STATISTICAL ANALYSIS PLAN

A Phase 2, Multi-center, Randomized, Double-Masked and Placebo-Controlled Study Evaluating the Efficacy and Safety of YP-P10 Ophthalmic Solution Compared to Placebo in Subjects with Dry Eye

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Statistical Analysis Plan Approval

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List of Abbreviations

ADaM	Analysis Data Model
AE	Adverse Event
ANOVA	Analysis of Variance
ATC	Anatomical Therapeutic Chemical
BID	*Bis in die* (Twice Daily)
CAE®	Controlled Adverse Environment®
CI	Confidence Interval
CRF	Case Report Form
CRO	Contract Research Organization
CS	Clinically Significant
CSR	Clinical Study Report
DED	Dry Eye Disease
eCRF	Electronic Case Report Form
ETDRS	Early Treatment of Diabetic Retinopathy Study
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IOP	Intraocular Pressure
IP	Investigational Product
ITT	Intent-to-Treat
IWRS	Intractive Web Response System
LOCF	Last Observation Carried Forward
logMAR	Logarithm of the Minimum Angle of Resolution
LS	Least Squares
MedDRA	Medical Dictionary for Regulatory Activities
MCMC	Markov Chain Monte Carlo
mm	Millimeters
mmHg	Millimeters of Mercury
MMRM	Mixed-Effect Model for Repeated Measures
NC	Not Calculable
NCS	Not Clinically Significant
NEI	National Eye Institute
OSDI©	Ocular Surface Disease Index
PDF	Portable Document Format
PP	Per Protocol
PT	Preferred Term
RTF	Rich Text Format
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis System®
SD	Standard Deviation
SDC	Statistics & Data Corporation
SDTM	Study Data Tabulation Model
SE	Standard Error

SOC	System Organ Class
TE-SAE	Treatment-Emergent Serious Adverse Event
TEAE	Treatment-Emergent Adverse Event
TFBUT	Tear Film Break-Up Time
VA	Visual Acuity
VAS	Visual Analog Scale
WHODrug	World Health Organization Drug Dictionary

1. Introduction

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and reporting in detail for the efficacy and safety assessments, as well as relevant data collected in protocol YPP10-001, version 5.0 dated 03MAR2023.

This SAP is being written with due consideration of the recommendations outlined in the most recent International Conference on Harmonisation (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials, the most recent ICH E3 Guideline, entitled Guidance for Industry: Structure and Content of Clinical Study Reports, and the most recent ICH E9 (R1) addendum on estimands and sensitivity analysis in clincal trials to the guideline on statistical principles for clinical trials.

The statistical analysis methods presented in this document will supersede the statistical analysis methods described in the clinical protocol. If additional analyses are required to supplement the planned analyses described in this SAP, they may be completed and will be identified in the clinical study report.

2. Study Objectives

The objective of this study is to compare the safety and efficacy of YP-P10 Ophthalmic Solution to placebo for the treatment of the signs and symptoms of the dry eye.

3. Study Design and Procedures

3.1 General Design

This study is a randomized, double-masked, placebo-controlled, and multi-center study to compare the efficacy and safety of YP-P10 Ophthalmic Solution to YP-P10 Placebo Ophthalmic Solution (vehicle) for treating dry eye. Approximately [redacted] subjects will be randomized with a ratio of [redacted] into one of the three groups at Visit 2 (Day 1):

1) 0.3% YP-P10 Ophthalmic Solution (low dose, N = [redacted])
2) 1% YP-P10 Ophthalmic Solution (high dose, N = [redacted])
3) YP-P10 Placebo Ophthalmic Solution (placebo, N = [redacted])

Subjects will be instructed to administer study drug one drop in each eye, twice daily (BID) for 12 weeks.

Of the [redacted] randomized subjects, approximately [redacted] subjects will be of first, second, or third generation Japanese descent, verified by review of subject's family tree, government-approved ID (e.g., birth certificate), and affirmative response to a Japanese lifestyle questionnaire. Inclusion of Japanese subjects will only be applicable at one site (Aesthetic Eye Care Institute, CA).

Subjects, Sponsor, Contract Research Organization (CRO), and site personnel will be masked to treatment assignment. During the 7-day run-in period prior to randomization, all subjects will receive vehicle in each eye BID. During the screening period, two 90-minute exposures to the Controlled Adverse Environment (CAE®) will be conducted to ascertain eligibility to enter the study at Visit 1 (Day -7) and Visit 2 (Day 1).

Subjects who qualify after the initial screening visit will enter the run-in phase, where they will self-administer vehicle BID for approximately 7 days. Those who qualify at Visit 2 (Day 1) will be randomized to receive study drug in a double-masked fashion for 12 weeks. Subjects will self-administer drops BID and will complete daily diary assessments as instructed.

The CAE® exposure will occur at Visit 1 (Day -7) and Visit 2 (Day 1); with Pre-CAE®, during CAE®, and Post-CAE® assessments of ocular signs and symptoms.

Study drug will be discontinued at Visit 6 (Day 85). Subjects will exit from the study at this visit.

The total number of expected participants, including screen failures, is approximately [redacted] subjects.

Table 1 shows the scheduled study visits, the planned study day and the acceptable visit window for each study visit:

Table 1. Study Visit Windows

[redacted]

3.2 Schedule of Visits and Measurements

The schedule of visits and assessments is provided in Appendix 1.

4. Study Endpoints

4.1 Efficacy Endpoints

4.1.1 Primary Efficacy Endpoints

The primary efficacy endpoints of sign and symptom are:

Sign: Mean change from baseline (Visit 2 [Day 1] Pre-CAE®) to Visit 6 (Day 85) in total corneal fluorescein staining score of the study eye using the modified National Eye Institute (NEI) scale.

- Corneal fluorescein staining will be assessed at five regions [redacted] on the cornea of each eye of a subject at Pre-CAE® of Visit 1 and Visit 2, and Visits 3-6. Grading of the corneal staining will be based on the [redacted]

- The total corneal staining score is calculated as [redacted].
- The mean change from baseline at Visit 6 (Day 85) in total corneal fluorescein staining will be calculated as [redacted]

Symptom: Mean change from baseline (Visit 2 [Day 1] Pre-CAE®) to Visit 6 (Day 85) in ocular discomfort score of both eyes using the Visual Analog Scale (VAS).

- Ocular discomfort measured by [redacted] will be assessed at all visits, including pre-CAE® of Visit 1 (Day -7) and Visit 2 (Day 1), and Visit 3 (Day 15) through Visit 6 (Day 85). [redacted]
- The mean change from baseline Visit 2 (Day 1) Pre-CAE® to Visit 6 (Day 85) in ocular discomfort using [redacted] will be calculated as the [redacted]

4.1.1.1 Statistical Hypotheses

The statistical hypotheses are two-sided hypotheses.

[redacted]

[redacted]

4.1.1.2 ESTIMANDS

The following intercurrent events will potentially occur during trial conduct.

Estimand 1 for the Primary Analyses:

Describes strategies of handling intercurrent events that potentially occur during the trial conduct for the primary analyses of the primary efficacy endpoints. The proposed strategies will potentially provide relatively conservative treatment effect based on the assumptions associated with each intercurrent event.

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

Estimand 2 for Sensitivity Analyses:

- [redacted]
- [redacted]
- [redacted]
- [redacted]

4.1.2 SECONDARY EFFICACY ENDPOINTS

The secondary efficacy endpoints include:

- Fluorescein staining of the cornea on the [redacted]

- Corneal fluorescein staining on the [redacted] will be assessed for each eye at all visits, including pre-CAE® of Visit 1 (Day -7) and Visit 2 (Day 1), and Visit 3 (Day 15) through Visit 6 (Day 85)

- Lissamine green staining of the conjunctiva on the [redacted] by region: [redacted]
  - Lissamine green staining using [redacted] will be assessed for each eye at all visits, including pre-CAE® of Visit 1 (Day -7) and Visit 2 (Day 1), and Visit 3 (Day 15) through Visit 6 (Day 85)
  - The conjunctival sum will be calculated as the sum of grading score of six regions [redacted] for study eye, ranging from [redacted] per eye
- Mean change from baseline to each follow-up visit in conjunctival redness (Ora Calibra® Conjunctival Redness Scale)
  - Conjunctival redness using Ora Calibra® Scale will be assessed in each eye at both pre- and post-CAE® of Visit 1 (Day -7) and Visit 2 (Day 1), and Visit 3 (Day 15) through Visit 6 (Day 85)
  - The scale ranges from [redacted]
- Mean change from baseline to each follow-up visit in Unanesthetized Schirmer's Test in the study eye
  - Unanesthetized Schirmer's Test will be assessed in each eye at pre-CAE® of Visit 1 (Day -7) and Visit 2 (Day 1), and Visit 3 (Day 15) through Visit 6 (Day 85)
- Proportion of subjects demonstrating [redacted] increase from baseline to each follow-up visit in the Unanesthetized Schirmer's Test
  - Change from baseline in the Unanesthetized Schimer's Test will be dichotomized to [redacted]
- Mean change from baseline to each follow-up visit in Tear Film Break-Up Time (TFBUT) in the study eye
  - TFBUT will be assessed in each eye at all visits including Pre-CAE® and Post-CAE® of Visit 1 (Day -7) and Visit 2 (Day 1), and Visit 3 (Day 15) through Visit 6 (Day 85).
- Mean change from baseline to each follow-up visit in Ocular Surface Disease Index© (OSDI©)
  - OSDI is assessed at pre-CAE® of Visit 1 (Day -7) and Visit 2 (Day 1), and Visit 3 (Day 15) through Visit 6 (Day 85)

- The subjects will be asked the [redacted] questions on the OSDI questionnaire to assess the severity of dry eye disease at the subject level. [redacted]

  The total OSDI score will be assessed on a scale of [redacted]

  Total OSDI score and subtotal OSDI scores will be calculated as follows:

  [redacted]

  The number of questions answered in the denominator will exclude questions with a response of "N/A". OSDI will be analyzed for total OSDI score and subtotal scores.

