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

STUDY ID:

RFD530-P001

PROTOCOL

NCT04805593

Device Protocol for RFD530-P001
Title: Clinical Investigation of the WaveLight® EX500 Excimer Laser for Hyperopic LASIK

Protocol Number:	RFD530-P001
Development Stage of Project:	Product Support
Sponsor Name and Address:	Alcon Research, LLC and its affiliates ("Alcon") 6201 South Freeway Fort Worth, Texas 76134-2099
Test Product:	WaveLight® EX500 excimer laser system

Investigator Agreement:

- I have read the clinical study described herein, recognize its confidentiality, and agree to conduct the described trial in compliance with Good Clinical Practice (GCP), the ethical principles contained within the Declaration of Helsinki, this protocol, all applicable regulatory authority regulations, and conditions of approval imposed by the reviewing IRB or regulatory authority.
- I will supervise all testing of the device involving human subjects and ensure that the requirements relating to obtaining informed consent and IRB review and approval are met in accordance with applicable local and governmental regulations.
- I have read and understand the appropriate use of the investigational product(s) as described in the protocol, current Investigator's Brochure, product information, or other sources provided by the Sponsor.
- I understand the potential risks and side effects of the investigational product(s).
- I agree to maintain adequate and accurate records in accordance with government regulations and to make those records available for inspection.
- I agree to comply with all other requirements regarding the obligations of clinical Investigators and all other pertinent requirements of the Sponsor and government agencies.
- I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed of their obligations in meeting the above commitments.

Have you ever been disqualified as an Investigator by any Regulatory Authority? ☐ No ☐Yes
Have you ever been involved in a study or other research that was terminated? ☐ No ☐Yes If yes, please explain here:

Principal Investigator:

Signature Date

Name and professional position:

Address:

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1 GLOSSARY OF TERMS

Names of test product(s)	Throughout this document, test product(s) will be referred to as the WaveLight EX500 excimer laser system or EX500.
Name of Control Product(s)	N/A
Adverse Device Effect (ADE)	Adverse event related to the use of an investigational medical device (investigational product) or control product. *Note: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation; any malfunction; and use error or intentional misuse of the investigational medical device (investigational product) or control product.*
Adverse Event (AE)	Untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device (investigational product). *Note: This definition includes events related to the investigational medical device, comparator, or the procedures involved. For users or other persons, this definition is restricted to events related to the use of investigational medical devices (investigational product) or control product.* Requirements for reporting Adverse Events in the study can be found in Section 11.
Anticipated Serious Adverse Device Effect (ASADE)	An effect which by its nature, incidence, severity or outcome has been identified in the risk assessment.
Device Deficiency	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety, or performance. *Note: This definition includes malfunctions, use errors, and inadequacy in the*

	information supplied by the manufacturer including labelling. *This definition includes device deficiencies related to the investigational medical device or the comparator.* Requirements for reporting Device Deficiencies in the study can be found in Section 11.
Enrolled Subject	Any subject who signs an informed consent form for participation in the study.
Interventional Clinical Trial	A research trial that prospectively assigns, whether randomly or not, human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes, and/or a research trial in which diagnostic or monitoring procedures beyond standard of care are conducted and generate outcomes for use in analysis of data.
Investigational Product	Is defined as a preventative (vaccine), a therapeutic (drug or biologic), device, diagnostic, or palliative used as a test or control product in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form.
Malfunction	Failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or clinical investigation plan (CIP), or Investigator's brochure (IB).
Non-serious Adverse Event	Adverse event that does not meet the criteria for a serious adverse event.

Postmarketing/Postauthorization study	Any study conducted within the conditions laid down in product labelling and other conditions laid down for the marketing of the product or under normal conditions of use. A postmarketing study falls either within the definitions of an interventional or a non- interventional study and may also fall within the definition of a postapproval study.
Product Complaints	Any oral, electronic, or written communication that alleges deficiencies related to the identity (labeling), quality, durability, reliability, safety, effectiveness, or performance of a marketed product, including failure of the product, labeling or packaging to meet specifications, whether or not the product is related to or caused the alleged deficiency. A complaint may allege that an adverse event or medical device malfunction has occurred.
Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Serious Adverse Event (SAE)	Adverse event that led to any of the following: • Death. • A serious deterioration in the health of the subject, users or other persons as defined by one or more of the following: a. a life-threatening illness or injury. *Note: Life-threatening means that the individual was at immediate risk of death from the event as it occurred, ie, it does not include an event which hypothetically might have caused death had it occurred in a more severe form.*

	b. any potentially sight-threatening event or permanent impairment to a body structure or a body function including chronic diseases. c. in-patient hospitalization or prolonged hospitalization. *Note: Planned hospitalization for a pre-existing condition, without serious deterioration in health, is not considered a serious adverse event. In general, hospitalization signifies that the individual remained at the hospital or emergency ward for observation and/or treatment (usually involving an overnight stay) that would not have been appropriate in the physician's office or an out-patient setting. Complications that occur during hospitalization are adverse events. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred, the event should be considered serious.* *d.* a medical or surgical intervention to prevent a) or b). *e.* any indirect harm as a consequence of incorrect diagnostic test results when used within manufacturer's instructions for use. • Fetal distress, fetal death, congenital abnormality or birth defect including physical or mental impairment. *Note: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without*

	serious deterioration in health, is not considered a serious adverse event. Refer to Section 11 for additional SAEs.
Serious Health Threat	Signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons. *Note: This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.*
Unanticipated Serious Adverse Device Effect (USADE)	Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the risk assessment.
Use Error	Act or omission of an act that results in a different medical device response than intended by manufacturer or expected by user. *Note:* *a) Use error includes the inability of the user to complete a task.* *b) Use errors can result from a mismatch between the characteristics of the user, user interface, task or use environment.* *c) Users might be aware or unaware that a use error has occurred.* *d) An unexpected physiological response of the patient is not by itself considered a use error.* *e) A malfunction of a medical device that causes an unexpected result is not considered a use error."*

