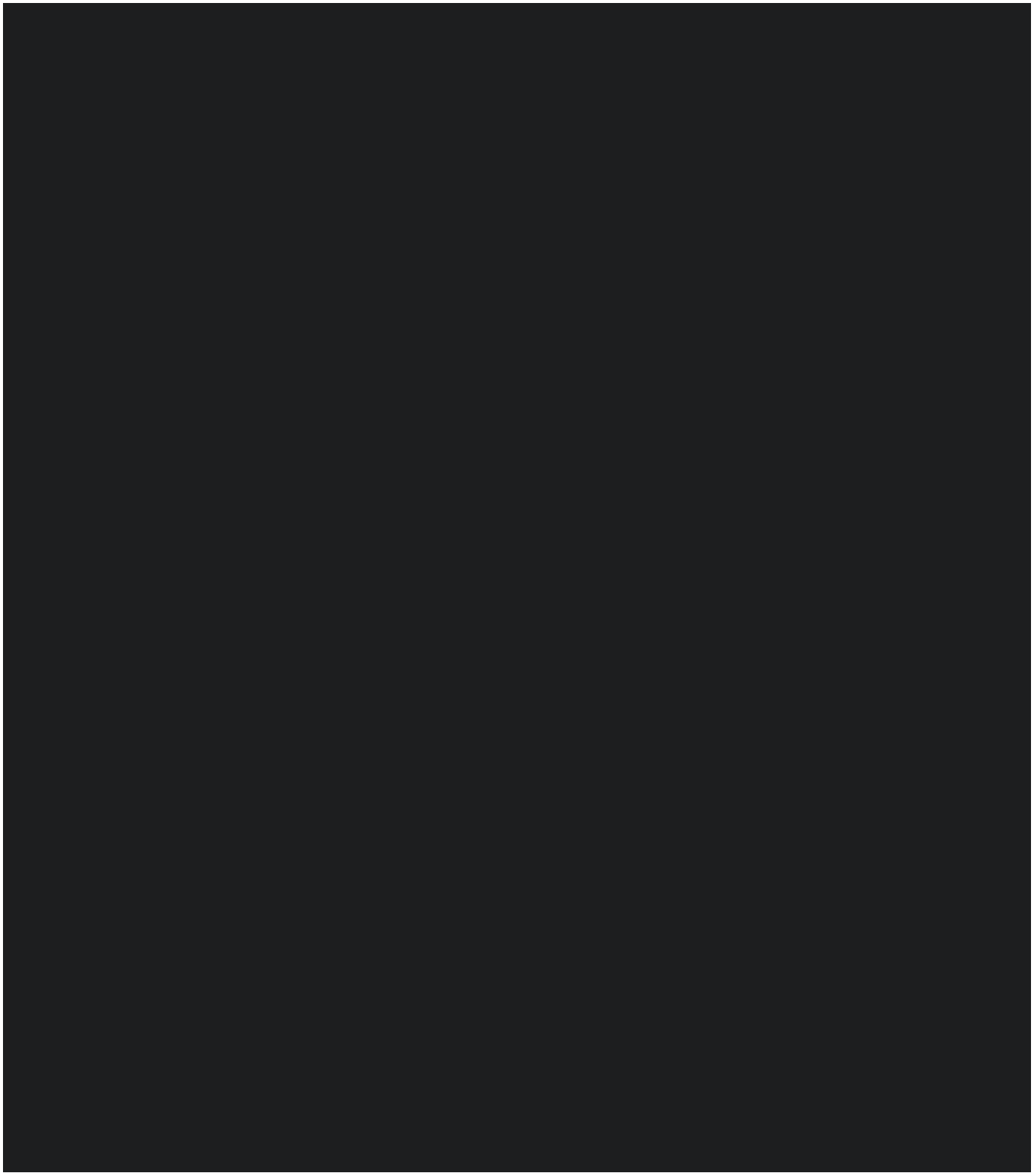
10.1.9. Publication Policy

- 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.

10.1.10. Compliance with Protocol

The investigator is responsible for compliance with the protocol at the investigational site. A representative of the sponsor will make frequent contact with the investigator and his/her research staff and will conduct regular monitoring visits at the site to review participant and study intervention accountability records for compliance with the protocol. Protocol deviations will be discussed with the investigator upon identification. Significant protocol deviations will be reported to the IRB/IEC according to the IRB/IEC's reporting requirements.



10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. 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 intervention, whether or not considered related to the study intervention. • 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 intervention. For devices, disease signs and symptoms that existed prior to the study intervention are not considered AEs. **AE of Special Interest (AESI)** An adverse event of special interest (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 AESI(s) have been identified for the study intervention(s) in this protocol (see Section 8.3.7): 1. Hy's law cases 2. Inadequate control of diabetes: hyperglycemia and hypoglycemia Serious AESIs must be reported to the sponsor within 24 hours via the SAE form. Nonserious AESIs do not require submission on an SAE form; should be recorded on the appropriate page of the eCRF. **Potential Hy's Law Cases** For potential Hy's law cases, refer to Appendix 9.

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); for example: o The test result is associated with accompanying symptoms, and/or o The test result requires additional diagnostic testing or medical/surgical intervention, and/or o The test result leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or o The test result is considered to be an AE by the investigator or sponsor. • 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 intervention 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 intervention or a concomitant medication. Overdose per se will not be reported as an AE or SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AEs or SAEs if they fulfil the definition of an AE or SAE. Also, lack of efficacy or failure of expected pharmacological action also constitutes 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 DG, and they will not be reported as AEs or SAEs: nausea, abdominal pain, upper abdominal pain, vomiting, postprandial fullness, bloating, and early satiety.
- 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

10.3.2. 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 intervention 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 is to be considered serious. Hospitalization for elective intervention 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 is to 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 are usually considered serious. Examples of such events include invasive or malignant cancers, intensive intervention 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.

10.3.3. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording
• When an AE or 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 or 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 AE or SAE eCRF 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 or SAE.

Assessment of Intensity

MILD	A type of AE 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 AE 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 AE 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 intervention and each occurrence of each AE or 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 intervention administration will be considered and investigated.
- The investigator will also consult the investigator's brochure 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

10.3.4. Reporting of SAEs

SAE Reporting to Sponsor or Designee Within 24 Hours
• Email is the preferred method to transmit SAE information. [redacted] • Facsimile transmission of the 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/SADE form within the designated reporting time frames. • Contacts for SAE reporting can be found on the protocol title page.

