STATISTICAL ANALYSIS PLAN

A Multi-Center, Double-Masked, Randomized, Vehicle-Controlled, Phase 2b Evaluation of the Onset and Duration of ADX-102 Ophthalmic Drops (0.5% and 0.1%) Compared to Vehicle of ADX-102 Ophthalmic Drops in the Conjunctival Allergen Challenge (Ora-CAC®) Model of Acute Allergic Conjunctivitis

Sponsor: Aldeyra Therapeutics, Inc.
131 Hartwell Ave.
Lexington, MA 02421

Protocol Number: ADX-102-AC-004

Author: [redacted]

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Version: 1.0

SDC
Statistics & Data Corporation

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Statistical Analysis Plan Approval

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List of Abbreviations

AE	Adverse Event
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical Classification
BOCF	Baseline Observation Carried Forward
CAC	Conjunctival Allergen Challenge
CRF	Case Report Form
CS	Clinically Significant
CSR	Clinical Study Report
eCRF	Electronic Case Report Form
ETDRS	Early Treatment of Diabetic Retinopathy Study
HIPAA	Health Information Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IOP	Intraocular Pressure
IP	Investigational Product
ITT	Intent-to-Treat
LOCF	Last Observation Carried Forward
logMAR	Logarithm of the Minimum Angle of Resolution
LS	Least Squares
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
NCS	Not clinically significant
PDF	Portable Document Format
PP	Per-Protocol
PT	Preferred Term
RTF	Rich Text Format
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDC	Statistics and Data Corporation, Incorporated
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
VA	Visual Acuity
WHO DDE	World Health Organization Drug Dictionary Enhanced

1. Introduction

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and reporting for protocol ADX-102-AC-004, Final 1.0 dated 19OCT2016.

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 and the most recent ICH E3 Guideline, entitled Guidance for Industry: Structure and Content of Clinical Study Reports (CSR).

This SAP describes the data that will be analyzed and the subject characteristics, efficacy, and safety assessments that will be evaluated. This SAP provides details of the specific statistical methods that will be used. 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 CSR.

2. Study Objectives

The objective of this study is to evaluate the efficacy of ADX-102 ophthalmic drops (0.1% and 0.5%) compared to vehicle of ADX-102 ophthalmic drops for the treatment of the signs and symptoms of acute allergic conjunctivitis.

3. Study Variables

3.1 Primary Variables

The primary efficacy variable is the following:

- Ocular itching evaluated by the subject at 10(±1), 15(±1), and 20(±1) minutes post-conjunctival allergen challenge (CAC) at Visits 3 and 4 (0-4 scale, allowing half unit increments).

[redacted]

3.3 Exploratory Variables

There are no exploratory efficacy variables in this study.

3.4 Safety Variables

The safety variables include the following:

- Adverse Events (AE) (reported, elicited and observed);
- Visual Acuity (VA) at Distance Utilizing an Early Treatment Diabetic Retinopathy Study (ETDRS) chart;
- Slit-lamp Biomicroscopy;
- Intraocular Pressure (IOP);
- Dilated Fundoscopy.

3.5 Statistical Hypotheses

[redacted]

4. Study Design and Procedures

4.1 General Study Design

This is a multi-center, double-masked, randomized, vehicle-controlled, phase 2b study evaluating the efficacy of ADX-102 ophthalmic drops (0.1% and 0.5%) compared to vehicle of ADX-102 ophthalmic drops for the treatment of the signs and symptoms of acute allergic conjunctivitis.

The trial will comprise 4 office visits over a period of approximately 5 weeks. Visits 1 and 2 will be used to select a subject population that responds reproducibly to two CACs administered approximately 7 days apart. Subjects who meet the entry criteria for itching and redness response to CAC at Visits 1 and 2 will be randomized (1:1:1) at Visit 3 (Day 1, Enrollment/Randomization) to receive either ADX-102

ophthalmic drops (0.1%), ADX-102 ophthalmic drops (0.5%), or vehicle of ADX-102 ophthalmic drops bilaterally. Subjects will undergo the 1-hour (+5 minutes) duration of action CAC approximately 1 hour from the time of their study drug instillation. Subjects will return approximately 14 days later for Visit 4 (Day 15± 3, 10-Minutes Onset of Action CAC), at which time they will be treated with the same treatment they received at Visit 3 and challenged approximately 10 minutes after dosing. At Visit 4, final exit procedures will also be conducted and subjects will exit the study.

