Short Title:

Statistical Analysis Plan
RFL605-P001 / NCT02987660

Full Title:

Statistical Analysis Plan
RFL605-P001

Protocol Title:	Comparison of Topography Guided LASIK with WaveLight EX500 to SMILE with Zeiss VisuMax
Project Number:	A02827
Protocol TDOC Number:	TDOC-0052425
Author:	[redacted]
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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 Objectives:

The primary objective of the study is to demonstrate that Topography Guided Laser in situ keratomileusis (LASIK) is superior to Small incision lenticule extraction (SMILE) in the percentage of eyes with manifest refraction cylinder ≤ 0.5 D at 3 months.

Decision Criteria for Study Success:

The primary objective will be considered met if the percentage of eyes with manifest refraction cylinder within (≤) 0.5 D in the Topography Guided LASIK arm is statistically significantly different from the SMILE arm at 3 months (Month 3) in favor of the Topography Guided LASIK arm.

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List of Abbreviations

A	Axis
ADE	Adverse device effect
AE	Adverse event
ATC	Anatomical therapeutic classification
BCVA	Best corrective visual acuity
C	Cylinder
CI	Confidence interval
CSR	Clinical study report
DBL	Database lock
eCRF	Electronic case report form
ICF	Informed consent form
IOP	Intraocular pressure
ITT	Intent-to-Treat
LASIK	Laser in situ keratomileusis
MedDRA	Medical Dictionary for Regulatory Activities
MRSE	Manifest refraction spherical equivalent
OD	Right eye
OS	Left eye
OU	Both eyes
RSVP	Refractive Status and Vision Profile
SAP	Statistical analysis plan
SADE	Serious adverse device effect
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SMILE	Small incision lenticule extraction
SQDES	Short questionnaire for dry eye syndrome
SOC	System organ class
TEAE	Treatment-emergent AE
UCVA	Uncorrected visual acuity
WHO	World Health Organization

1 Study Objectives and Design

This statistical analysis plan (SAP) describes the statistical analysis outlined in Section 15 of the study protocol (Clinical Trial Protocol Version 1.0) along with any additional analyses, specifications or deviations from the protocol planned before database lock (DBL).

1.1 Study Objectives

The primary objective of the study is:

- To demonstrate that Topography Guided Laser in situ keratomileusis (LASIK) is superior to Small incision lenticule extraction (SMILE) in the percentage of eyes with manifest refraction cylinder $\leq$ 0.5 D at 3 months.

The secondary objectives are:

- To demonstrate that Topography Guided LASIK is superior to SMILE in mean manifest refraction cylinder at 3 months.
- To demonstrate that Topography Guided LASIK is superior to SMILE in mean uncorrected visual acuity (UCVA) at 3 months.

The safety objectives are:

- To evaluate the adverse events (AEs) associated with Topography Guided LASIK and SMILE.
- To evaluate post-surgery BCVA after Topography Guided LASIK and SMILE.
- To evaluate mesopic uncorrected contrast sensitivity after Topography Guided LASIK and SMILE.

- To evaluate quality of vision and vision related quality of life after Topography Guided LASIK and SMILE.

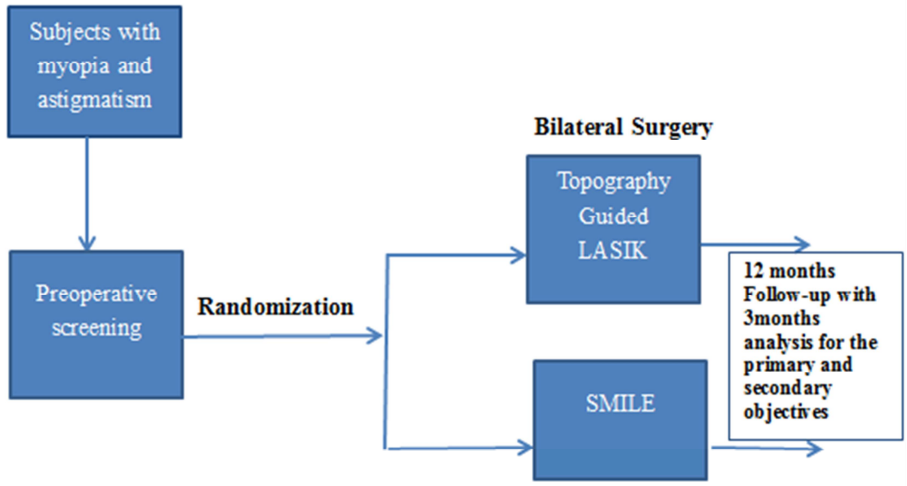
1.2 Study Description

This is a prospective, parallel group, multi-center, randomized, observer masked study. The study will enroll subjects requiring refractive correction of myopia and astigmatism who meet the protocol inclusion and exclusion criteria. The expected duration of subject participation in the study is up to 15 months with 7 planned study visits (including Pre-surgery Visit).