- Mean change from baseline to each follow-up visit in [redacted] symptom assessment
  - The symptoms Burning/stinging, itching, foreign body sensation, blurred vision, eye dryness, photophobia, and pain will be measured by [redacted] at Pre-CAE® of Visit 1 (Day -7) and Visit 2 (Day 1), and at Visit 3 (Day 15) through Visit 6 (Day 85).
  - [redacted]
- Daily compliance diary
- Drop comfort (Ora Calibra® Drop Comfort Scale and Questionnaire)
  - In the Ora Calibra® Drop Comfort Scale, subjects are asked to rate each eye following drop instillation on a [redacted], where [redacted]. The scale will be completed by subjects at Visit 2 (Day 1), Post-CAE® immediately upon instillation, [redacted] post instillation, and [redacted] post instillation. zWithin-visit change in drop comfort will be calculated for each eye by taking the difference between drop comfort at [redacted] or at [redacted] post instillation and drop comfort immediately upon instillation, where negative values indicate an increase in drop comfort.
  - In the Ora Calibra® Drop Comfort Questionnaire, [redacted]

[redacted]

For each endpoint, change from baseline will be calculated for each subject as [redacted]

4.2 Safety Endpoints

The safety endpoints include the following:

- Adverse events (AE)
- Visual acuity (VA)
- Slit-lamp biomicroscopy
- Intraocular pressure (IOP)
- Dilated Fundoscopy

5. Study Treatments

5.1 Methods of Assigning Subjects to Treatment Groups

Each subject who meets all the inclusion and none of the exclusion criteria at Visit 1 (Day -7) and Visit 2 (Day 1) will be assigned a randomization number at the end of Visit 2 (Day 1). The Interactive Web Response System (IWRS) will be used to assign all randomization numbers.

Randomization and kit numbers will be assigned to each subject as they are entered into the IWRS. Subjects will be stratified by the following sign and symptom at baseline (Table 2):

- Stratification Factor 1: Total corneal fluorescein staining score of the study eye [redacted] at Visit 2 (Day 1), Pre-CAE® [redacted]
- Stratification Factor 2: Ocular discomfort score using the VAS at Visit 2 (Day 1), Pre-CAE® [redacted];

Table 2. Two Stratification Factors for Randomization at Visit 2, Pre-CAE®

[redacted]

The site staff will dispense kit(s) required at each visit. Both the randomization number and the dispensed study drug kit number(s) will be recorded on the subject's source document and electronic case report form (eCRF). Subjects, Sponsor, CRO, and site personnel will be masked to treatment assignment.

5.2 Masking and Unmasking

All subjects, investigators, and study personnel, including Yuyu Pharma, Inc., Statistics & Data Corporation (SDC), and Ora, Inc. site personnel involved with the conduct of the study, data quality assurance, and statistical analyses will be masked with regard to treatment assignments until database lock. When medically necessary, the investigator may need to determine what treatment group has been assigned to a subject. When possible (i.e., in non-emergent situations), Ora, Inc. and Yuyu Pharma, Inc. personnel should be notified before unmasking study drug. Ora, Inc. and Yuyu Pharma, Inc. must be informed immediately about any unmasking event.

If an investigator identifies a medical need for unmasking the treatment assignment of a subject, they should contact Ora, Inc. and/or the medical monitor prior to unmasking the identity of the investigational product (IP), if possible. Ora, Inc. will ask the site to complete and send them the Unmasking Request Form. Ora, Inc. will notify Yuyu Pharma, Inc. and jointly will determine if the unmasking request should be granted. They may consult the medical monitor as needed. The result of the request will be documented on the Unmasking Request Form. The investigator will unmask the subject's treatment assignment using IWRS upon approval of the request. The investigator will complete the Unmasking Memo form and include it in the subject's study file and provide a copy for the Trial Master File. For each unmasked request, the reason, date, signature, and name of the person who unmasked the subject must be noted in the subject's study file.

Unmasked subjects will be discontinued from the study. Unmasked subjects will be followed for safety monitoring until resolution of the AE or study completion, whichever occurs last.

6. Sample Size and Power Considerations

This study is expected to enroll a total of [redacted] randomized subjects, with [redacted] subjects in each group. Of the [redacted] randomized subjects, approximately [redacted] subjects will be of first, second, or third generation Japanese descent, verified by review of subject's family tree, government-approved ID (e.g., birth certificate), and subject's affirmative response to a Japanese lifestyle questionnaire. Approximately [redacted] subjects will be screened to enroll [redacted] randomized subjects. Assuming approximately 10% drop out rate, [redacted] subjects per group are expected to complete the study. A sample size of [redacted] subjects per group will provide 80% power to detect a statistically significant standardized treatment effect size of [redacted] between YP-P10 Ophthalmic Solution and placebo at the two-sided significance level of [redacted] for each primary endpoint.

7. Data Preparation

7.1 Input Data

Study data will primarily be recorded on the eCRFs supplied by SDC using iMednet v2020.1.0.

When all prerequisites for database lock have been met, the database will be locked. Following database lock, approval will be obtained from Yuyu Pharma, Inc. to unmask the study. Any changes to the database after data have been locked can only be made with the approval of Yuyu Pharma, Inc. in consultation with SDC.

Final analysis will be carried out after the following have occurred:

- Database lock has occurred with written authorization provided by appropriate SDC and Yuyu Pharma, Inc. personnel.
- Protocol deviations have been identified and status defined (major/minor deviations) prior to database lock.
- Analysis populations have been determined.
- Randomized treatment codes have been unmasked.

7.2 Output Data

Data from Electronic Data Capture (EDC) and external data will be transferred to Biostatistics and incorporated into standard formats following the Study Data Tabulation Model (SDTM). Data will then be mapped to analysis datasets using the Analysis Data Model (ADaM). Both SDTM- and ADaM-formatted data will be used to create the subject listings, while all tables and figures will be based on the ADaM-formatted data.

SDTM will follow the SDTM Version 1.7 model and will be implemented using the SDTM Implementation Guide Version 3.3 and the SDTM Controlled Terminology Version 2022-03-25. ADaM data will follow the ADaM Version 2.1 model and will be implemented using the ADaM Implementation Guide Version 1.1. Both SDTM and ADaM will be validated using Pinnacle 21. Any discrepancies in the validation will be noted in reviewer's guides accompanying the final data transfers.

Define.xml will be created for SDTM and ADaM using the Define-XML Version 2.0 model.

8. Analysis Populations

8.1 Intent-to-Treat Population

The intent-to-treat (ITT) population includes [redacted]

8.2 Per Protocol Population

The per protocol (PP) population includes [redacted]

[redacted]

8.3 Safety Population

The safety population includes [redacted]

9. Missing Data Handling

For the primary efficacy endpoints, missing patterns and reasons will be examined. Missing data for primary efficacy endpoints will be imputed as follows:

- For missing-at-random, the data will be imputed using treatment-group-based Markov Chain Monte Carlo (MCMC) on the ITT population.
- For missing-not-at-random due to intercurrent events, the imputation methods are defined in the estimands in Section 4.1.1.2.

For the secondary efficacy endpoints, missing data will not be imputed.

Imputation of missing data will be executed for partial or missing dates where complete dates are required to flag data as treatment-emergent or concomitant with treatment. Partial/missing start and end dates for AEs and concomitant medications will be imputed as follows:

Partial/missing start date:

- Dates with missing day only will be imputed as the 1st of the month unless the month and year are same as the month and year of first dose of study medication, in which case missing day will be imputed as the first dose day of study medication.
- Dates with both day and month missing will be imputed as 1 Jan unless the year is same as the year of first dose of study medication, in which case missing day and month will be imputed as the first dose day and month of study medication.
- Completely missing dates will be imputed as the first dose date of study medication unless the end date is on or before the first dose date of study medication, in which case missing date will be imputed as 1 Jan of the same year as the end date.

