Arena Pharmaceuticals, Inc.

APD334-005

An Extension Study of APD334-003 in Patients with Moderately to Severely Active Ulcerative Colitis

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Statistical Analysis Plan

Version 1.2

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LIST OF ABBREVIATIONS

AE	adverse event
BMI	body mass index
CI	confidence interval
CP	completers population
CRF	case report form
CRO	contract research organization
CRP	c-reactive protein
CSR	clinical study report
ECG	electrocardiogram
eCOA	electronic clinical outcomes assessments
EOS	end of study
EOT	end of treatment
HR	heart rate
[redacted]	
ICF	informed consent form
LOCF	last observation carried forward
MCS	mayo clinic score
MedDRA	Medical Dictionary for Regulatory Activities
MITT	modified intent-to-treat
OCT	optical coherence tomography
PFTs	pulmonary function tests
[redacted]	[redacted]
PI	principal investigator
[redacted]	[redacted]
PML	progressive multifocal leukoencephalopathy
PMS	partial mayo score
PROs	patient reported outcomes
PT	preferred term
q.d.	once daily
QT_c	QT interval corrected for heart rate
QTcB	QTc corrected by Bazett's
QTcF	QTc corrected by Fridericia's
S1P1	sphingosine 1-phosphate 1 receptor
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event
WBC	white blood cell
WHODRUG	World Health Organization Drug Dictionary

1. INTRODUCTION

This statistical analysis plan (SAP) describes the analyses and data presentations that will be applied to data gathered in clinical trial Protocol No. APD334-005 [redacted] in order to evaluate the long-term safety, tolerability and efficacy of APD344 in patients with moderately to severely active ulcerative colitis who have completed the APD334-003 induction study.

This SAP is finalized prior to database lock and data analysis start. Section 9 discusses the changes from the planned analysis from the protocol, and the major changes in the analysis that are made after database lock will be documented in the Clinical Study Report (CSR) with the rationales and details.

Etrasimod (APD334), hereafter referred to as etrasimod, is a new chemical entity in development for the treatment of autoimmune diseases [redacted]. Etrasimod is an orally available, selective, sphingosine 1-phosphate 1 receptor ($S1P_1$) agonist. The $S1P_1$ receptor is a physiological mediator which has been shown to regulate lymphocyte recirculation between lymphoid tissue and blood. Binding and internalization of the $S1P_1$ receptor may result in lymphocyte retention within lymphoid tissue, with subsequent reduction in peripheral lymphocyte count and lymphocyte availability for recruitment to sites of inflammation [redacted]. It is through this mechanism that etrasimod may potentially reduce inflammation in inflammatory bowel disease. Lymphocyte lowering has been correlated with clinical efficacy for S1P functional antagonists in multiple sclerosis, psoriasis, and ulcerative colitis. This same mechanism may also be useful in treating a variety of other inflammatory and autoimmune diseases [redacted].

Previous pre-clinical and clinical data showed the desired effects and the benefit/risk assessment based on data gathered on etrasimod justifies the further clinical development. For additional clinical information regarding etrasimod, refer to the latest version of Investigator Brochure [redacted].

This is an extension study to APD334-003 induction study to evaluate long-term safety, tolerability, and efficacy (i.e., ability to achieve and maintain clinical remission and response after 34 weeks of additional treatment) of etrasimod.

The SAP is based on the Protocol Amendment 04 (27 Mar 2017). The key changes from the previous versions of the protocols include:

- Amendment 02 (28 Sep 2015) to Amendment 03 (20 Oct 2016)
  - Changed study duration from 52 weeks to 46 weeks in total
  - Changed study design to single arm, open-label (2 mg once daily [q.d.]) for APD334-003 responders only and removal of Placebo group
  - Updated secondary [redacted] outcome measures to reflect study duration of 46 weeks total (including the APD334-003 study)
    [redacted]
  - Changed Week 52 to Week 46 as End-of-Treatment
  - Removed Primary Safety and Secondary Efficacy hypotheses
  - Removed sample size and power calculations

  - Changed 'Randomized' to 'Enrolled' and removed treatment groups
  - Removed between group differences and removal of formal statistical analysis

- Amendment 03 (20 Oct 2016) to Amendment 04 (27 Mar 2017)
  - Updated to add proportion of patients who achieve clinical response to secondary endpoints
  - Updated to reflect APD334-003 completers to be eligible for APD334-005 study

More details can be found in Section 12.

2. OBJECTIVES

2.1. Primary Objective

The primary objective of this study is to evaluate the long-term safety and tolerability of etrasimod in patients with ulcerative colitis who have completed the APD334-003 study.

2.2. Secondary Objective

The secondary objective of this study is to evaluate the effect of etrasimod on achieving and maintaining clinical response and/or remission in patients with ulcerative colitis after 46 weeks of treatment.

2.3. Exploratory Objective

To examine the effect of etrasimod treatment in patients with ulcerative colitis on:

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design and Plan

APD334-005 is a phase 2, open-label extension study to determine the long-term safety and tolerability of etrasimod as well as its ability to achieve and maintain clinical remission and response after 34 weeks of additional treatment in patients with ulcerative colitis who have completed the APD334-003 induction study.

Eligible patients must have completed the APD334-003 induction study and must meet the eligibility criteria for the APD334-005 at time of entry. All eligible patients will have the option to enroll and receive open-label 2 mg q.d. treatment with etrasimod. For this purpose, all patients shall be consented for APD334-005 prior to the final procedures being performed for APD334-003 (as some procedure results will be used for the extension study baseline).

Selected procedures from the Week 12 visit in study APD334-003 will be carried over to the APD334-005 study to be included as baseline information and assist in determining eligibility for the APD334-005 study. [redacted]. Following the Day 1 visit, there will be regular visits to monitor for safety and perform efficacy assessments throughout the treatment period. Final assessments will be conducted at Week 46 from Baseline of study APD334-003 (Week 34 of this study), or upon early termination from the study. A 2-week follow-up visit will be conducted to ensure appropriate patient safety [redacted]

The total study participation/duration is up to 36 weeks (34 weeks of treatment and a 2-week follow-up visit after final visit). The schedule of procedures and visits for the study is provided in Appendix 14.1.

[redacted] Patients who terminate early or discontinue from the study will not be replaced.

Note: Patients that were enrolled under Protocol Amendment 02 (28 Sep 2015) followed a different study design (i.e. patients were randomized to Placebo or 2 mg q.d. etrasimod and remained blinded, and final assessments were conducted at Week 52 instead of Week 46). More details about changes in the study design are covered in Sections 1 and 12.

3.2. Study Endpoints

3.2.1. Primary Endpoint

The primary endpoint for the study is long-term safety. The safety of etrasimod will be monitored throughout the study with safety endpoints being as follows:

- Treatment-emergent adverse events (TEAEs) up to 30 days following discontinuation of the study drug

- Treatment-emergent serious adverse events (SAEs) up to 30 days following discontinuation of the study drug

3.2.2. Secondary Endpoints

Secondary efficacy endpoints are achievement, durability and maintenance of clinical response and/or clinical improvement. They include the following:

- The proportion of patients who achieve clinical response at end of treatment in APD334-005; the proportion of patients who achieve clinical response at Week 12 in APD334-003 and maintain clinical response at end of treatment in APD334-005. [definition of clinical response: a patient has achieved clinical response if he/she meets criteria of clinical remission defined below, or meets criteria of clinical response i.e. a decrease in 3-component Mayo Clinic score of ≥ 2 points and at least 30% with either a decrease of rectal bleeding of ≥ 1 or rectal bleeding score of 0 or 1] at Week 46 compared to APD334-003 baseline]

- The proportion of patients who achieve clinical remission at end of treatment in APD334-005; the proportion of patients who achieve clinical remission at Week 12 in APD334-003 and also maintain clinical remission at end of treatment in APD334-005 [definition of clinical remission: individual subscores of the 3-component Mayo Clinic score as follows: an endoscopy score (using flexible proctosigmoidoscopy) of 0 or 1 (excluding friability), a rectal bleeding score of 0 or 1, and a stool frequency score of 0 or 1 with a decrease of ≥ 1 point] at Week 46 compared to APD334-003 baseline]

3.2.3. Exploratory Endpoints

[redacted]

3.3. Treatments

3.3.1. Study Drug

[redacted] Arena Pharmaceuticals will provide adequate supplies of etrasimod tablets. Etrasimod tablets will be provided as a 2 mg strength.

3.3.2. Placebo

Not applicable.

Note: Under Protocol Amendment 02 (28 Sep 2015), patients that were randomized to Placebo received [redacted] tablets [redacted] that matched the active tablets in size, shape and appearance.

4. GENERAL STATISTICAL CONSIDERATIONS

Continuous data will be summarized using descriptive statistics (i.e., n, mean, median, standard deviation (SD), 90% confidence interval (CI) for change or percent change from baseline, minimum and maximum). For the summary statistics of all numerical variables unless otherwise specified, minimum and maximum will be displayed to the same level of precision as reported. Mean, median and 90% CIs will be displayed to one level of precision greater than the data collected. Standard deviation will be displayed to two levels of precision greater than the data collected.

For proportion-based measures, n, frequencies, proportion and its 90% CI will be produced. The denominator for all percentages will be the number of patients within the treatment group for the analysis set of interest, unless otherwise stated. Percentages will be presented to 1 decimal place. When count data are presented, the percentage will be suppressed when the count is zero in order to draw attention to the non-zero counts. A row denoted “Missing” will be included in count tabulations where specified on the shells to account for dropouts and missing values.

There is no formal between group inferential comparisons for study endpoints due to lack of control group. Summary statistics will be provided for the primary safety endpoint, secondary efficacy endpoints, exploratory efficacy endpoints, and additional safety measures. All analysis summaries will be presented as follows:

Previously Treated in APD334-003 (APD334-005 treatment: 2 mg etrasimod)				**APD334-005 treatment:**	**APD334-005 treatment:**
Placebo	1 mg etrasimod	2 mg etrasimod	1 mg & 2 mg etrasimod	2 mg etrasimod	Placebo

Listings will include a subtitle to indicate both treatments, i.e. treatment received in APD334-003 study and treatment received in APD334-005 study.

If endoscopy was performed prior to Week 46, then last observation carried forward (LOCF) imputation method will be used for the endoscopy subscore. Any endoscopy performed during the APD334-005 extension study (after Week 12 visit) will be used for LOCF imputation.

All data summaries and statistical analyses will be performed using the SAS software version 9.3 or higher (SAS Institute, Cary, NC).

4.1. Time points and Day Ranges

Since it is not always possible for all study participants to come in for their clinic visits on the exact day specified in the protocol schedule, the 'Week' of a patients visit will be defined by the following relative day ranges.

[redacted]

[redacted]

[redacted]

4.2. Sample Size

Patient enrollment is limited by the number of patients who complete the APD334-003 study. Therefore, sample size calculation is not needed.

4.3. Randomization, Stratification, and Blinding

4.3.1. Randomization and Stratification

Not applicable for this open-label extension study.

Note: Patients that were enrolled under Protocol Amendment 02 (28 Sep 2015) were randomized to Placebo or 2 mg q.d. etrasimod and remained blinded. More details about changes in the study design are covered in Sections 1 and 12.

4.3.2. Blinding

The extension study is an open-label study, however in order to keep the blind of the induction study intact, the sponsor, patients, and personnel involved with the conduct of the APD334-005 study will continue to be blinded to the total white blood cell (WBC) and lymphocyte counts, as access to this information may lead to unintentional unblinding of a patient (due to Investigational Product's mechanism of action). A central contract research organization (CRO) physician(s) unblinded to the leucocyte count will continue to review and monitor the total WBC and lymphocyte counts for safety purposes in the trial. The study site personnel will not receive laboratory results for the total WBC or lymphocyte counts. Further details are included in the Covance Labs Data Transfer Specifications (COVANCE 2018).

