Clinical Investigation of the WaveLight® EX500 Excimer Laser for Hyperopic LASIK

STUDY ID:

RFD530-P001

STATISTICAL ANALYSIS PLAN

NCT04805593

Title:

Statistical Analysis Plan for Protocol RFD530-P001

Protocol Title:	Clinical Investigation of the WaveLight® EX500 Excimer Laser for Hyperopic LASIK
[redacted]	[redacted]
[redacted]	[redacted]
	[redacted]
[redacted]	[redacted]
Approvals:	See last page for electronic approvals.

Job Notes:

This is the first revision (Version 3.0) of Statistical Analysis Plan for this study. This version of the Statistical Analysis Plan is based on Version 2.0 of the study protocol.

Executive Summary:

Key Objectives:

The objective of this study is to evaluate efficacy and safety data on WaveLight EX500 excimer laser system treatment for the correction of hyperopia with and without astigmatism by laser in situ keratomileusis (LASIK) treatment.

Decision Criteria for Study Success:

In order to evaluate efficacy of the WaveLight EX500 excimer laser system for the correction of hyperopia with and without astigmatism, the following primary effectiveness endpoints are defined:

- Percentage of eyes with MRSE within ±0.50 D at refractive stability[1] (Target: > 50%)
- Percentage of eyes with MRSE within ±1.00 D at refractive stability[1] (Target: > 75%)

For confirming the safety of the WaveLight EX500 excimer laser system, the following is defined as primary safety endpoint.

- Percentage of eyes experiencing ocular adverse events

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1 STUDY OBJECTIVES AND DESIGN

1.1 Study Objectives

The purpose of this study is to collect efficacy and safety data on the WaveLight EX500 excimer laser system for the correction of hyperopia up to +3.0 D of sphere with and without astigmatic refractive errors up to +3.0 D at the spectacle plane, with a maximum manifest refraction spherical equivalent (MRSE) of +3.0 D to apply for registration in Japan.

1.2 Study Description

This is a prospective, single-arm, multi-center, interventional study with planned bilateral treatment.

Qualified subjects will receive bilateral LASIK treatment and be followed for 1 year. Subjects will be asked to attend a total of 9 visits (screening, surgery, day 1, 1 week, 1 month, 3 month, 6 month, 9 month, and 1 year). Total expected duration of subject participation is approximately 1 year.

Refractive surgery will be bilaterally performed for all subjects. Both eyes from each subject will be used for analysis.

1.3 Randomization

This is a single-treatment study. Randomization will not be implemented.

1.4 Masking

This is a single-treatment study. Masking will not be necessary for this study.

1.5 Interim Analysis

No interim analyses are planned for this study.

2 ANALYSIS SETS

2.1 Efficacy Analysis Sets

2.1.1 Full Analysis Set

Full Analysis Set (FAS) will include all eyes with successful refractive surgery having at least 1 postoperative visit. The primary analysis set for effectiveness analysis will be the FAS.

[redacted]

2.1.2.1 Refractive Stability

Stability analyses will be performed on eyes that have every follow-up exam from 1 month up to the stability time point [redacted] as well as on the eyes that have 2 consecutive exams, but not necessarily every follow-up exam. The following stability analyses will be performed for the time intervals between all consecutive pairs of scheduled postoperative refractions:

- Percentage of eyes that achieve:
    - a change of ≤ 1.00 D of MRSE between two refractions performed at 1 month and 3 months, and between subsequent refractions performed at least 3 months apart;
    - a change of ≤0.50 D of MRSE between two refractions performed at 1 month and 3 months, and between subsequent refractions performed at least 3 months apart;
- Mean overall change and change per month in MRSE between consecutive scheduled visits as determined by a paired analysis;
- Mean ±SD MRSE for the preoperative and each postoperative visit;
- Assessment of cylinder stability for correction of spherocylindrical refractive errors

Refractive stability is achieved at the latter of two postoperative manifest refractions performed at least 3 months apart or at 3 months after surgery when compared with the 1-month interval, when all of the following recommended criteria are met:

- At least 95% of the treated eyes have a change ≤ 1.00 D of MRSE between the 2 refractions;
- The mean rate of change in MRSE, as determined by a paired analysis, is ≤ 0.5 D per year (0.04 D/month) over the same time period;
- The mean rate of change of MRSE decreases monotonically over time, with a projected asymptote of zero or a rate of change attributable to normal aging;

- The 95% confidence interval for the mean rate of change in MRSE includes zero or a rate of change attributable to normal aging; and
- Stability is confirmed at least 3 months after the stability time point by a statistically adequate subgroup [redacted]

The primary effectiveness endpoints for the study can only be evaluated once refractive stability has been established [redacted] as well as on the eyes that had 2 consecutive exams, but not necessarily every follow-up exam.

