# STATISTICAL ANALYSIS PLAN

## APD371-202

## 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

**AUTHORS:** [redacted] AND [redacted]

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| | Name | Signature | Date |
|---|---|---|---|
| **Author:** | [redacted] | | |
| **Position:** | Associate Director | | |
| **Company:** | IQVIA | | |
| | | | |
| | **Name** | **Signature** | **Date** |
| **Author:** | [redacted] | | |
| **Position:** | Associate Research Pharmacokinetics Director | | |
| **Company:** | IQVIA | | |

Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

| | Name | Signature | Date |
|---|---|---|---|
| **Approved By:** | [redacted] | | |
| **Position:** | Sr. Director | | |
| **Company:** | Arena Pharmaceuticals | | |
| | | | |
| **Approved By:** | [redacted] | | |
| **Position:** | VP, Biostatistics & Data Management | | |
| **Company:** | Arena Pharmaceuticals | | |

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# TABLE OF CONTENTS

1. LIST OF ABBREVIATIONS ..... 8
2. INTRODUCTION ..... 11
3. STUDY OBJECTIVES ..... 11

3.1. Primary Objectives ..... 11

3.2. Secondary Objectives ..... 11

4. STUDY DESIGN ..... 12

4.1. General Description ..... 12

4.2. Schedule of Events ..... 13

4.3. Changes to Analysis from Protocol ..... 14

5. PLANNED ANALYSES ..... 14

5.1. Data Safety Monitoring Board (DSMB) ..... 14

5.2. Final Analysis ..... 14

6. ANALYSIS SETS ..... 15

6.1. Screened Set ..... 15

6.2. All Subjects Enrolled Set ..... 15

6.3. Full Analysis Set [FAS] ..... 15

6.4. Per Protocol Set ..... 15

6.5. Safety Set ..... 15

6.6. Pharmacokinetic Analysis Set ..... 16

7. GENERAL CONSIDERATIONS ..... 16

7.1. Reference Start Date and Study Day ..... 16

7.2. Baseline/Post-Baseline ..... 16

7.3. Retests, Unscheduled Visits and Early Termination Data ..... 18

7.4. Windowing Conventions ....18
7.5. Statistical Tests ....19
7.6. Common Calculations ....19
7.7. General Study Information ....20

8. SAMPLE SIZE JUSTIFICATION ....20
9. STATISTICAL CONSIDERATIONS ....21

9.1. Adjustments for Covariates and Factors to be Included in Analyses ....21
9.2. Multicenter Studies ....21
9.3. Missing Data ....21
9.4. Multiple Comparisons/ Multiplicity ....22
9.5. Examination of Subgroups ....22

10. OUTPUT PRESENTATIONS ....22
11. DISPOSITION AND PROTOCOL DEVIATIONS ....23
12. DEMOGRAPHICS AND BASELINE CHARACTERISTICS ....23

12.1. Derivations ....24

13. MEDICAL HISTORY ....24
14. CONCOMITANT MEDICAL CONDITIONS ....25
15. MEDICATIONS ....25
16. STUDY TREATMENT EXPOSURE ....25

16.1. Derivations ....26

17. STUDY TREATMENT COMPLIANCE ....26

17.1. Derivations ....26

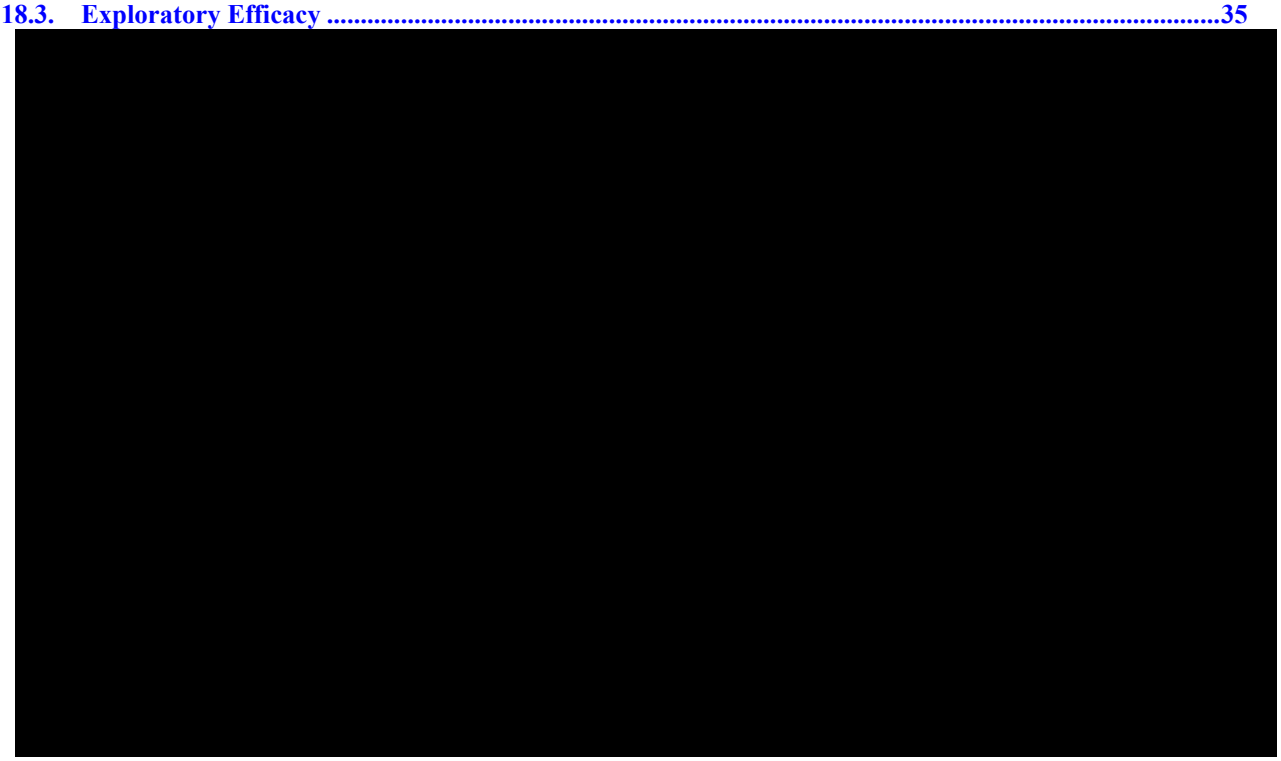
18. EFFICACY OUTCOMES ....28

18.1. Primary Efficacy ....28
18.1.1. Primary Efficacy Variable & Derivation ....28
18.1.2. Missing Data Methods for Primary Efficacy Variable ....28
18.1.3. Primary Analysis of Primary Efficacy Variable ....28
18.1.4. Sensitivity Analysis of Primary Efficacy Variable ....30

18.1.5. Supplementary Analysis of Primary Efficacy Variable ....31

**18.2. Secondary Efficacy ....31**
18.2.1. Secondary Efficacy Variables & Derivations ....31
18.2.2. Missing Data Methods for Secondary Efficacy Variables ....32
18.2.3. Analysis of Secondary Efficacy Variables....33
18.2.4. Sensitivity Analysis of Secondary and Key Exploratory Efficacy Variables ....34

**18.3. Exploratory Efficacy ....35**



**19. SAFETY OUTCOMES .... 49**

**19.1. Adverse Events....49**
19.1.1. All TEAEs ....49
19.1.2. Severity....50
19.1.3. Relationship to Study Treatment ....50
19.1.4. TEAEs Leading to Discontinuation of Study Treatment ....50
19.1.5. Teaes Leading to Study Discontinuation ....51
19.1.6. Serious and Non-Serious Teaes ....51
19.1.7. Teaes Leading to Death ....51
19.1.8. Teaes Of Special Interest ....51
19.1.9. Overall Summary of Adverse Events ....51

**19.2. Deaths ....52**

**19.3. Laboratory Evaluations ....52**
19.3.1. Laboratory Reference Ranges and Markedly Abnormal Criteria ....53

**19.4. 12-lead ECG ....53**

19.4.1. 12-Lead ECG: Outlier and Morphology Analyses....54

**19.5. Vital Signs....55**
19.5.1. Vital Signs Specific Derivations....57

**19.6. Physical Examination....57**

**20. PHARMACOKINETICS ANALYSIS....57**

**20.1. Plasma Concentration Data....58**

**20.2. Plasma Pharmacokinetic Parameters....59**

**21. IMPACT OF COVID-19....62**
**22. GENETIC AND BIOMARKERANALYSES....62**
**23. DATA NOT SUMMARIZED OR PRESENTED....62**
**24. REFERENCES....64**

[redacted]

**26. APPENDIX 2. PARTIAL DATE CONVENTIONS....67**

**Algorithm for Treatment Emergence of Adverse Events:....67**

**Algorithm for Prior / Concomitant Medications:....68**

**27. [redacted]**
**28. APPENDIX 4. EXAMPLE SAS CODE....77**

# 1. LIST OF ABBREVIATIONS

| Abbreviation | Meaning |
|---|---|
| AABS | average abdominal bloating score |
| AADS | average abdominal discomfort score |
| AAPS | average abdominal pain score |
| AE | adverse event |
| ANCOVA | analysis of covariance |
| APS | abdominal pain score |
| ATC | Anatomical Therapeutic Chemical |
| ATC3 | Anatomical Therapeutic Chemical: Therapeutic (Level 3) |
| AUC | area under the curve |
| BLQ | below the lower limit of quantification |
| BM | bowel movement |
| BMI | body mass index |
| BP | blood pressure |
| CC | complete cases |
| CI | confidence interval |
| CM | concomitant medication |
| CMH | Cochran-Mantel-Haenszel |
| CS | clinically significant |
| CSBM | complete spontaneous bowel movement |
| CSR | clinical study report |
| CV | coefficient of variation |
| DSMB | Data Safety Monitoring Board |
| ECG | electrocardiograms |
| eCRF | electronic case report form |
| EDC | electronic data capture |

| Abbreviation | Meaning |
|---|---|
| EQ-5D | European Quality of Life-5 |
| ET | early termination |
| FAS | Full Analysis Set |
| HADS | Hospital Anxiety and Depression Scale |
| HR | heart rate |
| IBS | irritable bowel syndrome |
| IBS-C | irritable bowel syndrome with predominant constipation |
| IBS-D | irritable bowel syndrome with predominant diarrhea |
| IBS-QoL | Irritable Bowel Syndrome-Quality of Life |
| IBS-SSS | Irritable Bowel Syndrome-Severity Scoring System |
| ICF | informed consent form |
| LS | least-squares |
| LTE | long-term extension |
| MAR | missing at random |
| MCMC | Markov Chain Monte Carlo |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MI | multiple imputation |
| MMRM | mixed-effects model repeated measures |
| NCS | not clinically significant |
| NRI | non-responder imputation |
| OC | observed cases |
| PCS | Potentially Clinically Significant |
| PGIC | Patient Global Impression of Change |
| PK | pharmacokinetic |
| PROMIS | Patient-Reported Outcomes Measurement Information System |
| PT | preferred term |

| Abbreviation | Meaning |
|---|---|
| SAE | serious adverse event |
| SAP | Statistical Analysis Plan |
| SBM | spontaneous bowel movement |
| SD | standard deviation |
| SI | International System of Units |
| SOC | System Organ Class |
| TEAE | treatment-emergent adverse event |
| TFL | table, figure, and listing |
| TID | 3 times per day |
| ULQ | upper limit of quantification |
| VAS | Visual Analog Scale |
| VS | vital signs |
| WHODD | World Health Organization Drug Dictionary |
| WK | week |

# 2. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy, safety, and pharmacokinetic (PK) data for the Main Study described in Protocol APD371-202. It describes the data to be summarized and analyzed, including specifics of the statistical methods to be implemented. This statistical analysis plan (SAP) is based on protocol version APD371-202 (Amendment 3, dated 03FEB2020) and focuses on analyses for the Main Study. There will be a separate SAP or an amendment to this SAP for the long-term extension (LTE) part of the study. A separate analysis plan will describe the genetic and biomarker analyses.

The table, figure and listing (TFL) shells are prepared in a separate file based on this analysis plan. Upon approval of the SAP, some updates (including but not limited to titles, footnotes, headings and re-numbering of tables, etc.) on TFL shells are allowed without a SAP amendment as long as the updates within TFL shells do not conflict with the contents of the SAP.

# 3. STUDY OBJECTIVES

## 3.1. PRIMARY OBJECTIVES

The primary objectives are:

- 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

## 3.2. SECONDARY OBJECTIVES

The secondary objectives are:

- 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 of olorinab and its predominant metabolites, [redacted], and [redacted], in subjects with IBS

# 4. STUDY DESIGN

## 4.1. GENERAL DESCRIPTION

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 predominant diarrhea (IBS-D) who are not on concomitant treatment for IBS. The 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 (at least 2 weeks; 14-19 days), 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 (male, female) and IBS subtype (IBS-C, IBS-D). The number of subjects enrolled with IBS-C will be approximately equal to the number of subjects enrolled with IBS-D. Subjects will be screened until approximately 60 subjects have been randomized per treatment group for a total of approximately 240 subjects. For subjects randomized under protocol amendment 1, there was an overnight observation period following randomization on Day 1, with orthostatic vital sign (VS) and 12-lead electrocardiogram (ECG) measured at multiple timepoints. Blood samples will be collected for measurement of plasma concentrations of olorinab and its metabolites. Samples will be used to evaluate the PK of olorinab and its predominant metabolites [redacted].

The PK sampling schemes specified in protocol amendment 1 include the following timepoints:

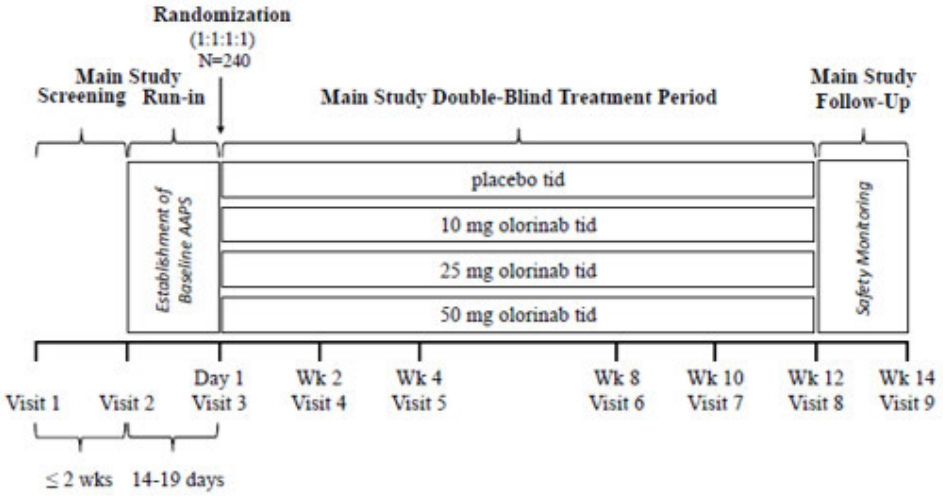
- Blood samples for the analysis of olorinab and metabolite plasma concentrations will be collected at study visits at Weeks 2 (Visit 4) through 10 (Visit 7) prior to the first daily dose. Blood samples will also be collected at Weeks 12 and 14 during the scheduled study visit. At Week 4 (Visit 5), in addition to samples collected prior to the first daily dose of study treatment, blood samples will be drawn 0.5, 1, and 2 hours after the first daily dose of study treatment. If a subject discontinues the study, a final PK sample will be collected at the Early Termination visit.
- Pharmacokinetic blood samples will be collected on Day 1 prior to and 0.5, 1, 2, 4, and 8 hours after the first dose of study treatment and 10 hours after the first dose of study treatment (2 hours after second dose). Additional samples will be collected on Day 2, prior to the first daily dose of study treatment and 2 and 4 hours after the first daily dose.

The PK sampling schemes specified in protocol amendment 2 and protocol amendment 3 (Main Study) include the following timepoints:

- Pharmacokinetic blood samples will be collected at study visits at Weeks 2 (Visit 4) through 10 (Visit 7) prior to the first daily dose. Blood samples will also be collected at Weeks 12 and 14 during the scheduled study visit. At Week 4 (Visit 5), in addition to samples collected prior to the first daily dose of study treatment, blood samples will be drawn 0.5, 1, and 2 hours after the first daily dose of study treatment administered at the clinic during the study visit. If a subject discontinues the study, a final PK sample will be collected at the Early Termination visit.

Pharmacokinetic blood samples will be collected on Day 1 prior to the administration of study treatment and 0.5, 1, and 2 hours after the administration of study treatment.

*Figure 1: Schematic Diagram of Main Study Design*




Abbreviations: 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 Main Study Treatment Period is Day 1. There is not a designated Day 0 in this study. For subjects randomized under protocol amendment 1, there was an overnight observation period following randomization on Day 1, with orthostatic vital sign (VS) and 12-lead electrocardiogram (ECG) measured at multiple timepoints. See orthostatic VS and ECG analyses under Safety Section for details.

## 4.2. SCHEDULE OF EVENTS

Schedule of events can be found in [redacted] of the protocol.

## 4.3. CHANGES TO ANALYSIS FROM PROTOCOL

There are no changes in analysis or definitions from those planned in the final protocol and no changes required due to COVID-19.

# 5. PLANNED ANALYSES

The following analyses will be performed for this study:

- Regular and ad hoc review of aggregate safety data by DSMB
- Final Analysis of the Main Study

No formal interim analyses are planned.

## 5.1. DATA SAFETY MONITORING BOARD (DSMB)

A DSMB SAP, describing the methodology and presentation of results and access to results will be provided by the Sponsor as a separate document.

## 5.2. FINAL ANALYSIS

All final, planned analyses identified in this SAP will be performed following Sponsor Authorization of this SAP, Database Lock, Sponsor Authorization of Analysis Sets and Unblinding of Treatment. PK analysis will be performed and is described in this analysis plan. [redacted]

After all subjects have completed the Main Study, outstanding data queries have been resolved/closed, and the data have been cleaned and finalized, the Sponsor will authorize breaking of the study blind and the final analysis of the data will be performed. The SAP must be approved and signed by the Sponsor before the database is locked and treatment assignment unblinded.

Any post-hoc, exploratory analyses completed to support planned study analyses, which were not identified in the SAP, will be documented and reported in the clinical study report. Any results from these unplanned analyses will also be clearly identified in the text of the clinical study report.

# 6. ANALYSIS SETS

Agreement and authorization of subjects included/excluded from each analysis set will be conducted prior to the unblinding of the study. A summary of analysis sets will be presented.

## 6.1. SCREENED SET

The screened set will include all subjects who provide informed consent for this study.

## 6.2. ALL SUBJECTS ENROLLED SET

The enrolled set will include all subjects who are enrolled in the Run-in Period of this study.

## 6.3. FULL ANALYSIS SET [FAS]

The full analysis set (FAS) will include all randomized subjects, irrespective of whether they received study treatment. Subjects will be classified according to randomized treatment.

## 6.4. PER PROTOCOL SET

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 protocol violations may include not meeting key inclusion/exclusion criteria, gross treatment non-compliance, receiving incorrect treatment, treatment unblinding by the investigator, or concomitant use of protocol-prohibited medications. The final determination on protocol violations, and thereby the composition of the Per Protocol set will be made prior to database lock of the Main Study and will be separately documented. Subjects will be summarized by treatment to which they were randomized, regardless of treatment actually received. If subjects are randomized but not treated, they will be excluded from Per Protocol set.

## 6.5. SAFETY SET

The safety set will include all subjects who are randomized and receive at least one dose of study treatment. Subjects will be classified according to actual treatment received. If there is any doubt whether a subject was treated or not, they will be assumed treated by the randomized treatment for the purposes of analysis.

## 6.6. PHARMACOKINETIC ANALYSIS SET

The pharmacokinetic analysis set will include all subjects in the FAS with at least 1 post-dose PK measurement who receive the active study drug, and who have at least 1 PK measurement at a scheduled post-dose or $C_{trough}$ PK timepoint after treatment started on Day 1 for at least 1 PK analyte [redacted], and who have no protocol violations or events with potential to affect the PK concentrations. Subjects will be classified according to the treatment received.

Only those in the PK analysis set who receive the active treatments will have PK (noncompartmental) or analyses (tabular or graphical summaries). In the case of a protocol violation/deviation or event that impacts PK, the affected PK sample data will be excluded from the summaries (i.e., the PK analysis set), but will still be reported in the study result listings. Protocol deviations impacting PK samples will be discussed in trial and adjudicated between IQVIA and Arena PK scientists and clinical pharmacologists, and the Protocol Deviation and its adjudication will be listed in listings.

# 7. GENERAL CONSIDERATIONS

## 7.1. REFERENCE START DATE AND STUDY DAY

Study Day will be calculated from the reference start date and will be used to show start/stop day of assessments and events. Reference start date is defined as Day 1, the date of randomization (Day 1 is the day of the first dose of study treatment) and will appear in every listing where an assessment date or event date appears.

- If the date of the event is on or after the reference date then:
  - Study day = (date of event – reference date) + 1.
- If the date of the event is prior to the reference date then:
  - Study day = (date of event – reference date) .

In the situation where the event date is partial or missing, Study Day, and any corresponding durations will appear as missing in the listings. In the situation where the subject is randomized but not treated, the reference date is defined as the baseline visit date.

## 7.2. BASELINE/POST-BASELINE

Unless otherwise specified, baseline is defined as the last non-missing measurement taken

prior to the reference start date. If measurements include time, the date/time will be used to define baseline; where time is not fully populated in the reference start date and fully populated in the measurement date, missing time values will be imputed to the earliest possible time measurement. Otherwise, only dates will be compared. In the case where the last non-missing measurement and the reference start date coincide and time is not collected, the measurement will be considered a baseline record, but adverse events (AEs) and medications commencing on the reference start date will be considered post-baseline records. For subjects randomized but not treated, baseline is defined as the last non-missing measurement taken on or before the baseline visit date.

Baseline AAPS is defined as the average abdominal pain score (APS) over the Run-in Period preceding the reference start date. The inclusion criteria to progress to randomization includes the requirement of "adequate compliance with entry of daily eDiary completed for ≥ 80% of days of the Run-in Period (Visit 2 to Visit 3 [Day 1])". Baseline AAPS will be calculated in the EDC system if at least 80% of the eDiary entries for APS are available and will be calculated as the average APS over all non-missing entries. If a subject has APS values recorded for less than 80% of the eDiary entries for the Run-in Period but is randomized, baseline AAPS will still be calculated based on the available APS.

Post-baseline AAPS at each week during the treatment period (Week 1 to Week 12) is calculated by taking the average value over each 7-day increment, beginning with the 7 days including and succeeding the Day 1 Visit, and continuing with 7-day increments for 12 weeks, regardless of the timing of the actual visits. AAPS during the follow-up period (Weeks 13 and 14) is calculated by taking the average value over the 7-day increment, beginning with the day after the last dose date, and continuing with 7-day increments for 2 weeks. If APS values are missing for more than 3 days in the 7-day window for the average weekly value, it will be reported as missing.

Post-baseline weekly AAPS by scheduled visit is calculated by taking the average value over the window of 7 days prior to and including the scheduled visit day if the endpoint is recorded for at least 4 of the 7 days in the window. If APS values are missing for more than 3 days in the 7-day window, the average value for the AAPS by scheduled visit will be reported as missing.

For other continuous endpoints collected in the Daily Diary form (e.g., bloating, discomfort, and number of bowel movements), baseline and post-baseline will be derived in the same manner.

## 7.3. RETESTS, UNSCHEDULED VISITS AND EARLY TERMINATION DATA

For by-visit analyses and summaries of efficacy and safety, data (including scheduled, retests, unscheduled, and early termination) will be assigned to visits after the application of the windowing conventions described in Section 7.4. All measurements will be considered in summaries of abnormalities or worst-case values post-baseline.

In the case of a retest (same visit number assigned), the measurement nearest to the visit date will be used for by-visit summaries. In the case of several measurements equally close to the visit date, the earliest non-missing measurement will be taken. If multiple assessments are available on the same day, then the average of the assessment will be used in the analysis except for laboratory and ECG data, where the assessment at the earliest time of the same day will be used. If both central and local assessments of the same laboratory test are available on the same day, the central assessment will take precedence over the local assessment. Listings will include scheduled, unscheduled, retest and early discontinuation data.

## 7.4. WINDOWING CONVENTIONS

All scheduled study visits are defined relative to Study Day 1, the date of randomization and first dose of study treatment. Scheduled visit windows are defined in Appendix 1 of the protocol. A windowing convention will be used to determine the analysis visit value for a given measurement and will be applicable for all by-visit summaries and analyses for efficacy and safety data. The early discontinuation visits and unscheduled visits will be eligible for allocation to an analysis visit. The 2-week follow-up visit will be summarized separately. [redacted] displays the specific visit windows used for the FAS, SAF and Per Protocol Set populations for efficacy and safety analysis. See [redacted] Additional Visit Windows for additional visit windows.

Windowing will be applied to the data prior to any missing data calculations. If one or more results for a variable are assigned to the same analysis visit, the result with the date closest to the protocol scheduled day will be used in the analysis. If two measurements in the same analysis visit window are equally close to the protocol scheduled study day, the earliest measurement will be used in the analysis. For ePRO measurements (PROMIS, EQ-5D, etc.), the stamp date in the device will be used to calculate the study day, and Day 1 will include those ePROs collected on Randomization Date or the date after randomization day (Day 1

and Day 2).

## 7.5. STATISTICAL TESTS

The default significance level will be 5%; confidence intervals (CIs) will be 95% and all tests will be two-sided, unless otherwise specified in the description of the analyses.

## 7.6. COMMON CALCULATIONS

For quantitative measurements:

- Change from baseline = (Test Value at Visit X – Baseline Value)

- Percent change from baseline = ((Test Value at Visit X – Baseline Value) / Baseline Value) x 100
- Proportion at Visit X = (Number of subjects satisfying criteria at Visit X / Total number of subjects at Visit X)
- Proportion achieving an improvement from Visit X to Visit Y = (Number of subjects achieving an improvement from Visit X to Visit Y / Total number of subjects with non-missing data for that parameter at both Visit X and Visit Y)

## 7.7. GENERAL STUDY INFORMATION

All analyses, except for PK, will be conducted using SAS® (version 9.4 or later, SAS Institute Inc., Cary, NC).

For PK, non-compartmental parameter calculations will be performed using Phoenix® WinNonlin® 8.0 or higher (Certara, L.P., Princeton, New Jersey). Graphics may be prepared using the same versions of SAS®. A general table with summary of study information will be generated, including date first subject signed ICF, last subject last visit date, database lock date and versions of the MedDRA, World Health Organization Drug Dictionary Global (Enhanced w/WHO Herbal Dictionary) (WHODD), and software used for analyses (SAS, WinNonlin) etc.

# 8. SAMPLE SIZE JUSTIFICATION

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).

# 9. STATISTICAL CONSIDERATIONS

## 9.1. ADJUSTMENTS FOR COVARIATES AND FACTORS TO BE INCLUDED IN ANALYSES

The following covariates and factors are used in the analyses. For details of their inclusion in the models, see the specific analysis section.

- Baseline AAPS value
- Treatment: (Placebo, Olorinab 10 mg, Olorinab 25 mg, Olorinab 50 mg) and, additionally for primary and secondary efficacy endpoints, (Placebo and Olorinab pooled; Placebo, Olorinab 10 mg, Olorinab 25 and 50 mg pooled)
- Stratification factors:
  - Sex: Male, Female
  - IBS subtype: IBS-C, IBS-D
- Week: Week 1 - Week 14
- Scheduled Visit: Day 1, Week 2, Week 4, Week 8, Week 10, Week 12, Week 14
- Treatment-by-week interaction
- Treatment-by-visit interaction

## 9.2. MULTICENTER STUDIES

This study will be conducted by multiple investigators at multiple investigational sites within the United States. Randomization to treatment arms is not stratified by center. Randomization to treatment arms is stratified by sex (male, female) and IBS subtype (IBS-C, IBS-D). Data from all sites will be pooled and statistical analyses will not be adjusted for investigational site or geographic region. Ad-hoc analyses may be conducted by site or by pooling sites.

## 9.3. MISSING DATA

Missing safety data will generally not be imputed, with the exceptions of AE relationship to study treatment (as described in Section 19.1.3), partial or missing AE start dates, and Concomitant Medication (CM) start dates. Details about date imputations are described in Appendix 2. Partial Date Conventions. No other missing safety data will be imputed.

Missing efficacy data will be handled as described in Sections 18.1.2, 18.2.2, and 18.3.21 of this analysis plan. Sensitivity analyses will be conducted to assess the robustness of the

primary and secondary endpoint results, as described in Sections 18.1.4 and 18.2.4, respectively. Missing PK data will be handled as described in Section 20.2 of this analysis plan.

## 9.4. MULTIPLE COMPARISONS/ 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.

## 9.5. EXAMINATION OF SUBGROUPS

The following subgroups will be assessed for the primary endpoint:

- Sex (Female, Male)
- IBS subtype (IBS-C, IBS-D)
- Stratification factor (Female IBS-C, Female IBS-D, Male IBS-C, Male IBS-D)
- Baseline AAPS (< Median, ≥ Median)
- Age (< Median, ≥ Median)
- Race (Caucasian, Non-Caucasian)
- Ethnicity (Hispanic, Non-Hispanic)
- Baseline BMI (< Median, ≥ Median)
- Baseline Duration of IBS (< Median, ≥ Median)
- Baseline IBS-SSS (<75 (remission), ≥ 75 and < 175 (mild), ≥ 175 and < 300 (moderate), ≥ 300 (severe))
- Baseline IBS-QoL (>40 (non-severe), ≤40 (severe))
- Baseline HADS anxiety scores (≥ 8 or < 8)
- Baseline HADS depression scores (≥ 8 or < 8)

Additional subgroups may be assessed, if deemed necessary. It should be noted that the study was not designed to detect treatment differences with statistical power within any of the above subgroups.

# 10. OUTPUT PRESENTATIONS

Appendix 1. Programming Conventions for Outputs shows conventions for presentation of data in outputs. The templates provided with this SAP describe the presentations for this study and therefore the format and content of the summary tables, figures, and listings to be

provided for the clinical study report.

