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Study ID: EB001-ABD201

Title: A Phase 2 Study to Evaluate Safety and Efficacy of EB-001 Intramuscular (IM) Injections in Reducing Musculoskeletal Pain in Subjects Undergoing Elective Abdominoplasty Surgery

Statistical Analysis Plan Version 4.0: 09 May 2018

STATISTICAL ANALYSIS PLAN

A Phase 2 Study to Evaluate Safety and Efficacy of EB-001 Intramuscular (IM) Injections in Reducing Musculoskeletal Pain in Subjects Undergoing Elective Abdominoplasty Surgery

Protocol Number: EB001 ABD201

Protocol Version 4.0 (09MAY2018)

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Bonti, Inc.

DOCUMENT VERSION CONTROL

Version Number	Date	Comments/Changes
V1.0	07NOV2018	Final SAP

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LIST OF IN-TEXT TABLES AND FIGURES

LIST OF ABBREVIATIONS (COMMONLY USED)

ADaM	Analysis Data Model
ADL	Activities of Daily Living
AE	Adverse Event
ANOVA	Analysis of variance
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
BMI	Body Mass Index
BP	Blood Pressure
CRF	Case Report Form
CSR	Clinical Study Report
CSU	Clinical Study Unit
EB-001	Botulinum Neurotoxin Serotype E Drug Product
ECG	Electrocardiogram
EOS	End of Study
ET	Early Termination
FEV1	Forced Expiry Volume 1
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
HR	Heart Rate
HSA	Human Serum Albumin
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IM	Intramuscular
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent to Treat
NPRS	Numerical Pain Rating Scale
NPRS-A	Numerical Pain Rating Scale Administered After an Activity
MEQ	morphine milligram equivalents

PACU	Post-Anesthesia Care Unit
PFT	Pulmonary Function Test
PGA	Patient Global Assessment
PP	Per Protocol
PR Interval	Time between the onset of atrial depolarization and the onset of ventricular depolarization
PT	Preferred Term
QRS duration	The interval from the beginning of the Q wave to the termination of the S wave, representing the time for ventricular depolarization
QT Interval	Interval representing the time for both ventricular depolarization and repolarization to occur
QTcB Interval	QTc interval using Bazett's correction (msec) = QT/(RR)½, where the QT interval is measured in msec and the RR interval is measured in seconds
QTcF Interval	QTc interval using Fridericia's correction (msec) = QT/(RR)⅓, where the QT interval is measured in msec and the RR interval is measured in seconds
RR Interval	Time elapsed between two consecutive R-waves.
SAE	Serious Adverse Event/Experience
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDTM	Standard Data Table Model
SOC	System Organ Class
SOT	Spread of Toxin
SpO2	Peripheral Capillary Oxygen Saturation
SRC	Safety Review Committee
SVC	Slow Vital Capacity
TEAE	Treatment Emergent Adverse Event
WHO	World Health Organization

1. PURPOSE OF THE ANALYSES

This statistical analysis plan (SAP) is based on protocol number EB001-ABD201 Amendment 3 Final Version 4.0 (09May2018) from Bonti. Inc. The SAP will be signed off before the final database lock. The SAP contains detailed information to aid in the performance of the statistical analysis and reporting of the study data for use in the final clinical study report (CSR). This SAP is being written with due consideration of the recommendations outlined in the most recent International Conference on Harmonization (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials, the most recent ICH E3 Guideline and the Guidance for Industry: Structure and Content of Clinical Study and the most recent FDA draft Guidance for Industry - Analgesic Indications: Developing Drug and Biological Products, dated February 2014.

This SAP describes the data sets that will be analyzed and the subject characteristics, safety, and efficacy assessments that will be evaluated. This SAP provides details of the specific statistical methods that will be used. If additional analyses are required to supplement the planned analyses described in this SAP, they may be completed and will be identified in the CSR.

The study was terminated early as per Sponsor's discretion. The decision was not related to any safety findings of the drug. Due to early termination of the study, descriptive summaries will be provided but no statistical comparisons will be performed for the data collected prior to the study close-out.

2. PROTOCOL SUMMARY

2.1 Study Objectives

[redacted]

2.1.2 Efficacy

To evaluate the efficacy of intraoperative administration of EB-001 IM into the RA muscles in reducing the pain and use of rescue pain medications in subjects undergoing elective abdominoplasty surgery. Efficacy will be assessed by efficacy endpoints listed in Sections 7.2.1 and 7.2.2 of the SAP.

2.2 Overall Study Design and Plan

This was planned to be a two-stage study but was terminated after 23 subjects were randomized in Stage 1. The following describes the original study design. The study was intended to be conducted at up to two surgical centers that specialize in elective abdominoplasty surgeries and to enroll up to 32-74 subjects in Stage 1 and 66 subjects in Stage 2, with up to 56-60 subjects

exposed to active drug. The study included a screening visit to determine subject eligibility. On the day of surgery, subjects were admitted to an inpatient clinic for 5 days post-operatively (Days 1-5). Intraoperatively, a single dose of EB-001 IM was given via IM injections into each RA muscles per the surgical procedure manual. Follow up visits were planned to be scheduled at days 8, 15, and 29.

The first stage was a placebo-controlled, single-blind (to subject and staff at study site), single ascending cohort study stratified by ethnicity (Hispanic and non-Hispanic) starting from Cohort 2. Four cohorts (8 subjects per cohort) were planned to be dosed at 4 ascending doses of EB-001. An optional Cohort 5 was to be considered. See Section 2.4.3 of the SAP for planned cohort details.

In the event an intolerable dose was identified, a lower (intermediary) dose could have been evaluated as proposed by the SRC. This lower dose could have been a repeat of the prior lower dose cohort or an intermediary dose between the intolerable dose and prior lower dose cohort.

In the first stage of the study, if an intolerable dose was identified (see Section 4.1.1 of Protocol), a lower dose could be evaluated as proposed by the SRC. This lower dose may be a repeat of the prior lower dose cohort or an intermediary dose between the intolerable dose and prior lower dose cohort. If the dose was an intermediary dose, a sentinel group consisting of 3 subjects (1 active: 2 placebo) would be dosed first. The SRC would review all available safety data of the prior sentinel group through at least Day 5 post-operatively, and 5 additional subjects (3 active: 2 placebo) would be dosed upon approval.

In addition, if the SRC deemed appropriate, before an intolerable dose was identified, a repeat dose, or a dose not exceeding the planned dose of the next cohort could have been evaluated.

If a repeat or lower dose (i.e., any dose at or lower than prior highest dose evaluated without meeting stopping criteria) was to be considered, subjects could be dosed without implementing sentinel dosing strategy.

All dose escalation/adjustments or additional cohorts and corresponding sample size were intended to be and were determined by the SRC.