Study visits will be referred to in all tables and listings as the expected study day corresponding to the visit to enable reviewers to understand the assessment timing without referring to the protocol visit schedule. The following table shows the scheduled study visits, their planned study day (note that there is no Day 0 and that Day 1 corresponds to the day of randomization), and the acceptable visit window for each study visit:

Scheduled Visit	Planned Study Day	Visit Window
Visit 1 (Screening/Titration CAC)	Day -21	+/- 3 Days
Visit 2 (Confirmation CAC)	Day -14	+/- 3 Days
Visit 3 (Enrollment/ Duration of Action CAC)	Day 1	NA
Visit 4 (Onset of Action CAC)	Day 15	+/- 3 Days

4.2 Schedule of Visits and Assessments

The schedule of visits and assessments is provided below.

Visit	Visit 1	Visit 2	Visit 3	Visit 4
Day	**-21±3**	**-14±3**	**1**	**15±3**
PROCEDURE				
General Assessments				
Informed Consent & HIPAA[1]	X			
Demographic Data[1]	X			
Medical & Medication History[1]	X			
Update Medical & Medication History		X	X	X
Allergic Skin Test	X			
Urine Pregnancy Test	X			X
Randomization			X	
AE Assessment			X	X
Allergen Challenge				
CAC	X	X	X	X
[redacted]				
Relief Drop Instillation[2]	X	X	X	X
Visual/Systems Exams				
Visual Acuity Utilizing an ETDRS chart	X	X	X	X[3]
Slit Lamp Biomicroscopy	X	X	X	X[3]

Visit	Visit 1	Visit 2	Visit 3	Visit 4
Day	-21±3	-14±3	1	15±3
Intraocular Pressure	X			X
Dilated Fundoscopy	X			X
Investigational Product (IP)				
IP Instillation			X[4]	X[5]
Exit from Study				X

[redacted]

5. Study Treatments

This study consists of three treatments arms:

- ADX-102 Ophthalmic Drops (0.1%);
- ADX-102 Ophthalmic Drops (0.5%);
- Vehicle of ADX-102 Ophthalmic Drops.

5.1 Method of Assigning Subjects to Treatment Groups

All subjects screened for the study who sign an ICF will be assigned a 3-digit screening number that will be entered in the Screening and Enrollment Log. Screening numbers will be assigned in a sequential order beginning with 001. Randomization will be used to avoid bias in the assignment of subjects to treatment and time point, to increase the likelihood that known and unknown subject attributes (e.g., demographics and baseline characteristics) are evenly balanced across treatment groups and across time points, and to enhance the validity of statistical comparisons.

Once a subject meets all qualification criteria at Visit 3 (Day 1), they will be enrolled and randomly assigned to masked treatment using a 1:1:1 (ADX-102 ophthalmic drops [0.1%]: ADX-102 ophthalmic drops [0.5%]: vehicle of ADX-102 ophthalmic drops) assignment ratio. Subjects will be assigned the lowest 4-digit randomization number available at the Investigative site within the appropriate stratum. The randomization number will be stratified by the average post-CAC itching scores [redacted] at baseline (Visit 2) to ensure balance for the primary endpoint of ocular itching. No randomization numbers will be skipped or omitted.

5.2 Masking and Unmasking

When medically necessary, the investigator may need to determine what treatment has been assigned to a subject. The investigator should make every effort to contact Ora to discuss the subject's emergency situation and the need to unmask a study subject prior to unmasking the IP.

If the investigator determines that emergency unmasking is necessary, the investigator should identify the given subject's study drug kit which contains a scratch off laminate under which the treatment is identified along with the associated lot number. In order to unmask, the investigator should scratch off the laminate, using a flat object and applying pressure, to reveal the treatment assigned for that subject. The emergency unmasking should be performed by the designated site personnel. The investigator must also indicate in source documents and in the electronic case report form (eCRF) that the mask was broken and provide the date, time, and reason for breaking the mask. Any AE or serious adverse event (SAE) associated with breaking the mask must be recorded and reported as specified in the study protocol. The investigator has the responsibility to contact Ora within 24 hours of breaking the blind.

Subjects will have the IP treatment discontinued immediately if treatment assignment is unmasked and will be discontinued from the study.