4.4. Analysis Populations

The analyses of all proportion-based and all continuous efficacy variables will use the Modified Intent-to-Treat (MITT) population as primary. In addition, all endpoints that include the endoscopy subscore will use Completers population (CP).

Analysis populations will be presented in a listing for all enrolled patients.

4.4.1. Modified Intent-To-Treat Population (MITT)

This MITT population consists of all patients, who received at least 1 dose of etrasimod or Placebo, have a baseline measurement, and have a post-enrollment measurement in the extension study for the specific efficacy endpoint being assessed. Note that MITT population can vary with endpoints since some patients may have the needed data for inclusion in the MITT population for some endpoints but not for others.

4.4.2. Completers Population (CP)

This CP population consists of all patients in the MITT population who completed the extension study based on the study completion status collected on the End of Study CRF page. No missing data will be imputed for this analysis. Any substantial differences between conclusions based on the MITT population and the CP population will be investigated. Note that CP population will be used only for endpoints that include the endoscopy subscore, unless otherwise stated.

4.4.3. Safety Population

The Safety population will include all patients who received study medication in the extension study.

5. PATIENT DISPOSITION

5.1. Disposition

The number of patients enrolled in the study will be tabulated overall and by country as described in Section 4. Tables will indicate the number and percentage of patients who were enrolled into the study, who completed treatment and/or completed the study and who discontinued treatment and/or discontinued study prematurely (early termination) for any of the following reasons:

- Adverse event(s) (AEs)
- Patient lost to follow up
- Patient withdrawal of consent
- Investigator decision
- Sponsor decision
- Death
- Other

All percentages will be based on the number of enrolled patients within the relevant category.

Patient disposition data will be presented in a listing.

5.2. Protocol Deviations

Protocol deviations will be summarized for the Safety population and will include the number of patients with at least one protocol deviation, total number of protocol deviations and summaries by subtype category.

Protocol deviations will be presented in a listing.

6. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Since this is an extension study to APD334-003 study, some of the baseline characteristics data (i.e. ulcerative colitis history, social history and medical history) for the relevant enrolled patients will be taken from the APD334-003 induction study.

6.1. Demographics

All baseline patient characteristics of demographics data will be presented for the Safety population. Demographic characteristics will be collected at Week 12 (APD334-003 study) / Day -1 (APD334-005 study).

The demographic characteristics consist of age (years), sex, race, and ethnicity. A patient's age in years is calculated using the date of the informed consent and date of birth.

The baseline characteristics consist of baseline height (cm), baseline weight (kg), and baseline body mass index (BMI) (kg/m^2). Body mass index is calculated as (body weight in kilograms) / $(\text{height in meters})^2$.

Continuous variables (i.e. age, height, weight and BMI) will be summarized using descriptive statistics (i.e. number of observations [n], mean, SD, median, minimum and maximum). Categorical data will be summarized by the number and percentage (n(%)) of patients within the relevant category i.e. age category (18-24; 25-34; 35-44; 45-54; 55-65; and >65), sex (Male, Female), race (American Indian or Alaska Native, Asian – Chinese, Asian – Japanese, Asian – Other, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other and Not allowed per country regulation) and ethnicity (Hispanic or Latino, Not Hispanic or Latino). Percentages will be based on the total number of patients in the Safety population.

Patient demographics and baseline characteristics will be presented in a listing. In addition patient weight data will be listed.

6.2. Baseline Disease Characteristics

Baseline ulcerative colitis disease information will be summarized for the Safety population as follows:

- Duration of ulcerative colitis (years) at APD334-003 screening visit by descriptive statistics
- Disease location (Proctosigmoiditis/Left sided colitis, Pancolitis/ Extensive colitis) at APD334-003 screening visit by n (%)
- History of Colonic Ulcerative Activity on Endoscopy (ulcerative colitis extending ≥ 15 cm proximal to the rectum) at APD334-003 screening visit by n (%)

- Ulcerative colitis prior [redacted]

Note: Prior ulcerative colitis treatment was collected at APD334-003 screening visit.

- Disease Activity (Mayo Clinic Scores) at APD334-005 baseline
- Fecal Calprotectin at APD334-005 baseline
- CRP at APD334-005 baseline
- [redacted]

Baseline ulcerative colitis disease information collected at APD334-003 screening visit, including hospitalization history, will be listed.

6.3. Alcohol, Tobacco and Caffeine Usage

Social history collected at APD334-003 screening visit i.e. tobacco, alcohol, caffeine and other substances used, will be listed for the Safety population.

6.4. Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 18.0 or later. The number and percentage of patients with any medical history at APD334-003 screening visit will be summarized overall and for each system organ class and preferred term. Percentages will be calculated based on number of patients in the Safety population.

Patient medical history data including specific details will be presented in a listing.

6.5. Inclusion and Exclusion Criteria

Inclusion and exclusion data will be listed only for patients that did not meet inclusion/exclusion criteria.

7. TREATMENTS AND MEDICATIONS

7.1. Concomitant Medications

Concomitant medications include any medications that are taken when on study treatment in APD334-005 study, including medications that started prior and are ongoing during study treatment.

The total number of concomitant medications and the number and percentages of patients with at least one concomitant medication will be summarized as described in Section 4. The number and percentages of all concomitant medications will be summarized by drug class and preferred term. All summaries will be performed using the Safety population.

Medications will be coded using the World Health Organization Drug Dictionary (WHODRUG, Version December 2017).

All medications will be listed.

7.2. Study Treatments

Investigational product will be dispensed to eligible patients under the supervision of the investigator or his/her designee at the Week 12 visit of the APD334-003 study.

[redacted]

Patients enrolled under Protocol Amendment 02 (28 Sep 2015) were randomized to Placebo or 2 mg q.d. etrasimod and were instructed to take their 2 mg etrasimod, or matching Placebo tablet in the same way as described in the paragraph above.

Study treatment administration, drug accountability and dosing details will be listed for the Safety population.

7.2.1. Treatment Compliance

Compliance will be assessed using patient data recorded in the drug accountability form of the electronic case report forms (eCRFs). On each day, a patient should take his/her assigned treatment.

The overall study drug compliance (%) will be calculated as follows:

Compliance (%) = [(actual number of tablets taken over the study period) / (designated total number of tablets that should have been taken over the study period)] * 100

The study period is defined as the number of days that the patient has been in the active treatment phase of the APD334-005 study.

Summary statistics on percentage of treatment compliance as well as the number and percentage of patients in each compliance category (<80%, 80-100%, and >100% compliant) will be presented as described in Section 4 using the Safety population.

Treatment compliance data will be listed for each patient.

7.2.2. Extent of Exposure

Duration of exposure is defined as the total number of days a patient is exposed to any study drug in APD334-005 study and will be presented as the sum of all days from the first dose date (Day 1) to the last dose date (i.e. date of last dose - the date of first dose + 1) using the dose administration page on the CRF. If the last dose date on the dose administration page is missing, or if a patient is lost to follow-up, but the drug accountability log confirms that the patient has taken study drug, the visit date following the last completed drug accountability log will be used.

The duration of exposure (in days and in weeks) to study drug will be summarized for all patients in the Safety population and will be presented in a table by summary statistics (as described in Section 4). The duration of exposure (cumulative) will then be classified into the following categories: > 0 days, ≥ 28 days, ≥ 56 days, ≥ 84 days, ≥ 112 days, ≥ 140 days, ≥ 168 days, ≥ 196 days, ≥ 224 days, ≥ 252 days and ≥ 280 days and will be presented as the number and percentage of patients in each duration category. Percentages will be computed from the number of patients in the Safety population.

In addition, the overall exposure will be summarized i.e. from Baseline of APD334-003 study to end of APD334-005 study. Duration of overall exposure is defined as the total number of days a patient is exposed to any study drug in APD334-003 and APD334-005 study and will be presented as the sum of all days from the first dose date (Day 1 of APD334-003 study) to the last dose date in the APD334-005 study (i.e. date of last dose - the date of first dose + 1) using the dose administration page on the CRF. If the last dose date on the dose administration page is missing, or if a patient is lost to follow-up, but the drug accountability log confirms that the patient has taken study drug, the visit date following the last completed drug accountability log will be used.

The duration of overall exposure (in days and in weeks) to study drug will be summarized for all patients in the Safety population and will be presented in a table by summary statistics (as described in Section 4). The duration of overall exposure (cumulative) will then be classified into the following categories: > 0 days, ≥ 28 days, ≥ 56 days, ≥ 84 days, ≥ 112 days, ≥ 140 days, ≥ 168 days, ≥ 196 days, ≥ 224 days, ≥ 252 days, ≥ 280 days, ≥ 308 days, ≥ 336 days and ≥ 364 days and will be presented as the number and percentage of patients in each duration category. Percentages will be computed from the number of patients in the Safety population.

A summary of each patient's exposure in APD334-005 study will be presented in a listing.

8. EFFICACY ANALYSIS

Summary statistical analyses will be performed for all efficacy measures.

There is no between group inferential comparison for study endpoints.

8.1. Efficacy Assessments

Efficacy assessments will be listed for each patient for the MITT population where relevant.

8.1.1. Flexible Proctosigmoidoscopy

A flexible proctosigmoidoscopy, performed with a video endoscope following a cleansing prep (oral or rectal cathartic) will be performed at Baseline [redacted] and [redacted] EOT. A repeat flexible proctosigmoidoscopy may be permitted by the Sponsor when the central reader indicates that the video endoscope data was acquired incorrectly, or did not meet the minimal required quality standards.

8.1.2. Stool Sample

A stool sample will be collected at time points listed in the schedule of procedures and visits (Section 14.1) for the analysis of fecal calprotectin, [redacted]

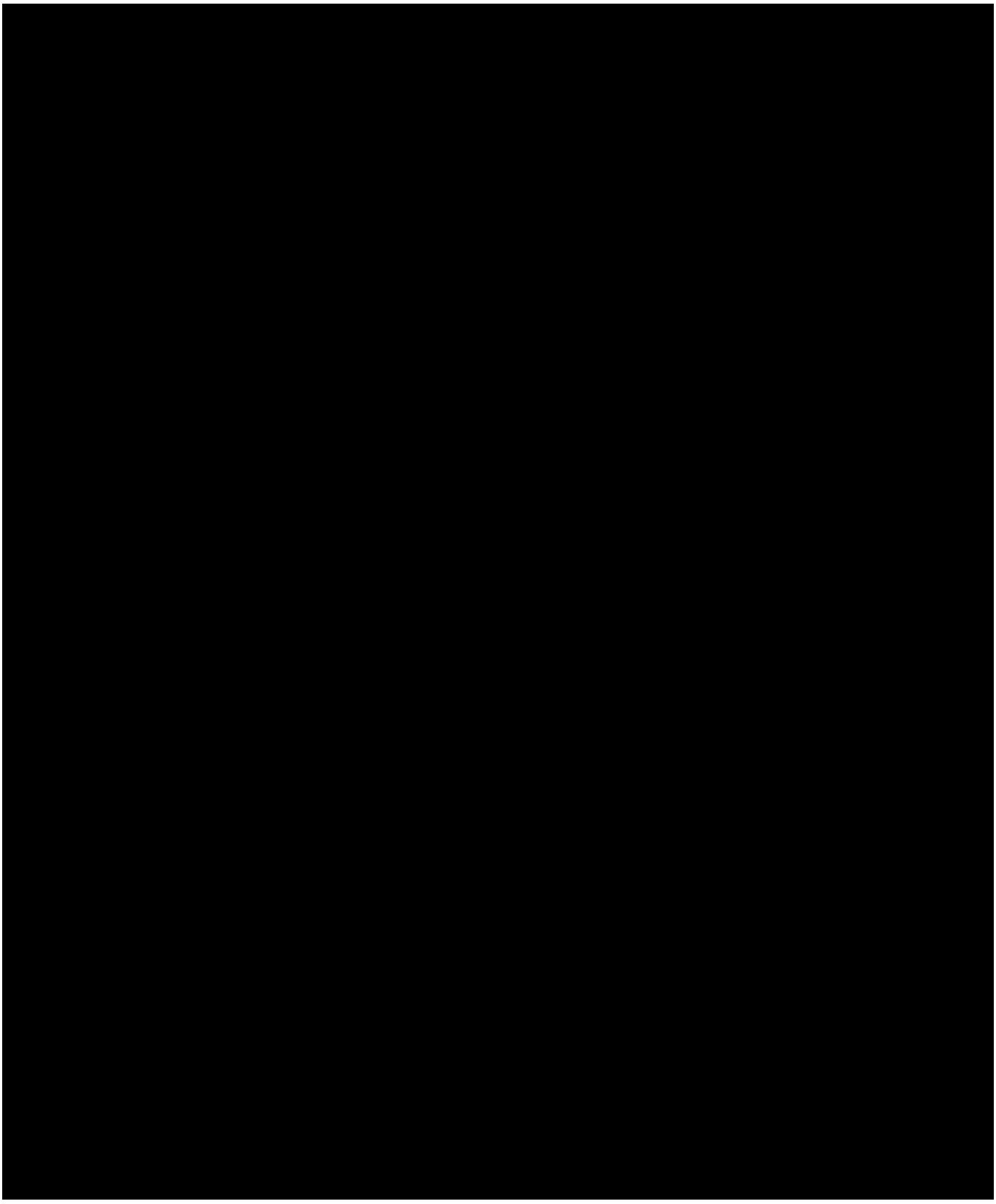
8.1.3. C-reactive protein (CRP)