The study involves a Pre-Surgery Visit (ranging from 1 to 45 days prior to the Surgery Visit) followed by a 12-month post-surgery period (see Figure 1-1). The visits are as follows:

- Pre-Surgery/ Screening Visit (Day -45 to Day -1)
- Surgery (Day 0)
- Day 1 (Day 1)
- Week 1 (Day 7 ± 2)
- Month 1 (Day 28 ± 7)
- Month 3 (Day 84 ± 14)
- Month 12 (Day 330 to Day 375)

Figure 1-1 Study design



1.3 Randomization

The randomization scheme will be generated and maintained by the Sponsor's (or designee) unmasked personnel who are not involved in the conduct or analysis of the study. Randomization will be implemented using Medidata Balance®.

The randomization will be stratified by study site to ensure a balance of surgery allocations within each investigational site. Randomization will be in a 1:1 ratio.

1.4 Masking

This is an observer masked study. This means that site personnel performing the manifest refraction subjective assessment and all UCVA testing after randomization will remain masked with regard to treatment assignment until after the final DBL.

Surgery assignment may be known to Alcon, Novartis, and other site personnel (e.g., nurses and technicians involved with the surgery, staff entering data in the electronic case report form (eCRF), site personnel administering other study related procedures, e.g. Refractive Status and Vision Profile [RSVP] and Short questionnaire for dry eye syndrome [SQDES] questionnaires). However they will not reveal the surgery assignment to masked site personnel at any time during the study.

1.5 Interim Analysis

There is no formal interim analysis planned for this study. However, the main analysis will occur after the last subject completes the 3 months post-surgery follow-up (Day 84 ± 14). Subjects will then be followed up for an additional 9 months post-surgery (i.e. in total 12 months [Day 330 to Day 375] after surgery) for safety [redacted] parameters.

2 Data Analysis General Information

All analyses will be performed using SAS® statistical software (Version 9.4 or a more recent version), unless otherwise noted.

Assessments documented in the database that occur as "bilateral" (i.e. both eyes [OU]) will be summarized and listed for each eye separately. To facilitate derivations and analysis based on the eye, database records for bilateral will be split into two records containing identical information as the original record with the exception of the laterality which shall be recoded to "Right" (i.e. right eye [OD]) and "Left" (i.e. left eye [OS]), respectively. It should be noted that dependent on the assessment and at the discretion of the medical team, the assessment may only be counted once.

Data will be summarized with respect to background and demographic characteristics, primary, secondary, [redacted] along with safety observations.

Descriptive statistics (the number of non-missing observations, mean, median, standard deviation [SD], minimum, and maximum values) will be presented for continuous variables. The following number of decimal places will be used: mean values to 1 more decimal place than the raw data; median, minimum, and maximum to the same number of decimal places as the raw data and SD to 2 more decimal places than the raw data.

For categorical variables for background and demographic characteristics, the number and percentage of subjects/ eyes for each category within a variable will be calculated for non-missing data. If a count of zero is obtained for categorical data, the zero count and percentage will still be displayed. A row (category) denoted "Missing" will be included in count tabulations if a non-zero count of missing values is present for either of the surgery groups. In addition, the corresponding percentage for this row will be displayed.

Change from baseline (pre-surgery) (where relevant) will only be summarized for subjects with both baseline (pre-surgery) and post-surgery data for the relevant visit.

Unless otherwise specified, all statistical tests will be two-sided, performed using a 5% significance level and 95% (two-sided) confidence intervals (CIs) will be presented.

All data will be listed by subject and eye (if applicable), unless stated otherwise.

2.1 General Definitions

All analyses will be based on assessments according to the investigator, with the exception of the subject reported outcomes (RSVP questionnaire, SQDES). This study will consist of the following epochs:

- a screening period
- a post-surgery period

Surgery/ treatment refers to:

- Topography Guided LASIK
- SMILE

2.2 Definition of Baseline Date

Baseline date is referred to as Surgery (Day 0) of the study. It is defined as the date of surgery, for treated subjects/ eyes.

2.3 Baseline and Post-baseline Definitions

The 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.

2.4 Unscheduled Visits

All data collected at unscheduled visits will be listed.

AEs, slit lamp examination findings and dilated fundus findings collected at unscheduled visits will be reported.

3 Analysis Sets

Assignment of study eyes to the appropriate analysis set(s) will be determined prior to DBL. For the purposes of this study, the treatment will be considered to have begun once the flap

creation is initiated for Topography Guided LASIK and once the laser touches the eye for SMILE.

The **Intent to treat (ITT) Analysis Set** will contain all study eyes for which study treatment has begun for the set of subjects that are randomized; all eyes will be assigned to the treatment to which they are randomized.

The **Safety Analysis Set** will contain all study eyes for which study treatment has begun; all eyes in the Safety Analysis Set will be assigned to the treatment actually received.

All subjects who satisfy the inclusion and exclusion criteria, and who sign the informed consent form (ICF), will be considered enrolled in the study.

The ITT Analysis Set will be used to display subject disposition, background and demographic characteristics, medical history, and the analysis of the effectiveness endpoints. The Safety Analysis Set will be used for the analysis of the safety endpoints.

It should be noted for subject-level (group-level) data, the analysis will be based on the subject-level version of the respective analysis set (i.e. the subject must have at least one eye for which treatment has begun).