6. Sample Size and Power Considerations

[redacted]

7. Data Preparation

All reported study data will be recorded on the eCRFs supplied by Statistics & Data Corporation (SDC) using iMedNet™. Only the Principal Investigator and authorized study staff according to the Delegation of Responsibilities log are entitled to make entries in the eCRF.

After data are entered into the clinical study database, electronic edit checks and data review will be performed. All data validation specifications and procedures are detailed in the Data Validation Manual as a separate document. When the database has been declared to be complete and accurate, the database will be locked. Any changes to the database after data have been locked can only be made with the approval of the Sponsor and Ora in consultation with SDC.

All analyses outlined in this document will be carried out after the following have occurred:

- All data management requirements are met according to SDC standard operating procedures, including data entry, performance of edit and validation checks, documentation and resolution of data queries, and database lock with written authorization provided by appropriate SDC and Sponsor personnel;
- Protocol deviations have been identified and status defined (major/minor deviations);
- Analysis populations have been determined; and
- Randomized treatment codes have been unmasked.

8. Analysis Populations

8.1 Intent-to-Treat

The Intent-to-Treat (ITT) population consists of all subjects who are randomized. All data will be included and no subjects will be excluded because of protocol violations. The ITT population will be analyzed as randomized and will be used for the efficacy analyses.

8.2 Per-Protocol

The Per-Protocol (PP) population is a subset of the ITT population and includes the subjects who completed the study through Visit 4 (Day 15) with no major protocol violations. This population will be analyzed as treated using observed data only for confirmatory analyses.

8.3 Safety

The safety population includes all randomized subjects who received the test article. The safety population will be analyzed as treated and will be used for the safety analyses. No data will be excluded for any reason.

9. General Statistical Considerations

9.1 Unit of Analysis

The subject will be considered the unit of analysis for all variables with exceptions of slit-lamp biomicroscopy and dilated fundus examination. For the variables using subject as the unit of the analysis, the average of both eyes of each subject will be used for statistical summaries and analyses in cases where data are collected for each eye. For slit-lamp biomicroscopy and dilated fundus examination results, the eye will be the unit of analysis and summaries will be provided for all eyes combined.

9.2 Missing or Inconclusive Data Handling

[redacted]

[redacted]

[redacted]

[redacted]

9.3 Definition of Baseline

For the primary efficacy variable (ocular itching scores at 10(±1), 15(±1), and 20(±1) minutes post-CAC), baseline will refer to the time-relevant measure at Visit 2 (e.g., ocular itching at 10 minutes post-CAC at Visit 2 will be the baseline for ocular itching at 10 minutes post-CAC at Visits 3 and 4).

[redacted] For all safety variables, baseline is defined as the last measurement prior to the first dose of study medication. Change from baseline will be calculated as follow-up visit minus baseline visit.

9.4 Data Analysis Conventions

All data analysis will be performed by SDC after the study is completed and the database has been locked and released for unmasking. 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. All study data will be listed by subject, treatment, visit and time point (as applicable) based on all randomized subjects unless otherwise specified.

Summaries for quantitative variables will include the number of observations (n), arithmetic mean, standard deviation (SD), median, minimum, and maximum. Minima and maxima will be reported with the same precision as the raw values; means and medians will be presented to one additional decimal place than reported in the raw values. Standard deviations will be presented to two additional decimal places than reported in the raw values. Summaries for qualitative variables will include frequency counts and percentages. All percentages will be rounded to one decimal place (i.e., XX.X%). Differences between active treatment groups and placebo will be calculated as active minus vehicle and change from baseline will be calculated as follow-up visit minus baseline visit.

All statistical tests will be two-sided with a significance level of 0.05 ($\alpha = 0.05$) unless otherwise specified. Confidence intervals (CI) for differences between treatment groups will be two-sided at 95% confidence. All p-values will be rounded to four decimal places; p-values less than 0.0001 will be presented as "<0.0001"; p-values greater than 0.9999 will be presented as ">0.9999".

Unless otherwise specified, summaries will be presented by treatment group and, where appropriate, visit and time point.

9.5 Adjustments for Multiplicity

[redacted]

10. Disposition of Subjects

Subject disposition will be presented in terms of the numbers and percentages of subjects who were randomized, completed the study, and discontinued from the study. Subjects who are not discontinued from the study will be considered study completers. Disposition will be summarized by treatment group and for all subjects.