10.4. Appendix 4: Abbreviations

Term/Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ALP	alkaline phosphatase
AST	aspartate aminotransferase
AT	aminotransferases
BID	twice daily
BP	blood pressure
CDISC	Clinical Data Interchange Standards Consortium
CFR	Code of Federal Regulations
CPT	common protocol template
CRF	case report form
DG	diabetic gastroparesis
DILI	drug-induced liver injury
DGSSD	diabetic gastroparesis symptom severity diary
DM	diabetes mellitus
ECG	electrocardiogram
eCRF	electronic case report form
FDA	Food and Drug Administration
FPFV	first participant first visit
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GE	gastric emptying
GERD	gastroesophageal reflux disease
GHS1α	Growth Hormone Secretagogue 1α
GP	gastroparesis
HbA1c	hemoglobin A1c
HIPAA	Health Insurance Portability and Accountability Act
HR	heart rate
HRT	hormonal replacement therapy
IC	informed consent
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
INR	international normalized ratio

Term/Abbreviation	Definition
IRB	Institutional Review Board
ISO	International Organization for Standardization
MedDRA	Medical Dictionary for Regulatory Activities
MSP	Medical Safety Physician
NASH	nonalcoholic steatohepatitis
NCI	National Cancer Institute
PCS	potentially clinically significant
PD	pharmacodynamic
PK	pharmacokinetic
Etc.	QT interval corrected for heart rate
QT interval	Time between Q wave and T wave in heart's electrical cycle
RLM	relamorelin
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SoA	schedule of activities
SUSAR	suspected unexpected serious adverse reactions
SOC	system organ class
TBL	total bilirubin
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
ULN	upper limits of normal
US	United States
WOCBP	Woman/women of childbearing potential

10.5. Appendix 5: Standard Discontinuation Criteria

CDISC Submission Value	CDISC Definition
Adverse event	Any untoward medical occurrence in a patient or clinical investigation subject 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)
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)
Physician 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 trial
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 subject	An indication that a study participant has removed itself from the study (NCI)

10.6. Appendix 6: Study Tabular Summary

Parameter Group	Parameter	Value
Trial information	Trial Title	Open-label Extension Study of Relamorelin for the Treatment of Diabetic Gastroparesis
	Clinical Study Sponsor	Allergan
	Trial Phase Classification	Phase 3 Trial
	Trial Indication	DG
	Trial Indication Type	Treatment
	Trial Type	Safety
	Trial Length	Until the product becomes commercially available or the sponsor terminates development
	Planned Country of Investigational Sites	multiple
	Planned Number of Subjects	~1000
	FDA-Regulated Device Study	No
	FDA-Regulated Drug Study	Yes
	Pediatric Study	No
Subject information	Diagnosis Group	NA
	Healthy Subject Indicator	No
	Planned Minimum Age of Subjects	18 years
	Planned Maximum Age of Subjects	NA
	Sex of Participants	Both
	Stable Disease Minimum Duration	3 months
Treatments	Investigational Therapy or Treatment	RLM
	Intervention Type	Drug
	Pharmacological Class of Invest. Therapy	Synthetic ghrelin analogue
	Dose per Administration	10
	Dose Units	µg
	Dosing Frequency	BID
	Route of Administration	SC
	Current Therapy or Treatment	RLM
	Added on to Existing Treatments	No
	Control Type	N/A
	Comparative Treatment Name	N/A
Trial design	Study Type	Interventional
	Intervention Model	Open-label
	Planned Number of Arms	1
	Trial is Randomized	No
	Randomization Quotient	N/A
	Trial Blinding Schema	N/A
	Stratification Factor	N/A
	Adaptive Design	No
	Study Stop Rules	No

10.7. Appendix 7: Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Women of Child Bearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

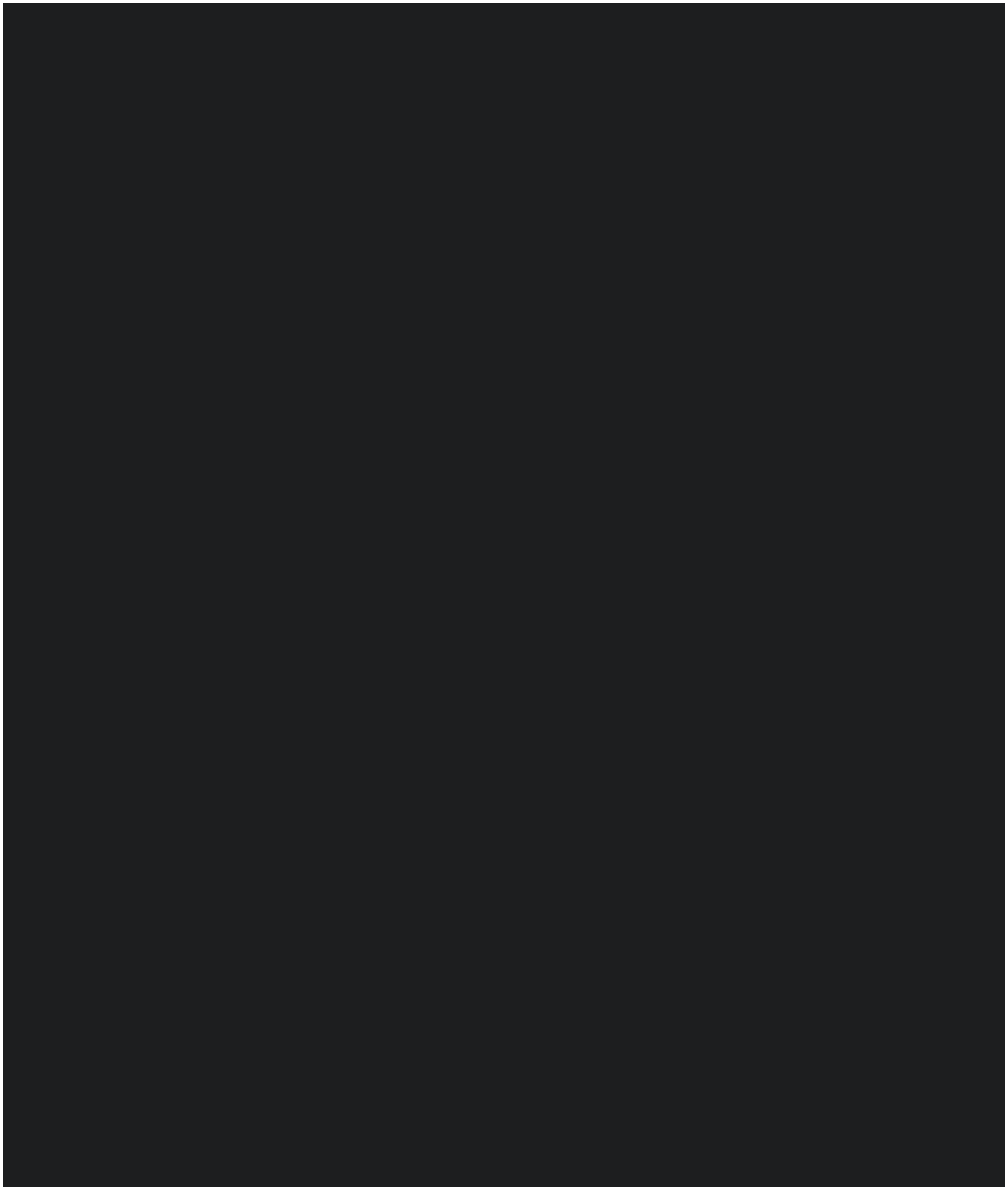
Women in the following categories are not considered WOCBP:

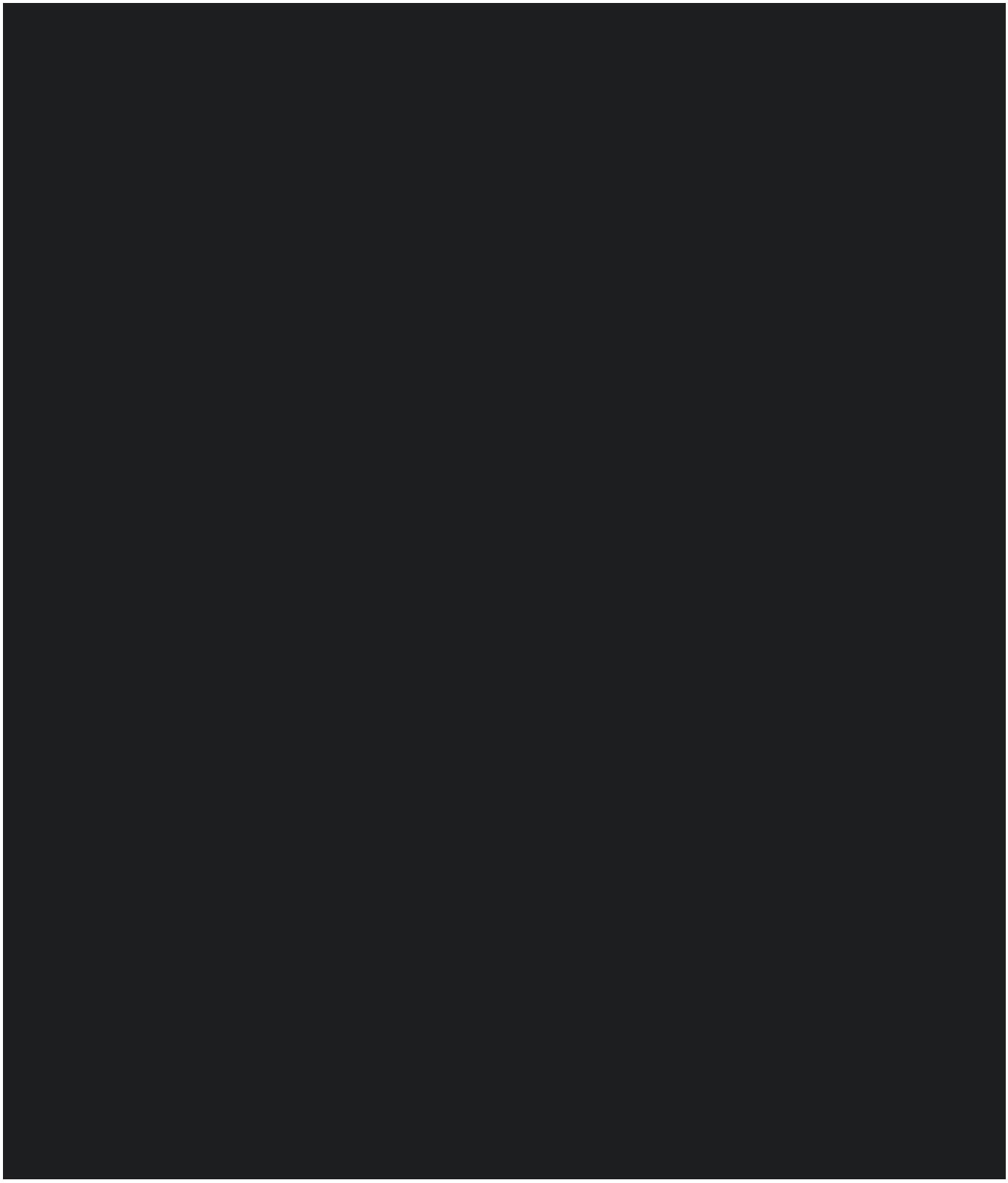
1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   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 FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or 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]





10.8. Appendix 8: Medical Device Incidents: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.8.1. 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 6.1 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 labeling 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 nonoccurrence 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 intervention is interrupted or compromised by a medical device failure.
- A misdiagnosis due to medical device failure leads to inappropriate intervention.
- A participant's health deteriorates due to medical device failure.

10.8.2. Documenting Medical Device Incidents

Medical Device Incident Documenting

[redacted]

10.9. Appendix 9: Liver Safety: Suggested Actions and Follow-up Assessments

Close monitoring should be initiated for the following participants:

- Participants with normal baseline serum aminotransferases (AT) who develop an increase of serum AT ≥ 3 × ULN
- Participants with elevated baseline AT who develop an increase of serum AT > 2 × the baseline value

The participant should return to the study site and be evaluated for potential drug-induced liver injury (DILI) as soon as possible, preferably within 48 to 72 hours from the time the investigator becomes aware of the abnormal results. Evaluation should typically include repeat testing of all 4 of the usual serum biochemical measures (ALT, AST, ALP, and TBL) to confirm the abnormalities and to determine if they are increasing or decreasing.

If it is difficult for the participant to return to the study site promptly, the participant should be retested locally, but normal laboratory ranges should be recorded, results should be made available to sponsor's study physician and the investigator immediately, and the data should be included in the eCRF. If repeat testing within this time frame is not possible, the study intervention should be discontinued.