The second stage was to be a randomized, placebo-controlled, double-blind, parallel 3-arm study. In this stage, there would be 2 doses of EB-001 (to be determined by the SRC after last dosing of last subject of Stage 1) and placebo in a 1:1:1 ratio for a total of 66 subjects stratified by ethnicity (Hispanic and non-Hispanic). The SRC would meet periodically to review safety data.

The study was terminated early (after 23 subjects were randomized and dosed) at the discretion of the sponsor.

2.3 Study Population

The study population consists of healthy males or females 23 to 55 years of age, inclusive, undergoing elective abdominoplasty surgery (Full length plication from xyphoid to pubis, removal of skin/fat flap) under general anesthesia (endotracheal or otherwise) without liposuction.

2.4 Treatment Regimens

[redacted]

2.4.2 Comparator Group

[redacted]

2.4.3 Planned Dose Cohorts

The planned cohorts were as follows:

Cohort 1 sentinel group (3 subjects; 1 active: 2 placebo) [redacted] The rest of the cohort (5 subjects; 3 active: 2 placebo) will be dosed at the same dose after review of all available data by the Safety Review Committee (SRC) is conducted, with safety data through at least Day 5 post-operatively.

Cohort 2 sentinel group (3 subjects; 1 active: 2 placebo) [redacted] after review of all available safety data from the prior cohort through at least Day 5 post-operatively. The rest of the cohort (5 subjects; 3 active: 2 placebo) will be dosed after review of all available data by the SRC is conducted, with safety data through at least Day 5 post-operatively.

Cohort 3 sentinel group (3 subjects; 1 active: 2 placebo) [redacted] after review of all available safety data from the prior cohorts through at least Day 5 post-operatively. The rest of the cohort (5 subjects; 3 active: 2 placebo) were to be dosed after review of all available data by the SRC was conducted, with safety data through at least Day 5 post-operatively.

Optional Cohort 4 sentinel group (3 subjects; 1 active: 2 placebo) [redacted] after review of all available safety data from the prior cohorts through at least Day 5 post-operatively. The rest of the cohort (5 subjects; 3 active: 2 placebo) will be dosed after review of all available data by the SRC is conducted, with safety data through at least Day 5 post-operatively.

Optional Cohort 5 (up to 42 subjects; 2 active: 1 placebo) will be dosed at a dose previously assessed after review of all available safety data from the prior cohorts through at least Day 5 post-operatively.

In the event an intolerable dose is identified, a lower (intermediary) dose may be evaluated as proposed by the SRC. This lower dose may be a repeat of the prior lower dose cohort or an intermediary dose between the intolerable dose and prior lower dose cohort.

After 23 subjects were randomized (enrollment after Cohort 3 was completed), the study enrollment was on hold and the study was later terminated at the discretion of the sponsor.

3. GENERAL ANALYSIS AND REPORTING CONVENTIONS

This section discusses general policies to be employed in the analysis and reporting of the data from the study. Departures from these general policies are provided in the specific detailed

sections of this SAP. When this situation occurs, the rules set forth in the specific section take precedence over the general policies.

All continuous study assessments will be summarized by treatment and time point (as applicable) using the descriptive statistics n, mean, SD, median, and range (minimum, and maximum). All of the categorical study assessments will be summarized by treatment and time point (as applicable) using frequency counts and rates of occurrence (%). Changes from baseline for continuous outcomes will be presented as their corresponding continuous measures for post-baseline visits. All study data will be listed by treatment dose level, subject, and time point (as applicable). The placebo group will consist of the placebo subjects from each of the different cohorts combined. For all analyses, the pooled set of placebo subjects from the various cohorts will be considered the placebo group.

No preliminary rounding will be performed; rounding will only occur after the analysis. To round, consider the digit to the right of the last significant digit: if <5, then round down; if ≥5, then round up. Means and medians will be presented with one more decimal place than the precision of the data. SDs will be presented with two more decimal places than the precision of the data. Percentages will be presented with one decimal place. Minimums and maximums will be presented with the same precision as the original data.

[redacted] The domain (Study data tabulation Model [SDTM]) and analysis (Analysis Data Model [ADaM]) data sets will be taken as input to the [redacted] programs that generate the report-ready tables, figures and listings. The submission ready SDTM and ADaM data sets will be provided to the sponsor along with display deliveries.

For all summaries, the pooled set of placebo subjects from the various cohorts will be considered the placebo group.

No testing will be conducted due to early termination of the study.

The following conventions will be used throughout the study analysis:

- Stop Time of dose administration is considered time 0.
- Assessment visit times are defined by time of treatment administration.
- Baseline value is defined as the last valid measurement prior to the start treatment administration.
- Change from baseline is defined as post-baseline value minus baseline value.
- Duration of an AE will be computed in hours in the first 96 hours during confinement and thereafter in days as the stop date of the event minus the start date plus 1. If reported as ongoing at the time of database lock, the stop date will be imputed as the date of the last visit or the last date of any AE for the subject in the database, whichever is later. Other missing dates will be imputed as described in Table 8-1.
- The number of days in the study is computed as: [Date of study completion or withdrawal minus the date of treatment administration (Day 0)] + 1.
- If duplicate values are obtained at a given visit (e.g., repeated vital sign measurements), the last value will be used unless it is noted that the measurement was in error for that value. Values that compromise interpretation will not be used in summaries (e.g., values

that were obtained post-dose will not be summarized as pre-dose values).

- If a pre-rescue NPRS is recorded in the same minute as a rescue medication is recorded, the NPRS will be assumed to have occurred PRIOR to the administration of rescue.
    - If a subject experiences inadequate analgesic relief and takes non- protocol specified rescue medication, they will be treated as 'discontinued' from the efficacy portion of the study. The date/time of the discontinuation will be assumed to be the date/time of the start of non-protocol specified rescue captured on protocol deviations eCRF. Early discontinuation from the efficacy portion affects the computation of the analgesic endpoints only.

4. ANALYSIS POPULATIONS

4.1 Efficacy Population

- The modified Intent to Treat (**mITT**) population will include all randomized patients who receive study drug and have at least one non- missing NPRS assessment within the primary endpoint timeline (12-96 hours, inclusive). In addition to the primary analysis of the primary endpoint, all efficacy analyses will be performed using this population. Analyses will be performed on subjects using their randomized treatment group.
- All **Randomized** Subjects: All participants who are successfully screened and randomized.

For all efficacy analyses, subjects will be analyzed based on the mITT population.

4.2 Safety Population

The Safety population will include all subjects exposed to any amount of study drug. All safety analyses will be performed using the safety population and be based upon the actual treatment received if different from that randomized.