The number and percentage of subjects prematurely discontinued from the study and the reasons for study discontinuation will be summarized by treatment group for all randomized subjects. The reasons for study discontinuation that will be summarized include: AE, protocol violation, lack of efficacy, administrative reasons, manifest clinically active signs or symptoms of allergic conjunctivitis during the pre-CAC ocular allergic signs & symptoms assessment at Visit 4, sponsor termination of study, investigator decision and other. A subject listing will be provided that includes the date of and reason for premature study discontinuation.

Subject listings will be provided that include informed consent date, inclusion and exclusion criteria violations and exclusions from the PP population.

Protocol violations will be summarized by treatment group for all randomized subjects for each violation category (informed consent, inclusion/exclusion, randomization, subject was not treated with assigned treatment, assessment/procedure not conducted per protocol requirements, missed visit, visit conducted out of window, assessment not done, site failure to report, subject use of prohibited concomitant medication, investigational product stored our of correct temperature control, waiver was granted, other) and severity (min, major) using counts and percentages. Percentages will be based on the total number of subjects randomized in each treatment group. A subject listing will be provided that includes the date

of the violation, the violation description and the classification of whether the violation was judged to be major or minor.

11. Demographic and Pretreatment Variables

11.1 Demographic Variables

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

Age (years) will be summarized, overall and by treatment, 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:

Age = (informed consent date – date of birth) / 365.25 truncated as an integer.

The number and percentage of subjects will be presented, overall and by treatment, for age category, sex, race, ethnicity and iris color for each eye separately.

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

11.2 Pretreatment Variables

At Visit 1, subjects signing the informed consent and Health Insurance Portability and Accountability Act (HIPAA) forms will be given a diagnostic test for allergic disease (skin test). Results from this test will be provided in a subject listing.

12. Medical History and Concomitant Medications

12.1 Medical History

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) 19.1.

Non-ocular medical history will be summarized using discrete summary statistics and presented by treatment group at the subject and event 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 reported once within that SOC. As with the PT, if a subject reports multiple conditions within the same SOC, that SOC will only be reported once.

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

12.2 Prior and Concomitant Medications

[redacted]

[redacted]

13. Exposure to Investigational Product

The number and percentage of subjects instilled with IP will be summarized by visit and treatment group for the Safey population. Percentages will be calculated based on the total number of subjects in each treatment group with responses.

A listing of IP instillation for all subjects will also be provided.

14. Efficacy Analyses

14.1 Primary Analysis

The primary efficacy variable is ocular itching evaluated by the subject at 10(±1), 15(±1), and 20(±1) minutes post-CAC measured at Visit 3 (1 hour post treatment) and Visit 4 (10-minutes post treatment).

Ocular itching will be evaluated using the following Ora Calibra™ Conjunctival Allergen Challenge Ocular Itching Scale:

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

14.2.1 Ocular Itching

Ocular itching will be evaluated by the subject (0 to 4 scale, with half unit increments) at 5(±1), 30(±1) and 60(±5) minutes post-CAC at Visits 3 and 4 using the same Ora Calibra™ Conjunctival Allergen Challenge Ocular Itching Scale as the primary efficacy analysis. Ocular itching for these time points will be analyzed in a similar manner to ocular itching at the primary analysis time points as described at the beginning of Section 14.2.

Simliar analyses will be conducted for subgroups defined by gender, age, allergen and baseline itching scores.

[redacted]

[redacted]

[redacted]

15. Exploratory Analyses

There is no planned exploratory analysis for this study.

16. Safety Analyses

The primary safety variable is the incidence of subjects with any AE during the entire study.

The secondary safety variables of visual acuity, slit-lamp biomicroscopy, IOP and dilated fundus examination will be summarized descriptively using quantitative and qualitative summary statistics as appropriate. Changes and shifts from baseline will also be summarized where applicable.

All safety analyses will be conducted using the Safety Population. No statistical inferential testing will be performed for safety variables.

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. An AE can arise from any use of the IP (e.g., off-label use, use in combination with another drug or medical device) and from any route of administration, formulation, or dose, including an overdose. An AE can arise from any delivery, implantation, or use of a medical device, including medical device failure, subject characteristics that may impact medical device performance (e.g., anatomical limitations), and therapeutic parameters (e.g., energy applied, sizing, dose release) associated with medical device.

All AEs spontaneously reported by the subject and/or in response to an open question from study personnel or revealed by observation, physical examination or other diagnostic procedures will be recorded in the source document and on the appropriate pages of the eCRF. Any clinically relevant deterioration in clinical finding is considered an AE and must be recorded. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event. Any pre-existing medical condition that worsens after administration of study medication will also be considered a new AE. Study medication includes the drug under evaluation or any other medications required by the protocol given during any stage of the study.

