CLINICAL STUDY PROTOCOL
SUMMARY OF CHANGES

Protocol title:	A Phase 2, Multi-Center, Randomized, Double-Blind, Placebo-Controlled Parallel-Group Study to Evaluate the Safety, Tolerability, and Efficacy of Olorinab in Subjects with Irritable Bowel Syndrome Experiencing Abdominal Pain
Protocol number:	APD371-202
Version:	Amendment 3.0, dated 03 February 2020
Replaces version:	Amendment 2, dated 15 November 2019

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment 3.0: 03 February 2020

Overall Rationale for the Amendment

The primary rationale for this amendment is to add an optional long-term extension period to the study. Additional minor updates have been made throughout the protocol to add clarity to intended study conduct.

Summary of Changes

Current Section No. and Name	Description of Change	Brief Rationale
Throughout	Minor editorial, formatting, and nomenclature revisions. Throughout the protocol, information about the new long-term extension (LTE) was added in new, separate subsections. The descriptor "Main Study" was added to text and section headings that apply to the original study. Section numbers were adjusted as needed for the addition of new sections describing the LTE. Updated amendment numbering scheme to 3.0.	Minor updates for improved accuracy, clarity, readability, and consistency with current Arena standards. The descriptors "Long-Term Extension" and "Main Study" were added throughout for clarity. Numbering of the protocol amendment was adjusted [redacted]
Title Page	Version information updated. Degrees for Sponsor's Responsible Medical Officer added.	Changes reflect the current protocol details. Medical Officer information was corrected.
Protocol History	Row added for Amendment 3.0.	Changes reflect the current protocol details.
Synopsis	Updates throughout.	Updated for consistency with changes made to the main body of the protocol (detailed below).
Table of Contents	Updated to reflect the addition of sections supporting the LTE.	Changes support the addition of the LTE and the current outline of the protocol.
List of Abbreviations and Definitions of Terms	Updated.	Per changes made throughout the protocol.
1.1 Background	Data from long-term repeated-dose oral toxicity studies were added.	New long-term toxicity data to support long-term dosing in humans were needed.
2.1 Main Study	New subheading 2.1, Main Study, added above the Main Study Objectives.	New subheading was added to clarify which objectives applied to the Main Study versus the LTE.
2.2 Long-Term Extension	New subheading 2.2, Long-Term Extension, was added and the new objectives of the LTE were added.	New objectives were needed for the LTE and new subheadings were added for organization and clarity.
3.1.1 Main Study	New subheading 3.1.1, Main Study, added above the text describing the Main Study design.	New subheading was added to clarify which study design text applied to the Main Study versus the LTE.
Figure 1	The descriptor "Main Study" was added to the study period headings within the figure.	"Main Study" was added as a descriptor for clarity and to distinguish the figure from the new LTE figure.

Current Section No. and Name	Description of Change	Brief Rationale
3.1.2 Long-Term Extension	New section and text describing the design of the LTE was added.	New section needed to describe the design of the LTE.
Figure 2	New figure added showing design of LTE.	New figure needed to show design of the LTE.
3.2 Scientific Rationale for Study Design	Text was added to describe the rationale for the LTE.	New text needed to support the addition of the LTE.
3.3.1 Main Study	New subheading 3.3.1, Main Study, added above the text describing the justification for the doses used in the Main Study.	New subheading was added to clarify which Justification for Dose text applied to the Main Study versus the LTE.
3.3.2 Long-Term Extension	New subheading 3.3.2, Long-Term Extension, was added and new text justifying the doses chosen for the LTE was added.	New section needed to support the addition of the LTE.
3.6 Main Study Treatment Period	Text added to explain that the last day of the Run-in Period is Day –1 and the first day of the Treatment Period is Day 1.	Clarified there is no Day 0 in the Main Study.
3.8 Long-Term Extension Screening and Treatment Periods	New section added to describe the LTE Screening and Treatment Periods.	New section needed to support the addition of the LTE.
3.9 Long-Term Extension Follow-Up/End of Study	New section added to describe the LTE Follow-Up and End-of-Study procedures.	New section needed to support the addition of the LTE.
3.10 Early Termination Visit	Text regarding the LTE Early Termination Visit was added.	New text needed to support the addition of the LTE.
3.11 Study Duration	Text describing the duration of the LTE was added.	New text needed to support the addition of the LTE.
4.1 Main Study	New subheading 4.1, Main Study, added above the list of inclusion criteria for the Main Study.	New subheading was added to clarify which inclusion and exclusion criteria applied to the Main Study versus the LTE.
[redacted]		

Current Section No. and Name	Description of Change	Brief Rationale
4.1 Main Study (Continued)	Key exclusion criterion 3 was revised to allow history of cholecystectomy > 6 months prior to Screening for subjects with IBS-C.	History of cholecystectomy in subjects with IBS-C is not expected to interfere for the scientific validity of the study or represent a safety concern for subjects.
4.1.2.2 Other Exclusion Criteria (exclusion criterion 14)	*Clostridium difficile* was updated to *Clostridioides difficile*.	Update was made due to the reclassification of *Clostridium difficile* to *Clostridioides difficile* based on the adoption by the US Centers for Disease Control and Prevention.
4.2 Long-Term Extension	New section heading added.	New section heading needed to support the addition of the LTE.
4.2.1 Inclusion Criteria	New section added and inclusion criteria for LTE added.	New section needed to support the addition of the LTE.
4.2.2 Exclusion Criteria	New section added and exclusion criteria for LTE added.	New section needed to support the addition of the LTE.
4.5 Screen Failures, Run-in Failures, and Rescreening Guidance	Text added to define LTE screen failures and to describe circumstances under which subjects may be rescreened for the LTE.	New text needed to support the addition of the LTE.
	Content regarding values recorded after Screening and before Baseline that fail eligibility thresholds were rewritten.	Text was revised and shortened for clarity and readability.
5 Study Treatment	Information about the powder-in-capsule formulation was removed.	The powder-in-capsule formulation is no longer needed.
	The formulation to be used during the LTE was described.	New text needed to support the addition of the LTE.
5.5 Measures to Minimize Bias: Randomization and Blinding	The procedures for maintaining and breaking the blind during the LTE were added.	New text needed to support the addition of the LTE.
5.6 Study Treatment Compliance	The study visits at which compliance will be calculated during the Main Study were changed from Visits 4 through 7 to Visits 4 through 8. For the LTE, added Visits 3 through 7 during which compliance will be calculated.	The visits to be used to calculate compliance during the Main Study were corrected to Visits 4 through 8 and added for the LTE.
5.7 Concomitant Therapy	Text describing the concomitant therapy to be recorded during the LTE was added.	New text needed to support the addition of the LTE.
5.7.2 Allowed Concomitant Therapy	[redacted]	

Current Section No. and Name	Description of Change	Brief Rationale
5.7.3 Rescue Medication for Constipation or Diarrhea Symptoms	Text was revised to specify the study periods during which rescue medications for constipation or diarrhea symptoms may be administered, and to prohibit their use during the Screening Period.	New text needed to support the addition of the LTE and to clarify that rescue medications for constipation or diarrhea are not allowed during the Screening or Run-in Periods.
5.7.4 Prohibited Concomitant Therapy	[redacted]	
Table 1 Prohibited Concomitant Medications	[redacted]	
7.2 Informed Consent	A sentence was added to specify that participation in the LTE is optional and subjects who participate in the LTE will sign an additional consent.	New text needed to support the addition of the LTE.
7.5 Efficacy Assessments	Text describing when the eDiary should be completed during the LTE was added.	New text needed to support the addition of the LTE.
7.7.2 Vital Signs and Schedule of Assessments for Main Study, footnote e	The words “at least” were added to the instruction that subjects must rest in the supine position for “at least” 5 minutes before vital signs are measured.	This change allows some flexibility to sites when performing vital signs measurements and is not expected to affect study results.
7.7.4 Clinical Laboratory Assessments	The maximum amount of blood to be collected from each subject during the LTE was added.	New text needed to support the addition of the LTE.
7.10 Pharmacokinetics	The pharmacokinetic analysis to be performed during the LTE was added.	New text needed to support the addition of the LTE.
8.2 Analysis Sets	The analysis sets for the LTE were added.	New text and table needed to support the addition of the LTE.
8.3 Statistical Analyses	Text was added to describe when the SAPs for the Main Study and LTE will be finalized and how results will be reported.	New text needed to support the addition of the LTE.
8.3.1.1 Main Study Endpoints	New subheading 8.3.1.1, Main Study Endpoints, added above the text describing the Main Study endpoints.	New subheading was added to clarify which study endpoints apply to the Main Study versus the LTE.

Current Section No. and Name	Description of Change	Brief Rationale
8.3.1.2 Long-Term Extension Endpoints	New section and text for LTE endpoints added.	New section needed to support the addition of the LTE.
8.3.6 Statistical Analyses for the Long-Term Extension	New section added to describe the statistical analyses for the LTE.	New section needed to support the addition of the LTE.
9.2 Informed Consent Process	New sentence added regarding informed consent for the LTE.	New text needed to support the addition of the LTE.
[redacted]		

Name: Clinical Study Protocol: APD371-202 Amendment 3.0 - Summary of Changes
Description: A Phase 2, Multi-Center, Randomized, Double-Blind, Placebo-Controll

User Nam [redacted] Capacity: [redacted]	Meaning: Approval Step Date: 03-Feb-2020 23:14:59 GMT+0000

CLINICAL STUDY PROTOCOL

Protocol title:	A Phase 2, Multi-Center, Randomized, Double-Blind, Placebo-Controlled Parallel-Group Study to Evaluate the Safety, Tolerability, and Efficacy of Olorinab in Subjects with Irritable Bowel Syndrome Experiencing Abdominal Pain
Protocol number:	APD371-202
Version:	Amendment 3.0, dated 03 February 2020
Compound:	Olorinab (APD371)
Study phase:	Phase 2
Short title:	Olorinab in IBS-C and IBS-D
Indication:	Abdominal pain due to irritable bowel syndrome
NCT number:	NCT04043455
Sponsor name:	Arena Pharmaceuticals, Inc.
Legal registered address:	6154 Nancy Ridge Drive San Diego, California 92121
Sponsor's Responsible Medical Officer:	[redacted], MD, MHS, FACC Chief Medical Officer & Head of Clinical Development
Clinical lead:	[redacted], PharmD, PhD Director, Clinical Development Arena Pharmaceuticals, Inc. Tel: +[redacted] E-mail: [redacted]
SAE reporting:	IQVIA Pharmacovigilance Tel: [redacted] Fax [redacted] E-mail: [redacted]
Sponsor approval:	This protocol was approved by the Sponsor's Responsible Medical Officer or delegate. The electronic signature manifest is appended.

Confidentiality Statement

PROTOCOL HISTORY

Document	Amendment Type	Date
Amendment 3.0	Global	03 February 2020
Amendment 2	Global	15 November 2019
Amendment 1	Global	15 May 2019
Original Protocol	Not applicable	7 March 2019

PROTOCOL SYNOPSIS

Sponsor: Arena Pharmaceuticals, Inc.
Name of investigational study drug: Olorinab (APD371)
Protocol title: A Phase 2, Multi-Center, Randomized, Double-Blind, Placebo-Controlled Parallel-Group Study to Evaluate the Safety, Tolerability, and Efficacy of Olorinab in Subjects with Irritable Bowel Syndrome Experiencing Abdominal Pain
Protocol number: APD371-202
Phase: 2
Countries/regions (planned): United States
Objectives: ***Main Study*** Primary Objectives • To compare the efficacy of different doses of olorinab versus placebo on improvement in abdominal pain severity in subjects with irritable bowel syndrome (IBS) • To compare the safety and tolerability of different doses of olorinab versus placebo in subjects with IBS Secondary Objectives • To compare the proportion of abdominal pain treatment responders for different doses of olorinab versus placebo • To compare change in pain frequency for different doses of olorinab versus placebo • To characterize the pharmacokinetics (PK) of olorinab and its predominant metabolites [redacted], and [redacted] in subjects with IBS ***Long-Term Extension (LTE)*** Primary Objective • To evaluate the safety and tolerability of long-term administration of olorinab in subjects with IBS

Study Design:

Main Study

The Main Study is designed to assess the efficacy, safety, and tolerability of olorinab in the treatment of abdominal pain in subjects with IBS with predominant constipation (IBS-C) or IBS with predominant diarrhea (IBS-D) who are not on concomitant treatment for IBS. This is a Phase 2, multi-center, randomized, double-blind, placebo-controlled, parallel-group study that includes a Screening Period (up to 4 weeks for subjects who consent to colonic biopsy, up to 2 weeks for all other subjects), a Run-in Period (2 weeks), a randomized Main Study Treatment Period (12 weeks), and a post-treatment Follow-Up Period (2 weeks), totaling 16-20 weeks. After the Run-in Period, eligible subjects will be equally randomized into 1 of 4 treatment groups (olorinab 10, 25, or 50 mg 3 times per day [tid] or placebo tid). Randomization will be stratified by sex and IBS subtype. The number of subjects enrolled with IBS-C will be approximately equal to the number of subjects enrolled with IBS-D.

LTE

The LTE is an optional extension period that is designed to assess the safety, tolerability, population PK (C_{trough}), and efficacy of long-term administration of olorinab in subjects who have completed the Main Study. The LTE will be conducted at the same study sites as the Main Study. Subjects who participate in the LTE will be subjects who complete LTE Visit 2 < 28 days after their Main Study Week 12 visit ("Continuing subjects") or subjects who complete their Main Study Week 12 visit ≥ 28 days prior to LTE Visit 2 ("Gap subjects"). Gap subjects will be required to have an LTE Screening visit approximately 14 days prior to randomization in the LTE. After completing eligibility assessments, subjects will enter a randomized LTE Treatment Period (52 weeks), and a post-treatment LTE Follow-Up Period (2 weeks). Gap subjects who are interested in participating in the LTE must enroll in the LTE within 8 weeks after the IRB approval date of Amendment 3.0. All subjects who meet LTE eligibility criteria will be assigned to olorinab treatment as follows:

- Subjects who received 25 mg or 50 mg olorinab during the Main Study will continue to receive the same dose.
- Subjects who received placebo or 10 mg olorinab during the Main Study will be re-randomized (1:1) in a double-blind manner to receive either 25 mg or 50 mg olorinab.

Number of subjects (planned):

Main Study subjects

Subjects will be screened until approximately 60 subjects have been randomized per study group for a total of approximately 240 subjects.

LTE subjects

Subjects who participate in the LTE will include study subjects who completed the Main Study Treatment Period and who meet the applicable inclusion and exclusion criteria for the LTE. Subject enrollment in the LTE will not be capped.

Eligibility criteria:

Main Study

Inclusion criteria:

Subjects must meet the following inclusion criteria to be eligible for enrollment into the study:

1. Male and female subjects ≥ 18 and ≤ 70 years of age at Visit 1 (Screening)

[redacted]

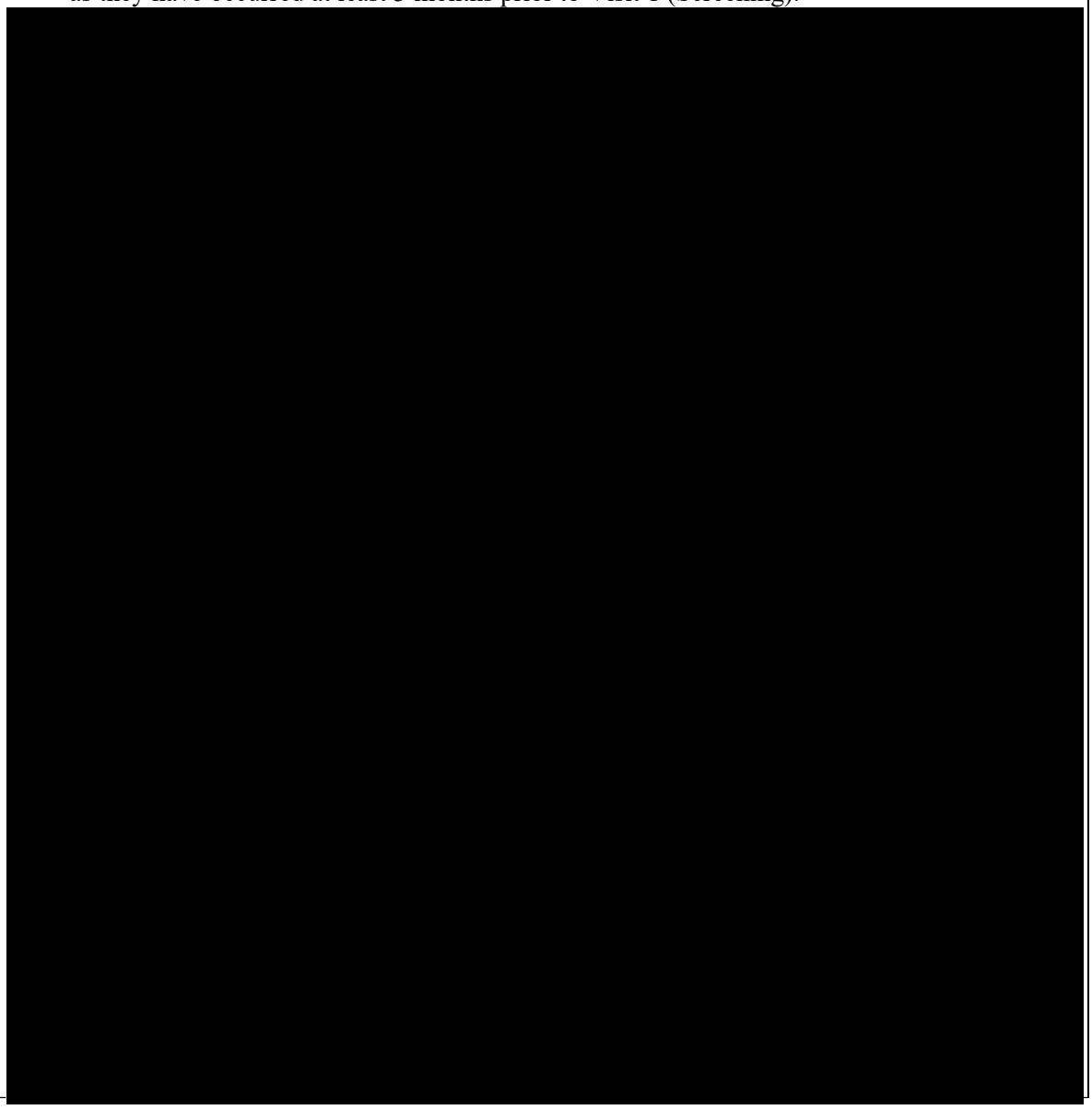
3. Clinical diagnosis of IBS-C or IBS-D according to Rome IV criteria at Visit 1 (Screening)
4. Per the Rome IV diagnostic algorithm for IBS, subjects 50 years of age and over are to have had one of the following with a result that rules out causes of abdominal pain other than IBS:
    a. Colonoscopy (within 10 years of Visit 1 [Screening])
    b. Flexible sigmoidoscopy and double contrast barium enema (within 5 years of Visit 1 [Screening])
    c. Computed tomography (CT) colonography (within 5 years of Visit 1 [Screening])

[redacted]

Key exclusion criteria:

Subjects are excluded from the study if they meet any of the following key exclusion criteria. Additional exclusion criteria are listed in Section 4.1.2.

1. Diagnosis of IBS with mixed bowel habits (IBS-M) or unsubtyped IBS (IBS-U)
2. Clinically relevant changes in dietary, lifestyle, or exercise regimen within 30 days prior to Visit 1 (Screening) that may confound efficacy assessments in the clinical judgment of the Investigator (or designee)
3. Any colonic or major abdominal surgery (eg, bariatric surgery [including gastric banding], stomach surgery, small/large bowel surgery, or abdominal large vessel surgery). History of cholecystectomy is exclusionary for subjects with IBS-D. For subjects with IBS-C, a history of cholecystectomy more than 6 months prior to Visit 1 (Screening) is allowed. Procedures such as appendectomy, hysterectomy, caesarean section, or polypectomy are allowed as long as they have occurred at least 3 months prior to Visit 1 (Screening).



[redacted]

LTE

Inclusion criteria:

Subjects must meet the following inclusion criteria to be eligible for enrollment into the LTE:

1. All subjects must have completed the Main Study (including both Visit 8 [Week 12] and Visit 9 [Week 14]).

[redacted]

Exclusion criteria:

Subjects are excluded from the LTE if they meet any of the following exclusion criteria:

1. Subject meets any exclusion criteria from the Main Study, at the time of assessing eligibility for the LTE, unless approved by the Sponsor in advance.
2. Subject had less than 75% overall compliance with eDiary entries during the Main Study.
3. Subject deviated from the prescribed dosage regimen during the Main Study (ie, overall study treatment compliance less than 85% or more than 115%), unless approved by the Sponsor in advance.