Partial/missing end date:

- Dates with missing day only will be imputed as the last day of the month unless the month and year are the same as the month and year of the last dose of study medication, in which case missing day will be imputed as the last dose day of study medication.
- Dates with both day and month missing will be imputed as 31 Dec unless the year is same as the year of the last dose of study medication, in which case missing day and month will be imputed as the last dose day and month of study medication.

- If the ongoing flag is missing or "Yes" then the date will not be imputed unless death date is available, in which case the missing date will be imputed as the death date. If ongoing is "No" then the missing end date will be imputed as the last dose date.
- If the imputed date is after the date of death, then the end date will be set equal to the date of death.

The original dates will be displayed in data listings and the imputed dates will be used in derivations only (study day, treatment-emergence status, etc).

10. Statistical Methods

10.1 Unit of Analysis

Safety endpoints and primary symptom efficacy endpoints will be analyzed for both eyes. For subject-level efficacy endpoints, the unit of analysis will be the subject. For other eye-level efficacy endpoints, the unit of analysis will be the study eye, or the "worst eye," as defined by the following:

Study Eye: [redacted]

10.2 Definition of Baseline

Baseline measures are defined as [redacted]

10.3 Data Analysis Conventions

Statistical programming and analyses will be performed using SAS® Version 9.4 or higher. Output will be provided in rich text format (RTF) for tables and portable document format (PDF) for tables, listings, and figures using landscape orientation.

Summaries for continuous and ordinal variables will include the [redacted]

[redacted]

All summaries will be presented by treatment group and visit where appropriate, unless otherwise specified. Listings will be presented for all data collected on the eCRFs, sorted by subject id number, visit/time point, and parameter as applicable based on all randomized subjects unless otherwise specified.

10.4 Adjustments for Multiplicity

Hierarchical fixed sequence testing strategy will be used to maintain the study-wise two-sided type I error rate of [redacted] for testing multiple primary efficacy endpoints and multiple doses.

The hierarchical order is specified as the following (Figure 1):

- [redacted]
- [redacted]
- [redacted]
- [redacted]

If any test in the hierarchical order fails to show statistical significance, then the test results below the hierarchical order will not be claimed in this study.

The tests for the secondary efficacy endpoints are considered exploratory in this study. There will be no type I error control procedures for secondary efficacy endpoints.

Figure 1: Testing Sequence of the Primary Efficacy Endpoints:

11. Disposition of Subjects

Subject disposition will be presented [redacted] The reasons for study discontinuation will be summarized and include:

- Adverse Event (s)
- Protocol Violation(s)
- Administrative Reasons
- Sponsor Termination of the Study
- Subject Choice
- Other

Disposition will be summarized by [redacted]

[redacted]

The number and percentage of subjects with any protocol deviation will also be summarized for the following categories:

- Informed Consent
- Inclusion/Exclusion and Randomization
- Test Article/Study Drug Instillation and Assignment at Site
- Improper Protocol Procedures at Site
- Site's Failure to Report SAE / AE
- Visit out of Window
- Subject's Non-compliance with Test Article / Study Drug
- Subject's use of Prohibited Concomitant Medication
- Subject's Failure to Follow Instructions
- Other

[redacted]

The number of subjects in the following categories will be summarized based on the number of subjects screened:

- Number of subjects screened
- Number and percentage of screen failure subjects and the reason for screen failure

[redacted]

There will also be a listing of screen failures.

12. Demographic and Pretreatment Variables

12.1 Demographic Variables

The demographic variables collected in this study include age, sex, race, ethnicity, country, and iris color. Subjects who record more than one race will be grouped into a single category denoted as "Other." Iris color will be summarized for study eye. Demographic variables will be summarized separately for the ITT and Safety populations.

Age (years) will be summarized by treatment group and overall, using continuous descriptive statistics. Age will also be categorized as follows: < 65 years and ≥ 65 years. Age will be reported in years and calculated using the following formula:

The number and percentage of subjects will be presented by treatment group and overall, for age category, sex, race, ethnicity, and iris color (OD and OS).

A subject listing that includes all demographic variables will be provided.

12.2 Baseline Disease Characteristics

Baseline disease characteristics will be summarized by treatment group for the study eye when appropriate for the following assessments:

- Total Corneal Fluorescein Staining
- Ocular Discomfort
- Fluorescein Staining (
- Lissamine Green Staining
- Conjunctival Redness (Ora Calibra Scale)
- Unanesthetized Schirmer's Test
- TFBUT
- OSDI
- Burning/stinging, Itching, Foreign body sensation, Blurred vision, Photophobia, Pain, Eye Dryness as measured by

12.2.1 Corneal Fluorescein Staining (Ora Calibra Scale)

At Visit 1 (Day -7) and Visit 2 (Day 1), both Pre-CAE® and Post-CAE®, grading of the

[redacted]

12.2.2 Ocular Discomfort during the CAE (ORA Calibra Scale)

At Visit 1 (Day -7) and Visit 2 (Day 1) during CAE® exposure, subjects will be asked to [redacted]

12.2.3 Ocular Discomfort & 4-Symptom Questionnaire (ORA Calibra Scale)

At Visit 1 (Day -7), Pre-CAE® and Visit 2 (Day 1), Pre-CAE®, subjects will [redacted]

13. Medical History and Concomitant Medications

13.1 Medical History

Medical history will be coded to Medical Dictionary for Regulatory Authorities (MedDRA) Version 25.0. Non-ocular medical history will be summarized using discrete summary statistics and presented by treatment group at the subject level by System Organ Class (SOC) and Preferred Term (PT) using the ITT population. Ocular medical history will be similarly summarized at the subject level. If a subject reports the same PT multiple times within the same SOC, that PT will only be counted once withing that SOC. As with the PT, if a subject reports multiple conditions within the same SOC, that SOC will only be reported once. In the summaries, SOCs and PTs within a SOC will be listed in order of descending frequency across all subjects.

Listings of medical history will be generated separately for ocular and non-ocular data.

13.2 Concomitant Medications

Concomitant medications will be coded using World Health Organization Drug Dictionary (WHODrug) Global (B3, March 2022) and summarized to the therapeutic drug class (Anatomical Therapeutic Chemical [ATC] 4 classification) and preferred names. If the ATC 4 classification is not provided, then the next lowest classification that is provided in the coding dictionary will be used.

Concomitant medications are defined as those medications listed as having been taken (1) prior to initiation of study drug administration and continuing for any period of time following the first administration of study drug or (2) at any time following the first administration of study drug.

Prior medications are reported medications that have been taken prior to initiation of study drug administration.

Concomitant medications will be summarized separately for ocular and non-ocular concomitant medications using the ITT population. Medications will be tabulated for each treatment group using frequencies and percentages. Subjects may have more than one medication per ATC text. At each level of subject summarization, a subject will be counted once if he/she reports one or more medications. Percentages will be based on the number of subjects in each treatment group. In the summaries, ATC classes and preferred names within an ATC class will be listed in descending frequency across all subjects.

Listings of prior and concomitant medications will be generated separately for ocular and non-ocular concomitant medicatons.

14. Dosing Compliance and Treatment Exposure

Subject listings for run-in and study drug assignment, instillation, and accountability, in addition to a listing for subject diary data, will be produced in addition to the listings described in this section.

14.1 Dosing Compliance

Subjects will be instructed on proper use of the subject daily diary and proper instillation and storage of study drug at the end of Visit 1 (Day -7) through Visit 6 (Day 85) and given written instructions. To assess dosing and symptom assessment compliance, the subject daily diaries will be collected at Visit 1 (Day -7) through Visit 6 (Day 85), and the subject's used and unused study drug ampules will be collected at Visit 3 (Day 15) through Visit 6 (Day 85). Dosing compliance will be based on the used and unused (excluding the extra ampules) ampule count. If the subject is less than 80% or more than 125% compliant with dosing based on the expected number of used ampules, then the subject will be deemed non-compliant and a dosing deviation should be recorded.

Dosing compliance (% compliance) will be assessed by calculating the number of actual doses received and comparing that to the number of expected doses as follows:

[redacted]

A categorical dosing compliance variable will also be derived as non-compliant (<80%), compliant (≥80% and ≤125%), and over compliant (>125%).

[redacted]

A subject listing of dosing compliance will also be produced.

14.2 Treatment Exposure

Extent of treatment exposure for completed or discontinued subjects will be calculated in days using the following:

[redacted]

Extent of treatment exposure for subjects who were lost to follow-up will be calculated in days using the following:

[redacted]

Extent of treatment exposure for each subject exposed to study drug will be summarized with continuous descriptive statistics for each treatment group using the Safety population. A subject listing of treatment exposure will also be produced.

15. Efficacy Analyses

15.1 Primary Efficacy Endpoints

15.1.1 Primary Analyses of Primary Efficacy Endpoints

The primary analyses of the change from baseline Visit 2 (Day 1), Pre-CAE® to Visit 6 (Day 85) for the primary efficacy endpoints will be analyzed using [redacted]

[redacted]

The missing data of the primary endpoints will be imputed as specified in Section 9 of this SAP. The strategies of handling the intercurrent events in the primary analysis are described in Estimand 1 in Section 4.1.1.2.