2 LIST OF ACRONYMS AND ABBREVIATIONS

Table 2–1 List of Acronyms and Abbreviations Used in This Protocol

Abbreviation	Definition
ADE	Adverse device effect
AE	Adverse event
ANSI	American National Standards Institute
ASADE	Anticipated serious adverse device effect
BCDVA	Best corrected distance visual acuity
°C	Degrees Celsius
[redacted]	[redacted]
[redacted]	[redacted]
CFR	Code of Federal Regulations
CIP	Clinical investigation plan
CRF	Case report form
[redacted]	
D	Diopter
eCRF	Electronic case report form
EDC	Electronic data capture
ETDRS	Early Treatment of Diabetic Retinopathy Study
EX500	WaveLight EX500 excimer laser system
°F	Degrees Fahrenheit
FAS	Full analysis set
FDA	US Food and Drug Administration
FS200	WaveLight FS200 femtosecond laser unit
GCP	Good Clinical Practice
GmbH	Gesellschaft mit beschränkter Haftung - company with limited liability
hPa	hectopascal
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Conference for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent ethics committee
IDE	Investigational Device Exemptions
IOP	Intraocular pressure
IP	Investigational product
IRB	Institutional review board
ISO	International Organization for Standardization
LASIK	Laser-assisted in situ keratomileusis
LED	Light emitting diode
[redacted]	
m	Meter
max	Maximum
min	Minimum

Abbreviation	Definition
mmHg	Millimeter of mercury
MOP	Manual of procedures
MRSE	Manifest refraction spherical equivalent
N	Number
N/A	Not applicable
PMDA	Pharmaceuticals and Medical Devices Agency
[redacted]	[redacted]
RMSh	Root mean square height
SADE	Serious adverse device effect
SAE	Serious adverse event
SAF	Safety analysis set
SD	Standard deviation
SOP	Standard operating procedure
UCDVA	Uncorrected distance visual acuity
US	United States
USADE	Unanticipated serious adverse device effect
USV	Unscheduled visit
VA	Visual acuity
WFO	Wavefront Optimized

3 PROTOCOL SUMMARY

Investigational product type	Device
Study type	Interventional
Investigational products	Test Product: WaveLight EX500 excimer laser system
Purpose and rationale	Refractive surgery by excimer laser system is recognized as an effective treatment for myopia and hyperopia with or without astigmatism. Japan's guideline for refractive surgery allows correction for hyperopia with and without astigmatism. However, the WaveLight EX500 excimer laser system has not been approved for hyperopic treatment in Japan. 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.
Objective(s)	To collect efficacy and safety data on the WaveLight EX500 excimer laser system for the correction of hyperopia with and without astigmatism by laser in situ keratomileusis (LASIK) treatment.
Endpoint(s)	Primary Effectiveness Endpoint — Target Percentage of eyes with MRSE within ±0.50 D at refractive stability* — >50% Percentage of eyes with MRSE within ±1.00 D at refractive stability* — >75% *The definition of refractive stability refers to ANSI Z80.11-2012 (R2017) F.3.

	Primary Safety • Percentage of eyes experiencing ocular adverse events
Assessment(s)	Effectiveness [redacted] • Manifest refraction Safety • Patient reported outcome • Best corrected photopic distance visual acuity (BCDVA) • Manifest refraction • Intraocular pressure (IOP) • Slit lamp examination • Dilated fundus examination [redacted]
Study Design	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.
Subject population	Subjects 18 years of age or older who desire to have LASIK will be consented and screened for meeting the inclusion and exclusion criteria. Planned number of subjects enrolled/consented: approximately 70 eyes (35 subjects) Planned number of treated/randomized subjects: approximately 60 eyes (30 subjects)

	Planned number of completed subjects: approximately 50 eyes (25 subjects)
Key inclusion criteria (See Section 8.1 for a complete list of inclusion criteria)	Subjects must meet all inclusion criteria as listed in Section 8.1. Key Inclusion Criteria include: • Hyperopia up to +3.0 D of sphere with and without astigmatic refractive error up to +3.0 D at the spectacle plane, with a maximum MRSE of +3.0 D • Intended to treat bilaterally • Best corrected photopic distance visual acuity of 20/20 or better • Uncorrected photopic distance visual acuity of 20/40 or worse • Stable refraction (within ±0.50 D), as determined by MRSE for a minimum of 12 months prior to surgery
Key exclusion criteria (See Section 8.2 for a complete list of exclusion criteria)	Subjects must not meet exclusion criteria as listed in Section 8.2. Key Exclusion Criteria include: • History or evidence of active or inactive corneal disease or retinal vascular disease, keratoconus, glaucoma (or suspect), or cataract • Previous intraocular or corneal surgery • Intent to have monovision treatment • Increased risk for developing strabismus post-treatment
Data analysis and sample size justification	The safety analysis set (SAF) will include all eyes for which refractive surgery is attempted with test device (regardless of success or failure). Full Analysis Set (FAS) will include all eyes with successful refractive surgery having at least 1 postoperative visits. The primary analysis set for effectiveness analysis will be the FAS. [redacted]

	[redacted] Subject evaluability will be determined prior to locking database. No interim analysis is planned. 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 analyses will be conducted. Test 1: Percentage of eyes with MRSE within ±0.50 D at refractive stability is greater than the target level of 50% Test 2: Percentage of eyes with MRSE within ±1.00 D at refractive stability is greater than the target level of 75%. For the statistical test of primary effectiveness variables, the exact test of a binomial proportion will be used, and the p-values will be provided for Test 1 and Test 2. [redacted] Type 1 error at each test is set as one-sided 2.5%. Refractive surgery will be bilaterally performed for all subjects. Both eyes from each subject will be used for analysis.

	[redacted] Each safety variable will be summarized descriptively. Incidence of adverse events will be calculated. [redacted]
Key words	• LASIK • Hyperopia • Astigmatism
Associated materials	• WaveLight EX500 Laser System • WaveCard

Table 3–1 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.