It is critical to initiate close monitoring immediately upon detection and confirmation of signals of potential DILI as early as possible and not to wait until the next scheduled visit or monitoring interval. Close monitoring of the participant should be initiated in conjunction with the sponsor and consideration given to the following:

- Obtain a more detailed history of symptoms and prior or concurrent diseases.
- Obtain a history of concomitant drug use, including nonprescription medications, herbal products and dietary supplements, alcohol and recreational drug use, and special diets.
- Obtain a history of exposure to environmental chemical agents.
- Initiation of appropriate evaluations including applicable laboratory tests (eg, direct bilirubin, INR), physical assessments, and other assessments (eg, imaging)
    - Rule out other potential causes of biochemical abnormalities, eg, acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; NASH; hypoxic/ischemic hepatopathy; and biliary tract disease.
- Consider gastroenterology or hepatology consultations.

If any of the following criteria are met, discontinuation of study intervention should be considered (if indicated, prior to receipt of confirming retest biochemistry laboratory test results) and the sponsor notified of the discontinuation:

- 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

- ALT or AST ≥ 5 × ULN for more than 2 weeks
- ALT or AST ≥ 8 × ULN

If the study intervention is discontinued, the participant may be re-challenged with study intervention only after consultation with the Allergan MSP. All participants showing potential DILI should be followed until all abnormalities return to normal or to the baseline state.