15.1.2 Sensitivity Analyses of the Primary Efficacy Endpoints

The sensitivity analyses of the primary efficacy endpoints will be conducted based on the ITT population with Estimand 2 using the same ANOVA model specified in the primary analyses.

The sensitivity analyses of the primary endpoints will also be conducted using an analysis of covariance (ANCOVA) model including baseline values and treatment group as covariates on the ITT population with Estimand 1.

The sensitivity analyses of the primary endpoints will also be conducted with the ITT and PP populations using the observed data only using the same ANOVA model.

[redacted]

As an additional sensitivity analysis, tipping point analysis will be conducted to assess the robustness of the primary analyses.

15.1.3 Figures

The LS means for the primary endpoints will be displayed in a line chart with [redacted]

15.2 Analyses of Secondary Efficacy Endpoints

The secondary efficacy endpoints, including the following, will be analyzed by visits as displayed in Appendix 1:

- Change from baseline to each follow-up visit in corneal fluorescein staining [redacted] of study eye by region: [redacted]
- Change from baseline to each follow-up visit in conjunctival lissamine green staining [redacted] of study eye by region: [redacted]
- Change from baseline to each follow-up visit in conjunctival redness (Ora Calibra® Conjunctival Redness Scale) of study eye
- Change from baseline to each follow-up visit in unanesthetized Schirmer's Test of study eye
- Proportion of subjects demonstrating [redacted] increase from baseline to each follow-up visit in the Unanesthetized Schirmer's Test
- Change from baseline to each follow-up visit in Tear Film Break-Up Time (TFBUT) of study eye

- Change from baseline to each follow-up visit in Ocular Surface Disease Index® (OSDI®)
- Change from baseline to each follow-up visit in symptom assessment by [redacted]
- Drop comfort (Ora Calibra® Drop Comfort Scale and Questionnaire)

[redacted]

[redacted]

[redacted].

Subject listings will be provided for all secondary efficacy endpoint assessments for all randomized subjects.

[redacted]

For drop comfort assessment, separate listings will be produced for the Ora Calibra® Drop Comfort Scale and the Ora Calibra® Drop Comfort Questionnaire.

16. Safety Analyses

All safety analyses will be conducted using the Safety population.

16.1 Adverse Events

An AE is defined as any untoward medical occurrence associated with the use of an IP in humans, whether or not considered IP-related. An AE can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IP, without any judgment about causality. Any pre-existing medical condition that worsens after first administration of the IP will also

be considered a new AE. The AE reporting period ends upon study exit. The IP includes the investigational drug under evaluation and any comparator drug, vehicle, or any other medications required by the protocol given during any stage of the study. All AEs will be coded using MedDRA Version 25.0.

Treatment-emergent adverse events (TEAEs) are defined as undesirable events not present prior to medical treatment, or an already present event that worsens either in intensity or frequency following the treatment.

Severity of an AE is defined as a qualitative assessment of the degree of intensity of an AE as determined by the Investigator or reported to him/her by the subject. The assessment of severity is made irrespective of relationship to IP or seriousness of the event and should be evaluated according to the following scale:

- *Mild*: Event is noticeable to the subject, but is easily tolerated and does not interfere with the subject's daily activities.
- *Moderate*: Event is bothersome, possibly requiring additional therapy, and may interfere with the subject's daily activities.
- *Severe*: Event is intolerable, necessitates additional therapy or alteration of therapy, and interferes with the subject's daily activities.

The relationship of each AE to the IP should be determined by the investigator using these explanations:

- *Definitely Related*: Relationship exists when the AE follows a reasonable sequence from the time of IP administration, follows a known response pattern of the drug class, is confirmed by improvement on stopping the IP and no other reasonable cause exists.
- *Probably Related*: Relationship exists when the AE follows a reasonable sequence from the time of IP administration, follows a known response pattern of the drug class, is confirmed by improvement on stopping the IP and the suspect IP is the most likely of all causes.
- *Possibly Related*: Relationship exists when the AE follows a reasonable sequence from the time of IP administration, but could also have been produced by the subject's clinical state or by other drugs administered to the subject.
- *Unlikely to be Related*: Relationship uncertain to the investigational product. Likely to be related to factors other than investigational product but cannot be ruled out with certainty.
- *Not Related*: Concurrent illness, concurrent medication, or other known cause is clearly responsible for the AE, the administration of the IP and the occurrence of the AE are not reasonably related in time, or exposure to IP has not occurred.

The expectedness of an AE should be determined based upon existing safety information about the IP using these explanations:

- *Unexpected*: An AE that is not listed in the Investigator's Brochure (IB) or is not listed at the specificity or severity that has been observed.

- *Expected*: An AE that is listed in the Investigational Brochure (IB) at [redacted]
- *Not applicable*: An AE unrelated to the IP.

An overall summary will be presented that includes the number of events and the number and percentage of subjects who experienced at least one AE, ocular AE, and non-ocular AE by treatment group and among all subjects. This summary will also include the number of events and the number and percentage of subjects who experienced at least one treatment-emergent adverse event (TEAE), as well as breakdowns of TEAEs further categorized by ocular and non-ocular, severity, relationship to study drug, expectedness, and the number of subjects with TEAEs causing premature treatment discontinuation. Lastly, the summary will include serious adverse events (SAEs) and treatment-emergent serious adverse events (TE-SAEs) categorized by ocular and non-ocular, severity, and relationship to study drug, as well as the number of subjects with TE-SAEs causing premature treatment discontinuation and leading to death.

In addition to the overall AE summary, summaries will be provided for the following categories of AEs:

- Ocular and non-ocular TEAEs by SOC and PT
- Ocular and non-ocular TEAEs by SOC, PT, and maximal severity
- Ocular and non-ocular TEAEs by SOC, PT, and maximal relatedness
- Ocular and non-ocular TEAEs by SOC, PT, and study day of onset

If a subject reports the same PT multiple times within the same SOC, that PT will only be reported once within that SOC. As with the PT, if a subject reports multiple AEs within the same SOC, that SOC will only be reported once. SOCs and PTs within a SOC will be listed in order of descending frequency across all subjects.

Separate listings will be generated for all AEs, ocular AEs, non-ocular AEs, and SAEs. Pregnancy test results will also be presented in a listing.

16.2 Visual Acuity (ETDRS)

The observed and change from baseline in visual acuity will be summarized for each eye (study eye and fellow eye) using [redacted]

A subject listing of visual acuity will also be produced.

16.3 Slit-Lamp Biomicroscopy Examination

The results will be summarized using [redacted]. A subject listing of the slit-lamp biomicroscopy parameters will also be produced.

16.4 Intraocular Pressure (IOP)

The IOP values and changes from baseline for each eye (study eye and fellow eye) will be summarized using [redacted]

A subject listing of IOP will also be produced.

16.5 Dilated Fundoscopy Examination

The results will be summarized using [redacted] A subject listing of the dilated fundoscopy parameters will also be produced.

17. Subgroup Analyses

Subgroup analyses will be performed in selected subgroups on the ITT population with the observed data only. If the number of subjects in a subgroup is [redacted], it may be combined with other subgroups for the subgroup analyses.

17.1 Subgroup Analyses by Demographic Characteristics

The demographic characteristics subgroups are the following:

- Age Group: <65 years, ≥65 years
- Sex: Female, Male
- Race: White, Black or African American, Asian, or Other (including American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, and other)
- Ethnicity: Hispanic or Latino, Not Hispanic or Latino

Subgroup analysis of the primary efficacy endpoints will be performed in the demographic subgroups based on the ITT population with the observed data only. The primary efficacy endpoint will be analyzed using the similar methods described for the primary analysis of the primary efficacy endpoints by the ANOVA model. LS means and their respective SEs of the change from baseline for each treatment group and LS mean differences comparing active treatment (low dose and high dose) to placebo, respectively, will be presented from the model with SEs, two-sided 95% CIs, and two-sided p-values.

17.2 Subgroup Analysis by Japanese Subgroup

The Japanese subgroups are the following:

- Japanese, non-Japanese

17.2.1 Demographic and Baseline Disease Characteristics

Demographic variables will be summarized by Japanese subgroups on the ITT and Safety populations.

The number and percentage of subjects will be presented by Japanese subgroups and overall, further by treatment group, for age category, sex, race, ethnicity, and iris color (OD and OS).

Baseline disease characteristics will be summarized by Japanese subgroup, further by treatment group for the study eye when appropriate for the following assessments:

- Total Corneal Fluorescein Staining
- Ocular Discomfort
- Fluorescein Staining
- Lissamine Green Staining
- Conjunctival Redness (Ora Calibra Scale)
- Unanesthetized Schirmer's Test
- TFBUT
- OSDI
- Burning/stinging, Itching, Foreign body sensation, Blurred vision, Photophobia, Pain, Eye Dryness as measured by

17.2.2 Medical History and Concomitant Medications

Ocular and non-ocular medical history will be summarized separately at the subject level by Japanese subgroups and overall, and by SOC and PT using the ITT population.