Blood samples for analysis of CRP will be collected at time points listed in the schedule of procedures and visits (Section 14.1).

8.1.4. Electronic Clinical Outcomes Assessments (eCOA)

Patient reported outcomes (stool frequency and rectal bleeding) will be captured daily using a handheld electronic device from CRF Health [redacted]. Diary entries will be reviewed by site personnel during scheduled visits and at any unscheduled visit(s) due to disease exacerbation. The CRF Health eDiary software runs on the device and includes all the security features required of an eCOA solution for 21 CFR Part 11 compliance.

[redacted]



8.2. Primary Efficacy Analysis

There is no primary efficacy endpoint in this study, therefore no primary efficacy analysis is performed.

8.3. Secondary Efficacy Analysis

Secondary efficacy endpoints are listed in Section 3.2.2.

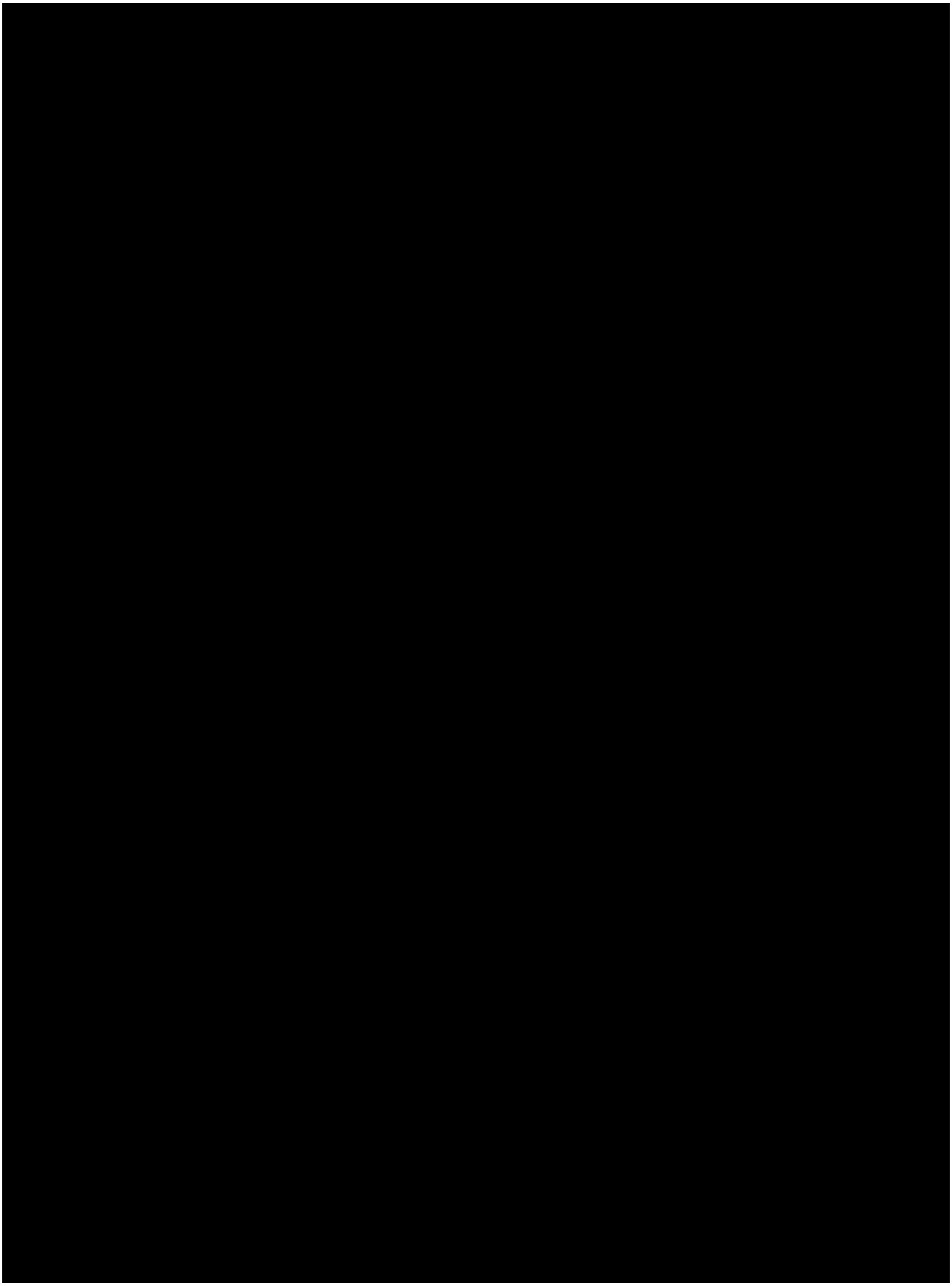
The secondary efficacy outcome of achievement or maintenance of clinical response will be based on the proportion of patients who achieve or maintain clinical response at end of treatment compared to APD334-003 baseline using the MITT and CP populations. Summary statistics i.e. total number of patients (N), frequencies (n), proportion (%) and its 90% CI for patients that achieved or maintained clinical response (responders) at end of treatment in APD334-005 will be produced as described in Section 4.

Similar summary statistical analyses will be produced for the second secondary efficacy outcome i.e. clinical remission at Week 46 compared to APD334-003 baseline.

Each secondary efficacy endpoint will be summarized, within the same presentation, by the following:

- Proportion of patients that achieved clinical response/clinical remission at Week 12 in APD334-003
- Proportion of patients that achieved clinical response/clinical remission at end of treatment in APD334-005
- Proportion of patients that achieved clinical response/clinical remission at both Week 12 in APD334-003 and end of treatment in APD334-005

8.4. Exploratory Efficacy Analyses



[redacted]

8.6. Multiplicity

Multiplicity is not applicable for this study.

9. SAFETY ANALYSIS

The safety of etrasimod will be monitored throughout the study with safety endpoints being as follows:

- Treatment-emergent adverse events (TEAEs) up to 30 days following discontinuation of the study drug
- Treatment-emergent serious adverse events (SAEs) up to 30 days following discontinuation of the study drug

Additional safety assessments will include:

- Physical & neurological examinations including ophthalmoscopy (and optical coherence tomography [OCT], where available)
- Progressive multifocal leukoencephalopathy (PML) checklist
- Clinical laboratory tests to include hematology, serum chemistry, coagulation, and urinalysis
- Vital sign measurements
- Pulmonary Function Tests (PFTs)
- ECGs
- AE reporting

For analyses based on laboratory measurements, vital signs and ECGs, summary tabulations (n, mean, SD, median, minimum and maximum for actual and change [or percent change] from baseline) will be presented. For analyses based on AEs, frequency and percentage will be presented. The analyses for all safety outcomes (categorical or continuous measures) will use the Safety population.

For analysis based on laboratory measurements, at least 1 laboratory test post-enrollment measurement in the extension study is required for inclusion in the Safety population. When assessing change from baseline, a baseline measurement is also required. Baseline for the safety analysis is defined as the last pre-enrollment measurement (i.e. APD334-005 Day 1 pre-dose). No missing data will be imputed for the safety analysis.

9.1. Adverse Events

A TEAE is defined as an AE that meets any of the following conditions:

- begins on or after the first dose of study drug in APD334-005 study

- begins before the first dose of study drug in APD334-005 study and worsens in severity on or after the first dose of study drug in APD334-005 study
- occurs in APD334-003 study and is ongoing in APD334-005 study
- occurs in APD334-003 study and end date is in APD334-005 study
- is completely missing an onset date and end date
- is completely missing an onset date and the end date is on or after the first dose of study drug in APD334-005 study

For the purpose of inclusion in TEAE tables, incomplete AE onset and end dates will be imputed as follows:

Missing onset dates (where UK and UKN indicate unknown or missing day and month respectively):

- UK-MMM-YYYY: If the month and year are different from the month and year of the first dose of study drug, assume 01-MMM-YYYY. If the month and year are the same as the first dose of study drug month and year, and the end date (after any imputation) is on or after the first dose of study drug, then assume the date of the first dose of study drug. If the month and year are the same as the first dose of study drug month, and year and the end date (after any imputation) is prior to the first dose of study drug, then assume the end date for the onset date
- DD-UKN-YYYY/UK-UKN-YYYY: If the year is different from the year of first dose of study drug, assume 01-JAN-YYYY of the collected year. If the year is the same as the first dose of study drug year, and the end date (after any imputation) is on or after the first dose of study drug, then assume the date of the first dose of study drug. If the year is the same as the first dose of study drug, and the end date (after any imputation) is prior to the first dose of study drug, then assume the end date for the onset date

Missing end dates (where UK and UKN indicate unknown or missing day and month respectively):

- UK-MMM-YYYY: Assume the last day of the month
- DD-UKN-YYYY/UK-UKN-YYYY: Assume 31-DEC-YYYY

All AEs will be classified by System Organ Class (SOC) and Preferred Term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA**,** version 20.1).

Patients with at least one TEAE will be summarized for the following:

- Overall summary of TEAEs
- Summary of TEAEs by SOC and PT
- Summary of TEAEs by Relationship to Study Drug
- Summary of TEAEs by Severity
- Serious TEAEs by SOC and PT
- TEAEs that leading to permanent discontinuation of study drug by SOC and PT
- TEAEs with severity grade ≥ 3 by SOC and PT

Patients will be monitored from Informed Consent Form (ICF) signature to 30 days after the last dose of study drug for adverse reactions to the study drug and/or procedures.

9.1.1. Overall Summary of Treatment Emergent Adverse Events

An overall summary of TEAEs will be presented in a table and will include the number and percentage of patients with any TEAE, number of TEAEs, patients with serious TEAEs, TEAEs leading to death and patients that discontinued from study treatment and/or study due to TEAEs. In addition, the table will include number and percentage of patients in each category of severity (i.e. Grade 1 to Grade 5) for all TEAEs and for related TEAEs, and number and percentage of patients in each category of relationship to study drug (i.e. "Related" and "Not Related").