# 11. DISPOSITION AND PROTOCOL DEVIATIONS

All subjects who provide informed consent will be accounted for in this study.

Subject disposition and withdrawals will be provided for the FAS. This summary will note subjects who complete the Week 12 visit as well as subjects who complete the Week 14 visit. An analysis set listing will also be provided. Inclusion and exclusion criteria will be presented for the screened set.

Protocol deviations will be displayed for the FAS. Deviations will be categorized as Critical/Major or Minor. Critical/major deviations will be summarized by treatment (placebo, olorinab 10 mg, olorinab 25 mg, olorinab 50 mg), olorinab 25 and 50 mg pooled, and olorinab pooled for the following categories as described in the Protocol Deviation and Classification Guidance document. All critical/major deviations will also be listed.

- Informed Consent Criteria
- Eligibility and Entry Criteria
- Concomitant Medication Criteria
- Laboratory Assessment Criteria
- Study Procedures Criteria
- SAE Criteria
- Randomization Criteria
- Visit Schedule Criteria
- Investigational Product Compliance
- Efficacy Criteria
- Administrative Criteria
- Source Document Criteria
- Regulatory or Ethics Approvals Criteria
- Other Criteria

A summary of protocol deviations related to COVID-19 will also be presented, as well as a listing of subjects with study conduct impacted by COVID-19.

# 12. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Demographics and baseline characteristics data will be presented for the FAS and Safety Set.

The data will be summarized by treatment, olorinab 25 and 50 mg pooled, and olorinab 10, 25, and 50 mg pooled without statistical testing. The following demographic and baseline characteristics will be reported for this study:

- Age on consent (years)
- Sex at birth: Female and Male
- Child-bearing potential for women: Yes, No
- Race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islanders, Multiple, White, Not Reported
- Race group: White, Non-White, Not Reported
- Ethnicity: Hispanic or Latino, Non-Hispanic or Latino, Not Reported, Unknown
- Weight (kg)
- Height (cm)
- BMI (kg/$m^2$)
- [redacted]
- Time since IBS diagnosis (years) – calculated relative to date of randomization
- IBS subtype: IBS-C, IBS-D
- eDiary Compliance Rate (%)
- Baseline AAPS
- Baseline AAPS Category: (≤ 7, >7)
- [redacted]

## 12.1. DERIVATIONS

- BMI (kg/ $m^2$) = weight (kg)/ height $(m)^2$
- Time since IBS diagnosis (years) = (date of randomization – date of IBS diagnosis + 1) / 365.25
  - Partial dates are imputed to the earliest possible date
- Weight (kg) = Weight (lb) * 0.4536
- Height (cm) = Height (in) * 2.54
- Height (m) = Height (in) * 0.0254 = Height (cm) * 0.01

# 13. MEDICAL HISTORY

Medical History conditions are defined as those conditions which stop prior to Screening. Medical History will be collected on the Medical History eCRF and coded using Medical

Dictionary for Regulatory Activities (MedDRA, version 23.0 or higher). Medical History will be summarized for the Safety Set by system organ class (SOC) and preferred term (PT).

# 14. CONCOMITANT MEDICAL CONDITIONS

Concomitant medical conditions are conditions (other than the indication being studied) which started prior to or at Screening and are ongoing at the date of Screening. Concomitant medical conditions will be captured on the Medical History eCRF page and coded using MedDRA version 23.0 or higher. Concomitant medical conditions will be summarized for the Safety Set by SOC and PT.

# 15. MEDICATIONS

Medications will be collected on the Prior or Concomitant Medications eCRF and coded using WHODD version 01Mar2020 or higher.

The prior and concomitant medications are defined below. See Appendix 2. Partial Date Conventions for handling of partial dates for medications. In the case where it is not possible to define a medication as prior or concomitant, the medication will be classified by the worst case; i.e., concomitant.

- 'Prior' medications are medications which started and stopped prior to the first dose of study treatment.
- 'Concomitant' medications are medications which started prior to, on or after the first dose of study treatment and continued into the main study period.

Prior and concomitant medications will be summarized separately by ATC Level 3 and Preferred Drug name for the Safety set. In addition, prior and concomitant medications related to IBS will be summarized.

# 16. STUDY TREATMENT EXPOSURE

The date of first and last study treatment administration will be taken from the eCRF "On Site Dosing Administration" form. Interruptions, compliance, and dose changes are not taken into account for duration of exposure. Study duration and treatment duration will be summarized as continuous variables for each treatment, olorinab 25/50 mg pooled, and pooled olorinab using descriptive statistics. The duration of treatment will also be summarized categorically: ≤ 4 weeks, > 4 to ≤ 8 weeks, > 8 weeks. Additionally, the total

subject-years of exposure and subject-years on study will be included in the summary.

Treatment formulation (capsules or tablets), number of capsules/tablets taken, missed, and frequency and percentage of subjects who missed at least one dose or who had at least one dose interruptions recorded on the Dosing Administration eCRF will also be summarized. Treatment compliance will also be summarized using both descriptive statistics and summarized categorically: < 85%, ≥ 85 to ≤ 115%, and > 115%.

## 16.1. DERIVATIONS

- Study Duration (days) = date of last study visit – date of screening visit + 1
- Treatment duration (days) = date of last study treatment administration – date of first study treatment administration + 1
- Treatment duration (weeks) = (date of last study treatment administration – date of first study treatment administration + 1)/7.
- Total subject-years on study = sum of duration of time on study across all subjects divided by 365.25
- Total subject-years of exposure = sum of duration of treatment exposure across all subjects divided by 365.25

# 17. STUDY TREATMENT COMPLIANCE

Compliance to study treatment will be summarized for the Safety Set. Total number of tablets expected, total number of tablets taken, total number of tablets missed, overall compliance to study treatment, frequency and percentage with overall compliance with the following categories: <85%, ≥85% to ≤115%, and >115%. By-visit compliance will also be summarized.

Subjects with administration compliance greater than 115% and subjects who do not return any study treatment or study packaging will be asked for the reason for the overcompliance or missing study treatment. Their responses will be recorded on the Drug Accountability eCRF and will be listed.

## 17.1. DERIVATIONS

Compliance to study treatment is based on the Drug Accountability eCRF and will be calculated as the number of capsules/tablets taken (total dispensed – total returned) divided

by the prescribed number of capsules/tablets, expressed as a percentage (see calculations below).

The study treatment is given three times daily (tid), and it is assumed that the subject should take study treatment from the morning of the visit day at which their treatment is initially dispensed to the evening before their last treatment return date, as subjects are advised to wait to take their dose at the study site until all assessments and procedures have been completed on study days. For example, if the initial dispensation date is Day 1 and the last return date is Day 85, then the subject should have taken 3 capsules/tablets each day on Days 1 to 84; hence, the total number of prescribed capsules would be 84×3 = 252. Multiple bottles may be dispensed at one visit; in these cases, "Per Visit" compliance will be non-missing if at least one bottle is returned.

- "Per Visit" Compliance to study treatment at Visit X will be calculated as follows:

$$\frac{([\text{N of Capsules dispensed at Visit (X)}] - [\text{N of Capsules returned at Visit X+1}])}{\{\,[\text{Date of Visit X+1}] - [\text{Date of Dispensing at Visit (X)}]\,\}\times 3} \times 100$$

- Overall Compliance to study treatment will be calculated as follows:

$$\frac{\begin{array}{c}\{([\text{N of Capsules dispensed at Visit 1}] - [\text{N of Capsules returned at Visit 2}]) \\ +\cdots+ \\ ([\text{N of Capsules dispensed at Visit (X}-1)] - [\text{N of Capsules returned at Visit X}])\}\end{array}}{[\text{Date of Visit X}] - [\text{Date of Dispensing at Visit 1}]\times 3} \times 100$$

For subjects who permanently stop the study treatment before Week 12, the "Date of Visit X" in Overall Compliance calculations will be replaced by the date of study withdrawal.

# 18. EFFICACY OUTCOMES

## 18.1. PRIMARY EFFICACY

### 18.1.1. PRIMARY EFFICACY VARIABLE & DERIVATION

The primary efficacy variable is the change in the AAPS from baseline to Week 12, where baseline is based on the randomization date (Day 1). Baseline AAPS and AAPS by week during the treatment period is derived as described in Section 7.2. Baseline AAPS is a required datapoint for eligibility; therefore, no missing data for baseline AAPS is expected. For the treatment period, if any AAPS value is completely missing, the primary efficacy analysis will be conducted on the non-missing data.

### 18.1.2. MISSING DATA METHODS FOR PRIMARY EFFICACY VARIABLE

Missing AAPS will not be imputed for the primary analysis. The primary analysis method, MMRM, will utilize all data available during the Main Study treatment period from subjects included in the FAS. Analysis of sensitivity to missing data for the primary endpoint will be performed as described in Section 18.1.4.

### 18.1.3. PRIMARY ANALYSIS OF PRIMARY EFFICACY VARIABLE

The primary efficacy analysis will be performed using the FAS population. The primary efficacy endpoint will be analyzed using a MMRM analysis with treatment group (placebo, olorinab 10 mg, olorinab 25 mg, olorinab 50 mg), stratification factors (sex and IBS subtype), week, and treatment-by-week interaction as factors and baseline AAPS as a covariate. Week will include each week from Week 1 to Week 12 based on eDiary data beginning from Day 1 (Randomization). In addition, two additional MMRMs will be completed with the following treatment groupings: 1) placebo, olorinab 10 mg, and olorinab 25 and 50 mg pooled and 2) placebo and pooled olorinab.

The primary objective of this study is to test the hypothesis that the change in AAPS from baseline to Week 12 is the same across treatment group (placebo, olorinab 10 mg, 25 mg, and 50 mg). The alternative hypothesis is that the change in AAPS from baseline to Week 12 differs between placebo and one of the olorinab treatments (10 mg, 25 mg, or 50 mg) or olorinab 25 mg/50 mg pooled.

Four hypothesis tests for the primary endpoint using the primary analysis methodology

described above are specified below.

- MMRM model with treatment groups (placebo, 10 mg, 25 mg, and 50 mg), and with **3** pre-specified comparisons of placebo vs. the individual treatment groups of olorinab (10 mg, 25 mg, and 50 mg)
- MMRM with treatment "groups" placebo, 10 mg, and pooled olorinab [25 mg + 50 mg], and with 1 pre-specified comparison of placebo vs. the pooled olorinab group [25 mg + 50 mg]

No multiplicity control is planned for this Phase 2 study. If any of the four pre-specified hypothesis test analyses demonstrates statistical significance at the 0.05 (2-sided) significance level at Week 12, then the study successfully demonstrated that the primary endpoint was met.

Change from baseline to Week 12 by scheduled visit is considered the supporting primary efficacy endpoint. It will be analyzed using a model of MMRM with treatment (placebo, olorinab 10 mg, olorinab 25 mg, olorinab 50 mg), stratification factors (sex and IBS subtype), visit, and treatment-by-visit interaction as factors and baseline AAPS as a covariate. Visits will include all scheduled visits except Visit 9 (Week 14). The analysis will also be repeated using the treatment groupings described in the preceding paragraph. If one of the MMRM models demonstrates statistically significant difference between placebo and one of the active doses of olorinab at Week 12, olorinab may be declared to achieve a statistically better reduction in AAPS than placebo.

All models will be run under the assumption of an unstructured covariance matrix. If the unstructured covariance matrix results in a lack of convergence, the heterogeneous Toeplitz covariance structure, followed by the heterogeneous autoregressive covariance structure, followed by compound symmetry will be used. The Newton-Raphson with ridging optimization technique will be used to aid with convergence. The Kenward-Rogers method will be used to estimate the denominator degrees of freedom. An example of the SAS PROC MIXED code used for the repeated measures models is provided in Appendix 4. Example SAS Code.

Descriptive statistics, including the number of observations, mean, SD, median, minimum, and maximum will be provided by treatment at each scheduled visit or each week. Additionally, p-values for within-treatment group change (for the primary efficacy variable, change in AAPS from baseline to Week 12) resulting from a one sample t-test using least squares mean estimates and associated standard errors will be presented by treatment. Least square mean differences between treatment groups ([i.e., olorinab 10 mg vs. placebo,

olorinab 25 mg vs. placebo, and olorinab 50 mg vs. placebo], [olorinab pooled vs. placebo] or [olorinab 10 mg vs. placebo, olorinab 25 and 50 mg pooled vs. placebo]), the corresponding standard errors, 95% CIs, and p-values will also be presented.

### 18.1.4. SENSITIVITY ANALYSIS OF PRIMARY EFFICACY VARIABLE

The robustness of the primary endpoint result will be assessed for the FAS using various sensitivity analyses. The following analyses will be used:

- ANCOVA with observed cases (OC): Treatment comparisons of the change in the AAPS from baseline to Week 12 will be made using an ANCOVA model with treatment and stratifications (sex and IBS subtype) as factors and baseline AAPS as a covariate. Type III sums of squares for least-squares (LS) will be used for the statistical comparison; the least squares mean differences, 95% CI, and p-value for each least squares mean difference value will be reported.
- ANCOVA with multiple imputation (MI): MI under the missing at random (MAR) assumption will be performed. Any missing AAPS data from Week 1 to Week 12 at the planned assessments will be imputed using MI under MAR. MAR assumes the missing value is independent of unobserved outcomes given observed data (i.e., subjects with missing AAPS can be modeled based on subjects with observed AAPS). Unscheduled visits are not included in the analysis for this approach. The following steps will be implemented:
  - ✓ Step 1: Non-monotone missing data will first be imputed to a monotone missing pattern using the multivariate joint Gaussian imputation model that utilizes the Markov Chain Monte Carlo (MCMC) method in the SAS PROC MI procedure. The number of imputations will be 100 and SEED = 4161. Each imputed dataset will only have missing data at the end of subjects' records (monotone missing data pattern). A separate imputation model will be used for each treatment group and only subjects with non-missing baseline AAPS will be included. If convergence cannot be met using a separate imputation model for each treatment group, data for all treatments will be imputed using the same model. The stratification variables at each planned visit will be included in the imputation models.
  - ✓ Step 2: The remaining monotone missing data will be imputed using sequential regression MI, where a separate regression model is estimated for the imputation of each variable (i.e. measurement at each time point). Each regression model will include explanatory variables for treatment, baseline AAPS, and the stratification factors. The number of imputations will be 1 and SEED = 4161.
  - ✓ Step 3: An ANCOVA model with treatment, randomization stratification (sex and

IBS subtype) as factors and baseline AAPS as a covariate will be run for each of the 100 datasets to obtain 100 estimators of interest.

- ✓ Step 4: SAS PROC MIANALYZE will be used to produce overall pooled estimates (mean of 100 estimates) of least squares mean differences between placebo and each treatment with associated standard errors, CIs, and pooled p-values presented. Additionally, SAS PROC MIANALYZE will be used to produce p-values for within-treatment group change based on a one sample t-test using pooled least squares mean estimates and associated standard errors. Summary statistics presented for Week 12 records will be based on the mean of the imputed records per subject per time point.

The missing AAPS values will be imputed first and change from baseline values will be calculated based on imputed AAPS scores.

There could be certain adjustments to the MI model specified in Step 2 above due to unexpected data issues after unblinding treatment. All post-unblinding modifications to the MI model or approaches to address missing data will be described in the Clinical Study Report (CSR).

- Nonparametric Wilcoxon Rank-Sum Test: The Wilcoxon Rank-Sum Test will be used to compare change in AAPS at Week 12 between treatment (each dose of olorinab vs placebo, olorinab 25 and 50 mg pooled versus placebo, and pooled olorinab vs placebo).

### 18.1.5. SUPPLEMENTARY ANALYSIS OF PRIMARY EFFICACY VARIABLE

All analyses described in Sections 18.1.3 and 18.1.4 will be repeated using the Per Protocol Set.

## 18.2. SECONDARY EFFICACY

### 18.2.1. SECONDARY EFFICACY VARIABLES & DERIVATIONS

The secondary efficacy analyses will be performed for the FAS. The secondary efficacy endpoints are:

- 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 Treatment Period
- The proportion of subjects achieving a ≥ 40% improvement in AAPS from baseline to Week 12
- The proportion of subjects achieving a ≥ 40% improvement in AAPS from baseline for at least 6 of the 12 weeks during the Treatment Period
- The proportion of subjects achieving a ≥ 50% improvement in AAPS from baseline to Week 12
- The proportion of subjects achieving a ≥ 50% improvement in AAPS from baseline for at least 6 of the 12 weeks during the 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

The secondary variables will be derived from the information recorded on the Daily Diary.

Baseline and post-baseline AAPS are calculated as described in Section 7.2.

### 18.2.2. Missing Data Methods for Secondary Efficacy Variables

For the continuous endpoint of percent change in AAPS from baseline to Week 12, the MMRM models described in Section 18.1.3 will be used. For the continuous endpoint of change in number of pain free days per week from baseline to Week 12, the by-week MMRM model described in Section 18.1.3 will be used. For the change in number of pain free days per week endpoint, a subject with a missing value for a given day when there are non-missing values during the week will be assumed to not be pain free for that day.

For the binary endpoints of proportion of subjects achieving a ≥ 30% improvement in AAPS from baseline to Week 12 and 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, all missing post-baseline AAPS values will be imputed using MI under the MAR assumption as described in Steps 1 and 2 of Section 18.1.4. The following steps will then follow:

- Step 3: Subjects will be classified as responders or non-responders per imputed data based on the endpoint criteria specified in Section 18.2.1 for the endpoint of interest. For each dataset, the proportion of responders and non-responders will be calculated.
- Step 4: The Cochran-Mantel-Haenszel (CMH) test, stratified by sex and IBS subtype, will be run for each of the 100 datasets to obtain 100 odds ratio estimates of interest (active treatment over placebo). Common risk difference estimates, CIs, and two-sided p-values will also be calculated for active treatment minus placebo based on

Mantel-Haenszel weights. For the 100 odds ratio estimates and difference estimates in each treatment, the estimates will be passed directly to PROC MIANALYZE, along with their associated standard errors. In some cases, an odds ratio estimate may be calculated as missing due to a value of zero in the denominator for certain treatment comparisons; the missing value for that imputation cannot be passed to PROC MIANALYZE. As a result there may be fewer than 100 odds ratio estimates used to calculate the pooled estimate in these instances.

- Step 5: SAS PROC MIANALYZE will be used to produce an overall pooled estimate (mean of 100 estimates) of the odds ratio with associated CI, and of the percentage difference estimate with associated standard error, CI, and two-sided pooled p-values. Counts and percentages of responders will also be summarized using SAS PROC MIANALYZE.

The MI model will be pre-defined before database lock. However, there could be certain adjustments due to unexpected data issues after unblinding treatment. All post-unblinding modifications to the MI model or approaches to address missing data will be described in the CSR.

The robustness of the secondary endpoint results will be assessed using various sensitivity analyses, described in Section 18.2.4.

### 18.2.3. Analysis of Secondary Efficacy Variables

For the continuous secondary efficacy endpoints, percent change in AAPS from baseline to Week 12 and change in number of pain free days per week from baseline to Week 12, the same methodology used for the primary efficacy endpoint will be used for the analysis. The analyses for percent change in AAPS from baseline at Week 12 will include both evaluation at the scheduled visit for Week 12 (Visit 8) and Week 12 based on baseline day as described in Section 18.1.3. The analyses for change in number of pain free days per week from baseline at Week 12 above will include the evaluation at Week 12 based on baseline day as described in Section 18.1.3.

For the binary secondary efficacy endpoints (proportion of subjects with a $\geq 30\%$, $\geq 40\%$, and $\geq 50\%$ improvement in AAPS from baseline to Week 12 and proportion of subjects achieving a $\geq 30\%$, $\geq 40\%$, and $\geq 50\%$ improvement in AAPS from baseline for at least 6 of the 12 weeks during the Main Study Treatment Period), a CMH test will be conducted to compare placebo against each of the olorinab treatments (10 mg, 25 mg, 50 mg, pooled 25 and 50 mg, and olorinab pooled), stratified by the randomization factor (sex and IBS

subtype). The responder rate and the odds ratio relative to placebo will be presented with corresponding CIs, and the percentage of difference from placebo will be presented together with corresponding 95% CIs and the p-values. The 95% CI for the responder rate of each treatment group will be generated using the normal approximation method. Missing data will be imputed using MI, as described in Section 18.2.2.

### 18.2.4. SENSITIVITY ANALYSIS OF SECONDARY AND KEY EXPLORATORY EFFICACY VARIABLES

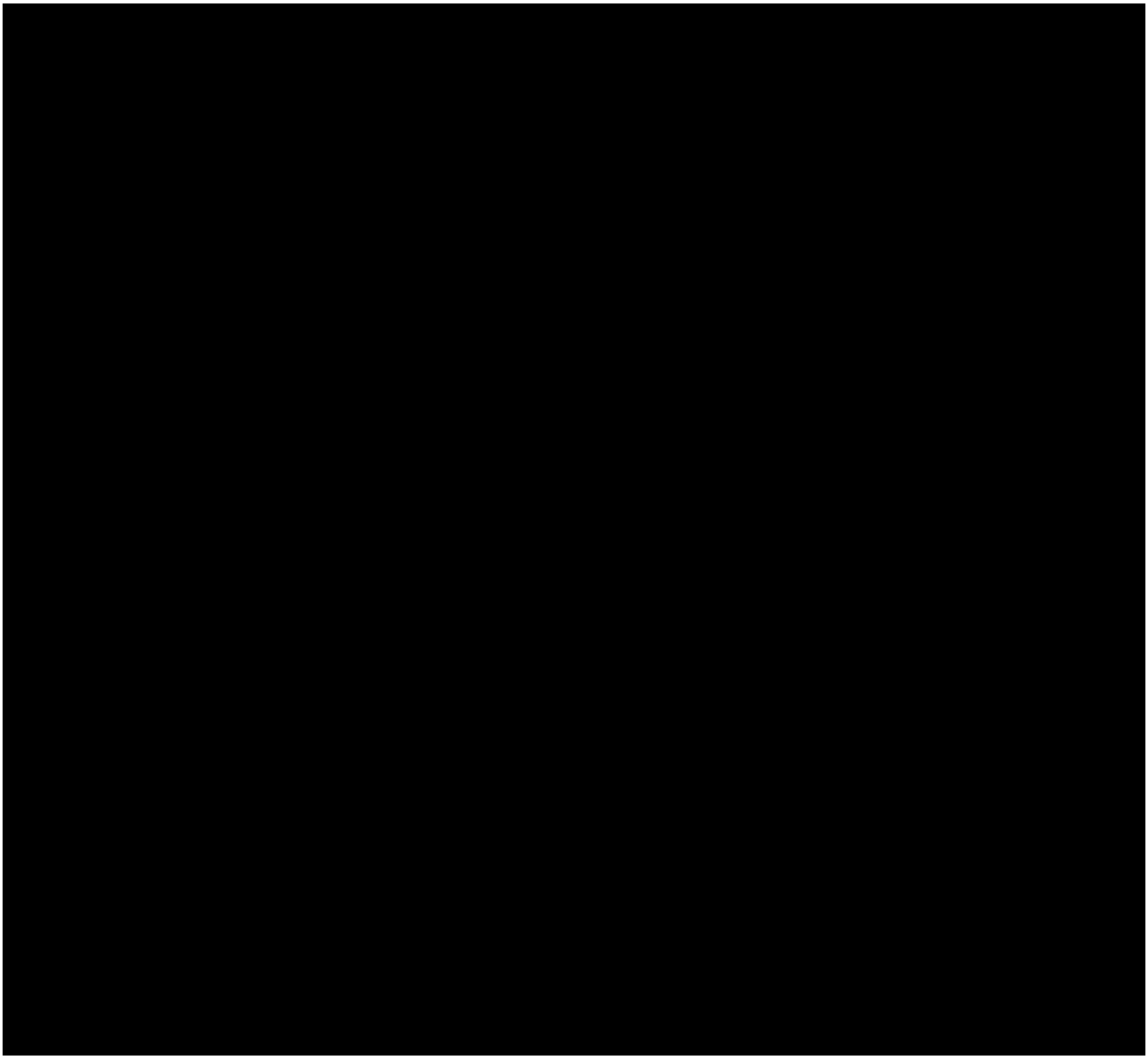
The robustness of the secondary endpoints' results will be assessed using various sensitivity analyses. The following analyses will be used:

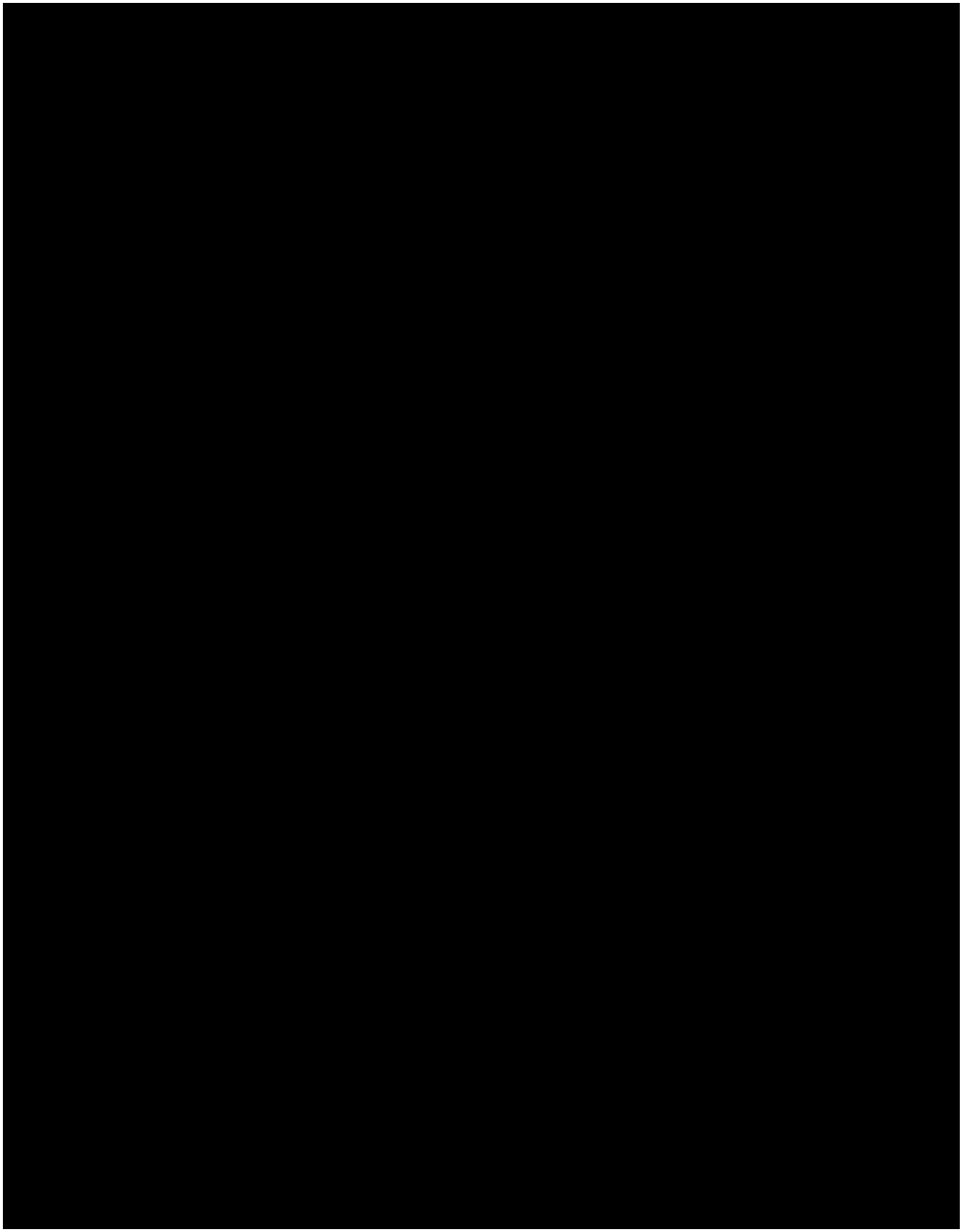
- For continuous endpoints, the ANCOVA with OC, ANCOVA with MI, and Non-parametric Wilcoxon Rank-Sum Test will be implemented as described in Section 18.1.4.
- For binary endpoints based on AAPS and bowel motility endpoints (including the three composite responder endpoints for IBS-C and IBS-D), the sensitivity to missing data assumptions will be evaluated with the following models:
    - CMH with OC: The CMH test described in the analysis of secondary efficacy variables Section will be repeated on the population of subjects with observed data for the given analysis.
    - CMH with NRI (non-responder imputation): The CMH test described in the analysis of secondary efficacy analysis Section will be completed on all subjects in the FAS. Subjects will be considered a non-responder if they do not meet the endpoint criteria (e.g. a ≥ 30% improvement in AAPS) or are missing data at the time point of interest. All non-responders at the time point of interest, as well as subjects who discontinue study treatment at any time prior to that time point for any reason, will be defined as non-responders for the analysis. Randomized subjects without at least 1 post-baseline observation will also be defined as non-responders in NRI analyses.
    - Logistic regression (OC): A logistic regression model using observed cases will be used to analyze treatment comparisons between the proportion of subjects achieving a ≥ 30% improvement in AAPS from baseline to the given time point, with the explanatory variable of treatment (placebo, olorinab 10 mg, olorinab 25 mg, olorinab 50 mg), randomization stratification factor (sex and IBS subtype) and baseline AAPS as a covariate. In addition, two additional logistic regression models will be completed with the following treatment groupings: 1) placebo, olorinab 10 mg, and olorinab 25 and 50 mg pooled and 2) placebo and pooled olorinab. The endpoint of subjects

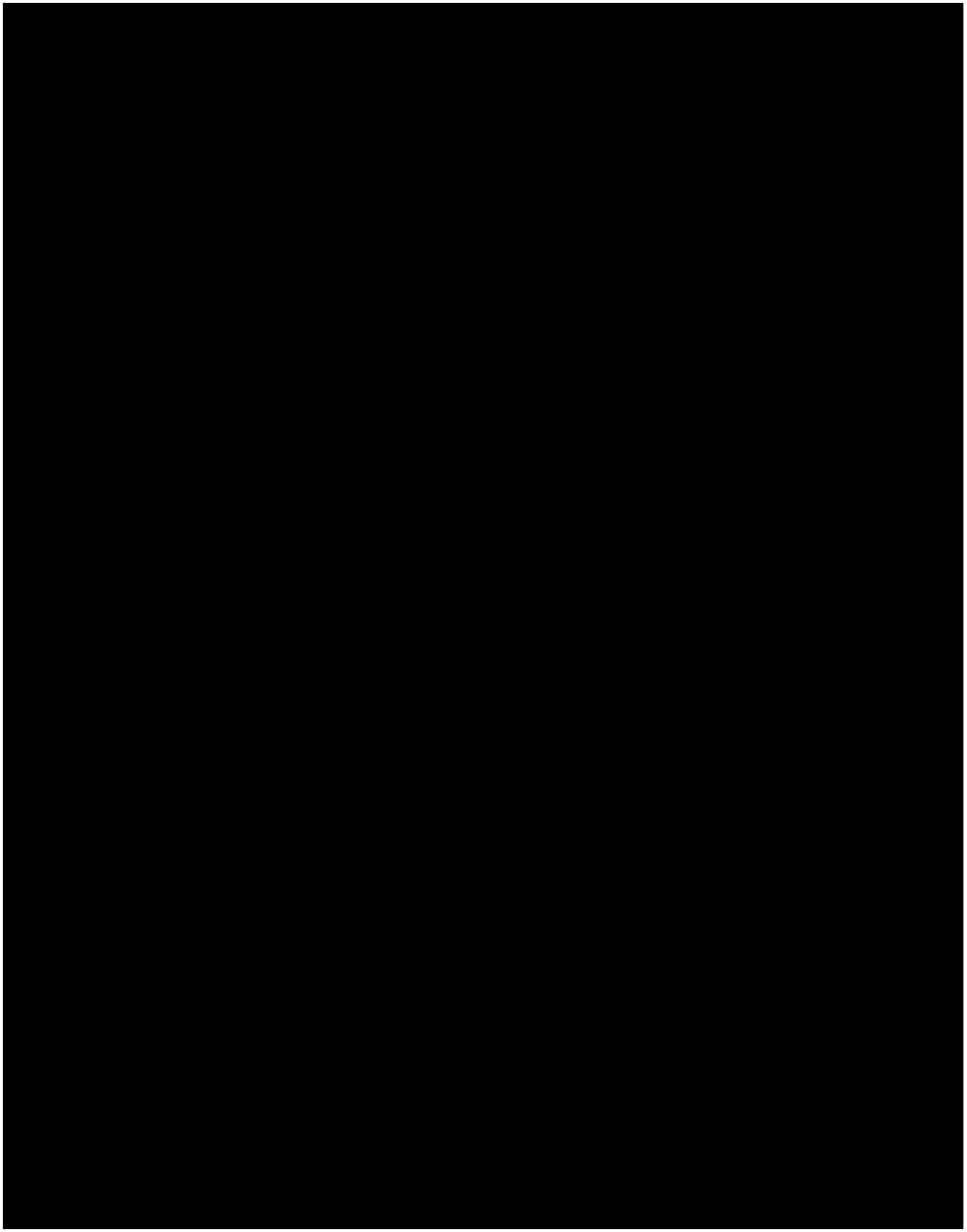
achieving a ≥ 30% improvement in AAPS from baseline for at least 6 of the 12 weeks during the Treatment Period will also be analyzed using the same logistic regression models.