Concomitant medications will be summarized separately for ocular and non-ocular concomitant medications by Japanese subgroups and overall, and by ATC and preferred name using the ITT population.

17.2.3 Primary Efficacy Endpoints Analyses

Subgroup analyses of the primary efficacy endpoints will be performed in the Japanese subgroups based on the ITT population with the observed data only. The primary efficacy endpoint will be analyzed using the

[redacted]

17.2.4 Secondary Efficacy Endpoints Analyses

Subgroup analyses of the secondary efficacy endpoints will be performed in the Japanese subgroups based on the ITT population with the observed data only.

The secondary efficacy endpoints will be analyzed using the [redacted]

17.2.5 Safety Analyses

Safety analyses by Japanese subgroups will be conducted using the Safety population. The analyses by Japanese subgroups are similar as main safety analyses in Section 16 of this SAP.

17.3 Subgroup Analysis by Two Stratification Factors

The two stratification factors are the following:

- Stratification Factor 1: Visit 2 (Day 1) Pre-CAE® total corneal fluorescein staining score: [redacted]
- Stratification Factor 2: Visit 2 (Day 1) Pre-CAE ocular discomfort score [redacted]

[redacted]

18. Interim Analyses

No interim analyses are planned for this study.

19. Changes from Protocol-Stated Analyses

There are no changes from protocol-stated analyses

20. References

There are no applicable references for this SAP.

21. Revision History

Documentation of revision to the SAP will commence after approval of the final version 1.0.

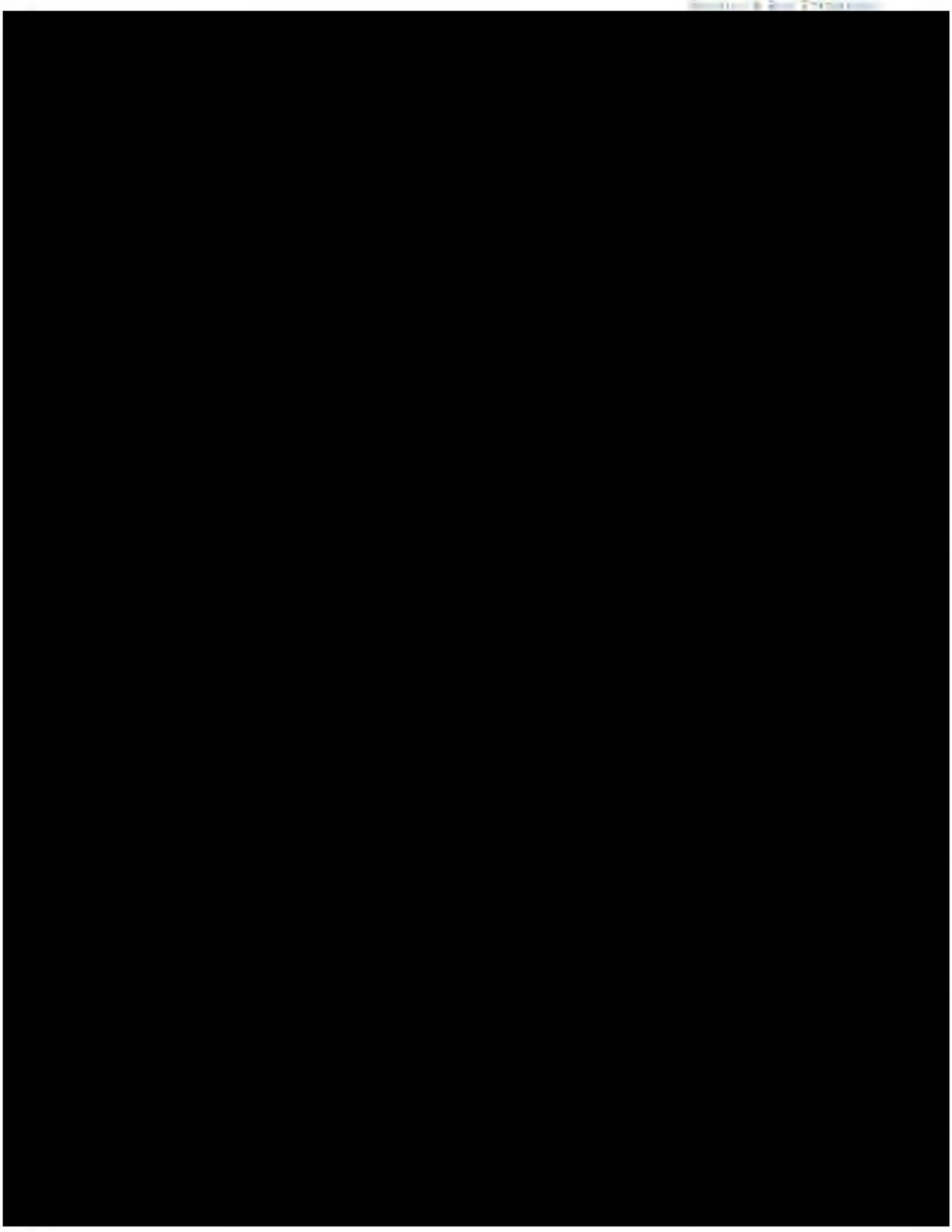
22. Potential Impact of COVID-19

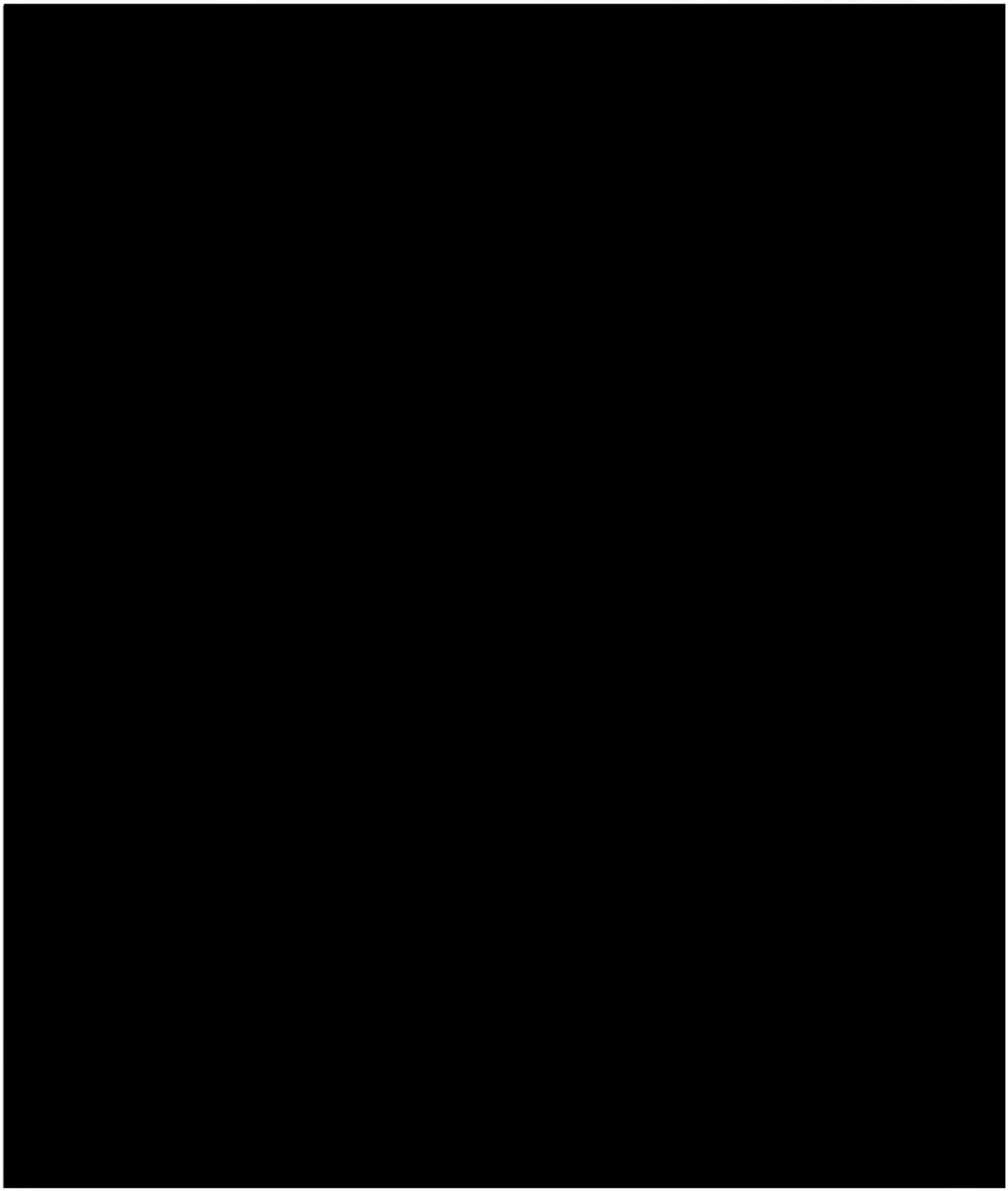
There are no potential impact noted.