[redacted]

Treatment groups and duration:

Main Study

This study will include a Screening Period (up to 4 weeks for subjects consenting to biopsy, up to 2 weeks for all other subjects), a Run-in Period (2 weeks), a randomized Main Study Treatment Period (12 weeks), and a post-treatment Follow-Up Period (2 weeks) for a total duration of 16 to 20 weeks. Throughout the Main Study Treatment Period, subjects will self-administer oral study treatment (olorinab 10, 25, or 50 mg, or placebo) tid with water. This study will not allow dose adjustments.

LTE

The LTE will include a 2-week LTE Screening Period for Gap subjects only; continuing subjects may enter the LTE without a separate LTE Screening Period. Once enrolled, all subjects will enter a 52-week LTE Treatment Period followed by a 2-week LTE Follow-Up Period. Subjects who participate in the LTE will have a total study duration as follows:

- Gap Subjects: Main Study (16 to 20 weeks), an LTE Screening Period (2 weeks), an LTE Treatment Period (52 weeks), and an LTE Follow-Up Period (2 weeks), for a total duration of 72 to 76 weeks.
- Continuing Subjects: Main Study (16 to 20 weeks), an LTE Treatment Period (52 weeks), and an LTE Follow-Up Period (2 weeks), for a total duration of 70 to 74 weeks.

Subjects will self-administer oral study treatment (olorinab 25 or 50 mg) tid with water. This study will not allow dose adjustments.

Endpoints

Main Study

Primary

- Change in average abdominal pain score (AAPS) from Baseline to Week 12
- Adverse events (AEs) and clinically relevant changes in vital signs and clinical laboratory results

Secondary

- The proportion of subjects achieving a ≥ 30% improvement in AAPS from Baseline to Week 12
- The proportion of subjects achieving a ≥ 30% improvement in AAPS from Baseline for at least 6 of the 12 weeks during the Main Study Treatment Period
- Percent change in AAPS from Baseline to Week 12
- Change in number of pain free days per week from Baseline to Week 12
- PK parameters including, but not limited to, observed maximum concentration (C_{max}), time of observed maximum (peak) concentration after drug administration (t_{max}), and observed trough (pre-dose) concentration (C_{trough})

LTE

Primary

- AEs, clinically relevant changes in vital signs, and clinical laboratory results.

Statistical methods:

Main Study

Sample size:

It is assumed that change in AAPS from Baseline to Week 12 will be normally distributed with a standard deviation (SD) of 1.9. Assuming a 1:1:1:1 randomization, 240 subjects (60 per treatment group) is sufficient to achieve at least 80% power to detect a treatment effect of 1.0 between each of the olorinab treatment groups and placebo by a 2-sample t-test using a 2-sided significance level of 0.05.

Note, under the same assumptions there is at least 95% power to detect a treatment effect of 1.0 between the pooled olorinab treatment group (180 subjects) and placebo (60 subjects).

A blinded review of the data to evaluate the assumption regarding the SD of the change in AAPS from Baseline at Week 12 may be conducted. The planned sample size will not be reduced as a result of the sample size re-estimation. Details will be specified in the Main Study Statistical Analysis Plan (SAP).

Testing strategy:

No formal testing strategy or adjustments of the type I error will be employed for the primary, secondary, or exploratory endpoints. Estimates and confidence intervals (CI) for treatment groups and from pairwise comparisons will be used in an exploratory manner.

Statistical analysis:

The primary endpoint, change in AAPS from Baseline to Week 12, will be analyzed using a mixed-effects model repeated measures (MMRM) analysis with treatment, stratification factors, visit, and treatment-by-visit interaction as factors and Baseline AAPS as a covariate. Least squares means, standard errors (SEs), and 95% CIs for the treatments and their difference will be presented together with the p-values.

Unless otherwise specified, continuous endpoints will be analyzed using a MMRM analysis with treatment, the stratification factors, visit, and treatment-by-visit interaction as factors and Baseline AAPS and Baseline value (if applicable) as covariates. Least squares means, SEs, and 95% CIs for the treatments and their difference will be presented together with the p-values.

Categorical endpoints will be analyzed by either the Cochran-Mantel-Haenszel method, Fisher's exact test, or by logistic regression with a model that includes treatment and stratification factors as factors and Baseline AAPS and Baseline value (if applicable) as covariates. The odds ratio of each olorinab treatment group relative to placebo and percentage of difference from placebo will be presented together with corresponding 95% CIs and the p-values.

Time-to-event endpoints will be displayed using Kaplan-Meier plots and analyzed with Cox regression with a model that includes treatment and stratification factors as factors and Baseline AAPS and Baseline value (if applicable) as covariates. The hazard ratio will be presented together with 95% CIs and the p-values.

Pairwise comparisons of each olorinab treatment group compared to placebo will be conducted. In addition, analyses of the pooled olorinab treatment groups compared placebo will be conducted.

Where statistical assumptions (eg, proportional hazards, normality, proportional odds) are not met, alternative approaches will be evaluated (eg, non-parametric analysis, log transformation).

Pharmacokinetic analysis:

A descriptive summary of observed plasma concentrations will be displayed by time and by treatment group. The Pharmacokinetic Set will be used to analyze plasma levels. Full details of PK analysis will be provided in the SAP for the Main Study.

Safety analysis:

All safety data will be listed and summarized by treatment group. All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and tabulated by System Organ Class and Preferred Term. Incidence of AEs, serious AEs (SAEs), and treatment-emergent AEs (TEAEs) leading to study treatment discontinuation will be summarized and presented in descending order of frequency. Laboratory parameters will be summarized by treatment group at each scheduled assessment timepoint using descriptive statistics. Associated laboratory parameters such as hepatic enzymes, renal function, and hematology values will be grouped and presented together. Individual subject values will be listed and values outside of the standard reference range will be noted. Shift tables and analyses of changes from Baseline will be produced. The change from Baseline for each of the vital signs and electrocardiogram (ECG) parameters will be summarized. Incidence of abnormal vital signs parameters and outlier ECG results will be tabulated.

Interim analysis:

No formal interim analyses are planned.

LTE

The LTE has 2 treatment groups, 25 mg and 50 mg. Based on subjects' treatment assignment in the Main Study and the LTE, subjects can be classified into 6 unique treatment groups: "Placebo|25 mg", "Placebo|50 mg", "10 mg|25 mg", "10 mg|50 mg", "25 mg|25 mg", and "50 mg|50 mg".

Safety analyses will be performed as described above for the Main Study. In addition, new AEs that occur after the first dose in the LTE or TEAEs which occurred in the Main Study period and increase in severity after the first dose of LTE study treatment will also be summarized by the 6 unique treatment groups.

A descriptive summary of observed plasma concentrations will be provided by treatment group.

Summary statistics will be provided for efficacy endpoints by unique treatment group. Proportion-based endpoints including responders will be summarized with frequency count and percentage. Continuous endpoints will be summarized with descriptive statistics including mean, median, standard deviation, minimum, and maximum. There is no formal between-treatment comparison for efficacy endpoints.

Additional analyses may be performed in some subgroups of medical interest, such as sex, age, race, and IBS subtype. Details of the analyses will be provided in the SAP for LTE.

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[redacted]

[redacted]

LIST OF APPENDICES

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Explanation
5-HT_3	5-hydroxytryptamine receptor 3
5-HT_4	5-hydroxytryptamine receptor 4
AAPS	average abdominal pain score
ADR	adverse drug reaction
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
APS	abdominal pain score
AUC_{inf}	area under the plasma versus time concentration curve from time zero to the last quantifiable measure
bpm	beats per minute
BUN	blood urea nitrogen
C_{ave}	average concentration
$CB_{1\ (or\ 2)}$	cannabinoid receptor 1 or 2
CBD	cannabidiol
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	observed maximum concentration
CMH	Cochran-Mantel-Haenszel
CONSORT	Consolidated Standards of Reporting Trials
CT	computed tomography
CTCAE	common terminology criteria for adverse events
C_{trough}	observed trough (pre-dose) concentration
DBP	diastolic blood pressure
DGP	deamidated gliadin peptide
DNA	deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic case report form

Abbreviation	Explanation
EDC	electronic data capture
eDiary	electronic diary
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
EQ-5D	European Quality of Life 5
FAS	Full Analysis Set
GCP	Good Clinical Practice
GERD	gastroesophageal reflux disease
GI	gastrointestinal
HADS	Hospital Anxiety and Depression Scale
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HDPE	high-density polyethylene
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HR	heart rate
IBD	inflammatory bowel disease
IBS	irritable bowel syndrome
IBS-C	irritable bowel syndrome with predominant constipation
IBS-D	irritable bowel syndrome with predominant diarrhea
IBS-M	irritable bowel syndrome with mixed bowel habits
IBS-QoL	Irritable Bowel Syndrome-Quality of Life
IBS-SSS	Irritable Bowel Syndrome-Severity Scoring System
IBS-U	unsubtyped irritable bowel syndrome
ICF	informed consent form
ICH	International Council for Harmonisation
IgA	immunoglobulin A
IgG	immunoglobulin G
INR	international normalized ratio
IRB	Institutional Review Board
IUD	intrauterine device

Abbreviation	Explanation
IUS	intrauterine system
IWRS	Interactive Web Response System
LDH	lactate dehydrogenase
M1	[redacted]
M2	[redacted]
M4	[redacted]
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDMA	methylenedioxymethamphetamine
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effects model repeated measures
OTC	over the counter
PGIC	Patient Global Impression of Change
PIC	powder in capsule
PK	pharmacokinetic
PP	Per Protocol
PRO	patient-reported outcome
PROMIS	Patient-Reported Outcomes Measurement Information System
PT	prothrombin time
PTT	activated partial thromboplastin time
QTc	corrected QT interval
QTcB	corrected QT interval by Bazzett
QTcF	corrected QT interval by Fridericia
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SD	standard deviation
SE	standard error
SNRI	serotonin and norepinephrine reuptake inhibitor

Abbreviation	Explanation
SOP	standard operating procedure
SSRI	selective serotonin reuptake inhibitors
T3	triiodothyronine
T4	thyroxine
TEAE	treatmentemergent adverse event
THC	tetrahydrocannabinol
tid	3 times per day
t_{max}	time of observed maximum (peak) concentration after drug administration
TMF	trial master file
tTG	tissue transglutaminase
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
WBC	white blood cell

1. INTRODUCTION

Irritable bowel syndrome (IBS) is a functional gastrointestinal (GI) disease defined according to Rome IV criteria by recurrent abdominal pain associated with defecation or a change in bowel habits (Lacy 2016). Patients with IBS may also experience other abdominal symptoms of cramping, bloating, and abdominal distension and have lower scores in quality of life measures compared to others with chronic diseases (ten Berg 2006). There are 3 main subtypes of IBS: IBS-C (predominant constipation), IBS-D (predominant diarrhea), and IBS-M (mixed bowel habits). Research (Rey de Castro 2015) suggests that the frequency and severity of pain attacks has been shown to be generally similar across subtypes, but with some differences in duration and frequency of IBS symptomatic episodes (Hellstrom 2011, Weinland 2011).

In Western countries, the prevalence of IBS has been estimated at approximately 10-15%, but with considerably greater country and region variability globally (Hungin 2005, Saito 2002, Sperber 2017). IBS accounts for more than 50% of referrals to GI specialists (Jones 2000, Sandler 1984). Although the underlying cause of IBS is unknown, evidence suggests that multiple biological factors, including motility, epithelial hyperpermeability, dysbiosis, inflammation and immune dysfunction, visceral hypersensitivity, epigenetics/genetics, altered brain-gut interactions, and various psychosocial factors (eg, response to past and present stressors, cognitive status, coping behaviors) may all contribute to the pathogenesis of this disorder (Drossman 2016, Enck 2016).

Many patients with IBS report abdominal pain as their most severe IBS symptom (Drossman 2009). Attempts to address IBS-related pain with centrally acting pain medications such as opioids, gabapentin, and tricyclic antidepressants has resulted in limited success, primarily due to the safety profile of these medications. Therefore, treatment of pain in this population remains under developed (Camilleri 2018).

1.1. Background

Cannabinoid receptors 1 and 2 (CB_1 and CB_2, respectively) play critical roles in pain perception. CB_1/CB_2 agonists have been shown to alleviate acute, chronic inflammatory, postsurgical, cancer, and neuropathic pain in animal models. However, the therapeutic potential of nonselective CB_1/CB_2 agonists is limited by the psychotropic effects resulting from activation of CB_1 located in the brain. In well-validated rodent models of inflammatory, neuropathic pain and postoperative pain, CB_2-selective agonists have been shown to exhibit analgesic, anti-hyperalgesic, and anti-allodynic activity without psychotropic consequences (Guindon 2008).

Supporting a role for CB_2 in visceral pain in humans, CB_2 are upregulated on inflamed intestinal epithelia, myenteric and submucosal plexi, and immune cells of patients with Crohn's disease (Wright 2005, Wright 2008). Expression of CB_2 is also increased on colonic mucosa in patients with IBS (Cremon 2017).

Olorinab (APD371) is a peripherally acting, full agonist of CB_2, with 1000-fold higher selectivity for CB_2 over CB_1 that is being developed for the treatment of abdominal pain in patients with IBS. A detailed description of the chemistry, pharmacology, efficacy, and safety of olorinab is provided in the Investigator's Brochure. In various preclinical studies, olorinab has

shown antinociceptive efficacy (Adams 2018), including a preclinical model of colitis-induced visceral hypersensitivity (Castro 2018) and chronic visceral hypersensitivity (Brierley 2019).

1.2. Benefit/Risk Assessment

Olorinab showed significant efficacy after acute dosing in rodent models of chronic visceral hypersensitivity, osteoarthritis pain, chemotherapy-induced neuropathic pain, and diabetes-related neuropathic pain [redacted]. Subchronic dosing or constant infusion with olorinab provided sustained suppression of allodynia without inducing tachyphylaxis or changes in body weight [redacted]. Collectively, these results suggest that olorinab may be beneficial in suppressing similar chronic pain states in humans.

Single daily doses of olorinab up to 400 mg and multiple doses of up to 200 mg tid were generally well tolerated in Studies APD371-001 [redacted] and APD371-002 [redacted], respectively. The most frequently reported treatment-emergent adverse events (TEAEs) were diarrhea, dizziness, dry mouth, headache/sinus headache, nausea, and somnolence.

A dose-related trend toward increased heart rate (HR) was noted by vital sign and telemetry measures in a single ascending dose study, but the increases were not associated with symptoms or adverse events (AEs) and did not meet the predefined safety criteria for cessation of dose escalation. No notable changes in electrocardiogram (ECG) parameters apart from HR were evident. Decreased HR was observed in a multiple ascending dose study following repeated administration of olorinab; however, HR remained in a physiologically acceptable range for each

subject throughout the study. During the Phase 2a study, there was no apparent dose-dependent change in HR observed and there were no TEAEs related to changes in HR.

In the single ascending dose study, the mean values for systolic blood pressure (SBP) and diastolic blood pressure (DBP) were within the normal range at Baseline and at all post-dose timepoints assessed, and there were no clinically significant changes in the mean values of the different treatment groups. In the multiple ascending dose study, all individual supine SBP and DBP measurements remained in a physiologically acceptable range for each subject throughout the study; all individual changes observed were asymptomatic and no AEs were reported that were related to changes in blood pressure. On Day 1, changes in mean supine SBP and DBP for the lowest olorinab dose group were generally comparable to the placebo group. Mean supine SBP and DBP exhibited a mild decrease from Baseline as early as 1 hour after the first dose on Day 1 in the two higher dose groups and reached a nadir at 6 hours. In general, mean changes in supine blood pressure in the Phase 2a study during the first day of dosing were variable and small. After Day 1, mean supine and orthostatic SBP and DBP values collected before the first daily dose over the course of the 8-week study remained relatively stable for both dose groups.

Preliminary efficacy results from the Phase 2a study demonstrated significant decreases in abdominal pain (as measured by AAPS) starting on Week 1 and sustained through Week 8.

The benefit-risk profile supports further clinical development of olorinab.

2. OBJECTIVES

2.1. Main Study

Primary Objectives

- To compare the efficacy of different doses of olorinab versus placebo on improvement in abdominal pain severity in subjects with IBS
- To compare the safety and tolerability of different doses of olorinab versus placebo in subjects with IBS

Secondary Objectives

- To compare the proportion of abdominal pain treatment responders for different doses of olorinab versus placebo
- To compare change in pain frequency for different doses of olorinab versus placebo
- To characterize the pharmacokinetics (PK) of olorinab and its predominant metabolites [redacted], and [redacted] in subjects with IBS

2.2. Long-Term Extension

Primary Objective

- To evaluate the safety and tolerability of long-term administration of olorinab in subjects with IBS

[redacted]

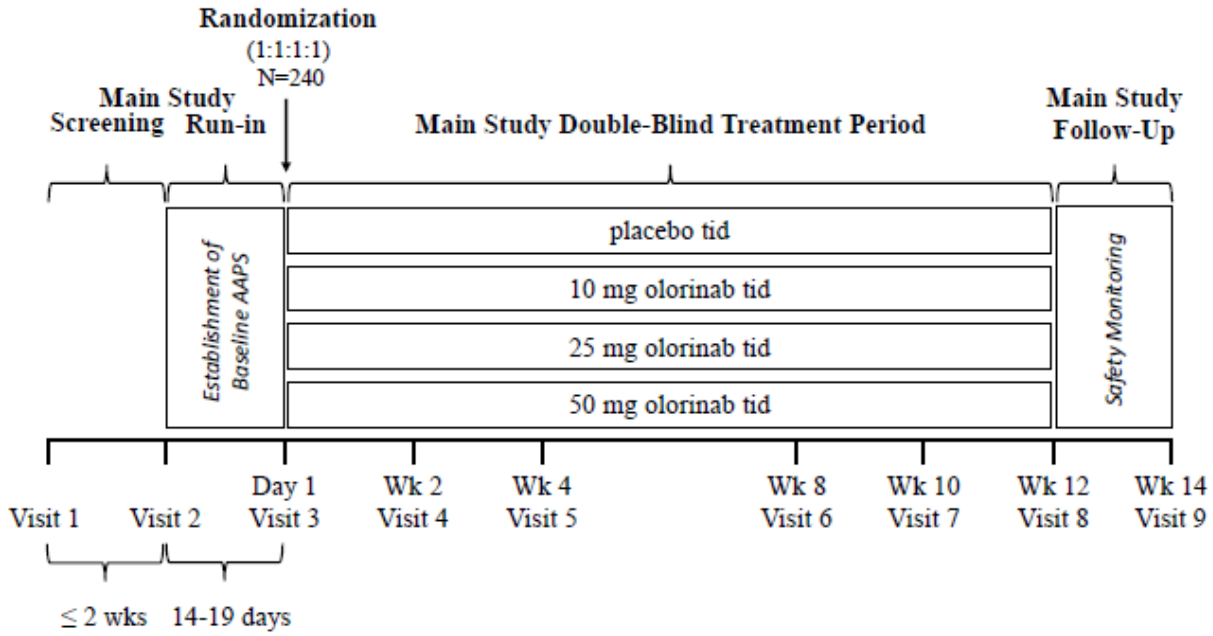
3. STUDY DESIGN

3.1. Overall Design

3.1.1. Main Study

The Main Study is designed to assess the efficacy, safety, and tolerability of olorinab in the treatment of abdominal pain in subjects with IBS with IBS-C or IBS-D who are not on concomitant treatment for IBS. This study is a Phase 2, multi-center, randomized, double-blind, placebo-controlled, parallel-group study that includes a Screening Period (up to 4 weeks for subjects who consent to colonic biopsy, up to 2 weeks for all other subjects), a Run-in Period (2 weeks), a randomized Main Study Treatment Period (12 weeks), and a post-treatment Main Study Follow-Up Period (2 weeks), totaling 16-20 weeks (Figure 1). After the Run-in Period, eligible subjects will be equally randomized into 1 of 4 treatment groups (olorinab 10, 25, or 50 mg tid or placebo tid). Randomization will be stratified by sex and IBS subtype. The number of subjects enrolled with IBS-C will be approximately equal to the number of subjects enrolled with IBS-D. An optional Long-Term Extension (LTE) is described in Section 3.1.2.

Figure 1: Schematic Diagram of Main Study Design



AAPS, average abdominal pain score; tid, 3 times per day; Wk, week

Notes: The Screening Period may be extended to up to a total of 4 weeks for subjects who consent to colonic biopsy. The last day of the Run-in Period is Day –1 and the first day of the Treatment Period is Day 1. There is not a designated Day 0 in this study. For Continuing subjects, Visit 9 of the Main Study may take place on the same day as Visit 2 of the Long-Term Extension.