4.3 Disposition of Subjects

All subjects and the populations for which they qualify will be listed. If a subject is randomized but does not complete the surgery or receive study drug, they will not be counted in any analyses. Subjects who are screened and who fail screening or withdraw consent prior to randomization or are randomized but not treated will be listed and summarized in total and by reason. Subjects who are randomized, subjects who are included in each study population (mITT, and Safety), subjects who are treated, subjects who complete follow-up (safety only and safety/efficacy), and subjects who withdraw early from the study and the reason for withdrawal will be summarized by treatment group and overall in a subject disposition summary table. Subjects who are discontinued from the efficacy portion of the study or who discontinue the study but agree to be followed for safety will also be presented.

4.4 Major Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol or Good Clinical Practice (GCP) requirements. All deviations will be addressed in study source documents and transcribed into the electronic case report form (eCRF). All protocol deviations will be designated as major or minor prior to database lock by the sponsor's medical monitor.

All protocol deviations will be presented in a by-subject listing. Any site-specific deviations noted by the clinical monitors will be documented in the final CSR.

[redacted]

6. MEASUREMENTS OF TREATMENT COMPLIANCE

Study medication exposure will be provided in a data listing. Because study medication is administered at the study center by trained study personnel, compliance with study medication is not expected to be an issue and no summary will be provided.

7. EFFICACY EVALUATION

7.1 Overview of Efficacy Analysis Issues

7.1.1 Handling of Dropouts or Missing Data

If a subject receives protocol specified rescue medication, a windowed LOCF imputation method will be used and the pre-rescue pain NPRS/NPRS-A score for each assessment (pain at rest, pain after walking) will be carried forward for 4 hours. Intermittent missing pain scores (due to subject sleeping, etc.) will not be imputed, and AUC will be calculated based on non-missing values.

In AUC analyses, no other imputation will be performed for subjects who have missing values due to early drop out. In addition, there will be no imputation of missing data for safety or other efficacy assessments.

7.1.2 Assessment Time Windows

Assessment times will be based on the nominal protocol-specified assessment times.

7.2 Efficacy Outcomes

Overall pain assessment at rest using NPRS will be performed every 2 hours ((±15 minutes) post-dose after the subject is awake and lucid from surgery, until discharge. Assessments will also be made after subjects are discharged on Days 6-29 and will be entered into the Pain Assessment Diary (see Section 7.1.1.31.1 of the protocol).

Pain assessment after an activity using NPRS-A will be performed at baseline (prior to surgery), every 8 hours (±15 minutes) post-dose on Day 1, and every 6 hours on day 2 and after, after the subject is awake and lucid from surgery until discharge. The Investigator will ask subjects to sit up in the bed unassisted at an angle of approximately 45 degrees or more, swing legs out, put feet down, stand up, and walk approximately 10 feet. Subjects will then be asked to rate their level of worst pain when performing the activities using the NPRS-A. NPRS-A will also be assessed at each follow-up visit on days 8, 15, and 29 (End of Study (EOS)/ Early Termination (ET)).

During the in-patient period (up to Day 5), NPRS / NPRS-A assessments scheduled between 00:00 and 06:00 may be skipped if the subject is sleeping. However, the 12-hour pain assessment must be completed even when the assessment falls between 00:00 and 06:00.

NPRS and NPS-A are ranged based on an 11-point numerical scale, where 0 means no pain and 10 means the worst pain imaginable.

In the event rescue medication is used, an assessment of pain using the NPRS prior to administering rescue medication will be recorded. If subjects cannot perform NPRS-A prior to taking rescue medication due to intolerable pain, this assessment may be omitted.

7.2.1 Primary Efficacy Endpoint

Area under the curve (AUC) of subject's assessment of pain using NPRS between 12- and 96-hour post-surgery ($AUC_{12\text{-}96}$).

7.2.2 Secondary Efficacy Endpoints

- AUC assessment of overall pain profile using NPRS:
  - Over the first 96 hours post-surgery ($AUC_{0\text{-}96}$)
  - Over the first 72 hours post-surgery ($AUC_{0\text{-}72}$)
  - Over the first 48 hours post-surgery ($AUC_{0\text{-}48}$)
  - Over the first 24 hours post-surgery ($AUC_{0\text{-}24}$)
  - Over the period of 12 to 24 hours post-surgery ($AUC_{12\text{-}24}$)
  - Over the period of time t to 96 hours post-surgery (($AUC_{t\text{-}96}$), whereas t is any time during confinement
- Pain assessment at rest after discharge using NPRS at Days 6 through 29.
- Pain assessment after sitting up in the bed unassisted at an angle of approximately 45 degrees or more, swinging legs out, putting feet down, standing up, and walking approximately 10 feet using NPRS-A (NPRS administered after an activity) over the first 96 hours and at Days 8, 15, 29.
- Patient global assessment (PGA) of pain control
- Use of rescue medications over various postsurgical periods

7.3 Analysis Methods

7.3.1 AUC Outcomes

All AUC calculations will be done using the standard trapezoidal rule

$$\text{AUC} = \sum_{i=0}^{x} \left(\frac{NPRS_i + NPRS_{i+1}}{2}\right) * (T_{i+1} - T_i)$$

Where: NPRSi = NPRS at time i, and ($T_{i+1} - T_i$) is the Time difference in hours between time i and time i+1. The AUC calculation of NPRS-A will be calculated using the same formula, substituting $NPRS\text{-}A_i$ in place of $NPRS_i$.

In the event that protocol specified rescue medication is used during the time period of AUC calculation, for purposes of AUC calculation, the NPRS and/or NPRS-A score taken prior to the dispensation of rescue medication will be used as the NPRS and/or NPRS-A score for the following 4-hour period and the observed AUC score will be ignored.

The individual NPRS and NPRS-A scores through Day 5 (prior to discharge) will be presented graphically over time by cohort and presented in subject listings.

The computed AUCs will be listed for the individual subjects along with the respective endpoints that they were calculated on.

7.3.2 NPRS and NPRS-A Outcomes

The individual NPRS and NPRS-A outcomes after discharge will be summarized at each time point similar to the primary analysis.

7.3.3 Patient Global Assessment (PGA) of Pain Control

To assess pain control, each subject will be asked the following question: “Overall, how well your pain has been controlled during the last 24 hours?” at 96±2 hours (Days 5), and on Days 8, 15, and 29 (EOS/ET), using a 4-point categorical scale (Poor (0), Fair (1), Good (2), Excellent (3)).

PGA summary tables will include the proportion of subjects with each score, by cohort and time point. PGA scores will be listed.