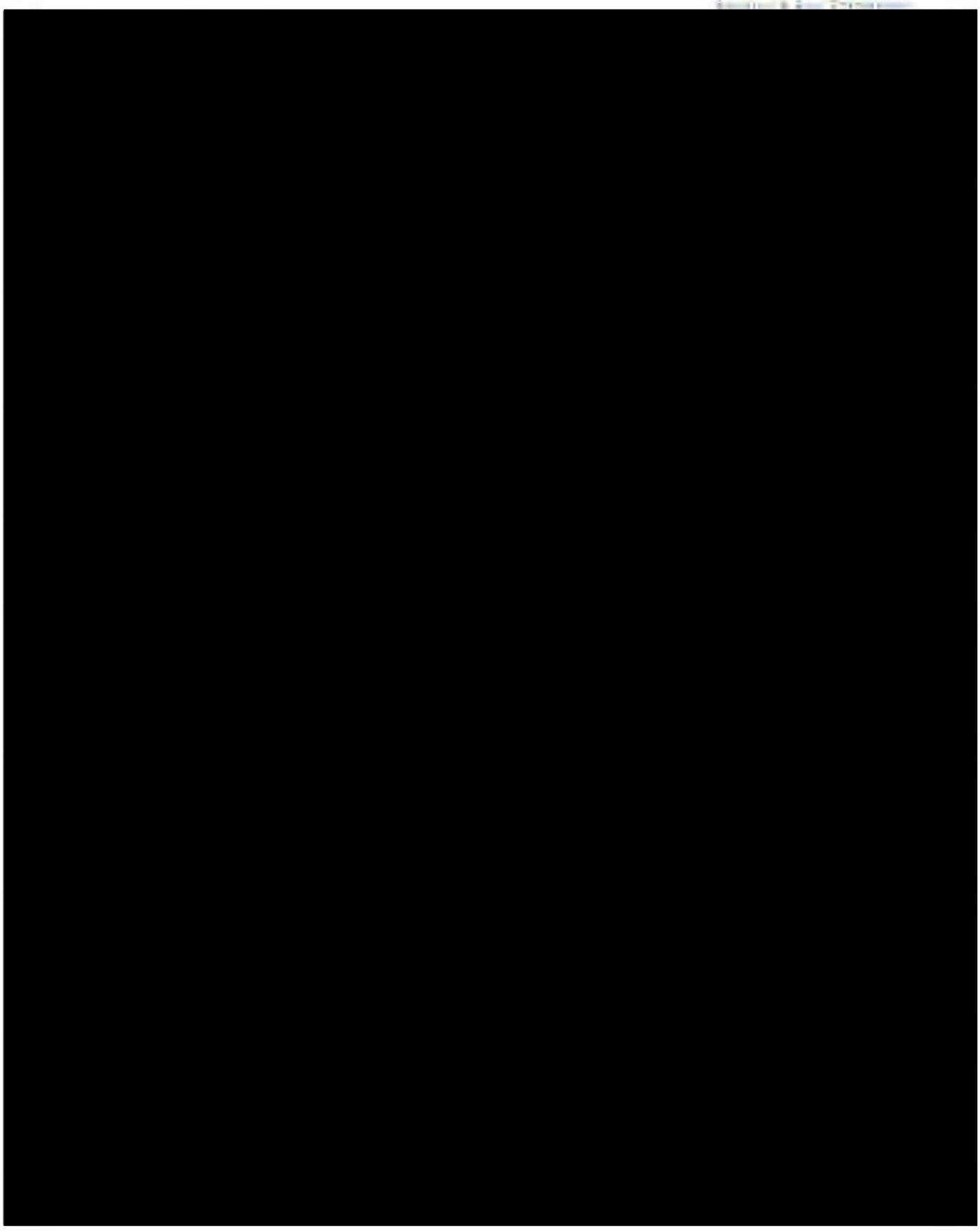
23. Tables

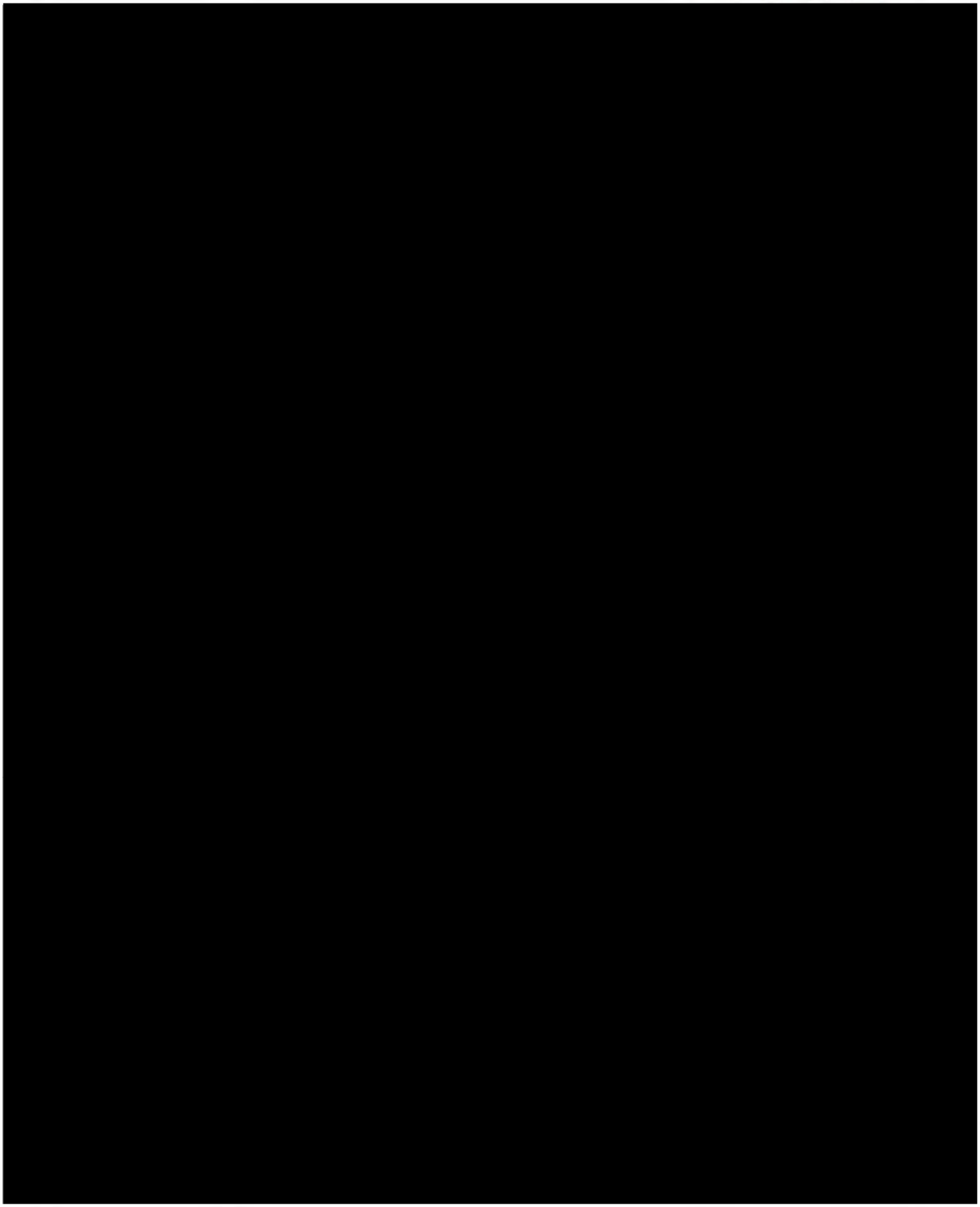
Tables that will be included in the topline delivery are shown in **boldface** font