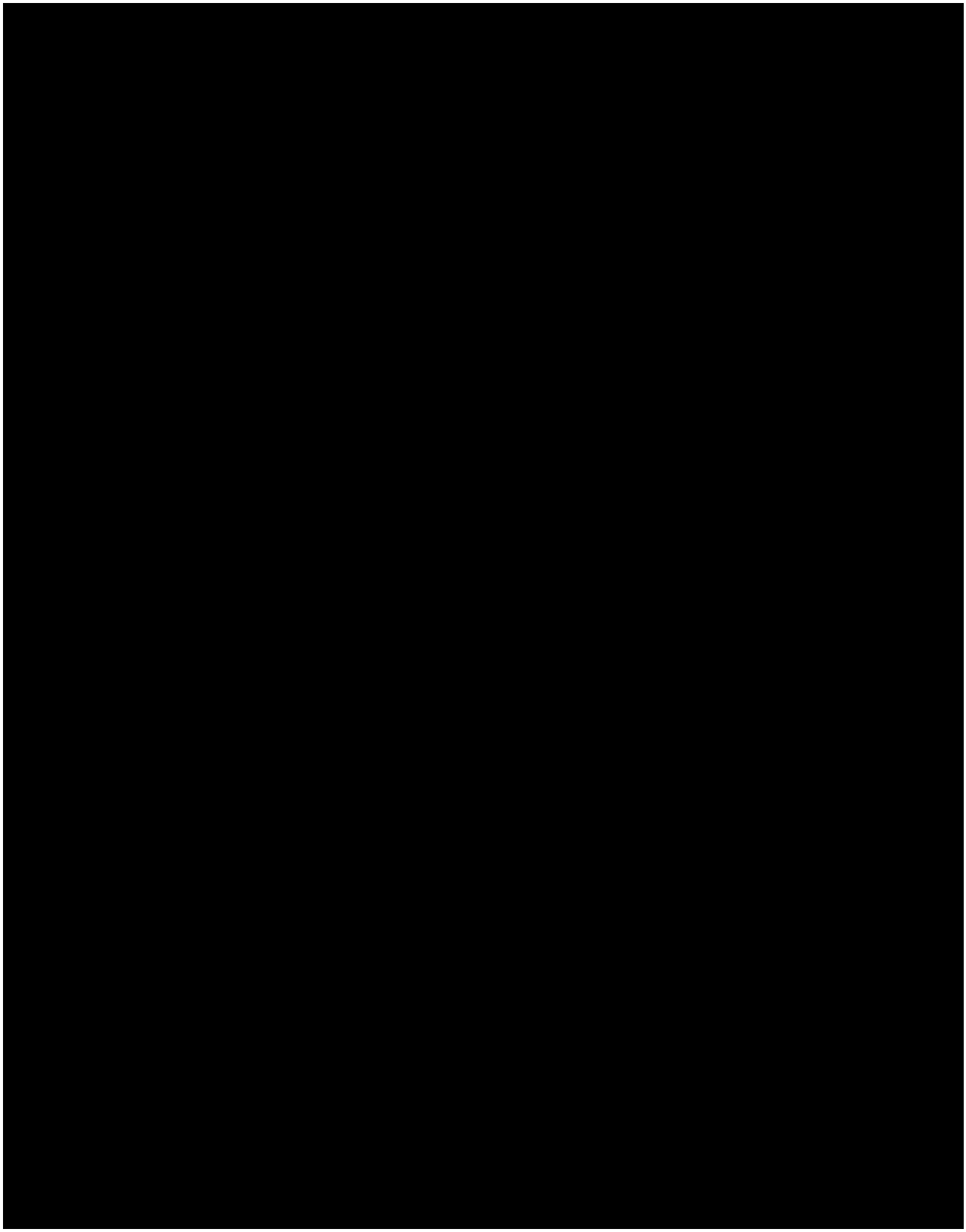
- Sensitivity to analysis set: The secondary analysis will be repeated for the Per Protocol Set.

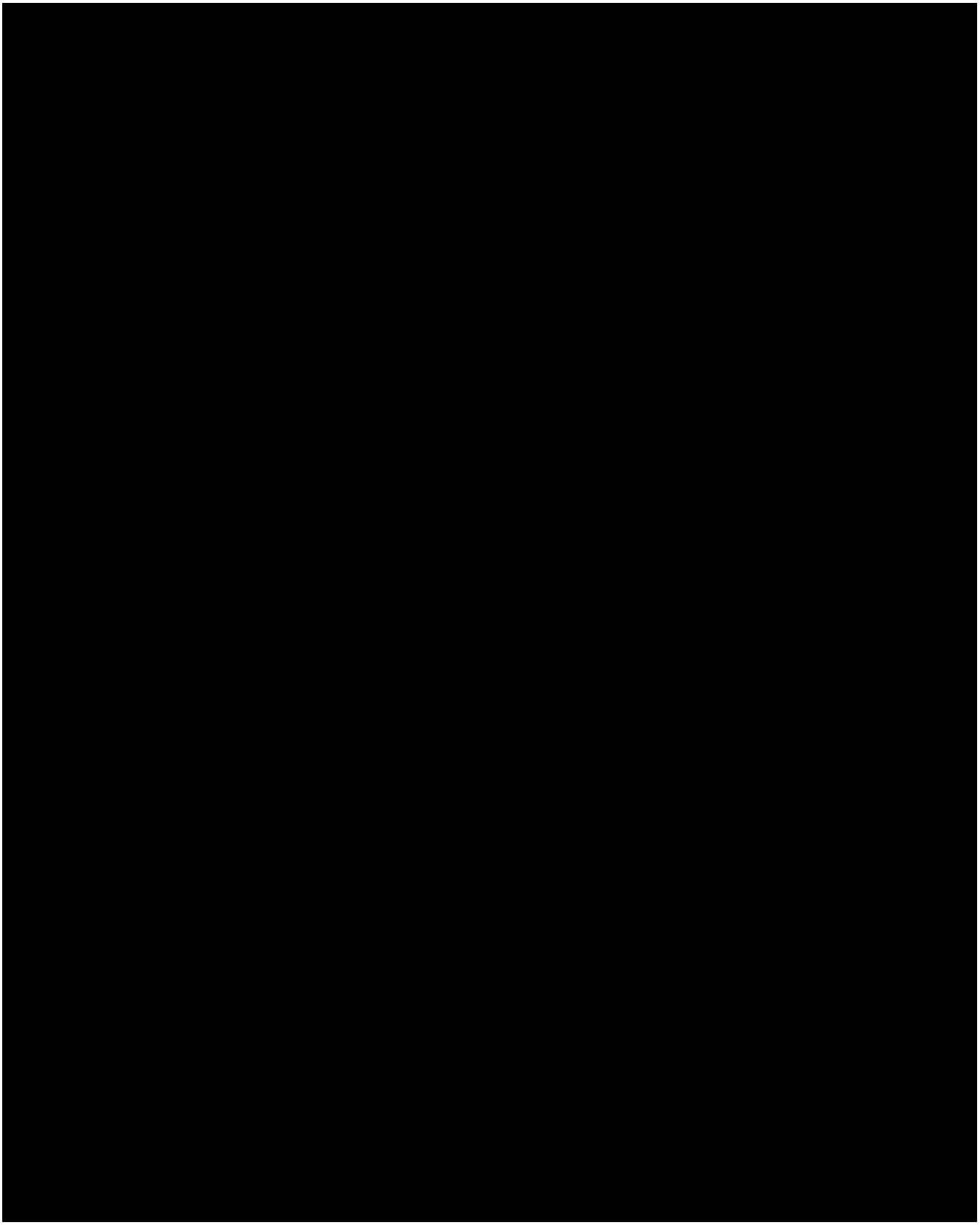
The sensitivity analyses for the composite responder endpoint based on AAPS reduction and no worsening in bowel motility as defined in Section 18.3.8, will be performed using CMH with OC and CMH with NRI in FAS only.