4 Subject Characteristics and Study Conduct Summaries

Subject characteristics and study conduct summaries include tables and listings such as a subject disposition table, background and demographic characteristics tables (including age, sex, race, and ethnicity), listing of study surgery assignment by investigator, and listing of subjects excluded from the analysis sets. Descriptive summary statistics will be presented by surgery group and overall for the ITT Analysis Set, unless otherwise specified.

No inferential tests for differences in subject characteristics between surgery groups will be performed.

4.1 Subject Disposition

A subject disposition table will be presented that displays the number of subjects enrolled in addition to the number and percentage of subjects (based on the number of randomized subjects) randomized, treated, completed, and discontinued. This table will also contain counts for each reason for premature study discontinuation. Furthermore a listing of reasons for early study discontinuation will also be provided.

The number of subjects within each of the analysis sets used in the study will be given. The reasons for exclusion from each set will be listed.

Finally, an accountability table as in Table F.1 in Appendix F of ANSI Z80.11-2012 will be provided.

4.2 Background and Demographic Characteristics

Background and demographic characteristics will be summarized on the subject-level version of the ITT and Safety Analysis Sets (i.e. the subject must have at least one eye for which treatment has begun) by surgery group and overall. The number and percentage of subjects will be presented for the categorical variables and descriptive statistics for the continuous variables.

Demographics

Categorical variables

- age (years) (<65, ≥65)
- sex (Female, Male, 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)

Continuous variable

- age (years)

Ocular characteristics

Categorical variables

- curvature (D) (for K1/Flat, K2/Steep)
- meridian (degrees) (for K1/Flat, K2/Steep)

Continuous variable

- axial length (mm) (for each eye)
- corneal thickness (μm) (for each eye)
- pupil size (mm) (for each eye)

4.3 Medical History

Medical history data will be listed by surgery group for all randomized subjects.

4.4 Prior and Concomitant Medications

Prior medications will be defined as drugs taken and stopped prior to surgery. Any medication given at least once between surgery and the last day of study visit will be a concomitant medication, including those which were started pre-surgery and continued into the post-surgery period.

Prior or concomitant medication will be identified based on recorded start dates of medication taking. Medications will be identified by anatomical therapeutic classification (ATC) according to the World Health Organization (WHO) Drug Reference List dictionary (201603 or a more recent version).

Prior and concomitant medications will be listed by surgery group for all randomized subjects.