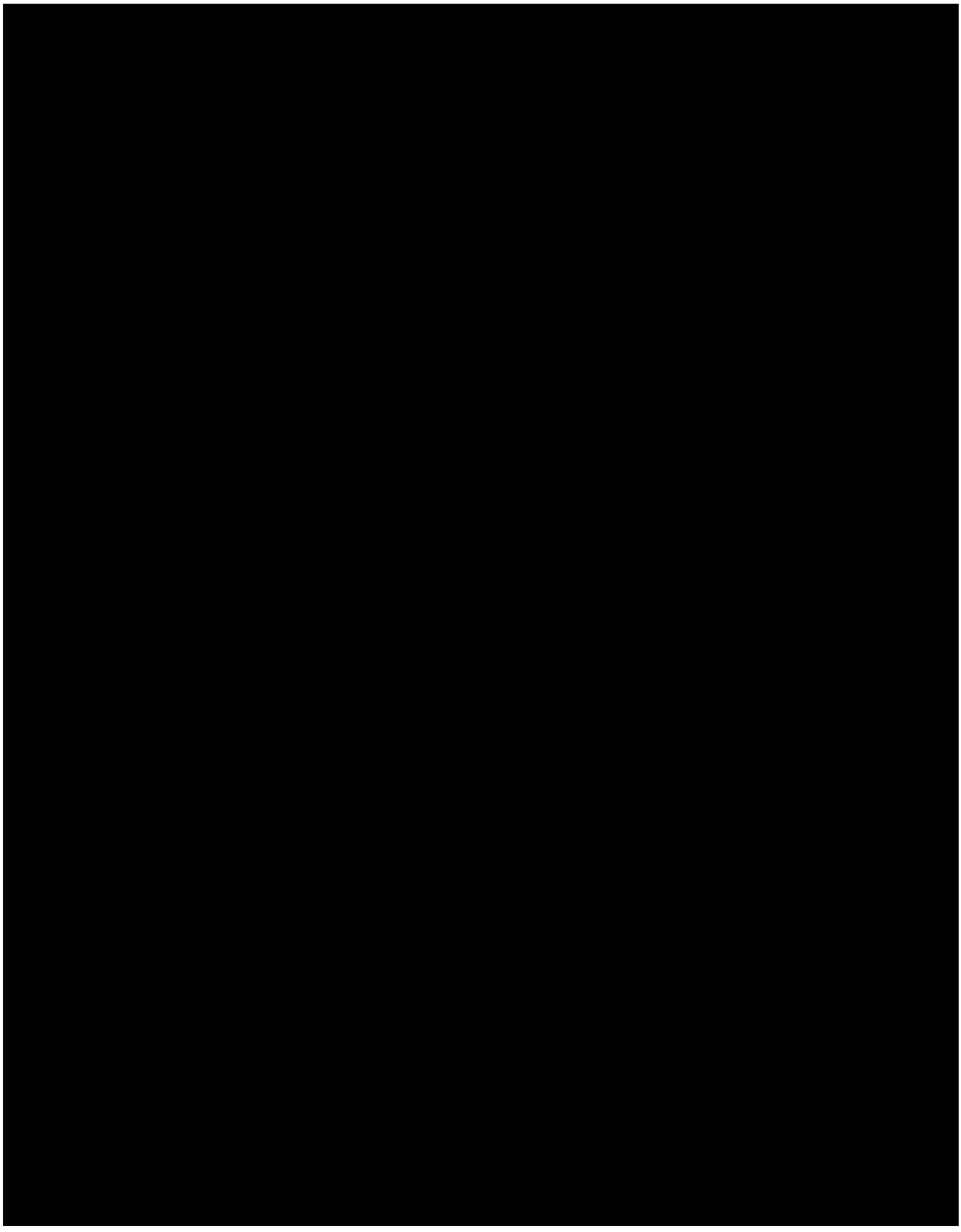
[redacted]