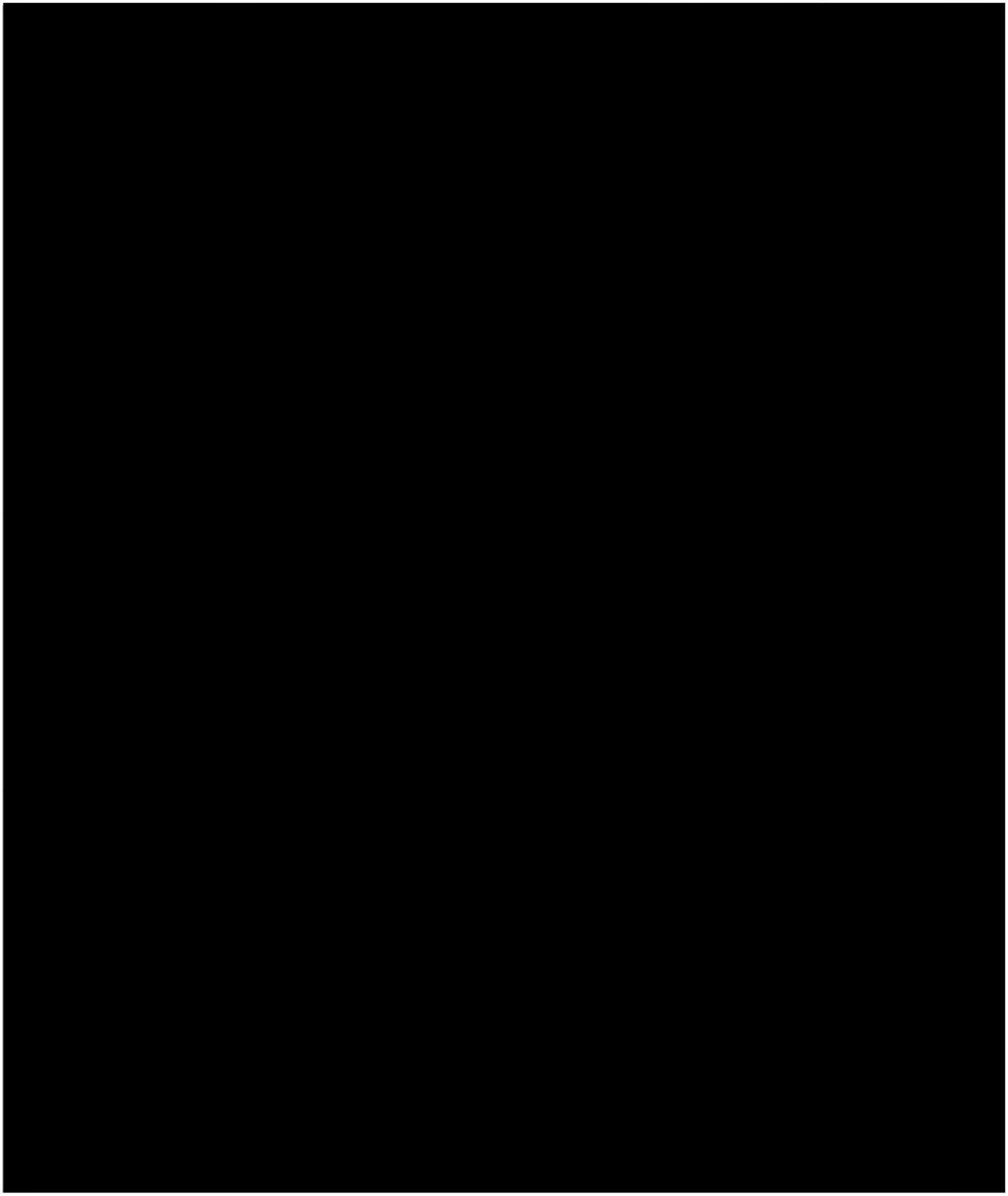
[redacted]