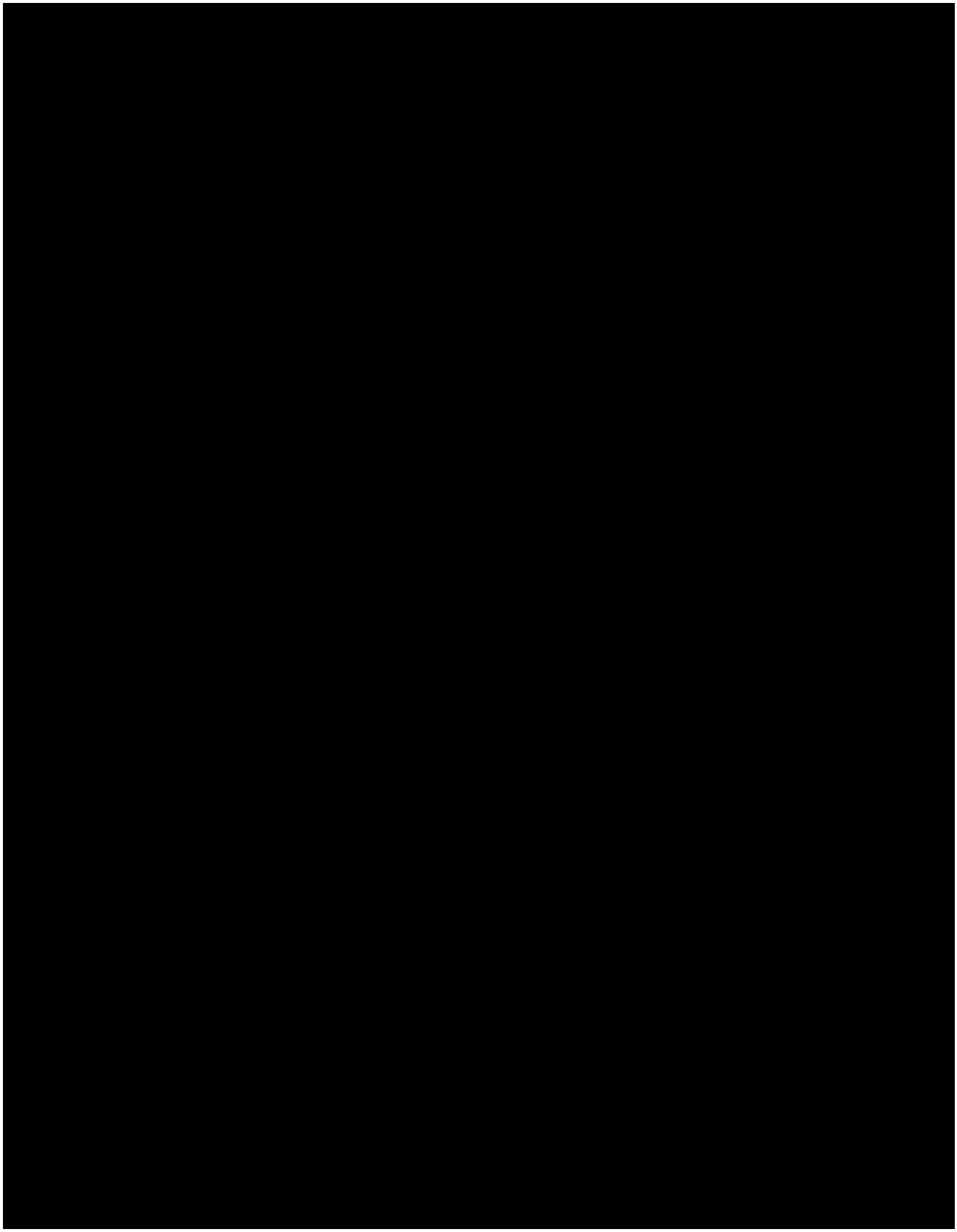


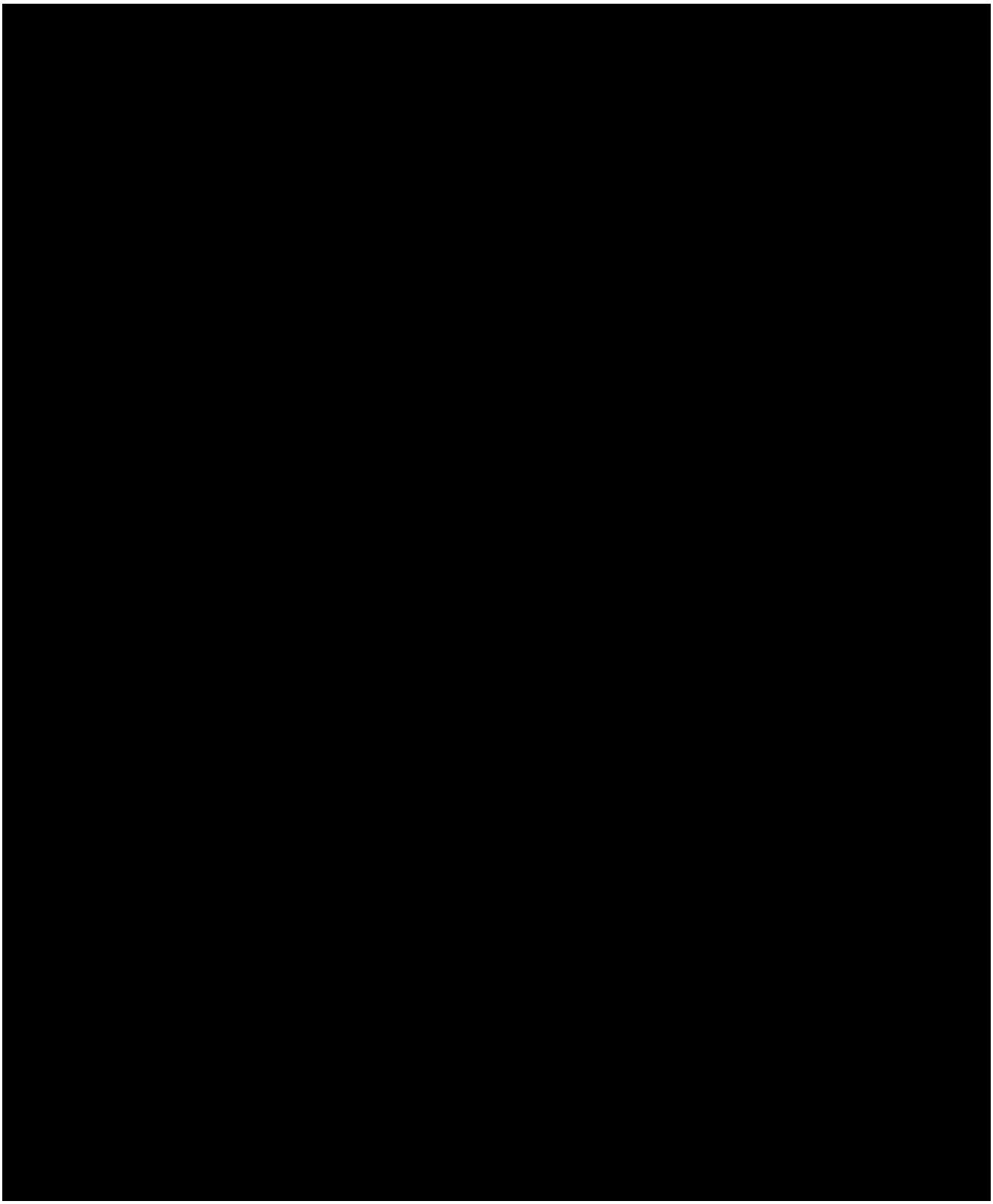


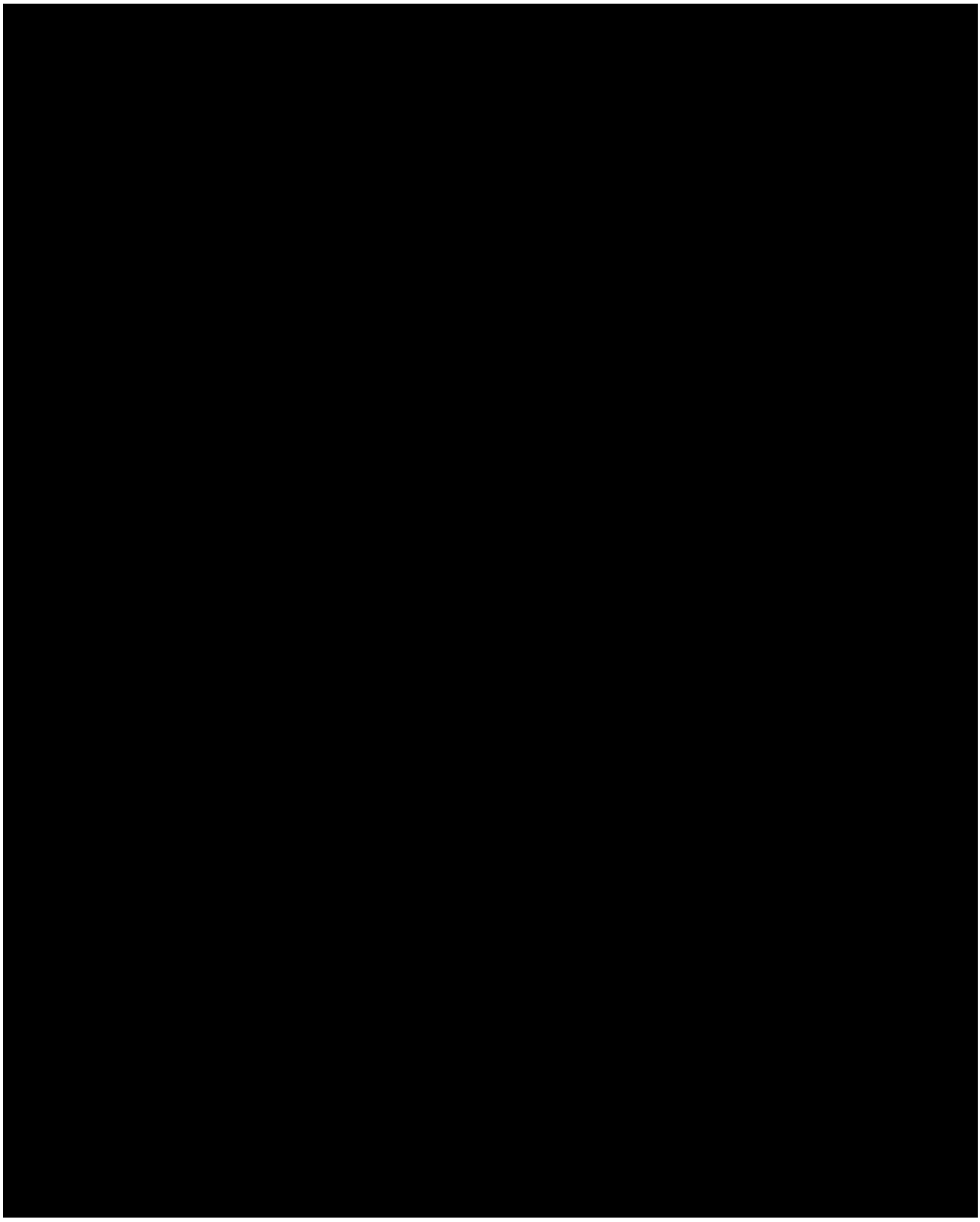


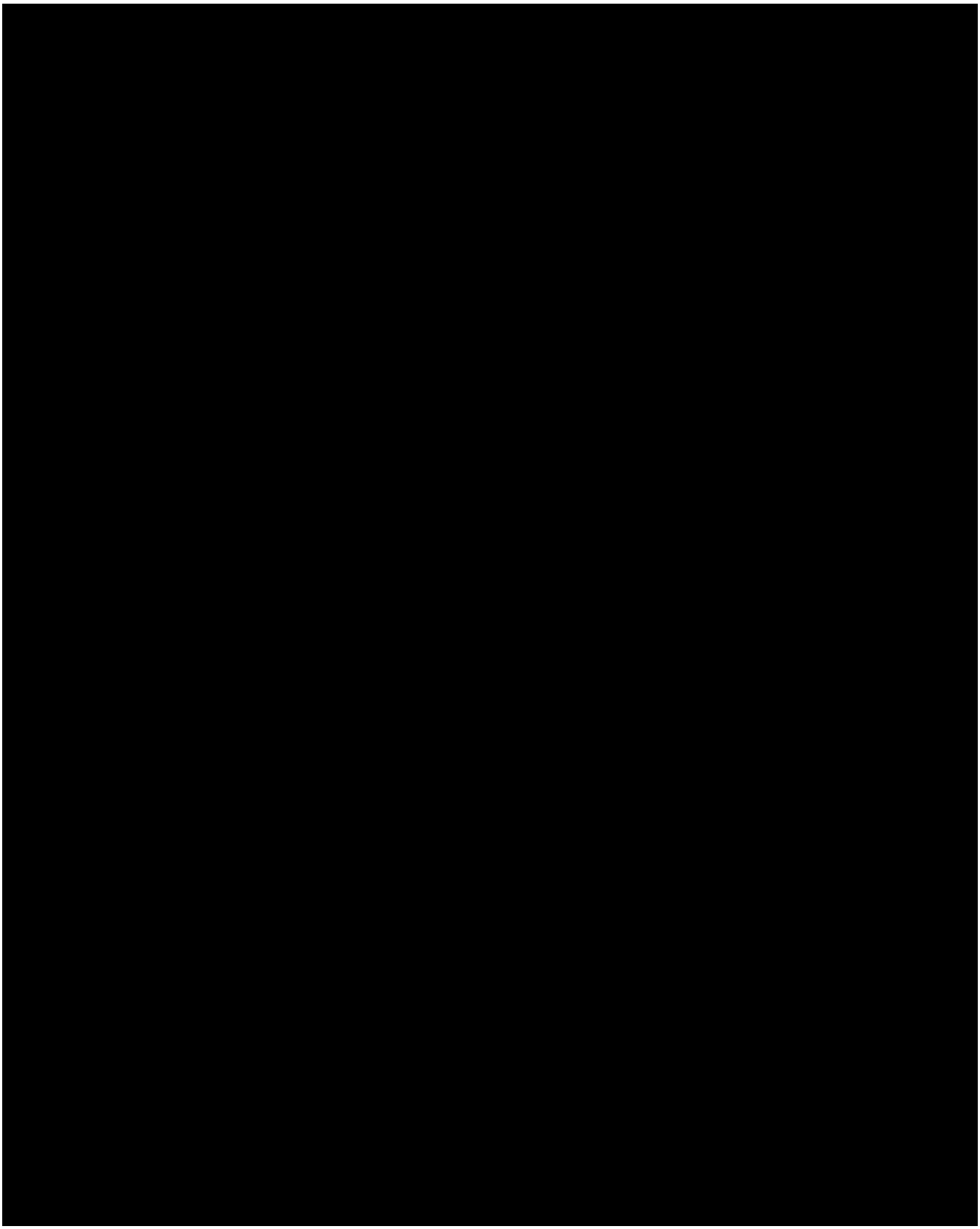


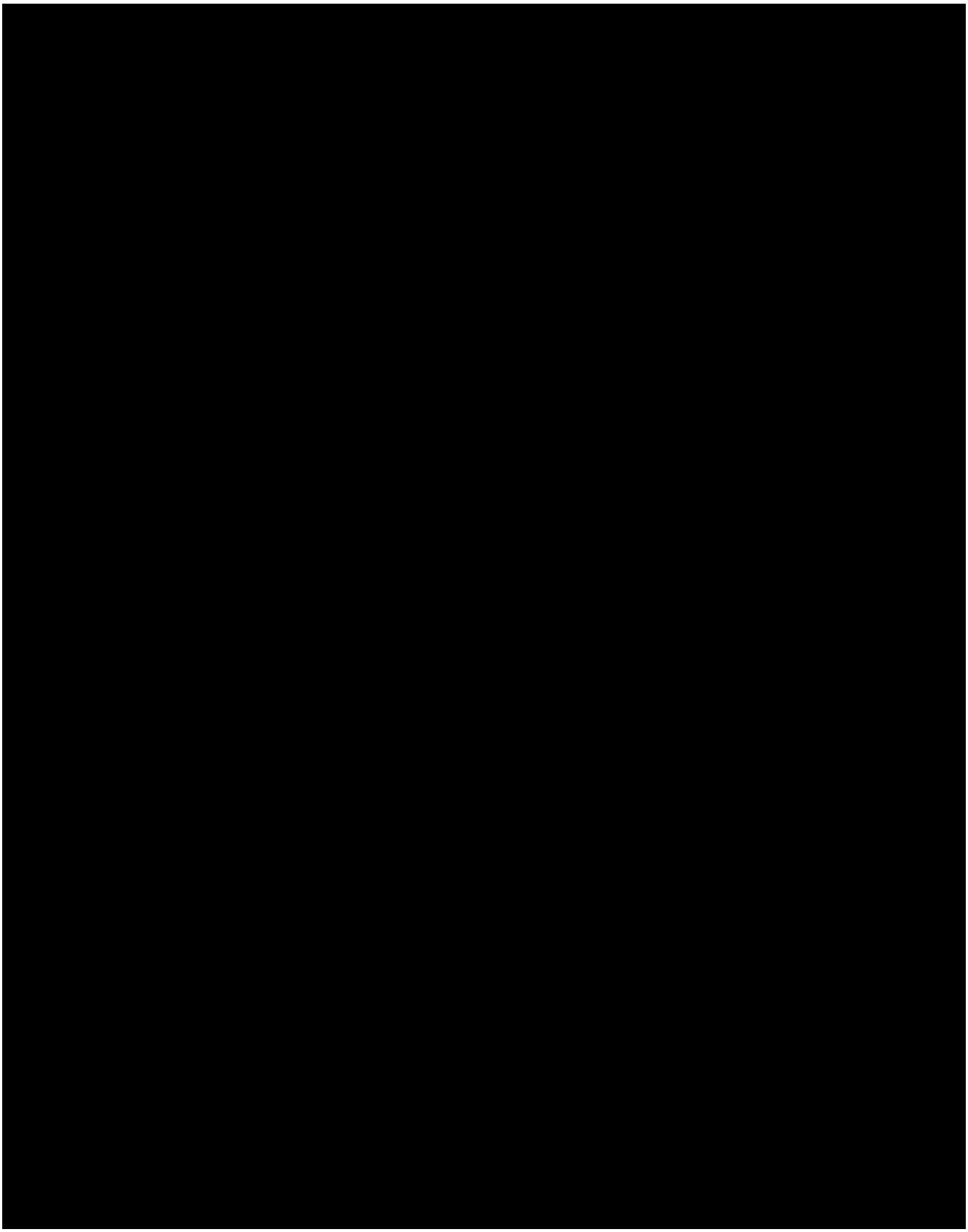


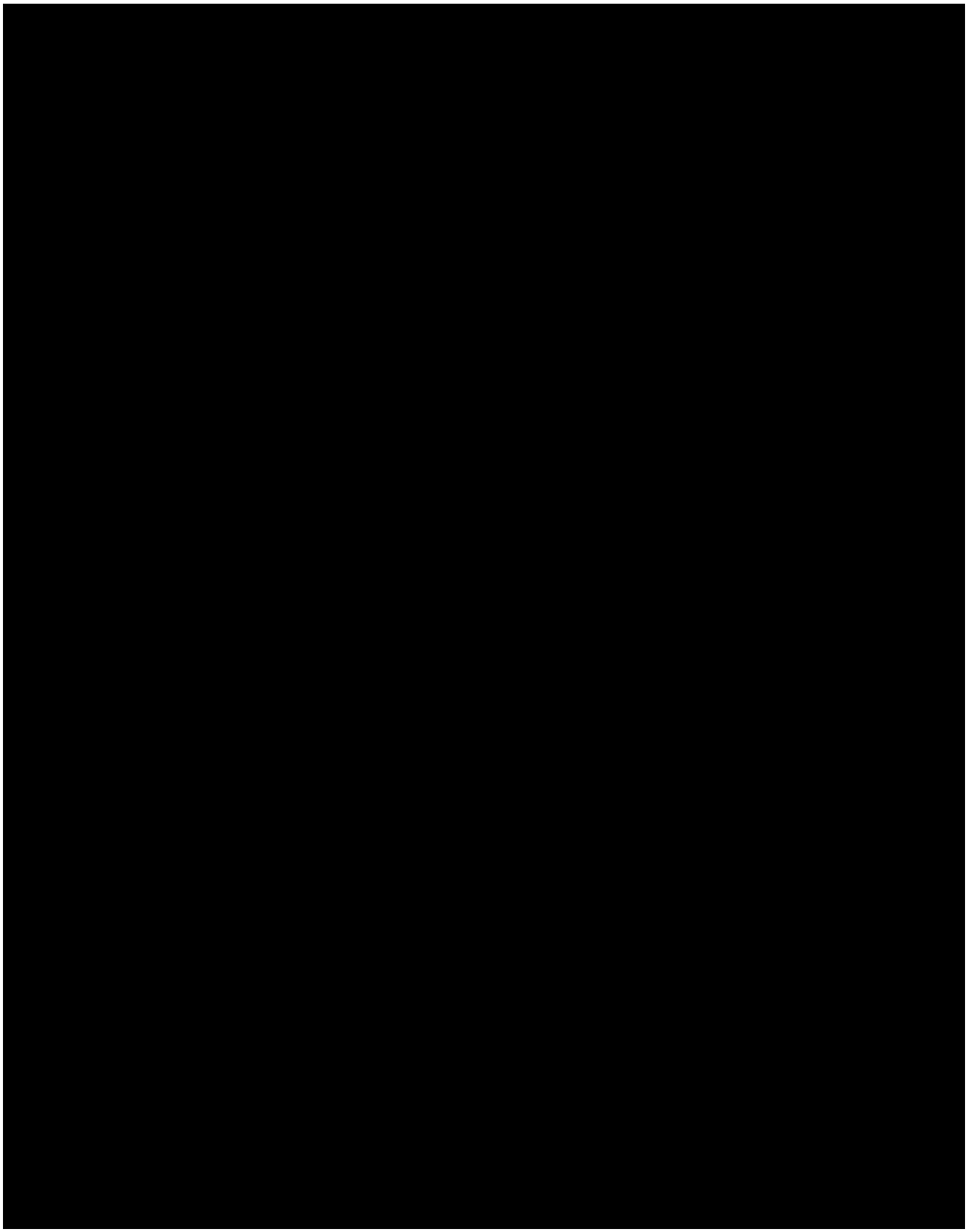


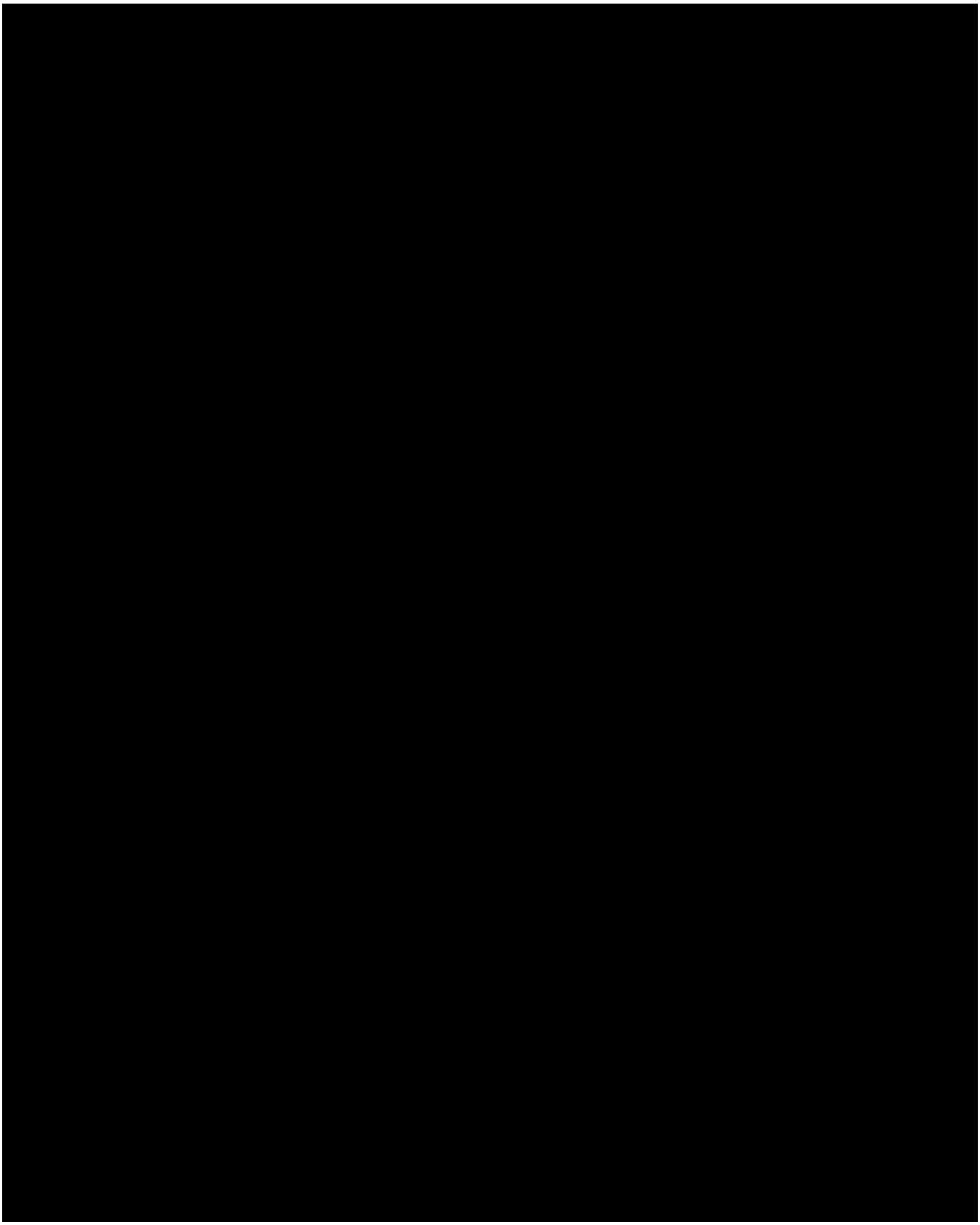


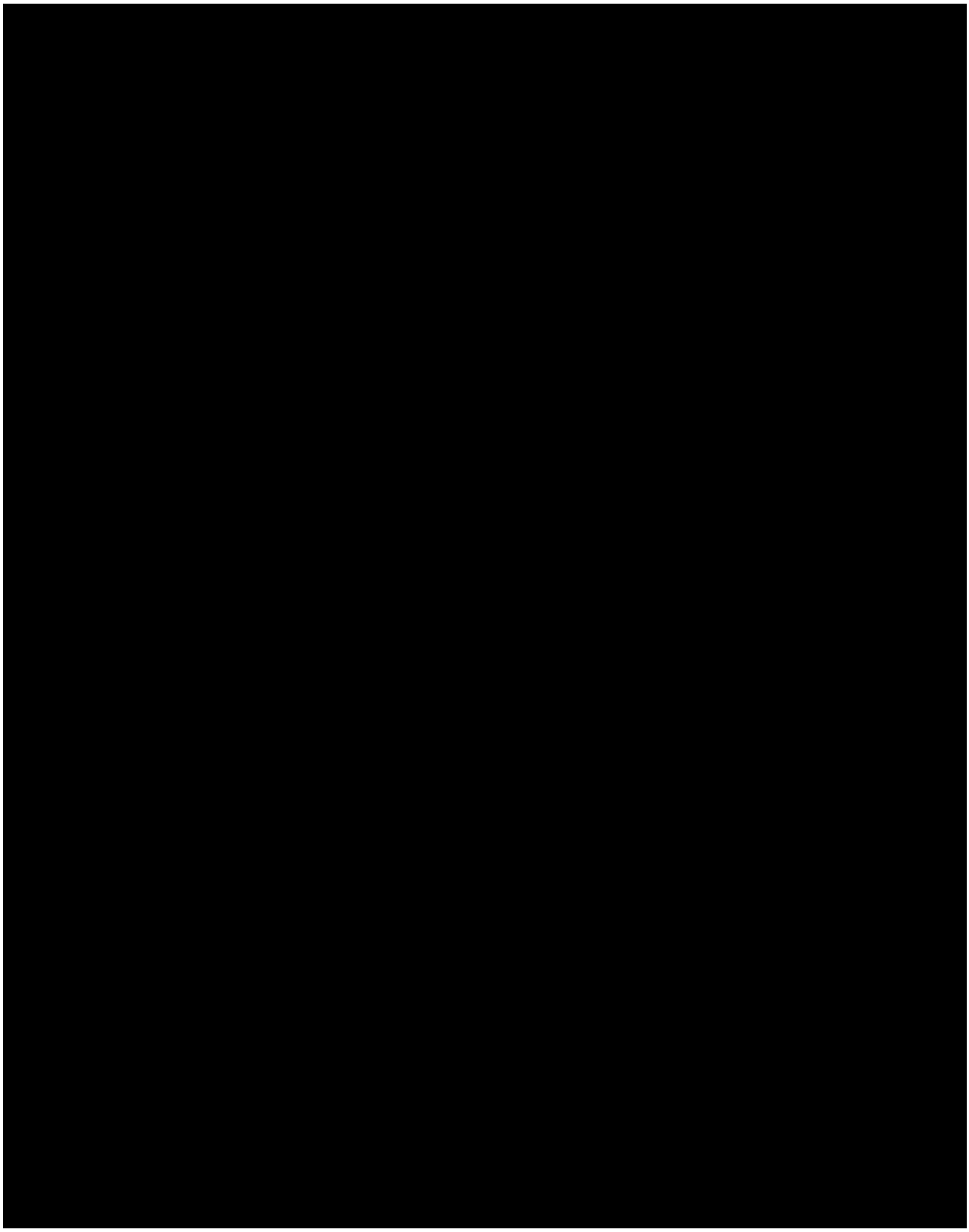


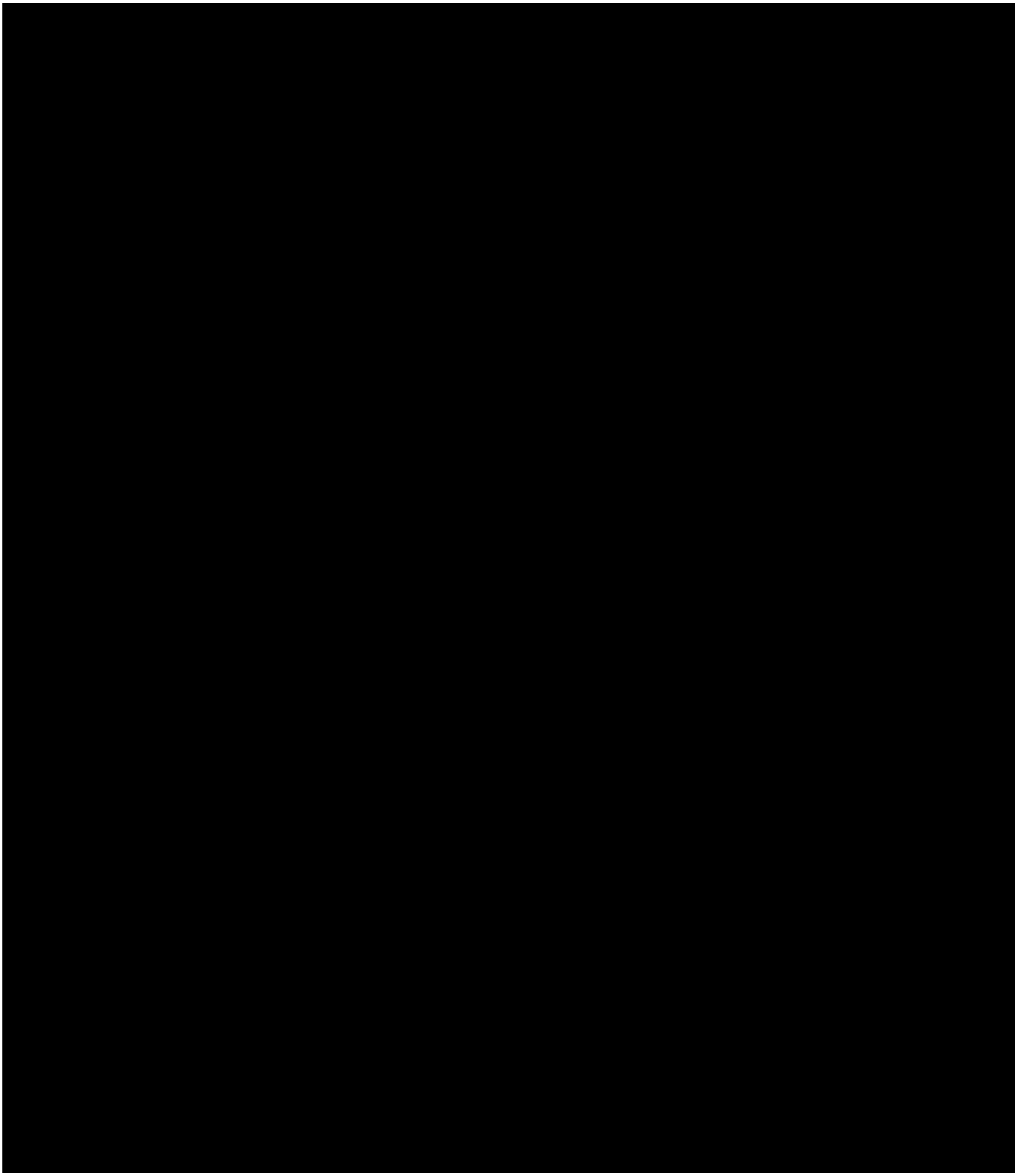












[redacted]

# 19. SAFETY OUTCOMES

All analyses for safety outcomes will be based on the safety analysis set. All safety data will be listed and summarized by actual treatment group. There will be no statistical comparisons between the treatments for safety data, unless otherwise specified. Unless otherwise stated, treatments displayed will include placebo, olorinab 10 mg, olorinab 25 mg, olorinab 50 mg, olorinab 25 and 50 mg pooled, and pooled olorinab.

## 19.1. ADVERSE EVENTS

AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, Version 23.0 or higher. Treatment-emergent adverse events (TEAEs) are defined as:

- An AE that occurs after the first dose of study treatment (olorinab or placebo) that was not present before the first dose of treatment, OR
- An AE that increases in severity after the first dose of study treatment (olorinab or placebo), if the event was present before the first dose of treatment.

All TEAEs will be coded and summarized by system organ class (SOC) and preferred term (PT) and will be presented by descending order of frequency. AEs occurring before the first dose of study treatment will be summarized separately. Listings will include all AEs (TEAEs and Non-TEAEs).

See Appendix 2. Partial Date Conventions for handling of partial dates for AEs for the purpose of assigning treatment-emergent flags. In the case where it is not possible to define an AE as treatment-emergent or not, the AE will be classified by the worst case; i.e. treatment emergent.

### 19.1.1. ALL TEAEs

All TEAEs will be summarized by SOC and PT in each treatment and with olorinab 25 and 50 mg pooled and olorinab active treatments pooled and presented by descending order of

frequency in any treatment. TEAEs will also be summarized by maximum severity and relationship to study treatment. A separate summary of related TEAEs and related TEAEs by maximum severity will also be provided.

### 19.1.2. SEVERITY

Severity is classified by grade using the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0) system as defined below. The CTCAE grade will be assessed by a nurse and/or physician and will be recorded in the AE severity Section on the Adverse Events eCRF.

**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 (e.g., 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.

TEAEs with a missing severity but identified as a life-threatening serious adverse event (SAE) or one requiring initial or prolonged hospitalization will be classified as Grade 4 (Potentially Life-threatening), otherwise missing severity will be classified as Grade 3 (severe). If a subject reports a TEAE more than once within that SOC/ PT, the AE with the greatest severity will be used in the corresponding severity summaries.

### 19.1.3. RELATIONSHIP TO STUDY TREATMENT

Relationship is classed as “not related”, “unlikely related”, “probably related”, or “related” (increasing severity of relationship) by the Investigator. A “related” TEAE for the purpose of TEAE summaries is defined as a TEAE with a relationship to study treatment as “related” or “probably related” to study treatment. TEAEs with a missing relationship to study treatment will be regarded as “related” to study treatment. “Unlikely related” will be counted as non-related TEAE. If a subject reports the same AE more than once within the same SOC/ PT, the AE with the strictest causality will be used in the corresponding relationship summaries. All TEAEs will be summarized by SOC, PT, and relationship to study treatment.

### 19.1.4. TEAEs Leading to Discontinuation of Study Treatment

TEAEs leading to permanent discontinuation of study treatment will be identified by action taken being recorded as "Drug withdrawal" on the AE page of the eCRF. All TEAEs leading to discontinuation of study treatment will be summarized by SOC and PT. A listing of all TEAEs leading to discontinuation of study treatment will also be presented.

### 19.1.5. TEAEs Leading to Study Discontinuation

TEAEs leading to study discontinuation will be noted on the End of Study eCRF. All TEAEs leading to study discontinuation will be summarized by SOC and PT.

### 19.1.6. Serious and Non-Serious TEAEs

Serious adverse events (SAEs) are those events recorded as "Serious" on the Adverse Events page of the eCRF. All serious TEAEs will be summarized by SOC and PT. All non-serious TEAEs will also be summarized by SOC and PT. A serious AE listing will also be presented.

### 19.1.7. TEAEs Leading to Death

TEAEs leading to Death are those events which are recorded as "Fatal" on the Adverse Events page of the eCRF. A summary of TEAEs leading to death by SOC and PT will be prepared by treatment.

### 19.1.8. TEAEs Of Special Interest

To date, no AEs of special interest have been identified related to olorinab. Potential AEs of special interest may be identified by clinical or medical reviewers. In addition to appropriate reporting of these events as an AE or SAE, supplementary detailed information may be collected. Any identified AEs of special interest will be summarized by SOC and PT separately. A listing will also be provided.

### 19.1.9. Overall Summary of Adverse Events

In addition to the summaries by SOC and PT as described in Sections 19.1.1 to 19.1.5, an overview of TEAEs will be summarized (not broken down by SOC or PT) by number and frequency of subjects and by number of AEs by treatment:

- Any AE (including non-TEAEs)

- Any TEAE
- Any related TEAE
- TEAEs by maximum severity
- Related TEAEs by maximum severity
- TEAEs by relationship to study treatment
- TEAEs leading to death
- Serious TEAEs
- Non-serious TEAEs
- Related Serious TEAEs
- TEAEs leading to study treatment discontinuation
- TEAEs leading to study treatment interruption
- TEAEs leading to study discontinuation
- Related TEAEs leading to study treatment discontinuation
- Related TEAEs leading to study treatment interruption
- Related TEAEs leading to study discontinuation
- TEAE leading to death

## 19.2. DEATHS

For any reports of death during the study as recorded on the End of Study page of the eCRF, the information will be presented in a listing.

## 19.3. LABORATORY EVALUATIONS

Results from the central laboratory will be included in the reporting of this study for chemistry, hematology, coagulation, urinalysis, thyroid chemistry, celiac, basal metabolic panel, virology, and serum pregnancy. A list of laboratory assessments to be included in the outputs is included in Table 3 in the protocol. If local and central laboratory assessments are available from the same day, central laboratory assessments will be used in the analysis.

Presentations will use SI Units. Quantitative laboratory measurements reported as "< X", i.e. below the lower limit of quantification (BLQ), or "> X", i.e. above the upper limit of quantification (ULQ), will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the listings.

Laboratory parameters such as hepatic enzymes, renal function and hematology values will be grouped and presented together. The following summaries will be provided for laboratory data:

- Value and change from baseline by visit (for quantitative measurements)
- Incidence of abnormal values according to laboratory reference ranges by visit
- Shift from baseline to end of treatment according to laboratory reference range (for quantitative measurements and categorical measurements)
- Summary of subjects with treatment-emergent abnormal lab results
- Listing of subject's laboratory assessments at all timepoints. Values outside of the central laboratory reference range will be flagged. Values obtained from local laboratory will be flagged.

### 19.3.1. LABORATORY REFERENCE RANGES AND MARKEDLY ABNORMAL CRITERIA

Quantitative laboratory measurements will be compared with the relevant laboratory reference ranges in SI units and categorized as:

- Low: Below the lower limit of the laboratory reference range.
- Normal: Within the laboratory reference range (upper and lower limit included).
- High: Above the upper limit of the laboratory reference range.
- Treatment-emergent high result: a change from a value less than or equal to the high limit at all baseline visits to a value greater than the high limit at any time during the treatment period.
- Treatment-emergent low result: a change from a value greater than or equal to the low limit at all baseline visits to a value less than the low limit at any time during the treament period.

## 19.4. 12-LEAD ECG

Results from the central 12-lead ECG Reading Centre will be included in the reporting of this study. The ECGs will be read and interpreted by the central ECG laboratory. For subjects enrolled before protocol amendment 2, there was an over-night observation period following randomization, and ECGs were collected at multiple timepoints on Day 1 and Day 2 (see below).

- Day 1: Prior to the first dose of study treatment and 2, 4, and 8 hours after the first dose (prior to the second dose), and 10 hours after the first dose (2 hours after the second dose).
- Day 2: Prior to the first dose of study treatment, and 2 and 4 hours after the first dose.

At all other indicated visits after baseline, ECGs were collected once per visit, prior to

administration of the first daily dose of study treatment.

For subjects enrolled after protocol amendment 2, on Day 1, ECG was collected prior to the first dose of study treatment and 2 hours after administration of study treatment. At all other indicated visits after baseline, ECGs were collected once per visit, prior to administration of the first daily dose of study treatment.

The following ECG parameters will be reported for this study on the central read for each safety ECG:

- PR Interval (msec)
- QRS Interval (msec)
- QT Interval (msec)
- QTcF Interval (msec) [derived]
- QTcB Interval (msec) [derived, optional]
- Heart Rate (HR) (bpm)
- Overall interpretation of ECG (Investigator's judgment):
  - Normal
  - Abnormal, Not Clinically Significant (Abnormal NCS)
  - Abnormal, Clinically Significant (Abnormal CS)

The following summaries will be provided by treatment group for ECG data:

- Value and change from baseline by visit (for quantitative measurements)
- Shift in normal/abnormal NCS/abnormal CS from baseline to worst investigator overall interpretation of clinical significance post-baseline
- Shift in markedly abnormal categories from baseline to post-baseline by visit

### 19.4.1. 12-LEAD ECG: OUTLIER AND MORPHOLOGY ANALYSES

The following Outlier and Morphology findings will be summarized with frequency count and percentage by treatment:

- HR, tachycardic
- HR, bradycardic
- Short PR <120 ms
- Prolonged PR >220ms
- QRS >120 ms
- QT new >500 ms

- QT new > 450 ms (male)
- QT new > 470 ms (female)
- QTcF new >500 ms
- QTcF new >480 ms
- QTcF >30 ms increase from baseline
- QTcF >60 ms increase from baseline
- New atrial fibrillation
- New atrial flutter
- New abnormal U waves
- New ST segment depression changes
- New ST segment elevation changes
- New T wave inverted
- New 2nd degree heart block
- New 3rd degree heart block
- New complete RBBB
- New complete LBBB
- New MI

## 19.5. VITAL SIGNS

Orthostatic vital signs (VS) include the collection of blood pressure (BP) and HR after the subject has been resting in the supine position for at least 5 minutes and then again after 1 and 3 minutes of standing. For subjects enrolled before protocol amendment 2, there was an over-night observation period following randomization, and the orthostatic VS were collected at multiple timepoints on Day 1 and Day 2 (see below).

- Day 1: Prior to the first dose of study treatment and 2, 4, 8 hours after the first dose (prior to the second dose), and 10 hours after the first dose (2 hours after the second dose).
- Day 2: Prior to the first dose of study treatment and 2 and 4 hours after the first dose.

At all other visits after baseline, orthostatic vital signs were collected once per visit, prior to administration of the first daily dose of study treatment. For Day 1 and Day 2, the assessment at the earliest time of the same day will be used for analysis.

For subjects enrolled after protocol amendment 2, orthostatic BP and HR assessments were collected once per visit, prior to administration of the first daily dose of study treatment for the post-baseline visits.

The following VS data will be summarized using descriptive statistics by treatment group as well as for active treatment groups pooled.

- The actual measurement values of vital signs (BP and HR at Supine, Standing 1 and 3 minutes) at each visit/timepoint
- Change from baseline for orthostatic VS (BP and HR at Supine, Standing 1 and 3 minutes): calculated as post-baseline values minus the value prior to the first dose on Day 1.
- Change from supine to standing in orthostatic vital signs (BP and HR): calculated as the standing measurement minus the supine measurement by visit/timepoint. It will be calculated for 1-minute standing and 3-minute standing separately.

Body temperature and respiratory rate were collected once per visit, prior to the administration of the first daily dose of study treatment (for visits occurring during the Treatment Period). Change from baseline will be summarized in a similar manner. Baseline is defined as the last measurement collected before the first dose on Day 1.

Vital sign values meeting the criteria as defined in
Table 2 below will be categorized as potentially clinically significant (PCS) findings. These findings will be summarized with frequency count and percentage for each treatment as well as for the active treatments pooled, both overall and by visit for the pre-dose period (including Screening, Run-in and Day 1/Pre-dose) and for the post-dose period The summaries and counts will be presented at both the subject level (counting subjects with PCS findings) and event level (counting all PCS events).

**Table 2: Vital Sign PCS Criteria**

| Parameter | PCS Category | PCS Criteria |
|---|---|---|
| Systolic BP (mm Hg) | High | (> 155 Standing or ≥ 140 Supine) and Supine increase from baseline ≥ 20 |
| | Low | (≤ 80 Standing or ≤ 90 Supine) and Supine decrease from baseline ≥ 20 |
| Diastolic BP (mm Hg) | High | (> 105 Standing or ≥ 90 Supine) and Supine increase from baseline ≥ 15 |
| | Low | (< 35 Standing or < 40 Supine) and Supine decrease from baseline ≥ 15 |
| Pulse Rate (bpm) | High | ≥ 120 Standing or ≥ 100 Supine |
| | Low | < 40 Standing or Supine |
| Orthostatic Systolic BP (mm Hg) | Low | Supine to Standing decrease ≥ 20 |

| Parameter | PCS Category | PCS Criteria |
|---|---|---|
| Orthostatic Diastolic BP (mm Hg) | Low | Supine to Standing decrease ≥ 10 |
| Orthostatic Pulse Rate (bpm) | High | Supine to Standing increase ≥ 30 |
| Respiratory Rate (brpm) | High | ≥ 28 |
| | Low | ≤ 8 |
| Temperature (°C) | High | > 38 |
| | Low | < 35 |

Abbreviation: bpm = beats per minute; BP = blood pressure; brpm = breaths per minute; PCS = potentially clinically significant.
Note: Standing is from Standing 1 or Standing 3 measurement.

### 19.5.1. VITAL SIGNS SPECIFIC DERIVATIONS

- Temperature ($^0$C) = (5/9) (Temperature ($^0$F) – 32)

## 19.6. PHYSICAL EXAMINATION

All physical examination assessments will be listed.

# 20. PHARMACOKINETICS ANALYSIS

The PK analyses for the Main Study are described in the subsequent paragraphs.
All PK concentrations will be reported and analyzed with the same precision as the source data provided by the bio-analytical laboratory regardless of how many significant figures or decimals the data carry. The unrounded derived PK parameters will be considered the source data for the calculation of descriptive statistics and rounded for reporting purposes in by-subject listings. Pharmacokinetic parameters will be listed with the following rounding/precision conventions:

- Parameters directly obtained from source data (e.g., $C_{max}$, dose-normalized $C_{max}$, and $C_{trough}$) will be reported and analyzed with the same precision as the source concentration data.
- Parameters obtained from actual elapsed sample collection times (e.g., $t_{max}$) will be reported with the same precision as the actual elapsed sampling time value (2 decimal places) of the source data.
- All other pharmacokinetic parameters will be listed to one significant figure greater than precision of bioanalytical data

Summary statistics for PK concentrations will include: number of observations (n), mean, SD, coefficient of variation (CV%), geometric mean, geometric CV%, minimum, median, and maximum.

Summary statistics for PK parameters, except $t_{max}$, will include: n, arithmetic mean, arithmetic SD, CV%, minimum, median, maximum, geometric mean, and geometric CV%; geometric mean and geometric CV% will be calculated from available individual values that are greater than 0. For geometric mean calculation, the mean of log transformed values will be calculated, and then transformed back to the original scale by exponentiation.

The PK parameter $t_{max}$ will be summarized using n, median, minimum, and maximum.

An n $\geq$3 will be required for calculations of descriptive statistics. If n <3, no descriptive statistics will be calculated; only n, minimum, and maximum, will be presented.

For the reporting of descriptive statistics, the mean, SD, geometric mean, and geometric CV% will be presented to one digit more precision than rounding of the source data. The minimum, median, and maximum will be presented to the same precision as rounding of the source data. Coefficient of variation will always be reported to 1 decimal place.

## 20.1. PLASMA CONCENTRATION DATA

Individual PK blood sample collection times, derived sampling time deviations where scheduled times are specified, and plasma concentrations of olorinab and the metabolites [redacted] and [redacted] will be listed.