2.2 Safety Analysis Set

The safety analysis set (SAF) will include all eyes for which refractive surgery is attempted with test device (regardless of success or failure). SAF will be the primary analysis set for the safety analyses.

3 SUBJECT CHARACTERISTICS AND STUDY CONDUCT SUMMARIES

For all analysis datasets (SAF and FAS), demographics (age, race, ethnicity, sex) and baseline characteristics (manifest refraction [sphere, cylinder], manifest refraction spherical equivalent [MRSE], uncorrected distance visual acuity [UCDVA], best corrected distance visual acuity [BCDVA], mesopic pupil size, flap diameter, flap thickness, optical zone and residual stroma thickness) will be summarized. For age (18-40, 41-64, ≥ 65 years), race, ethnicity, sex and mesopic pupil size (≤ 6.5 mm, > 6.5 mm), the N and percentage will be summarized. Also, descriptive statistics (arithmetic mean, standard deviation, N, median, minimum and maximum) will be summarized for age, manifest refraction (sphere, cylinder), MRSE, logMAR UCDVA, logMAR BCDVA, mesopic pupil size, flap diameter, flap thickness, optical zone and residual stroma thickness. Study conduct summaries will be presented in a subject disposition table for all enrolled subjects.

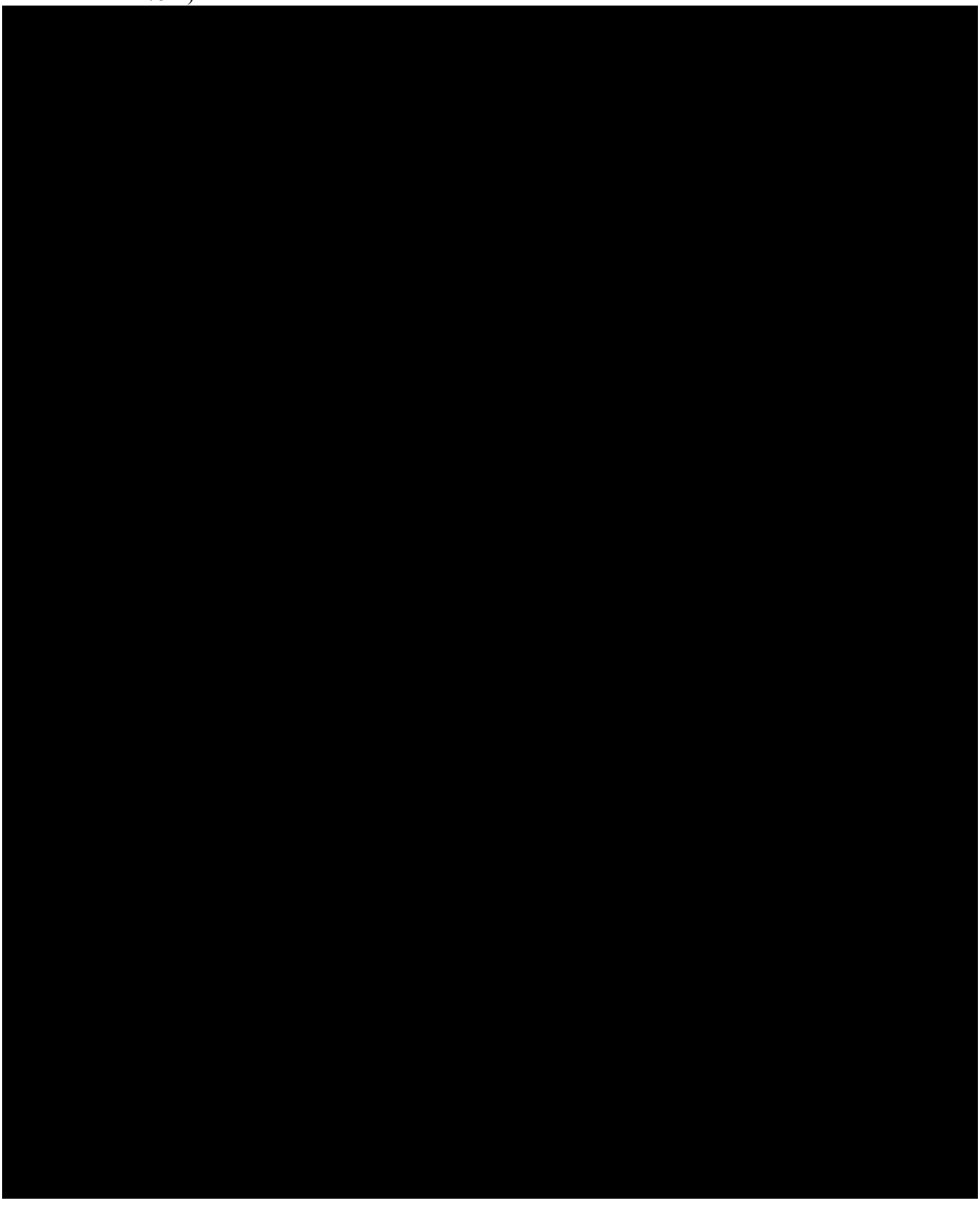
4 EFFICACY ANALYSIS STRATEGY

4.1 Efficacy Endpoints

In order to evaluate efficacy of the WaveLight EX500 excimer laser system for the correction of hyperopia with and without astigmatism, the following primary effectiveness endpoints are defined:

- Percentage of eyes with MRSE within ±0.50 D at refractive stability[1] (Target: > 50%)

- Percentage of eyes with MRSE within ±1.00 D at refractive stability[1] (Target: > 75%)



[redacted]

4.2 Efficacy Hypotheses

The statistical test for primary variables will be performed using the exact test of a binomial proportion. The null and alternative hypotheses are:

Test 1;

H_0: π_1 (EX500) = 50.0%

H_1: π_1 (EX500) > 50.0%

Test 2:

H_0: π_2 (EX500) = 75.0%

H_1: π_2 (EX500) > 75.0%

where π_1(EX500) is the population proportion of eyes in the EX500 group with MRSE within ±0.50 D at refractive stability, and π_2(EX500) is the population proportion of eyes in the EX500 group with MRSE within ± 1.00 D at refractive stability for EX500 group. The constants 50.0% in Test 1 and 75.0% in Test 2 are the target levels for these MRSE parameters referred to from the FDA Checklist of Information Usually Submitted in an IDE (1996).

The p-values will be provided for Test 1 and Test 2. [redacted]

4.3 Statistical Methods for Efficacy Analyses

The FAS will be used for this analysis. The number and percentage of eyes meeting each of the primary effectiveness endpoints will be calculated. The effectiveness criteria will be considered to have been met if the percentage meets or exceeds the target rate at the time of refractive stability for all primary effectiveness endpoints. [redacted]