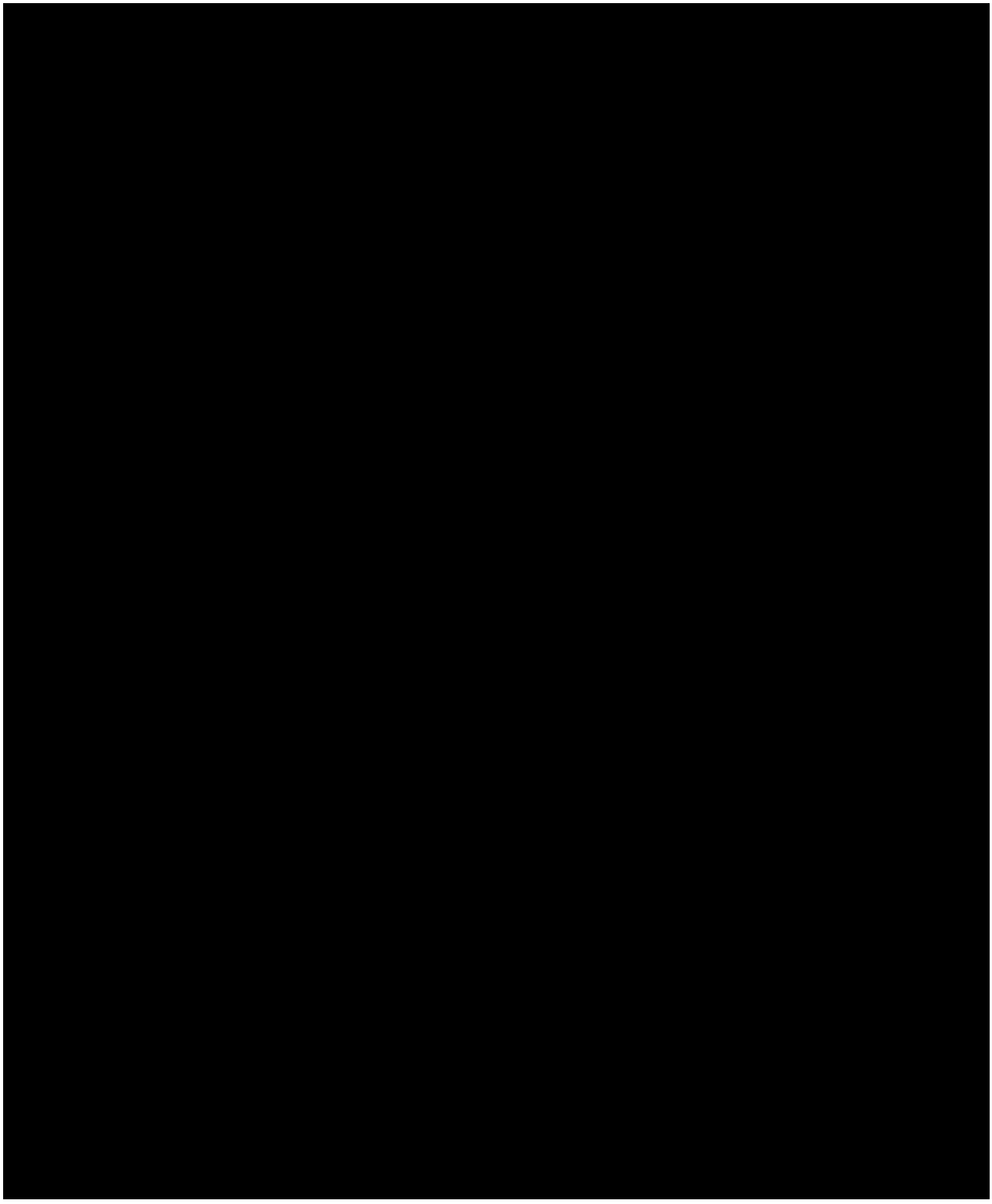
11. Refer to Protocol Sections 10.2.2 and 11, eCRF Guidelines, and MOP for collection and documentation requirements.

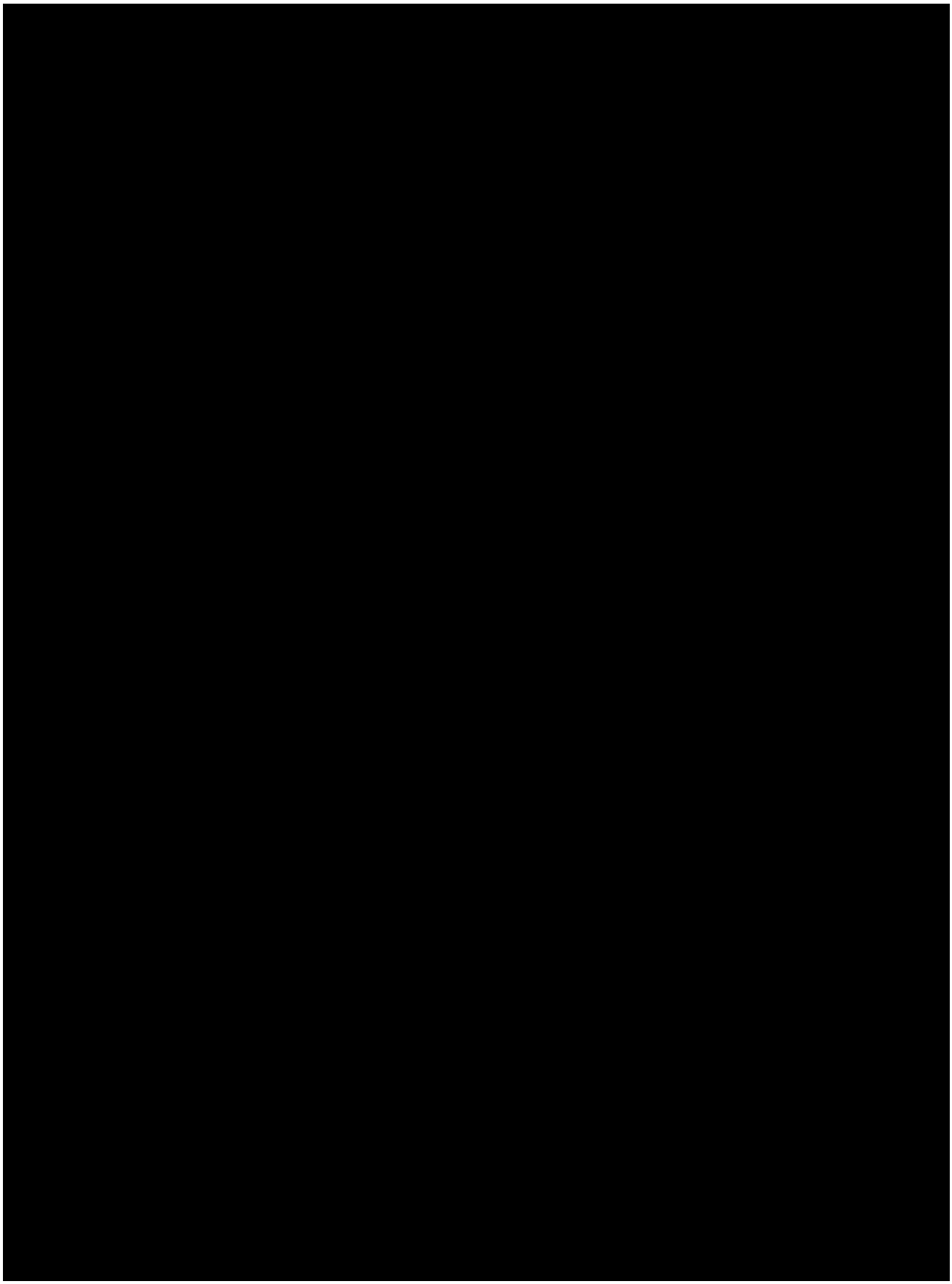
4 PROTOCOL AMENDMENTS

Modification of the protocol is prohibited without prior written agreement in the form of a protocol amendment. All amendments must be created by the Study Sponsor and must be approved by the IRB/IEC and global and regional Health Authorities, as applicable, prior to implementation except when required to mitigate immediate safety risks or when the changes involve only logistical or administrative revisions.