3.1.2. Long-Term Extension

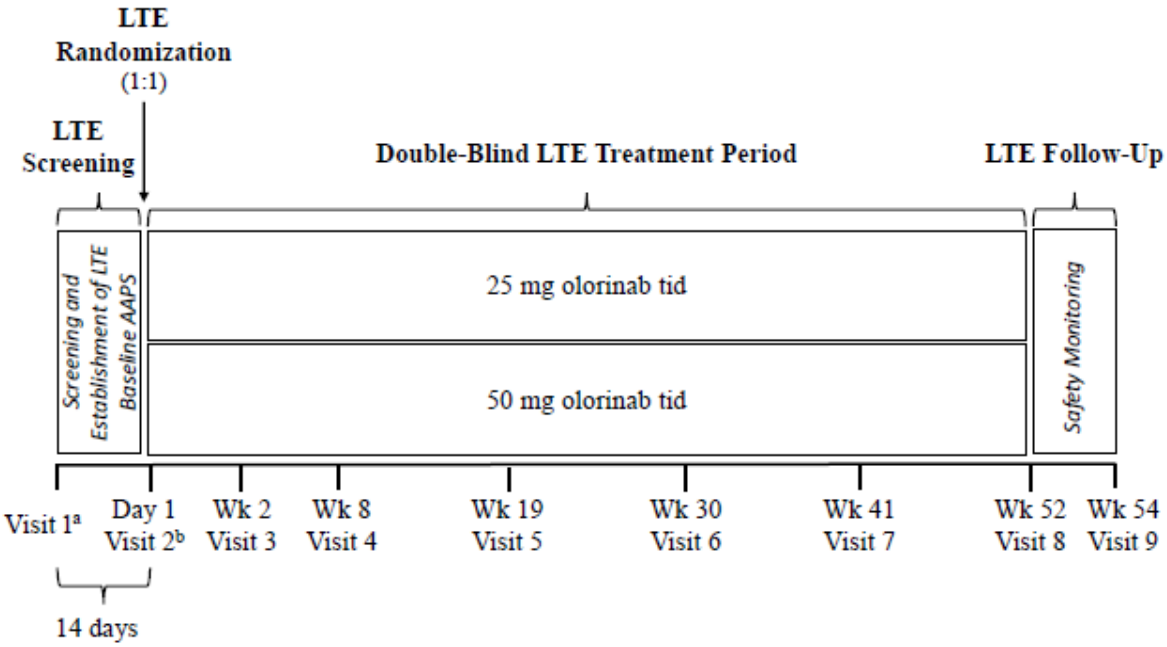
The LTE is an optional extension period that is designed to assess the safety, tolerability, population PK (C_{trough}), and efficacy of long-term administration of olorinab in subjects who have completed the Main Study. The LTE will be conducted at the same study sites as the Main Study. Subjects who participate in the LTE will be subjects who complete LTE Visit 2 < 28 days

after their Main Study Week 12 visit ("Continuing subjects") or subjects who complete their Main Study Week 12 visit ≥ 28 days prior to LTE Visit 2 ("Gap subjects"). Gap subjects will be required to have an LTE Screening visit approximately 14 days prior to randomization in the LTE. After completing eligibility assessments, subjects will enter a randomized LTE Treatment Period (52 weeks), and a post treatment LTE Follow-Up Period (2 weeks) (Figure 2).

Gap subjects who are interested in participating in the LTE must enroll in the LTE within 8 weeks after the IRB approval date of Amendment 3.0. All subjects who meet LTE eligibility criteria will be assigned to olorinab treatment as follows:

- Subjects who received 25 mg or 50 mg olorinab during the Main Study will continue to receive the same dose.
- Subjects who received placebo or 10 mg olorinab during the Main Study will be re-randomized (1:1) in a double-blind manner to receive either 25 mg or 50 mg olorinab.

Figure 2: Schematic Diagram of Long-Term Extension Design



AAPS, average abdominal pain score, LTE, long-term extension; tid, 3 times per day; Wk, week
[a] Gap subjects start the LTE at Visit 1.
[b] Continuing subjects start the LTE at Visit 2.

3.2. Scientific Rationale for Study Design

IBS is a GI disorder characterized by abdominal pain associated with defecation or change in bowel habits (Lacy 2016). Symptoms are chronic and may be episodic in nature, varying widely among patients (Miller 2014, Weinland 2011). In clinical studies of IBS, a run-in period of 1-3 weeks is recommended to monitor presence and consistency of symptoms according to study entry criteria (EMA 2014, FDA 2012, Miller 2014, Spiegel 2017). Accordingly, this study will incorporate a Main Study Run-in Period of at least 2 weeks (14-19 days), which will be used to

train subjects on the proper completion of patient-reported outcome (PRO) instruments, to confirm subject eligibility with respect to abdominal pain severity, and to establish baseline values of various assessments.

Based on its mechanism of action as a selective CB_2 agonist and data from previous nonclinical and clinical studies, it is anticipated that olorinab may have an effect on abdominal pain in patients with IBS, but will not have an effect on motility or bowel symptoms of constipation or diarrhea (Mathison 2004). Per FDA Guidance for Industry, *Irritable bowel syndrome - clinical evaluation of drugs for treatment* (FDA 2012), abdominal pain score (APS) is the recommended instrument for measuring pain in IBS. The instrument is a patient-reported outcome that uses an 11-point numeric rating scale ranging from 0 (no abdominal pain) to 10 (worst possible abdominal pain). The scale has been validated and has been widely used in clinical studies on pain in IBS (Spiegel 2009). Subjects in this study will record their worst abdominal pain over the previous 24 hours in a daily electronic diary (eDiary). Abdominal pain in IBS can fluctuate daily. To better capture a summary of subject pain, the AAPS (for Baseline: the average of all APS scores during the Run-In Period; for post-baseline visits: the average of the APS score over the 7 days before the scheduled visit) will be used to summarize subject pain and compare changes in pain over time. In the absence of significant safety findings, a greater decrease in AAPS in olorinab-treated subjects compared to placebo-treated subjects over the course of this study will provide supportive evidence that olorinab provides a direct benefit to subjects.

This study has been designed as a randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study to reduce bias and account for placebo effect in the evaluation of the safety and efficacy of multiple dose levels of olorinab. The addition of an LTE, during which subjects will receive olorinab 25 mg tid or 50 mg tid for approximately 1 year, is included to allow subjects access to olorinab for an extended period of time and for the collection of long-term safety data.

3.3. Justification for Dose

3.3.1. Main Study

The safety, tolerability, and PK of olorinab have been evaluated in 2 Phase 1 dose escalation studies. Olorinab has also been evaluated in an 8-week Phase 2a, proof-of-concept study in subjects with quiescent to mildly active Crohn's disease. In a single ascending dose study, single oral doses of 10 to 400 mg of olorinab were administered to healthy, adult volunteers. TEAEs were predominantly mild in severity and the majority of TEAEs occurred in subjects administered doses ≥ 120 mg. No TEAEs led to discontinuation and there were no serious AEs (SAEs). A dose-dependent trend of increases in supine HR was observed at doses ≥ 250 mg. Systemic exposure of olorinab (observed maximum concentration [C_{max}] and area under the plasma versus time concentration curve from time zero to the last quantifiable measure [AUC_{inf}]) increased with dose in a manner that was less than dose proportional.

In a multiple ascending dose study, multiple oral doses of olorinab 50, 100, and 200 mg were administered tid for 10 days to healthy, adult volunteers. Most TEAEs were mild in severity. Olorinab was associated with mean decreases from baseline in supine SBP and DBP, respectively, that were evident beginning at 1-hour post-dose on Day 1 and Day 10, in the 100 and 200 mg groups. Blood pressure values returned to baseline or above baseline values upon

discontinuation of treatment. The 200 mg dose was associated with mean decreases in supine HR of approximately 10 to 15 beats per minute (bpm) compared to baseline throughout the Treatment Period. In the 50 mg and 100 mg groups, changes in HR relative to baseline were small and variable.

In a Phase 2a study, doses of 25 and 100 mg of olorinab were administered tid for 8 weeks in a randomized, open-label study in 14 subjects with quiescent to mildly active Crohn's disease. PK results indicated that the systemic exposure of olorinab was dose proportional.

Decreases in AAPS compared to baseline were similar for both olorinab treatment groups starting on Week 1 and sustained through Week 8 in the Phase 2a study. The lack of dose-dependency on AAPS may indicate possible pharmacological saturation of CB_2 at 25 mg tid. Resultant C_{max} and average concentration (C_{ave}) plasma concentrations that were generally equal to or higher than those that achieved notable efficacy in rat models of pain are also consistent with a potential pharmacological saturation of CB_2 at 25 mg tid and above.

The absence of a placebo group in the Phase 2a study in combination with high placebo response rates reported in previous studies of patients with IBD and IBS confound the confirmation of clinical efficacy as it relates to a dose-response relationship. Therefore, the pharmacologically active 25 mg tid dose will be bracketed with 10 and 50 mg doses tid.

PK modelling predicts that the 25 mg and 50 mg tid dose levels will provide mean C_{ave} values that correspond to those that show efficacy in the rat. Similar modelling to predict mean C_{max} and C_{ave} after a 10 mg dose results in values lower than rat efficacious values. Therefore, inclusion of the 10 mg dose is intended to contribute to the characterization of the efficacy dose response for olorinab.

In summary, olorinab doses of 10, 25, and 50 mg tid have been selected for the Main Study based on their safety and tolerability profile from prior studies. Furthermore, these doses are expected to result in a range of efficacies, which will inform dose selection in future clinical studies.

3.3.2. Long-Term Extension

Chronic abdominal pain is a common feature in patients with IBS. In the LTE, subjects will receive olorinab doses of 25 or 50 mg which are expected to be in the therapeutic range for pain relief, and were shown to be safe and well tolerated in previous Phase 1 and Phase 2 studies.

3.4. Main Study Screening and Enrollment

Potential subjects will provide written informed consent before any study-specific procedure is performed. The Screening Period will last for up to 2 weeks. For subjects who consent to collection of a colonic biopsy sample for biomarker analysis, the Screening Period may be extended 2 additional weeks for a total Screening Period of up to 4 weeks; collection of colonic biopsy tissue must be performed at least 1 week prior to entering the Run-in Period. A summary of screening and enrollment events is provided in the [redacted]). Inclusion and exclusion criteria are listed in Section 4.1.1 and Section 4.1.2, respectively. Eligible subjects meeting all inclusion and none of the exclusion criteria requirements may be enrolled.

3.5. Main Study Run-in Period

Subjects who are enrolled in the study will enter the Run-in Period. The Run-in Period will last at least 2 weeks (14-19 days) and will end on Day −1. No study treatment will be administered during the Run-in Period. At the beginning of the Run-in Period, subjects will be trained on daily eDiary entry. Subjects will be instructed to complete daily eDiary entries in the evening, generally at the same time every day, throughout the Run-in Period. As a follow-up to training, study staff will attempt to contact subjects within approximately 3 days after Visit 2 (Day 1 of Run-in) to confirm whether subjects are able to see the eDiary questions, to confirm whether the eDiary devices are appropriately synchronizing, and to help troubleshoot any potential eDiary technical issues in a timely manner as appropriate. This contact attempt should be documented in the subject's source document. At the end of the Run-in Period and prior to randomization at Visit 3 (Day 1), subject eligibility will be determined based on the following:

- Compliance with eDiary completion requirements
- AAPS score during the Run-in Period ≥ 4
- Continued eligibility as defined by the inclusion/exclusion criteria
- Subject did not use any rescue medication during the Run-in Period

Subjects who do not meet the criteria listed above will be considered Run-in failures and will not progress in the study. Subjects who do meet the criteria listed above will move on to the Main Study Treatment Period.

3.6. Main Study Treatment Period

The Main Study Treatment Period will begin on Day 1. The last day of the Run-in Period is Day −1 and the first day of the Main Study Treatment Period is Day 1. There is not a designated Day 0 in this study.

Subjects who have completed the Run-in Period and remain eligible for the study will be randomized to receive olorinab 10, 25, or 50 mg or placebo tid. All Main Study Treatment Period study visits (Visits 4, 5, 6, 7, and 8) that occur after Visit 3 (Day 1) should be scheduled relative to the actual date of Day 1. Subjects will receive study treatment for 12 weeks (± 3 days) and will continue to perform daily eDiary entries. Study visits and assessments will be conducted per the [redacted].

3.7. Main Study Follow-Up/End of Main Study

Subjects who have completed the Main Study Treatment Period will return for a Main Study Follow-Up Visit at Week 14, approximately 2 weeks (± 3 days) after completion of the Main Study Treatment Period. When possible, subjects who have stopped taking study treatment prior to the end of the Main Study Treatment Period (Early Termination) will also conduct a Follow-Up visit approximately 2 weeks (± 3 days) after discontinuation of study treatment. Subjects will complete daily eDiary entries throughout the Main Study Follow-Up Period. Visit assessments are detailed in the [redacted]).

3.8. Long-Term Extension Screening and Treatment Periods

Subjects who complete the Main Study (including both Visit 8 [Week 12] and Visit 9 [Week 14]) and meet eligibility criteria for the LTE may continue to receive olorinab at doses of 25 mg or 50 mg for approximately 52 weeks starting as soon as approximately 2 weeks after their last dose of study drug in the Main Study Treatment Period. Subjects will provide written informed consent before any procedures specific to the LTE are performed.

For Continuing subjects who enter the LTE (ie, subjects who completed Visit 8 [Week 12] < 28 days before LTE Visit 2), the first visit in the LTE period (LTE Visit 2) may take place on the same day as the Main Study Follow-Up Visit 9 [Week 14]. Eligibility for Continuing subjects for the LTE will be confirmed as indicated in Section 4.2.

For Gap subjects (ie, subjects who completed Visit 8 [Week 12] ≥ 28 days before LTE Visit 2), an additional 14-day LTE Screening Period will be required before LTE dosing can commence. During the LTE Screening visit (LTE Visit 1), eligibility for the LTE will be confirmed as indicated in Section 4.2. At the LTE Screening visit, subjects will be re-trained on daily eDiary entry as described in Section 3.5.

Subjects will complete the eDiary daily throughout the LTE.

[redacted]. During the LTE Treatment Period, the site staff will contact each subject by telephone approximately 3 weeks before each study visit to remind them of the importance of their eDiary entries and of their upcoming visit.

3.9. Long-Term Extension Follow-Up/End of Study

Subjects who have completed the LTE Treatment Period will return for a Follow-Up Visit at LTE Week 54, approximately 2 weeks (± 7 days) after completion of the LTE Treatment Period. When possible, subjects who have stopped taking study treatment prior to the end of the LTE Treatment Period (Early Termination) will return for an LTE Follow-Up Visit approximately 2 weeks (± 7 days) after discontinuation of study treatment. [redacted]

3.10. Early Termination Visit

Subjects who stop taking study treatment prior to the end of the Main Study Treatment Period will return to the clinic for a Main Study Early Termination Visit. Subjects enrolled in the LTE who stop taking olorinab prior to the end of the LTE Treatment Period will return to the clinic for an LTE Early Termination Visit. Early Termination Visit assessments are detailed in the [redacted] Every effort should be made to schedule Early Termination procedures within 3 days of the last dose of study treatment and before initiation of any new treatments which could affect endpoints. After completion of the Early Termination Visit, subjects should also return (when possible) for a Follow-Up Visit approximately 2 weeks (± 3 days [for the Main Study] or ± 7 days [for the LTE]) after discontinuation of study treatment. Site staff will work with subjects who withdraw early to obtain as much follow-up data as possible.

3.11. Study Duration

For subjects who participate only in the Main Study, study duration from the time of consent to the last visit for each subject will be 16 to 20 weeks. A subject is considered to have completed the Main Study if they complete all phases of the study including Visit 8 (Week 12) and the Follow-Up Visit at Week 14.

For Continuing subjects who participate in the LTE, study duration from the time of consent to the last visit for each subject will be 70 to 74 weeks.

For Gap subjects who participate in the LTE, the duration of time that the subject participates in the study will be 72 to 76 weeks, not including the time that the subject is not enrolled in the study after completion of the Follow-Up Visit (Week 14) in the Main Study and before the subject returns for the LTE Screening Visit.

The end of the study is defined as the date of the last clinic visit (scheduled or unscheduled) of the last subject in the study.

4. STUDY POPULATION

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

4.1. Main Study

4.1.1. Inclusion Criteria

Subjects must meet the following inclusion criteria to be eligible for enrollment into the study:

1. Male and female subjects ≥ 18 and ≤ 70 years of age at Visit 1 (Screening)

[redacted]

3. Clinical diagnosis of IBS-C or IBS-D according to Rome IV criteria at Visit 1 (Screening)
4. Per the Rome IV diagnostic algorithm for IBS, subjects 50 years of age and over are to have had one of the following with a result that rules out causes of abdominal pain other than IBS:
    a. Colonoscopy (within 10 years of Visit 1 [Screening])
    b. Flexible sigmoidoscopy and double contrast barium enema (within 5 years of Visit 1 [Screening])
    c. Computed tomography (CT) colonography (within 5 years of Visit 1 [Screening])

[redacted]

[redacted]

4.1.2. Exclusion Criteria

Subjects are excluded from the study if any of the following exclusion criteria apply.

4.1.2.1. Key Exclusion Criteria

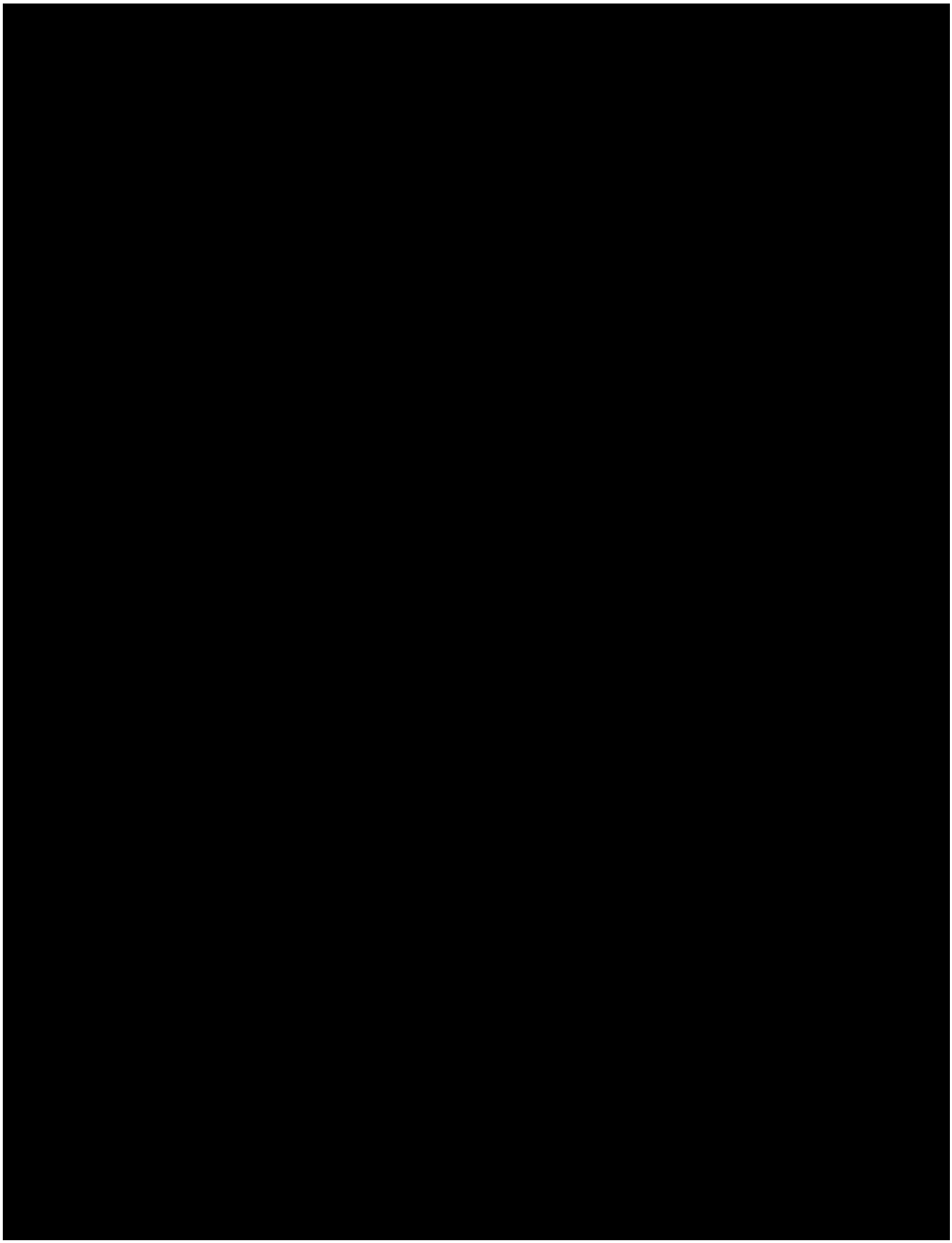
1. Diagnosis of IBS-M or unsubtyped IBS (IBS-U)
2. Clinically relevant changes in dietary, lifestyle, or exercise regimen within 30 days prior to Visit 1 (Screening) that may confound efficacy assessments in the clinical judgment of the Investigator (or designee)
3. Any colonic or major abdominal surgery (eg, bariatric surgery [including gastric banding], stomach surgery, small/large bowel surgery, or abdominal large vessel surgery). History of cholecystectomy is exclusionary for subjects with IBS-D. For subjects with IBS-C, a history of cholecystectomy more than 6 months prior to Visit 1 (Screening) is allowed. Procedures such as appendectomy, hysterectomy, caesarean section, or polypectomy are allowed as long as they have occurred at least 3 months prior to Visit 1 (Screening).