Plasma concentrations of each analyte will be summarized at the scheduled visit by scheduled time (where applicable) and stratified by formulation and treatment. Summaries for overall treatment group will also be presented.

Concentrations that are BLQ will be treated as missing for the computation of geometric descriptive statistics, and zero for the computation of the remaining descriptive statistics. Concentrations that are missing will be omitted from the calculation of descriptive statistics. Concentrations associated with sampling time deviations will be included in the summaries, providing:

- For pre-dose timepoint, the samples are collected before the next dose,
- For post-dose timepoints, the samples are collected after the previous scheduled time

and before the next scheduled time, and the time deviation is not significant, as adjudicated by PK scientist and clinical pharmacologist (in which case their time deviance and its adjudication will be noted in protocol deviations).

Only samples collected on Day 1 will be included in the Day 1 summaries (i.e., 0 day for the time window). For the summaries of visits after Day 1, under assumption for steady-state, samples collected on a day outside of the time window of ±3 days allowed in the protocol will still be included in the summaries for the corresponding scheduled visit.

For each PK analyte, figures of arithmetic mean (SD) concentration-time serial profiles overlaid by treatment group, by dosage form and overall will be presented for Day 1, Day 2, and Week 4. By-subject plots of concentration-time serial profiles, overlaying parent and all metabolites will also be presented for Day 1, Day 2, and Week 4, with the 3 assessment days represented as panels in a single plot. All concentration-time profiles will be depicted on linear and semi-logarithmic scales.

Additional data presentation of pre-dose ($C_{trough}$) concentrations is described in Section 20.2.

## 20.2. PLASMA PHARMACOKINETIC PARAMETERS

Plasma PK parameters for olorinab and the metabolites [redacted] and [redacted] after the first dose of the corresponding day on Day 1, Day 2, and at Week 4 will be calculated by noncompartmental methods. Actual elapsed time from dosing will be used. The following data handling conventions apply to the PK analyses for all analytes on Day 1, Day 2, and at Week 4, unless otherwise indicated:

- Pre-dose samples that are BLQ will be assigned a numerical value of zero.
- Any pre-dose concentration values that are quantifiable on Day 1 will be included in the PK analysis and identified in the CSR and the subject will be considered for potential exclusion from the pharmacokinetic analysis set. Although quantifiable concentration values at pre-dose on Day 1 are considered as anomalous, the PK parameters shall be listed and included in the parameter summaries for all such cases as a conservative approach to retain data for the study in patient population.
- Missing pre-dose samples:
  - On Day 1, will be assigned a numerical value of zero and the subject will be considered for potential exclusion from the pharmacokinetic analysis set,
  - On Day 2 and at Week 4, will be kept as missing and $C_{trough}$ will not be calculated.
- Post-dose BLQ concentrations will be assigned a value of zero if they precede quantifiable data points in the initial portion of the profile.

- A BLQ value that occurs between quantifiable data points prior to $C_{max}$, will be assigned concentration of zero.
- Following $C_{max}$, BLQ values embedded between 2 quantifiable data points will be treated as missing.
- Trailing BLQ values after the last quantifiable concentration will be set to zero.

In addition, for calculating Day 1 $AUC_{(0-8)}$:

- Actual time of sample collection, regardless of time deviations, rather than scheduled time shall be used to derive AUC0-8.
- If concentration at t=8 h is available but collection time is missing, $AUC_{(0-8)}$ will be calculated using scheduled time.
- If concentration at t=8 h is missing, $AUC_{(0-8)}$ will not be calculated
- $AUC_{all}$ shall be used as an estimate of $AUC_{(0-8)}$ if concentrations fall to BLQ at or before reaching t=8 h.

The same nominal dose administered will be used for both the powder in capsule (PIC) and tablet formulations (as the dose input for the olorinab analysis and for calculating dose-normalized exposures for the different analytes).

The following PK parameters will be calculated for olorinab and the metabolites [redacted] unless otherwise indicated:

| | |
|---|---|
| $C_{trough}$ | Observed plasma concentration at the end of the dosing interval, obtained from the value measured prior to the next dose.<br>(Unit: ng/mL). |
| $C_{max}$ | Maximum concentration in plasma<br>(Unit: ng/mL). |
| $C_{max}$ /D | Dose-normalized $C_{max}$.<br>(Unit: ng/mL/mg). |
| $t_{max}$ | Time of maximum concentration<br>(Unit: h). |
| $MRC_{max}$ | Molar-corrected metabolite to parent (olorinab) $C_{max}$ ratio ,calculated as follows:<br>$\frac{\text{metabolite Cmax}}{\text{olorinab Cmax}} \times \frac{\text{olorinab MW}}{\text{metabolite MW}}$<br>$MRC_{max}$ will be calculated for [redacted] and [redacted]. |
| $AUC_{(0-8)}$ | Area under the concentration-time curve of the analyte in plasma during the dosing interval.<br>(Unit: ng*h/mL) |
| $AUC_{(0-8)}$ /D | Dose-normalized $AUC_{(0-8)}$<br>(Unit: ng*h/mL/mg). |
| $MRAUC_{(0-8)}$ | Molar-corrected metabolite to parent (olorinab) $AUC_{(0-8)}$ ratio, calculated as follows:<br>$\frac{\text{metabolite AUC}(0-8)}{\text{olorinab AUC}(0-8)} \times \frac{\text{olorinab MW}}{\text{metabolite MW}}$<br>$MRAUC_{(0-8)}$ will be calculated for [redacted] and [redacted]. |

The areas under the curve will be calculated by linear up/log down trapezoidal summation, where at least 3 quantifiable post-dose concentrations are available.

[redacted]

The parameter $C_{trough}$ will be obtained from concentrations measured pre-dose at Weeks 2, 4, 8, 10, and 12. Other parameters ($C_{max}$, $C_{max}$/D, $t_{max}$ and $MRC_{max}$) will be calculated for Day 1, Day 2 (protocol Amendment 1 only), and Week 4. In addition, for subjects who are randomized under protocol Amendment 1 with more timepoints in the PK sampling schemes, $C_{trough}$ obtained from concentrations measured at 8-hour timepoint on Day 1 and pre-dose on Day 2, and $AUC_{(0-8)}$ and $MRAUC_{(0-8)}$ on Day 1 will also be calculated.

Individual plasma PK parameters will be listed and summarized for each analyte at the scheduled visit and by treatment, formulation, and IBS subtype. Day 1 PK parameters will be summarized separately for subjects who are randomized under protocol Amendment 1 and after protocol Amendment 1. In the event that subject numbers are too low to summarize Day 1 PK parameters by treatment, formulation, and IBS subtype (less than 3 subjects in each subgroup), parameters may be summarized by treatment and formulation, and additionally by treatment and IBS subtype.

$C_{trough}$ of each analyte will be summarized per day, treatment, formulation, and IBS subtype, for all pre-dose trough concentrations sampled within the following time brackets: 12 hours of the previous day's dose (immediate prior dose was not more than 12 hours before trough sample) and within one hour of dosing (trough sample taken at or not more than one hour before) on the trough assessment day. Summaries for overall treatment group will also be presented. For each analyte, figures of geometric mean (geometric CV%) $C_{trough}$ profiles overlaid by treatment group will be presented on linear scales. Individual values and geometric means of $C_{max}$ will be plotted versus dose for Day 1, Day 2, and at Week 4. In addition, plots of individual values and geometric means of $AUC_{(0-8)}$ versus dose on Day 1 will be presented for the overall treatment group of subjects who are randomized under protocol amendment 1.

# 21. IMPACT OF COVID-19

The study has been closely monitored during the period of COVID-19 and the impact of COVID-19 to data analyses is minimal. The below analyses related to COVID-19 are planned to document any impacts of the pandemic. Post hoc explanatory data analyses may be planned after database lock if the data warrants the request.

- Summary of major protocol deviations caused by COVID-19
- A listing of any adverse events related to COVID-19
- A listing of any subjects with phone or remote visits due to COVID-19.

# 22. GENETIC AND BIOMARKERANALYSES

Genetic and biomarker analyses will be completed by Sponsor and will be described in a separate analysis plan if needed.

# 23. DATA NOT SUMMARIZED OR PRESENTED

The other variables and/or domains not summarized or presented are:

- Comments
- Meals (Day 1)

These domains and/or variables will not be summarized or presented but will be available in the clinical study database, SDTM and/or ADaM datasets.

# 24. REFERENCES

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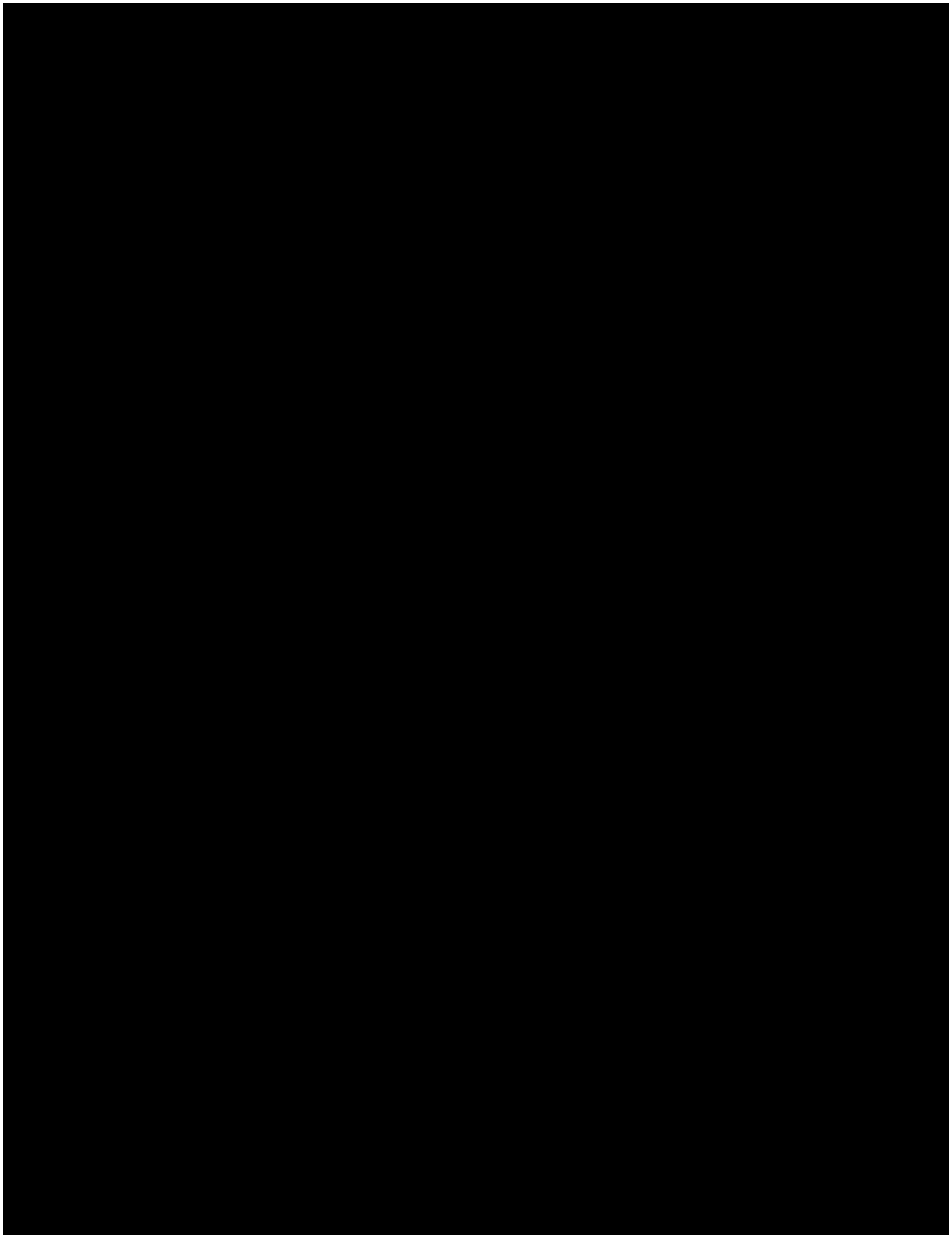
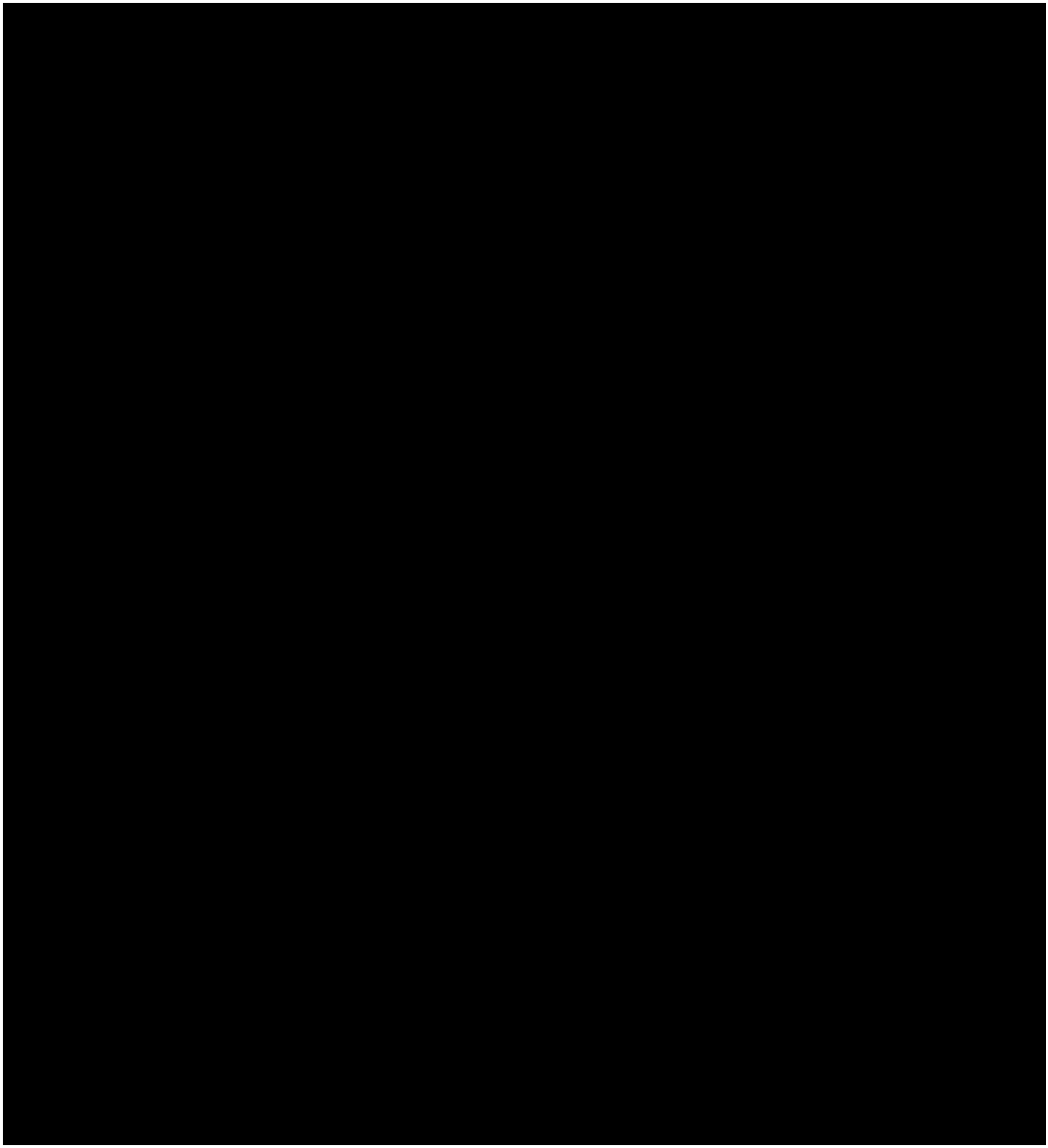
Liang, K., Zeger, S., Longitudinal Data Analysis for Continuous and Discrete Responses for Pre-Post Designs. Sankhyta: The Indian Journal of Statistics. 2000. 62(B): 134-148.

Little, R., & Yau, L. (1996). Intent-to-Treat Analysis for Longitudinal Studies with Drop-Outs. Biometrics , vol 52, 1324-1333.

[redacted]





# 26. APPENDIX 2. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings.

## ALGORITHM FOR TREATMENT EMERGENCE OF ADVERSE EVENTS:

| AE START DATE | AE STOP DATE | ACTION |
|---|---|---|
| Known | Known, Partial or Missing | If AE start date < study treatment first dose date, then not TEAE<br>If AE start date ≥ study treatment first dose date, then TEAE |
| | | |
| Partial, but known components show that it cannot be on or after date of first dose of study treatment | Known, Partial or Missing | Not TEAE |
| | | |
| Partial, could be on or after date of first dose of study treatment | Known | If AE stop date < study treatment first dose date, then not TEAE<br>If AE stop date ≥ study treatment first dose date, then TEAE |
| | Partial | Impute AE stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then:<br>If AE stop date < study treatment first dose date, then not TEAE<br>If AE stop date ≥ study treatment first dose date, then TEAE |
| | Missing | Assumed TEAE |

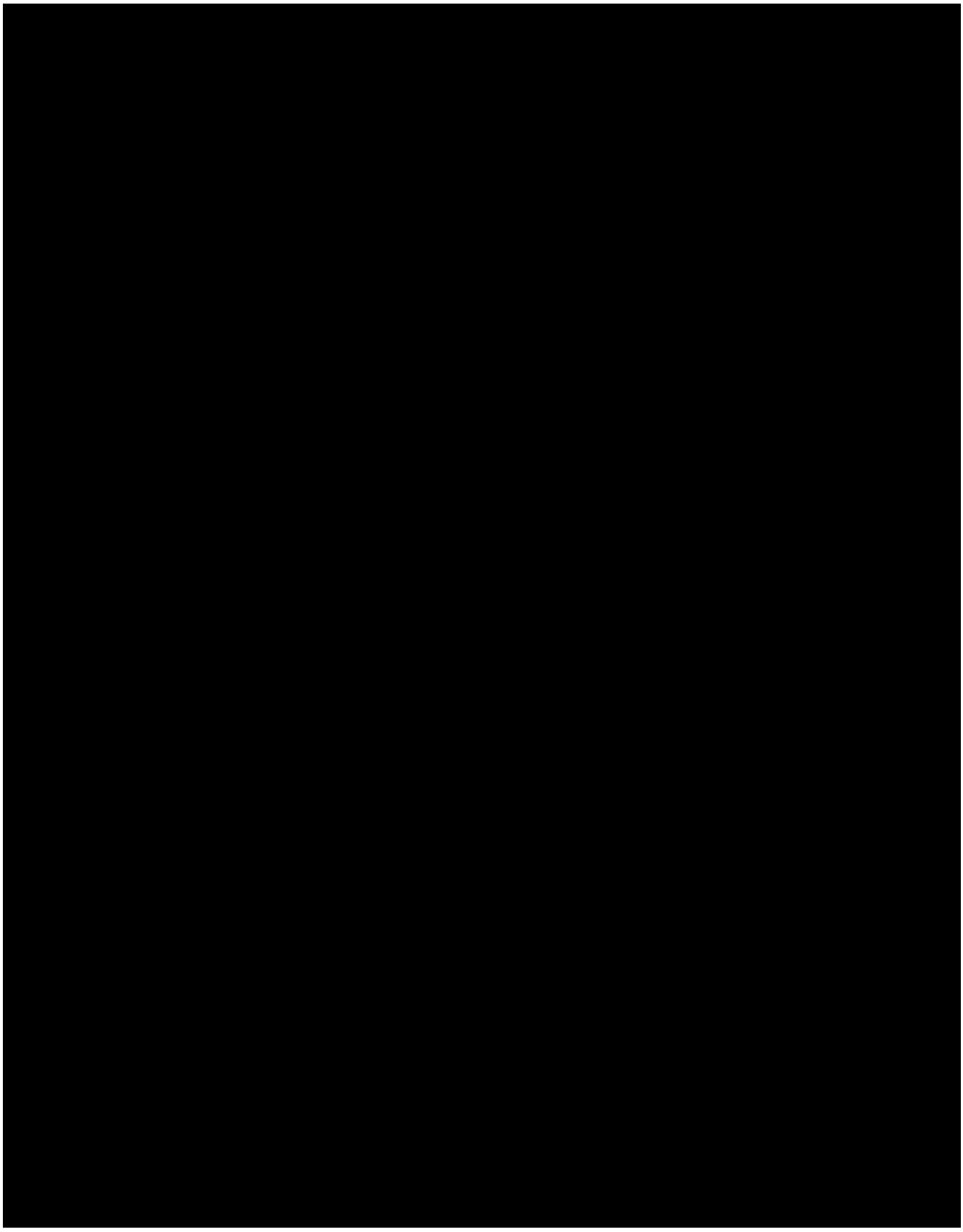
| AE START DATE | AE STOP DATE | ACTION |
|---|---|---|
| | | |
| Missing | Known | If AE stop date < study treatment first dose date, then not TEAE<br>If AE stop date ≥ study treatment first dose date, then TEAE |
| | Partial | Impute AE stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then:<br>If AE stop date < study treatment first dose date, then not TEAE<br>If AE stop date ≥ study treatment first dose date, then TEAE |
| | Missing | Assumed TEAE |

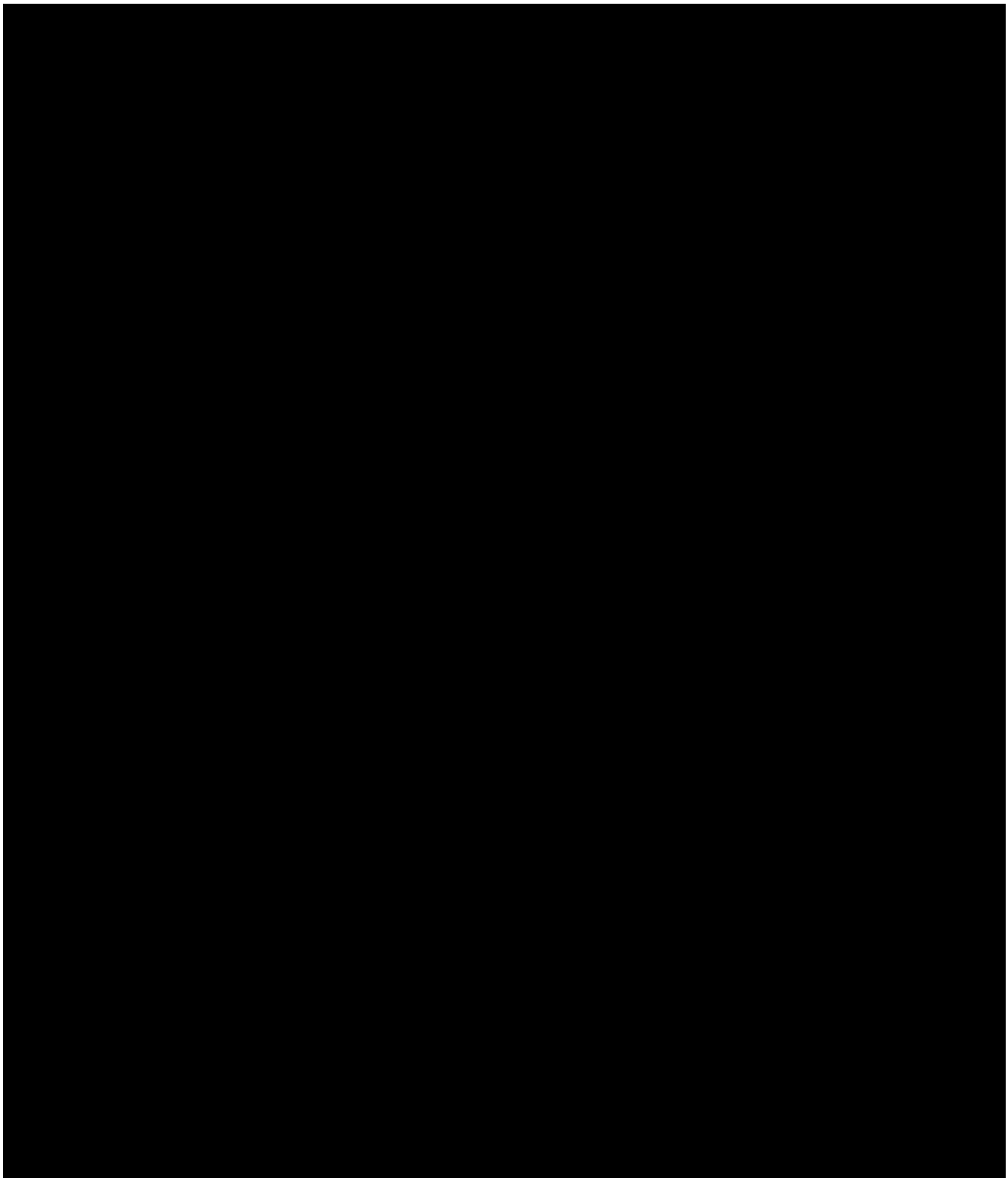
**ALGORITHM FOR PRIOR / CONCOMITANT MEDICATIONS:**

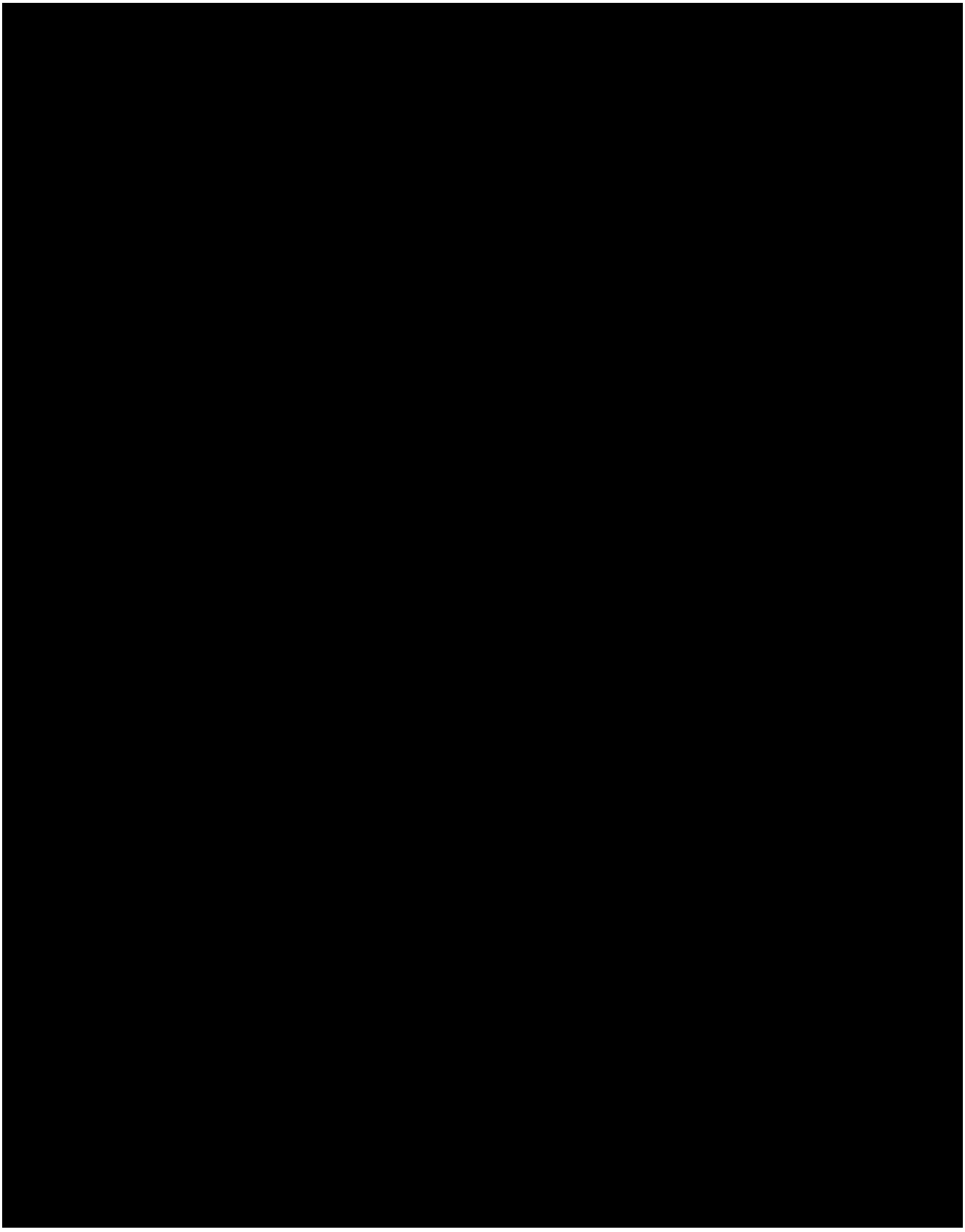
| START DATE | STOP DATE | ACTION |
|---|---|---|
| Known | Known | If medication stop date < study treatment first dose date, assign as prior<br>If medication stop date ≥ study treatment first dose date, assign as concomitant |
| | Partial | Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then:<br>If medication stop date < study treatment first dose date, assign as prior<br>If medication stop date ≥ study treatment first dose date, assign as concomitant |
| | Missing | If medication stop date is missing could never be assumed a prior medication, assign as concomitant |