Amendments may necessitate that the informed consent and other study-related material be revised. If the consent form is revised, all subjects currently enrolled in the study must sign the approved, revised informed consent (re-consent), as required by the IRB/IEC.







5 INTRODUCTION

5.1 Rationale and Background

Refractive surgery using the Wavelight EX500 excimer laser system is recognized as a safe and effective treatment for hyperopia with or without astigmatism (El-Naggar 2017, Motwani 2017, Durrie 2010). The Wavelight EX500 excimer laser is approved by the FDA for treatment of hyperopic subjects. Although, Japan's guideline for refractive surgery allows correction for hyperopia with and without astigmatism. The WaveLight EX500 excimer laser system has not been approved for hyperopic treatment in Japan. The purpose of this study is to collect safety and efficacy data to apply for registration in Japan.

5.2 Purpose of the Study

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 MRSE of +3.0 D, to apply for registration in Japan.

At the end of the study, a clinical study report will be prepared in accordance with applicable regulatory requirements and standards.

There are no immediate plans to submit the results of this postmarket study for publication; however, the results may be offered for publication if they are of scientific interest, or if the results relate to a product that is subsequently approved or cleared for marketing.

5.3 Risks and Benefits

As with any refractive surgical procedure, there are potentials risks with the use of the WaveLight EX500 excimer laser system. However, there are no additional warnings or precautions associated with these outside of the risks identified for other LASIK procedures.

There may also be unknown risks to the use of WaveLight EX500 excimer laser system. Any risk to subjects in this clinical study will be minimized by compliance with the eligibility criteria and study procedures, clinical oversight and monitoring.

More information on summary of the literature, description of the investigational device, guidance for the Investigator, as well as known and potential risks and benefits can be found in the Procedure Manual and User Manual for WaveLight EX500 excimer laser system and the user manual.

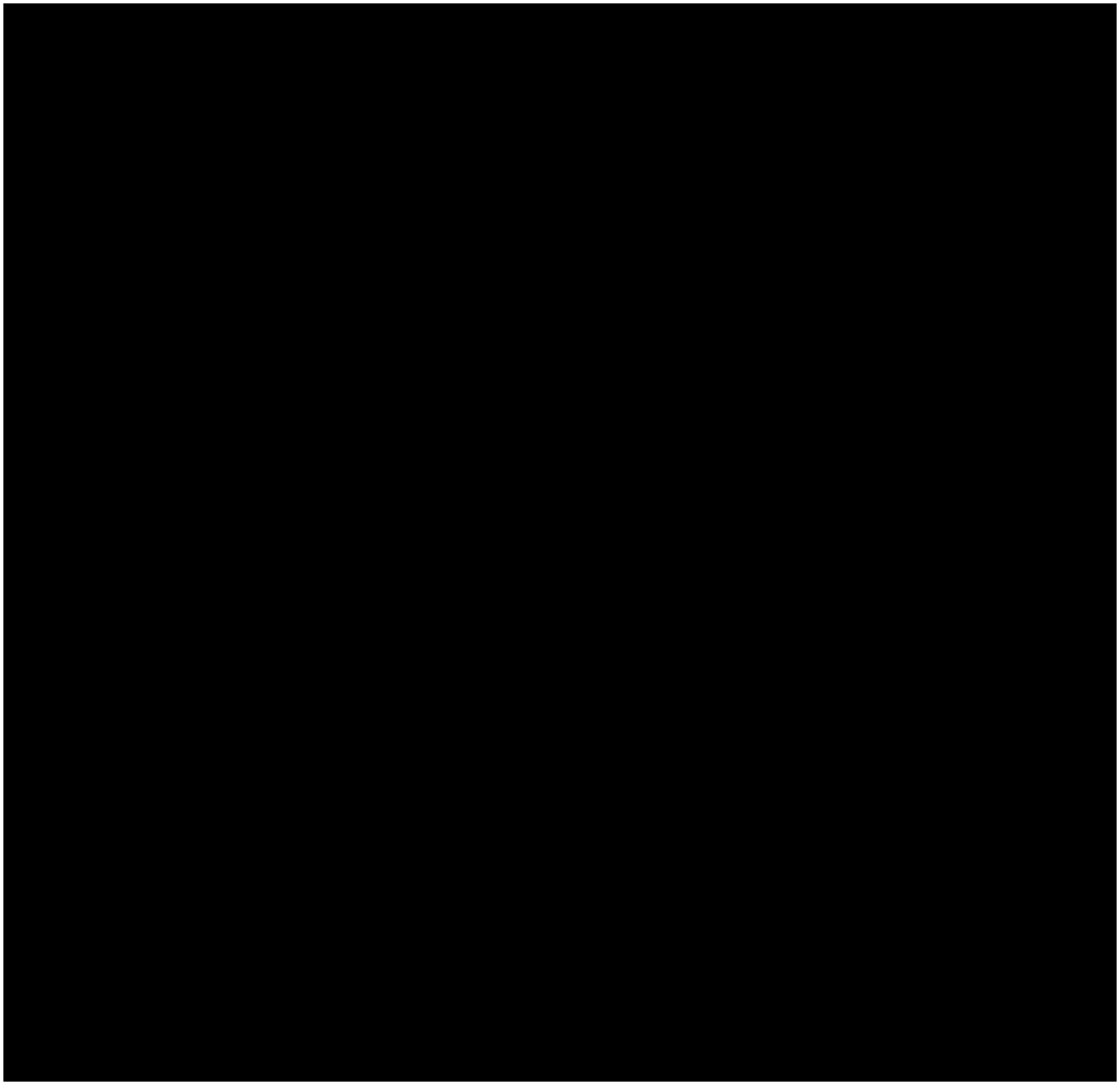
6 STUDY OBJECTIVES

6.1 Primary Objective(s)

Table 6–1 Primary Objective(s)