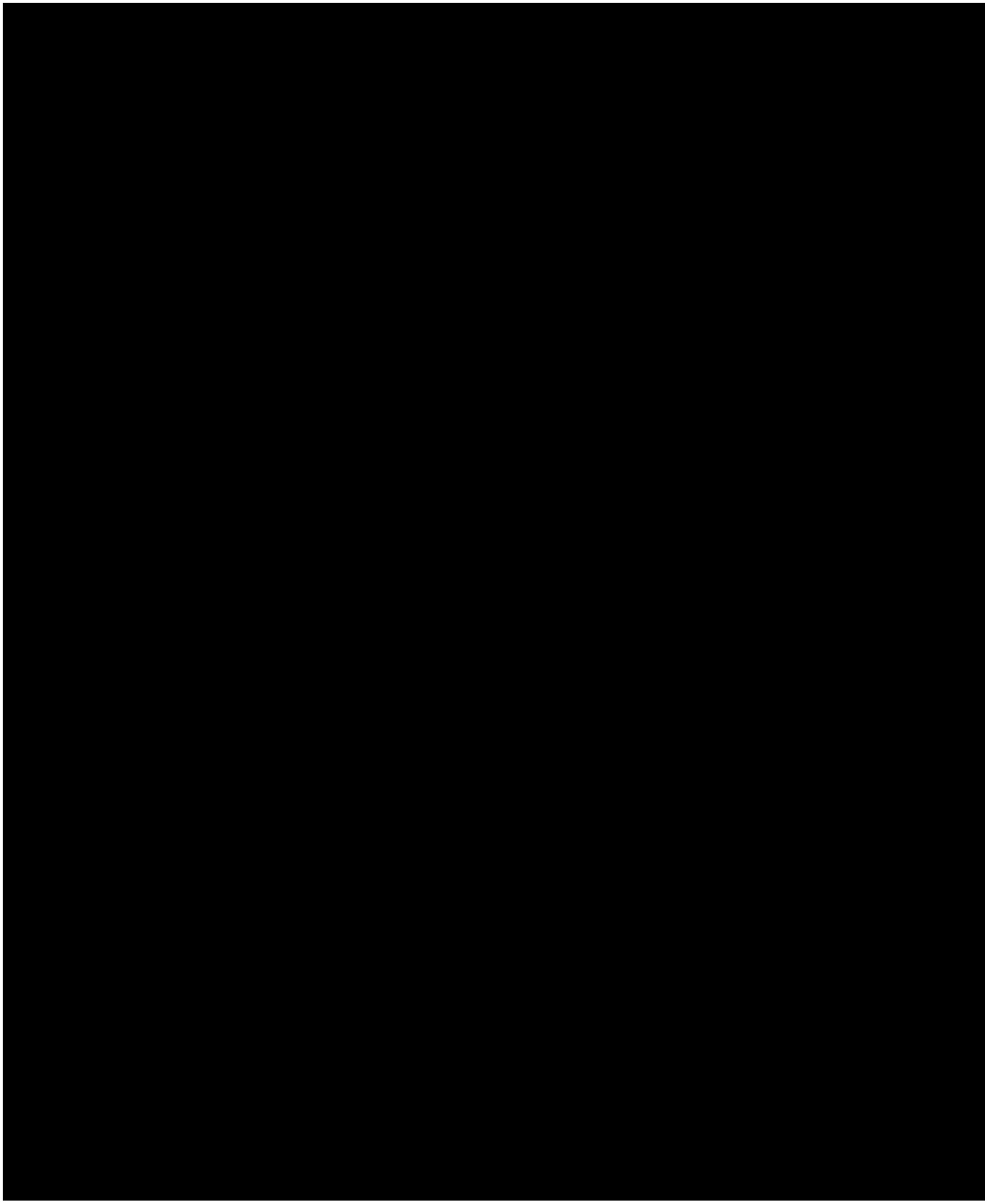
[redacted]

[redacted]

4.1.2.2. Other Exclusion Criteria

[redacted]



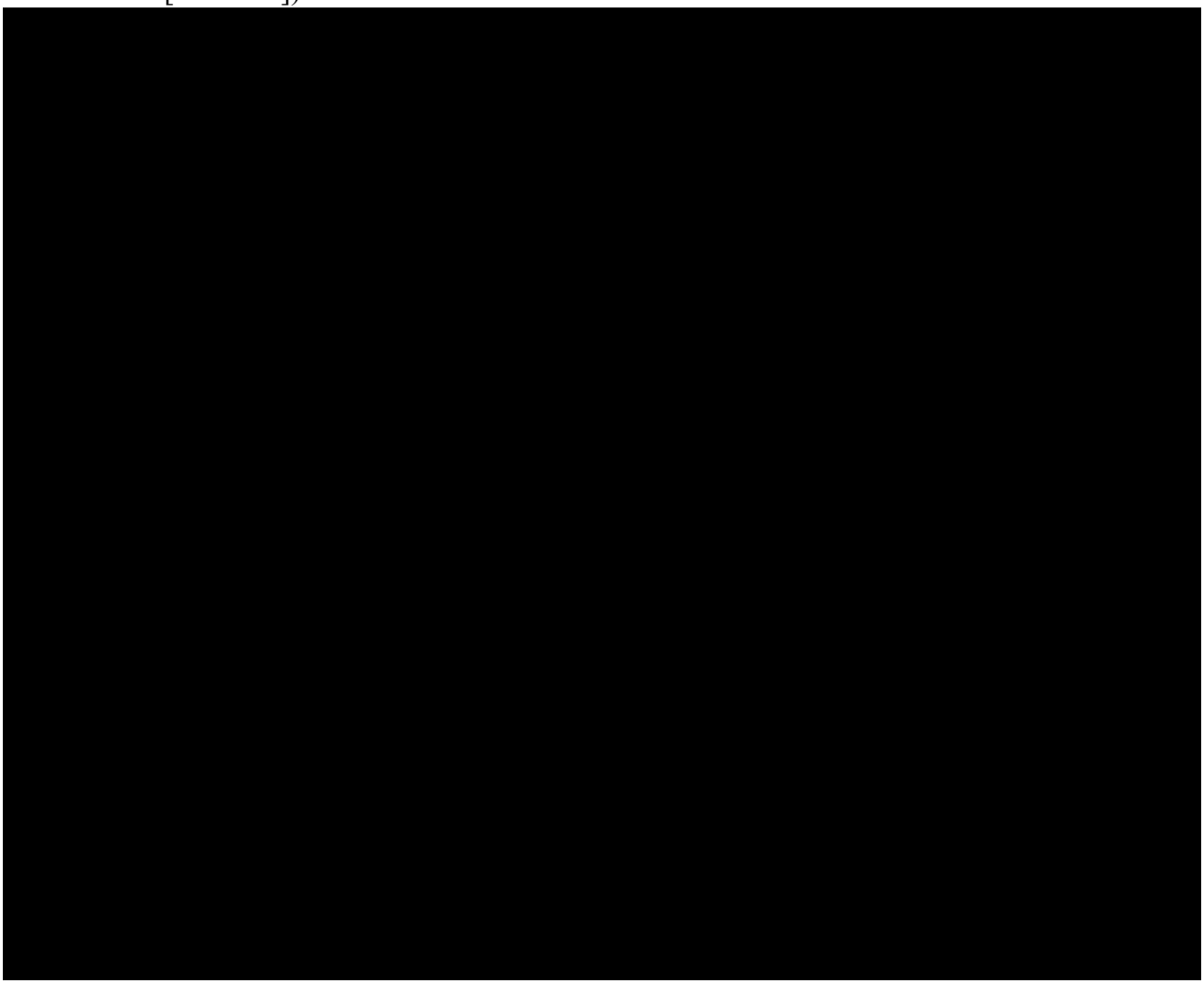


4.2. Long-Term Extension

4.2.1. Inclusion Criteria

Subjects must meet the following inclusion criteria to be eligible for enrollment into the LTE:

1. All subjects must have completed the Main Study (including both Visit 8 [Week 12] and Visit 9 [Week 14]).



4.2.2. Exclusion Criteria

Subjects are excluded from the LTE if they meet any of the following exclusion criteria:

1. Subject meets any exclusion criteria from the Main Study at the time of assessing eligibility for the LTE, unless approved by the Sponsor in advance.
2. Subject had less than 75% overall compliance with eDiary entries during the Main Study.
3. Subject deviated from the prescribed dosage regimen during the Main Study (ie, overall study treatment compliance less than 85% or more than 115%), unless approved by the Sponsor in advance.

[redacted]

4.3. Rome IV Criteria for IBS Diagnosis

Diagnosis of IBS and IBS subtype will be confirmed by the Investigator or designee. The following criteria must be fulfilled for the last 3 months with symptom onset at least 6 months before diagnosis:

Recurrent abdominal pain, on average, at least 1 day/week in the last 3 months, associated with 2 or more of the following criteria (Schmulson 2017):

- Related to defecation
- Associated with a change in frequency of stool
- Associated with a change in form (appearance) of stool

Subjects will be classified as having IBS-C or IBS-D using the following definitions, according to the Investigator's assessment of the subject's defecation patterns when untreated for constipation or diarrhea:

IBS-C More than one-fourth (25%) of bowel movements with Bristol Stool Scale Types 1-2 and less than one-fourth (25%) with Types 6-7.

IBS-D More than one-fourth (25%) of bowel movements with Bristol Stool Scale Types 6-7 and less than one-fourth (25%) with Types 1-2.

Bristol Stool Scale definitions are provided in [redacted].

4.4. Lifestyle Considerations

The Sponsor will be informed of all restriction violations. The Sponsor will decide whether a subject with restriction violations will be allowed to continue study participation. Subjects may be rescheduled to return to the clinic for their visit as appropriate if they have not followed designated restrictions required prior to blood sampling. Every effort should be made to keep rescheduled visits within the window of the respective study visit.

4.4.1. Meals and Dietary Restrictions

- Subjects may not eat or drink grapefruit-containing foods or beverages from the start of the Run-in Period throughout the duration of the study.
- Caffeine is restricted on Day 1.
- Subjects should arrive at the clinic after fasting (no food or drink except water) overnight for at least 8 hours and should withhold the morning dose of study treatment until after fasted blood draws. On Day 1 (Main Study Visit 3) and Week 4

(Main Study Visit 5), which include post-dose blood samples, subjects can be provided a snack to be consumed between the 0.5 and 1 hour PK blood sample. At all visits, caffeine is restricted until after the last vital signs have been taken.

- Subjects will be instructed to refrain from the use of alcohol within 24 hours of study visits.
- Subjects will be instructed to refrain from making significant dietary changes throughout the duration of the study.

4.4.2. Water Restrictions

There are no water restrictions.

4.4.3. Activity

- Subjects will be instructed to refrain from strenuous exercise (relative to the subject's fitness level and typical exercise routine) within 24 hours prior to each study visit.
- Subjects will be instructed to refrain from making significant changes to their activity levels and exercise routines throughout the duration of the study.
- On Day 1 and Week 4, which include post-dose blood samples, strenuous exercise should be avoided until all blood samples have been collected.
- On Day 1 and Week 4, which include post-dose blood samples, subjects should not assume a supine position after administration of study treatment, except as needed for vital sign assessments, until the completion of the blood sample at 2 hours post-dose.

4.5. Screen Failures, Run-in Failures, and Rescreening Guidance

Main Study screen failures are defined as subjects who consent to participate in the Main clinical study but are not subsequently enrolled into the study at Visit 2 (Run-in). LTE screen failures are defined as subjects who consent to participate in the LTE but are not subsequently enrolled into the LTE. Run-in failures are defined as subjects who are enrolled at Main Study Visit 2 (Run-in) but do not randomize at Visit 3 (Day 1). A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, reason for screen failure, eligibility criteria, any concomitant medications, and any SAEs. If a screen failure occurs because of a restricted concomitant medication, the medication should be documented in the eCRF.

Individuals may re-qualify for study enrollment in the Main Study or LTE within 2 weeks of Main Study Visit 1 (Screening) or LTE Visit 1 (Screening), as applicable, following an abnormal laboratory test, vital signs, or ECG finding by having that test repeated once with acceptable results as judged by the Investigator (or designee). The Investigator may consult with the Medical Monitor as needed.

If a result for laboratory, vital signs, or ECG obtained after Screening but before randomization fails eligibility thresholds outlined below as applicable, the subject must be withdrawn unless the value is assessed and documented as not a clinically significant change from the qualifying Screening value by the Investigator (or designee).

Subjects who have not been randomized and do not meet the remaining inclusion and exclusion criteria may be rescreened for the Main Study with a new screening number if the Investigator assesses that the subject is an appropriate candidate for re-screening. The Investigator may consult with the Medical Monitor if there are any questions related to rescreening a subject. Subjects may not be rescreened more than once without prior approval of the Medical Monitor and rescreening must occur at least 2 weeks after the date of screen failure. Subjects who do not meet the minimum pain requirements for study entry, as defined in Inclusion Criterion 10, and subjects who have been randomized are not eligible for rescreening.

5. STUDY TREATMENT

Olorinab (APD371) is a highly selective, full agonist of CB_2.

Olorinab is provided in 2 formulations: powder in capsule (PIC) and tablet. Both tablets and capsules are immediate-release formulations, therefore the same bioavailability is expected. Both formulations include the following strengths: 10 mg, 25 mg, and 50 mg. [redacted]

Olorinab drug substance, drug product (capsules and tablets), and matching placebo (capsules and tablets) are manufactured in compliance with current Good Manufacturing Practices. Capsules and tablets are packaged in the following configuration: 63 count in 100-cc high-density polyethylene (HDPE) bottles heat-induction sealed with child-resistant screw cap. Bottles will be labeled in compliance with local country requirements and shipped to participating clinical study sites for study use.

Although 2 different dosage forms (capsules and tablets) of study treatment will be used in this study, individual subjects will remain on the same dosage form assigned at the time of randomization throughout the Main Study Treatment Period. During the LTE, all subjects will receive the tablet dosage form, regardless of which dosage form they were assigned to during the Main Study.

5.1. Dosage and Administration

[redacted]

5.2. Instructions for Missed Doses

Subjects should be instructed that if they forget to take a dose, they should take their missed dose as soon as they realize the dose has been missed as long as the next planned dose is at least 3 hours away; otherwise, they should skip their missed dose and they should take their next dose at the regular time. Subjects should be instructed to contact the Investigator if they miss more than 9 consecutive doses (ie, all doses have been missed for at least a 72-hour period). If the

subject vomits the study treatment, he/she should be instructed not to take another dose in the same dosing period, but to take the next dose at the regular time.

5.3. Dose Interruptions

All study treatment interruptions of greater than 5 consecutive days will be noted in the electronic case report form (eCRF) with the start date, duration, and reason for the interruption (if known) specified. If the interruption was caused by an AE, only the primary AE leading to interruption of study treatment, per the judgment of the Investigator, should have an action taken of study treatment interrupted. If a study treatment interruption greater than 5 days is required for a medical reason, the Investigator must contact the Medical Monitor.

5.4. Handling/Storage/Accountability

Sufficient study treatment will be provided to participating clinical study sites to support study conduct. All study treatment must be stored in a secure, limited access area. [redacted]
Procedures for reporting any shipment damage or temperature excursions are specified in the Pharmacy Manual.

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit and storage for all study treatments received. Any discrepancies must be reported to Sponsor or designee. All issues must be resolved before use of the study treatment.

Only subjects randomized in the study may receive study treatment and only authorized site staff are permitted to supply or administer study treatment.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

At completion of the study, all study treatment will be reconciled and either retained or destroyed according to direction from the Sponsor and applicable country regulations. On-site destruction may be permitted under the guidance of local regulations and applicable site standard operating procedures (SOPs). Prior to taking any action with study treatment, the Investigator or designee will contact the Sponsor or designee for approval of such action. Final reconciliation will be performed at study completion. Further guidance and information for the final disposition of used and unused study treatment will be provided in a separate Pharmacy Manual.

5.5. Measures to Minimize Bias: Randomization and Blinding

This is a double-blind study with limited access to the randomization code. All study treatment bottles will be identical in appearance, and olorinab and placebo will be identical in appearance within each type of formulation (capsules or tablets). The treatment each subject receives will not be disclosed to the Investigator, study site staff, subject, study vendors, or Sponsor personnel involved with the conduct of the study (with the exception of the clinical supply staff and safety staff). The Interactive Web Response System (IWRS) will store treatment codes and maintain kit numbers for dispensed study treatment. All subjects will be centrally assigned to randomized study treatment group using an IWRS. Before the study is initiated, the login information and directions for the IWRS will be provided to each site.

The IWRS will be programmed with blind-breaking instructions. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a subject's treatment assignment is warranted. Subject safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the Investigator should make every effort to contact the Sponsor prior to unblinding a subject's treatment assignment unless this could delay emergency treatment of the subject. If a subject's treatment assignment is unblinded, the subject should immediately stop taking all study treatment and the Sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and eCRF, as applicable.

After the Main Study has completed and the database for that portion of the study has been locked, that database will be unblinded for analysis. However, the investigators (except as necessary for data review), sites, and subjects will remain blinded to the treatment assignments throughout study conduct (including conduct of the LTE).

5.6. Study Treatment Compliance

Study treatment will be dispensed at the study visits scheduled in the [redacted].

Subjects will document study treatment administration once daily in the subject eDiary. At Visit 3, subjects will be instructed on how to record treatment administration in the subject eDiary.

Starting with Visit 4, subjects will be instructed to bring unused study treatment and used study treatment packaging to each study visit to assess compliance with study treatment administration. Returned study treatment should be counted at each visit. Compliance with the scheduled dose should be assessed based on the following:

- Study treatment accountability
- Non-directed verbal questioning
- Review of eDiary responses regarding study treatment administration

Deviation(s) from the prescribed dosage regimen will be recorded in the eCRF. If compliance is not between 85% and 115%, inclusive, at Main Study Visits 4 through 8 or LTE Visits 3 through 7, the subject will be counseled by the Investigator or designee about the importance of compliance with the regimen.

Subjects with administration compliance greater than 115% and subjects who do not return any study treatment or study treatment packaging will be asked for the reason for the overcompliance or missing study treatment and their response will be recorded in the eCRF.

The Sponsor retains the right to require the withdrawal of any subject who violates the protocol.

5.7. Concomitant Therapy

Medication restrictions are outlined in the inclusion and exclusion criteria (Section 4.1.1 and Section 4.1.2 for the Main Study and Section 4.2.1 and Section 4.2.2 for the LTE) and in the lifestyle considerations (Section 4.4). Restrictions apply until study completion or discontinuation from randomized study treatment.

Dosages for allowed background concomitant medications should be stable prior to screening and maintained constant during the study (ie, until study completion or discontinuation from randomized study treatment) unless otherwise specified in this protocol or instructed by the Investigator (who will contact the Medical Monitor for consultation prior to any such changes). The Medical Monitor must be informed in a timely manner if study site personnel are informed of any use of restricted medications or treatments which could affect safety of the subject or study endpoints during the study (until study completion or Early Termination). The Sponsor, in consultation with the Medical Monitor, will decide whether a subject with such medication changes will be allowed to continue randomized study treatment.

