Short Title:

Comparison of the Cataract Refractive Suite and Standard Manual Techniques
Statistical Analysis Plan
CTK246-P001 / NCT02974140

Full Title:

A prospective, Multicenter, Randomized Evaluation of Refractive Predictability When Using the Cataract Refractive Suite and Standard Manual Techniques
Statistical Analysis Plan
CTK246-P001

Protocol Title:	A prospective, multicenter, randomized evaluation of refractive predictability when using the Cataract Refractive Suite and standard manual techniques
Project Number:	Cataract Refractive Suite/A02835
Protocol TDOC Number:	TDOC- 0052629
Author:	▮▮▮▮▮▮▮

Statistician |
Template Version:	Version 4.0, approved 16MAR2015
Approvals:	See last page for electronic approvals
Job Notes:	

This is the original (Version 1.0) Statistical Analysis Plan for this study. This version of the Statistical Analysis Plan is based on Version 1.0 of the study protocol.

Executive Summary:

Key objective: to compare the refractive predictability (prediction error) between the Cataract Refractive Suite (CRS) and standard manual technique at 1 month postoperative.

Decision criterion: percentage of eyes in which the Manifest refraction spherical equivalent (MRSE) at 1 month is $\leq 0.5D$ relative to predicted MRSE when comparing the CRS group with standard manual technique.

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List of Abbreviations

ADE	Adverse device effects
AE	Adverse event
ATC	Anatomical Therapeutic Chemical
██████	████████████████████████
CDE	Cumulative dissipated energy
CI	Confidence Interval
CRS	Cataract Refractive Suite
DBL	Database lock
FAS	Full analysis set
IOL	Intraocular lens
IOP	Intraocular pressure
████	████████████
████	█████████████████████
MedDRA	Medical Dictionary for Regulatory Activities
MRSE	Manifest refraction spherical equivalent
████	██████████████
PD	Protocol deviation
PT	Preferred term
SADE	Serious adverse device effects
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SOC	System organ class
████	██████████████
████	█████████
VA	Visual acuity
WHO	World Health Organization

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1   Study Objectives and Design

This statistical analysis plan (SAP) describes the statistical analysis outlined in Section 15 of the study protocol along with any additional analyses, specifications, or deviations from the protocol planned before database lock (DBL).

1.1   Study Objectives

The primary objective is to compare the refractive predictability between the CRS and standard manual technique at 1 month post-operative.

Secondary objectives include:

1. To compare the amount of cumulative dissipated energy (CDE) expended in the eye between the CRS and standard manual technique.

2. To assess the average estimated aspiration fluid used during surgery between the CRS and standard manual technique.

3. To assess the average aspiration time spent during surgery between the CRS and standard manual technique.

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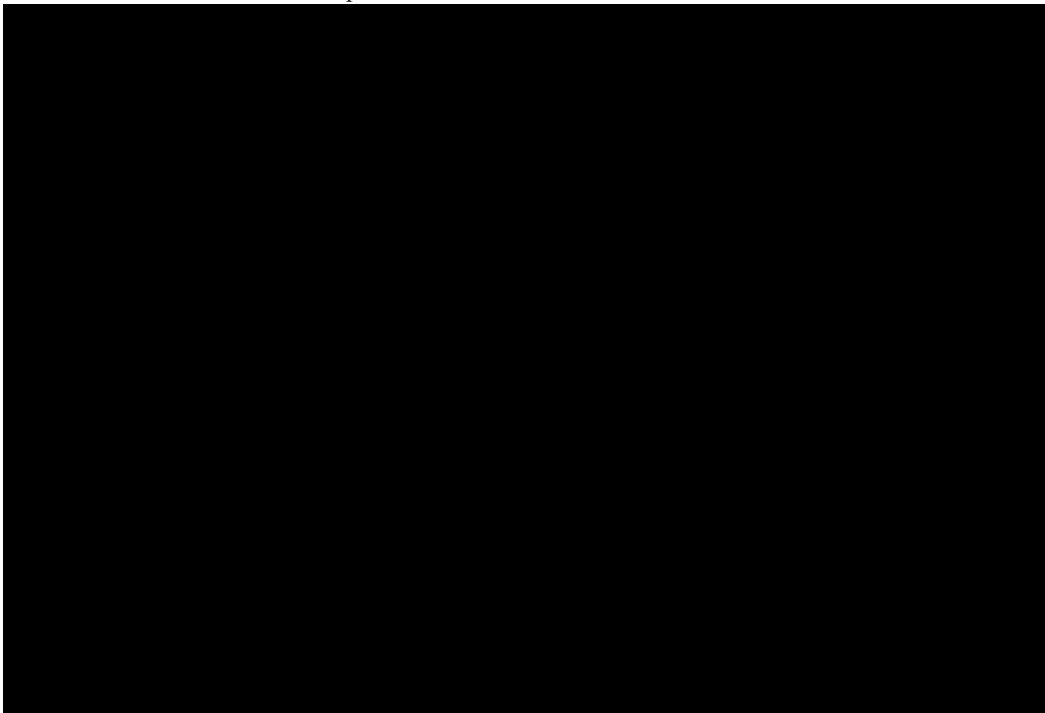
1.2   Study Description

This is a prospective, multi-center, observer masked, randomized, active control, contralateral design study. Subjects with bilateral cataracts will be enrolled at approximately 12 investigational sites and undergo cataract surgery.