Ocular complaints should not be addressed as AEs unless the complaint is outside the normal limits for allergic conjunctivitis symptoms after allergen exposure or is associated with clinical sequelae (i.e., adverse slit-lamp examination finding).

[redacted]

Treatment-emergent adverse events (TEAEs) are defined as any event that occurs or worsens on or after the day that randomized study treatment is initiated.

An AE is considered serious if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death;
- A life-threatening AE;

  Note: An AE is considered "life-threatening" if, in the view of either the investigator or Sponsor/designee, its occurrence places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization;

  Note: The term "inpatient hospitalization" refers to any inpatient admission (even if less than 24 hours). For chronic or long-term inpatients, inpatient admission includes transfer within the hospital to an acute/intensive care inpatient unit. Inpatient hospitalization does not include: emergency room visits; outpatient/same-day/ambulatory procedures; observation/short stay units; rehabilitation facilities; hospice facilities; nursing homes; or clinical research/phase 1 units.

  Note: The term "prolongation of existing hospitalization" refers to any extension of an inpatient hospitalization beyond the stay anticipated or required for the reason for the initial admission as determined by the investigator or treating physician.
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;

  Note: A SAE specifically related to visual threat would be interpreted as any potential impairment or damage to the subject's eyes (e.g., hemorrhage, retinal detachment, central corneal ulcer or damage to the optic nerve).
- A congenital anomaly/birth defect.

Important medical events that may not result in death, are life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

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

- *Suspected*: A reasonable possibility exists that the IP caused the AE.
- *Not Suspected*: A reasonable possibility does not exist that the IP caused the AE.

  Note: "Reasonable possibility" means there is evidence to suggest a causal relationship between the investigational product and the AE. Types of evidence that would suggest a causal relationship between the investigational product and the AE include: a single occurrence of an event that is uncommon and known to be strongly associated with investigational product exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome); one or more occurrences of an event that is not commonly associated with investigational product exposure, but is otherwise uncommon in the population exposed to the investigational product (e.g., tendon rupture); an aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the investigational product-treatment group than in a concurrent or historical control group.

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.

An overall summary will be presented that includes the number of AEs and the number and percentage of subjects who experienced at least one AE, by treatment group and for all subjects combined. This summary will also include breakdowns of AEs further categorized as ocular or non-ocular, SAEs, AEs by maximum severity and relationship to IP, number of subjects with AEs leading to subject withdrawal and number of subjects with AEs resulting in death. TEAEs summarized for the same categories will also be included.

Additional summaries of AEs will be provided showing the number of AEs and the number and percentage of subjects who experienced at least one AE. These summaries will be presented at the subject and event level by SOC and PT. 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 conditions within the same SOC, that SOC will only be reported once. In the summary, SOC will be listed in ascending alphabetical order; PTs will be listed in order of descending frequency for all subjects within each SOC. These summaries will be presented for ocular and non-ocular AEs separately and include the following:

- All AEs;
- All TEAEs;
- All TEAEs suspected to be related to the IP;
- All SAEs;
- All TEAEs by maximal severity; and

Subject listings will be provided for all adverse events, serious adverse events, adverse events leading to death and adverse events leading to study treatment discontinuation.

16.2 Visual Acuity (ETDRS)

VA will be measured at every study visit prior to the CAC. For Visit 4, it will be measured again post-CAC. Visual acuity (logMAR) will be summarized by treatment using the average of both eyes for each subject with quantitative summary statistics. The number of subjects with worsening of acuity of 10 letters or more from baseline will also be summarized with counts and with percentages based on the total number of subjects in each treatment group with responses. Results for VA will be presented in a data listing.

16.3 Slit-Lamp Biomicroscopy Examination

A slit-lamp biomicroscopy examination will be performed at each visit prior to the CAC and again post-CAC for Visit 4, and will consist of the examination of the following items:

- Eyelid;
- Conjunctiva;
- Cornea;
- Lens; and
- Anterior Chamber.

The results will be graded as normal, abnormal not clinically significant (NCS) or abnormal clinically significant (CS). The results will be summarized using counts and percentages for each treatment group for all eyes combined. Percentages will be based on the number of subjects eyes in each treatment

group with responses. A shift table will also be produced showing changes from baseline in slit-lamp examination results for each treatment and post-baseline assessment.