Any medication or vaccine (including OTC or prescription medicines, vitamins, and/or herbal supplements) other than study treatment that the subject has received within the 3 months prior to Screening, is receiving at the time of Screening, or receives during the study must be recorded in the concomitant medication log along with:

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

For Gap subjects who enroll in the LTE, any medication or vaccine (as described above) that the subject has received during the Gap period between Main Study Visit 9 (Week 14) and LTE Visit 1 must be recorded in the concomitant medication log.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

5.7.1. Required Concomitant Therapy

Not applicable

5.7.2. Allowed Concomitant Therapy

The following concomitant medications, sometimes used to treat IBS symptoms, are allowed throughout the course of this study provided that doses are unchanged for at least 90 days prior to screening and that the subject agrees to maintain the same dose of the medication throughout the study:

- Tricyclic antidepressants, tetracyclic antidepressants, SSRIs, SNRIs, or anticonvulsants (eg, pregabalin or gabapentin) for conditions other than IBS pain
- Benzodiazepines or non-benzodiazepine hypnotics, administered at bedtime for conditions other than IBS pain

The following concomitant medications are allowed throughout the course of this study as long as doses are stable for at least 30 days prior to Visit 1 (Screening) of the Main Study or the LTE, as applicable, and the subject agrees to maintain stable doses (within ± 20% total daily dose), or approximate frequency of ‘as needed’ use of medication throughout study participation:

[redacted]

5.7.3. Rescue Medication for Constipation or Diarrhea Symptoms

Rescue medications for constipation or diarrhea symptoms may not be taken for more than 3 days within any 30-day period. Subjects who do not comply with requirements will be reassessed on a case-by-case basis for continuing study eligibility by the Investigator in consultation with the Sponsor. The following medications will be permitted as rescue medication for constipation or diarrhea symptoms after a minimum of 3 days of increased symptoms during the Main Study Treatment Period, Main Study Follow-Up Period, LTE Screening Period, LTE Treatment Period, or LTE Follow-Up Period:

- Loperamide, for diarrhea, restricted to no more than 8 mg in a 24-hour period and no more than 14 mg in a 48-hour period
- Bisacodyl, for constipation, restricted to no more than 15 mg administered orally or 10 mg suppository in cases of severe constipation

The study restrictions regarding the use of rescue medication will be explained to subjects during informed consent. Rescue medications for constipation and diarrhea symptoms are not permitted during the Screening or Run-in Periods. Subjects who require rescue medication for constipation and diarrhea symptoms during the Run-in Period will be considered Run-in failures and may be eligible for re-screening.

All rescue medication will be documented in the concomitant medication log.

5.7.4. Prohibited Concomitant Therapy

Restricted or prohibited concomitant treatments are summarized below. Restrictions and prohibitions are effective from the time of informed consent through the final Follow-Up Visit (Main Study Visit 9 or LTE Visit 9) or Early Termination.

[redacted]

Table 1: Prohibited Concomitant Medications

Interaction	Drugs
Moderate or strong CYP3A4 inducers and inhibitors[a]	https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers
IBS medication	[redacted]

[redacted]

Note: The medications list at the linked website is not exhaustive. The Medical Monitor may be consulted for questions related to restricted medication.

5.8. Dosing in Excess of Instructed Daily Treatment

Subjects will be instructed to contact the Investigator if they take more than 6 capsules or tablets of study treatment (> 2 times the recommended daily dose) within a 24-hour time period. Once notified, the Investigator should document the event in the subject's source documents. The Sponsor does not recommend specific treatment for an overdose; there is no known antidote to the study treatment. In the absence of associated AEs as assessed per the clinical judgement of the Investigator, no further action is required.

If a subject reports receiving > 2 times the recommended daily dose within a 24-hour period, and if symptoms are present, the Investigator or designee should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the subject to assess for any AEs/SAEs and laboratory abnormalities.
3. Obtain a plasma sample for PK analysis of the last dose of study treatment if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the excess dose in the eCRF.

Subjects who do not comply with study treatment instructions will be counseled on correct dosing and administration of study treatment as soon as possible after a non-compliance with study treatment administration is identified. Decisions regarding dose interruptions, or withdrawal of the subject from the study will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject.

5.9. Dose Modification

Dose modification is not permitted in this study.

5.10. Treatment After the End of the Study

Additional treatment will not be available after completion of the Main Study Treatment Period for subjects who participate only in the Main Study, or after the LTE Treatment Period for subjects who participate in the LTE. Investigators (or designees) will consult with subjects to determine appropriate care for their condition upon completion of the study.

6. DISCONTINUATION OF STUDY TREATMENT AND SUBJECT DISCONTINUATION/WITHDRAWAL

6.1. Discontinuation of Study Treatment

A subject's study treatment may be discontinued early for any of the following reasons:

- AE
- Withdrawal by subject
- Investigator decision
- Study termination by Sponsor (the study may be terminated early if, in the opinion of the Sponsor, Medical Monitor, data safety monitoring board (DSMB), Investigator, or Institutional Review Board [IRB] an unacceptable risk to the safety and welfare of subjects is posed by the continuation of the study)
- Death
- Protocol deviation
- Pregnancy (Section 7.9)
- Other

6.2. Safety Criteria for Stopping Study Treatment

A subject's study treatment may be interrupted or discontinued if any of the following conditions are met:

[redacted]

If the study treatment is interrupted due to any of the criteria listed above, the subject may be evaluated as part of an unscheduled visit to assess their status. Additional subsequent visits may be scheduled as required to assess event outcomes. The Investigator, in consultation with the Medical Monitor, and Sponsor will determine the next course of action, which may include allowing the subject to resume treatment with the study treatment.

Subjects that are discontinued from the study will be followed up by the Investigator until event resolution.

6.3. Safety Criteria for Stopping the Study

The recommended study stopping criteria are defined in a separate DSMB charter.

6.4. Subject Discontinuation of Study

Subjects will be free to withdraw from the study at any time should they wish to do so. Any subject may be discontinued early from the study for any of the following reasons:

- AE
- Withdrawal by subject
- Investigator decision
- Lost to follow-up (Section 6.5)
- Study termination by Sponsor
- Death
- Protocol deviation
- Pregnancy
- Other

Subjects who withdraw from the study will be encouraged to return to the site to complete an Early Termination visit [redacted] Subjects who withdraw from the study will not be replaced by additional subjects.

6.5. Lost to Follow-Up

A subject will be considered lost to follow-up if he/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 subject fails to return to the clinic for a required study visit:

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

- Before a subject is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's source document.
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study.

Closure of specific sites or termination of the study as a whole will be addressed as described in Section 9.7.

7. STUDY ASSESSMENTS AND PROCEDURES

[redacted]

7.1. General Instructions

- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue study treatment.
- Adherence to the study design requirements, including those specified in the [redacted], is essential and required for study conduct.
- Study visits should be scheduled in the morning.
- The Investigator will maintain a screening/enrollment log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure or Run-in failure, as applicable.

7.2. Informed Consent

The Investigator will obtain and document informed consent for each subject screened for this study. All subjects will be informed in writing of the nature of the protocol (including study restrictions and the use of rescue medications) and investigational therapy, its possible hazards, and their right to withdraw at any time, and will sign a form indicating their consent to participate prior to the initiation of study procedures. Genetic testing is optional; subjects who agree to genetic testing will sign additional consent. Participation in the LTE study is optional; subjects who agree to participation in the LTE study will sign additional consent. Health Insurance Portability and Accountability Act (HIPAA) authorization forms will also be signed as applicable at each site.

7.3. Eligibility

Initial and ongoing subject eligibility will be assessed based on protocol inclusion and exclusion criteria.

7.4. Demography and Other Subject Characteristics

Subject demographic information and other subject characteristic information, such as general medical history, height, weight, baseline disease characteristics relevant to the study (including date and details of diagnosis, associated illness and diseases), and social history (eg, tobacco use, alcohol use) will be collected. Recent (ie, within 3 months of Main Study Screening or LTE Screening) blood donations, illnesses, and any participation in other investigational drug studies will also be recorded.

7.4.1. Evaluation of Specific Ongoing Conditions of Interest

Subjects with the following ‘ongoing’ conditions listed in their medical history at the time of enrollment will be asked to rate their pain related to each applicable condition. At the end of the Main Study Treatment Period, subjects will repeat the evaluation of pain related to all applicable conditions.

- Migraine
- Fibromyalgia
- Other chronic pain (to be specified)
- Endometriosis
- Interstitial cystitis/ bladder pain syndrome
- Chronic pelvic pain

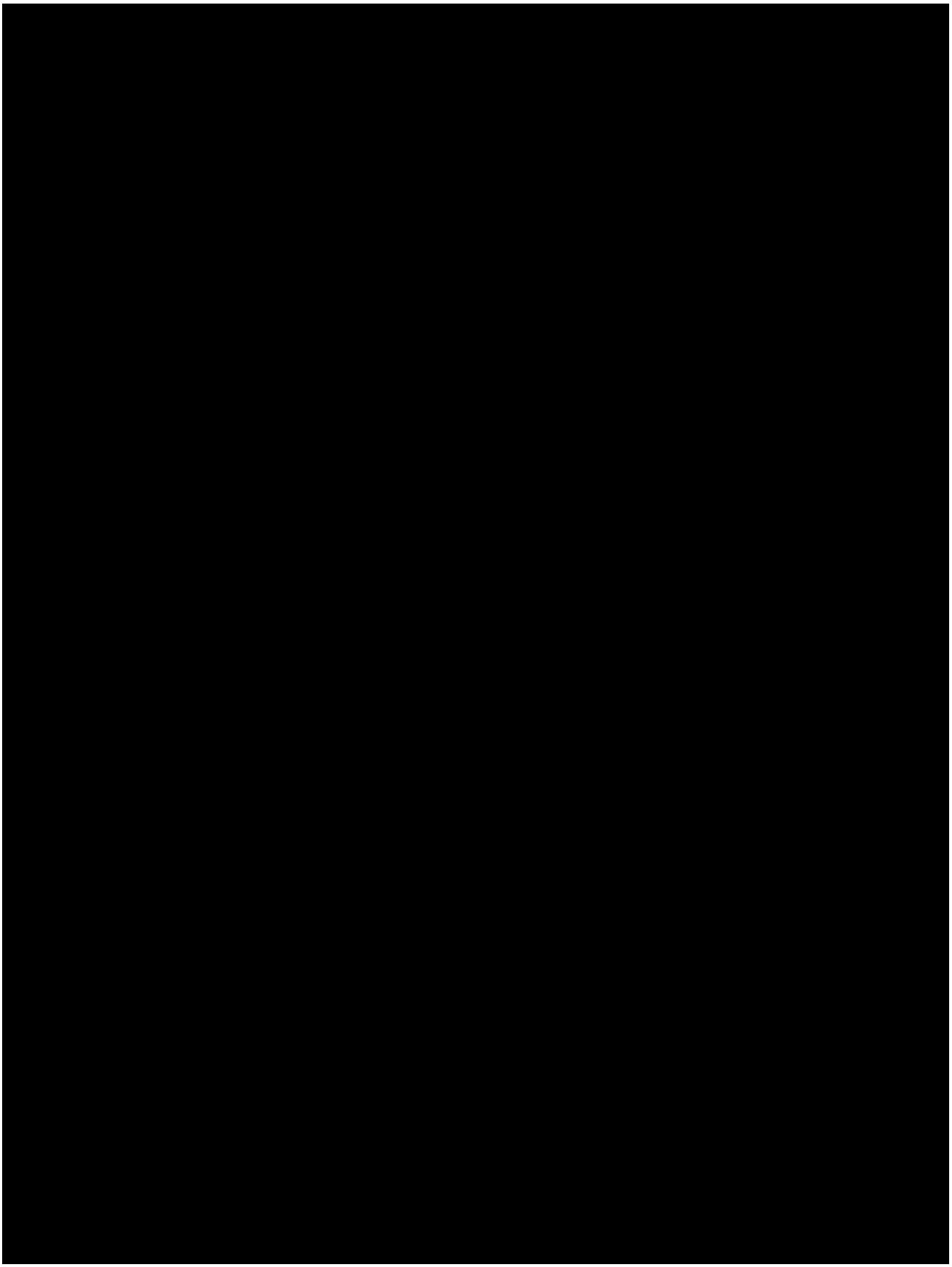
7.5. Efficacy Assessments

All patient-reported efficacy data, including daily eDiary data will be captured electronically using hand-held devices. Daily eDiary entry will include: APS, [redacted] and treatment administration. Subjects will be instructed to complete daily eDiary entries in the evening, generally at the same time each day. eDiary entries will be completed at the times shown in the [redacted]

7.5.1. Abdominal Pain Score

The APS is a single-question, 11-point numeric rating scale in which 0 represents no abdominal pain and 10 represents the worst possible abdominal pain. Once per day, subjects will use the APS to report their worst abdominal pain over the previous 24 hours. AAPS values collected during the Run-in Period will be used to determine subject eligibility for randomization. Daily APS will be collected throughout the study at the times shown in the [redacted].

[redacted]



[redacted]

7.6. Order of Events and Priority for Timed Assessments

Every effort should be made to perform procedures as closely as possible to the scheduled times indicated in the [redacted]. In chronological order, the order for completing visit procedures is pre-dose assessments (orthostatic vital signs or supine vital signs [as applicable] followed by body temperature and respiratory rate, physical examination, blood draw for trough PK and clinical laboratory assessments, and urine sample; ECG may be collected during the resting period prior to orthostatic vital signs or after the collection of respiratory rate), subject questionnaires, drug accountability and dispensing, study treatment administration, and all other assessments. For timed post-dose procedures scheduled at the same nominal timepoint, ECG may be collected during the resting period prior to orthostatic vital signs or after the collection of respiratory rate; blood draws should be collected after the completion of vital signs and ECG.

7.7. Safety Assessments

[redacted]

7.7.1. Physical Examinations

A full physical examination (including examination of general appearance, skin/dermatologic, lymph nodes, head, eyes, ears, nose and throat, neck, chest, thorax/lungs, and the following systems: cardiovascular, GI, neurologic, hematologic, and musculoskeletal) will be performed by medically qualified personnel at the timepoints specified in the [redacted].

An abbreviated physical examination (including examination of general appearance, thorax/lungs, cardiovascular system, and abdomen as well as assessments of any changes in the subject's health since the last visit) will per performed at the timepoints specified in the [redacted] All findings will be documented in subject source documents.

A symptom-driven physical examination will be performed at the timepoints specified in the [redacted] and at unscheduled timepoints if deemed necessary by the Investigator. Any new abnormalities or worsening may be recorded as AEs at the Investigator's discretion.

7.7.2. Vital Signs

Vital signs measurements will include blood pressure, HR, body temperature, and respiratory rate. Vital signs measures will be collected as defined in the [redacted]

Vital signs will be measured prior to any blood draw that occurs at the same timepoint.

Blood pressure and HR should be measured by an automated device. Proper technique should be utilized during the measurement of blood pressure and HR to include the following:

- Subjects should be allowed a 5-minute rest period before each assessment
- Readings should be taken on the subject's non-dominant arm consistently throughout the study
- The subject's arm should be bare and supported at heart level
- An appropriately sized cuff (cuff bladder encircling at least 80% of the arm) should be utilized. Subject's legs should not be crossed during the evaluation

Supine HR and blood pressure are measured after the subject has been resting in the supine position for at least 5 minutes. Orthostatic HR and blood pressure are measured after the subject has been resting in the supine position for at least 5 minutes and then after 1 and 3 minutes of standing. Supine vital signs and orthostatic measures will be collected at the timepoints indicated in the [redacted]

The Investigator or designee will be responsible for interpretation of vital signs at the time of the subject's visit. Clinically significant abnormalities will be documented in the eCRF and may be reported as AEs at the Investigator's discretion. Occurrence of orthostatic hypotension (defined as a decrease in SBP of 20 mm Hg relative to supine or a decrease in DBP of 10 mm Hg relative to supine) or postural tachycardia (defined as an increase of 30 bpm relative to supine or a maximum of 120 bpm) that occur at 1 or 3 minutes of standing will be documented on the eCRF. If orthostatic hypotension or postural tachycardia events are associated with symptoms they may also be documented as AEs at the discretion of the Investigator.

7.7.3. Electrocardiography

All ECGs will be recorded from a 12-lead ECG machine. Every attempt should be made to ensure the subject ECG readings are obtained using the same machine throughout the study at timepoints indicated in the [redacted]

It is recommended to collect ECGs at least 30 minutes after the end of the subject's most recent meal. All ECGs will be recorded with subjects in supine position. Supine rest time prior to ECGs should be at least 5 minutes.

Parameters to be provided on the confirmed read for each safety ECG are HR, and the following intervals: RR, PR, QRS, QT, QTc (QTcF required, QTcB optional). The ECGs will be read and

interpreted by the central ECG laboratory and the Investigator (or qualified designee) will be responsible for assessment of the clinical significance of ECGs. Clinically significant abnormalities will be documented in the eCRF and may be reported as AEs at the Investigator's discretion.

7.7.4. Clinical Laboratory Assessments

All laboratory assessments required by the protocol will be performed by a central laboratory unless otherwise stated. The maximum amount of blood collected from each subject at a single visit will not exceed 85 mL. The maximum amount of blood collected from each subject over the duration of the Main Study, including any extra assessments that may be required will not exceed 350 mL. The maximum amount of blood collected from each subject over the duration of the LTE will not exceed 135 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with samples. Additional details regarding clinical laboratory sample collection, preparation, and shipment are provided in the Laboratory Manual.

Clinical safety laboratory tests should be completed pre-dose after the subject has fasted overnight (at least 8 hours). Clinical laboratory tests, including basic metabolic panel, and screening for drugs of abuse will be conducted at timepoints specified in the [redacted]

The Investigator must review the laboratory report and document their review. Clinically significant worsening from baseline occurring during the study may be recorded as AEs at the Investigator's discretion. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline (Main Study Visit 3 or LTE Visit 2, as applicable) or are no longer considered clinically significant by the Investigator or Medical Monitor.

- If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Sponsor should be notified.
- All protocol-required laboratory assessments, as defined in the [redacted] must be conducted in accordance with the Laboratory Manual.
- If laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in subject management or are considered clinically significant by the Investigator (eg, AE), then the results must be recorded in the eCRF.

7.7.4.1. Clinical Chemistry, Hematology, and Coagulation

Clinical chemistry, hematology, and coagulation parameters that will be assessed during the study are identified in Table 3.

Subjects will be in a seated or supine position during blood collection.

7.7.4.2. Urinalysis

Urinalysis parameters that will be assessed during the study are identified in Table 3.

Table 3: Clinical Laboratory Tests

<table>
<tr><td colspan="3">Virology
HIV, HBsAg, and HCV</td></tr>
<tr><td>Pregnancy Testing
Serum or urine pregnancy test human chorionic gonadotropin (hCG)</td><td colspan="2">Drugs of Abuse
Amphetamine, barbiturates, benzodiazepines, cocaine, marijuana, methadone, methamphetamine, methylenedioxymethamphetamine, opioid, oxycodone, phencyclidine, THC, and THC derivatives</td></tr>
<tr><td>Hematology
Hematocrit
Hemoglobin
MCH
MCHC
MCV
Platelet count
RBC count
WBC count with differential

Coagulation
PT
PTT
INR</td><td>Serum Chemistry
Albumin
ALP
ALT
AST
Bicarbonate[a]
BUN[a]
Calcium[a]
Chloride[a]
Creatinine[a]
Creatine kinase
Glucose[a]
LDH
Phosphorus
Potassium[a]
Sodium[a]
Total bilirubin
Direct bilirubin
Total cholesterol
Total protein
Triglycerides
Uric acid

Additional Thyroid Chemistry
TSH
T4 free
T3 free
Thyroid binding protein</td><td>Urinalysis
Appearance
Bilirubin
Color
Glucose
Ketones
Microscopic examination of sediment
Nitrite
Occult blood
pH
Protein
Specific gravity
Urine drug screen
Urobilinogen</td></tr>
</table>

[a] Assessments included in the basic metabolic panel.
ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; hCG, human chorionic gonadotropin; HIV, human immunodeficiency virus; INR, international normalized ratio; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; LDH, lactate dehydrogenase; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; PT, prothrombin time; PTT, activated partial thromboplastin time; RBC, red blood cell; T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone; THC, tetrahydrocannabinol; WBC, white blood cell

7.7.5. Screening/Ongoing Study Eligibility

Laboratory tests conducted at Main Study and LTE Screening are detailed in Table 3. Some assessments may be repeated at specified visits in the [redacted] to confirm continuing eligibility.

7.7.5.1. Drugs of Abuse

A standard urine drug screen will be performed to determine subject eligibility. Subjects who test positive for amphetamine, barbiturates, cocaine, marijuana, methadone, methamphetamine,

methylenedioxymethamphetamine, opioid, oxycodone, phencyclidine, THC, and THC derivatives will not be eligible for study participation (ie, considered Screen Failures [Section 4.5]). If a subject has a positive result on a urine drug screen as a result of a prescribed medication that treats a concomitant illness that is not excluded or restricted per the protocol (Section 5.7.4), it is not required to exclude the subject from the study. Additional urine drug screening will be performed at every scheduled visit throughout the study. Positive urine drug screening results during the Treatment Period will be assessed on a case by case basis.

7.7.5.2. Pregnancy Testing

A serum human chorionic gonadotropin (hCG) pregnancy test will be performed on female subjects of childbearing potential to determine eligibility. Additional urine pregnancy tests (hCG) will be conducted at visits as specified in the [redacted] Any subject with a positive pregnancy test at any time during the study must stop taking study treatment immediately. Refer to Section 7.9 for additional information on pregnancy events.

Negative pregnancy test results must be documented for all female subjects of childbearing potential prior to dosing at applicable study visits. Women who are surgically sterile or those who are postmenopausal are not considered to be of childbearing potential; otherwise women are considered to be of childbearing potential.

[redacted]

7.7.5.4. Clinical Chemistry, Hematology, and Coagulation

Clinical chemistry, hematology, coagulation parameters, and basic metabolic panel that will be assessed during the study are identified in Table 3.