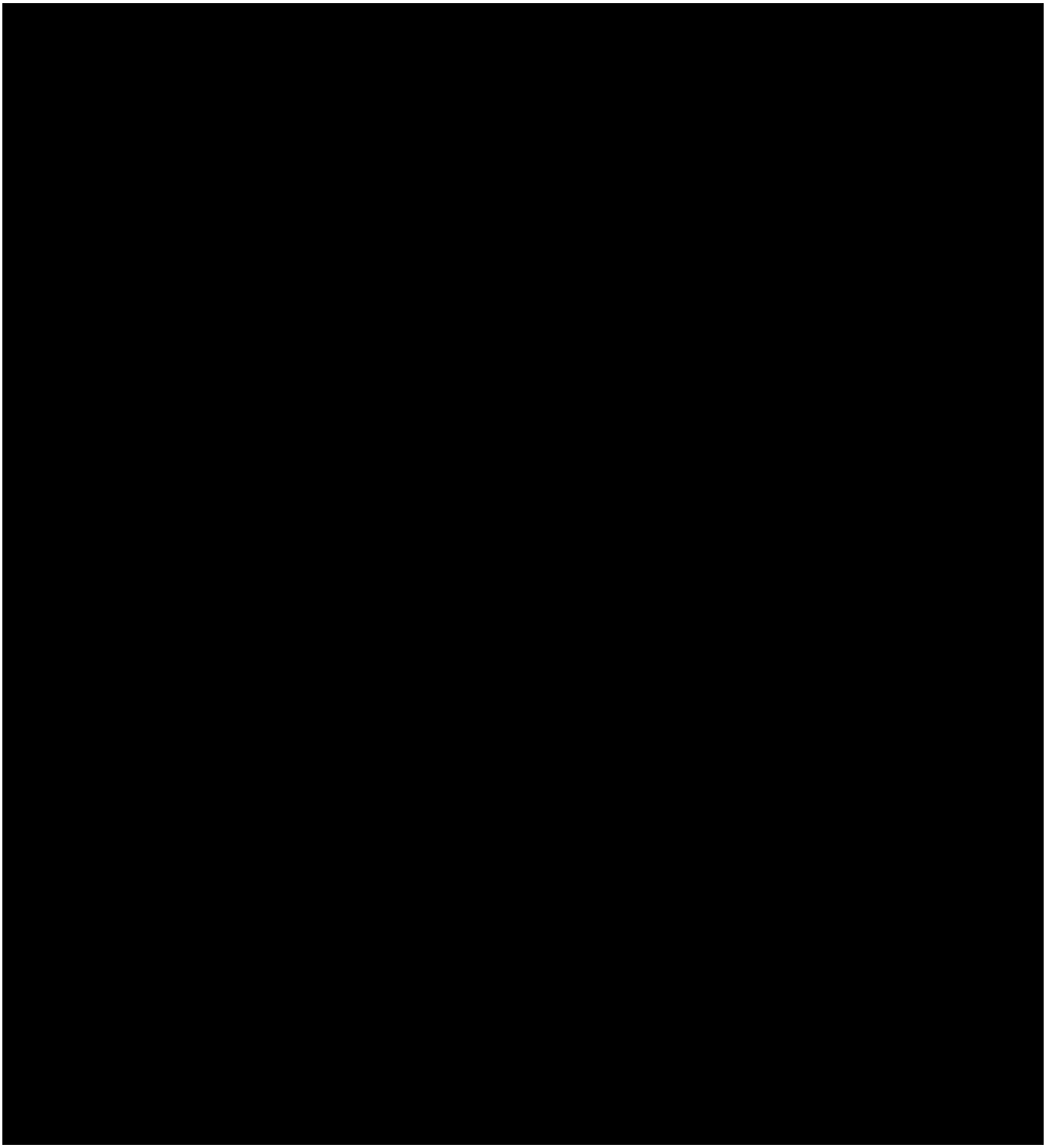
| START DATE | STOP DATE | ACTION |
|---|---|---|
| | | |
| Partial | Known | Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then:<br>If medication stop date < study treatment first dose date, assign as prior<br>If medication stop date ≥ study treatment first dose date, assign as concomitant |
| | Partial | Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then:<br>If medication stop date < study treatment first dose date, assign as prior<br>If medication stop date ≥ study treatment first dose date, assign as concomitant |
| | Missing | Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then:<br>If medication stop date is missing could never be assumed a prior medication, assign as concomitant |
| | | |
| Missing | Known | If medication stop date < study treatment first dose date, assign as prior<br>Else assign as concomitant |

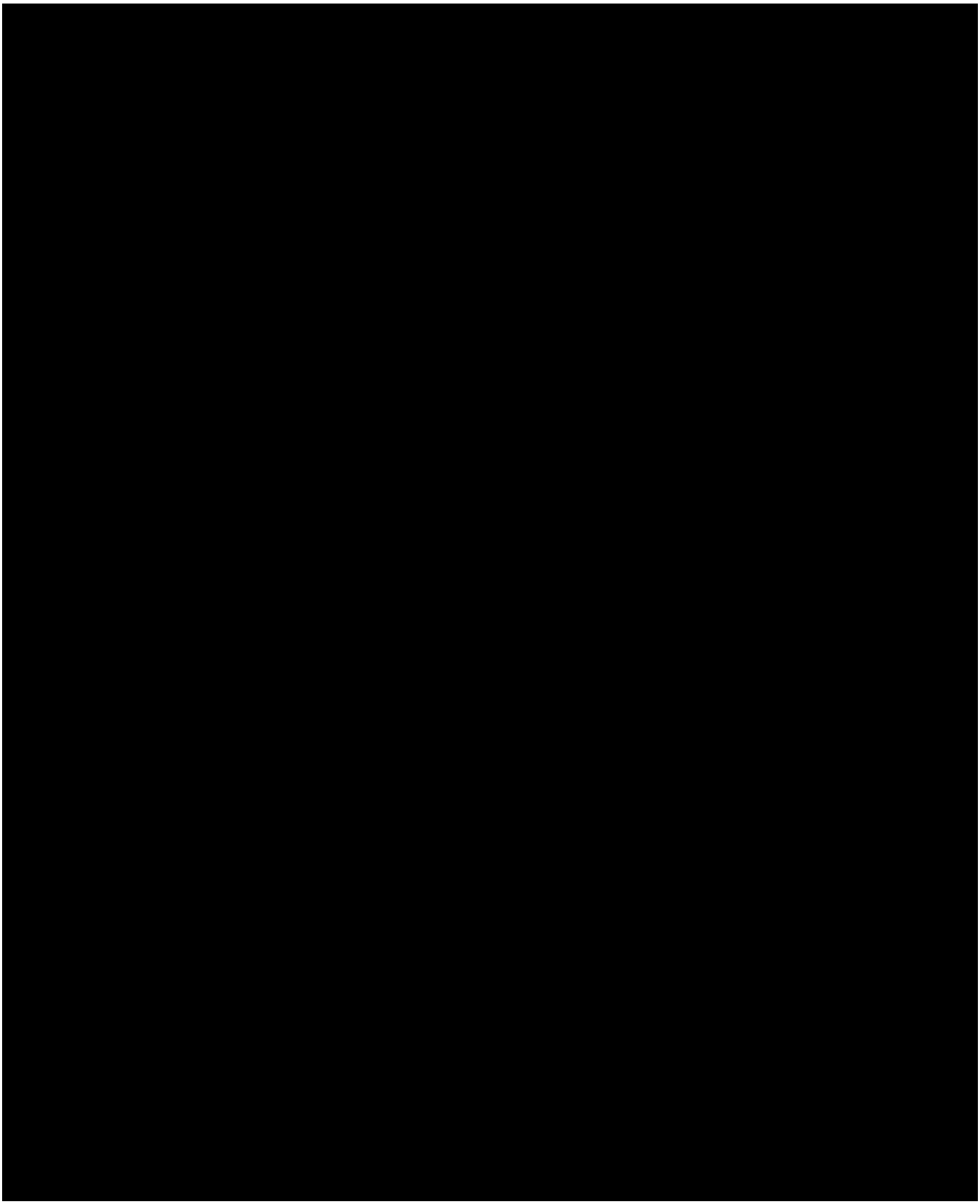
| START DATE | STOP DATE | ACTION |
|---|---|---|
| | Partial | Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then:<br>If medication stop date < study treatment first dose date, assign as prior<br>If medication stop date ≥ study treatment first dose date, assign as concomitant |
| | Missing | Assign as concomitant |











# STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

**Statistical Analysis Plan V1.0 (Dated 15JAN2021) for Protocol APD371-202 Amendment 3.**

| | Name | Signature | Date |
|---|---|---|---|
| **Author:** | [redacted] | | |
| **Position:** | Associate Director | | |
| **Company:** | IQVIA | | |

| | Name | Signature | Date |
|---|---|---|---|
| **Author:** | [redacted] | | |
| **Position:** | Associate Research Pharmacokinetics Director | | |
| **Company:** | IQVIA | | |

Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

| | Name | Signature | Date |
|---|---|---|---|
| **Approved By:** | [redacted] | | |
| **Position:** | Sr. Director | | |
| **Company:** | Arena Pharmaceuticals | | |

| | |
|---|---|
| **Approved By:** | [redacted] |
| **Position:** | VP, Biostatistics & Data Management |
| **Company:** | Arena Pharmaceuticals |

## Electronic Signature Manifestation

This page is a manifestation of the electronic signature(s) used in compliance with the organization's electronic signature policies and procedures.

| Signer Full Name | Meaning of Signature | Date and Time |
|---|---|---|
| [redacted] | Document Approval (I certify that I have the education, training and experience to perform this task) | 15 Jan 2021 23:37:46 UTC |
| | Document Approval (I certify that I have the education, training and experience to perform this task) | 21 Jan 2021 14:58:11 UTC |

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|---|---|---|---|
| **Author:** | [redacted] | | |
| **Position:** | Associate Director | | |
| **Company:** | IQVIA | | |

| | Name | Signature | Date |
|---|---|---|---|
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| **Company:** | Arena Pharmaceuticals | | |

| | |
|---|---|
| **Approved By:** | [redacted] |
| **Position:** | VP, Biostatistics & Data Management |
| **Company:** | Arena Pharmaceuticals |

# STATISTICAL ANALYSIS PLAN

## APD371-202

## 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

**AUTHOR:** [redacted]

**VERSION NUMBER AND DATE: 1.0 17MAY2021**

# STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

**Statistical Analysis Plan V1.0 (Dated 17MAY2021) for Protocol APD371-202 Amendment 3.**

| | Name | Signature | Date |
|---|---|---|---|
| **Author:** | [redacted] | | |
| **Position:** | Associate Director | | |
| **Company:** | IQVIA | | |
| | | | |

Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

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| **Approved By:** | [redacted] | | |
| **Position:** | Sr. Director | | |
| **Company:** | Arena Pharmaceuticals | | |
| | | | |
| **Approved By:** | [redacted] | | |
| **Position:** | VP, Biostatistics & Data Management | | |
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# TABLE OF CONTENTS

1. LIST OF ABBREVIATIONS ..... 8
2. INTRODUCTION ..... 11
3. STUDY OBJECTIVES ..... 11

3.1. Primary Objectives ..... 11

3.2. Exploratory Objectives ..... 11

4. STUDY DESIGN ..... 12

4.1. General Description ..... 12

4.2. Schedule of Events ..... 13

4.3. Changes to Analysis from Protocol ..... 13

5. PLANNED ANALYSES ..... 13

5.1. Final Analysis ..... 13

6. ANALYSIS SETS ..... 14

6.1. Enrolled Set ..... 14

6.2. Full Analysis Set [FAS] ..... 14

6.3. Safety Set ..... 14

7. GENERAL CONSIDERATIONS ..... 15

7.1. Reference Start Date and Study Day ..... 15

7.2. Baseline/Post-Baseline ..... 15

7.3. Retests, Unscheduled Visits and Early Termination Data ..... 16

7.4. Windowing Conventions ..... 16

7.5. Common Calculations ..... 18

7.6. General Study Information ..... 18

8. STATISTICAL CONSIDERATIONS ..... 18

8.1. Adjustments for Covariates and Factors to be Included in Analyses ....18

8.2. Multicenter Studies....18

8.3. Missing Data....19

8.4. Multiple Comparisons/ Multiplicity....19

8.5. Examination of Subgroups....19

9. OUTPUT PRESENTATIONS.... 19

10. DISPOSITION AND PROTOCOL DEVIATIONS.... 19

11. DEMOGRAPHICS AND BASELINE CHARACTERISTICS.... 20

11.1. Derivations ....21

12. MEDICAL HISTORY .... 21

13. CONCOMITANT MEDICAL CONDITIONS.... 21

14. MEDICATIONS.... 22

15. STUDY TREATMENT EXPOSURE .... 22

15.1. Derivations ....23

16. STUDY TREATMENT COMPLIANCE .... 23

16.1. Derivations ....23

17. EFFICACY OUTCOMES .... 24

17.1. Primary Efficacy....24

17.2. Secondary Efficacy ....24

17.3. Exploratory Efficacy ....24

[redacted]

[redacted]

**18. SAFETY OUTCOMES ..... 31**

**18.1. Adverse Events ..... 32**
18.1.1. All TEAEs ..... 32
18.1.2. Severity ..... 32
18.1.3. Relationship to Study Treatment ..... 33
18.1.4. TEAEs Leading to Discontinuation of Study Treatment ..... 33
18.1.5. Teaes Leading to Study Discontinuation ..... 33
18.1.6. Serious and Non-Serious Teaes ..... 34
18.1.7. Teaes Leading to Death ..... 34
18.1.8. Teaes Of Special Interest ..... 34
18.1.9. Overall Summary of Adverse Events ..... 34

**18.2. Deaths ..... 35**

**18.3. Laboratory Evaluations ..... 35**
18.3.1. Laboratory Reference Ranges and Markedly Abnormal Criteria ..... 35

**18.4. 12-lead ECG ..... 36**
18.4.1. 12-Lead ECG: Outlier and Morphology Analyses ..... 36

**18.5. Vital Signs ..... 37**
18.5.1. Vital Signs Specific Derivations ..... 38

**18.6. Physical Examination ..... 39**

**19. PHARMACOKINETICS ANALYSIS ..... 39**
**20. IMPACT OF COVID-19 ..... 39**
**21. GENETIC AND BIOMARKER ANALYSES ..... 39**
**22. DATA NOT SUMMARIZED OR PRESENTED ..... 39**
**23. REFERENCES ..... 40**
**24. APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS ..... 41**

**Output Conventions ..... 41**

**Decimals, Percentages, and P-values ..... 41**

**Dates & Times ..... 41**

**Spelling Format ..... 41**

**Presentation of Treatment Groups ..... 41**

**Presentation of Visits ..... 43**

Listings .....43

25. APPENDIX 2. PARTIAL DATE CONVENTIONS..... 44

Algorithm for Treatment Emergence of Adverse Events: .....44

Algorithm for Prior / Concomitant Medications: .....45

26. [redacted]

# 1. LIST OF ABBREVIATIONS

| Abbreviation | Meaning |
|---|---|
| AABS | average abdominal bloating score |
| AADS | average abdominal discomfort score |
| AAPS | average abdominal pain score |
| AE | adverse event |
| APS | abdominal pain score |
| ATC | Anatomical Therapeutic Chemical |
| ATC3 | Anatomical Therapeutic Chemical: Therapeutic (Level 3) |
| BM | bowel movement |
| BMI | body mass index |
| BP | blood pressure |
| CI | confidence interval |
| CM | concomitant medication |
| CS | clinically significant |
| CSBM | complete spontaneous bowel movement |
| CSR | clinical study report |
| DSMB | Data Safety Monitoring Board |
| ECG | electrocardiograms |
| eCRF | electronic case report form |
| EDC | electronic data capture |
| EQ-5D | European Quality of Life-5 |
| ET | early termination |
| FAS | Full Analysis Set |
| HADS | Hospital Anxiety and Depression Scale |
| HR | heart rate |
| IBS | irritable bowel syndrome |

| Abbreviation | Meaning |
|---|---|
| IBS-C | irritable bowel syndrome with predominant constipation |
| IBS-D | irritable bowel syndrome with predominant diarrhea |
| IBS-QoL | Irritable Bowel Syndrome-Quality of Life |
| IBS-SSS | Irritable Bowel Syndrome-Severity Scoring System |
| ICF | informed consent form |
| LTE | long-term extension |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NCS | not clinically significant |
| OC | observed cases |
| PCS | Potentially Clinically Significant |
| PGIC | Patient Global Impression of Change |
| PK | pharmacokinetic |
| PROMIS | Patient-Reported Outcomes Measurement Information System |
| PT | preferred term |
| SAE | serious adverse event |
| SAP | Statistical Analysis Plan |
| SBM | spontaneous bowel movement |
| SD | standard deviation |
| SI | International System of Units |
| SOC | System Organ Class |
| TEAE | treatment-emergent adverse event |
| TFL | table, figure, and listing |
| TID | 3 times per day |
| VAS | Visual Analog Scale |
| VS | vital signs |
| WHODD | World Health Organization Drug Dictionary |

| Abbreviation | Meaning |
|---|---|
| WK | week |

# 2. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analyses of efficacy, safety, and pharmacokinetic (PK) data for the Long-Term Extension (LTE) Period described in Protocol APD371-202. It describes the data to be summarized and analyzed, including specifics of the statistical methods to be implemented. This statistical analysis plan (SAP) is based on protocol version APD371-202 (Amendment 3, dated 03FEB2020). A separate analysis plan will describe the genetic and biomarker analyses.

The table, figure and listing (TFL) shells are prepared in a separate file based on this analysis plan. Upon approval of the SAP, some updates (including but not limited to titles, footnotes, headings and re-numbering of tables, etc.) on TFL shells are allowed without a SAP amendment as long as the updates within TFL shells do not conflict with the contents of the SAP.

# 3. STUDY OBJECTIVES

## 3.1. PRIMARY OBJECTIVES

The primary objective is:

- To evaluate the safety and tolerability of long-term administration of olorinab in subjects with irritable bowel syndrome (IBS)

## 3.2. EXPLORATORY OBJECTIVES

The exploratory objectives are:

- To measure the population PK ($C_{trough}$) of olorinab and its predominant metabolites [redacted] and [redacted] in subjects with IBS during long-term administration of olorinab
- To evaluate the efficacy of long-term administration of olorinab in subjects with IBS

# 4. STUDY DESIGN

## 4.1. GENERAL DESCRIPTION

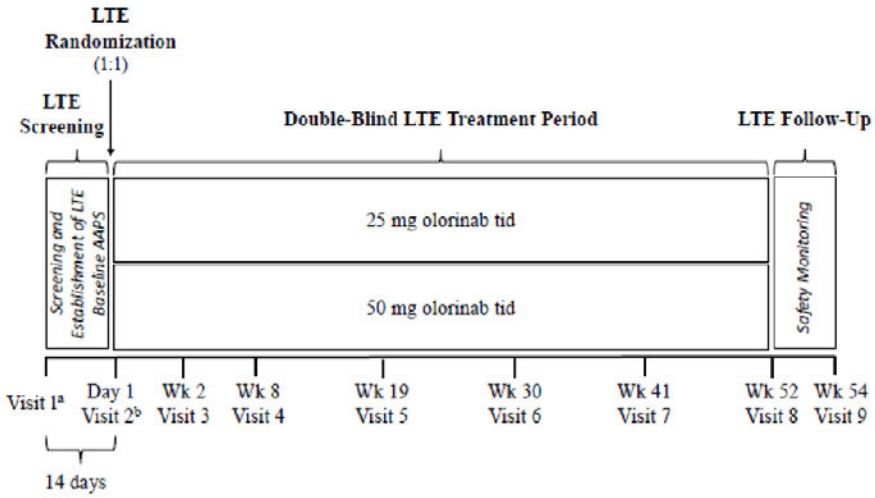
The LTE is an optional extension period that is designed to assess the safety, tolerability, population PK ($C_{trough}$), and efficacy of long-term administration of olorinab in subjects who have completed the Main Study. The LTE will be conducted at the same study sites as the Main Study. Subjects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

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.

*Figure 1: Schematic Diagram of Long-Term Extension Design*




Abbreviations: 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.

## 4.2. SCHEDULE OF EVENTS

Schedule of events can be found in Appendix 1 of the protocol.

## 4.3. CHANGES TO ANALYSIS FROM PROTOCOL

After completing the analysis for the Main Study Period, the decision was made to terminate the study early and end the LTE for all subjects. Analyses for the LTE will reflect all data collected until the study is terminated. Population PK endpoints, $C_{trough}$ of olorinab and its primary metabolites, will not be included in this SAP. Removal of PK exhibits (TFLs) was agreed upon on 01APR2021.

# 5. PLANNED ANALYSES

The following analyses will be performed for this study:

- Final Analysis of the LTE Study

## 5.1. FINAL ANALYSIS

All final, planned analyses identified in this SAP will be performed following Sponsor Authorization of this SAP, Database Lock, Sponsor Authorization of Analysis Sets and

Unblinding of Treatment. PK analysis datasets will be created but no formal PK tables, figures or listings will be produced.

After all subjects have completed or terminated the LTE, outstanding data queries have been resolved/closed, the data have been cleaned and finalized, and the database is locked, the Sponsor will authorize breaking of the study blind and the final analysis of the data will be performed. The SAP must be approved and signed by the Sponsor before the database is locked and treatment assignment unblinded.

Any post-hoc, exploratory analyses completed to support planned study analyses, which were not identified in the SAP, will be documented and reported in the clinical study report. Any results from these unplanned analyses will also be clearly identified in the text of the clinical study report.

# 6. ANALYSIS SETS

Agreement and authorization of subjects included/excluded from each analysis set will be conducted prior to the unblinding of the study. A summary of analysis sets will be presented.

## 6.1. ENROLLED SET

The enrolled set will include all subjects who signed the ICF for LTE.

## 6.2. FULL ANALYSIS SET [FAS]

The full analysis set (FAS) will include all randomized subjects in LTE, irrespective of whether they received study treatment. Subjects will be classified according to randomized treatment.

## 6.3. SAFETY SET

The safety set will include all subjects who received at least one dose of study treatment. Subjects will be classified according to actual treatment received. If there is any doubt whether a subject was treated or not, they will be assumed treated by the randomized treatment for the purposes of analysis.

# 7. GENERAL CONSIDERATIONS

## 7.1. REFERENCE START DATE AND STUDY DAY

Study Day will be calculated from the reference start date and will be used to show start/stop day of assessments and events. Reference start date is defined as Day 1, the date of LTE randomization (Day 1 is the day of the first dose of LTE study treatment) and will appear in every listing where an assessment date or event date appears.

- If the date of the event is on or after the reference date then:
  Study day = (date of event – reference date) + 1
- If the date of the event is prior to the reference date then:
  Study day = (date of event – reference date)

In the situation where the event date is partial or missing, Study Day, and any corresponding durations will appear as missing in the listings. In the situation where the subject is randomized but not treated, the reference date is defined as the LTE baseline visit date.

## 7.2. BASELINE/POST-BASELINE

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to the reference start date. If measurements include time, the date/time will be used to define baseline; where time is not fully populated in the reference start date and fully populated in the measurement date, missing time values will be imputed to the earliest possible time measurement. Otherwise, only dates will be compared. In the case where the last non-missing measurement and the reference start date coincide and time is not collected, the measurement will be considered a baseline record, but adverse events (AEs) and medications commencing on the reference start date will be considered post-baseline records. For subjects randomized but not treated, baseline is defined as the last non-missing measurement taken on or before the baseline visit date.

Main study baseline AAPS is defined as the average abdominal pain score (APS) over the main study Run-in Period preceding Visit 3. The detailed derivation can be found in the approved SAP for the Main Study.

LTE baseline AAPS is defined separately for continuing subjects and gap subjects. LTE baseline AAPS for continuing subjects is calculated using the Week 14 visit from the Main Study. Gap subject LTE baseline AAPS is calculated by taking the average value over the

window of 7 days prior to Day 1 in LTE.

Post-baseline weekly AAPS by scheduled visit is calculated by taking the average value over the window of 7 days prior to and including the scheduled visit day if the endpoint is recorded for at least 4 of the 7 days in the window. If APS values are missing for more than 3 days in the 7-day window, the average value for the AAPS by scheduled visit will be reported as missing.

For other continuous endpoints collected in the Daily Diary form (e.g., bloating, discomfort, and number of bowel movements), baseline and post-baseline will be derived in the same manner.

## 7.3. RETESTS, UNSCHEDULED VISITS AND EARLY TERMINATION DATA

For by-visit analyses and summaries of efficacy and safety, data (including scheduled, retests, unscheduled, and early termination) will be assigned to visits after the application of the windowing conventions described in Section 7.4. All measurements will be considered in summaries of abnormalities or worst-case values post-baseline.

In the case of a retest (same visit number assigned), the measurement nearest to the visit date will be used for by-visit summaries. In the case of several measurements equally close to the visit date, the earliest non-missing measurement will be taken. If multiple assessments are available on the same day, then the average of the assessment will be used in the analysis except for laboratory and ECG data, where the assessment at the earliest time of the same day will be used. If both central and local assessments of the same laboratory test are available on the same day, the central assessment will take precedence over the local assessment. Listings will include scheduled, unscheduled, retest and early discontinuation data.

## 7.4. WINDOWING CONVENTIONS

All scheduled study visits are defined relative to Study Day 1, the date of randomization and first dose of study treatment. Scheduled visit windows are defined in Appendix 1 of the protocol. A windowing convention will be used to determine the analysis visit value for a given measurement and will be applicable for all by-visit summaries and analyses for efficacy and safety data. The early discontinuation visits and unscheduled visits will be

eligible for allocation to an analysis visit. The 2-week follow-up visit will be summarized separately. [redacted] displays the specific visit windows used for the FAS and Safety Set populations for efficacy and safety analysis. See [redacted]. Additional Visit Windows for additional visit windows.

Windowing will be applied to the data prior to any missing data calculations. If one or more results for a variable are assigned to the same analysis visit, the result with the date closest to the protocol scheduled day will be used in the analysis. If two measurements in the same analysis visit window are equally close to the protocol scheduled study day, the earliest measurement will be used in the analysis. For ePRO measurements (PROMIS, EQ-5D, etc.), the stamp date in the device will be used to calculate the study day, and Day 1 will include those ePROs collected on the date of Randomization.

[redacted]

## 7.5. COMMON CALCULATIONS

For quantitative measurements:

- Change from main study baseline = (Test Value at Visit X – Main Study Baseline Value)
- Percent change from main study baseline = ((Test Value at Visit X – Main Study Baseline Value) / Main Study Baseline Value) x 100
- Change from LTE baseline = (Test Value at Visit X – LTE Baseline Value)
- Percent change from LTE baseline = ((Test Value at Visit X – LTE Baseline Value) / LTE Baseline Value) x 100
- Proportion at Visit X = (Number of subjects satisfying criteria at Visit X / Total number of subjects at Visit X)
- Proportion achieving an improvement from Visit X to Visit Y = (Number of subjects achieving an improvement from Visit X to Visit Y / Total number of subjects with non-missing data for that parameter at both Visit X and Visit Y)

## 7.6. GENERAL STUDY INFORMATION

All analyses will be conducted using SAS® (version 9.4 or later, SAS Institute Inc., Cary, NC).

A general table with summary of study information will be generated, including date first subject signed ICF, last subject last visit date, database lock date and versions of the Medical Dictionary for Regulatory Activities (MedDRA), World Health Organization Drug Dictionary Global (Enhanced w/WHO Herbal Dictionary) (WHODD), and SAS etc.

# 8. STATISTICAL CONSIDERATIONS

## 8.1. ADJUSTMENTS FOR COVARIATES AND FACTORS TO BE INCLUDED IN ANALYSES

No formal analyses with statistical tests between treatments will be conducted. Summary statistics will be presented for all analyses.

## 8.2. MULTICENTER STUDIES

This study will be conducted by multiple investigators at multiple investigational sites within the United States. Subjects who received placebo or Olorinab 10 mg in the Main Study will

be re-randomized (1:1) to receive either Olorinab 25 mg or Olorinab 50 mg. Subjects who received Olorinab 25 mg or Olorinab 50 mg in the Main Study will continue to receive the same dose. Data from all sites will be pooled and summary analyses will not be adjusted for investigational site or geographic region. Ad-hoc analyses may be conducted by site or by pooling sites.

## 8.3. MISSING DATA

Missing safety data will generally not be imputed, with the exceptions of AE relationship to study treatment (as described in Section 18.1.3), partial or missing AE start dates, and Concomitant Medication (CM) start dates. Details about date imputations are described in Appendix 2. Partial Date Conventions. No other missing safety data will be imputed.

## 8.4. MULTIPLE COMPARISONS/ MULTIPLICITY

Not applicable as no formal statistical comparisons between treatments are planned.

## 8.5. EXAMINATION OF SUBGROUPS

No subgroup analysis is planned for this study.

# 9. OUTPUT PRESENTATIONS

Appendix 1. Programming Conventions for Outputs shows conventions for presentation of data in outputs. The templates provided with this SAP describe the presentations for this study and therefore the format and content of the summary tables, figures, and listings to be provided for the clinical study report.

# 10. DISPOSITION AND PROTOCOL DEVIATIONS

All subjects who provide informed consent will be accounted for in this study.

Subject disposition and withdrawals will be provided for the FAS. This summary will note subjects who complete the Week 52 visit (end of treatment) as well as subjects who complete the Week 54 visit (end of study). An analysis set listing will also be provided. Inclusion and exclusion criteria will be presented for the screened set. A summary and listing of screen failures and reason for screen failure will be presented for the screened set.

Protocol deviations will be displayed for the FAS. Deviations will be categorized as Critical/Major or Minor. Critical/major deviations will be summarized by treatment as denoted in the Presentation of Treatment Groups in Appendix 1 for the following categories as described in the Protocol Deviation and Classification Guidance document. All critical/major deviations will also be listed.

- Informed Consent Criteria
- Eligibility and Entry Criteria
- Concomitant Medication Criteria
- Laboratory Assessment Criteria
- Study Procedures Criteria
- SAE Criteria
- Randomization Criteria
- Visit Schedule Criteria
- Investigational Product Compliance
- Efficacy Criteria
- Administrative Criteria
- Source Document Criteria
- Regulatory or Ethics Approvals Criteria
- Other Criteria

A summary of protocol deviations related to COVID-19 will also be presented, as well as a listing of subjects with study conduct impacted by COVID-19.