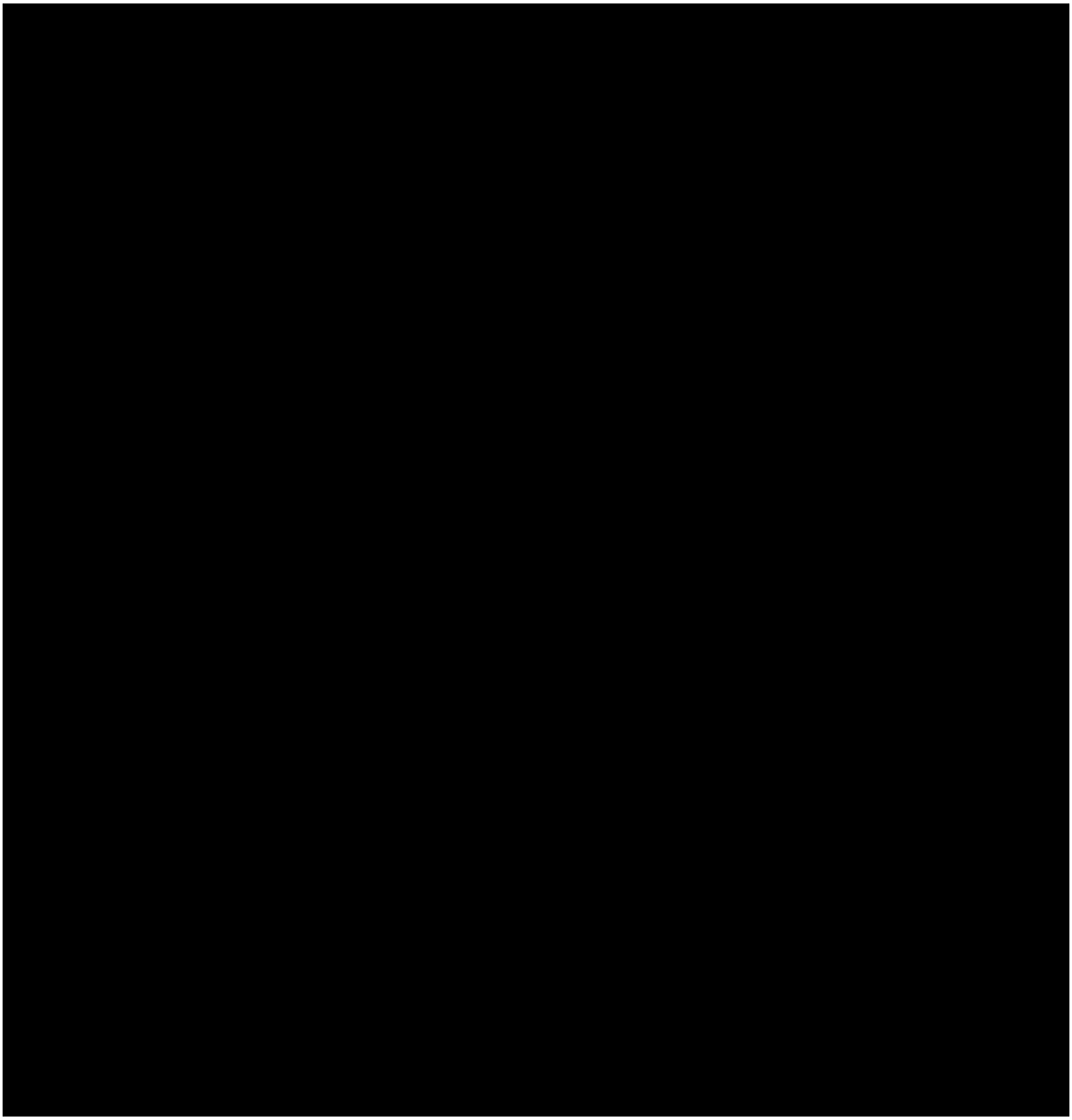


Table 4-1 summarizes the key efficacy analyses.

Table 4-1 Summary of Analysis Strategy for Key Efficacy Endpoints

Endpoint	Statistical Method	Analysis Set	Missing Data Approach
Primary			
Percentage of eyes with MRSE within ±0.50 D at refractive stability (Target: > 50%)	Exact test of a binomial proportion	FAS	Observed data only
Percentage of eyes with MRSE within ±1.00 D at refractive stability (Target: > 75%)	Exact test of a binomial proportion	FAS	Observed data only

[redacted]

The subject data listings of each effectiveness variable will be provided.

[redacted]

4.6 Interim Analysis for Efficacy

No interim analysis is planned.

5 SAFETY ANALYSIS STRATEGY

5.1 Safety Endpoints

In order to assess safety of the WaveLight EX500 excimer laser system for the correction of hyperopia with and without astigmatism, the following primary safety endpoint is defined:

- Percentage of eyes experiencing ocular adverse events

Also, Device Deficiencies, Intraocular Pressure, Slit Lamp Examination, Dilated Fundus Examination and Problems during Surgery will be summarized.