7.3.4 Rescue Medication

Rescue medication when needed is a maximum of 5 doses of 50 µg IV Fentanyl (up to 250 µg total) during the first 120 minutes after post-anesthesia care unit (PACU) arrival. After the first 120 minutes have elapsed, subjects during confinement may only receive oxycodone 5 mg every 4 hours, PRN. Following discharge from the hospital, subjects may use 500 mg acetaminophen PRN, a maximum of 6 times per day (not to exceed 3 g total dose in 24 hours). Subjects will be instructed not to take rescue medication until their pain reaches at least a moderate intensity, and to complete an entry in their Pain Assessment Diary prior to taking rescue medication. All post-discharge rescue medication usage must be recorded in the Rescue Medication Diary. Subjects’ rescue use will be captured on the Rescue Medication eCRF during the Inpatient portion of the study and in the Subject Rescue diary after discharge until Day 29. If additional rescue medication, other than the study rescue medications, appear on the concomitant medications page and can be identified, those medications will also be included in summaries as described below.

The summary will include all rescue taken by subjects regardless of their status (discontinued from efficacy or not).

Total amount of opioids (MEQ) used during the first 96 hours will be summarized overall (0-96hrs). Table 7-1 will be used to calculate the morphine milligram equivalents (MEQ) for each medication. The total opioid consumption for each day for each subject will be calculated as the sum of the MEQs of all of the medications taken on that day. For example, if a subject takes 5 MEQ morphine on Day 1 and Day 2, and 10 MEQ of Oxycodone on Day 2, the total consumption for Day 1 is 5 MEQ, and the total consumption for Day 2 is 15 MEQ. Subjects that take no opioids on a day will have a total opioid consumption value of zero for that day.

Table 7-1 Table of Morphine Milligram Equivalents

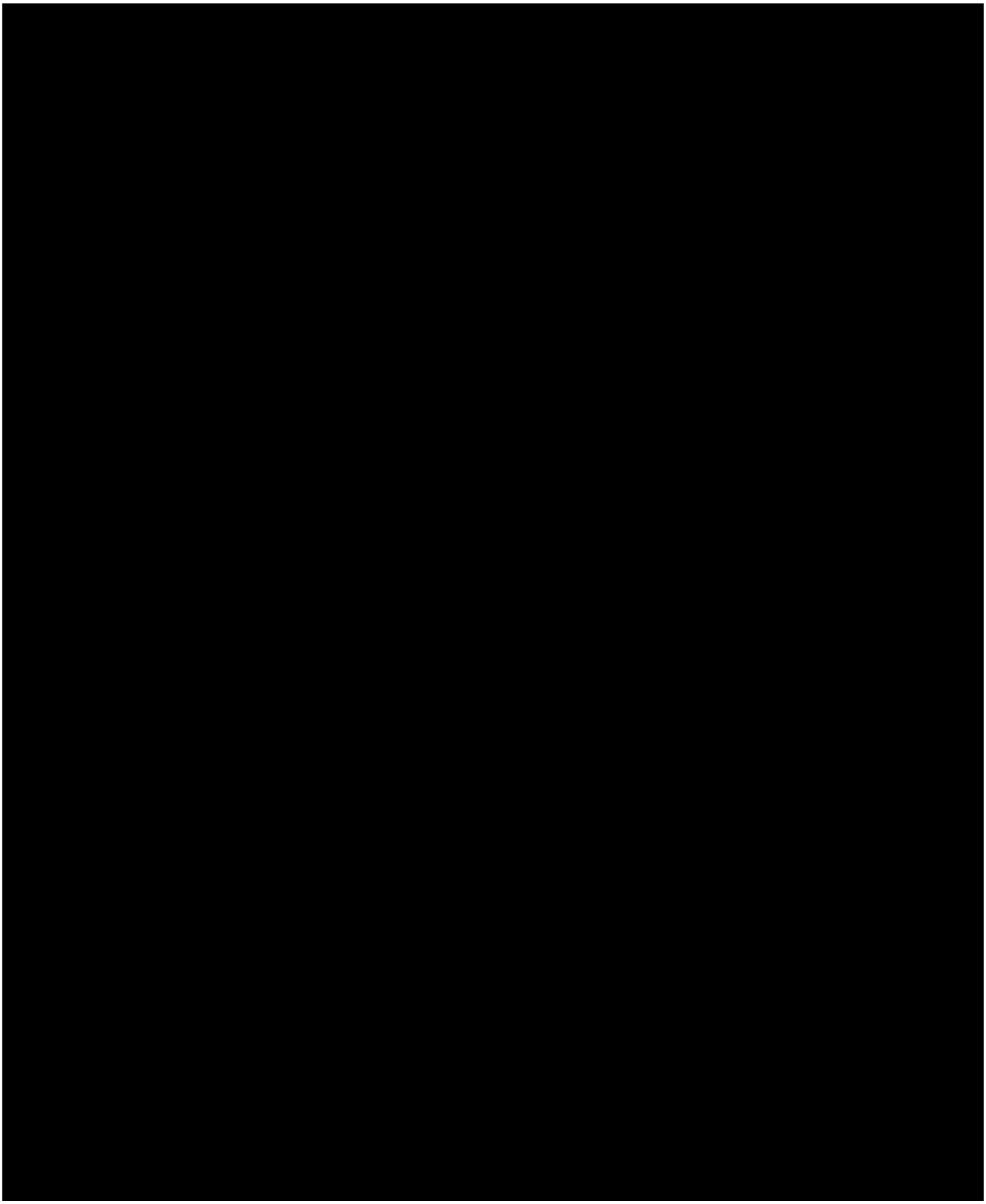
(from cdc.gov/drugoverdose/pdf)