Subjects will be in a seated or supine position during blood collection. All laboratory samples other than post-dose lab collections specified in the Schedule of Assessments should be collected prior to the administration of study treatment at applicable visits ([redacted]).

7.7.5.5. Urinalysis

Urinalysis parameters that will be assessed during the study are identified in Table 3.

7.8. Adverse Events

7.8.1. Definitions

7.8.1.1. Adverse Event

An AE is any untoward medical occurrence in a subject or clinical investigational subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

AEs can include, but are not limited to, any of the following:

- Unfavorable changes in general condition
- Subjective or objective signs/symptoms
- Concomitant disease or accidents
- Clinically relevant adverse changes in laboratory parameters over the course of the study
- Pre-existing conditions that worsen in severity or frequency or that have new signs/symptoms associated with them

Planned elective procedures or planned procedures not resulting from any worsening from a baseline condition are not considered AEs; however, any associated concomitant medications, contrast dyes, blood loss or blood transfusions must be reported in the clinical database as described in Section 7.8.2.2.

7.8.1.2. Serious Adverse Event

An AE should be classified as an SAE if it meets one of the following criteria:

Fatal:	AE resulted in death.
Life-threatening:	The AE placed the subject at immediate risk of death. This classification does not apply to an AE that hypothetically might cause death if it were more severe.
Hospitalization:	The AE required or prolonged an existing inpatient hospitalization. Hospitalizations for elective medical or surgical procedures or treatments planned before the signing of informed consent in the study or routine check-ups are not SAEs by this criterion. Admission to a palliative unit or hospice care facility is not considered to be a hospitalization. Hospitalizations or prolonged hospitalizations for scheduled therapy of the underlying cancer or study target disease need not be captured as SAEs.
Disabling/ incapacitating:	Resulted in a persistent or significant incapacity or substantial disruption of the subject's ability to conduct normal life functions.
Congenital anomaly or birth defect:	An adverse outcome in a child or fetus of a subject exposed to the molecule or study treatment regimen before conception or during pregnancy.
Medically significant:	The AE did not meet any of the above criteria but could have jeopardized the subject and might have required medical or surgical intervention to prevent one of the outcomes listed above or involves suspected transmission via a medicinal product of an infectious agent.

7.8.1.3. Adverse Drug Reaction

An adverse drug reaction (ADR) in the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established, is any

noxious and unintended response to a medicinal product related to any dose. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility (ie, the relationship cannot be ruled out).

7.8.1.4. Adverse Events of Special Interest

Based on the mechanism of action of olorinab and prior experience with other agents acting via a similar mechanism, potential AEs of special interest may be identified. In addition to appropriate reporting of these events as an AE or SAE, supplementary detailed information may be collected.

7.8.1.5. Severity

The severity of each AE will be assessed at the onset by a nurse/or physician. When recording the outcome of the AE the maximum severity of the AE experienced will also be recorded. The severity of each AE will be graded according to CTCAE, version 5.0:

Grade 1:	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2:	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
Grade 3:	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self-care activities of daily living (eg, preparing meals, shopping for groceries or clothes, using the telephone, managing money)
Grade 4:	Life-threatening consequences, urgent intervention indicated
Grade 5:	Death related to AE

7.8.1.6. Relationship

The Investigator is obligated to assess the relationship (causal relationship) between the study treatment and each occurrence of each AE/SAE. The AE relationship (causal relationship) to study treatment must be characterized as one of the following categories:

Not Related:	The AE does not follow a reasonable temporal sequence from administration of the study treatment, does not abate upon discontinuation of the study treatment, does not follow a known or hypothesized cause-effect relationship, and (if applicable) does not reappear when the study treatment is reintroduced, furthermore, there may exist a clear alternative medical explanation (eg, underlying disease state) or association with study procedure or study conduct.
Unlikely Related:	The temporal association between the AE and the study treatment is such that the study treatment is not likely to have any reasonable association with the AE.

Probably Related:	The AE follows a reasonable temporal sequence from administration of the study treatment and cannot be reasonably explained by the known characteristics of the subject's clinical state, environmental, or toxic factors, or other modes of therapy administered to the subject.
Related:	The AE follows a reasonable temporal sequence from administration of the study treatment, abates upon discontinuation of the study treatment, follows a known or hypothesized cause-effect relationship, and (if appropriate) reappears when the study treatment is reintroduced.

The Investigator will use clinical judgment to determine the relationship (causal relationship). Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to the study treatment administration should be considered and investigated. The Investigator should consult the Investigator's Brochure and the Product Information of marketed products within the drug class, when applicable. For each AE/SAE, the Investigator must document in the source documents 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 makes an initial assessment of causality for every event before the initial transmission of the SAE to the Sponsor. The Investigator may change his/her opinion of causality based on subsequent receipt of 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.

7.8.2. Eliciting and Recording Adverse Events

7.8.2.1. Eliciting Adverse Events

Subjects will be instructed that they may report AEs at any time. An open-ended or nondirected method of questioning should be used at each study visit to elicit the reporting of AEs.

7.8.2.2. Recording Adverse Events

The AE reporting period for safety surveillance begins when the subject is initially included in the study (date of first signature of informed consent) and continues up to 30 days after the last study treatment administration. If an AE is not resolved or stabilized by this time, the Sponsor in consultation with the Investigator will decide whether to continue to monitor the AE or closeout the event in the database if no further follow-up is necessary.

Any SAE suspected to be related to the study treatment must be reported whenever it occurs, irrespective of the time elapsed since the last administration.

Investigator and study personnel will record all AEs and SAEs whether received through an unsolicited report by a subject, elicited during subject questioning, discovered during physical examination, laboratory testing, and/or other means by recording them on the eCRF as appropriate. To avoid vague, ambiguous, or colloquial expressions, the AE should be recorded on the source documents and/or eCRFs using standard medical terminology that is as specific as possible, rather than the subject's own words. Whenever the Investigator is confident in making

a unifying diagnosis, all related signs, symptoms, and abnormal test results should be grouped together as a single AE in the source document and/or eCRF (eg, cough and rhinitis should be reported as an "upper respiratory tract infection").

The Investigator should assess when it may be appropriate for intermittent events of the same type to be grouped together as a single AE in the source document and/or eCRF (eg, "intermittent headache").

The following information should be recorded on the AE eCRF:

- Description including onset and resolution dates
- Whether it met SAE criteria
- Severity
- Relationship to study treatment or other causality
- Outcome

For SAEs, events occurring secondary to the primary event should be described on the eCRF in the narrative description field.

The following should be considered when recording SAEs:

- Death is an outcome of an event. The event that resulted in the death should be recorded and reported on the eCRF
- For hospitalizations, surgical, or diagnostic procedures, the illness leading to the surgical or diagnostic procedure should be recorded as the SAE, not the procedure itself. The procedure should be captured in the narrative as part of the action taken in response to the illness.

7.8.2.3. Diagnosis Versus Signs or Symptoms

In general, the use of a unifying diagnosis is preferred to the listing out of individual symptoms. Grouping of symptoms into a diagnosis should generally be limited to occasions when each component sign and/or symptom is a medically confirmed component of a diagnosis as evidenced by standard medical textbooks. If an aspect of a sign or symptom does not fit into a classic pattern of the diagnosis in the clinical judgement of the investigator, the individual symptom should generally be reported as a separate AE.

7.8.2.4. Reporting Serious Adverse Events

All SAEs are subject to reporting requirements.

7.8.2.5. Serious Adverse Events

All SAEs, whether or not considered related to study treatment, must be reported to the designated Sponsor Contact **within 24 hours of becoming aware of the event.** Enter the SAE information into the electronic data capture (EDC) system, and send other available pertinent information (eg, hospital records, laboratory results) to the designated Sponsor Contact:

IQVIA Pharmacovigilance
Phone: [redacted]
Fax: [redacted]
Email: [redacted]

If additional follow-up information is required or becomes available for a previously reported SAE, entry of the new information into EDC should be completed **within 24 hours of awareness.**

Elective hospitalization and/or surgery for clearly preexisting conditions (eg, a surgery that has been scheduled prior to the subject's entry into the study) will not be reported as an SAE. All other hospitalizations, including elective hospitalizations for any condition that was not preexisting, will be reported as an SAE.

Any SAE that is ongoing when the subject completes the study or discontinues the study will be followed by the Investigator until the event resolved, stabilized or returned to baseline (Main Study Visit 3 or LTE Visit 2, as applicable) status.

7.8.2.6. Serious, Unexpected Adverse Drug Reactions

All ADRs that are both serious and unexpected are subject to expedited reporting to regulatory agencies. An unexpected ADR is one for which the nature or severity is not consistent with information in the relevant source documents.

The following documents or circumstances will be used to determine whether an AE/ADR is expected:

1. For a medicinal product not yet approved for marketing in a country, the reference safety information section of a company's Investigator's Brochure will serve as the source document in that country
2. Reports that add significant information on specificity or severity of a known, already documented serious ADR constitute unexpected events. For example, an event more specific or more severe than described in the Investigator's Brochure would be considered "unexpected"

7.9. Pregnancy

If at any point a urine or serum hCG pregnancy test is positive, the subject will be withdrawn from the study treatment.

Details of all pregnancies that occur in female subjects and female partners of male subjects after the start of study treatment and until 30 days after the last dose will be collected.

Pregnancy (during maternal or paternal exposure to study treatment) does not meet the definition of an AE; however, to fulfill regulatory requirements, any pregnancy should be reported via the **Pregnancy Report Form** to the designated Sponsor Contact **within 24 hours of awareness** to collect data on the outcome of the birth for both the mother and the fetus.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and should be reported as such even if outside the SAE reporting period.

7.10. Pharmacokinetics

Blood samples of approximately 4 mL will be collected for measurement of plasma concentrations of olorinab and its metabolites as specified in the [redacted]. Fasting requirements and other restrictions for blood sampling are described in Section 4.4. Additional samples may be collected at additional timepoints or sampling days during the study if warranted and agreed upon between the Investigator and the Sponsor. A Laboratory Manual will be provided to instruct on material supplies, and sample collection, processing, storage, and shipping procedures. The actual date and time (24-hour clock time) of each sample will be recorded.

Samples will be used to evaluate the PK of olorinab and its predominant metabolites [redacted]. Samples collected for analyses of these olorinab plasma concentrations may also be used for profiling of drug binding proteins, bioanalytical method validation, stability assessments, metabolite assessments, to assess other actions of olorinab (and/or its metabolites) with plasma constituents, or for context pertaining to safety events arising during or after the study.

During the Main Study, calculated plasma PK parameters of olorinab and its metabolites will include but not necessarily be limited to the following:

- **C_{max}** – observed maximum concentration
- **t_{max}** – time of observed maximum (peak) concentration after drug administration
- **C_{trough}** – observed trough (pre-dose) concentration

During the LTE, only C_{trough} will be calculated.

Subject confidentiality will be maintained.

Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded. Detailed instructions regarding sample collection, processing, and shipping will be provided in a separate Laboratory Manual.

7.11. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

7.12. Genetics

A blood sample for deoxyribonucleic acid (DNA) isolation will be collected from subjects who have consented to participate in the genetic analysis component of the study. Participation is optional. Subjects who do not wish to participate in the genetic research may still participate in the study.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the subject. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

Details on processes for collection and shipment and destruction of these samples can be found in the Laboratory Manual.

Samples may be stored for a maximum of 20 years (or according to local regulations) following the last subject's last visit for the study at a facility selected by the Sponsor to enable further analysis of genetic samples.

7.13. Biomarkers

Colonic biopsy and blood biomarker samples will be collected from subjects who have consented to participate in the colonic biopsy and blood biomarker component of the study. Collection of blood samples for exploratory biomarker assessments will be collected at all sites. Blood samples may be tested for cytokines and chemokines. Collection of colonic biopsy samples for exploratory biomarker assessments will be collected at select sites only. Colonic biopsy tissue may be tested for components of the endocannabinoid system. Additional biomarkers in blood or colonic biopsies as deemed relevant to assess efficacy and mechanism of action of olorinab may be evaluated. Collection of colonic biopsy and biomarker samples will be conducted [redacted]

Details for collection, processing, and storage will be provided in the Laboratory Manual. Residual samples will be stored and may be used for additional analyses to further explore efficacy and mechanism of action of olorinab if the subject has granted optional consent for such testing. These additional analyses will only be conducted where allowed by the regulatory authorities and local ethics committees.

Samples may be stored for a maximum of 20 years (or according to local regulations) following the last subject's last visit for the study at a facility selected by the Sponsor to enable further analysis of biomarker responses to olorinab.

7.13.1. RNA Transcriptome Research

Transcriptome studies of blood samples and colonic biopsies will be conducted using ribonucleic acid (RNA)-Seq, and/or alternative equivalent technologies. This will enable the evaluation of changes in transcriptome profiles that may correlate with biological response relating to IBS and pain or the action of olorinab.

The same samples may also be used to confirm findings by application of alternative technologies.

7.13.2. Proteome Research

The biomarker blood sample and colonic biopsy samples will be collected to enable proteome studies performed by enzyme-linked immunosorbent assay (ELISA), mass spectrometry, or an alternative equivalent procedure. This will enable the evaluation of changes in proteome profiles that may correlate with biological response related to IBS and the mechanism of action of olorinab.

The samples may also be used to confirm findings by application of alternative technologies.

7.13.3. Metabolomic Research

Blood and colonic biopsy metabolome studies will be performed by mass spectrometry, liquid chromatography-mass spectrometry, gas chromatography-mass spectrometry, and/or Fourier-transform mass spectrometry, and equivalent methods. This may include analysis of

identified or uncharacterized metabolites and lipids that are known to be or emerge in the future as important in the pathogenesis of IBS and may be impacted by treatment with olorinab.

7.14. Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

8. STATISTICAL CONSIDERATIONS

8.1. Sample Size Determination

It is assumed that change in AAPS from Main Study Baseline to Week 12 will be normally distributed with a standard deviation (SD) of 1.9. Assuming a 1:1:1:1 randomization, 240 subjects (60 per treatment group) is sufficient to achieve at least 80% power to detect a treatment effect of 1.0 between each of the olorinab treatment groups and placebo by a 2-sample t-test using a 2-sided significance level of 0.05.

Note, under the same assumptions, there is at least 95% power to detect a treatment effect of 1.0 between the pooled olorinab treatment group (180 subjects) and placebo (60 subjects).

A blinded review of the data to evaluate the assumption regarding the SD of the change in AAPS from Baseline at Week 12 may be conducted. The planned sample size will not be reduced as a result of the sample size re-estimation. Details will be specified in the Statistical Analysis Plan (SAP) for the Main Study.

8.2. Analysis Sets

For purposes of analysis, the following analysis sets are defined for the Main Study (Table 4).

Table 4: Analysis Sets for Main Study

Analysis Set	Definition
Screened	The Screened Set will include all subjects who sign the ICF.
Enrolled	The Enrolled Set will include all subjects who are enrolled in the Run-in Period.
Full Analysis	The Full Analysis Set (FAS) will include all randomized subjects, irrespective of whether they received study treatment.
Per Protocol	The Per Protocol Set will include all subjects in the FAS without major protocol violations that might affect the evaluation of the effect of the study treatment on the primary endpoint. These violations will be pre-defined in the SAP and the Per Protocol Set will be specified prior to unblinding.
Pharmacokinetic	The Pharmacokinetic Set will include all subjects in the FAS with at least 1 post-dose PK measurement.
Safety	The Safety Set will include subjects randomly assigned to study treatment and who take at least one dose of study treatment.

For purposes of analysis, the following analysis sets are defined for the LTE (Table 5).

Table 5: Analysis Sets for Long-Term Extension

Analysis Set	Definition
Screened	The Screened Set will include all Gap subjects who signed the ICF for LTE.
Full Analysis	The Full Analysis Set (FAS) will include all randomized subjects in LTE, irrespective of whether they received study treatment.
Pharmacokinetic	The Pharmacokinetic Set will include all subjects in the FAS with at least 1 post-dose PK measurement in LTE.
Safety	The Safety Set will include subjects randomly assigned to study treatment and who take at least one dose of study treatment in LTE.

8.3. Statistical Analyses

Details regarding the statistical analyses will be provided in the SAPs. The SAP for the Main Study will be finalized prior to database lock (unblinding) of the Main Study and the SAP for the LTE will be finalized prior to database lock for the LTE. Results of the Main Study and the LTE may be reported in 2 separate clinical study reports.

Continuous variables will be summarized using the number of observations, mean, SD, median, minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages. For time-to-event variables, the number of subjects at risk over time, as well as the cumulative percentage of subjects experiencing the event of interest will be presented, based on Kaplan-Meier methodology.

Unless otherwise specified, continuous endpoints will be analyzed using a mixed-effects model repeated measures (MMRM) analysis with treatment, the stratification factors, visit, and treatment-by-visit interaction as factors and Baseline AAPS and Baseline value (if applicable) as covariates. Visit will include all scheduled visits except Visit 9 (Week 14). Least squares means, standard errors (SEs), and 95% confidence intervals (CIs) for the treatments and their difference will be presented together with the p-values.

Continuous endpoints derived from the eDiary (eg, score in abdominal pain, bloating, discomfort, number of bowel movements), will be analyzed using the MMRM above that includes scheduled visit, as well as a second MMRM model that includes treatment, the stratification factors, week, and treatment-by-week interaction as factors and Baseline AAPS and Baseline value (if applicable) as covariates. Week will include each week from Week 1 to Week 12. Least squares means, standard errors (SEs), and 95% confidence intervals (CIs) for the treatments and their difference will be presented together with the p-values.

Categorical endpoints will be analyzed by either the Cochran-Mantel-Haenszel (CMH) method, Fisher's exact test, or by logistic regression with a model that includes treatment and stratification factors as factors and Baseline AAPS and Baseline value (if applicable) as covariates. The odds ratio relative to placebo and percentage of difference from placebo will be presented together with corresponding 95% CIs and the p-values.

Time-to-event endpoints will be displayed using Kaplan-Meier plots and analyzed with Cox regression with a model that includes treatment and the stratification factors as factors and

Baseline AAPS and Baseline value (if applicable) as covariates. The hazard ratio will be presented together with 95% CIs and the p-values.

Where statistical assumptions (eg, proportional hazards, normality, proportional odds) are not met, alternative approaches will be evaluated (eg, non-parametric analysis, log transformation).

Pairwise comparisons of each olorinab treatment group compared to placebo will be conducted. In addition, analyses of the pooled olorinab treatment groups compared placebo will be conducted.

Efficacy data will be analyzed by randomized treatment, while safety data will be analyzed by actual treatment.

8.3.1. Endpoints

8.3.1.1. Main Study Endpoints

Primary

- Change in average abdominal pain score (AAPS) from Baseline to Week 12
- Adverse events and clinically relevant changes in vital signs and clinical laboratory results

Secondary

- The proportion of subjects achieving a ≥ 30% improvement in AAPS from Baseline to Week 12
- The proportion of subjects achieving a ≥ 30% improvement in AAPS from Baseline for at least 6 of the 12 weeks during the Main Study Treatment Period
- Percent change in AAPS from Baseline to Week 12
- Change in number of pain free days per week from Baseline to Week 12
- PK parameters including, but not limited to, C_{max}, t_{max}, and C_{trough}

Exploratory

[redacted]

[redacted]

8.3.1.2. Long-Term Extension Endpoints

Primary

- AEs, clinically relevant changes in vital signs, and clinical laboratory results

[redacted]

8.3.2. Main Study Efficacy Analyses

Statistical analysis methods for efficacy analyses in the Main Study are listed in Table 6.

Table 6: Statistical Analysis Methods for Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	The primary endpoint, change in AAPS from Baseline to Week 12, will be analyzed using a MMRM analysis with treatment, stratification factors, visit, and treatment-by-visit interaction as factors and Baseline AAPS as a covariate. An unstructured variance-covariance matrix will be used for the MMRM analysis. Least squares means, SEs, and 95% CIs for the treatments and their difference will be presented together with the p-values. The primary analysis will be conducted in the FAS. Sensitivity analyses will be detailed in the SAP.
Secondary	The proportion of subjects achieving a ≥ 30% improvement in AAPS from Baseline to Week 12 will be analyzed using the CMH test stratified by the stratification factors. The odds ratio relative to placebo and percentage of difference from placebo will be presented together with corresponding 95% CIs and the p-values. The proportion of subjects achieving a ≥ 30% improvement in AAPS for at least 6 of the 12 weeks during the Treatment Period will be analyzed using the CMH test stratified by the stratification factors. The odds ratio relative to placebo and percentage of difference from placebo will be presented together with corresponding 95% CIs and the p-values. The percent change in AAPS from Baseline to Week 12 and Change from Baseline to Week 12 in number of pain free days will be analyzed using the same MMRM analysis as specified for the primary endpoint above. The change and percent change in AAPS from Baseline to Week 12 and change from Baseline to Week 12 in number of pain-free days per week will be analyzed using another MMRM model with treatment, stratification factors, week, and treatment-by-week interaction as factors and Baseline AAPS as a covariate. An unstructured variance-covariance matrix will be used for the MMRM analysis. Least squares means, SEs, and 95% CIs for the treatments and their difference will be presented together with the p-values. A detailed description of PK analyses will be provided in the SAP. Additional details regarding the statistical methods for secondary endpoints will be described in the SAP.
[redacted]	

8.3.3. Main Study Pharmacokinetic Analysis

A descriptive summary of observed plasma concentrations will be displayed by time and by treatment group. The Main Study Pharmacokinetic Set will be used to analyze plasma levels. Full details of PK analysis will be provided in the SAP for the Main Study.