9.1.2. Treatment Emergent Adverse Events Summary by SOC and PT

Summaries of the total number of TEAEs and the number and percentage of patients with at least one TEAE will be provided. TEAEs will be presented by SOC and PT. At each level of patient summarization, a patient is counted once if the patient reported one or more events. Percentages will be calculated out of the number of patients in the Safety population.

The summary of TEAEs will be presented in descending order from the SOC with the highest total incidence (that is, summed across all treatment groups) to the SOC with the lowest total incidence. If the total incidence for any two or more SOCs is equal, the SOCs will be presented in alphabetical order. Within each SOC, the PTs will be presented in alphabetical order.

All TEAEs will be presented in a listing.

9.1.3. Relationship of Adverse Events to Study Drug

A summary of total number of TEAEs and number and percentage of patients with at least one TEAE by relationship (i.e. "Related" and "Not Related") to study drug will be presented in a table by incidence of occurrence.

The investigator will provide an assessment of the relationship of the event to the study drug. The possible relationships are "Not Related" or "Related". In the TEAE relationship table, if a patient reports multiple occurrences of the same TEAE, only the most closely related occurrence will be presented. Percentages will be calculated out of the number of patients in the Safety population.

The TEAE data will be categorized and presented by SOC, PT, and relationship.

9.1.4. Severity of Adverse Events

A summary of total number of TEAEs and number and percentage of patients with at least one TEAE by severity will be presented in a table.

The severity that will be presented represents the most extreme severity captured on the CRF page. The possible severities are Grade 1 to Grade 5 i.e. "Mild" "Moderate", "Severe", "Life-threatening" and "Death related", respectively. In the TEAE severity table, if a patient reported multiple occurrences of the same TEAE, only the most severe will be presented. Percentages will be calculated out of the number of patients in the Safety population.

The TEAE data will be categorized and presented by SOC, PT, and severity.

In addition, a similar table will be produced for TEAEs that have severity of Grade ≥ 3.

9.1.5. Serious Adverse Events

The seriousness of an AE should be assessed by the Investigator independently from the severity of the AE. A SAE is defined as any untoward medical occurrence that at any dose results in death, is life-threatening, is a congenital anomaly/birth defect, requires in-patient hospitalization or prolongation, or results in significant disability/incapacity.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

Summaries of the total number of SAEs and the number and percentage of patients with at least one SAE will be provided. SAEs will be presented by SOC and PT. At each level of patient summarization, a patient is counted once if the patient reported one or more events. Percentages will be calculated out of the number of patient in the Safety population.

The summary of SAEs will be presented in descending order from the SOC with the highest total incidence (that is, summed across all treatment groups) to the SOC with the lowest total incidence. If the total incidence for any two or more SOCs is equal, the SOCs will be presented in alphabetical order. Within each SOC, the PTs will be presented in alphabetical order.

All SAEs will be presented in a listing by patient using the Safety population. If there are no SAEs at the end of the study, the tables or listings will state that there are no SAEs in the study.

9.1.6. Adverse Events Leading to Study Discontinuation

A summary of total number of TEAEs and number and percentage of patients with at least one TEAE that caused permanent discontinuation of study medication (i.e. study medication discontinued and/or withdrawal from study) will be presented. TEAEs will be presented by SOC and PT. At each level of patient summarization, a patient is counted once if the patient reported one or more events. Percentages will be calculated out of the number of patients in the Safety population within the subgroup category.

The summary of TEAEs that caused permanent discontinuation of study medication will also be presented in descending order of frequency from the SOC with the highest total incidence (that is, summed across all treatment groups) to the SOC with the lowest total incidence. If the total incidence for any two or more SOCs is equal, the SOCs will be presented in alphabetical order. Within each SOC, the PTs will be presented in alphabetical order.

9.2. Clinical Laboratory Evaluations

Clinical laboratory evaluations (i.e. hematology, serum chemistry, coagulation and urinalysis) will be performed by a central laboratory. All summaries will be based on the units provided by the central laboratory, no conversion will be performed.

Summary tabulations (i.e. n, mean, SD, median, minimum and maximum) for the observed values and changes from baseline will be presented for clinical laboratory evaluations with numeric values for patients in the Safety population. Observed results at each visit and changes from baselines (APD334-003 baseline and APD334-005 baseline) to each scheduled post-baseline visit will be presented.

All relevant clinical laboratory tests will be classified as Low, Normal, and High according to the normal ranges. This categorical data will be summarized in shift tables comparing the results at last scheduled post-baseline visit with those at the baseline visit. Baseline for APD334-003 study is defined as last measurement before first dose of study medication in APD334-003 study, and baseline for APD334-005 study is defined as last pre-enrollment measurement (APD334-005 Day 1 pre-dose).

If any laboratory value falls above or below the upper or lower level of quantification, the value of the upper or lower level of quantification will be taken (e.g. <0.2 will become 0.2) for summaries but left as recorded in the listing.

All individual lab values will be listed by visit.

9.3. Vital Sign Measurements

Supine (laying face upward) blood pressure, heart rate/pulse, temperature, and respiratory rate will be measured after the patient has been resting for 5 minutes. Vitals signs will be measured prior to any blood draw that occurs at the same time point. Vital signs will be measured according to the time points in the schedules of procedures and visits (Section 14.1).

Summary tabulations (i.e. n, mean, SD, median, minimum and maximum) for the observed values and changes from baseline will be presented for vital sign data for patients in the Safety population. Changes from baselines (APD334-003 baseline and APD334-005 baseline) to each scheduled post-baseline time point and visit will be presented. Baseline for APD334-003 study is defined as last measurement before first dose of study medication in APD334-003 study, and baseline for APD334-005 study is defined as last pre-enrollment measurement (APD334-005 Day 1 pre-dose).

All vital sign data by patient will be presented in a listing.

9.4. Physical and Neurological Examination

Physical and neurological examinations will be listed.

9.5. Safety ECG (12-lead) [redacted]

Safety ECGs will be recorded from an ECG machine (12-lead). All safety ECGs will be obtained as single tracings, with the exception of the pre-treatment ECG obtained on Day 1, which is a triplicate recording.

All patients will have a standard 12-lead ECG performed during the study as clinically indicated. Intervals to be provided for each ECG are: RR, PR, QRS, QT, QT interval corrected for heart rate (QTc), QTc corrected by Bazett's (QTcB), and QTc corrected by Fridericia's (QTcF).

[redacted]

[redacted]

9.6. Lymphocyte Count

Summary tabulations (i.e. n, mean, SD, median, minimum and maximum) for the absolute lymphocyte counts, absolute changes from baselines [redacted], and percentage changes from baselines at each visit [redacted] will be presented for patients [redacted].

[redacted]

9.7. Other Safety Data

Other safety data will be listed and includes:

- PML Checklist
- Ophthalmoscopy with OCT
- PFT
- Pregnancy test details (only females who are not diagnosed as postmenopausal)

[redacted]

11. INTERIM ANALYSIS

No interim analyses is planned for this study.

12. CHANGES IN THE PLANNED ANALYSIS

Under Protocol Amendment 02 (28 Sep 2015) eligible responders on active treatment in the APD334-003 study (who choose to continue on to the APD334-005 study) underwent 1:1 randomization to 2 mg etrasimod q.d. or matching Placebo, while eligible Placebo responders in the APD334-003 study (who choose to continue on to the APD334-005 study) remained on Placebo. Responder patients stayed blinded. Non-responders in the APD334-003 study (who choose to continue on to the APD334-005 study) were administered with open-label 2 mg etrasimod. Under Protocol Amendment 03 (20 Oct 2016) eligible patients (who choose to continue on to the APD334-005 study) must have completed the APD334-003 study and were administered open-label 2 mg etrasimod. Data gathered on patients before Protocol Amendment 03 will follow the Protocol Amendment 03 analyses and data presentation as described in this SAP document. Patients that received 2mg etrasimod under any Protocol Amendment will be pooled into a 2 mg etrasimod group and patients that received placebo prior to Protocol Amendment 03 will be included in a second group. All listings will be presented by these two treatment groups, namely 2 mg etrasimod and Placebo, and by treatment previously received in APD334-003 study.

The following exploratory objectives have been added to the SAP in comparison with Protocol Amendment 04 (27 Mar 2017) to be consistent with the objectives in the APD334-003 study:

[redacted]

The following exploratory endpoints have been added to the SAP in comparison with Protocol Amendment 04 (27 Mar 2017) to be consistent with the endpoints in the APD334-003 study:

[redacted]

The following exploratory endpoints have been removed from the SAP in comparison with Protocol Amendment 04 (27 Mar 2017), as these are no longer needed:

[redacted]

The following subgroup analysis has been added to the SAP in comparison with Protocol Amendment 04 (27 Mar 2017):

[redacted]

The following subgroup analyses have been removed from the SAP in comparison with Protocol Amendment 04 (27 Mar 2017), as these have been already evaluated in APD334-003 study and are no longer needed:

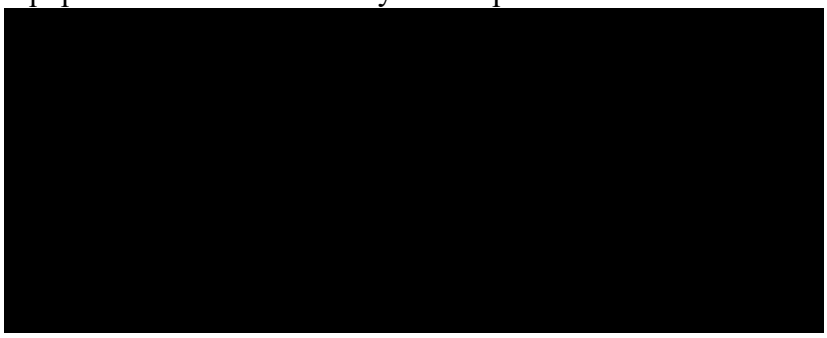
The 95% CIs have been changed to 90% CIs for all analyses in comparison with Protocol Amendment 04 (27 Mar 2017) to be consistent with the APD334-003 study.

The clinical remission definition has been updated to include "a rectal bleeding score of 0 or 1" in comparison with Protocol Amendment 04 (27 Mar 2017) to be consistent with the definition in final SAP of APD334-003 study.

The clinical response definition has been updated as "a patient has achieved clinical response if he/she meets criteria of clinical remission, or meet criteria of clinical response defined in the protocol." to be consistent with the definition in final SAP of APD334-003 study.

The following changes have been applied to the Analysis Populations to the SAP in comparison with Protocol Amendment 04 (27 Mar 2017):

- ITT population has been removed – no longer needed as APD334-005 is an open label study
- Definition of CP population has been updated to include "This CP population consists of all patients in the MITT population who completed the extension study" and "Note that CP population will be used only for endpoints that include the endoscopy subscore, unless otherwise stated." – to be consistent with the definition in final SAP of APD334-003 study
- CP population will be used only for endpoints that include the endoscopy subscore:



Sponsor was notified that laboratory tests for five patients [redacted] had been sent to local labs for the purpose of safety follow up on blood cell counts after last treatment. Such follow up may still be needed at time of database lock. The local laboratory results will be translated in English and archived in study file. Sponsor will write a section in CSR to describe the findings and to assess the safety issues for these [redacted] patients.