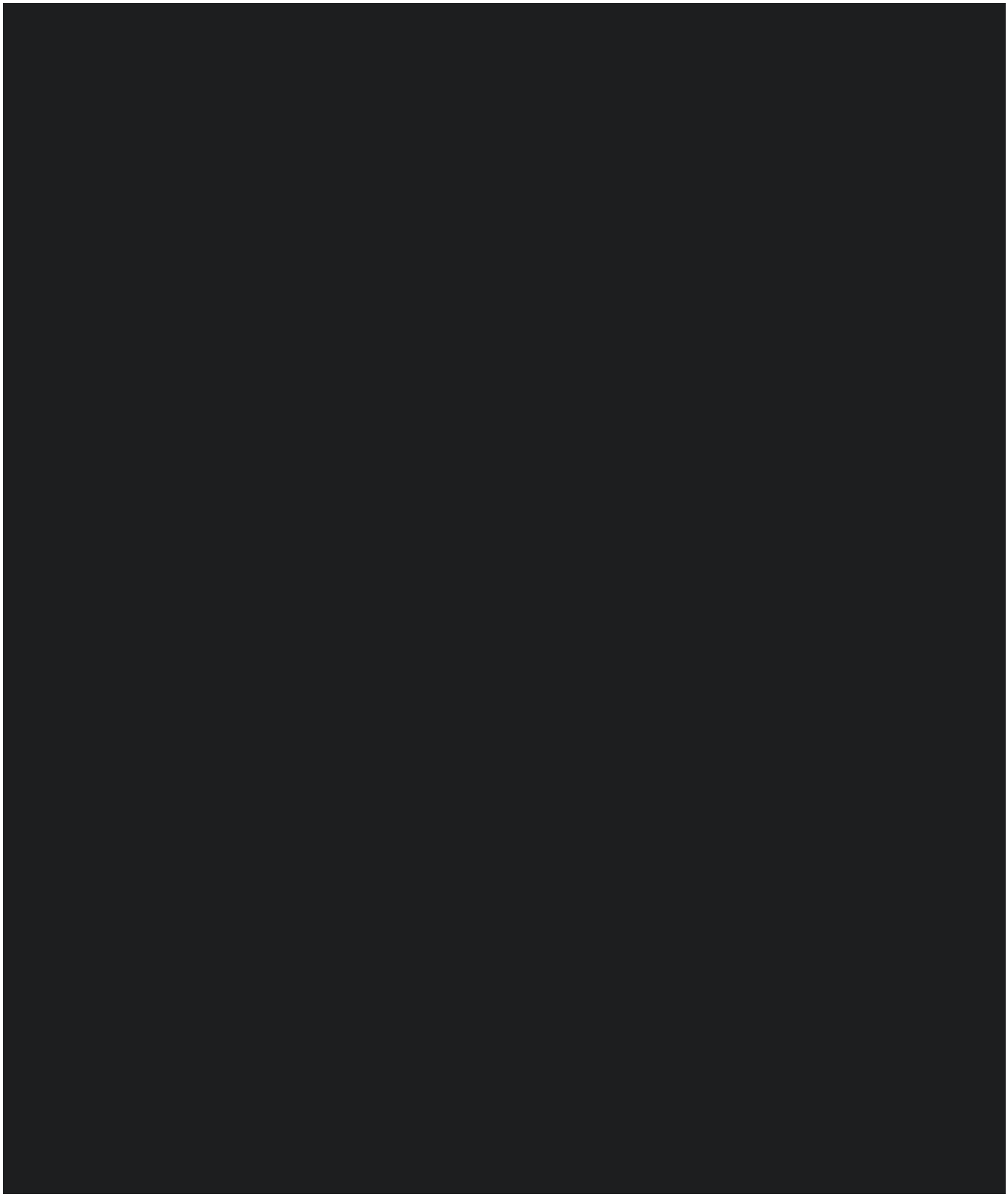
Reporting of Potential Hy's Law Cases

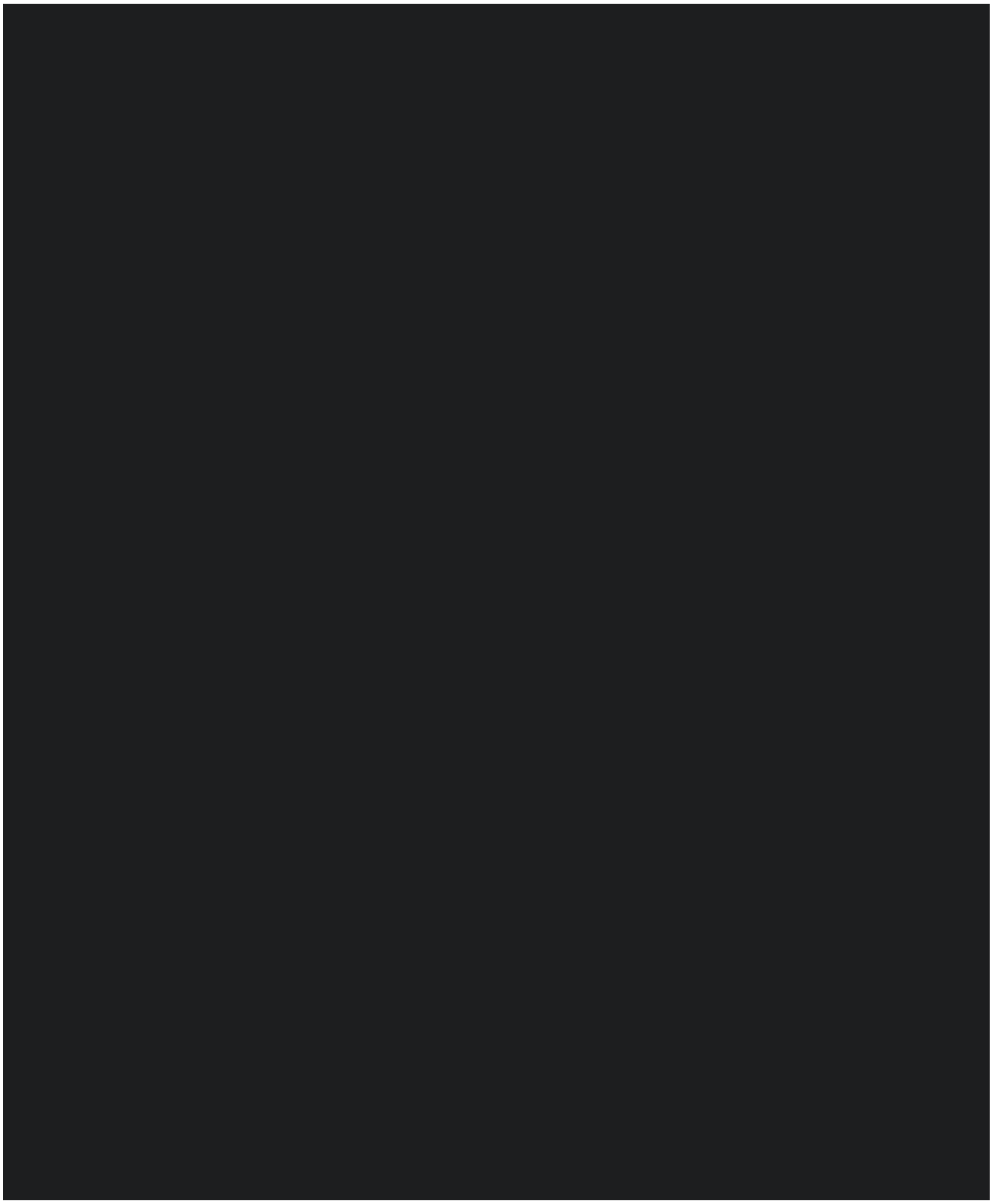
Potential Hy's law cases are defined by biochemical test results of hepatocellular injury and impaired hepatic function. They are considered Adverse Events of Special Interest (AESIs) and should be evaluated and followed further (ie, close monitoring