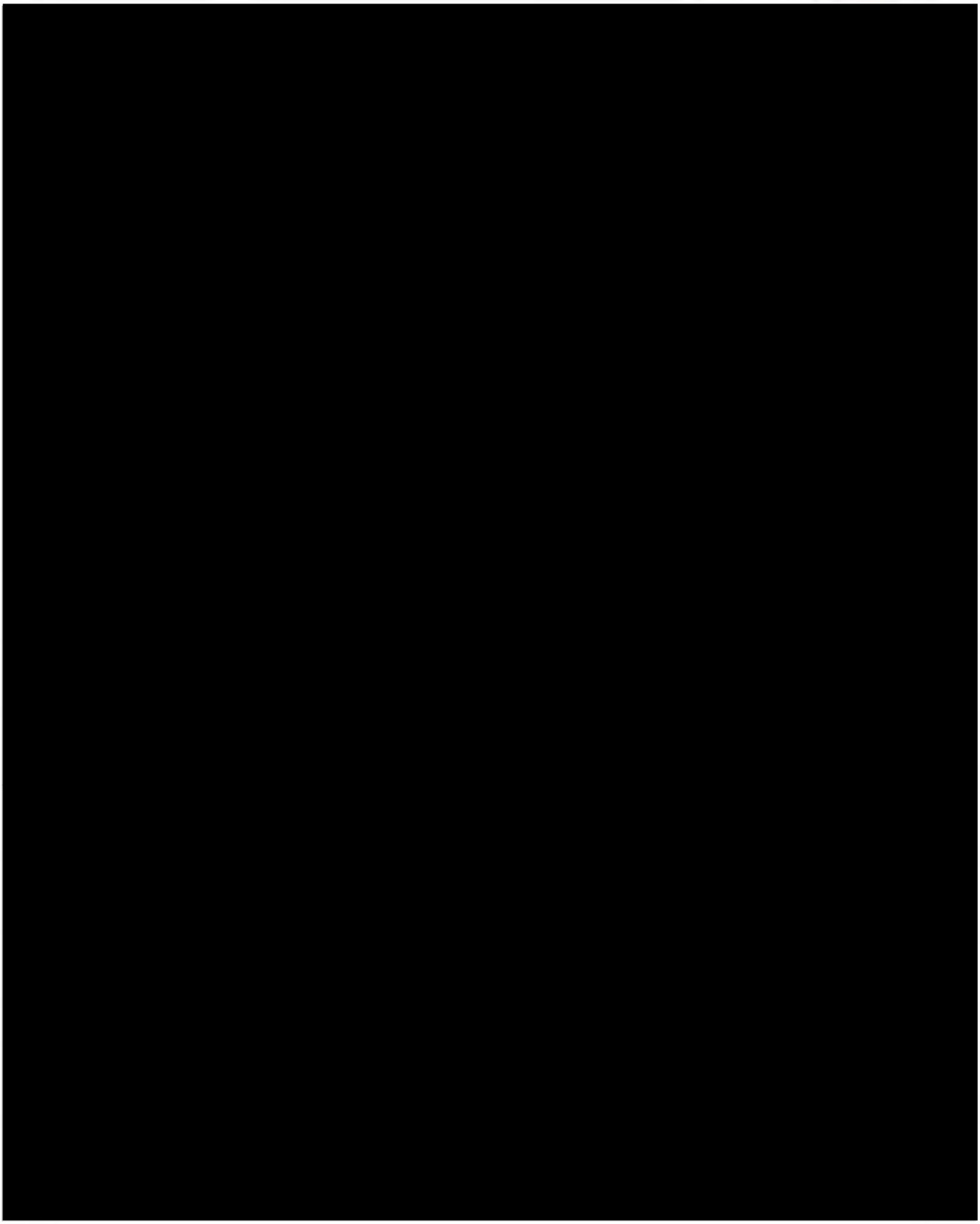


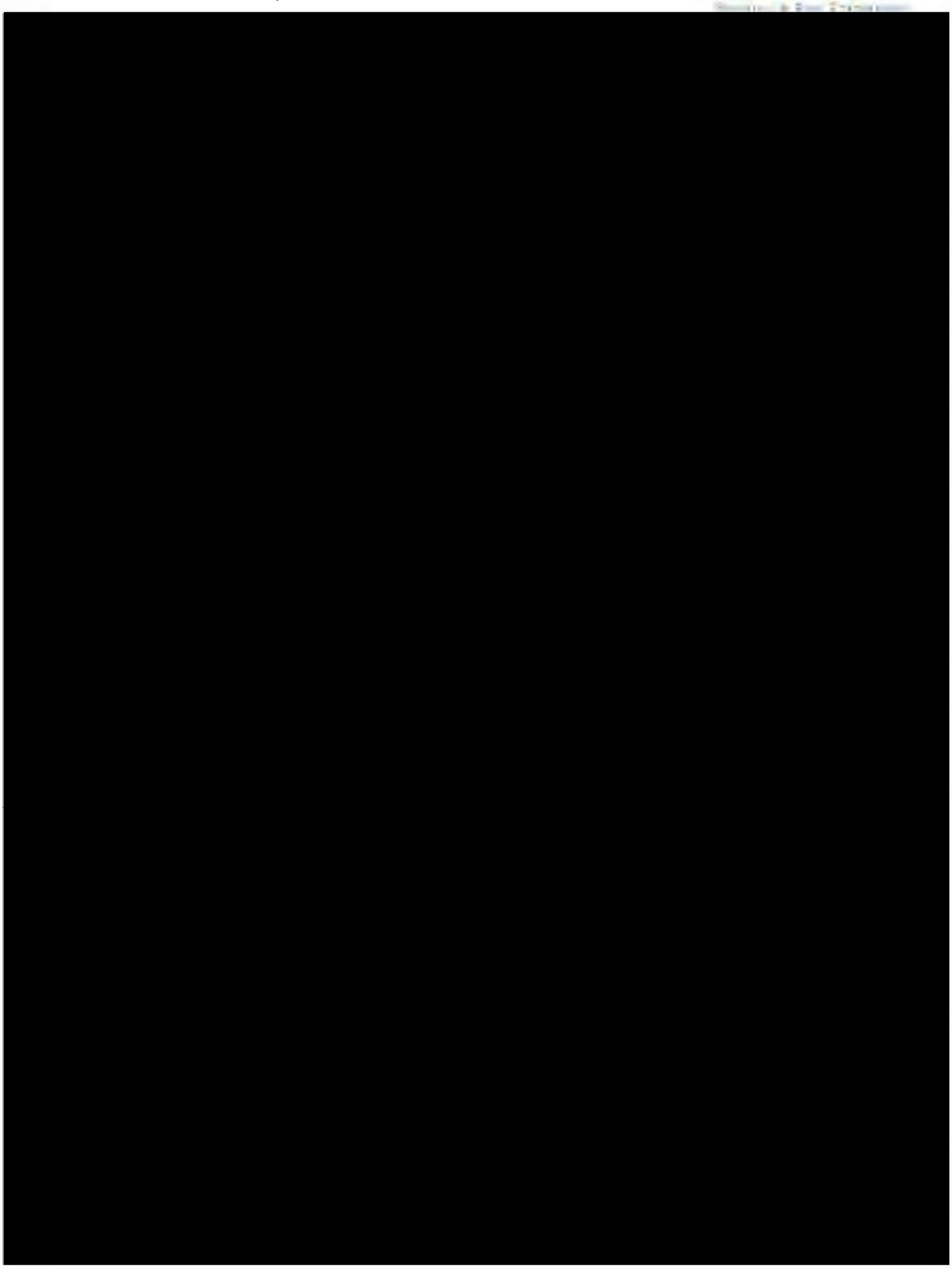




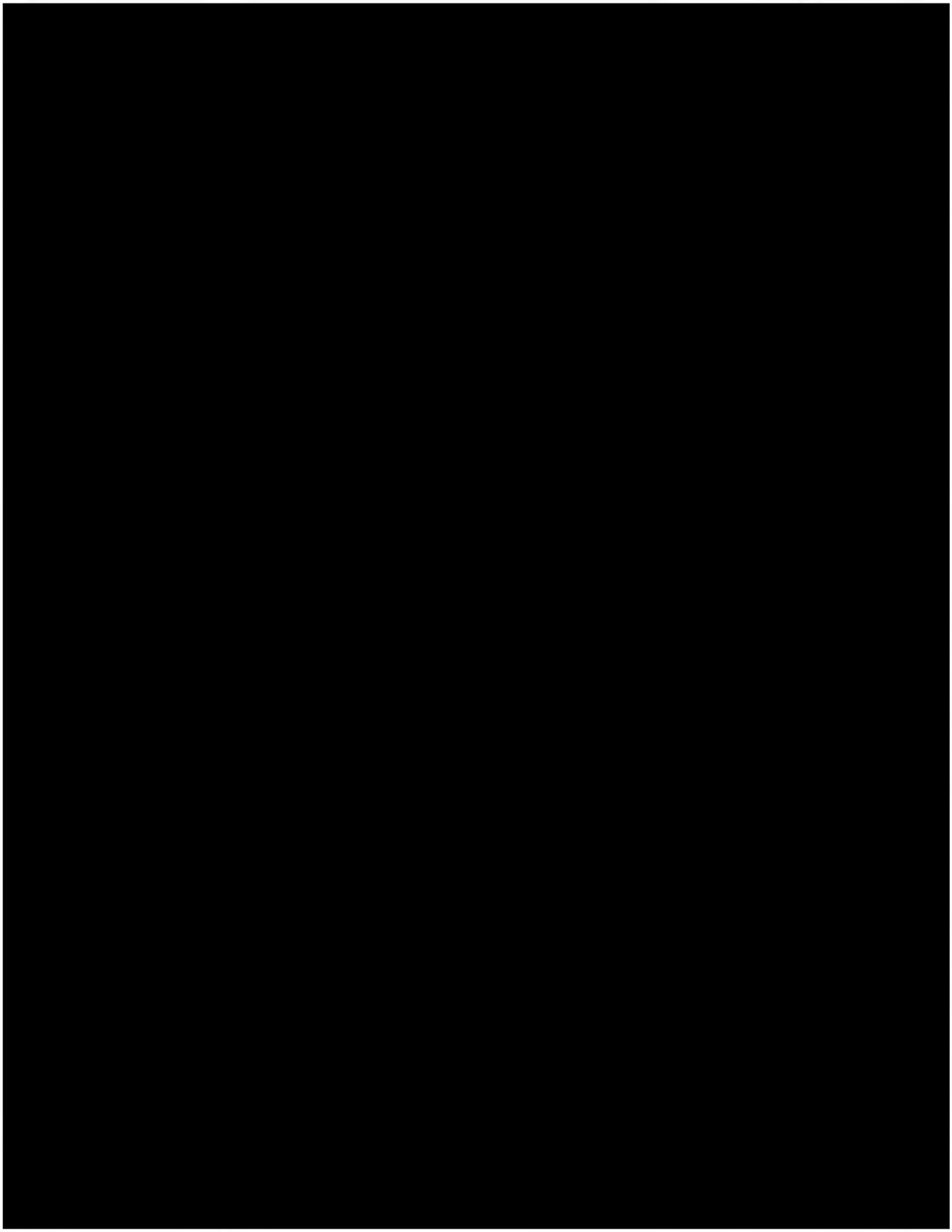




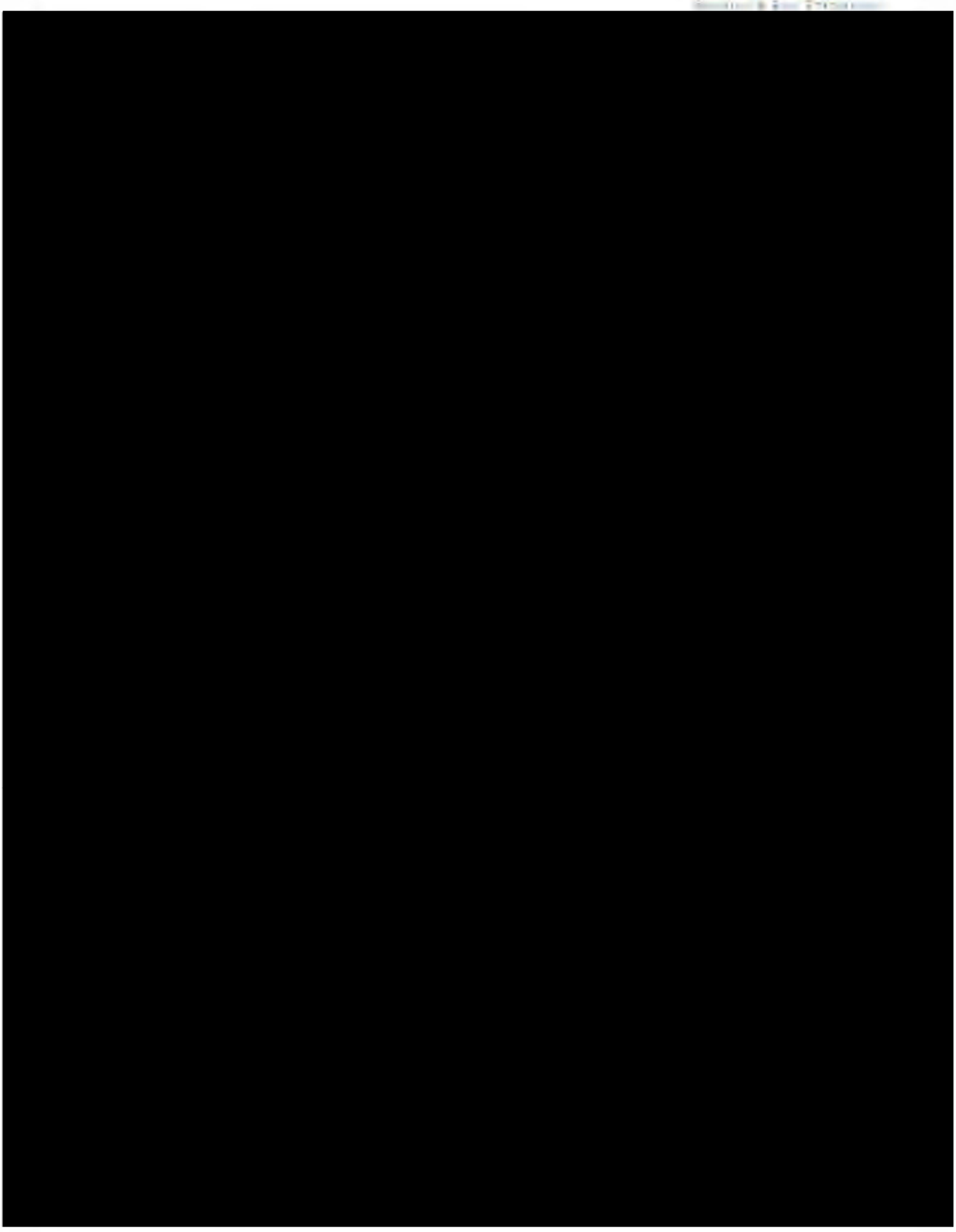




24. Listings



25. Figures



Appendix 1. Schedule of Visits and Assessments