Objective(s)	Endpoint(s)
To evaluate the correction accuracy of WaveLight EX500 excimer laser system treatment	• Percentage of eyes with MRSE within ±0.50 D at refractive stability (Target > 50%) • Percentage of eyes with MRSE within ±1.00 D at refractive stability (Target > 75%)

[redacted]



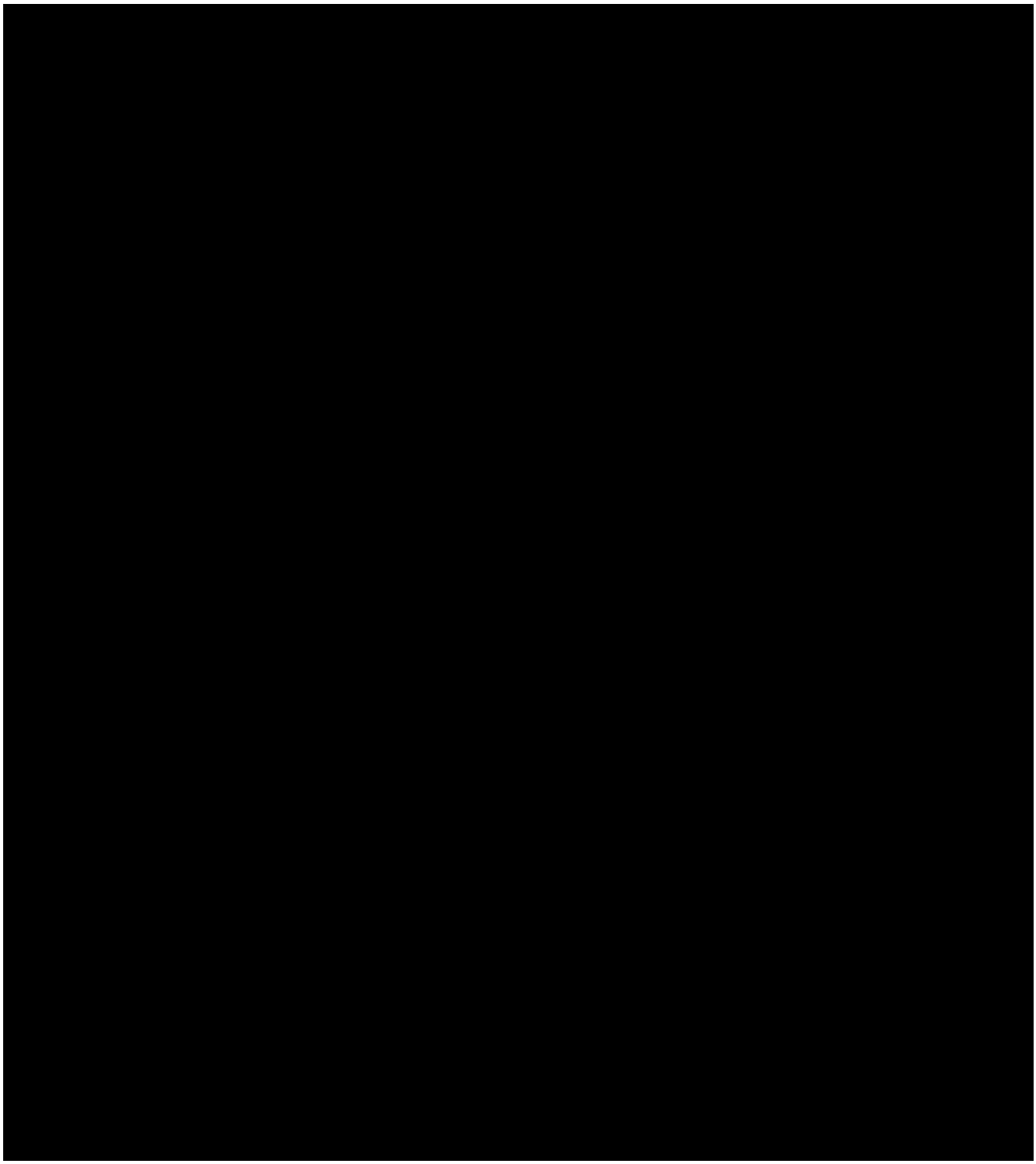
6.2 Secondary Objective(s)

Not Applicable.

6.4 Primary Safety Objective(s)

Table 6–4 Primary Safety Objective(s)

Objective(s)	Endpoint(s)
To confirm the safety of the WaveLight EX500 excimer laser system	Percentage of eyes experiencing ocular adverse events



6.5 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 definitions of refractive stability are described in Section 12.4.

7 INVESTIGATIONAL PLAN

7.1 Study Design

This is a prospective, single-arm, multi-center, interventional study with planned bilateral LASIK treatment with the WaveLight EX500 excimer laser system for subjects requiring refractive correction of hyperopia with or without astigmatism. All treated eyes will be targeted for emmetropia. The postoperative state of each treated eye will be compared to the preoperative state of the same eye.

Subjects will be evaluated initially for suitability as candidates for bilateral LASIK. Potential subjects willing to participate will be consented and screened. Approximately 30 qualified subjects (up to 60 eyes) will receive bilateral LASIK and be followed for 1 year. Total duration of subject participation is approximately 1 year and includes 9 study visits consisting of Screening, Surgery, 1 day, 1 week, 1 month, 3 month, 6 months, 9 months, and 12 months. Approximately 4 US study sites will participate in this clinical study. It is estimated that enrollment and follow-up of all subjects will take approximately 17 months. Additional information on the study population can be found in Section 8.