# 11. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Demographics and baseline characteristics data will be presented for the FAS and Safety Set. The data will be summarized by treatment as denoted in the Presentation of Treatment Groups in Appendix 1 without statistical testing. The following demographic and baseline characteristics will be reported for this study:

- Age on consent (years)
- Sex at birth: Female and Male
- Child-bearing potential for women: Yes, No
- Race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islanders, Multiple, White, Not Reported
- Race group: White, Non-White, Not Reported
- Ethnicity: Hispanic or Latino, Non-Hispanic or Latino, Not Reported, Unknown

- Weight (kg)
- Height (cm)
- BMI (kg/m$^2$)
- [redacted]
- Time since IBS diagnosis (years) – calculated relative to date of randomization in Main Study
- IBS subtype: IBS-C, IBS-D
- Main Study eDiary Compliance Rate (%)
- Main Study Baseline AAPS
- Main Study Baseline AAPS Category: (< 7, ≥7)
- LTE Baseline AAPS
- LTE Baseline AAPS Category: (< 7, ≥7)
- [redacted]

## 11.1. DERIVATIONS

- BMI (kg/ m$^2$) = weight (kg)/ height (m)$^2$
- Time since IBS diagnosis (years) = (date of randomization in the Main Study – date of IBS diagnosis + 1) / 365.25
  - Partial dates are imputed to the earliest possible date
- Weight (kg) = Weight (lb) * 0.4536
- Height (cm) = Height (in) * 2.54
- Height (m) = Height (in) * 0.0254 = Height (cm) * 0.01

# 12. MEDICAL HISTORY

Medical History conditions are defined as those conditions which stop prior to the first dose of study treatment in the LTE. Medical History will be collected on the Medical History eCRF and coded using MedDRA (version 23.0 or higher). Medical History will be summarized for the Safety Set by system organ class (SOC) and preferred term (PT).

# 13. CONCOMITANT MEDICAL CONDITIONS

Concomitant medical conditions are conditions (other than the indication being studied) which started prior to or on the date of the first dose of LTE study treatment and are ongoing

at the date of the first dose of LTE study treatment. Concomitant medical conditions will be captured on the Medical History eCRF page and coded using MedDRA version 23.0 or higher. Concomitant medical conditions will be summarized for the Safety Set by SOC and PT.

# 14. MEDICATIONS

Medications will be collected on the Prior or Concomitant Medications eCRF and coded using WHODD version 01Mar2020 or higher.

The prior and concomitant medications are defined below. See Appendix 2. Partial Date Conventions for handling of partial dates for medications. In the case where it is not possible to define a medication as prior or concomitant, the medication will be classified by the worst case, i.e., concomitant.

- 'Prior' medications are medications which started after or were ongoing during the last dose of main study treatment and stopped prior to the first dose of LTE study treatment.
- 'Concomitant' medications are medications which started prior to, on or after the first dose of LTE study treatment and continued into the LTE period.

Prior and concomitant medications will be summarized separately by ATC Level 3 and Preferred Drug name for the Safety set. In addition, prior and concomitant medications related to IBS will be summarized.

# 15. STUDY TREATMENT EXPOSURE

The date of first dose will be taken from the LTE Day 1 "On Site Dosing Administration" form, and the date of last dose will be taken from the LTE "End of Study" form. Interruptions, compliance, and dose changes are not taken into account for duration of exposure. Study duration and treatment duration will be summarized as continuous variables for each treatment as denoted in the Presentation of Treatment Groups in Appendix 1 using descriptive statistics. The duration of treatment will also be summarized categorically: ≤ 4, > 4 – 8, > 8 – 12, > 12 – 20, > 20 – 28, > 28 – 36, > 36 – 44, and > 44 weeks. Additionally, the total subject-years of exposure and subject-years on study will be included in the summary.

Number of tablets taken, missed, and frequency and percentage of subjects who missed at least one dose or who had at least one dose interruptions recorded on the Dosing Administration eCRF will also be summarized. Treatment compliance will also be summarized using both descriptive statistics and summarized categorically: < 85%, ≥ 85 to ≤ 115%, and > 115%.

## 15.1. DERIVATIONS

- Study Duration (days) = date of last study visit – date of LTE Day 1 visit + 1
- Treatment duration (days) = date of last LTE study treatment administration – date of first LTE study treatment administration + 1
- Treatment duration (weeks) = (date of last LTE study treatment administration – date of first LTE study treatment administration + 1)/7.
- Total subject-years on study = sum of duration of time on study across all subjects divided by 365.25
- Total subject-years of exposure = sum of duration of treatment exposure across all subjects divided by 365.25

# 16. STUDY TREATMENT COMPLIANCE

Compliance with study treatment will be summarized for the Safety Set. Total number of tablets expected, total number of tablets taken, total number of tablets missed, overall compliance with study treatment, frequency and percentage with overall compliance with the following categories: <85%, ≥85% to ≤115%, and >115%. By-visit compliance will also be summarized.

Subjects with administration compliance greater than 115% and subjects who do not return any study treatment or study packaging will be asked for the reason for the overcompliance or missing study treatment. Their responses will be recorded on the Drug Accountability eCRF and will be listed.

## 16.1. DERIVATIONS

Compliance to study treatment is based on the Drug Accountability eCRF and will be calculated as the number of capsules/tablets taken (total dispensed – total returned) divided by the prescribed number of capsules/tablets, expressed as a percentage (see calculations below).

The study treatment is given three times daily (tid), and it is assumed that the subject should take study treatment from the morning of the visit day at which their treatment is initially dispensed to the evening before their last treatment return date, as subjects are advised to wait to take their dose at the study site until all assessments and procedures have been completed on study days. For example, if the initial dispensation date is Day 1 and the last return date is Day 387, then the subject should have taken 3 capsules/tablets each day on

Days 1 to 386; hence, the total number of prescribed capsules would be 386×3 = 1,158. Multiple bottles may be dispensed at one visit; in these cases, "Per Visit" compliance will be non-missing if at least one bottle is returned.

- "Per Visit" Compliance to study treatment at Visit X will be calculated as follows:

$$\frac{([\text{N of Tablets dispensed at Visit (X)}] - [\text{N of Tablets returned at Visit (X+1)}])}{\{\,[\text{Date of Visit (X+1)}] - [\text{Date of Dispensing at Visit (X)}]\,\}\times 3} \times 100$$

- Overall Compliance to study treatment will be calculated as follows:

$$\frac{\begin{array}{c}\{([\text{N of Tablets dispensed at Visit 1}] - [\text{N of Tablets returned at Visit 2}]) \\ +\cdots+ \\ ([\text{N of Tablets dispensed at Visit (X}-1)] - [\text{N of Tablets returned at Visit X}])\}\end{array}}{[\text{Date of Visit X}] - [\text{Date of Dispensing at Visit 1}]\times 3} \times 100$$

For subjects who permanently stop the study treatment before Week 52, the "Date of Visit X" in Overall Compliance calculations will be replaced by the date of study withdrawal.

# 17. EFFICACY OUTCOMES

## 17.1. PRIMARY EFFICACY

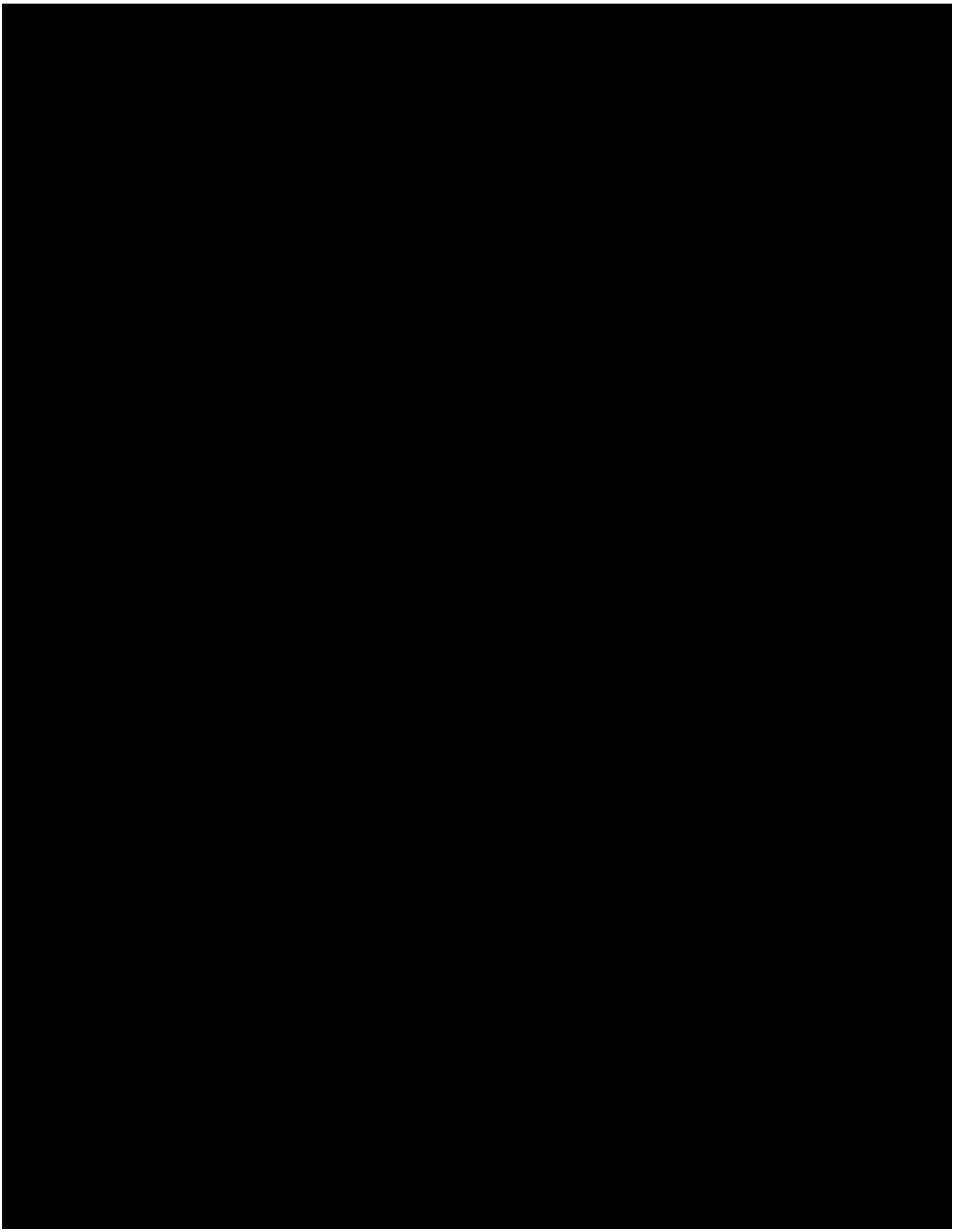
Not applicable. No primary efficacy analysis was conducted for the LTE.

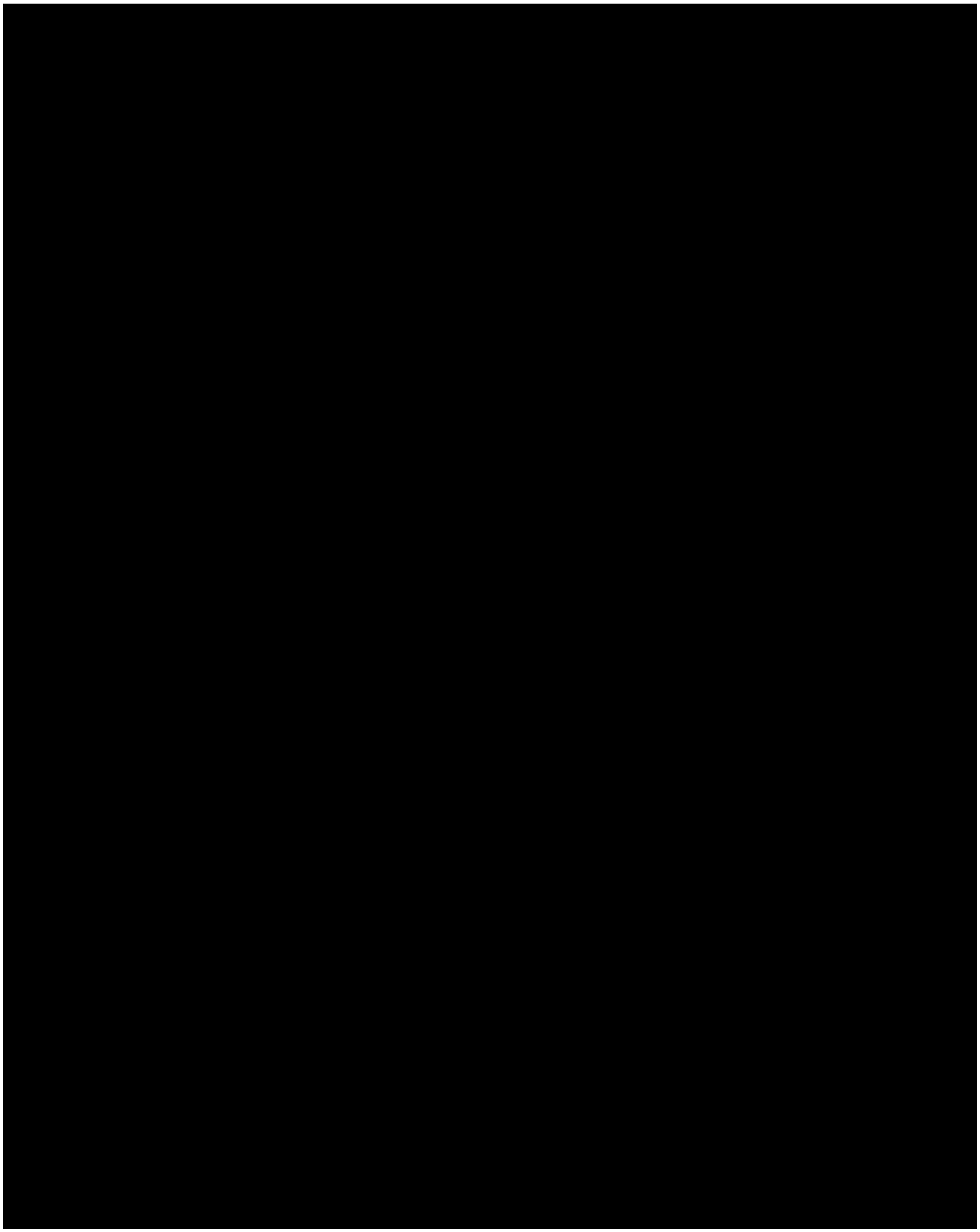
## 17.2. SECONDARY EFFICACY

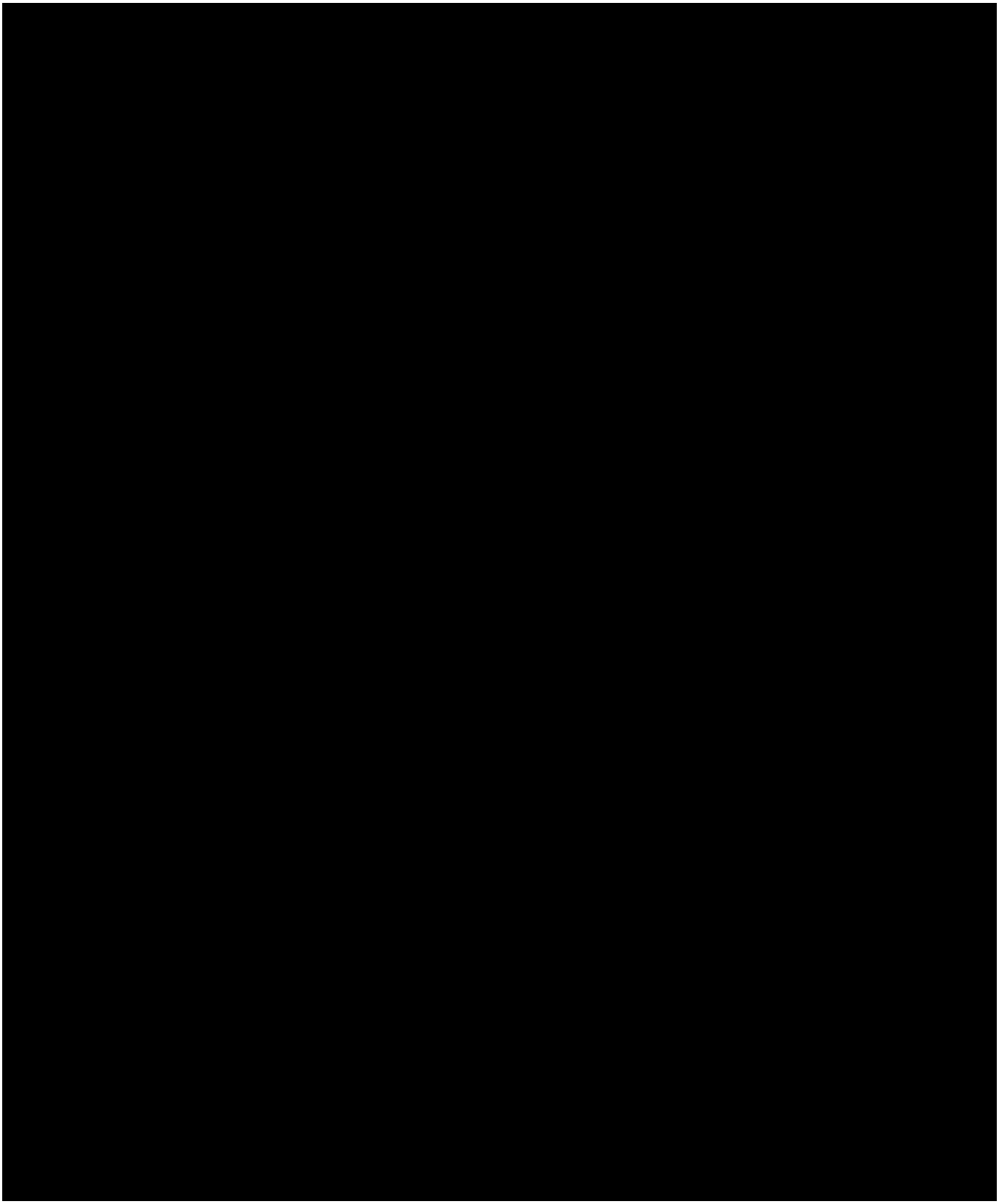
Not applicable. No secondary efficacy analysis was conducted for the LTE.

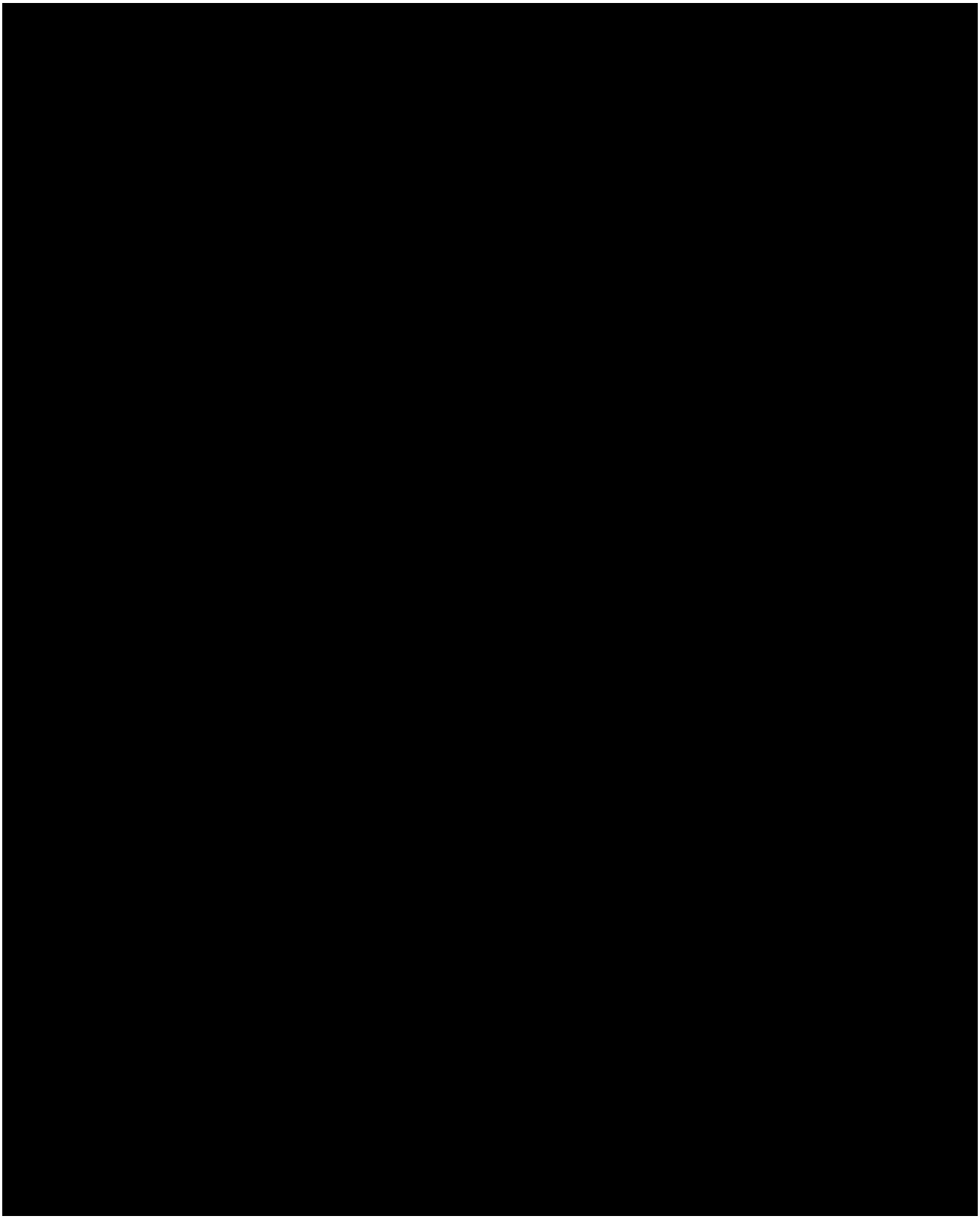
## 17.3. EXPLORATORY EFFICACY

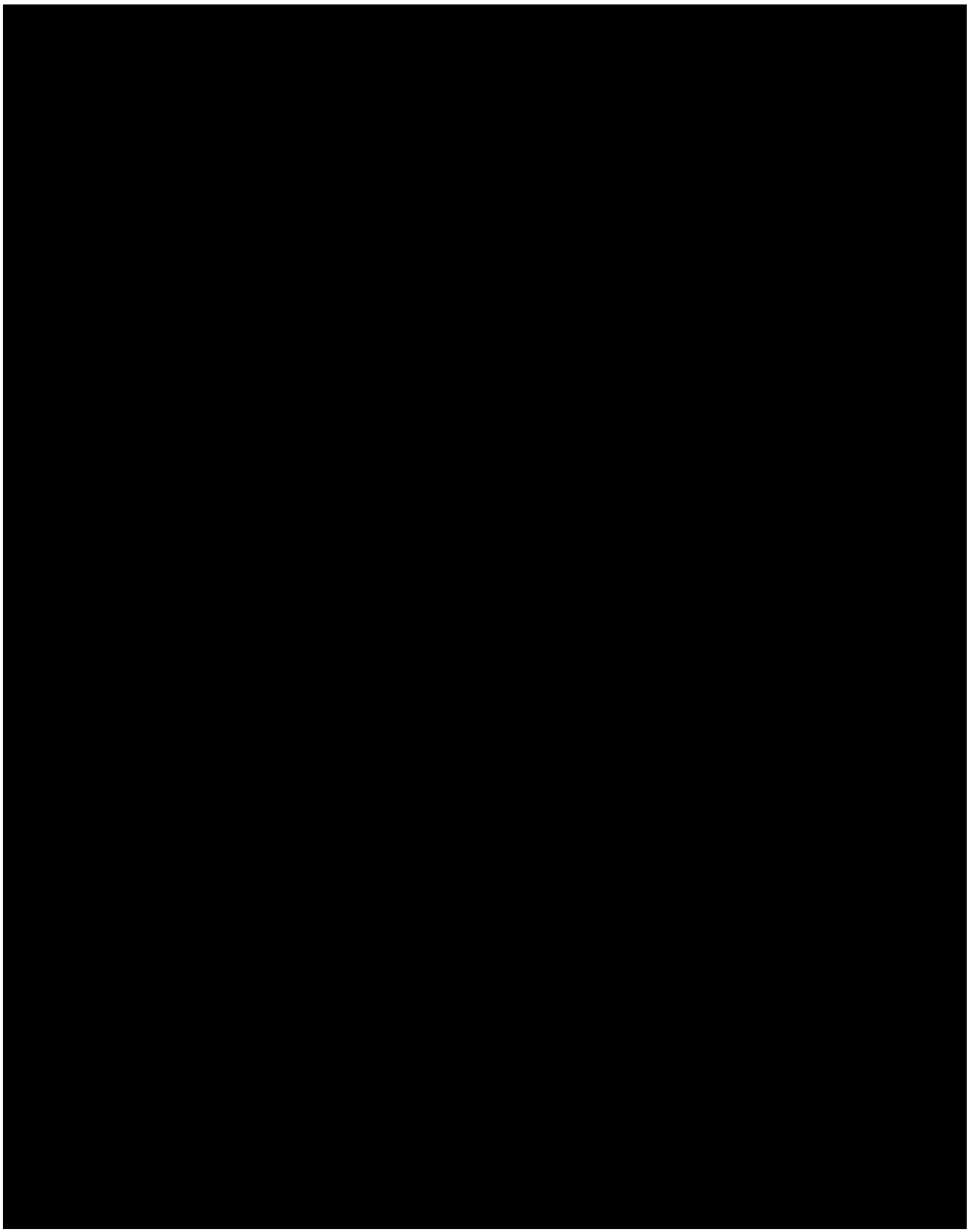
[redacted]

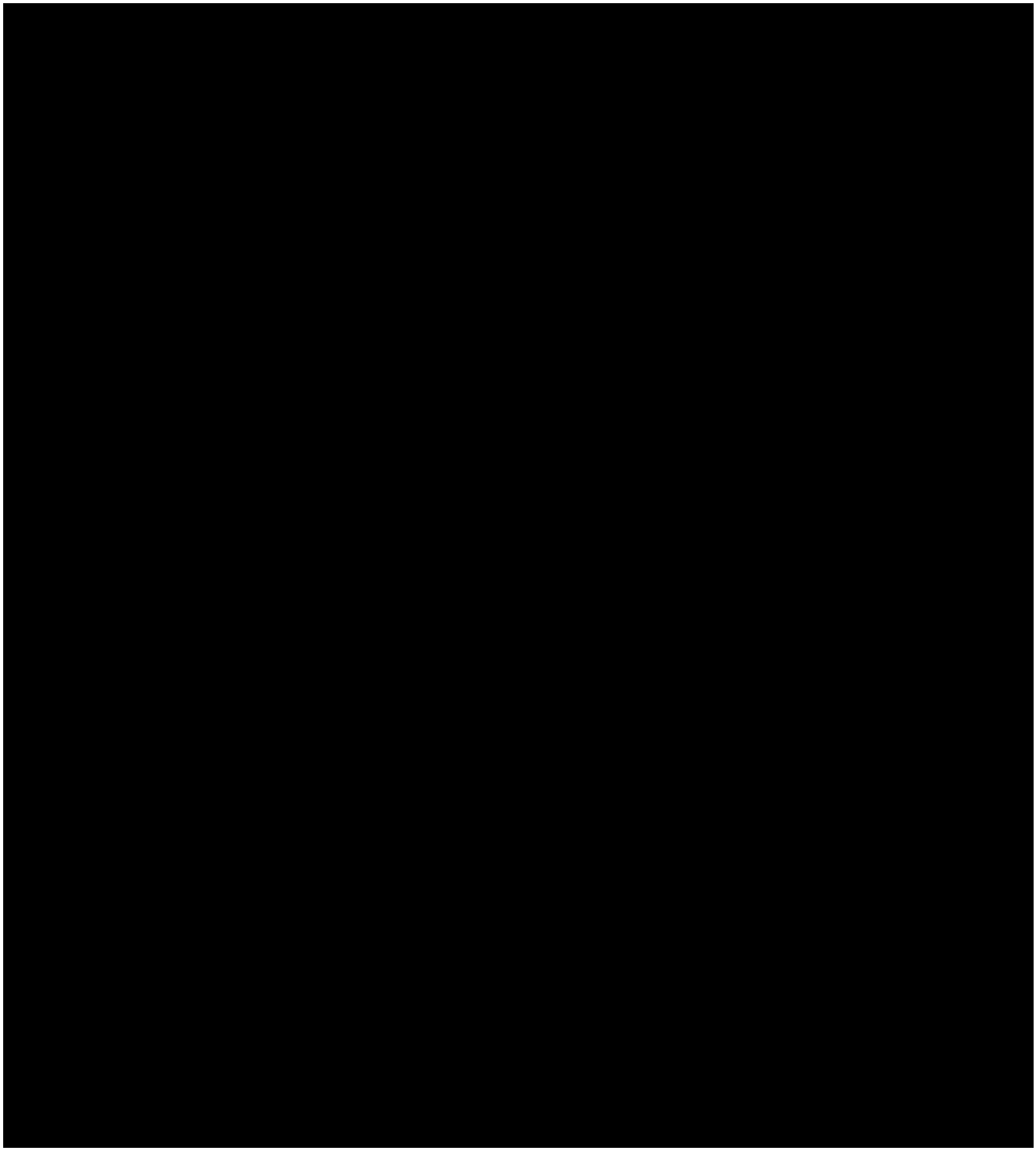












# 18. SAFETY OUTCOMES

All analyses for safety outcomes will be based on the safety analysis set. All safety data will be listed and summarized by actual treatment group. There will be no statistical comparisons

between the treatments for safety data, unless otherwise specified. Unless otherwise stated, exhibits will be displayed by treatment as denoted in the Presentation of Treatment Groups in Appendix 1.

## 18.1. ADVERSE EVENTS

AEs will be coded using MedDRA central coding dictionary, Version 23.0 or higher. New treatment-emergent adverse events (TEAEs) in LTE are defined as:

- An AE that occurs after the first dose of LTE study treatment that was not present before the dosing, OR
- An AE that increases in severity after the first dose of LTE study treatment if the event was present before the dosing treatment.

All TEAEs will be coded and summarized by system organ class (SOC) and preferred term (PT) and will be presented by descending order of frequency. AEs occurring before the first dose of study treatment will be summarized separately from new TEAEs occurring in the LTE. Listings will include all AEs (TEAEs and Non-TEAEs).

See Appendix 2. Partial Date Conventions for handling of partial dates for AEs for the purpose of assigning treatment-emergent flags. In the case where it is not possible to define an AE as treatment-emergent or not, the AE will be classified by the worst case, i.e. treatment emergent.