A subject listing of the slit-lamp biomicroscopy parameters will also be produced.

16.4 Intraocular Pressure (IOP)

IOP will be measured at Visits 1 (post-CAC®) and 4 (post-CAC) and will be summarized by treatment using the average of both eyes for each subject with quantitative summary statistics. At Visit 4, an IOP of ≥30 mmHg or an increase of 10 mmHg over baseline (Visit 1) will be considered an AE; the number of subjects meeting this criteria will be summarized with counts and with percentages based on the total number of subjects in each treatment group with responses. IOP will be listed for each eye at each visit.

16.5 Dilated Fundoscopy Examination

Dilated fundus examinations will be performed at Visits 1 (post-CAC) and 4 (post-CAC). Counts and percentages of normal and abnormal results will be presented for all eyes combined by visit and treatment group for the following regions: vitreous, retina, macula, choroid, and optic nerve. Percentages will be based on the number of subject eyes in each treatment group with responses. A shift table will also be produced showing changes from baseline in dilated fundus examination results for each treatment and post-baseline assessment. Results will be listed for both eyes at each visit.

17. Interim Analyses

No interim analysis is planned for this study.

[redacted]

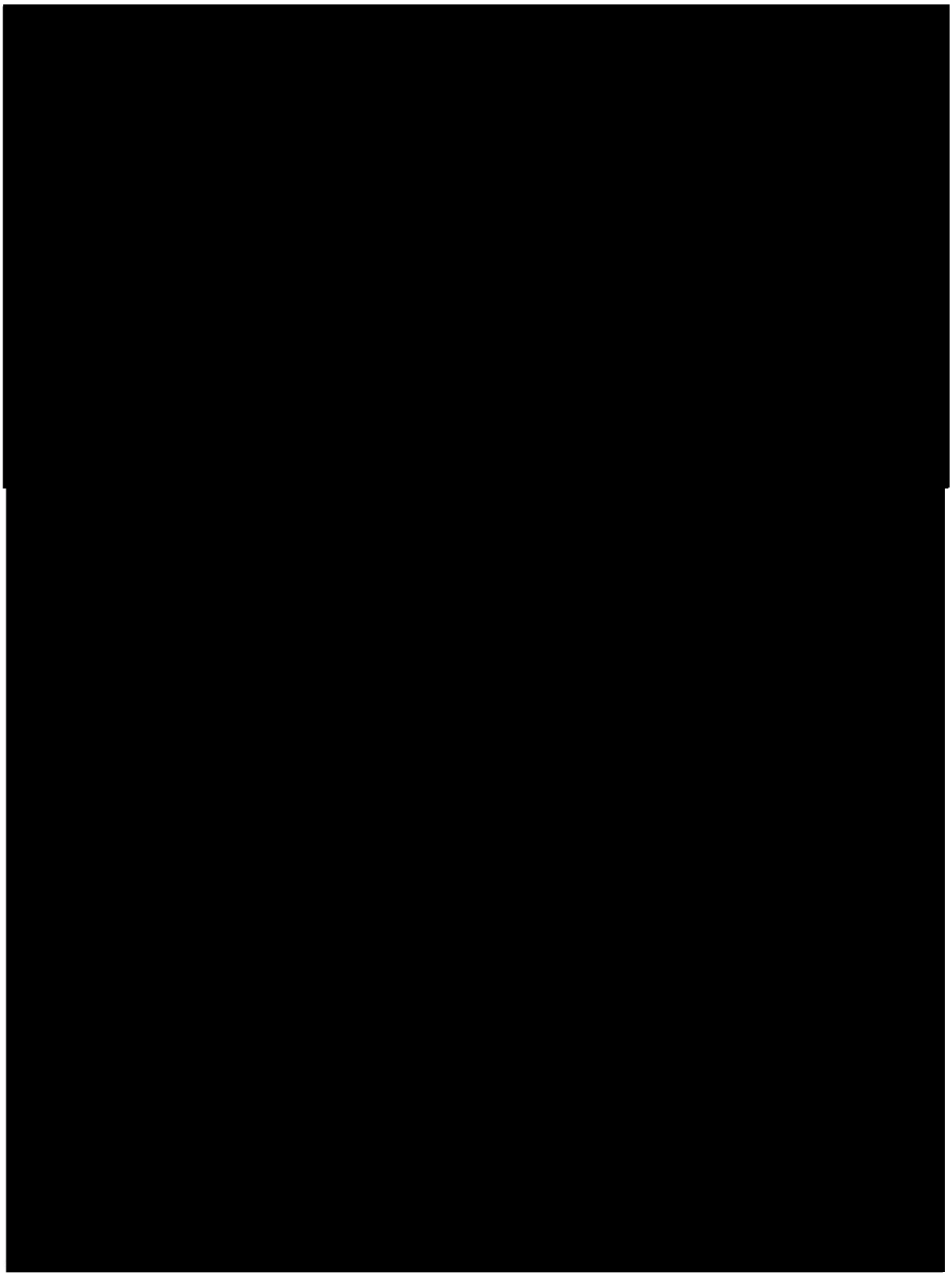
19. Revision History

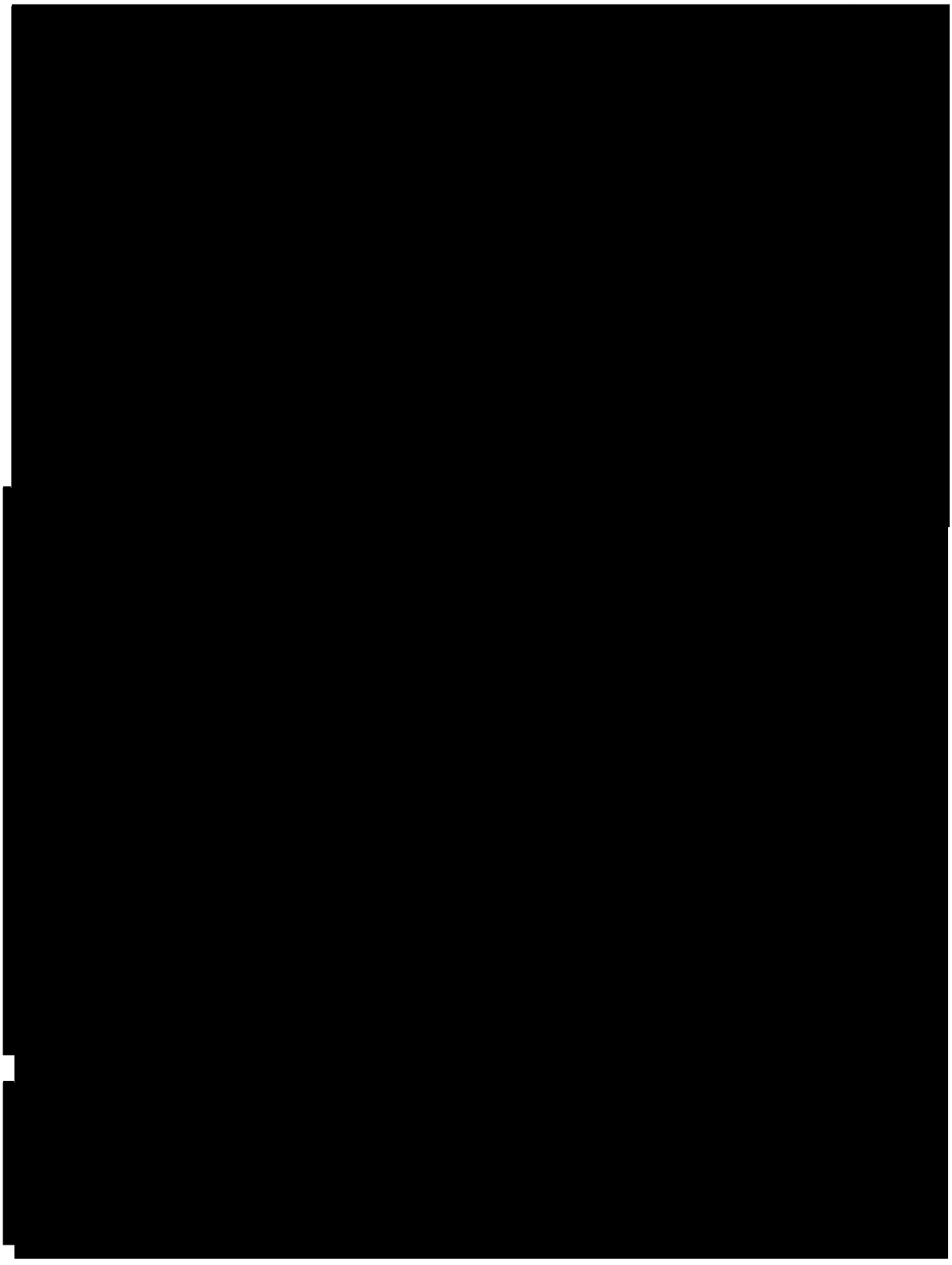
Documentation of revision to the SAP will commence after approval of the Final version 1.0.