Subjects will attend 8 planned study visits: a Screening visit from Day -30 to Day -1 followed by 7 visits during an approximate 5-month post-surgery period (see Figure 1-1).

Figure 1–1   **Study Design**
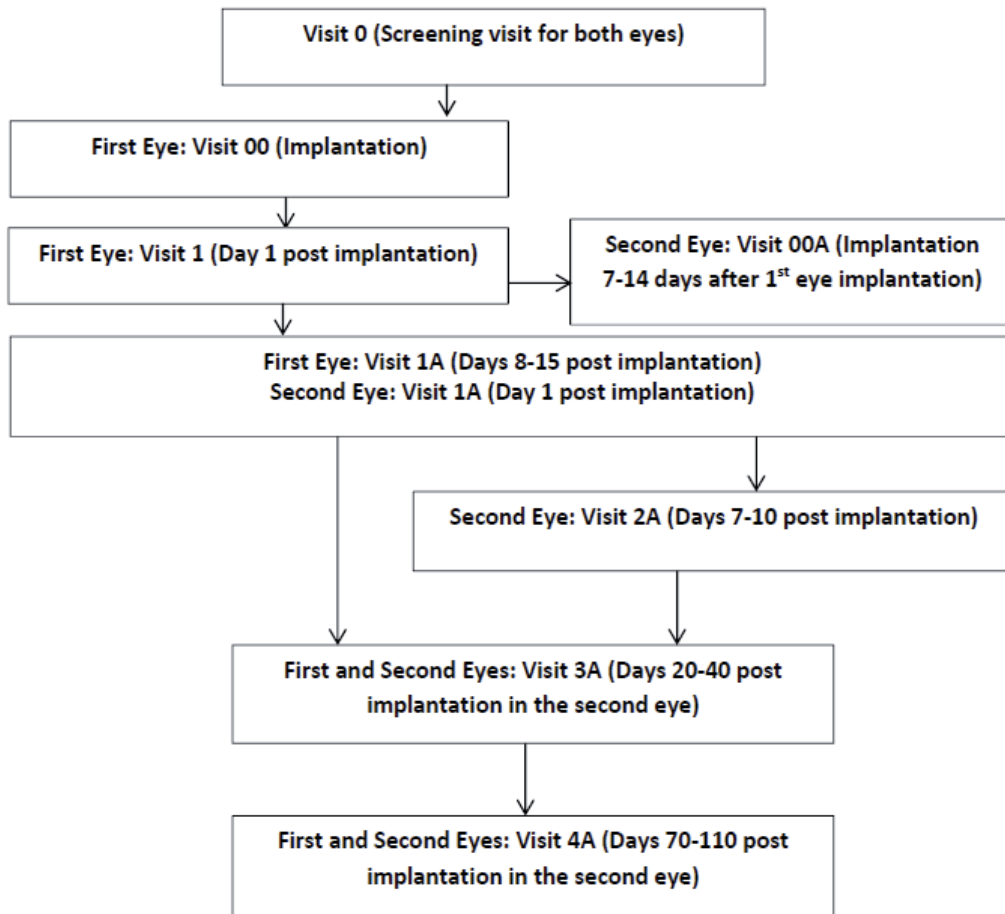
1.3 Randomization

A member of the Randomization Programming group at Alcon who is not part of the study team will generate the randomized allocation schedule for surgery procedure group. Randomization will be implemented in an Interactive Response Technology system.

1.4 Masking

This is an observer masked study. Site personnel who perform the manifest refraction subjective assessment and visual acuity testing after randomization will remain masked to the procedure group until after the final DBL. The same masking restriction applies to the analysts who perform the interim analysis. Surgery assignment may be known to Alcon, Novartis, and other site personnel. However they will not reveal the surgery assignment to masked site personnel or masked interim analysis team at any time during the study.

1.5 Interim Analysis

This study will initially randomize and treat 300 subjects. An interim analysis will be performed once 200 subjects have been randomized, treated and completed their assessment for the primary effectiveness endpoint at Month 1 (Visit 3A). Additional subjects may be enrolled based on the result of the interim analysis. The study will randomize and treat up to 500 subjects in total.

2 Data Analysis General Information

The statistical software used for the analyses will be SAS version 9.4 or later unless otherwise noted.

Descriptive statistics for continuous variables will include the number of observations, mean, standard deviation (SD), median, minimum, and maximum. .

For categorical variables frequency and percentage will be presented for non-missing data.

2.1 General Definitions

2.2 Baseline and Post-baseline

Baseline date is referred to as Surgery (Day 0) of the study. Note that baseline date is the date of surgery for each eye respectively as each eye is implanted on different days.

Baseline (pre-surgery) value for effectiveness and safety variables is the last available, non-missing, scheduled or unscheduled value collected prior to surgery.

All data collected after Surgery (Day 0) are defined as post-baseline data.

2.3   Unscheduled Visits

All unscheduled visit data will be listed as outlined in their relevant section if applicable.