5.2 Safety Hypotheses

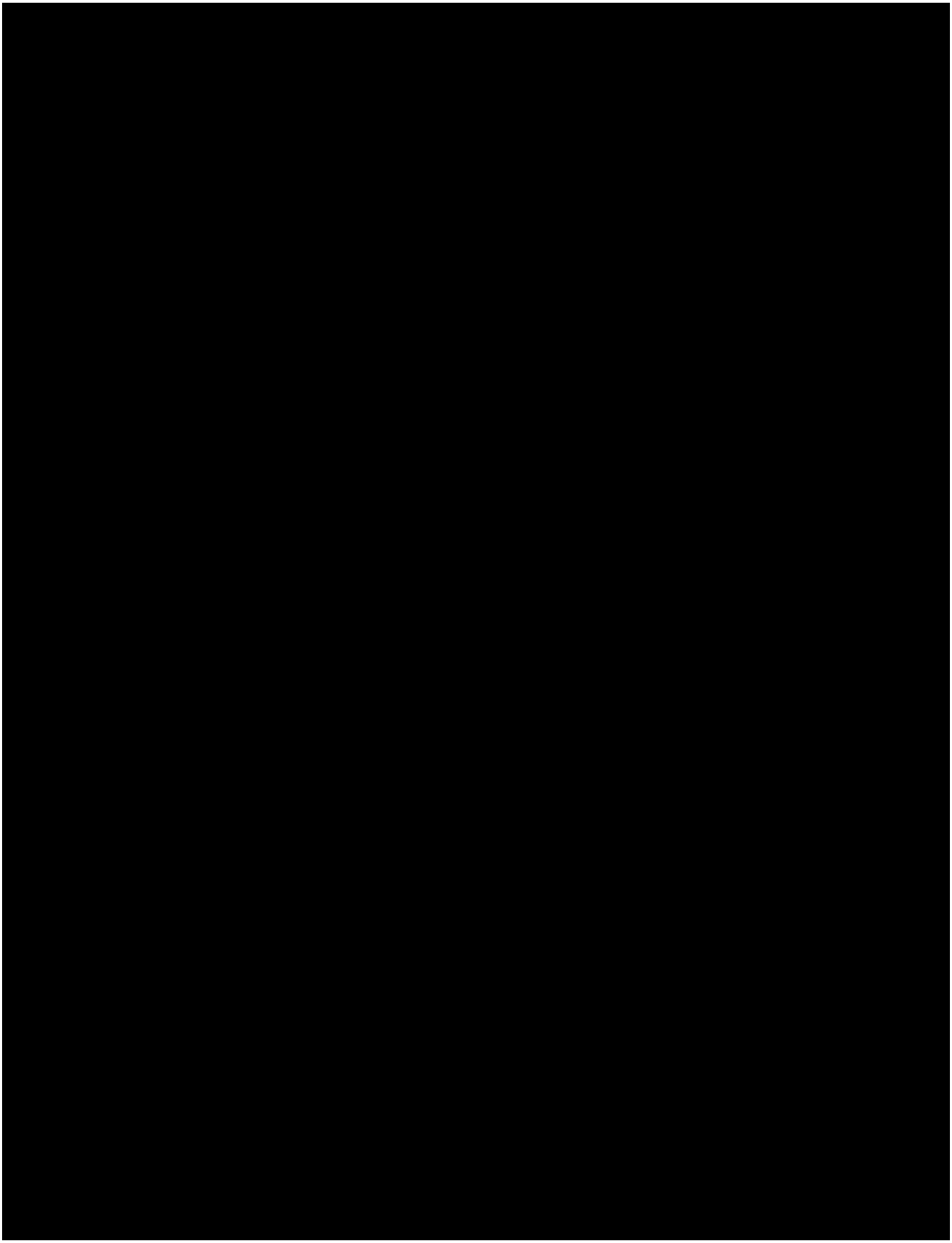
There are no formal safety hypotheses in this study. The focus of the safety analysis will be a comprehensive descriptive assessment of safety endpoints listed in Section 5.1.

5.3 Statistical Methods for Safety Analyses

Safety analyses will be conducted using the SAF through descriptive summaries (counts and percentages) and listings. In addition, separate subject listings will be provided for AEs that occur prior to refractive surgery using the test device (WaveLight® EX500 excimer laser).

5.3.1 Percentage of eyes experiencing ocular adverse events

Descriptive summaries (counts and percentages) for ocular AEs will be presented by System organ class. The listing of ocular AEs will be provided. In addition to an overall presentation of all ocular AEs, reports will be generated for special classes of AEs such as treatment-related AEs and serious AEs. If the nonocular AEs are reported, these AEs will be summarized by subject the same as the above.



5.3.10 Device Deficiencies

The applicable definition of a device deficiency is in the study protocol. A frequency table showing counts for each Device Deficiency category will be presented. In addition, a listing all device deficiencies, as recorded on the Device Deficiency Form will be provided.

5.3.11 Intraocular Pressure

Intraocular pressure (IOP) measurements will be recorded in mmHg. Descriptive summaries (arithmetic mean, standard deviation, N, median, minimum and maximum) of observed values and change from preoperative visit will be presented at each scheduled visit.