5 Effectiveness Analysis Strategy

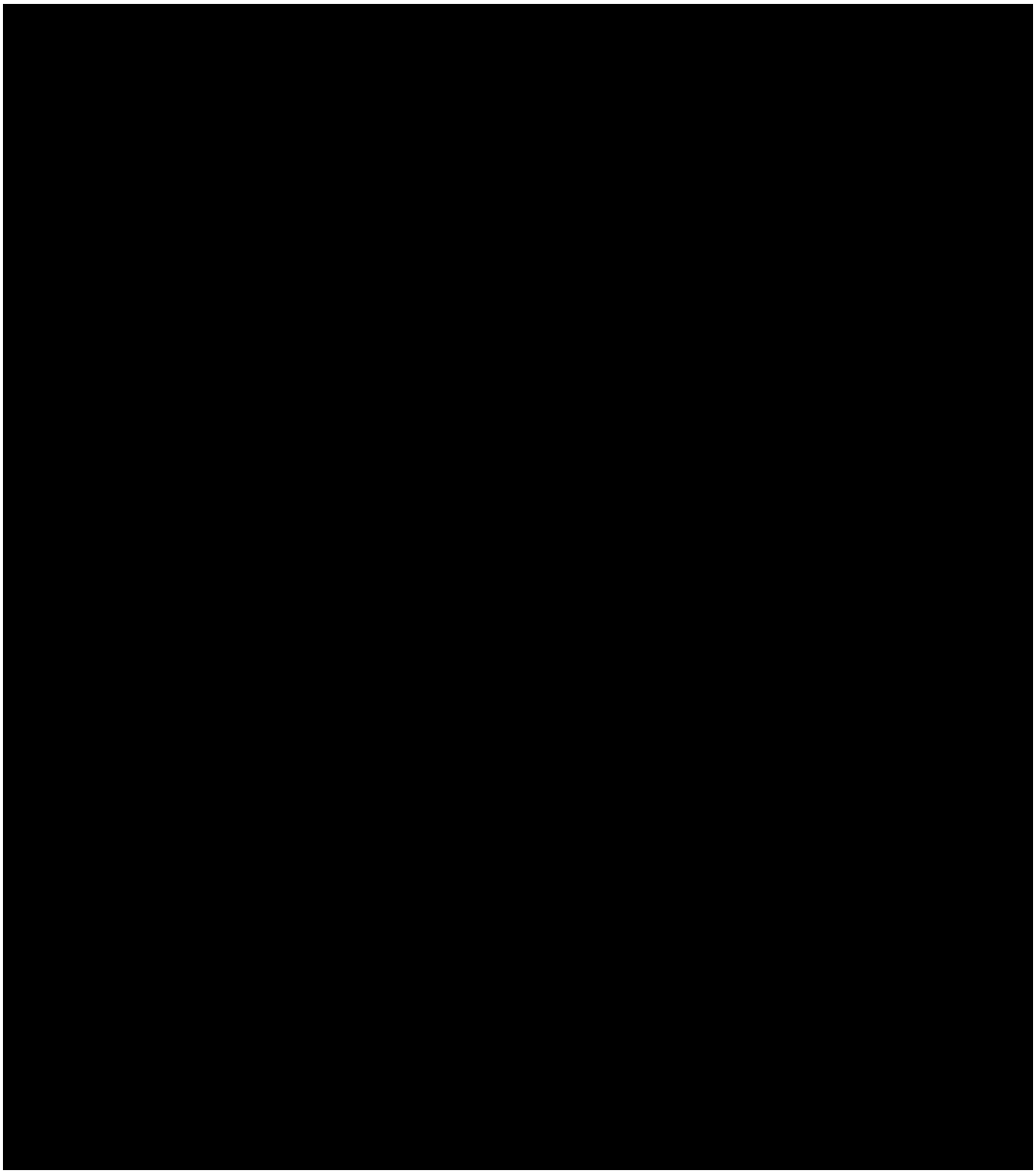
5.1 Effectiveness Endpoints

Primary Endpoint

- Percentage of eyes with manifest refraction cylinder ≤ 0.5 D at 3 months.

Secondary Endpoints

- Mean manifest refraction cylinder (D) at 3 months.
- Mean UCVA (logMAR) at 3 months.



5.2 Effectiveness Hypotheses

The primary effectiveness endpoint to be tested is that Topography Guided LASIK is superior to SMILE in the percentage of eyes with manifest refraction cylinder ≤ 0.5 D at 3 months (Month 3). The following null hypothesis will be tested at the two-sided 5% significance level (α=0.05):

H_0: $p_L = p_S$

H_1: $p_L \neq p_S$

where p_L and p_s refer to the percentage of eyes with manifest refraction cylinder within (≤) 0.5 D in the Topography Guided LASIK arm and SMILE arm, respectively.

The secondary effectiveness hypotheses to be tested are that:

- Topography Guided LASIK is superior to SMILE in mean manifest refraction cylinder at 3 months (Month 3).
    - The following null hypothesis will be tested (two-sided):

      H_0: $\mu_L = \mu_S$

      H_1: $\mu_L \neq \mu_S$

      where μ_L and μ_s denote the mean manifest refraction cylinder in the Topography Guided LASIK arm and SMILE arm, respectively.
- Topography Guided LASIK is superior to SMILE in mean UCVA at 3 months (Month 3).
    - The following null hypothesis will be tested (two-sided):

      H_0: $\mu_L = \mu_S$

      H_1: $\mu_L \neq \mu_S$

      where μ_L and μ_s denote the mean UCVA in the Topography Guided LASIK arm and SMILE arm, respectively.

5.3 Statistical Methods for Effectiveness Analyses

5.3.1 Primary Effectiveness Endpoint

The percentage of eyes with manifest refraction cylinder ≤ 0.5 D at 3 months (Month 3) will be analyzed for the ITT Analysis Set using the chi-square test quoted in Fleiss et al (Fleiss 2003) based on the two-sided 5% significance level (α=0.05). As the study surgery is bilateral, i.e. it is planned for both eyes for each subject to be treated on the day of surgery; the intracluster correlation/ agreement between eyes within subject will be taken into account.

Descriptive statistics at each visit will also be provided by surgery group for the percentage of eyes with manifest refraction cylinder ≤ 0.5 D for the ITT Analysis Set.