8.3.4. Main Study Safety Analyses

All safety analyses will be performed on the Main Study Safety Population. All safety data will be listed and summarized by treatment group. Additional statistical analysis methods for safety analyses are listed below.

8.3.4.1. Adverse Events

AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA).

For each treatment group, the proportion of subjects with TEAEs will be summarized overall, by severity, and by relationship to olorinab. A TEAE is defined as:

- An AE that occurs after initiation of olorinab that was not present at the time of treatment start.
- An AE that increases in severity after the initiation of olorinab, if the event was present at the time of treatment start.

Incidence of AEs, SAEs, and TEAEs leading to study treatment discontinuation will be summarized and presented in descending order of frequency. AEs occurring before the first dose of olorinab will be summarized separately.

8.3.4.2. Extent of Exposure

The duration of time on study and time on study treatment will be summarized for each treatment using descriptive statistics. The number of subjects on treatment for certain time intervals will also be summarized. The total subject-years and total subject-years on study will also be included in this summary.

8.3.4.3. Clinical Laboratory Results

Laboratory parameters will be summarized by treatment group at each scheduled assessment timepoint using descriptive statistics. Associated laboratory parameters such as hepatic enzymes, renal function, and hematology values will be grouped and presented together. Individual subject values will be listed and values outside of the standard reference range will be noted. Shift tables and analyses of changes from Baseline will be produced.

8.3.4.4. Vital Signs

The change from Baseline for each of the vital signs (blood pressure, HR, respiratory rate, body temperature) will be presented by treatment group. The incidence of abnormal vital signs parameters will be tabulated.

8.3.4.5. Physical Exams

Clinically significant physical examination abnormalities will be included in medical history or recorded and summarized as an AE.

8.3.4.6. Electrocardiography

The change from Baseline Descriptive statistics for each of the ECG parameters will be presented by treatment group. The incidence of outlier ECG results will be tabulated. Individual ECG values will be listed by visit and summarized using descriptive statistics. Parameters to be provided on the confirmed read for each safety ECG are HR and the following intervals: RR, PR, QRS, QT, and QTc (QTcF required, QTcB optional). The ECGs will be read and interpreted by the central ECG laboratory. Post-Baseline ECGs for each subject will be compared with the Baseline ECG. Any clinically significant change from Baseline may be recorded as an AE if deemed appropriate by the Investigator, or Investigator in consultation with the Medical Monitor. Outlier analysis will be performed on all subjects with QTcF values greater than 500 ms or change from Baseline > 60 ms in the absence of Baseline ECG abnormalities that preclude accurate surface ECG assessment of ventricular repolarization (eg, bundle branch block).

8.3.5. Other Analyses

[redacted]

8.3.6. Statistical Analyses for the Long-Term Extension

The LTE has 2 treatment groups, 25 mg and 50 mg. Based on subjects' treatment assignments in the Main Study and the LTE study, subjects can be classified into 6 unique treatment groups: "Placebo|25 mg", "Placebo|50 mg", "10 mg|25 mg", "10 mg|50 mg", "25 mg|25 mg", and "50 mg|50 mg".

Safety analyses will be performed as described above for the Main Study. In addition, new AEs that occur after the first dose in the LTE or TEAEs which occurred in the Main Study period and increase in severity after the first dose of LTE study treatment will also be summarized by the 6 unique treatment groups. Exposure will also be summarized by unique treatment group.

A descriptive summary of observed plasma concentrations will be provided by treatment group.

Summary statistics will be provided for efficacy endpoints by unique treatment group. Proportion-based endpoints including responders will be summarized with frequency count and percentage. Continuous endpoints will be summarized with descriptive statistics including mean, median, standard deviation, minimum, and maximum values. There is no formal between-treatment comparison for efficacy endpoints.

Additional analyses may be performed in some subgroups of medical interest, such as sex, age, race, and IBS subtype. Details of the analyses will be provided in the SAP for LTE.

8.4. Data Safety Monitoring Board

An independent data safety monitoring board (DSMB) has been established for the regular and ad hoc review of aggregate safety data. Membership of the DSMB, meeting frequency, and safety review criteria are defined in a separate DSMB charter. Recommendations for specific study stopping criteria are described in the DSMB charter. The DSMB will have access to aggregate blinded data but may also request to review unblinded data at their discretion as needed. At the conclusion of each meeting, the DSMB will provide a recommendation to the Sponsor's Safety Lead and the Study Lead Investigator.

8.5. Interim Analyses

No formal interim analyses are planned.

8.6. Missing Data

The efficacy analyses will be conducted on the FAS. The robustness of the primary endpoint result will be assessed using various sensitivity analyses (eg, complete-case, multiple imputation). In addition, sensitivity analyses may be used to assess the robustness of results for the secondary and exploratory endpoint using various methodology (eg, MMRM, complete-case, worst-case, non-responder, multiple imputation).

8.7. Testing Strategy/Multiplicity

No formal testing strategy or adjustments of the type I error will be employed for the primary, secondary or exploratory endpoints. Estimates and CIs for treatment groups and from pairwise comparisons will be used in an exploratory manner.

9. OPERATIONAL CONSIDERATIONS

9.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
  - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator's Brochure, and any other patient-facing documents (eg, advertisements) must be submitted to an IRB by the Investigator and reviewed and approved by the IRB before the study is initiated.
- Any amendments to the protocol will require IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB
  - Notifying the IRB of SAEs or other significant safety findings as required by IRB procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations
- The Sponsor is responsible for compliance with applicable sections of 21 CFR Part 312, SubPart D *(Responsibilities of Sponsors)*.

9.2. Informed Consent Process

The Investigator or his/her representative will explain the nature of the study and review protocol-specific subject requirements including requirements regarding background medications. The Investigator or his/her representative will answer any questions the subject has regarding study participation.

Subjects must be informed that their participation is voluntary. Subjects will be required to sign a statement of informed consent that meets the requirements of 21 CFR Part 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB or study center.

Informed consent will also include permission for the Investigator to obtain information on the subject's health status from next of kin, health care professionals, or public registries in the event

the subject withdraws early from randomized study treatment and fails to respond to attempts to schedule the Follow-Up Visit.

The informed consent process may also include additional consent for collection of colonic biopsy and blood samples for genetic analysis. The source document must include a statement that written informed consent was obtained before the subject 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.

If the ICF is updated, subjects 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 subject.

Subjects who are rescreened are required to sign a new ICF.

Subjects who participate in the LTE will be required to sign a separate ICF.

9.3. Data Protection

All information generated in this study is considered highly confidential and must not be disclosed to any person or entity not directly involved with the study unless prior written consent is provided from the Sponsor.

Subjects will be assigned a unique identifier by the Sponsor. Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

The subject 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 subject.

The subject 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 members, and by inspectors from regulatory authorities.

In addition, prior to study participation, the subject must be informed that the records identifying the subject will not be made publicly available.

9.4. Protocol Compliance

The Investigator/institution will conduct the study in compliance with the protocol agreed to by the Sponsor and regulatory authorities (if applicable) and that was approved by the IRB. The Investigator/institution and the Sponsor should sign the protocol, or an alternative contract, to confirm agreement.

The Investigator should not implement any deviation from, or changes to, the protocol without agreement by the Sponsor and prior review and documented approval from the IRB of an amendment, except where necessary to eliminate immediate hazard(s) to study subjects or when the change involves only logistical or administrative aspects of the study (eg, change in monitor, change of telephone number).

When an important deviation from the protocol is deemed necessary for an individual subject, the Investigator must contact the Sponsor. Such contact must be made as soon as possible to permit a review by the Sponsor to determine the impact of the deviation on the subject's participation and/or the assessment of safety or efficacy in the study. Any significant protocol deviations affecting subject eligibility and/or safety must be reviewed and/or approved by the IRB and regulatory authorities, as applicable, prior to implementation.

The Investigator should document and explain any deviation from the approved protocol.

9.5. Data Quality Assurance

Quality systems shall be implemented and maintained with written SOPs to ensure that the study is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s). Quality control shall be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

Prior to study activities being initiated at the site(s), the Sponsor or designee will train study site personnel on the protocol and applicable procedures. If new study site personnel are assigned to the study after the initial training, study sites should contact the study monitor in a timely manner as appropriate to coordinate training. All training should be documented.

All subject 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 review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or onsite monitoring) are provided in the Monitoring Plan.

The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.

The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).

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 subjects 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 for 2 years after the last marketing application approval, or if the application is not approved or never submitted, 2 years after the appropriate regulatory authorities have been notified of the discontinuation of clinical development of the

investigational product. 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.

9.6. Source Documents

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site. Source documents include information contained in original records and certified copies of results, observations or other facets required for the reconstruction and evaluation of the study that is contained in source documents. Examples of source documents may include (but are not limited to) hospital records, clinical and office charts, laboratory data/information, subjects' diaries or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, ECGs, X-rays, ultrasounds, right heart catheterization reports, ECHO, and PFTs. Data collected during the study must be recorded on the appropriate source documents.

Data reported on the eCRF or 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.

eCRFs must be completed for each subject screened/enrolled in this study. These forms will be used to transmit information collected during the study to the Sponsor and regulatory authorities, as applicable.

The Investigator will document subject data in his/her own subject files. These subject files will serve as source data for the study. All eCRF data required by this protocol will be recorded by investigative site personnel. All data entered into the eCRF will be supported by source documentation.

The Investigator or an authorized member of the Investigator's staff will make any necessary corrections to the eCRF. All changed information, including the date and person performing the corrections, will be available via the audit trail, which will be part of the electronic data capture system. For any correction, a reason for the alteration will be provided. The eCRFs will be reviewed periodically for completeness and acceptability by Sponsor personnel (or their representatives). The Sponsor (or their representatives) will also be allowed access to all source documents pertinent to the study in order to verify eCRF entries. The Investigator will review the eCRFs for completeness and accuracy and provide his or her electronic signature and date to eCRFs as evidence thereof.

The documentation related to the validation of the eCRFs will be maintained in the Trial Master File (TMF). The TMF will be maintained by the Contract Research Organization during the course of the clinical study and by the Sponsor upon completion of the study.

9.7. Study and Site Closure

The Sponsor or their 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 after 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 or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the Investigator
- Discontinuation of further study treatment development

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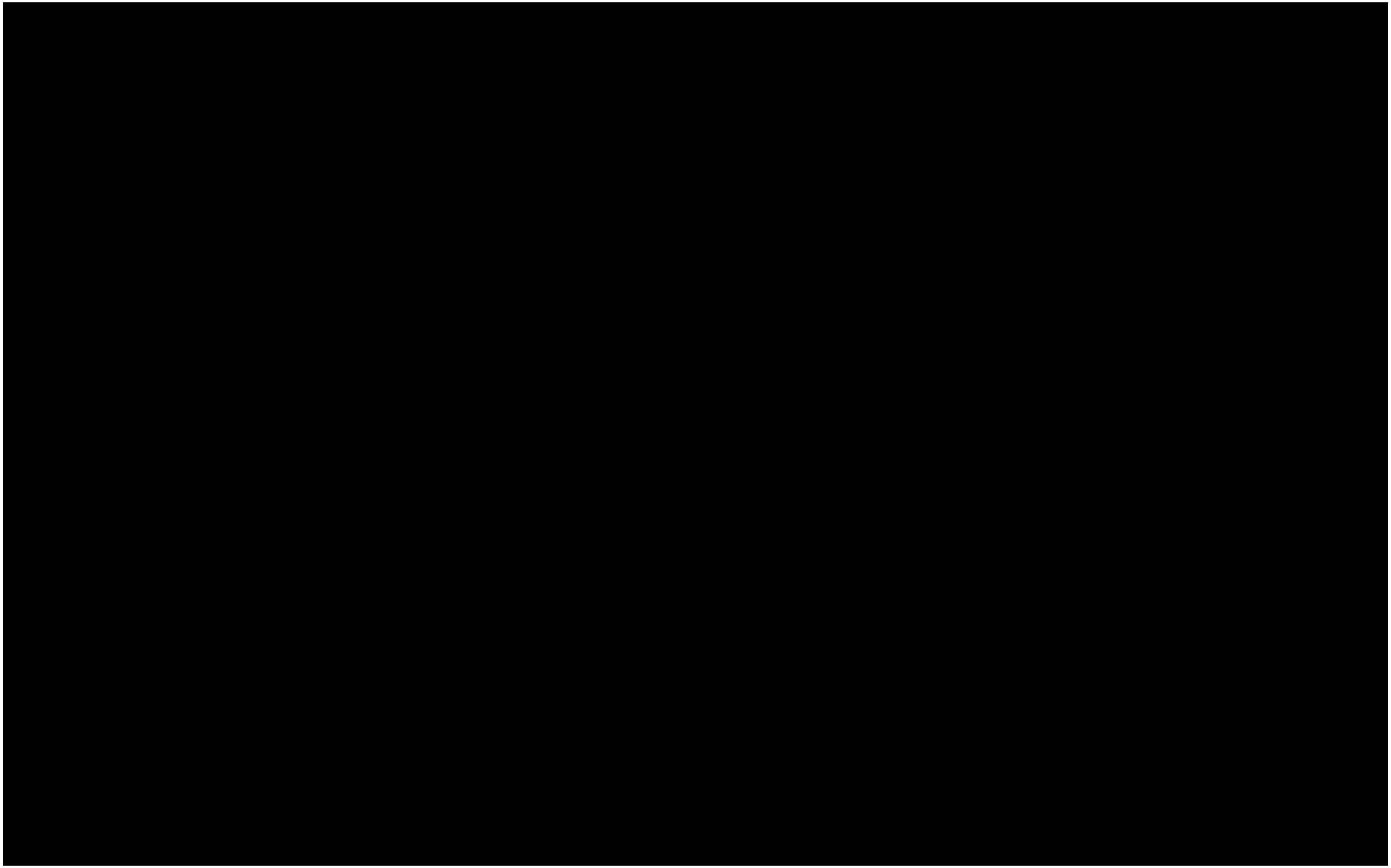