13. REFERENCES

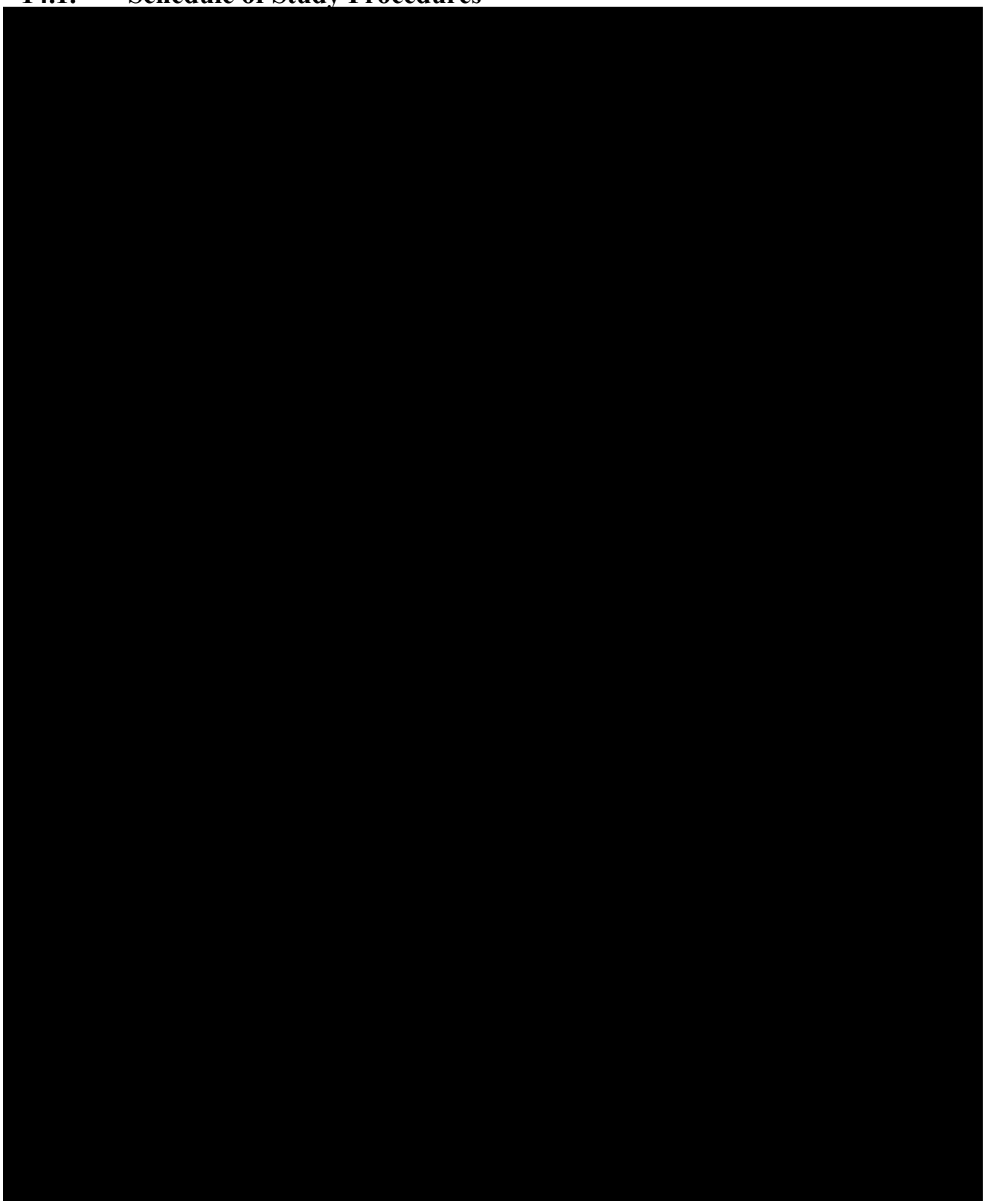
[redacted]. Investigator's brochure: Etrasimod (APD334) (Edition 06). San Diego, CA: Arena Pharmaceuticals, Inc.; October 25, 2018. On file at Arena.

COVANCE. Covance laboratory data transfer specifications. Covance;2018. On file at Arena.

[redacted] An extension study of APD334-003 in patients with moderately to severely active ulcerative colitis. San Diego, CA: Arena Pharmaceuticals, Inc.; March 27, 2017. Clinical Study Protocol APD334-005. On file at Arena.