20. Tables

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

[redacted]





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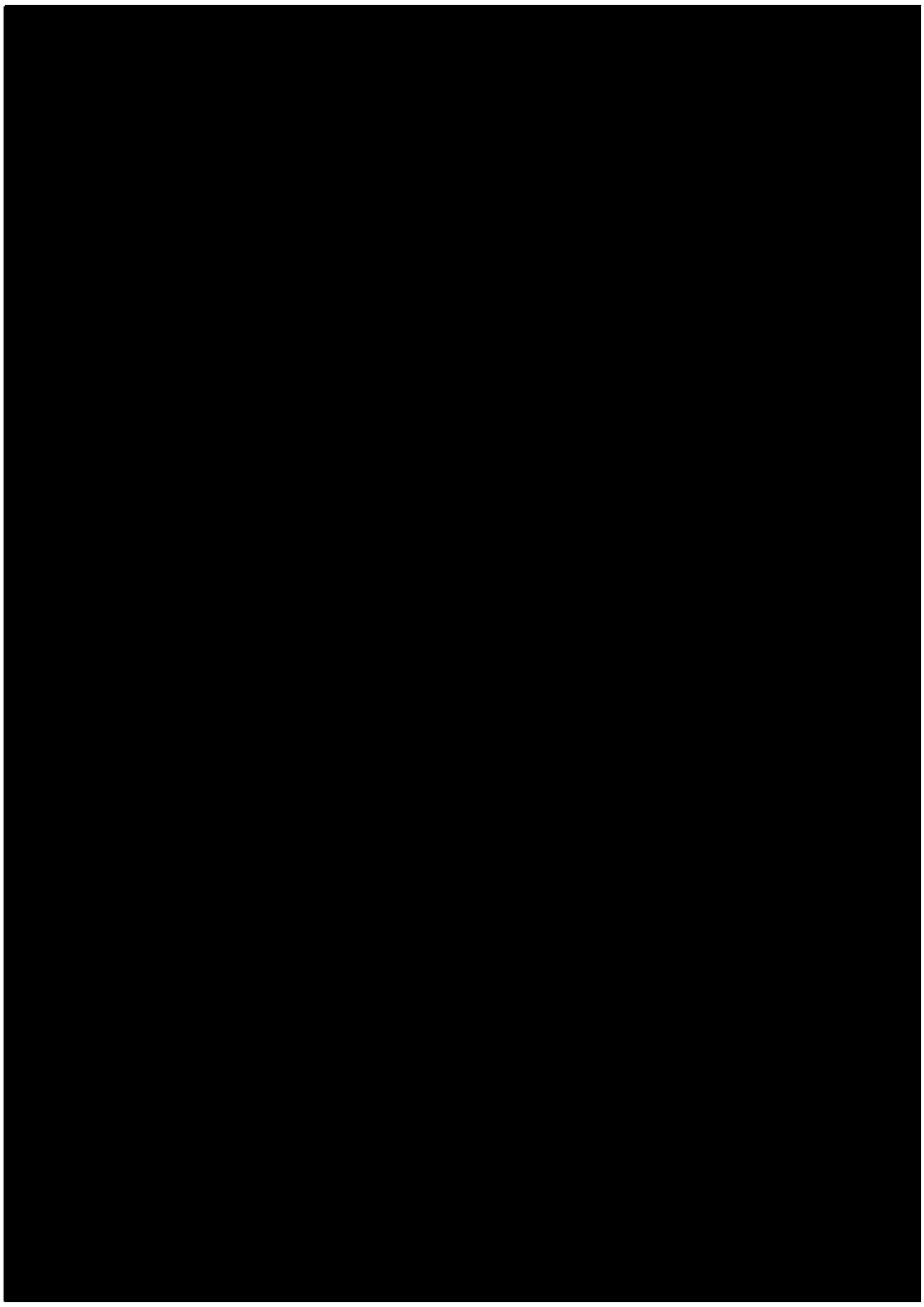
21. Listings

[redacted]



22. Figures