initiated) to determine whether these laboratory abnormalities are indicative of DILI. As indicated above, discontinuation of study intervention should also be considered. Criteria that identify a potential Hy's law case are as follows:

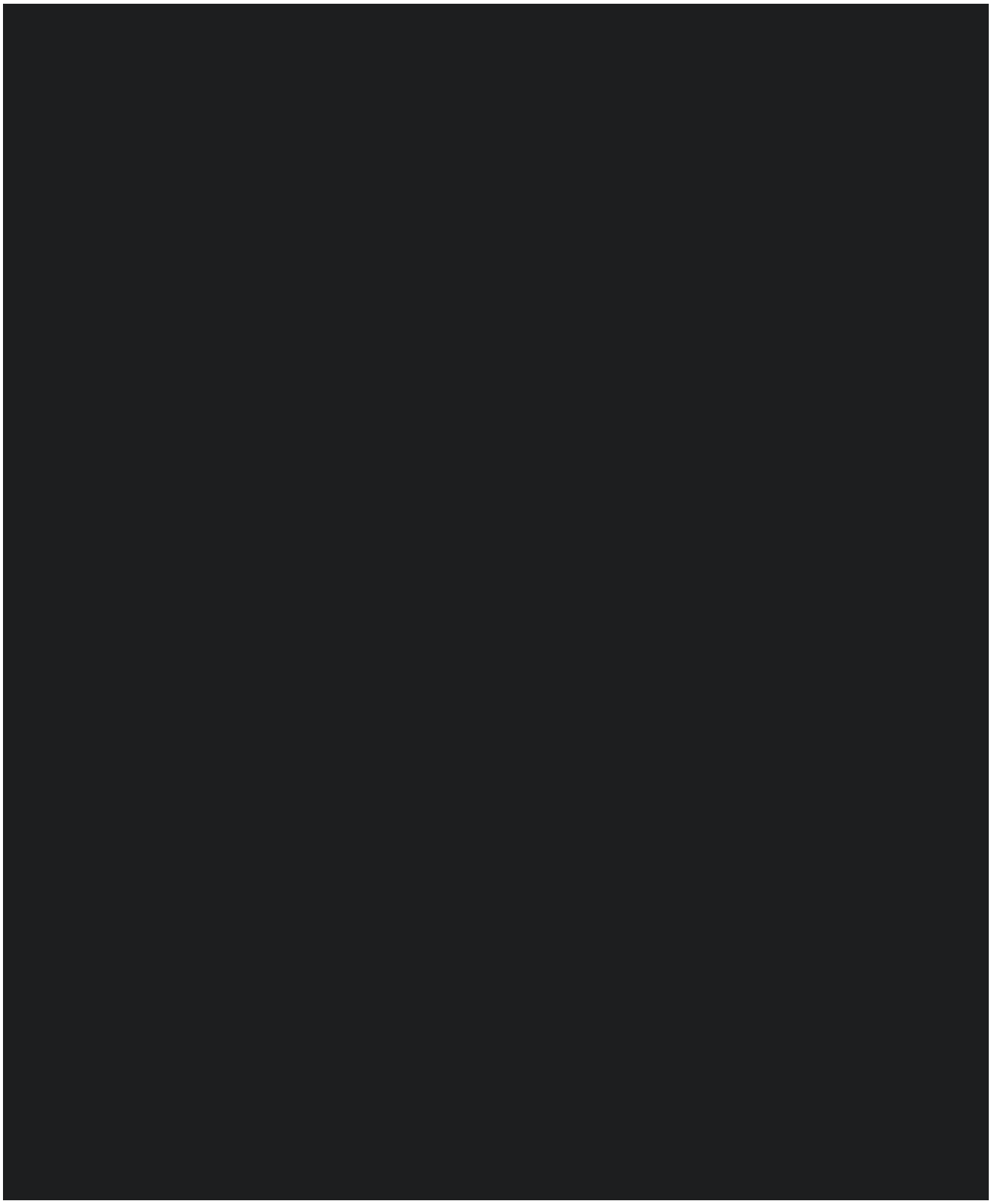
- ALT or AST ≥ 3 × ULN AND
- Total bilirubin ≥ 2 × ULN AND
- Alkaline phosphatase < 2 × ULN