Assessments will be obtained at baseline and at appropriate times after LASIK to evaluate the safety and effectiveness of the treatment. [redacted] Clinical assessments to be obtained at study visits are outlined in Table 3–1 and defined in Section 10.

The main analyses for effectiveness will be conducted at refractive stability for the FAS (Refractive Stability is defined in Section 12.4). Subjects are followed for at least 12 months (Day 330 to Day 420) for safety and supportive effectiveness assessments. All data analyses will be conducted at study completion.

7.2 Rationale for Study Design

The prospective, single-group study design, objectives, planned visits and assessments, and planned analysis at refractive stability are based on recommendations by ANSI Z80.11-2012 (R2017), the FDA Checklist of Information Usually Submitted in an IDE (1996), and ISO 14155:2011.

The study population includes subjects with hyperopia, with or without astigmatism, based on this being a prevalent refractive error for LASIK treatments today and the intended population for hyperopic LASIK.

Bilateral treatments of subjects will be implemented in this study based on past clinical study results that provide safety, effectiveness, and stability data (El-Naggar 2017, Motwani 2017, Durrie 2010).

7.2.1 Purpose and Timing of Interim Analyses and Resulting Design Adaptations

No interim analysis is planned. No changes to study design, after the initiation of the study, are planned.

7.3 Rationale for Duration of Treatment/Follow-Up

One year follow-up (Day 330 to 420) of subjects will be implemented in this study based on past clinical study results using EX500 for hyperopic LASIK (El-Naggar 2017) and follow-up recommended by ANSI Z80.11-2012 (R2017).

7.4 Data Monitoring Committee

Not applicable.

8 STUDY POPULATION

The study population consists of male and female subjects (18 years of age or older) who have hyperopia up to +3.0 D of sphere with or without astigmatic refractive errors up to +3.0 D at the spectacle plane, with a maximum MRSE of +3.0 D and desire to have LASIK. It is aimed to enroll (consent) approximately 35 subjects in approximately 4 sites in the United States, with a target of up to 30 subjects treated. Site-specific targets may vary based upon individual site capabilities. Estimated time needed to recruit subjects for the study is approximately 5 months. Because a 10% screening failure rate and up to 10% lost to follow-up rate is expected, approximately 30 subjects are expected to be treated in order to allow for treatment and follow-up of at least 25 subjects.

8.1 Inclusion Criteria

Written informed consent must be obtained before any study specific assessment is performed. Upon signing informed consent, the subject is considered enrolled in the study.

Subjects eligible for inclusion in this study must fulfill **all** of the following criteria:

1. Subject must be able to understand and sign an IRB/IEC approved Informed Consent form.
2. Willing and able to attend all scheduled study visits as required per protocol.
3. Minimum 18 years of age.
4. Hyperopia up to +3.0 D of sphere with and without astigmatic refractive error up to +3.0 D at the spectacle plane, with a maximum MRSE of +3.0 D.
5. Intended to treat bilaterally.
6. Intended to target emmetropia.
7. Best corrected photopic distance visual acuity of 20/20 or better.
8. Uncorrected photopic distance visual acuity of 20/40 or worse.
9. Less than 0.75 D spherical equivalent difference between cycloplegic and manifest refraction.
10. Stable refraction (within ±0.50 D), as determined by MRSE for a minimum of 12 months prior to surgery, verified by consecutive refractions and/or medical records or prescription history.
11. Demonstrate a stable refraction (within ±0.50 D) for contact lens wearers: within ±0.50 D MRSE on two consecutive exam dates under the following conditions:
    a. Lenses are not worn for at least 2 weeks (rigid or toric contact lenses) or 3 days (soft contact lenses) prior to the first refraction used to establish stability and through the day of surgery.
    b. The two subjective refractions are performed at least 7 days apart.

8.2 Exclusion Criteria

Subjects fulfilling **any** of the following criteria are not eligible for participation in this study.

1. Women of childbearing potential, defined as all women who are physiologically capable of becoming pregnant and who are not postmenopausal for at least 1 year or are less than 6 weeks since sterilization, are excluded from participation if any of the following apply:

    a. they are currently pregnant,

    b. have a positive urine pregnancy test result at Screening,

    c. intend to become pregnant during the study period,

    d. are breast-feeding.

    Note: Subjects who become pregnant during the study will not be discontinued; however, data will be excluded from the effectiveness analyses because pregnancy can alter refraction and visual acuity results.

2. Acute or chronic disease or illness that would increase the operative risk or confound the outcomes of the study (eg, dry eyes, immuno-compromised, connective tissue disease, clinically significant atopic disease, diabetes).

3. Current use of systemic medications that may confound the outcome of the study or increase the risk to the subject, including, but not limited to steroids, antimetabolites, isotretinoin, amiodarone hydrochloride.

4. Ocular condition that may predispose the subject to future complications, for example:

    - history or evidence of active or inactive of corneal disease (eg, herpes simplex keratitis, herpes zoster keratitis, recurrent erosion syndrome, corneal dystrophy)
    - evidence of retinal vascular disease
    - glaucoma or glaucoma suspect by exam findings and/or family history
    - keratoconus or keratoconus suspect

- cataract (including, but not limited to nuclear cataract, lens opacity or lens abnormalities such as lens subluxation)

5. Previous intraocular or corneal surgery that might confound the outcome of the study or increase the risk to the subject.

6. Intended to have monovision treatment.

7. An increased risk for developing strabismus post-treatment.

8. A known sensitivity to medications used in the study.

9. Other condition or assessment that causes subject to not be an acceptable candidate for treatment or study participation as clinically assessed and documented by the investigator.

10. Participation in other ocular clinical trials during the course of the study.

8.3 Rescreening of Subjects

Rescreening of subjects is allowed for the conditions listed below:

Rescheduling of surgery: If a subject reschedules surgery or surgery is rescheduled due to other reasons, and this rescheduling results in preoperative/screening assessments (Visit 0) falling outside of the -45 to -1 day window, assessments should be repeated and inclusion/exclusion criteria re-verified to ensure the subject still qualifies to proceed with study surgery.