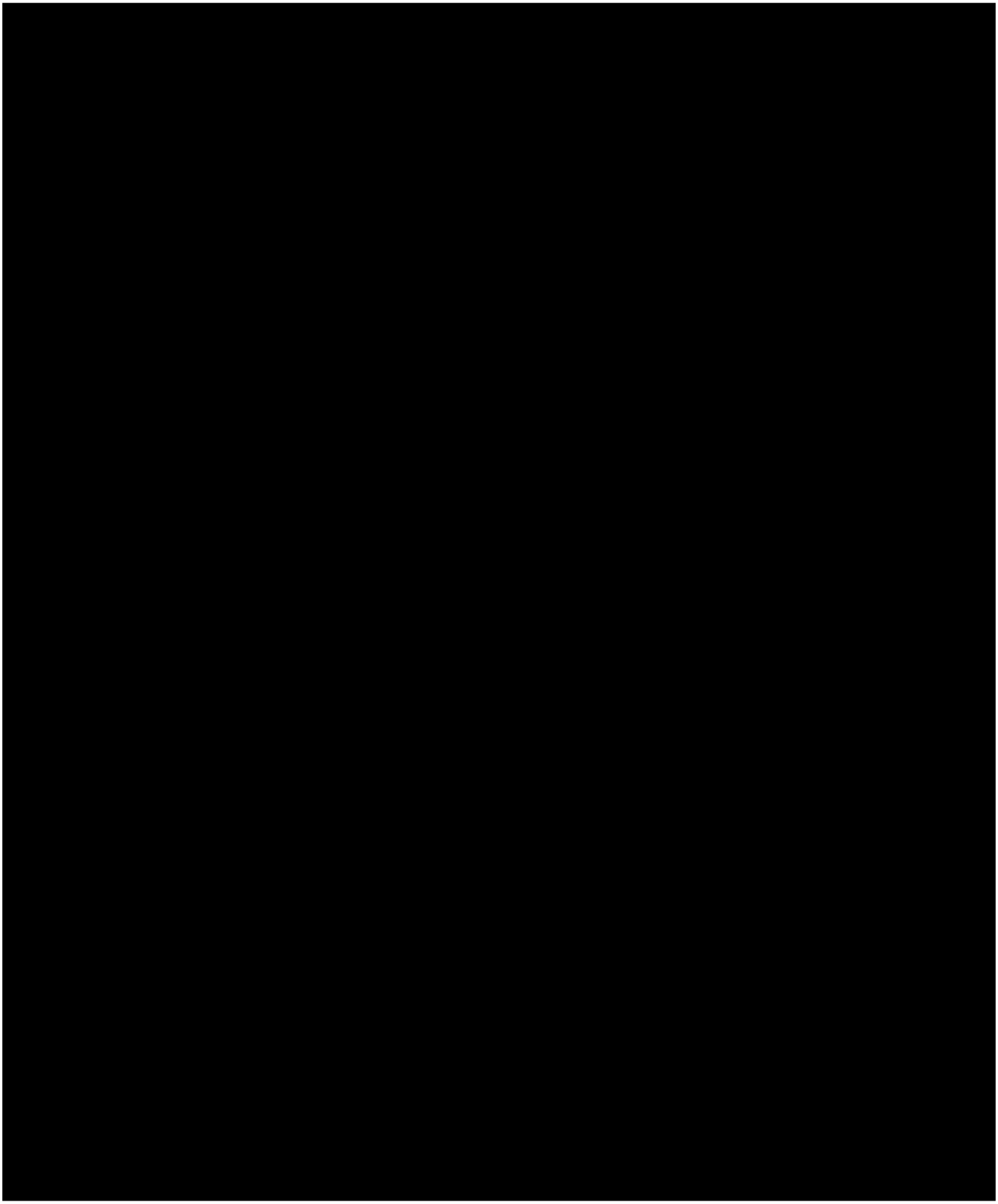
Opioid (Doses in mg/day)	Conversion Factor
Codeine	0.15
Fentanyl transdermal (in mcg/hr)	2.4
Hydrocodone	1
Hydromorphone	4
Morphine	1
Oxycodone	1.5
Oxymorphone	3

Total dose of Oxycodone used during the first 96 hours and the number of doses of Oxycodone will both be summarized separately Summaries will be shown both for overall (0-96hrs). Total Oxycodone use will also be presented graphically overall and by cohort.

A by-subject listing presenting the use of rescue medication by time of dosing will be given.

[redacted]





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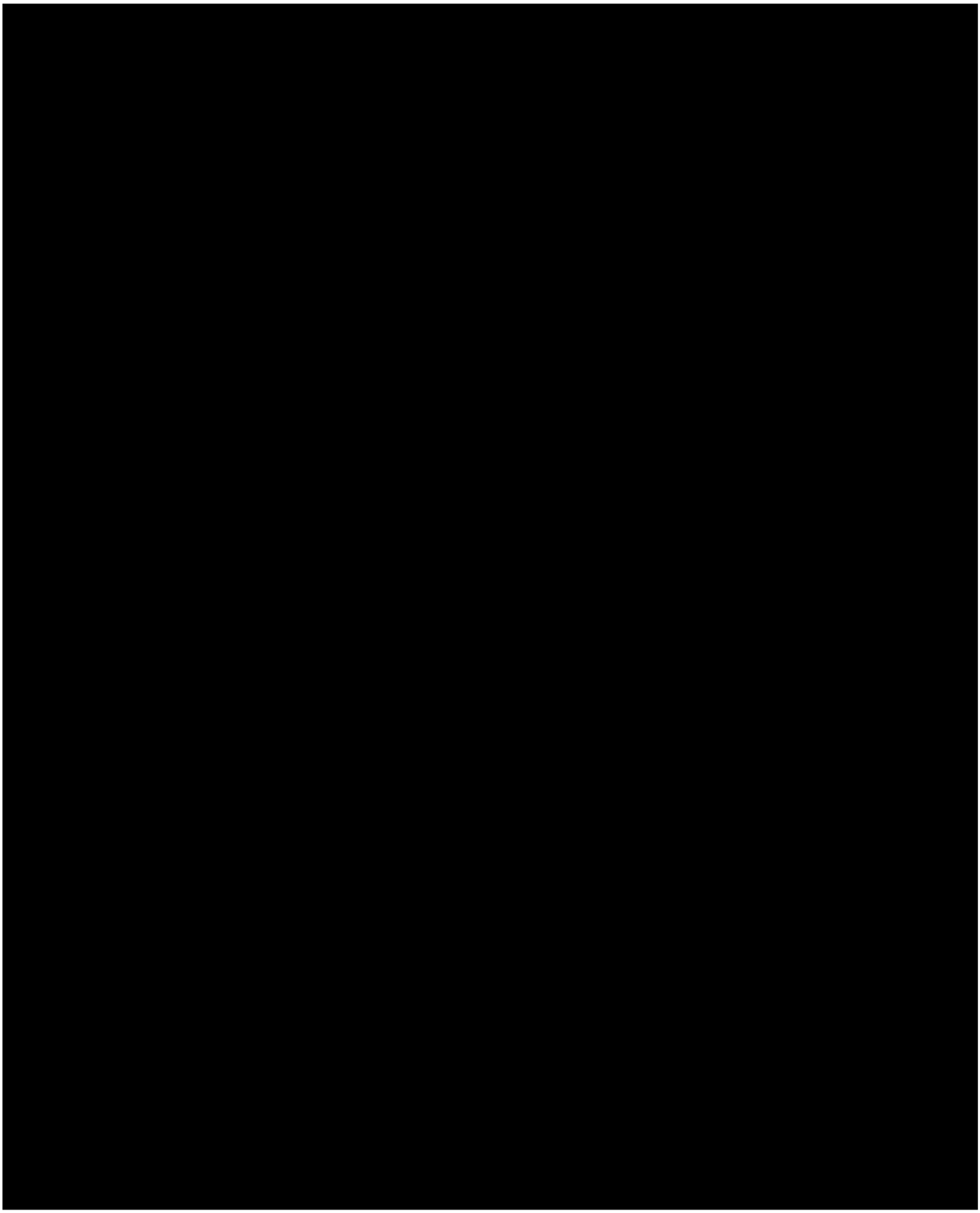