A listing will be provided which presents all observed data and all eyes with absolute change in IOP of greater than 10 mmHg at any visit compared to the same eye at preoperative visit.

5.3.12 Slit Lamp Examination

For each abnormal finding in case report form (CRF), counts and percentages of eyes will be presented by scheduled visit. A listing including all slit-lamp data at all visits will be provided.

For grading scales of Corneal Haze, Diffuse Lamellar Keratitis and Epithelium Ingrowth, counts and percentages of eyes in each category of grading scale by scheduled visits, counts and percentages of eyes with an increase ≥2 grades from preoperative visit (Visit 0) to any postoperative visit, and a shift table showing grading scales of each parameter at preoperative visit relative to the 6 month and 12 month visits will be presented. Also, a listing will be provided which presents all observed data and all eyes with an increase of ≥2 grades in any parameter at any visit compared to the grade of the same eye at preoperative visit.

5.3.13 Dilated Fundus Examination

For each abnormal finding in case report form (CRF), counts and percentages of eyes will be presented by scheduled visit. A listing including all dilated fundus examination data at all visits will be provided.

5.3.14 Problem during Surgery

Descriptive statistics (numbers and percentages) on eyes with problem with surgery will be presented. A listing of all eyes will be presented by subject, eye, with/without any problems during surgery and description of each problem.

5.4 Interim Analysis for Safety

No interim analyses are planned.

[redacted]

7 REFERENCES

1 ANSI Z80.11-2012 (R2017) American National Standard for Ophthalmics – Laser Systems for Corneal Reshaping

[redacted]

[redacted]

9 APPENDIX

9.1 Study Visits and Study Procedures and Assessments

Table 9-1 Schedule of Study Procedures and Assessments

	Screening[1]	Surgery	Postoperative							Other	
	Visit 0	Visit 00/ Visit 00A[2]	Visit 1/ Visit 1A	Visit 2/ Visit 2A	Visit 3/ Visit 3A	Visit 4/ Visit 4A	Visit 5/ Visit 5A	Visit 6/ Visit 6A	Visit 7 Visit 7A	Early Exit	USV[3]
Procedure/ Assessment	**Day -45 to -1**	**Day 0**	**Day 1**	**Day 5 to 9**	**Day 21 to 35**	**Day 70 to 98**	**Day 147 to 182**	**Day 245 to 301**	**Day 330 to 420**		
Informed Consent	X										
Inclusion/Exclusion	X	X[4]									
Demographics	X										
Medical History[5]	X										
Concomitant Medications[6]	X	X	X	X	X	X	X	X	X	X	X
Urine Pregnancy Test[7]	X										
Cycloplegic Refraction	X						X		X	X	
Mesopic Pupil Size	X										
Aberrometry	X										
Keratometry	X										
[redacted]											
Topography[8]	X										
UCDVA	X		X	X	X	X	X	X	X	X	X
Manifest/Subjective Refraction	X[9]			X	X	X	X	X	X	X	
BCDVA	X			X	X	X	X	X	X	X	
IOP	X				X	X	X	X	X	X	X
Slit Lamp Examination	X		X	X	X	X	X	X	X	X	X
Dilated Fundus Examination	X						X		X	X	X
LASIK surgery		X									
[redacted]											
Adverse Events[11]	X	X	X	X	X	X	X	X	X	X	X
Device Deficiencies	X	X	X	X	X	X	X	X	X	X	X

1. Screening should cover evaluation of both eyes with intent for bilateral treatment on the same surgery day.
2. 'A" denotes visit for 2nd eye treated. Although visits are listed for 1st and 2nd eye treatment, the expectation is to perform surgery and follow-up visits on the same day for both eyes.
3. Unscheduled visit – additional clinical assessments may be performed per the Investigator's discretion.
4. Confirm inclusion/exclusion criteria as needed.
5. Refer to Protocol Section 10.2.13, electronic case report form (eCRF) Guidelines, and Manual of Procedures (MOP) for collection and documentation requirements.
6. Refer to Protocol Sections 9.6 and 10.2.4, eCRF Guidelines, and MOP for collection and documentation requirements.
7. Required only for women of child-bearing age, not postmenopausal or surgically sterile women. Data is collected in source only.
8. Allow Investigator to use best judgement for post-op care.
9. Subjective Refraction to assess for inclusion stability at Screening (Visit 0) should be performed on the site's chart; subjective refraction for VA testing will be refraction on Sponsor provided electronic chart.