3   Analysis Sets

3.1   Effectiveness Analysis Sets

The full analysis set (FAS) will contain all eyes that are randomized and for which an IOL is successfully implanted; all eyes in the FAS will be assigned to the surgery procedure actually received for analysis purposes. The FAS will be the primary analysis set for all effectiveness summaries and analyses, as well as all baseline and study summaries (i.e. subject disposition, background and demographic characteristics, medical history).

3.2   Safety Analysis Set

The safety analysis set will contain all eyes for which LenSx is activated and laser cut is started for the test eyes and corneal incision is begun for the control eyes; all eyes in the safety analysis set will be assigned to the procedure group actually received. The safety analysis set will be the primary analysis set for all summaries and analyses of safety data.

4   Subject Characteristics and Study Conduct Summaries

4.1   Subject Disposition

A subject disposition table based on the FAS will be presented that displays the number and percentage of subjects who completed or discontinued the study prematurely including the reason for discontinuation. In addition the total number and percentage of subjects passing and failing screening will be presented for all screened patients. A patient accountability table for subjects with at least one eye in the FAS will be provided based on Table C.1 in ANSI Z80.12-2007.

The number of eyes within each of the analysis sets (Section 3.1 and Section 3.2) used in the study will be given. The reasons for exclusion from each set will be listed.

4.2   Protocol Deviations

The number of protocol deviations (PDs) will be tabulated by deviation code. In addition, a listing of PDs will be produced including the accompanying deviation code.

4.3   Demographics and other Baseline Characteristics

Characteristics by subject will be summarized overall, and characteristics by eye will be summarized by procedure group and overall.

Demographics and background characteristics for each subject:

- Age (in years, and year categories < 65 and ≥ 65)

- Gender (male / female / unknown / undifferentiated)

- Ethnicity (Hispanic or Latino / not Hispanic or Latino / not reported / unknown)

- Race (White / Black or African American / American Indian or Alaska Native / Asian / Native Hawaiian or Other Pacific Islander / other)

Ocular characteristics for each eye:

- Axial length (mm)

- Keratometry

Note: variables that have both baseline and post-baseline values will be summarized elsewhere in the SAP: Intraocular pressure (IOP), ███████████████████████ ████████████████████████████████████ manifest refraction, slit lamp examination.

4.4   Medical History

Relevant medical history (ocular and non-ocular) and current medical conditions by eye will be listed by surgery group for data in the FAS.

4.5   Prior and Concomitant Medications

Prior (or previous) medications are defined as those medications which were taken and stopped prior to surgery.

Concomitant medications are medications taken after surgery but prior to the last day of study visit. They also include medications initiated pre-surgery which continued into the post-surgery period. Note that this will not include routine preoperative, intraoperative and postoperative medications administered for the cataract surgery.

Prior or concomitant medication will be identified based on recorded or imputed start and end dates of medication taken. Prior and concomitant medications will be coded according to the

World Health Organization (WHO) Drug Reference List dictionary (201603 or a more recent version) which employs the Anatomical Therapeutic Chemical (ATC) classification system.

Prior and concomitant medications by eye will be listed by procedure group for data in the safety analysis set.

5 Effectiveness Analysis Strategy
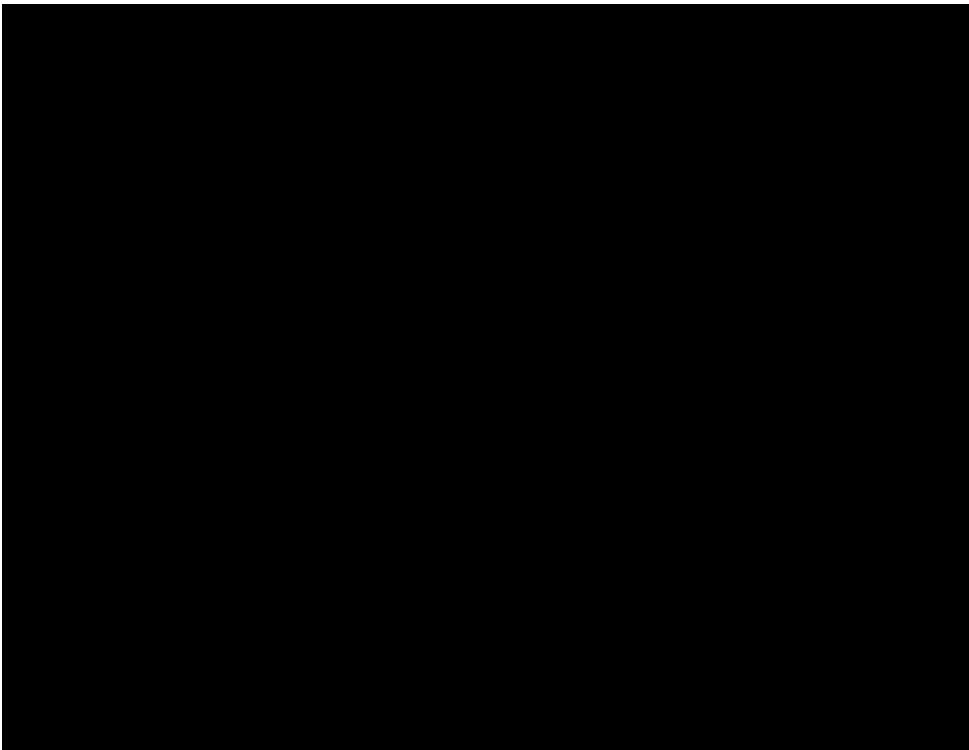
5.1 Effectiveness Endpoints

Primary endpoint

- Percentage of eyes in which the MRSE at 1 month is ≤ 0.5D relative to predicted MRSE

Secondary endpoints

- Mean CDE expended in the eye during surgery

- Mean estimated aspiration fluid used during surgery

- Mean aspiration time spent during surgery.