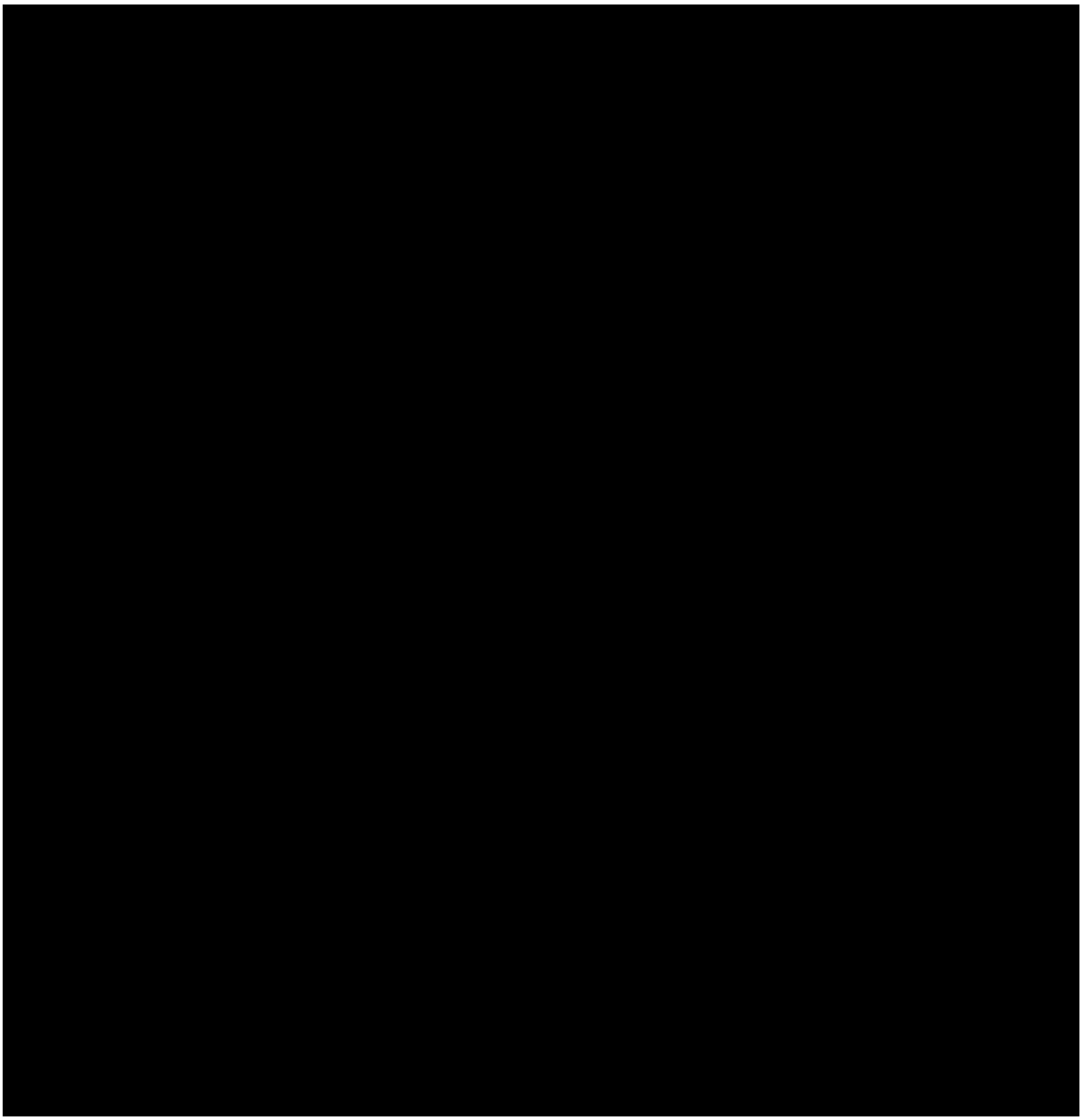
14. APPENDICES

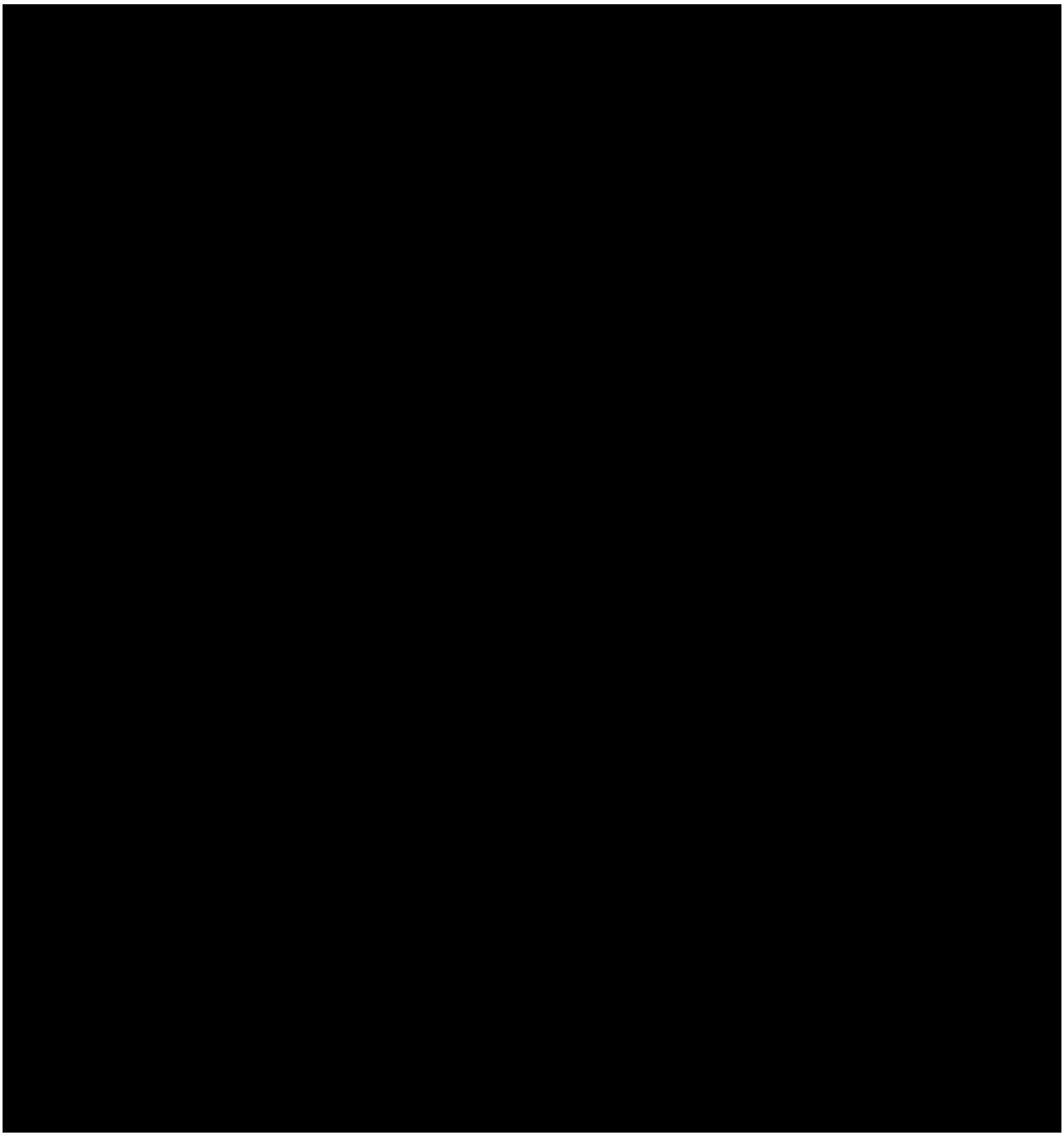
14.1. Schedule of Study Procedures

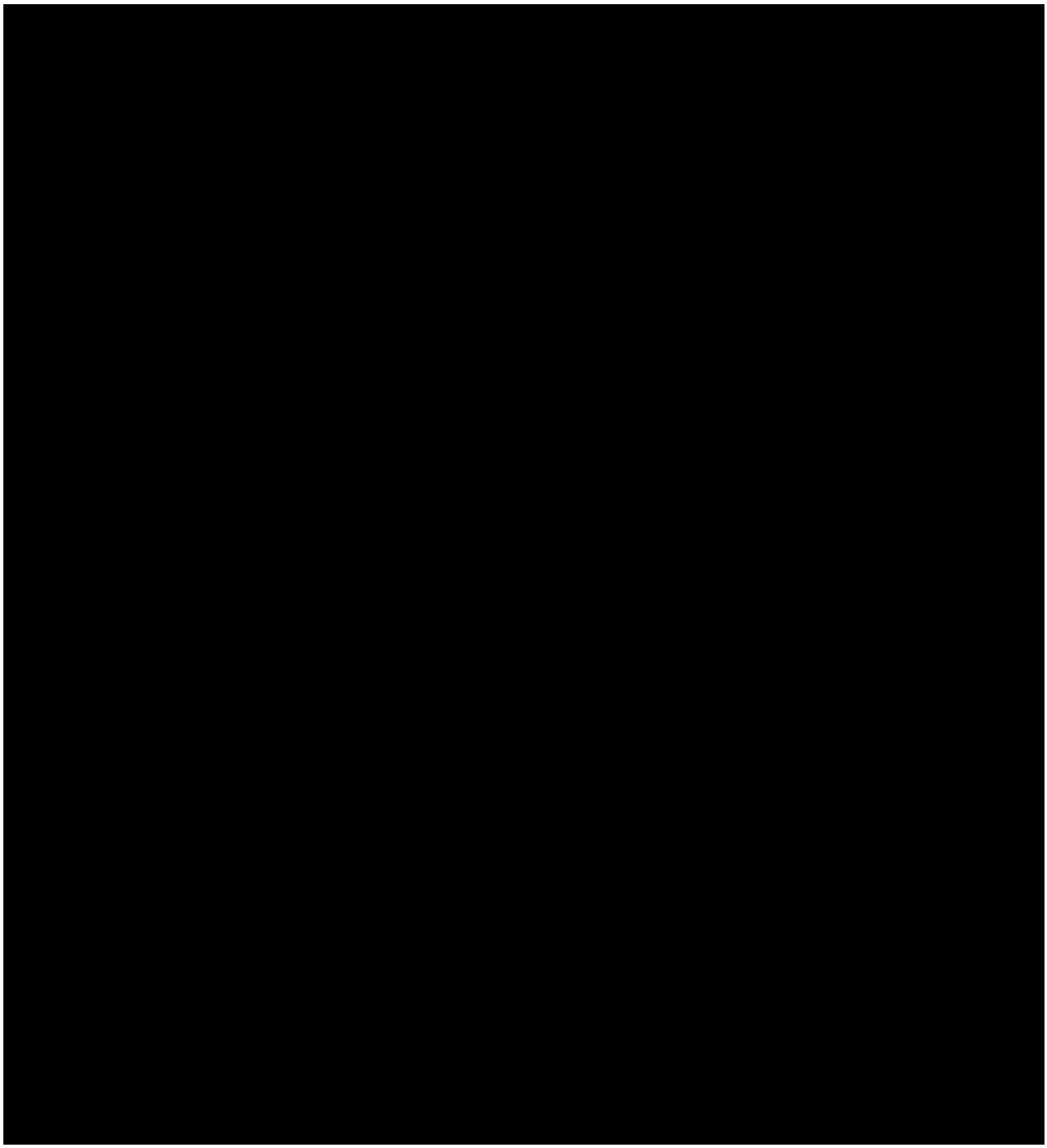


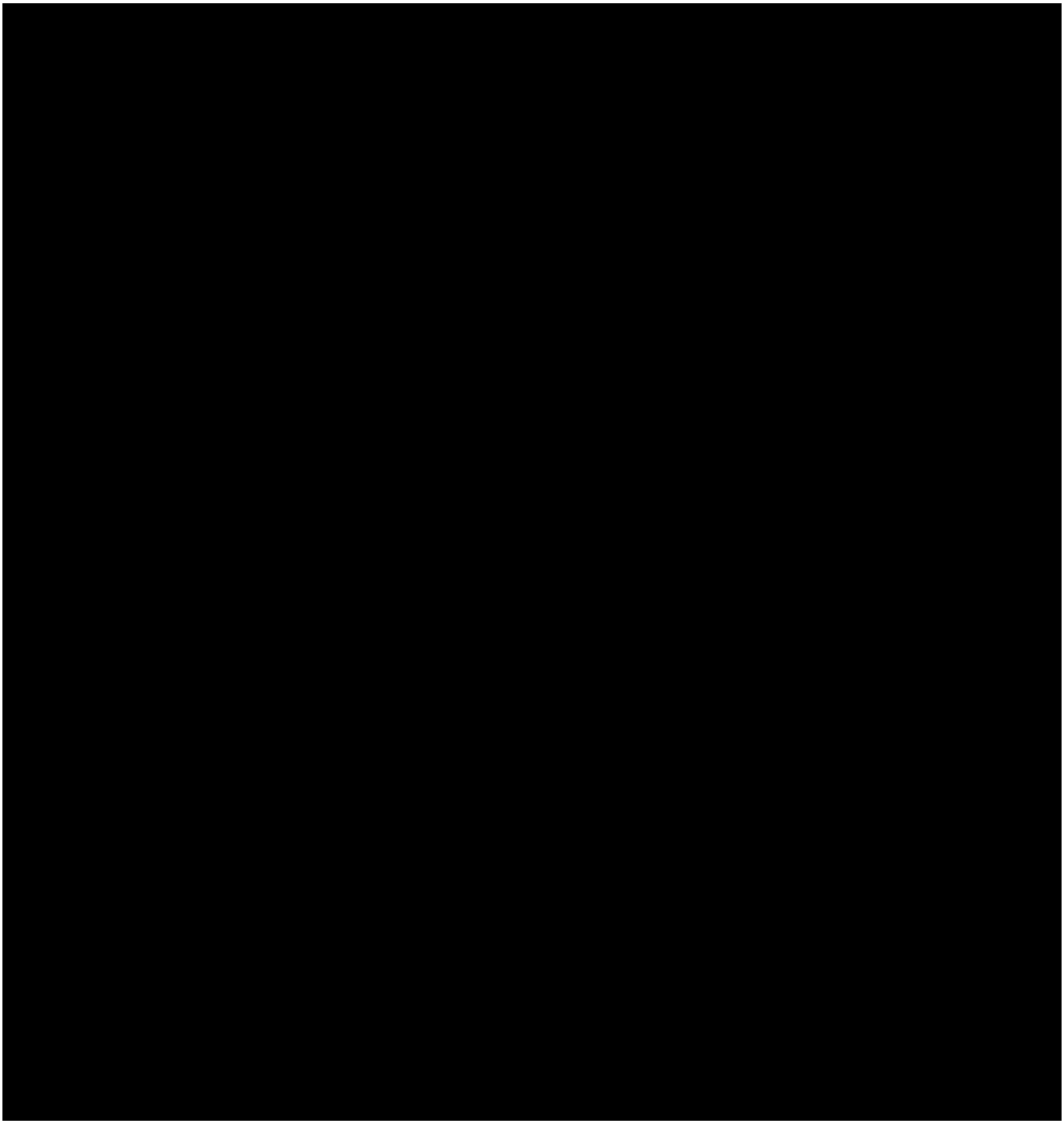
14.2. Listing of Efficacy Parameters and Study Populations Analysed

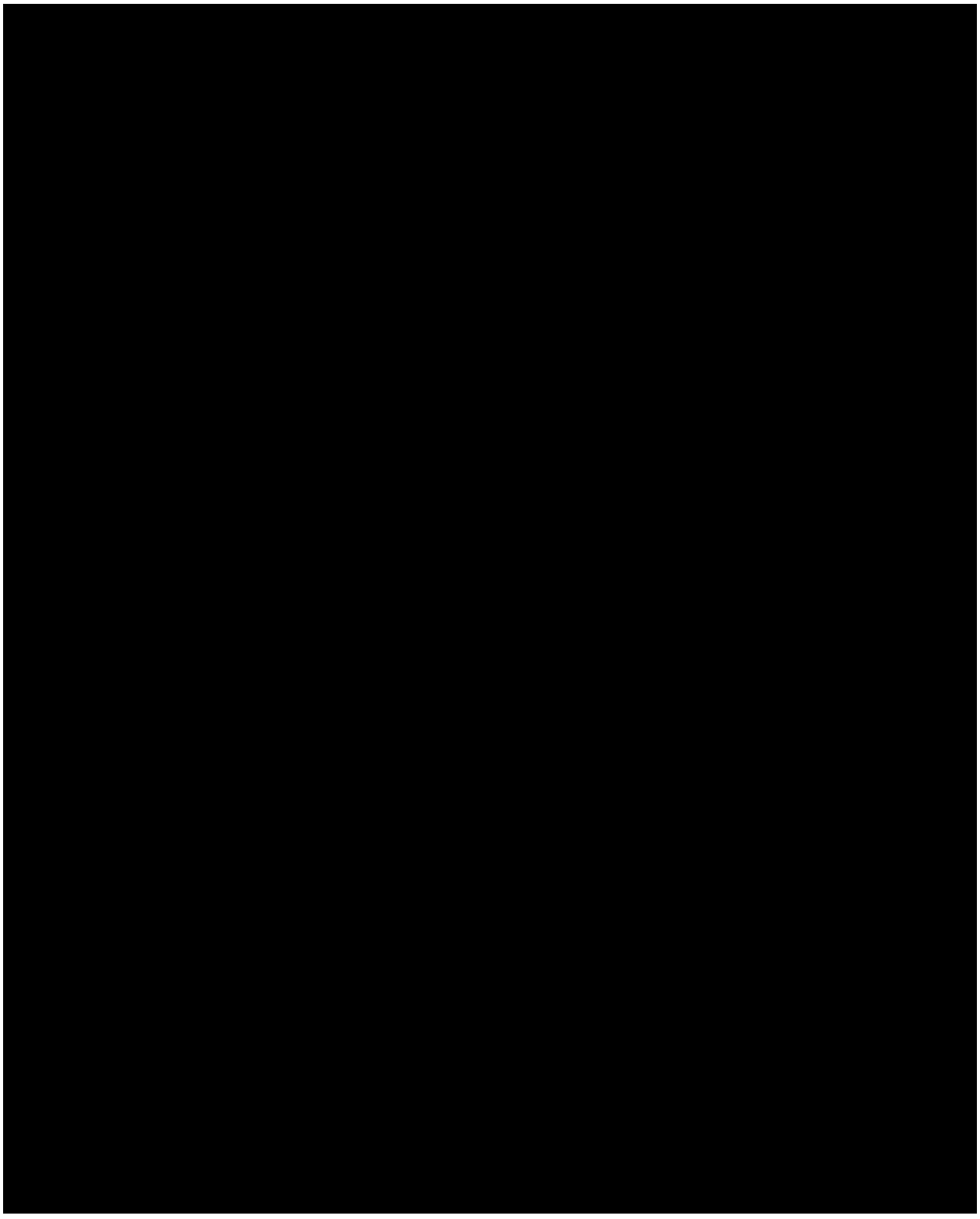
Efficacy Parameters	Response Analysed	Study Populations Analysed
Secondary Endpoints		
Clinical Response	Proportion	MITT, CP
Clinical Remission	Proportion	MITT, CP
Exploratory Endpoints		