[redacted]

11. Refer to Protocol Sections 10.2.2 and 11, eCRF Guidelines, and MOP for collection and documentation requirements.

[redacted]

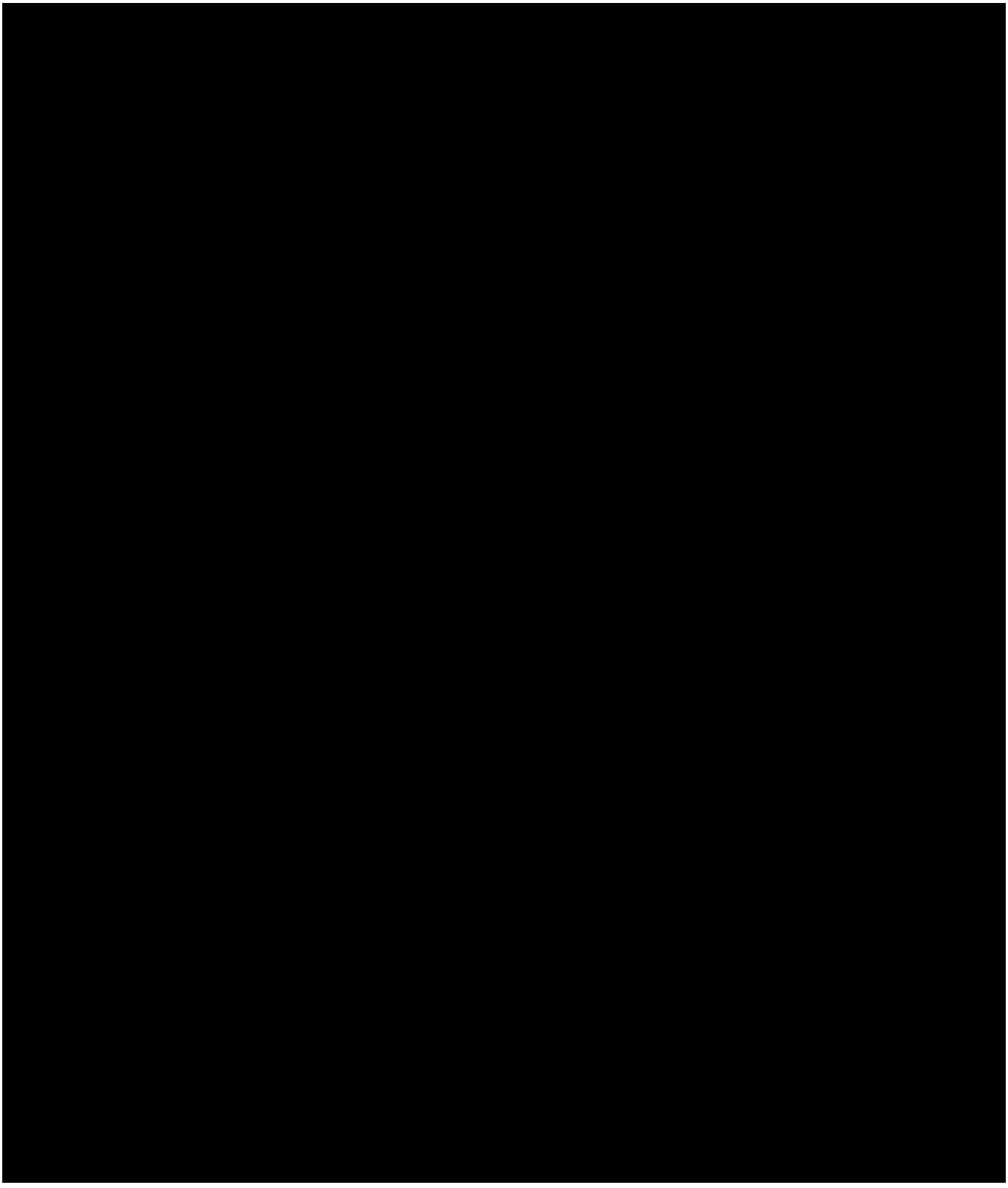
[redacted]

[redacted]

[redacted]

[redacted]

[redacted]



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