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5.2   Effectiveness Hypotheses

5.2.1   Primary Effectiveness Hypotheses

The primary effectiveness objective is to demonstrate superiority of the CRS compared to standard manual techniques with respect to refractive predictability at Month 1. The following hypotheses will be tested:

$$H_0: p_c \leq p_s$$

$$H_1: p_c > p_s$$

where p_c and p_s are the percentage of eyes with manifest refraction spherical equivalent within 0.5D of predicted postoperative spherical equivalent at Month 1 in the CRS and standard manual technique arms respectively.

5.2.2   Secondary Effectiveness Hypotheses

The null and alternative hypotheses are the same for all secondary analysis and can be presented as:

$$H_0: \mu_c \geq \mu_s$$

$$H_1: \mu_c < \mu_s$$

where μ_c denotes the mean value in the CRS group and μ_s denotes the mean value in the standard manual technique group for each of the respective secondary endpoints (mean CDE expended in the eye during surgery, mean estimated aspiration fluid used during surgery, and mean aspiration time spent during surgery).

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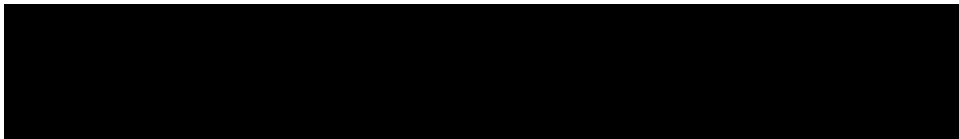
5.3   Statistical Methods for Effectiveness Analyses

All analysis in this section will be based on the FAS.

5.3.1   Primary Effectiveness endpoint

The primary effectiveness analysis will be analyzed using a one-sided McNemar's test at the 5% significance level. P-value for the difference in the population proportions will be estimated and presented.

The number and percentage of eyes with manifest refraction spherical equivalent $\leq 0.5D$ of predicted post-operative spherical equivalent will be presented by surgery procedure and visit.

5.3.2   Secondary Effectiveness Endpoints

Each of the null hypotheses will be tested using a one-sided paired t-test. Multiplicity adjustment will be discussed in Section 5.4.

Descriptive statistics for continuous variables will be provided by procedure group for each of the secondary effectiveness endpoints (mean CDE expended in the eye during surgery, mean estimated aspiration fluid used during surgery, mean aspiration time spent during surgery).