[redacted]

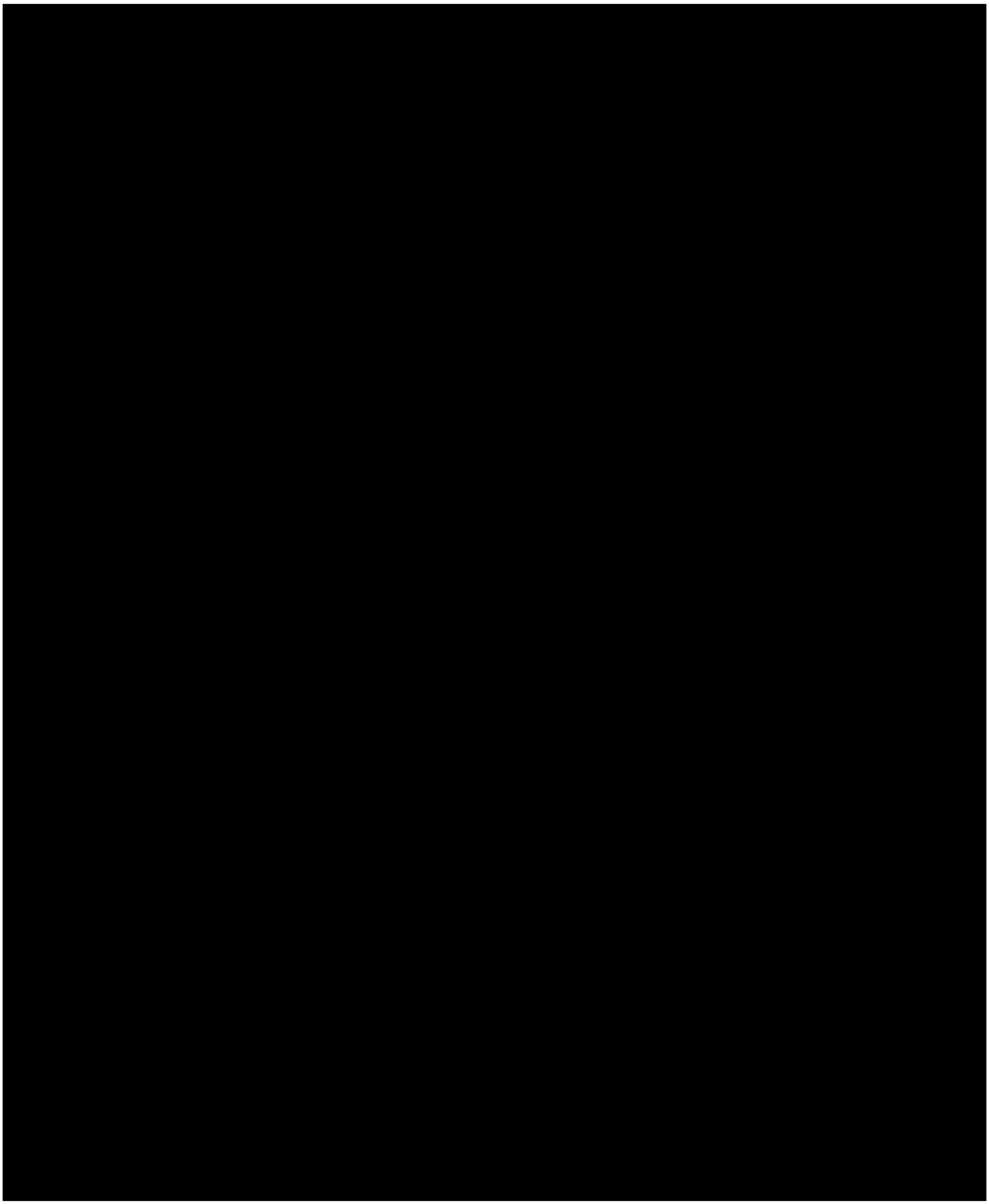
11. INTERIM ANALYSES AND DATA MONITORING

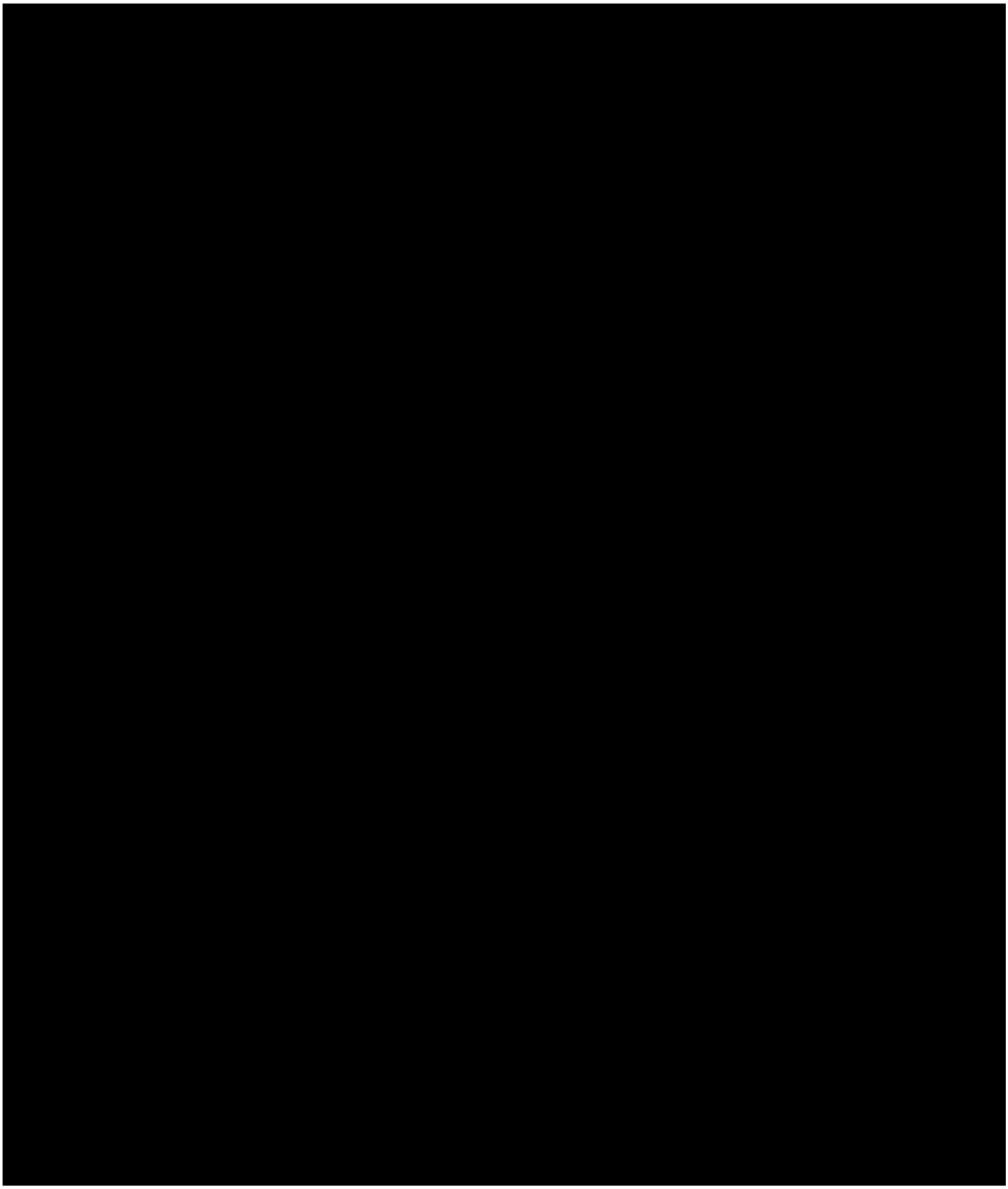
There are no planned interim analyses for this study. Blinded safety meetings were held by the SRC after each cohort.