5.3.2 Secondary Effectiveness Endpoints

5.3.2.1 Manifest refraction

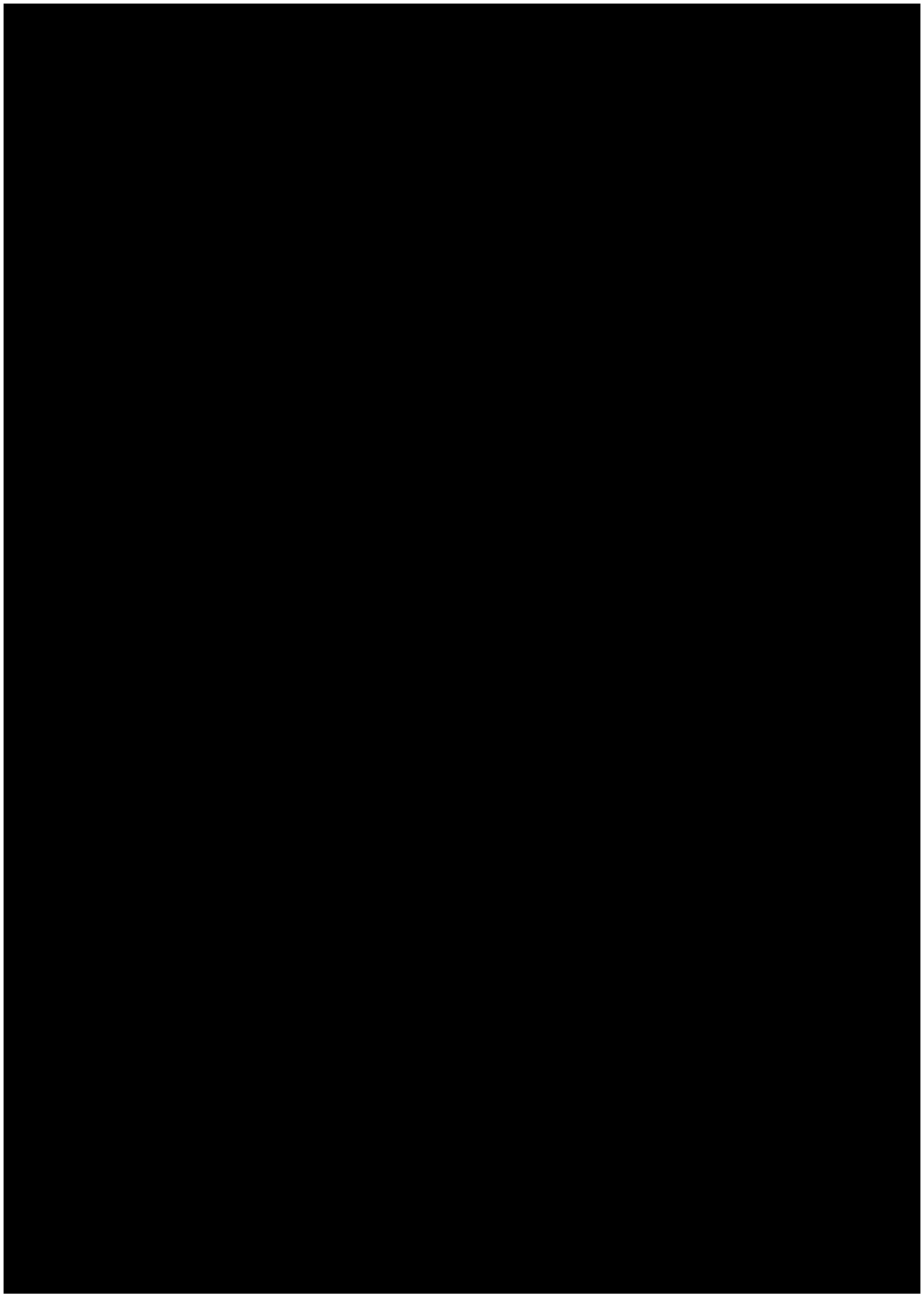
The mean manifest refraction cylinder at 3 months (Month 3) will be analyzed on eye level for the ITT Analysis Set using the statistic of Donner, et al (Donner 1981), which accounts for the intraclass correlation between eyes within subjects, based on the two-sided 5% significance level (α=0.05).

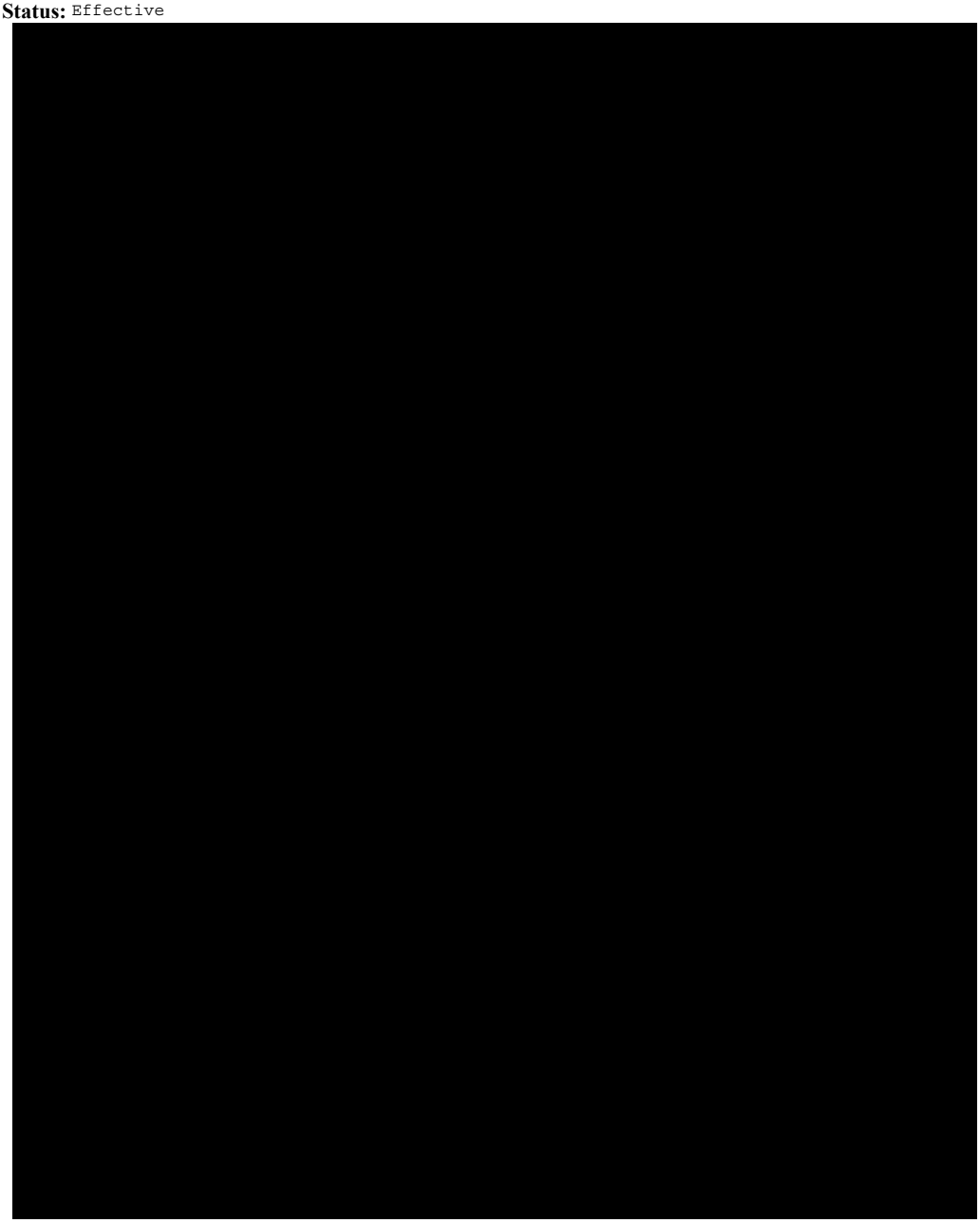
Descriptive statistics at each visit will also be provided by surgery group for the mean manifest refraction cylinder for the ITT Analysis Set.