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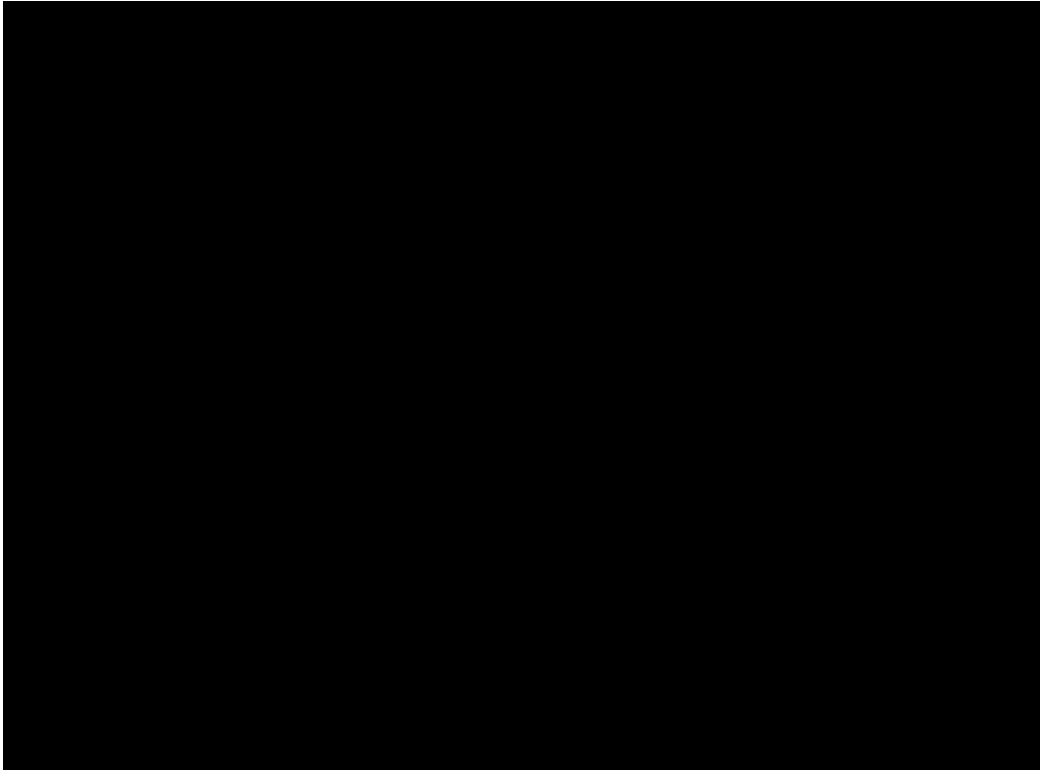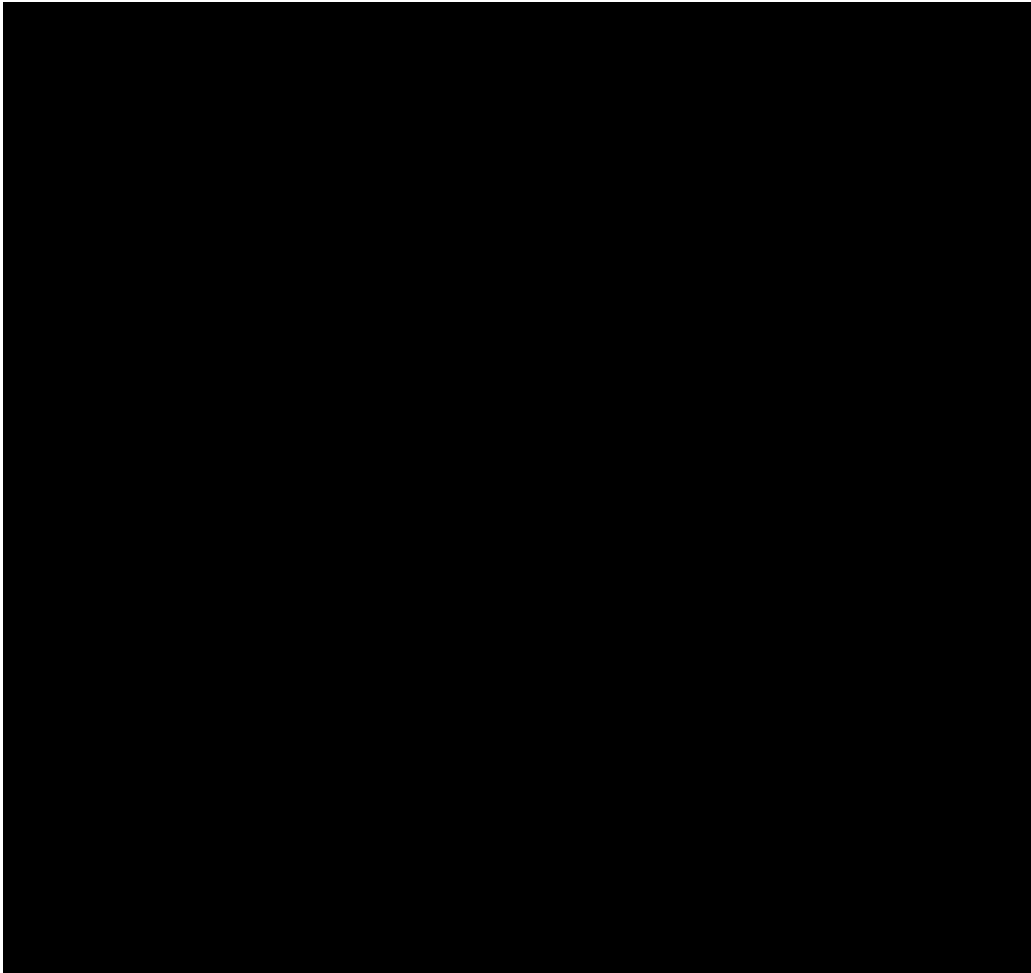
5.4   Multiplicity Strategy

In order to control the overall type I error rate over the family of primary and secondary hypotheses, the secondary effectiveness hypotheses will only be tested if the primary effectiveness null hypothesis is rejected at the one-sided 5% significance level ($\alpha=0.05$).

If the null hypothesis of the primary effectiveness endpoint is rejected, then the three secondary effectiveness endpoints will be tested using the Hochberg testing procedure. Let:

- H_{0i} refers to the corresponding null hypotheses (i=1, 2, 3)

- p_i refers to the p-values for H_{0i}, which will be calculated without any multiplicity adjustment. The p-values will be sorted in order of magnitude such that $p_1 \leq p_2 \leq p_3$

- Hochberg's step-up method will proceed as follows:

    - Step 1: If $p_3 < \alpha$ (where α is 0.05, 1-sided), reject all H_{0i} (i=1,2,3) and stop; otherwise go to Step 2.

    - Step 2: If $p_2 < \alpha/2$ (where α is 0.05, 1-sided), reject H_{01} and H_{02} and stop; otherwise go to Step 3.

    - Step 3: If $p_1 < \alpha/3$ (where α is 0.05, 1-sided), reject H_{01} and stop.

5.5   Handling of Missing Data

The analyses of the effectiveness endpoints will be based on observed data (i.e. no imputation will be performed). The influence of missing data is expected to be minimal.