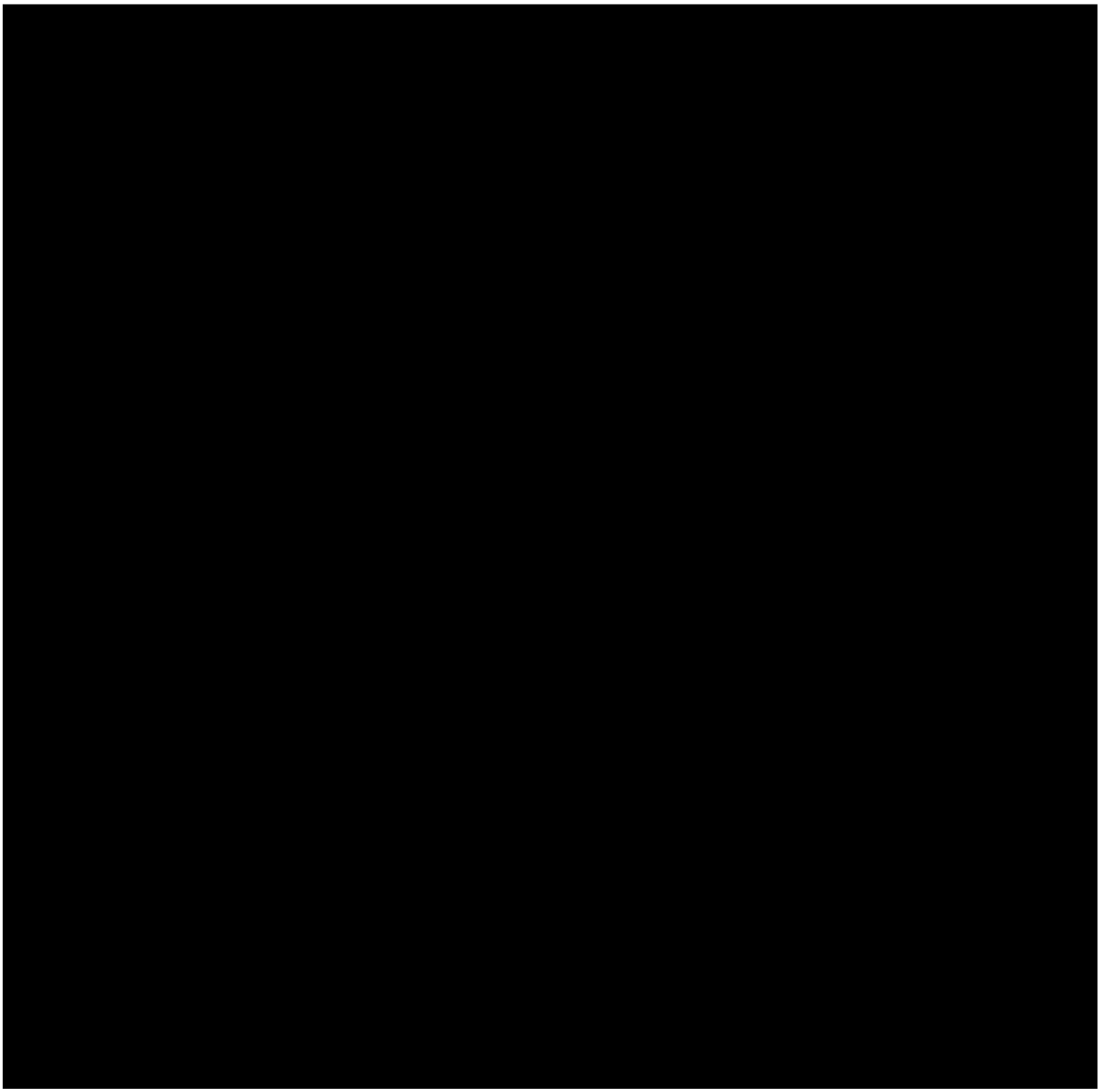
12. CHANGES TO THE ANALYSES PLANNED IN THE PROTOCOL

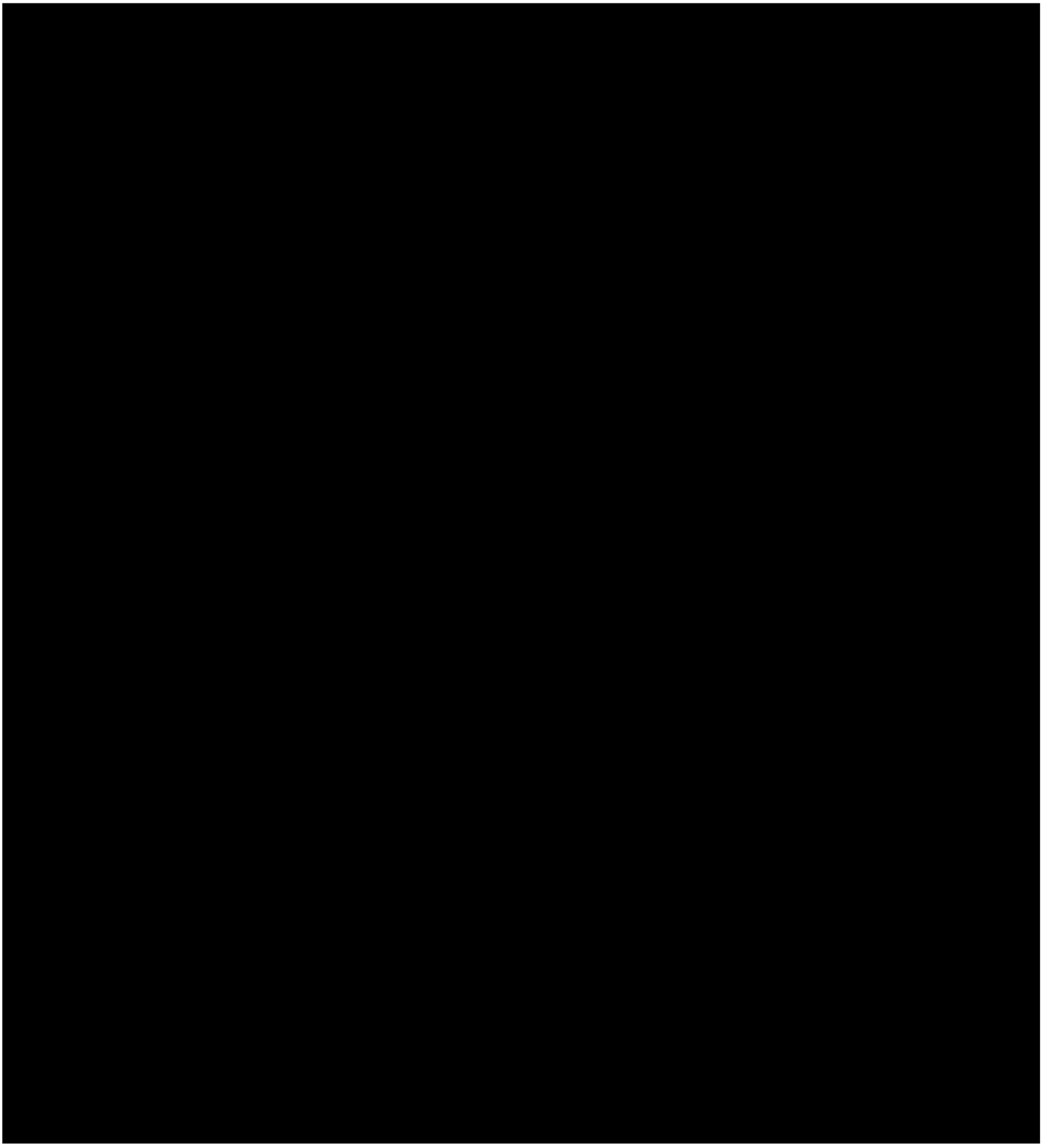
Any deviations from the statistical plan will be described and a justification given in the CSR.