5.3.2.2 UCVA

The mean UCVA at 3 months (Month 3) will be analyzed on eye level for the ITT Analysis Set using the statistic of Donner, et al (Donner 1981), which accounts for the intraclass correlation between eyes within subjects, based on the two-sided 5% significance level (α=0.05).

Descriptive statistics at each visit will also be provided by surgery group for the mean UCVA for the ITT Analysis Set.





5.4 Multiplicity Strategy

In order to control the type I error at the 5% significance level (α=0.05) over the family of primary and secondary hypotheses, the secondary effectiveness hypotheses will be relevant only if the primary effectiveness null hypothesis is rejected at the 5% significance level

(two-sided). The secondary hypotheses will then be tested using the Hochberg testing procedure.

For the secondary effectiveness endpoints, let:

- H_{0i} refers to the corresponding null hypotheses
- p_i refers to the p-values for H_{0i} , which will be calculated without any multiplicity adjustment where i = 1, 2 such that [1], [2] refer to the order from $p_{[1]} \leq p_{[2]}$.
- Hochberg's step-up method will proceed as follows:
    - Step 1: If $p_{[2]} < \alpha$ (where α is 0.05, two-sided), reject all H_{0i} (where i = 1, 2), and stop; otherwise go to Step 2.
    - Step 2: If $p_{[1]} < \alpha/2$ (where α is 0.05, two-sided), reject $H_{0[i]}$, i = 1, and stop.

The adjusted p-values in addition to the adjusted CIs for the secondary effectiveness endpoints will be presented.

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.

6 Safety Analysis Strategy

6.1 Safety Endpoints

The safety endpoints are:

- Mean intraocular pressure (IOP) (mmHg) at each study visit
- Mean mesopic uncorrected contrast sensitivity at each contrast level at each study visit
- Mean BCVA (logMAR) at each study visit
- Percentage of eyes with post-surgery BCVA that is $\geq$ 2 lines better, 1 to < 2 lines better, >0 to < 1 line better, no change, < 0 to < 1 line worse, 1 to < 2 lines worse, $\geq$ 2 lines worse than pre-surgery BCVA at each study visit
- Frequency of dry eye syndrome at each study visit
- Mean overall and subscale vision related quality of life score at each study visit
- Frequency of AEs

- Frequency of device deficiencies

6.2 Safety Hypotheses

There are no formal safety hypotheses in this study. The focus of the safety analysis will be a comprehensive descriptive assessment of safety endpoints listed in Section 6.1.

6.3 Statistical Methods for Safety Analyses

Except otherwise stated, the analysis set for all safety analyses is the Safety Analysis Set as defined in Section 3. It should be noted that the eye-level safety analyses will be performed using the Safety Analysis Set. For safety parameters collected on the subject-level (e.g. subject-reported outcome questionnaires, non-ocular AEs) the population of interest will be the set of subjects with at least one eye for which treatment has begun.

Baseline will be defined as the last measurement prior to surgery, except otherwise stated.

6.3.1 Adverse Events

The applicable definition of an AE is in the study protocol. All AEs occurring from when a subject signs the ICF to when a subject exits the study will be accounted for in the reporting. Analysis and presentation of AEs occurring during the 45 day pre-surgery period (the screening period) will be separated from those occurring during the post-surgery period where a comparative evaluation (descriptive only) of treatment-emergent AEs (TEAEs) is intended. A TEAE is an event not present prior to surgery (Topography Guided LASIK, SMILE) or any pre-existing event that worsens following surgery. The period for TEAE analysis starts from when study treatment has begun to 12 months post-surgery (Day 330 to Day 375). Study treatment will be considered to have begun once the flap creation is initiated for Topography Guided LASIK and once the laser touches the eye for SMILE.