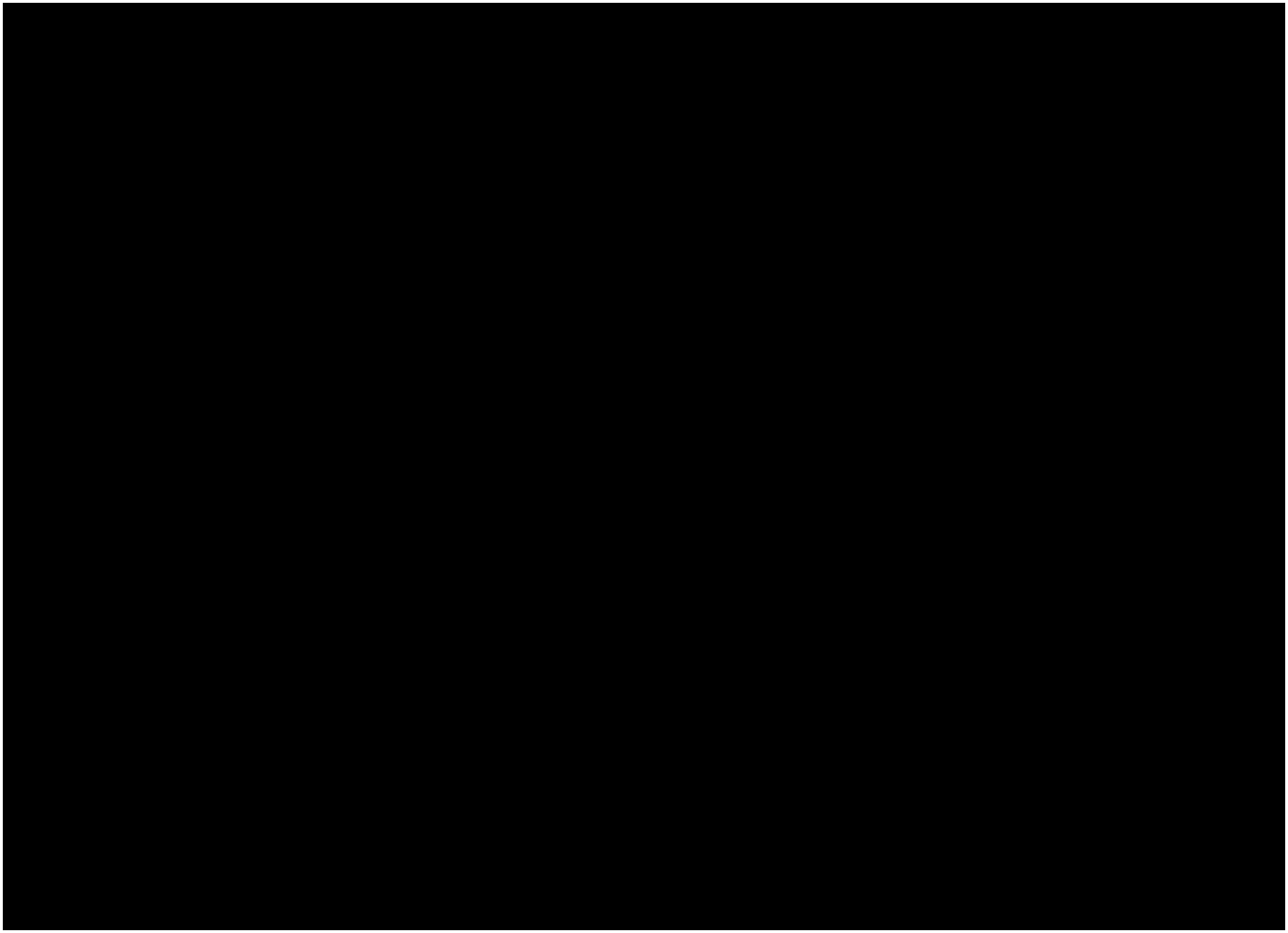

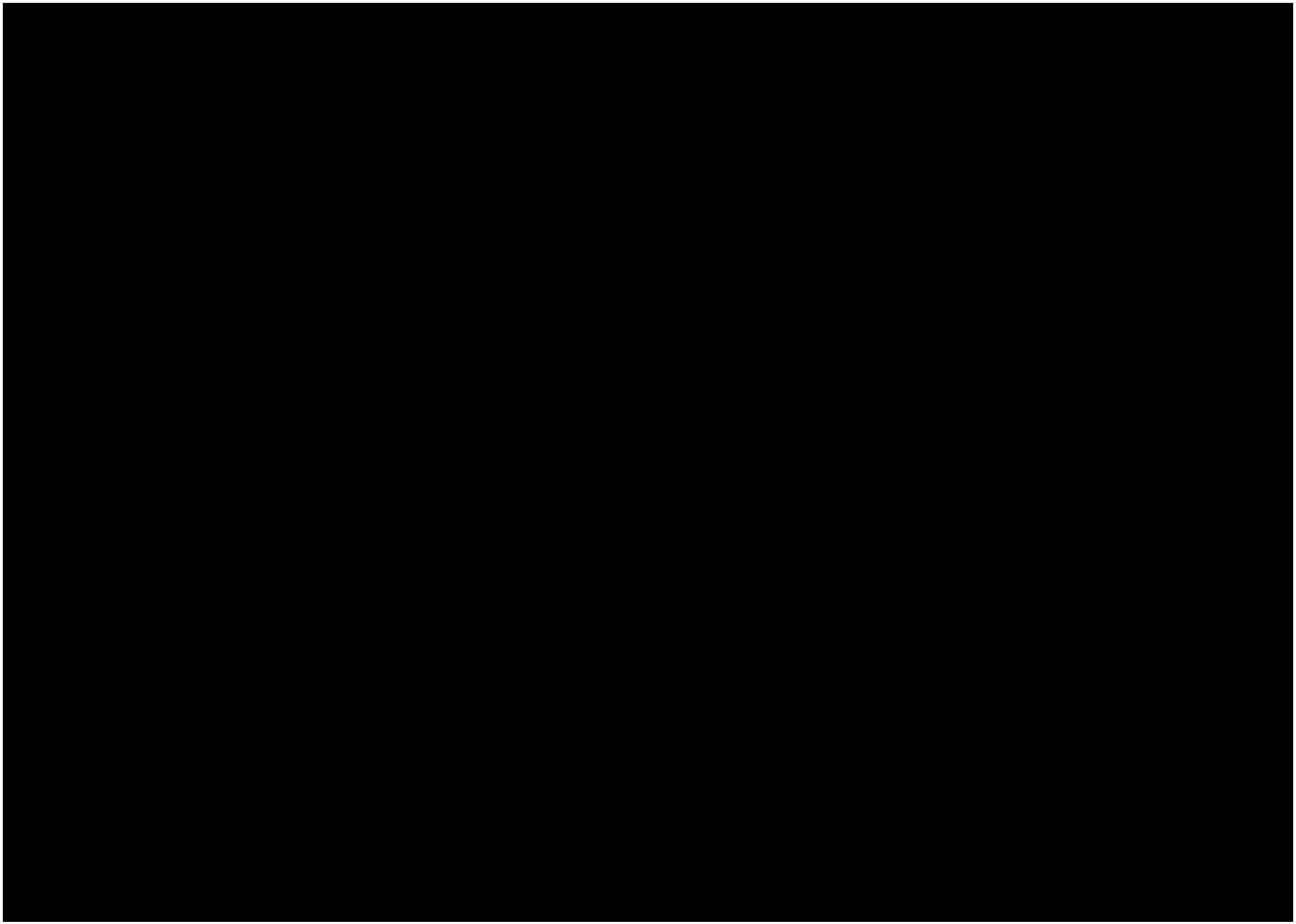

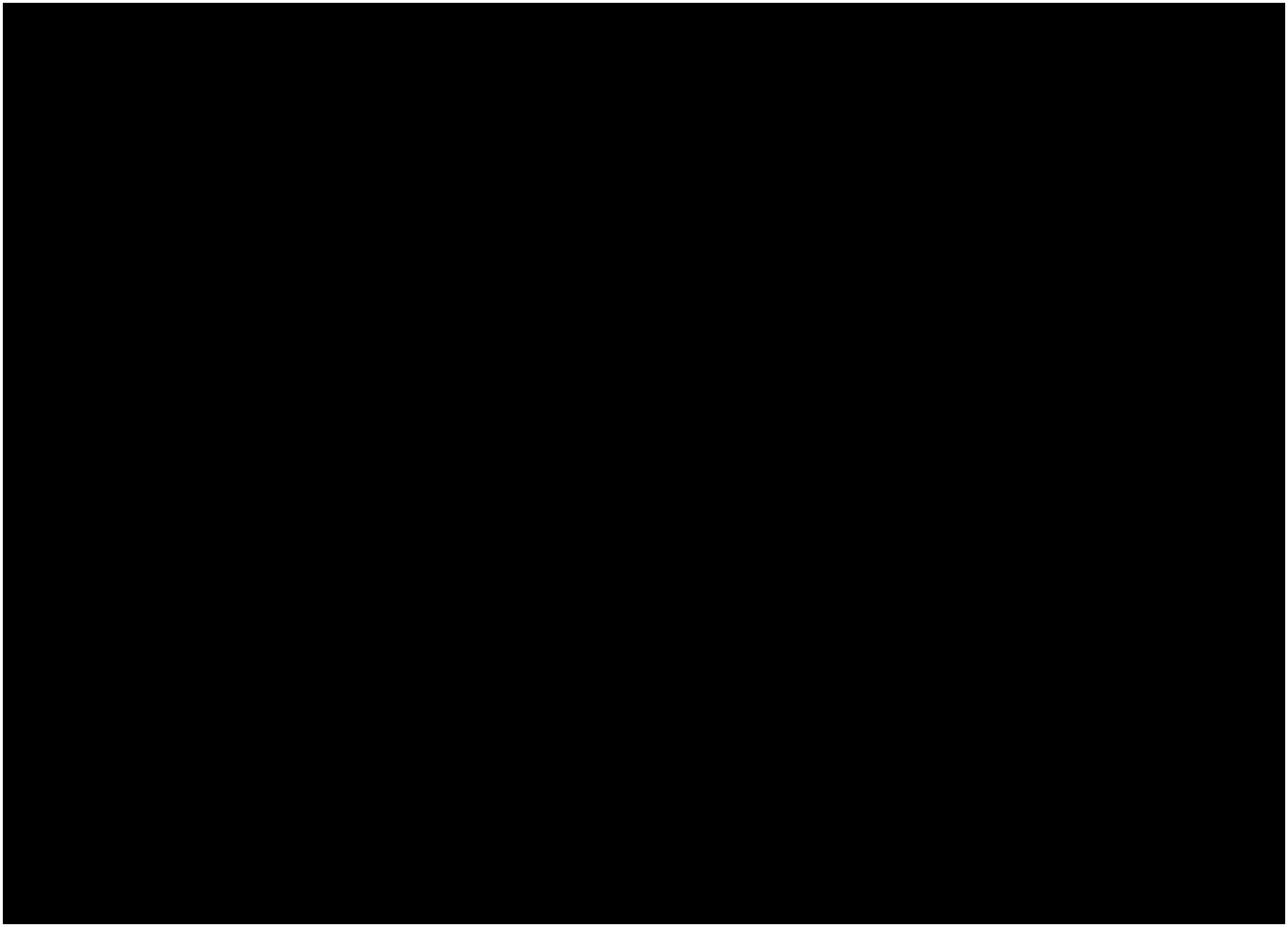

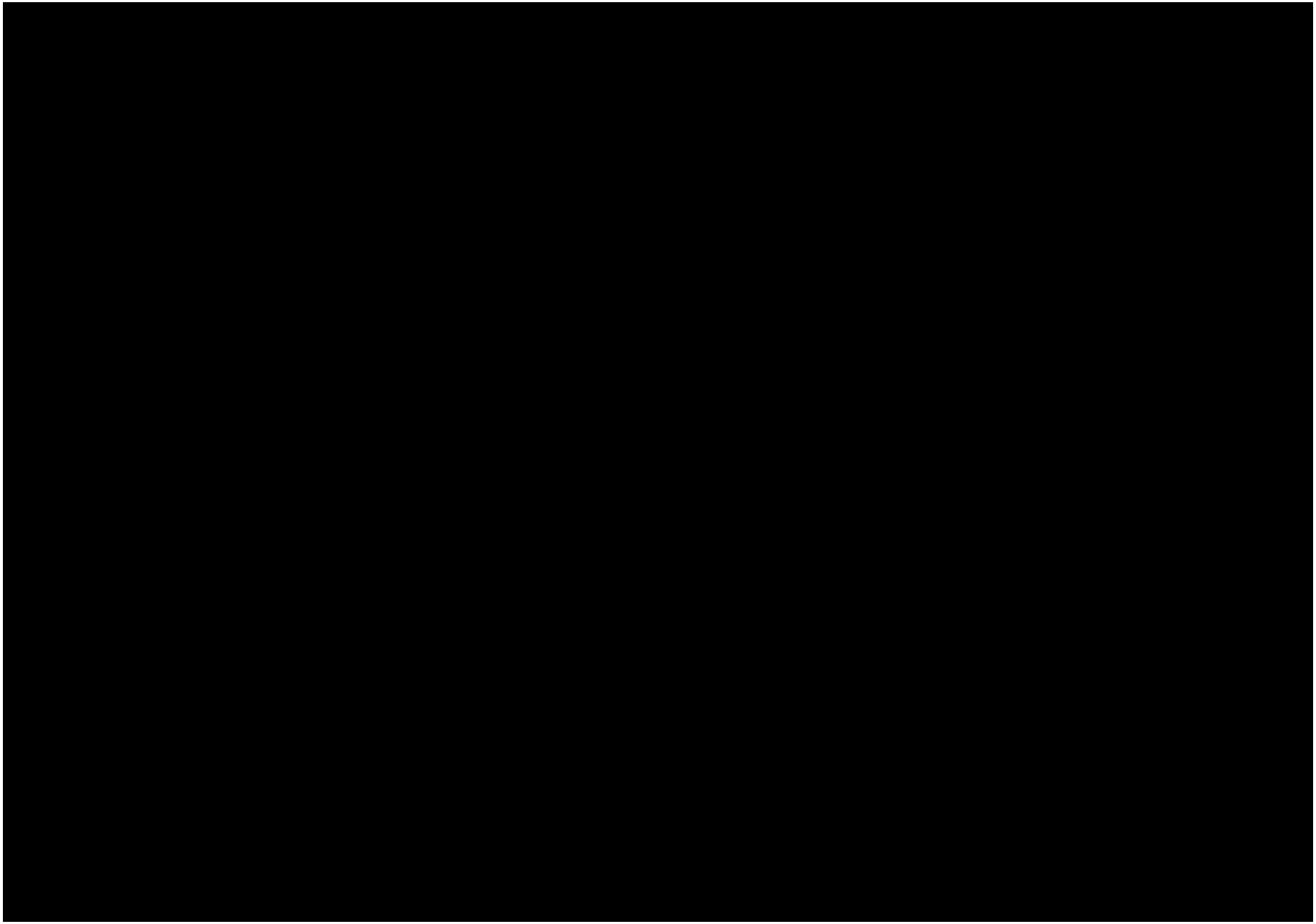

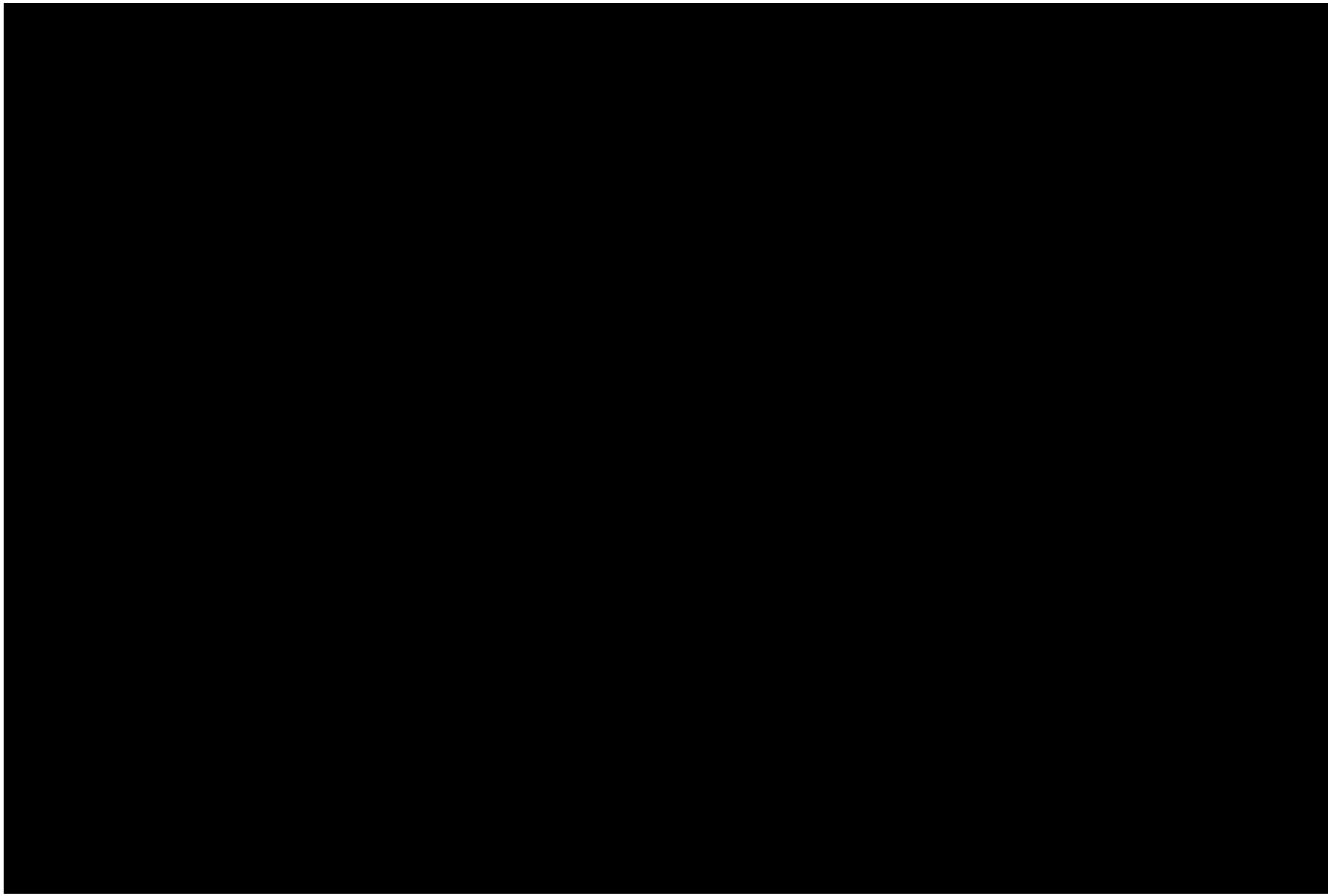

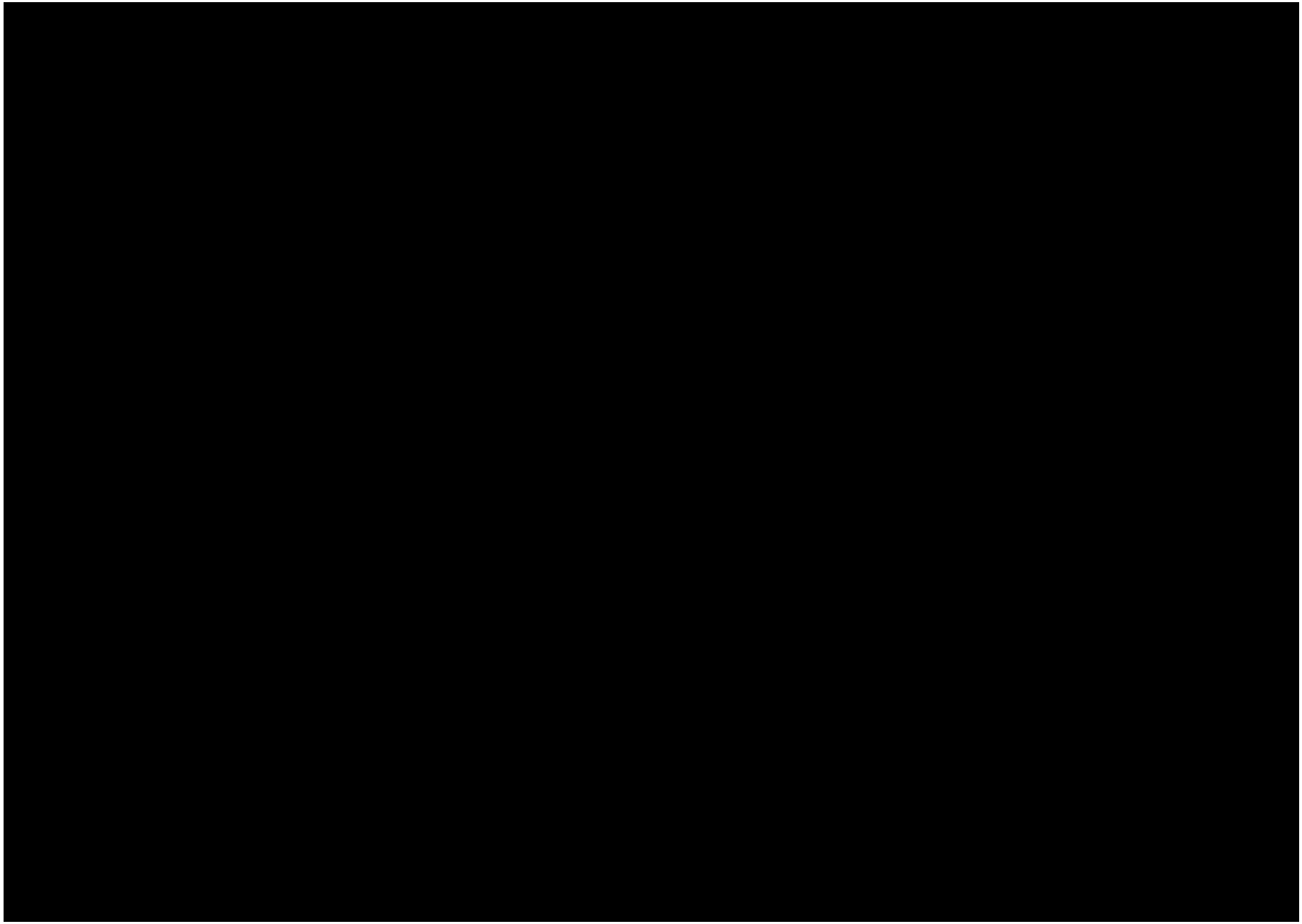

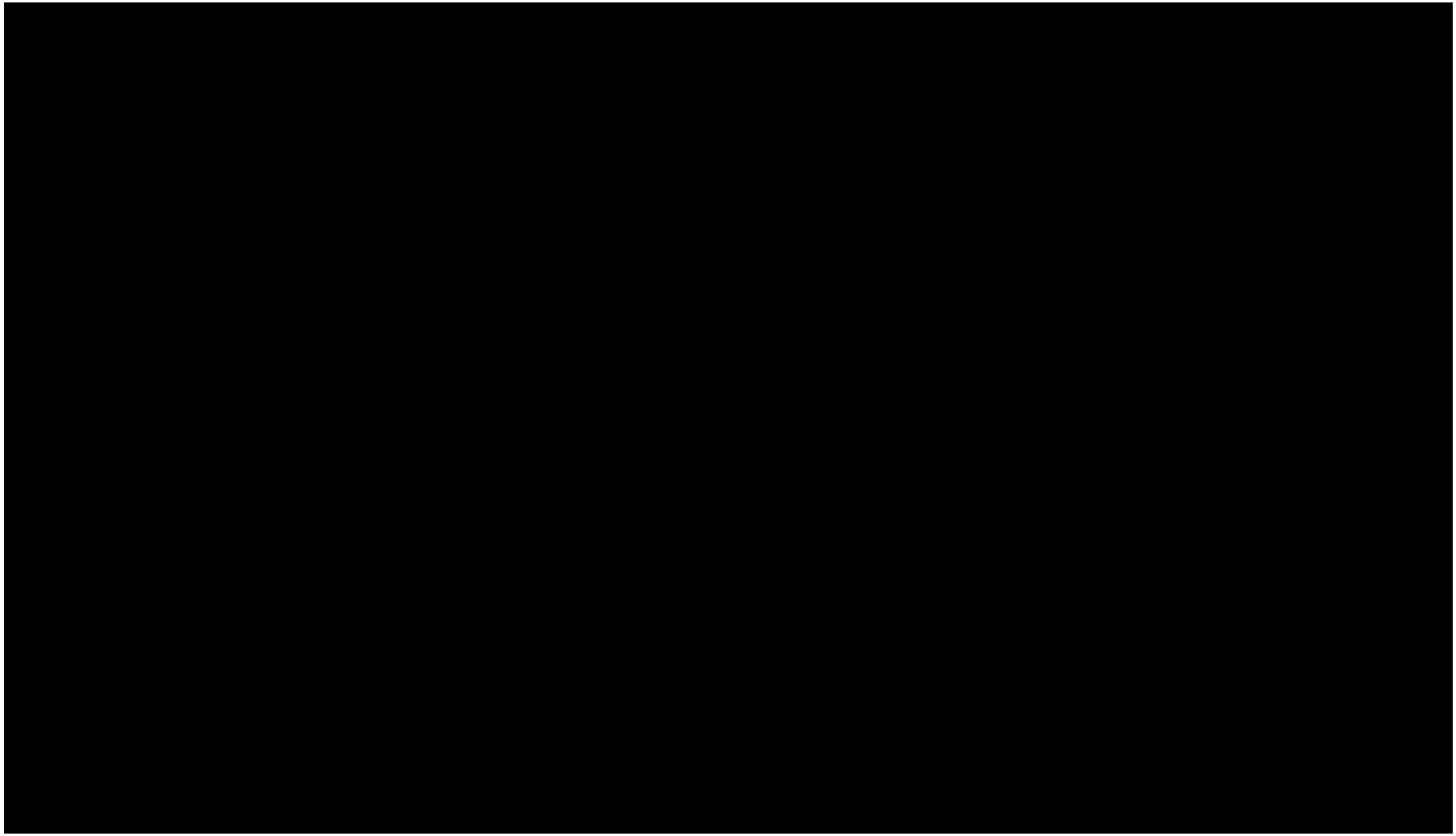

APPENDIX 2: INVESTIGATOR SIGNATURE

Study title: A Phase 2, Multi-Center, Randomized, Double-Blind, Placebo-Controlled Parallel-Group Study to Evaluate the Safety, Tolerability, and Efficacy of Olorinab in Subjects with Irritable Bowel Syndrome Experiencing Abdominal Pain

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol.

Investigator Signature	**Date**

Investigator Name and Credentials - Printed
Institution Name – Printed

Name: Clinical Study Protocol: APD371-202 Amendment 3.0
Description: A Phase 2, Multi-Center, Randomized, Double-Blind, Placebo-Controll

User Nam [redacted] Capacity: [redacted]	Meaning: Approval Date: 03-Feb-2020 23:11:40 GMT+0000