5.6   Interim Analysis for Effectiveness

An interim analysis for the purposes of sample size re-estimation will be performed when the first 200 subjects who are randomized and treated complete their assessment for the primary effectiveness endpoint at Month 1 (Visit 3A). Alcon staff not involved with the conduct of the trial will re-estimate the sample size based on the data from the first 200 subjects. These staff will provide the re-estimated sample size and the predicted conditional power of the final test statistic based on that sample size.

If the conditional power of the study is < 50% for the largest allowable sample size (500 subjects), no additional sample size beyond the originally planned 300 subjects will be added, and termination of the study may be considered. Because additional sample size will not be added if the conditional power of the study is <50% at the maximum allowable sample size, any effect of the sample size modification on the type I error should be minimal (Mehta, 2000).

6   Safety Analysis Strategy

6.1   Safety Endpoints

The safety endpoints are:

- Adverse events

- Slit lamp examination

- IOP

- Surgical problems

- Dilated fundus examination

- Device deficiencies

6.2   Safety Hypotheses

There are no formal safety hypotheses in this study.

6.3   Statistical Methods for Safety Analyses

The analysis set for safety analysis is the safety analysis set unless otherwise stated.

6.3.1   Extent of Exposure

6.3.2   Adverse Events

All AEs occurring from when a subject signs informed consent to when a subject exits the study will be accounted for in the reporting. Analysis and presentation of AEs occurring during the screening period will be separated from those occurring during the post-surgery period where a comparative evaluation of post-surgery AEs is intended. A post-surgery AEs is an AE that occurs that was not present prior to the study procedure or any pre-existing event that worsens following the study procedure. The period for post-surgery AEs analysis starts from when surgery procedure has begun to end of study.

Descriptive summaries (eye counts, event counts, and percentages) by procedure group for specific AEs will be presented by primary SOC and PT in the Medical Dictionary for Regulatory Activities (MedDRA; version 19.1 or later). Eye counts refer to the number of eyes with the respective AE of interest. Event counts refer to the number of occurrences of the respective AE of interest, regardless of whether an eye already had this event.

The SOCs will be presented in alphabetical order. PTs will be ordered with each SOC in decreasing order according to the total column. An eye with multiple ocular AEs of the same preferred term is only counted once toward the total of this preferred term and once toward the total of the SOC. Post-surgery AEs will be summarized for all eyes in the safety analysis set for the following tables:

- Ocular AEs

- Ocular serious AEs (SAEs)

- Adverse device effects (ADEs)

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- Serious ADEs (SADEs)

Listings describing details of AEs will be provided. These will include:

- Ocular AEs for all eyes in the safety analysis set

- Ocular AEs for all eyes not in the safety analysis set

- Non-ocular AEs for all enrolled subjects

- Deaths for all enrolled subjects

These listings will also include AEs that occur after signing the informed consent but prior to surgery. They will comprise all events occurring during this period in any subject who consented to participate in the study.

6.3.3   Device Deficiencies

The number of all device deficiencies will be tabulated by procedure group. A listing of all device deficiencies as recorded on the Device Deficiency page of the Global Library Forms will also be provided.

6.3.4   Slit Lamp Examination

A listing will be provided which presents all eyes with an abnormality in any slit-lamp parameter by visit. The listing will include the following variables: procedure group, investigator, subject, age, sex, race, ethnicity, visit, eye, parameter, baseline value and value at the visit. Other slit lamp examination findings will be listed along with their MedDRA dictionary primary SOC and PT codes.

6.3.5   Intraocular Pressure

IOP measurements will be recorded in mmHg and rounded to the nearest whole mmHg.

Descriptive summaries for continuous variables of observed IOP values and change from baseline values will be presented by procedure group and visit.

A listing will be provided which presents all subjects with an increase or decrease in IOP of more than 10 mmHg at any visit compared to the same eye at baseline. The listing will include the following variables: procedure group, investigator, subject, age, sex, race, ethnicity, visit, eye, baseline value, value at the visit, and change from baseline value.

6.3.6   Dilated Fundus Examination

A listing will be provided which presents all eyes with abnormality in any fundus parameter by visit. The listing will include the following variables: procedure group, investigator, subject, age, sex, race, ethnicity, visit, eye, baseline value and value at the visit.

6.3.7   Surgical Problems

The numbers and percentages of eyes with surgical problems will be presented by procedure group and surgical problem type. In addition, a listing of subjects with surgical problems will be provided. The listing will include the following variables: procedure group, investigator, subject, age, sex, race, ethnicity, eye, and description of surgical problem.

7   Sample Size and Power Calculations

The rates of success for the primary endpoint are assumed to be 83% and 75% for the CRS and standard manual technique arms respectively. These assumptions are based on data from the AnalyzOR Retrospective Data Exploration Study (Data on File)..

An estimate of the discordance in outcome between eyes is in the range 8% to 33%. For an initial sample size calculation, the midpoint value of this range, 21%, will be assumed. Based on these assumptions 267 subjects, treated contralaterally, are required to provide 90% power to reject the null hypothesis for a one sided McNemars test at the 5% level using the approximation from Miettinen (Miettinen 1968). If the proportion of discordance is 33% and all other assumptions stay the same a sample of 433 subjects are needed.