Descriptive summaries (subject counts and percentages, event counts) by surgery group for specific AEs will be presented by primary SOC and PT of the Medical Dictionary for Regulatory Activities (MedDRA) dictionary (Version 19.0 or a more recent version). The SOCs will be presented in alphabetical order. PTs will be ordered for each surgery group in decreasing proportion in the Topography Guided LASIK surgery group of interest (study surgery group 1). The following summary tables will be provided:

- Ocular AEs for all eyes in the Safety Analysis Set (TEAE only)
- Ocular SAEs for all eyes in the Safety Analysis Set (TEAE only)
- Adverse device effects (ADEs) for all eyes in the Safety Analysis Set (TEAE only)

- Serious ADEs (SADEs) for all eyes in the Safety Analysis Set (TEAE only)

Both subject and event counts will be presented for AEs. Subject counts refer to the number of subjects with the respective AE of interest. Subjects who experience multiple AEs for a PT will be counted once, similarly for subjects with multiple AEs per SOC, for subject counts. Event counts refer to the number of occurrences of the respective AE of interest, regardless of whether a subject already had this event.

Individual subject's listings will also 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
- Listing of deaths for all enrolled subjects

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

Although the surgery is planned to be bilateral, the investigator may decide to not perform the surgery on the second eye on the same day as the first eye. In the following scenarios, if during the 12-month post-surgery study period:

- no surgery is performed on the second eye
- surgery is performed on the second eye using non-study surgery

only AEs will be collected for this eye. These AEs (including those which are collected pre-surgery as well as those after the planned surgery) will be listed separately.

6.3.2 Best Corrected Visual Acuity

Observed values and change from baseline values for each treated eye will be presented descriptively (N, mean, median, SD, standard error [SE], minimum, and maximum) at each study visit for each surgery group.

Counts and percentages of eyes that experience pre-specified category of change from baseline to each post-surgery assessment will be presented according to the following categories: $\geq$ 2 lines better ($\geq$0.2), 1 to < 2 lines better (0.1 to <0.2), >0 to < 1 line better (>0 to <0.1), no change (0), < 0 to < 1 line worse (>-0.1 to <0), 1 to < 2 lines worse (-0.1 to >-0.2), $\geq$ 2 lines worse ($\leq$-0.2).

A listing will be provided which presents all subjects with ≥ 2 lines decrease (i.e. ≥ 2 lines worse) in BCVA from baseline to any visit for all randomized subjects. The listing will include the following variables: surgery group, investigator, subject, age, sex, race, ethnicity, visit, eye, baseline value, value at the visit, and a change from baseline value.

6.3.3 Biomicroscopy Findings/Slit Lamp Examination

A listing will be provided which presents all eyes with an abnormality in any slit-lamp parameter at any post-surgery visit. The listing will include the following variables: surgery 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 (Version 19.0 or a more recent version) primary SOC and PT codes.

6.3.4 Intraocular Pressure

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

Descriptive statistics (N, mean, median, SD, SE, minimum, and maximum) of observed values and change from baseline values will be presented at each study visit by surgery group.

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: surgery group, investigator, subject, age, sex, race, ethnicity, visit, eye, baseline value, value at the visit, and change from baseline value.

6.3.5 Dilated Fundus Examination

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

6.3.6 Mesopic Uncorrected Contrast Sensitivity

Descriptive statistics (N, mean, median, SD, SE, minimum, and maximum) of observed values in logCS (with and without glare) and change from baseline values will be presented at each study visit and contrast level (spatial frequencies of 1.5, 3.0, 6.0, 12.0, and 18.0 cd/m^2) by surgery group.

6.3.7 Subject Reported Outcomes

For RSVP, the individual items for the overall RSVP questionnaire will categorized into 8 subscales (concern, expectations, physical/social functioning, driving, symptoms, optical problems, glare, and problems with corrective lenses), and the mean score for each subscale will be calculated. The subscale scores will then be re-scaled into a score of 0 to 100. Descriptive statistics (N, mean, median, SD, SE, minimum, and maximum) of observed values and change from baseline values for the overall score and the eight subscale scores will be presented at each study visit by surgery group.

For SQDES, a subject is defined as having dry eye syndrome if there was occurrence of both dryness and irritation of the eyes either constantly or often (that is, severe symptoms) or a report of a previous clinical diagnosis of dry eye syndrome. A shift table showing the status of dry eye syndrome at baseline relative to each study visit will be presented by surgery group. In addition, a frequency table of SQDES status at each study visit by surgery group will be provided.

6.3.8 Surgical Problems

Descriptive summaries (counts and percentages) for eyes with surgical problems will be presented. In addition, a listing of subjects with surgical problems will be provided. The listing will include the following variables: surgery group, investigator, subject, age, sex, race, ethnicity, eye, and description of surgical problem.

6.3.9 Nomogram

A listing of subjects where the nomogram was used will be provided. The listing will include the following variables: surgery group, investigator, subject, age, sex, race, ethnicity, eye, and the optical infinity nomogram adjusted manifest refraction parameters (sphere, cylinder, and axis).

6.3.10 Surgical report

The surgical report will contain the treatment plan for surgery.