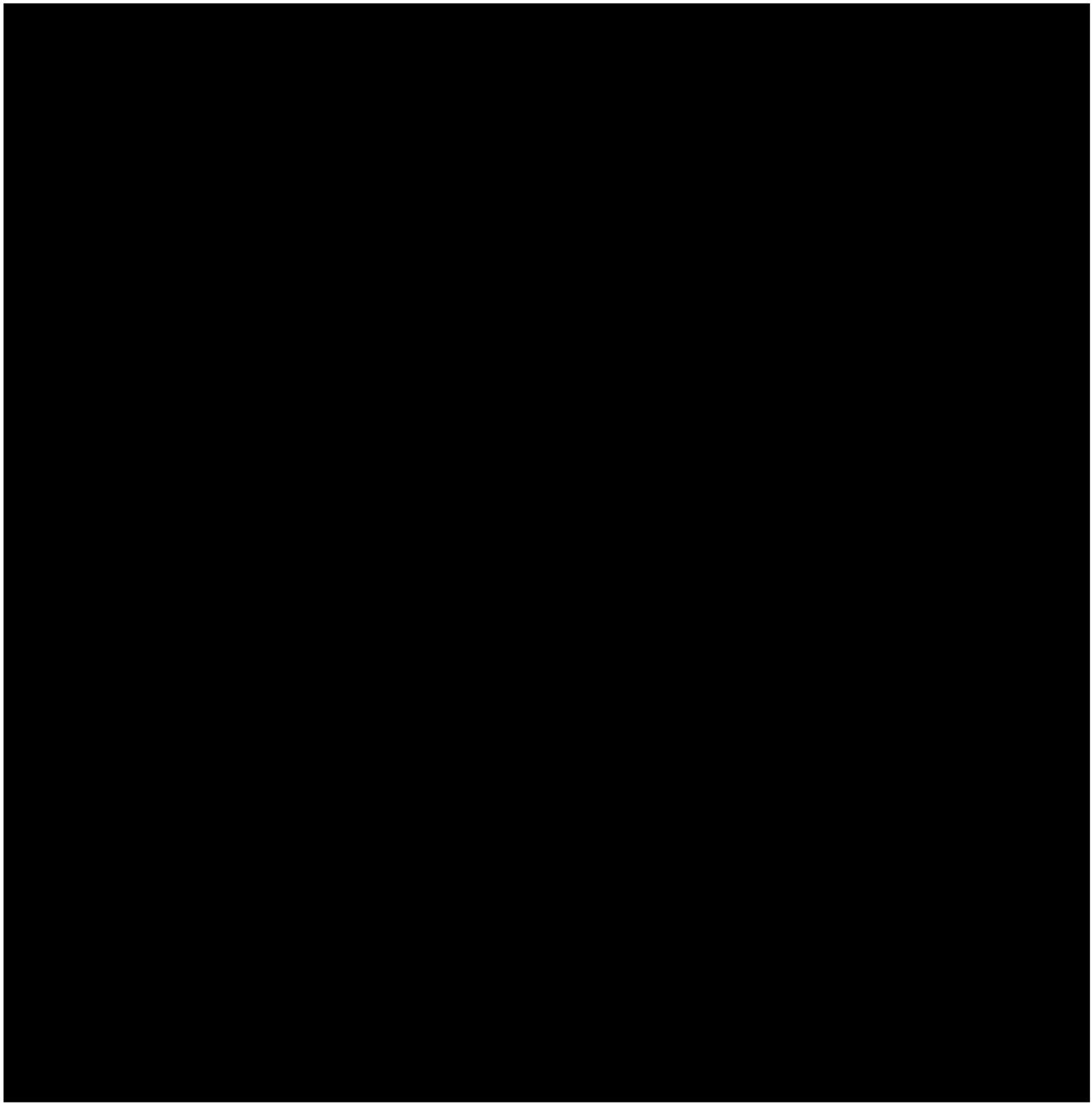
[redacted]











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Parties agreed to: Earvin Liang, Jennifer Nezzer, Song Liou