The initially planned sample size of 267 is inflated to allow for up to 10% drop out; this inflation yields a sample size of 300 subjects. Inflation of the sample size of 433 to allow for up to 10 % drop out yields a sample size of 485; the sample size of 500 is selected so that the maximum sample size will be divisible by the block size of 50.

The study will also employ an adaptive design with potential sample size adjustment based on the proportion of discordance from the interim analysis. This study will enroll approximately 350 subjects to initially randomize and treat 300 subjects (that could potentially increase to approximately 580 subjects enrolled and 500 subjects randomized). Based on the calculation from the interim analysis an additional 200 subjects may be randomized and treated thus the study will randomize and treat a total sample size in the range of 300 to 500 subjects. Any additional sample size will be added in blocks of 50 in order to prevent any back-calculation of the interim study results.

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8   References

Mehta CR, Pocock SJ. Adaptive increase in sample size when interim results are promising: a practical guide with examples. Statistics in medicine; 2000; 00:1-6

Miettinen OS. The matched pairs design in the case if all-or-none responses. Biometrics 1968;24:339–352

9   Revision History

This is the original (Version 1.0) SAP for this study. This version of the SAP is based on Version 1.0 of the study protocol.

10   Appendix

10.1   Imputation rules

10.1.1   AE date imputation

The following table explains the notation used in the logic matrix. Please note that completely missing start dates will not be imputed.

	Day	Month	Year
Partial Adverse Event Start Date	Not used	MON	YYYY
Surgery Start Date	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

	MON MISSING	MON < TRTM	MON = TRTM	MON > TRTM
YYYY MISSING	(1) No convention	(1) No convention	(1) No convention	(1) No convention
YYYY < TRTY	(2.a) Before Surgery Start	(2.b) Before Surgery Start	(2.b) Before Surgery Start	(2.b) Before Surgery Start
YYYY = TRTY	(4.a) Uncertain	(4.b) Before Surgery Start	(4.c) Uncertain	(4.c) After Surgery Start
YYYY > TRTY	(3.a) After Surgery Start	(3.b) After Surgery Start	(3.b) After Surgery Start	(3.b) After Surgery Start

Before imputing AE start date, find the AE start reference date.

1. If the (imputed) AE end date is complete and the (imputed) AE end date < surgery start date then AE start reference date = min(informed consent date, earliest visit date).
2. Else AE start reference date = surgery start date

Impute AE start date -

1. If the AE start date year value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the AE year value is missing, the imputed AE start date is set to NULL.
2. If the AE start date year value is less than the surgery start date year value, the AE started before surgery. Therefore:
   a. If AE month is missing, the imputed AE start date is set to the mid-year point (01JULYYYY).
   b. Else if AE month is not missing, the imputed AE start date is set to the mid-month point (15MONYYYY).
3. If the AE start date year value is greater than the surgery start date year value, the AE started after surgery. Therefore:
   a. If the AE month is missing, the imputed AE start date is set to the year start point (01JANYYYY).
   b. Else if the AE month is not missing, the imputed AE start date is set to the later of (month start point (01MONYYYY), AE start reference date + 1 day).

4. If the AE start date year value is equal to the surgery start date year value:
   a. And the AE month is missing the imputed AE start date is set to the surgery reference start date + 1 day.
   b. Else if the AE month is less than the surgery start month, the imputed AE start date is set to the mid-month point (15MONYYYY).
   c. Else if the AE month is equal to the surgery start date month or greater than the surgery start date month, the imputed AE start date is set to the later of (month start point (01MONYYYY), surgery start reference date + 1 day).

If complete (imputed) AE end date is available and the imputed AE start date is greater than the (imputed) AE end date, then imputed AE start date should be set to the (imputed) AE end date.

10.1.2   Concomitant medication date imputation

10.1.2.1 CM start date imputation

The following table explains the notation used in the logic matrix. Please note that completely missing start dates will not be imputed.

	Day	Month	Year
Partial CM Start Date	Not used	MON	YYYY
Surgery Start Date	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

	MON MISSING	MON < TRTM	MON = TRTM	MON > TRTM

	MON MISSING	MON < TRTM	MON = TRTM	MON > TRTM
YYYY MISSING	(1) Uncertain	(1) Uncertain	(1) Uncertain	(1) Uncertain
YYYY < TRTY	(2.a) Before Surgery Start	(2.b) Before Surgery Start	(2.b) Before Surgery Start	(2.b) Before Surgery Start
YYYY = TRTY	(4.a) Uncertain	(4.b) Before Surgery Start	(4.a) Uncertain	(4.c) After Surgery Start
YYYY > TRTY	(3.a) After Surgery Start	(3.b) After Surgery Start	(3.b) After Surgery Start	(3.b) After Surgery Start

1. If the CM start date year value is missing, the imputed CM start date is set to one day prior to surgery start date.

2. If the CM start date year value is less than the surgery start date year value, the CM started before surgery. Therefore:
   a. If the CM month is missing, the imputed CM start date is set to the mid –year point (01JULYYYY).
   b. Else if the CM month is not missing, the imputed CM start date is set to the mid-month point (15MONYYYY).