### 18.1.1. ALL TEAES

All TEAEs will be summarized by SOC and PT and by treatment as denoted in the Presentation of Treatment Groups in Appendix 1 and presented by descending order of frequency in any treatment. TEAEs will also be summarized by maximum severity and relationship to study treatment. A separate summary of related TEAEs and related TEAEs by maximum severity will also be provided.

### 18.1.2. SEVERITY

Severity is classified by grade using the Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0) system as defined below. The CTCAE grade will be assessed by a nurse and/or physician and will be recorded in the AE severity Section on the Adverse Events eCRF.

**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 (e.g., 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.

TEAEs with a missing severity but identified as a life-threatening serious adverse event (SAE) or one requiring initial or prolonged hospitalization will be classified as Grade 4 (Potentially Life-threatening), otherwise missing severity will be classified as Grade 3 (severe). If a subject reports a TEAE more than once within that SOC/ PT, the AE with the greatest severity will be used in the corresponding severity summaries.

### 18.1.3. Relationship to Study Treatment

Relationship is classed as “not related”, “unlikely related”, “probably related”, or “related” (increasing severity of relationship) by the Investigator. A “related” TEAE for the purpose of TEAE summaries is defined as a TEAE with a relationship to study treatment as “related” or “probably related” to study treatment. TEAEs with a missing relationship to study treatment will be regarded as “related” to study treatment. “Unlikely related” will be counted as non-related TEAE. If a subject reports the same AE more than once within the same SOC/ PT, the AE with the strictest causality will be used in the corresponding relationship summaries. All TEAEs will be summarized by SOC, PT, and relationship to study treatment.

### 18.1.4. TEAEs Leading to Discontinuation of Study Treatment

TEAEs leading to permanent discontinuation of study treatment will be identified by action taken being recorded as “Drug withdrawal” on the AE page of the eCRF. All TEAEs leading to discontinuation of study treatment will be summarized by SOC and PT. A listing of all TEAEs leading to discontinuation of study treatment will also be presented.

### 18.1.5. TEAEs Leading to Study Discontinuation

TEAEs leading to study discontinuation will be noted on the End of Study eCRF. All TEAEs

leading to study discontinuation will be summarized by SOC and PT.

### 18.1.6. SERIOUS AND NON-SERIOUS TEAES

Serious adverse events (SAEs) are those events recorded as "Serious" on the Adverse Events page of the eCRF. All serious TEAEs will be summarized by SOC and PT. All non-serious TEAEs will also be summarized by SOC and PT. A serious AE listing will also be presented.

### 18.1.7. TEAES LEADING TO DEATH

TEAEs leading to Death are those events which are recorded as "Fatal" on the Adverse Events page of the eCRF. A summary of TEAEs leading to death by SOC and PT will be prepared by treatment.

### 18.1.8. TEAES OF SPECIAL INTEREST

To date, no AEs of special interest have been identified related to olorinab. Potential AEs of special interest may be identified by clinical or medical reviewers. In addition to appropriate reporting of these events as an AE or SAE, supplementary detailed information may be collected. Any identified AEs of special interest will be summarized by SOC and PT separately. A listing will also be provided.

### 18.1.9. OVERALL SUMMARY OF ADVERSE EVENTS

In addition to the summaries by SOC and PT as described in Sections 18.1.1 to 18.1.5, an overview of TEAEs will be summarized (not broken down by SOC or PT) by number and frequency of subjects and by number of AEs by treatment:

- Any AE (including non-TEAEs)
- Any TEAE
- Any related TEAE
- TEAEs by maximum severity
- Related TEAEs by maximum severity
- TEAEs by relationship to study treatment
- TEAEs leading to study treatment discontinuation
- TEAEs leading to study treatment interruption
- TEAEs leading to study discontinuation
- Related TEAEs leading to study treatment discontinuation
- Related TEAEs leading to study treatment interruption

- Related TEAEs leading to study discontinuation

## 18.2. DEATHS

For any reports of death during the study as recorded on the End of Study page of the eCRF, the information will be presented in a listing.

## 18.3. LABORATORY EVALUATIONS

Results from the central laboratory will be included in the reporting of this study for chemistry, hematology, coagulation, urinalysis, thyroid chemistry, celiac, and virology. pregnancy. A list of laboratory assessments to be included in the outputs is included in Table 3 in the protocol. If local and central laboratory assessments are available from the same day, central laboratory assessments will be used in the analysis.

Presentations will use SI Units. Quantitative laboratory measurements reported as "< X", i.e. below the lower limit of quantification (BLQ), or "> X", i.e. above the upper limit of quantification (ULQ), will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the listings.

Laboratory parameters such as hepatic enzymes, renal function and hematology values will be grouped and presented together. The following summaries will be provided for laboratory data:

- Value and change from LTE baseline by visit (for quantitative measurements)
- Incidence of abnormal values according to laboratory reference ranges by visit
- Shift from LTE baseline to end of treatment according to laboratory reference range (for quantitative measurements and categorical measurements)
- Summary of subjects with treatment-emergent abnormal lab results
- Listing of subject's laboratory assessments at all timepoints. Values outside of the central laboratory reference range will be flagged. Values obtained from local laboratory will be flagged.

### 18.3.1. LABORATORY REFERENCE RANGES AND MARKEDLY ABNORMAL CRITERIA

Quantitative laboratory measurements will be compared with the relevant laboratory reference ranges in SI units and categorized as:

- Low: Below the lower limit of the laboratory reference range.

- Normal: Within the laboratory reference range (upper and lower limit included).
- High: Above the upper limit of the laboratory reference range.
- Treatment-emergent high result: a change from a value less than or equal to the high limit at all baseline visits to a value greater than the high limit at any time during the treatment period.
- Treatment-emergent low result: a change from a value greater than or equal to the low limit at all baseline visits to a value less than the low limit at any time during the treament period.

## 18.4. 12-LEAD ECG

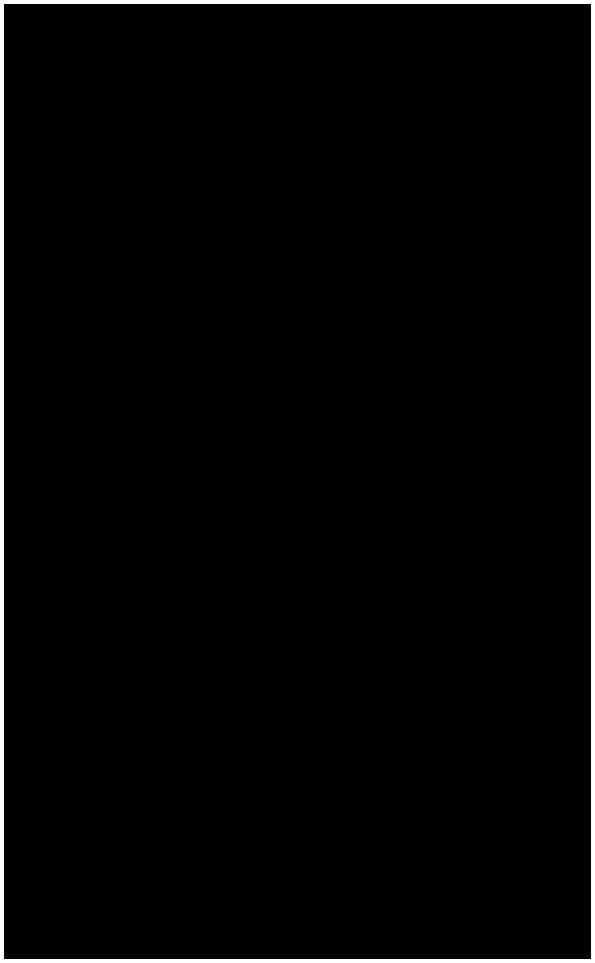
Results from the central 12-lead ECG Reading Centre will be included in the reporting of this study. The ECGs will be read and interpreted by the central ECG laboratory. At all scheduled visits, ECGs were collected once per visit, prior to administration of the first daily dose of study treatment.

The following ECG parameters will be reported for this study on the central read for each safety ECG:

- PR Interval (msec)
- QRS Interval (msec)
- QT Interval (msec)
- QTcF Interval (msec) [derived]
- QTcB Interval (msec) [derived, optional]
- Heart Rate (HR) (bpm)
- Overall interpretation of ECG (Investigator's judgment):
    - Normal
    - Abnormal, Not Clinically Significant (Abnormal NCS)
    - Abnormal, Clinically Significant (Abnormal CS)

The following summaries will be provided by treatment group for ECG data:

- Value by visit (for quantitative measurements)



## 18.5. VITAL SIGNS

Orthostatic vital signs (VS) include the collection of blood pressure (BP) and HR after the subject has been resting in the supine position for at least 5 minutes and then again after 1 and 3 minutes of standing. For gap subjects, orthostatic VS were collected at the screening and for continuing subjects, orthostatic VS were collected at the main study Week 14 visit. Screening orthostatic vital signs will be included in data listings of vital signs.

For all other visits, supine vital signs were collected once per visit, prior to administration of the first daily dose of study treatment.

Baseline VS is defined as the supine VS collected prior to or on the date of the administration of the first daily dose of LTE study treatment on Day 1.

The following VS data will be summarized using descriptive statistics by treatment group as denoted in the Presentation of Treatment Groups in Appendix 1.

- The actual measurement values of vital signs at each visit/timepoint
- Change from LTE baseline: calculated as post-baseline values minus the VS baseline value.

Body temperature and respiratory rate were collected once per visit, prior to the administration of the first daily dose of study treatment (for visits occurring during the Treatment Period).

Vital sign values meeting the criteria as defined in

Table 2 below will be categorized as potentially clinically significant (PCS) findings. These findings will be summarized with frequency count and percentage for each treatment as well as for the active treatments pooled, both overall and by scheduled visit. The summaries and counts will be presented at both the subject level (counting subjects with PCS findings) and event level (counting all PCS events).

**Table 2: Vital Sign PCS Criteria**

| Parameter | PCS Category | PCS Criteria |
|---|---|---|
| Systolic BP (mm Hg) | High | ≥ 140 Supine and Supine increase from baseline ≥ 20 |
| | Low | ≤ 90 Supine and Supine decrease from baseline ≥ 20 |
| Diastolic BP (mm Hg) | High | ≥ 90 Supine and Supine increase from baseline ≥ 15 |
| | Low | < 40 Supine and Supine decrease from baseline ≥ 15 |
| Pulse Rate (bpm) | High | ≥ 100 Supine |
| | Low | < 40 Supine |
| Respiratory Rate (brpm) | High | ≥ 28 |
| | Low | ≤ 8 |
| Temperature (°C) | High | > 38 |
| | Low | < 35 |

Abbreviation: bpm = beats per minute; BP = blood pressure; brpm = breaths per minute; PCS = potentially clinically significant

### 18.5.1. VITAL SIGNS SPECIFIC DERIVATIONS

- Temperature ($^0$C) = (5/9) (Temperature ($^0$F) – 32)

## 18.6. PHYSICAL EXAMINATION

All physical examination assessments will be listed.

# 19. PHARMACOKINETICS ANALYSIS

Pharmacokinetic analyses may be completed by Sponsor and will be described in a separate analysis plan if needed.

# 20. IMPACT OF COVID-19

The study has been closely monitored during the period of COVID-19 and the impact of COVID-19 on data analyses is minimal. The below analyses related to COVID-19 are planned to document any impacts of the pandemic. Post hoc exploratory data analyses may be planned after database lock if the data warrants the request.

- Summary of major protocol deviations caused by COVID-19
- A listing of any adverse events related to COVID-19
- A listing of any subjects with phone or remote visits due to COVID-19.

# 21. GENETIC AND BIOMARKER ANALYSES

Genetic and biomarker analyses will be completed by Sponsor and will be described in a separate analysis plan if needed.

# 22. DATA NOT SUMMARIZED OR PRESENTED

The other variables and/or domains not summarized or presented are:

- Comments
- Meals (Day 1)

These domains and/or variables will not be summarized or presented but will be available in the clinical study database, SDTM and/or ADaM datasets.

# 23. REFERENCES

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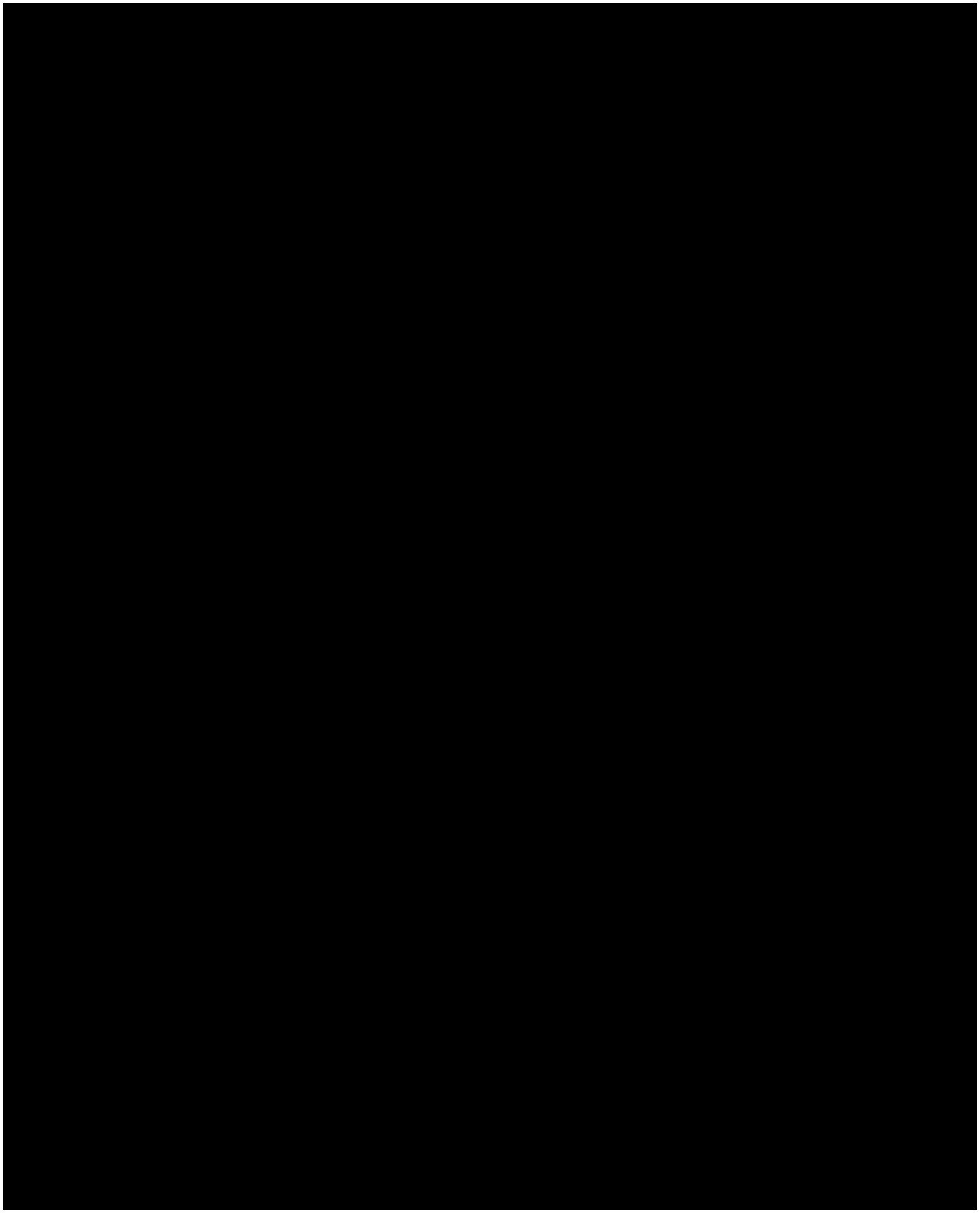
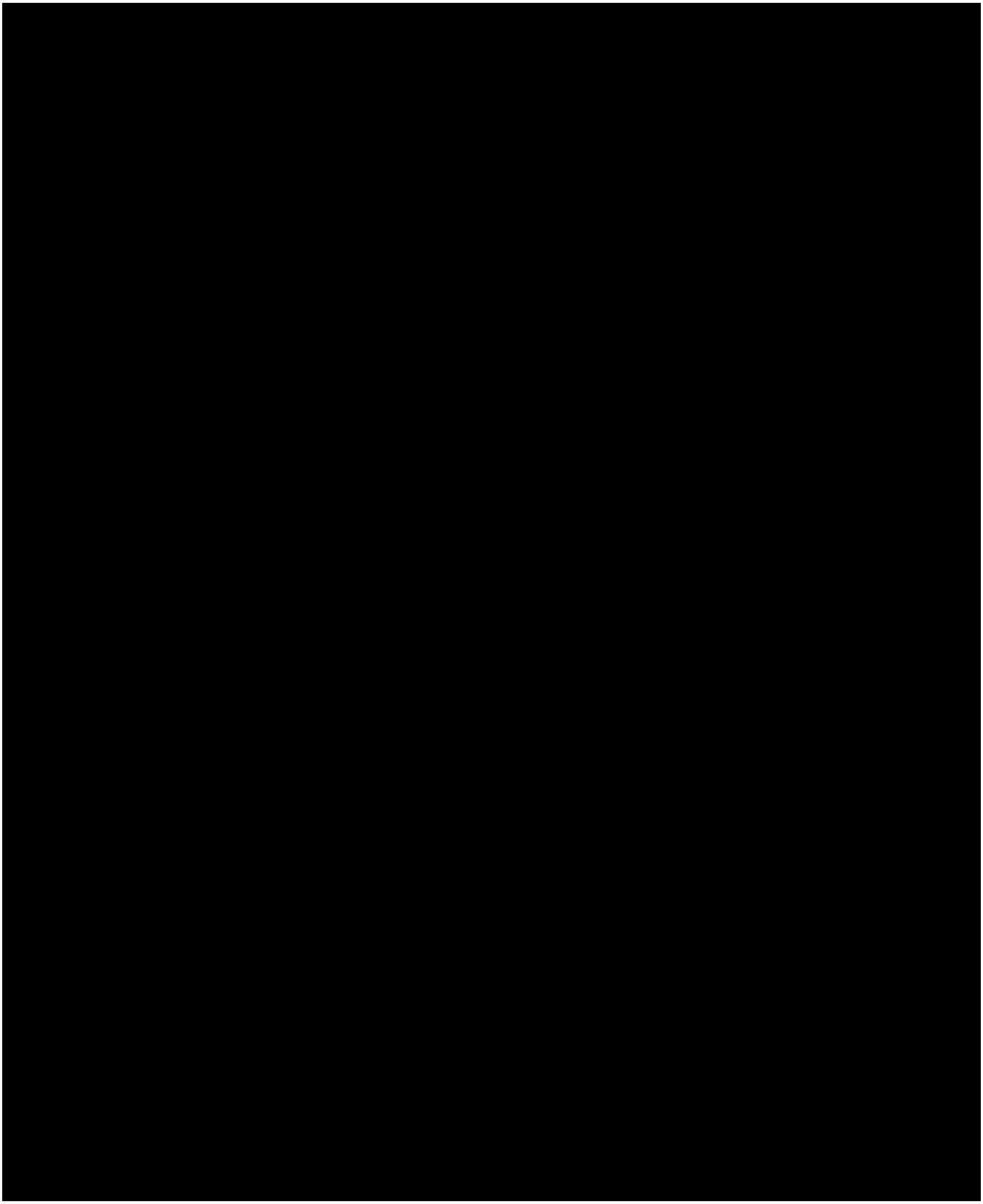
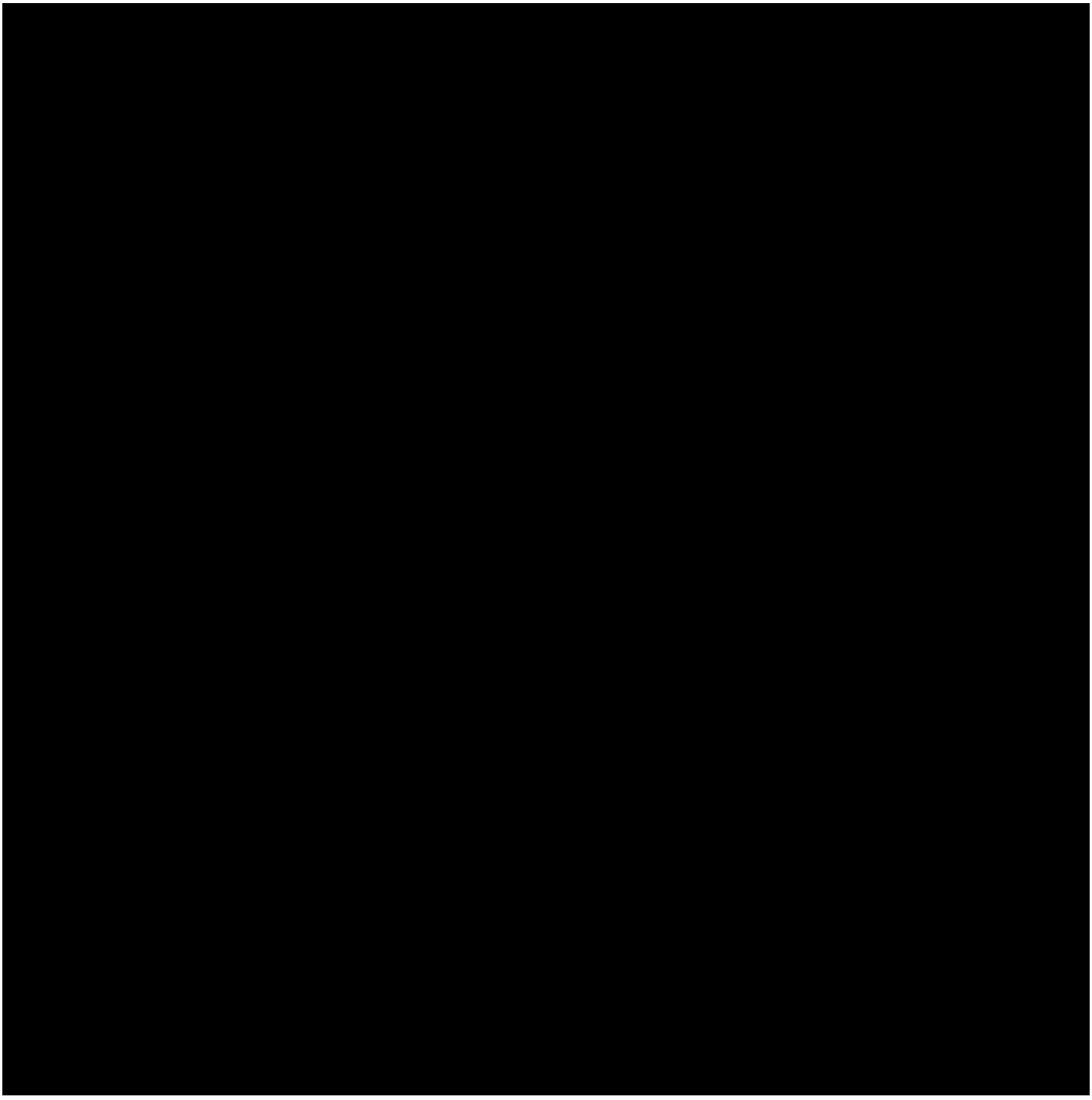
[redacted].







# 25. APPENDIX 2. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings.

## ALGORITHM FOR TREATMENT EMERGENCE OF ADVERSE EVENTS:

| AE START DATE | AE STOP DATE | ACTION |
|---|---|---|
| Known | Known, Partial or Missing | If AE start date < study treatment first LTE dose date, then not TEAE<br>If AE start date ≥ study treatment first LTE dose date, then TEAE |
| | | |
| Partial, but known components show that it cannot be on or after date of first dose of study treatment | Known, Partial or Missing | Not TEAE |
| | | |
| Partial, could be on or after date of first dose of study treatment | Known | If AE stop date < study treatment first LTE dose date, then not TEAE<br>If AE stop date ≥ study treatment first LTE dose date, then TEAE |
| | Partial | Impute AE stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then:<br>If AE stop date < study treatment first LTE dose date, then not TEAE<br>If AE stop date ≥ study treatment first LTE dose date, then TEAE |
| | Missing | Assumed TEAE |

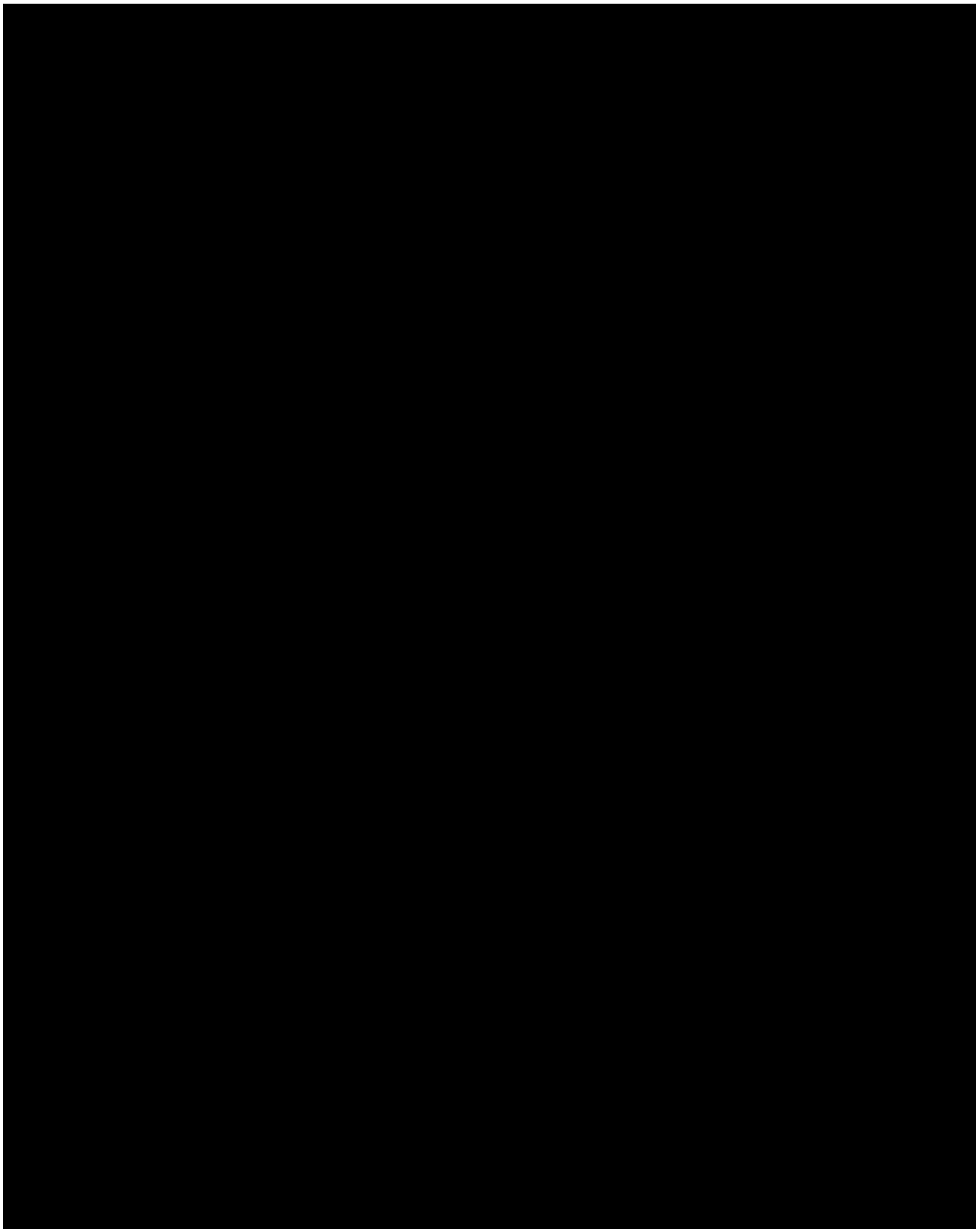
| AE START DATE | AE STOP DATE | ACTION |
|---|---|---|
| | | |
| Missing | Known | If AE stop date < study treatment first LTE dose date, then not TEAE<br>If AE stop date ≥ study treatment first LTE dose date, then TEAE |
| | Partial | Impute AE stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then:<br>If AE stop date < study treatment first LTE dose date, then not TEAE<br>If AE stop date ≥ study treatment first LTE dose date, then TEAE |
| | Missing | Assumed TEAE |

## ALGORITHM FOR PRIOR / CONCOMITANT MEDICATIONS:

| START DATE | STOP DATE | ACTION |
|---|---|---|
| Known | Known | If medication stop date < study treatment first LTE dose date, assign as prior<br>If medication stop date ≥ study treatment first LTE dose date, assign as concomitant |
| | Partial | Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then:<br>If medication stop date < study treatment first LTE dose date, assign as prior<br>If medication stop date ≥ study treatment first LTE dose date, assign as concomitant |
| | Missing | If medication stop date is missing could never be assumed a prior medication, assign as concomitant |

| START DATE | STOP DATE | ACTION |
|---|---|---|
| | | |
| Partial | Known | Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then:<br>If medication stop date < study treatment first LTE dose date, assign as prior<br>If medication stop date ≥ study treatment first LTE dose date, assign as concomitant |
| | Partial | Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then:<br>If medication stop date < study treatment first LTE dose date, assign as prior<br>If medication stop date ≥ study treatment first LTE dose date, assign as concomitant |
| | Missing | Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then:<br>If medication stop date is missing could never be assumed a prior medication, assign as concomitant |
| | | |
| Missing | Known | If medication stop date < study treatment first LTE dose date, assign as prior<br>Else assign as concomitant |

| START DATE | STOP DATE | ACTION |
|---|---|---|
| | Partial | Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then:<br>If medication stop date < study treatment first LTE dose date, assign as prior<br>If medication stop date ≥ study treatment first LTE dose date, assign as concomitant |
| | Missing | Assign as concomitant |



## Electronic Signature Manifestation

This page is a manifestation of the electronic signature(s) used in compliance with the organization's electronic signature policies and procedures.

| Signer Full Name | Meaning of Signature | Date and Time |
|---|---|---|
| [redacted] | Document Approval (I certify that I have the education, training and experience to perform this task) | 17 May 2021 14:49:42 UTC |
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