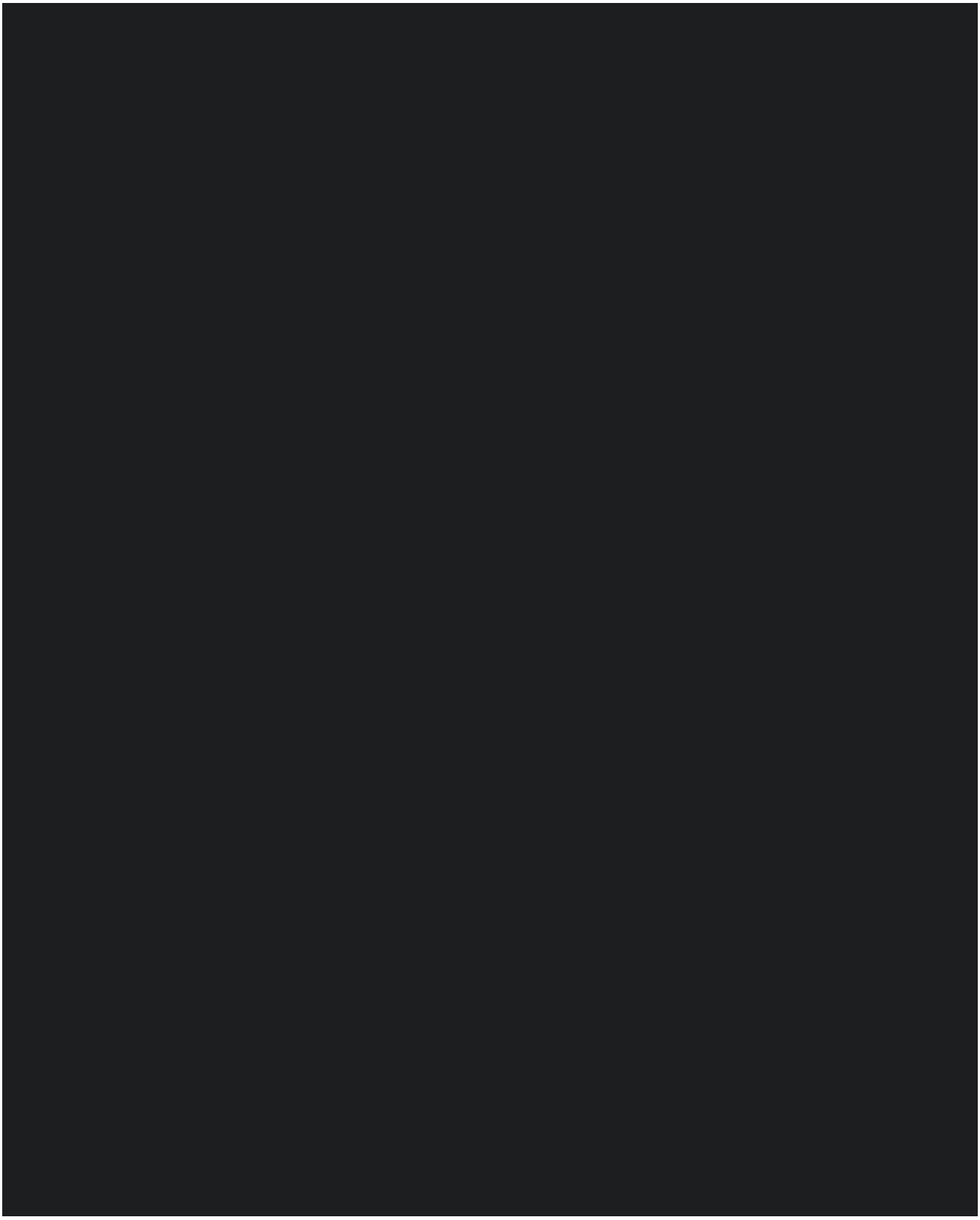
Sites must report every participant who meets the Hy's law criteria if this occurs within the time the participant signs the ICF until 30 days after the last dose of study intervention.

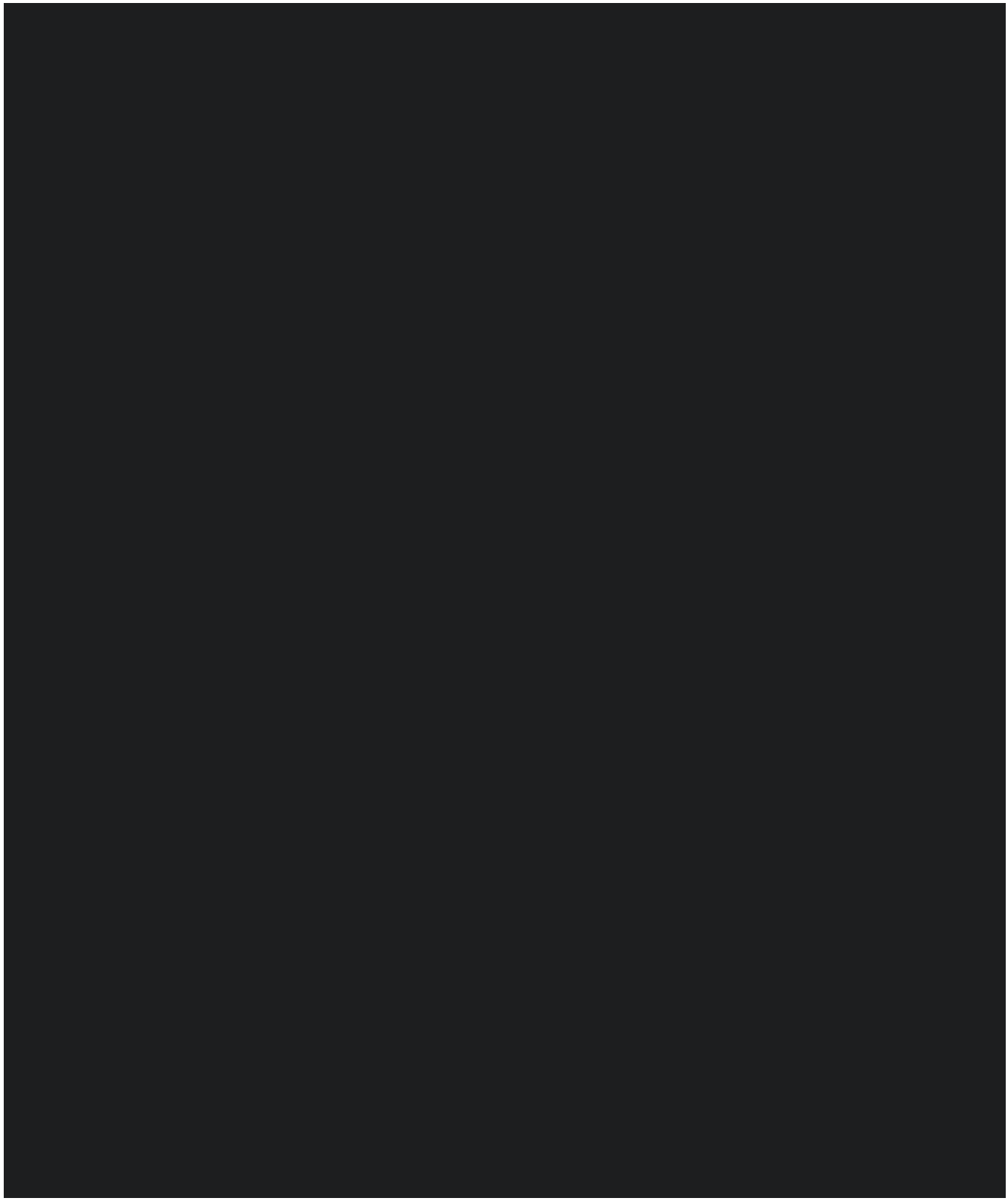
A laboratory alert for a potential DILI case will be sent immediately to the sponsor and investigators when the above criteria have been met, even if no clinical symptoms have been experienced. [redacted]