3. If the CM start date year value is greater than the surgery start date year value, the CM started after surgery. Therefore:
   a. If the CM month is missing, the imputed CM start date is set to the year start point (01JANYYYY).
   b. Else if the CM month is not missing, the imputed CM start date is set to the month start point (01MONYYYY).

4. If the CM start date year value is equal to the surgery start date year value:
   a. And the CM month is missing or the CM month is equal to the surgery start date month, then the imputed CM start date is set to one day prior to surgery start date.
   b. Else if the CM month is less than the surgery start date month, the imputed CM start date is set to the mid-month point (15MONYYYY).
   c. Else if the CM month is greater than the surgery start date month, the imputed CM start date is set to the month start point (01MONYYYY).

If complete (imputed) CM end date is available and the imputed CM start date is greater than the (imputed) CM end date, then imputed CM start date should be set to the (imputed) CM end date.

10.1.2.2 CM end date imputation

1. If the CM end date year value is missing, the date uncertainty is too high to impute a rational date. Therefore, if the CM end year value is missing or ongoing, the imputed CM end date is set to NULL.

2. Else, if the CM end date month is missing, the imputed end date should be set to the earliest of the (surgery follow up period date, 31DECYYYY, date of death).

3. If the CM end date day is missing, the imputed end date should be set to the earliest of the (surgery follow-up period date, last day of the month, date of death).

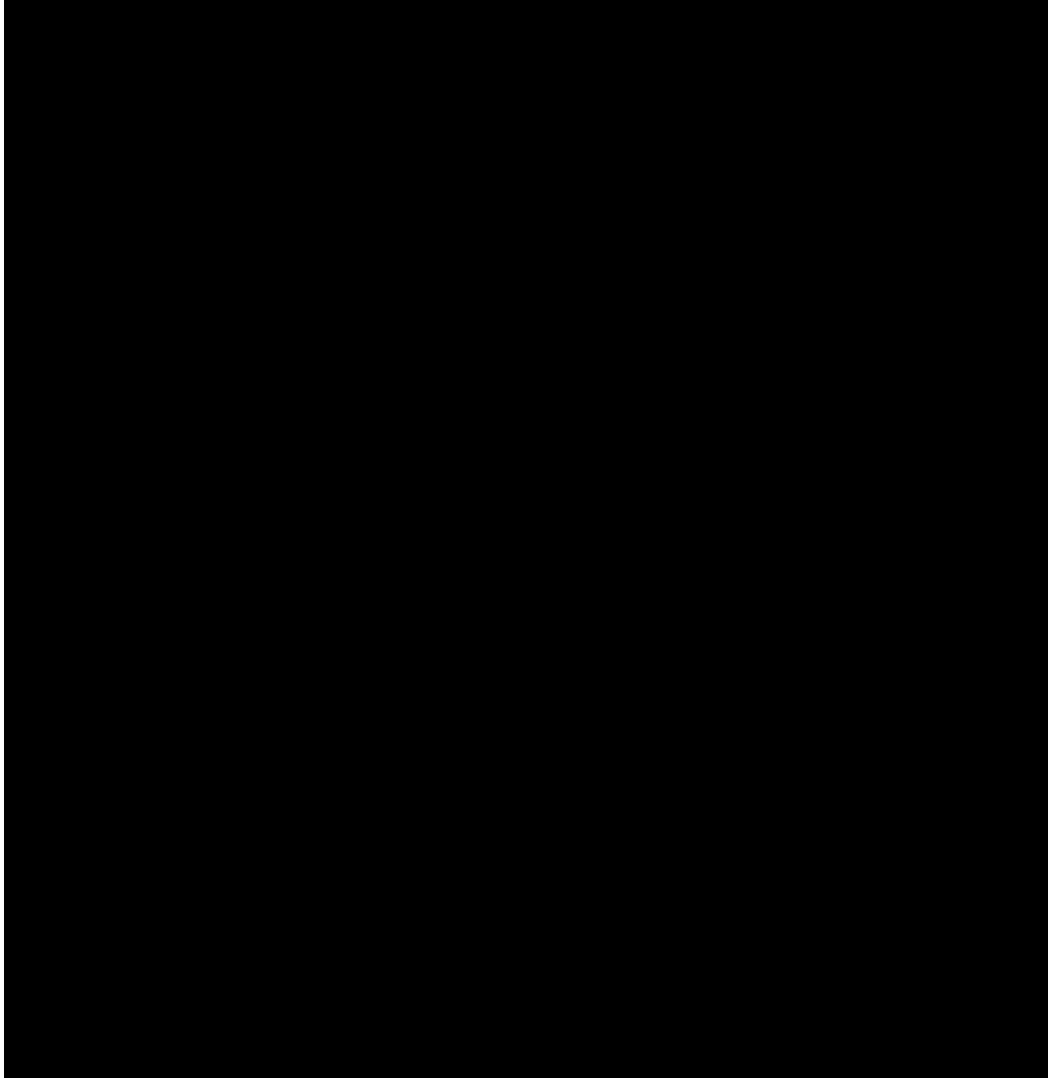4. If the imputed CM end date is less than the existing CM start date, use the CM start date as the imputed CM end date.