Descriptive statistics (N, mean, median, SD, SE, minimum, and maximum) of observed values will be provided by surgery group for the following parameters:

- Topography Guided LASIK
    - flap thickness (µm)

- optical zone (mm)

- SMILE
  - cap thickness (µm)
  - lenticule diameter (mm)

6.3.11 Device Deficiencies

Descriptive summaries (counts and percentages) of all device deficiencies will be tabulated with a breakdown by surgery group. A listing of all device deficiencies, as recorded on the Device Deficiency Form, will also be provided.

7 Sample Size and Power Calculations

The sample size calculation is based on conservative estimates of the interim results from a pilot study comparing Topography Guided LASIK to SMILE (single center investigator initiated trial) (data not published).

Based on the assumed rates of 90% vs 80% of eyes with manifest refraction cylinder less than or equal to 0.5 D at 3 months for Topography Guided LASIK and SMILE, respectively, and an intracluster correlation coefficient (i.e. correlation between eyes within subject) of 0.39, a sample size of 185 subjects (185 groups contributing 2 eyes each) per treatment group will provide 90% power to reject the hypothesis for the primary effectiveness objective (based on the two sided 5% significance level). In total, 740 eyes (individual-level) from 370 subjects (group-level) are required for this study.

To ensure the required sample size is achieved, approximately 225 subjects (contributing 2 eyes each) will be enrolled per treatment arm. This will take into account drop-outs prior to surgery. It is expected that 200 subjects (contributing 2 eyes each) will receive bilateral surgery per treatment arm. Of these subjects, it is expected that a further 7% may drop out during the 3 months post-surgery.

8 References

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Eydelman MB, Drum B, Holladay J, Hilmantel G, Kezirian G, Durrie D et al. Standardized analyses of correction of astigmatism by laser systems that reshape the cornea. J Refract Surg 2006;22:81-95

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9 Revision History

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.

10 Appendix

10.1 Imputation rules

10.1.1 AE Date Imputation

10.1.1.1 AE End Date

For the purpose of date imputation, the study treatment follow-up period date is defined as the last available visit date, i.e. including unscheduled visits after the end of study visit.

8. If the AE end date month is missing, the imputed end date should be set to the earliest of the (study treatment follow-up period date, 31DECYYYY, date of death).
9. If the AE end date day is missing, the imputed end date should be set to the earliest of the (study treatment follow up-period date, last day of the month, date of death).
10. If AE year is missing or AE is ongoing, the end date will not be imputed.

If the imputed AE end date is less than the existing AE start date then use AE start date as AE end date.

10.1.1.2 AE Start Date

AEs with completely missing onset dates will be considered to be treatment emergent. AEs with partially missing onset dates will also be included as treatment emergent when the month (if it exists) and the year occur on or later than the month and year of first administration of study treatment.

Partial AE start dates are imputed with reference to the first administration of study treatment (TRTSTD) as outlined in the table below.

The date value is split into day, month, and year sections and referenced in the imputation table as outlined below:

	Day	Month	Year
Partial AE Start Date	Not used	MON	YYYY

	Day	Month	Year
Study Treatment Start Date (TRTSTD)	Not used	TRTM	TRTY

The following matrix explains the logic behind the imputation.

Comparison of month section	MON missing	MON<TRTM	MON=TRTM	MON>TRTM
YYYY missing	NC	NC	NC	NC
YYYY<TRTM	(D) = 01JULYYYY Before Study Treatment Start	(C) = 15MONYYYY Before Study Treatment Start	(C) = 15MONYYYY Before Study Treatment Start	(C) = 15MONYYYY Before Study Treatment Start
YYYY=TRTY	(B) = TRTSTD+1 Uncertain	(C) = 15MONYYYY Before Study Treatment Start	(A) = TRTSTD+1 Uncertain	(A) = 01MONYYYY After Study Treatment Start
YYYY>TRTY	(E) = 01JANYYYY After Study Treatment Start	(A) = 01MONYYYY After Study Treatment Start	(A) = 01MONYYYY After Study Treatment Start	(A) = 01MONYYYY After Study Treatment Start

The following table is the legend to the logic matrix.

Relationship	
Before Study Treatment start	Partial date indicates AE start date prior to Study Treatment Start Date
After Study Treatment start	Partial date indicates AE start date after Study Treatment Start Date
Uncertain	Partial date insufficient to determine relationship of AE start date to Study Treatment Start Date
Imputation calculation	
NC / Blank Uncertain	No convention
(A) After Treatment Start or Uncertain	MAX(01MONYYYY, TRTSTD+1)
(B) Uncertain	TRTSTD+1
(C) Before Study Treatment Start	15MONYYYY
(D) Before Study Treatment Start	01JULYYYY
(E) After Study Treatment Start	01JANYYYY

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

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

To 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 study treatment start date year value, the AE started before study treatment. 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 study treatment start date year value, the AE started after study treatment. 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 study treatment start date year value:
    a. And the AE month is missing, the imputed AE start date is set to the AE reference start date + 1 day.
    b. Else if the AE month is less than the study treatment 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 study treatment start date month or greater than the study treatment start date month, the imputed AE start date is set to the later of (month start point [01MONYYYY], AE 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.