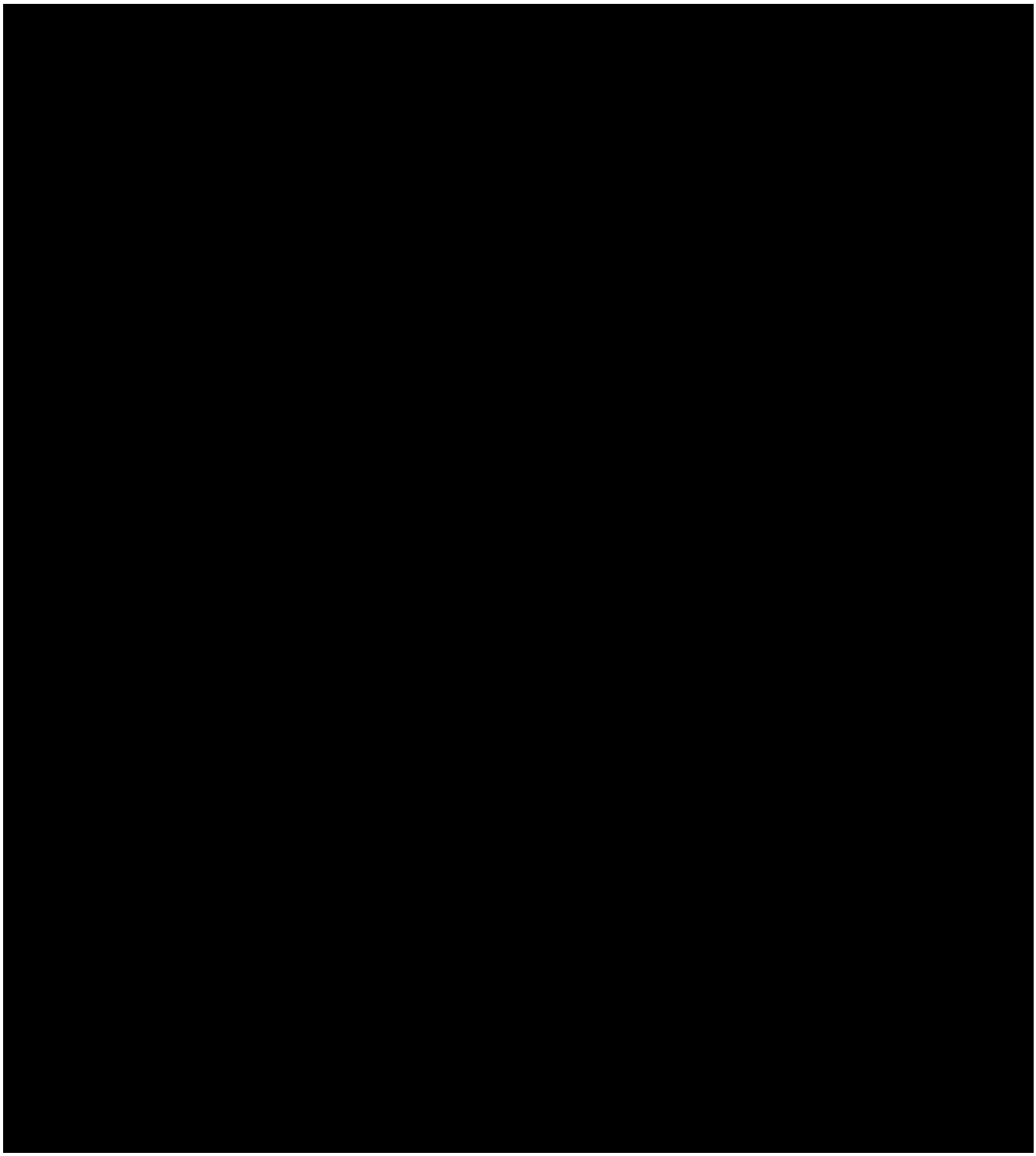


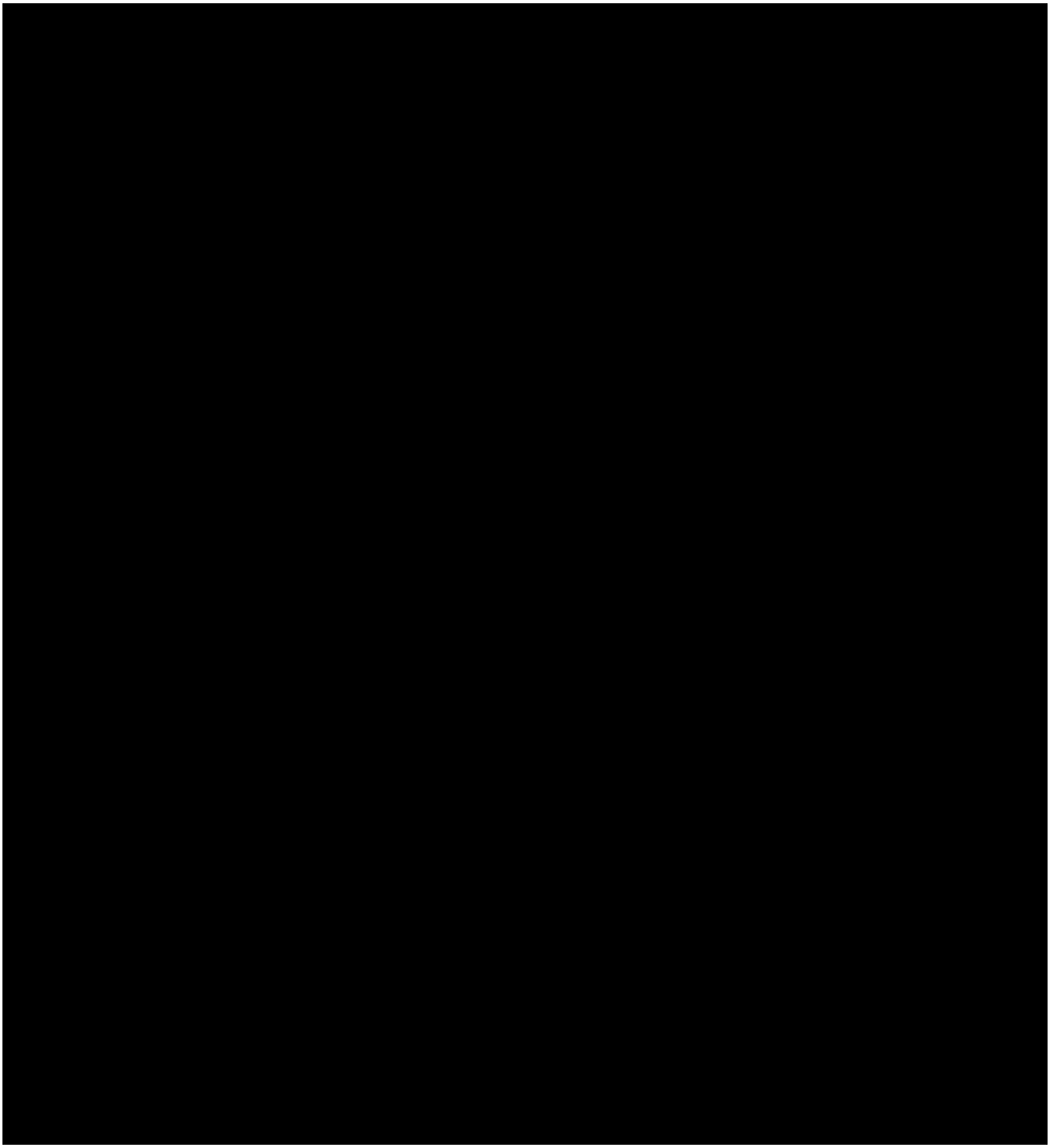


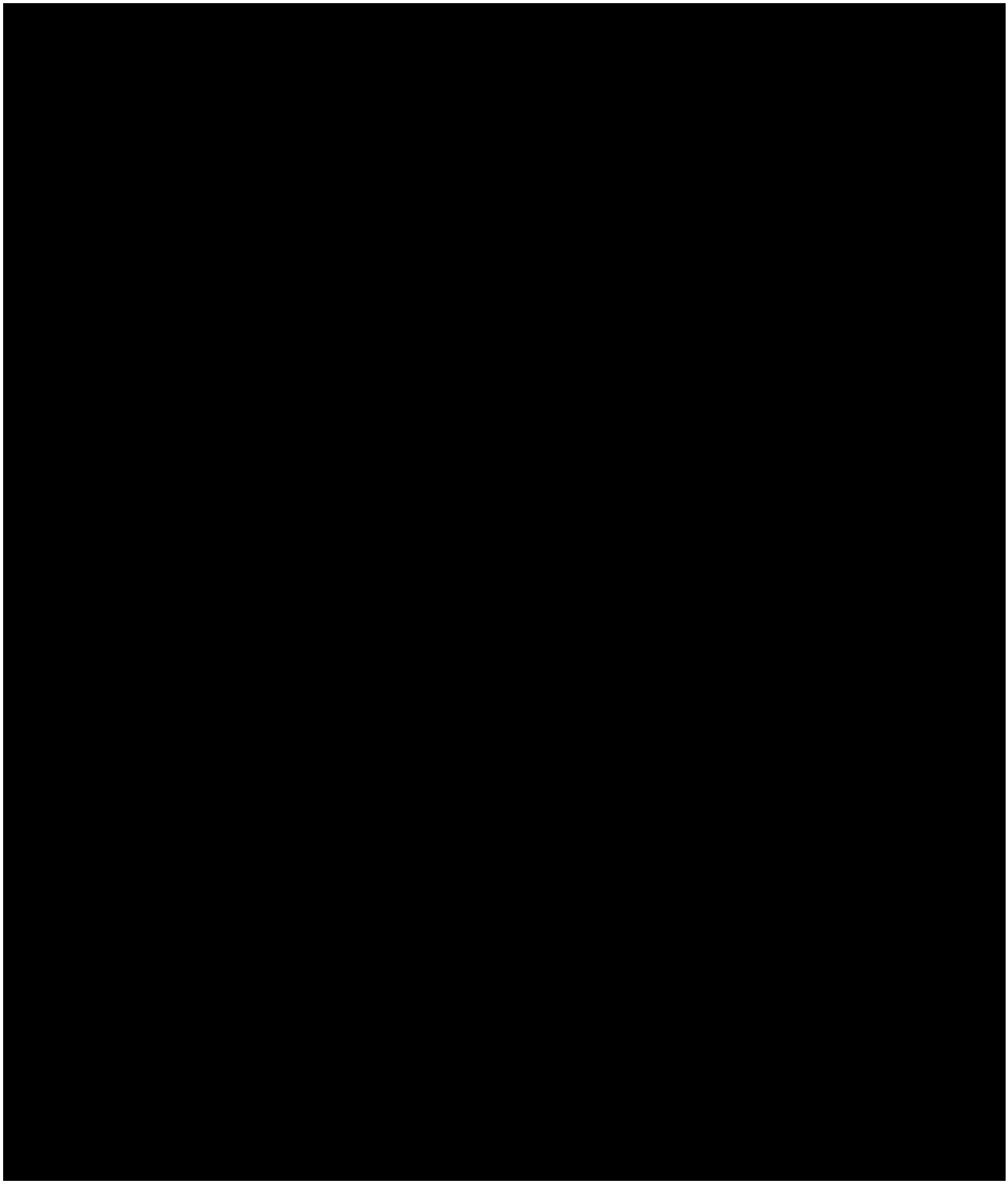


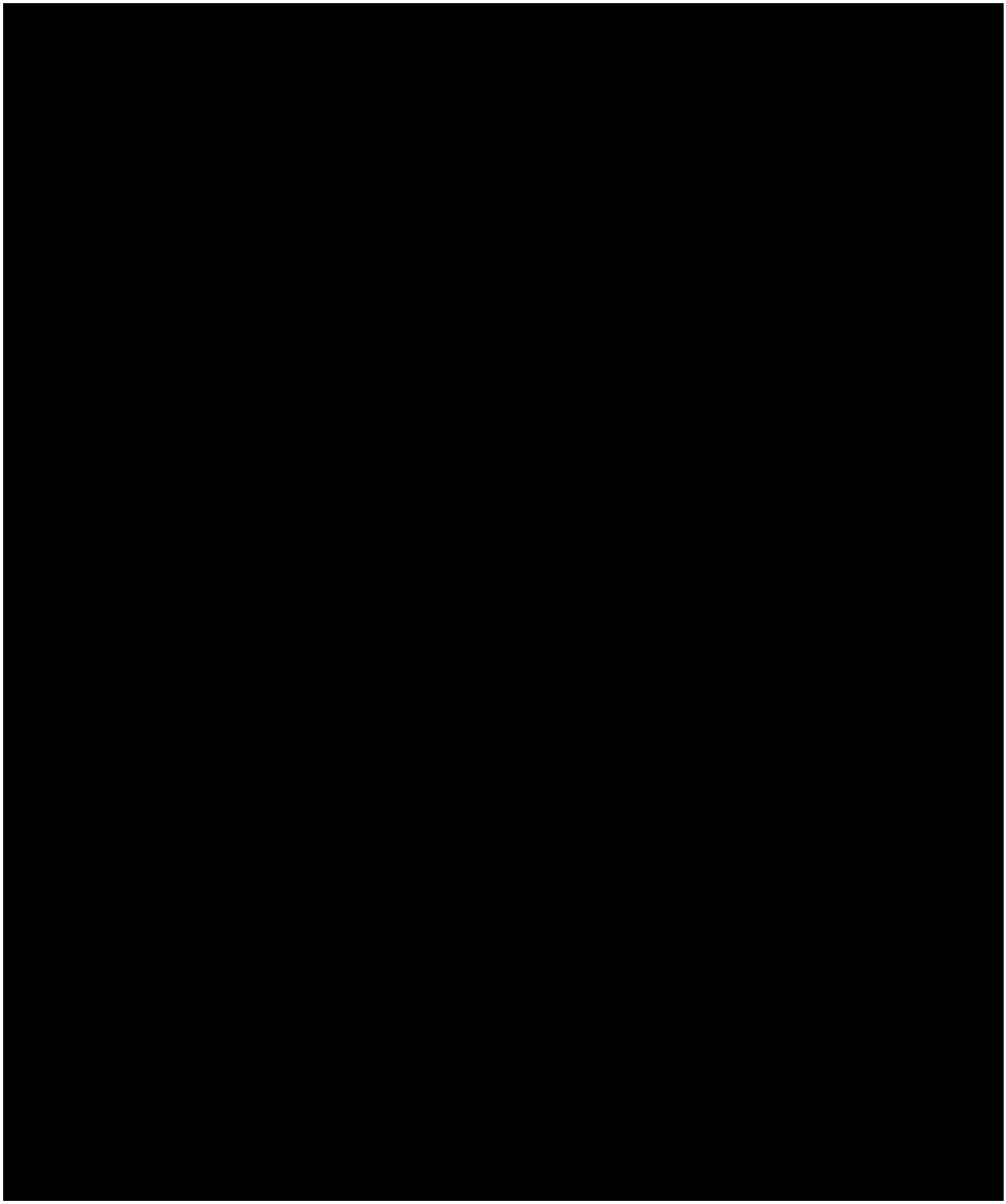


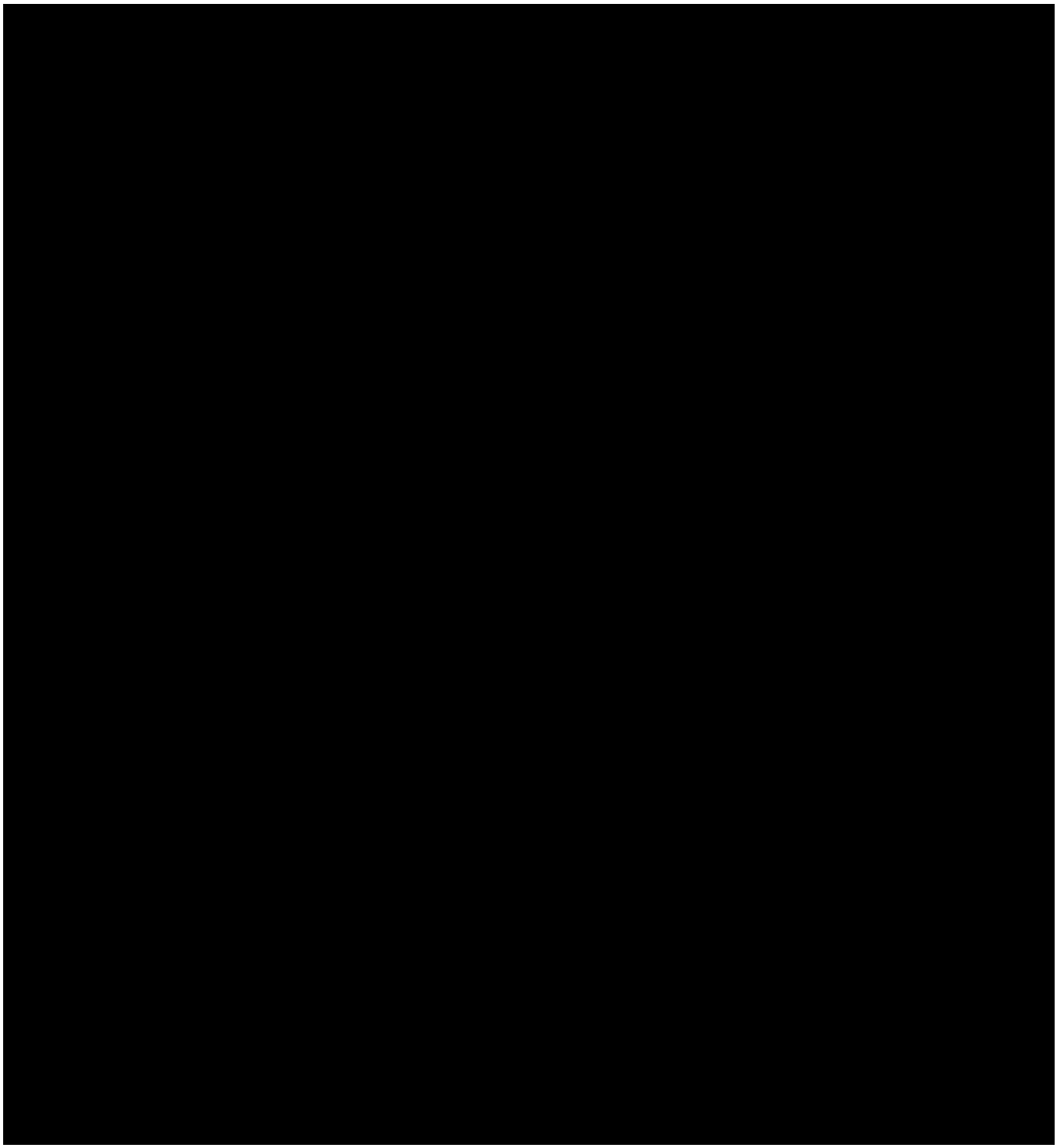


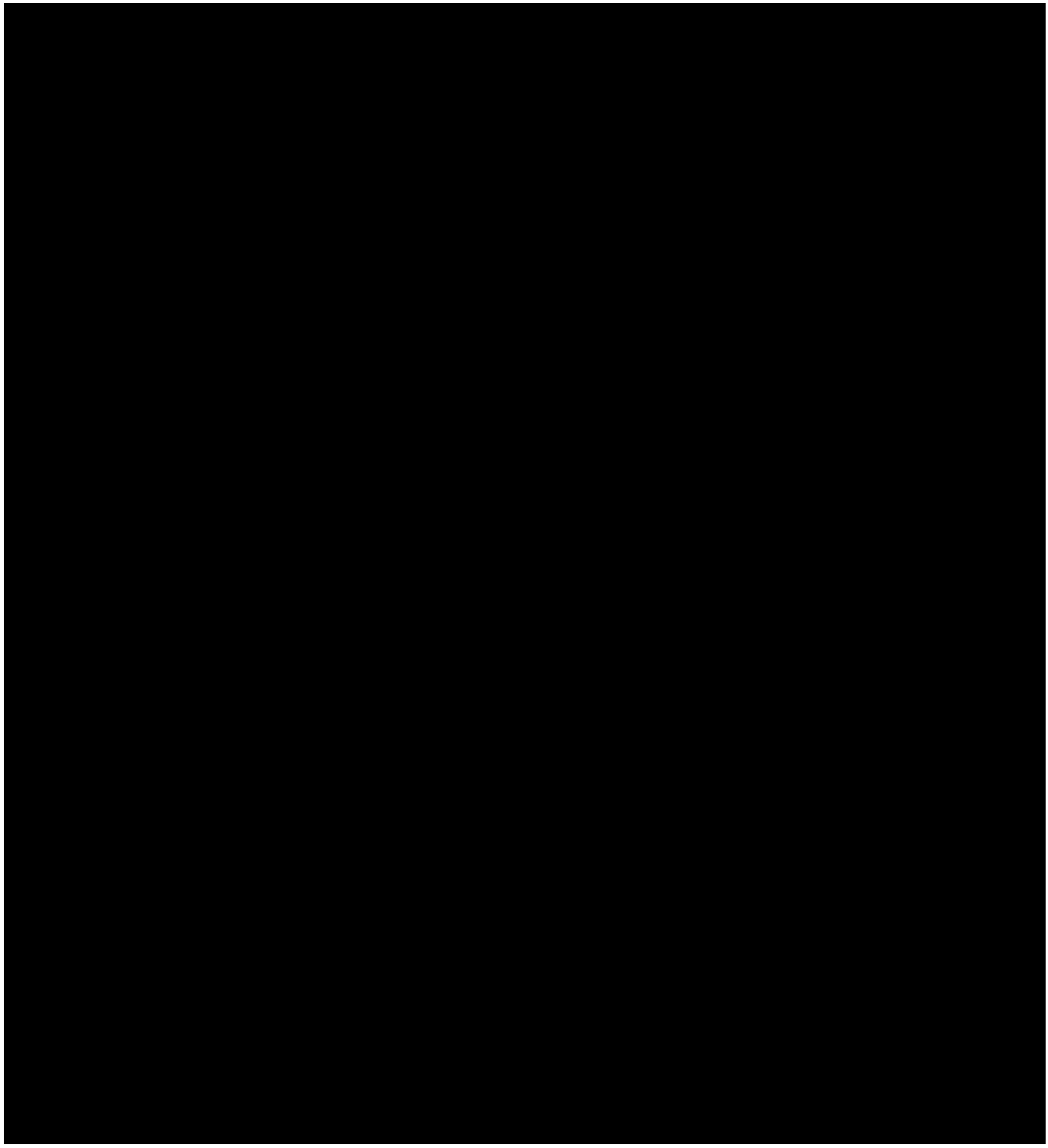












This is a representation of an electronic record that was signed electronically, and this page is the manifestation of the electronic signature.

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Title: [redacted], Biostatistics
Date: Tuesday, 27 November 2018, 02:20 PM Pacific Daylight Time
Meaning: Author Approval
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UserName: [redacted]
Title: [redacted], Biostatistics & Data Management
Date: Tuesday, 27 November 2018, 02:23 PM Pacific Daylight Time
Meaning: Approval
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