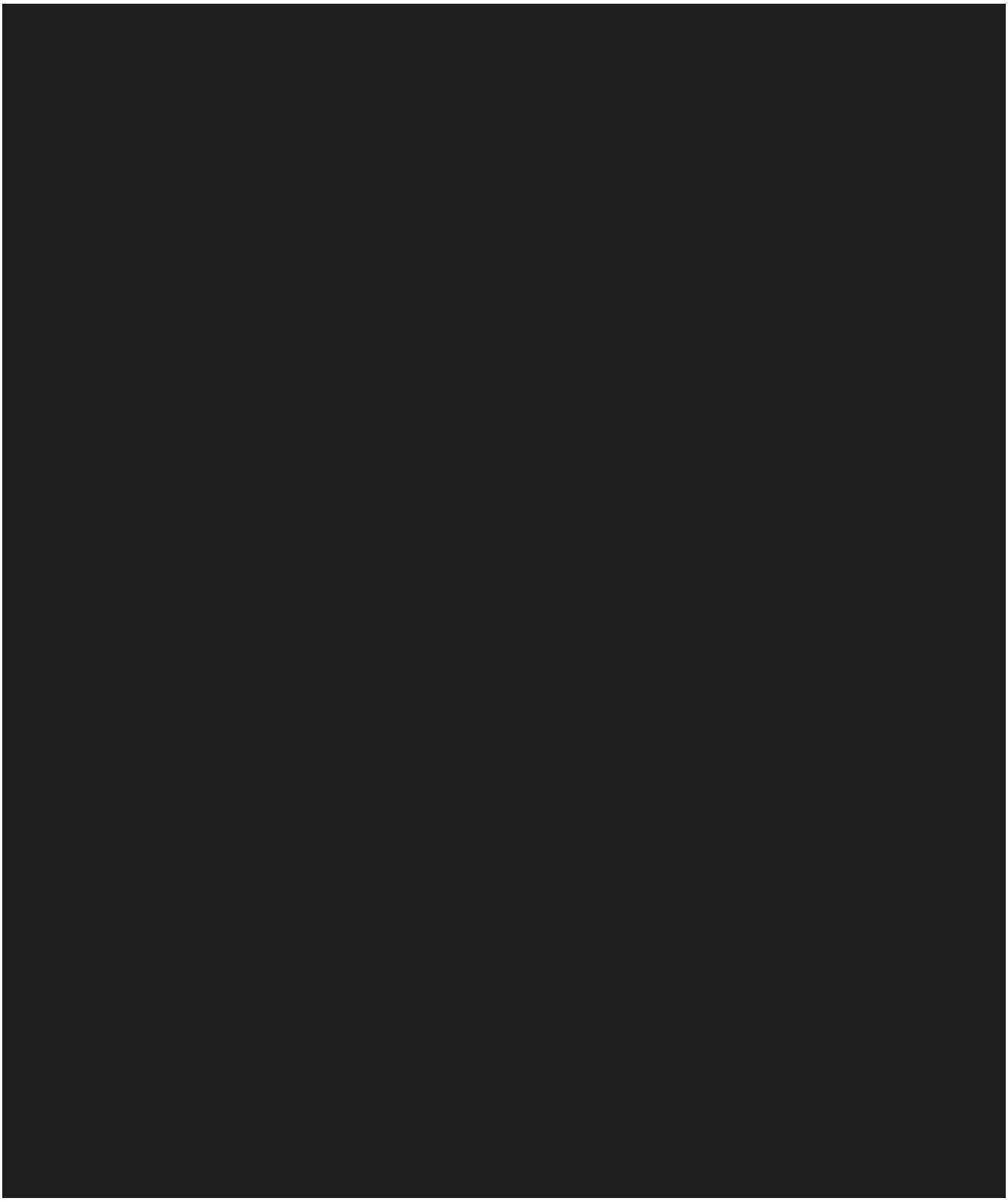


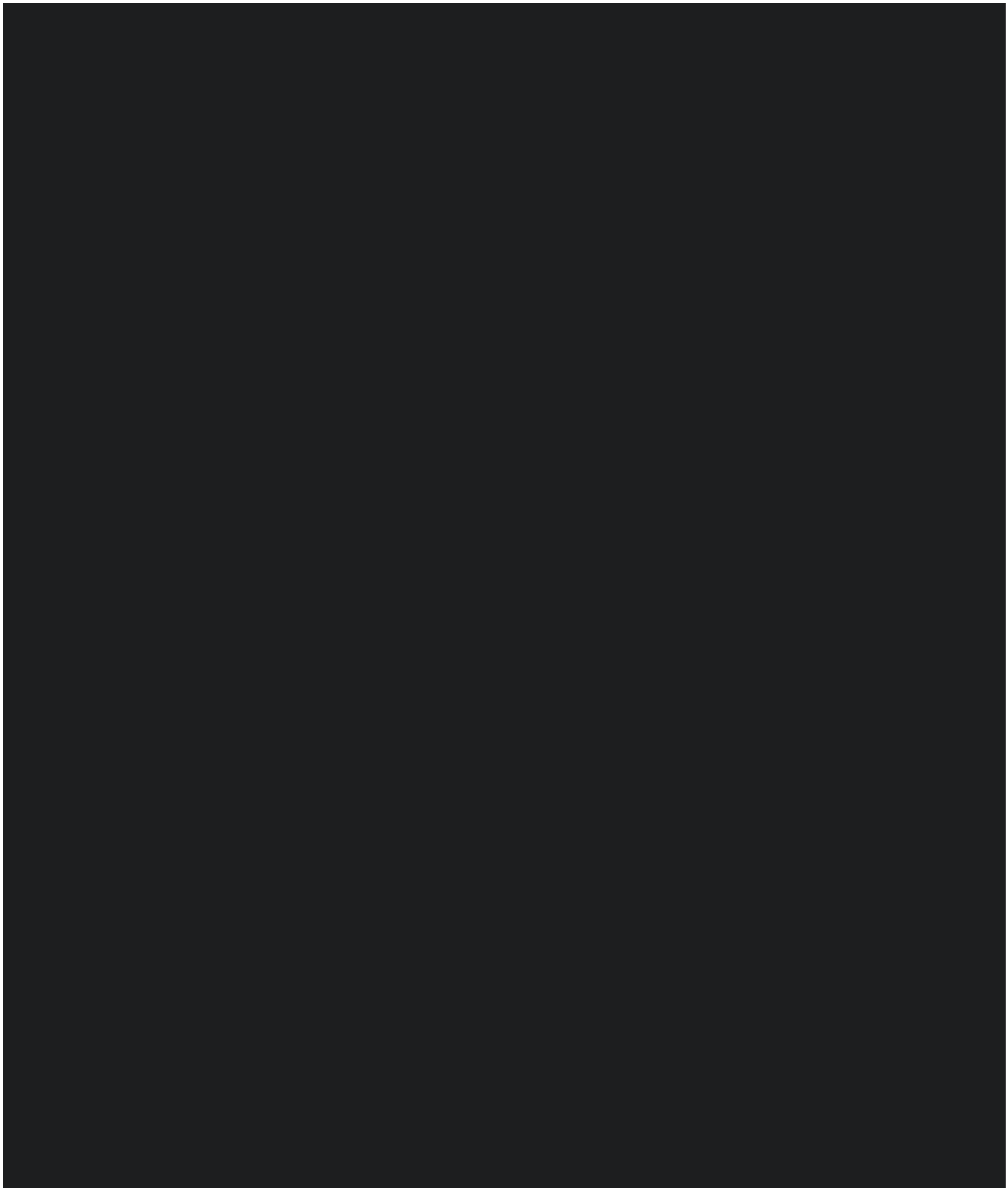


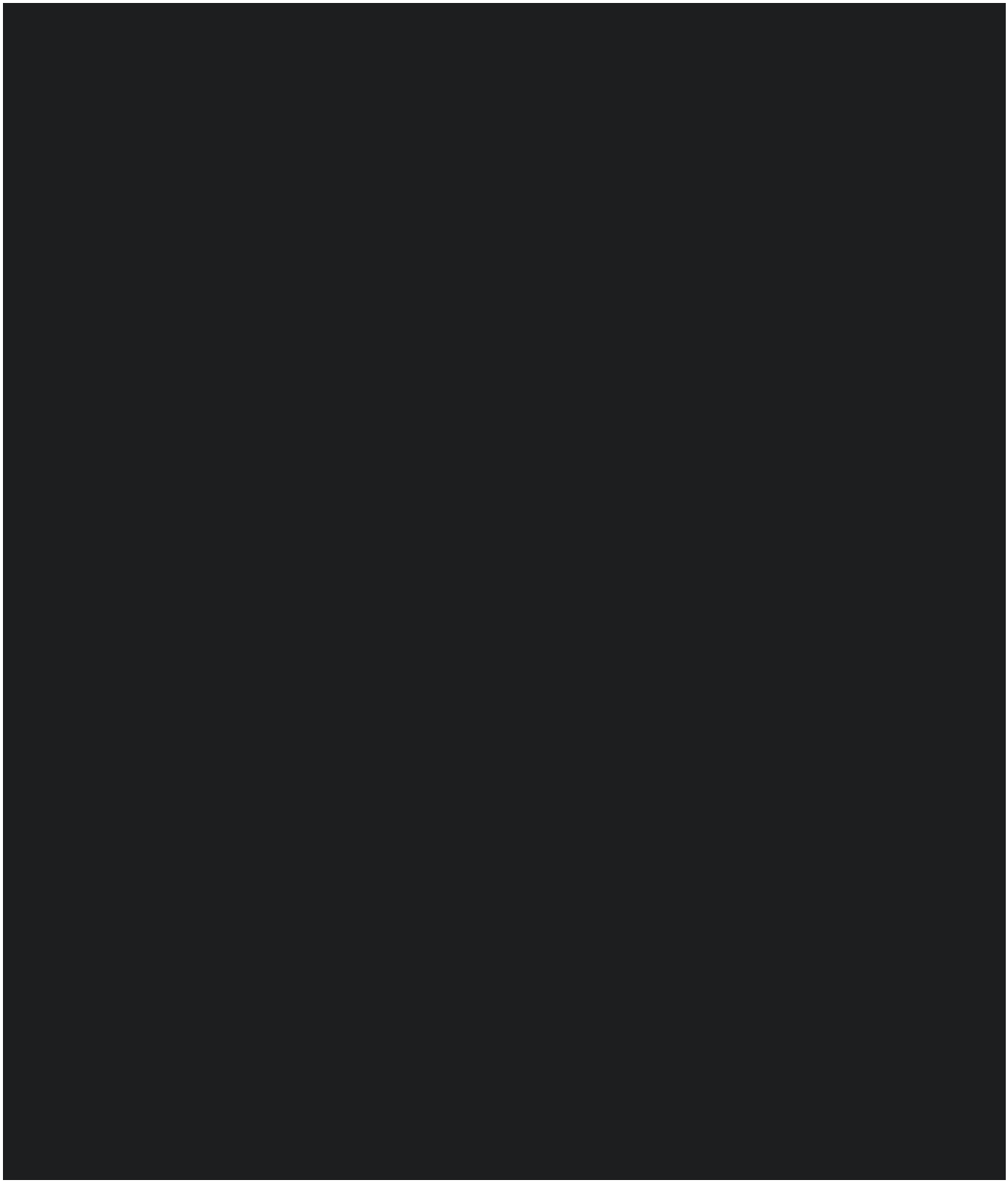












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