Criteria not met: Rescreening of subjects who did not meet inclusion/exclusion criteria is allowed one time per subject. Rescreening is allowed only if criteria previously not met could reasonably have changed since the prior screening. Criteria that could change and rescreening would be allowed include: Inclusion 3, 8, or if changes in refractive stability or receipt of additional past records can show stability for criteria 9-11, and Exclusion Criteria 1, 3, or 6. Repeat assessments only for criteria not met as long as the assessments are within the 45-day screening window. If the repeat assessments fall outside the 45-day screening window, all screening procedures must be repeated and inclusion/exclusion criteria re-verified.

[redacted]

9 TREATMENTS ADMINISTERED

9.1 Investigational Product(s)

Test Product(s): WaveLight EX500 excimer laser system

Control Product(s) (If applicable): Not applicable

Table 9–1 Test Product – WaveLight EX500 Excimer Laser System

Test Product	WaveLight EX500 excimer laser system
Manufacturer	WaveLight GmbH Am Wolfsmantel 5 91058 Erlangen, Germany
Indication for use and intended purpose in the current study	The WaveLight EX500 excimer laser system is an FDA approved stationary scanning-spot excimer laser system used in refractive surgery for the treatment of myopia, myopic astigmatism, hyperopia, hyperopic astigmatism, and mixed astigmatism, including customized refractive surgery based on data delivered by WaveLight's diagnostic devices.
Product description and parameters available for this study	For treatments, at least the following components of the system have to be operated: • Laser Console - containing operating elements, laser head, optical transmission system, energy, and system controls; o Eyetracker, scanner motors, gas supply, plume evacuator, headup display, video system, N2 generator focusing and fixation lights, system software and ablation profiles with scanning spot patterns, operating microscope with illumination, LED slit illumination system, and test systems • Patient Bed - with moving motors and bed control • System Notebook (WaveNet Planning System) – containing software for programming treatment parameters
Formulation	N/A
Usage	In this study, the Wavefront Optimized (WFO) Ablation profile of the WaveLight EX500 excimer laser system will be used for

	bilateral LASIK treatment of hyperopia with and without astigmatism. Prior to usage for the laser portion of the treatment, a corneal flap must be created. For this study, the WaveLight FS200 femtosecond laser unit (FS200) will be utilized to create the flap. The WaveLight EX500 excimer laser system is intended for use solely by the physicians trained in the use of this laser system and its accessories. During its operation, the WaveLight EX500 excimer laser system does not come into contact with the eye, and treatment usually lasts 1.3 seconds per diopter.
Operating Conditions	Temperature: + 64°F (+ 18°C) to + 86°F (+ 30°C) above dew point Humidity: 20% to 70% at + 77°F (+ 25°C), not condensing Air pressure (recommended): 800 hPa to 1060 hPa (Barometric)
Supply	Each selected investigational site must have an FS200 and an EX500.

The Investigator will be responsible for ensuring that the products are used in accordance with their respective indications and procedural guidance provided in the appropriate User and Procedure Manuals. [redacted]

More information on the test product can be found in the WaveLight EX500 User Manual.

9.2 Other Medical Device or Medication Specified for Use During the Study

During the clinical study, additional medical devices and/or medications that are required in conjunction with the treatment include the following:

- FS200: The FDA approved FS200 will be used for creation of the corneal flap according to MOP and associated user manuals, and is to be performed by a qualified ophthalmic surgeon.

- Patient Interface: The disposable patient interface designed for use with the FS200 will be used according to the approved user guide.
- WaveCard: A study-specific WaveCard will be used for clinical study treatment. This WaveCard is serial-number-specific for a particular laser and has a defined number of treatments. This WaveCard will be provided to the site and labeled with the protocol number.
- Medications given for WaveLight EX500 excimer laser system LASIK will be per the Investigator's standard of care for LASIK.

9.3 Treatment Assignment / Randomization

After signing the ICF, a subject must be entered into the EDC system and will be assigned a subject number upon entry. This subject number will be used to identify the subject through the clinical study. Subjects who qualify based on inclusion and exclusion criteria should be treated as schedules allow surgery to be performed. This is a single-group study, as recommended by ANSI Z80.11 2012(R2017), and all subjects will be planned for bilateral LASIK with a target of emmetropia; therefore, no randomization will be used.

9.4 Treatment Masking

The clinical study design is a single-arm treatment and therefore all members associated with the study (at the site and the Study Sponsor) are unmasked to the assigned treatment.

9.5 Accountability Procedures

Upon receipt of Investigational Products (IP), the Investigator or delegate must conduct an inventory of the WaveCard by serial number, complete study-specific confirmation of receipt procedures as described in the MOP, and retain any required documentation in the Investigator's clinical study records. Throughout the study, the Investigator or delegate must maintain records of IP use for each subject (eg, WaveCard use documentation). This record must be made available to the study monitor for the purposes of verifying the accounting of IP use. Any discrepancies and/or deficiencies between the observed disposition and the written account must be recorded along with an explanation. All IPs sent to the Investigator must be accounted for by Study Sponsor personnel, and in no case be used in an unauthorized manner.

- Return to the Study Sponsor investigational product associated with a device deficiency. Refer to Section 11 of this protocol for additional information on the reporting of device deficiencies and to the MOP for information on return of study products associated with these events.

The Investigator is responsible for proper disposition of all unused IPs at the conclusion of the study, according to the instructions provided in the MOP.

9.6 Changes to concomitant medications, treatments/ procedures

After the subject is enrolled into the study, the Investigator must instruct the subject to notify the study site about:

- Any new medications
- Alterations in dose or dose schedules for current medications,
- Any medical procedure or hospitalization that occurred or is planned
- Any non-drug therapies (including physical therapy and blood transfusions).

The Investigator must document this information in the subject's case history source documents.

Preoperative and postoperative medications should be given as per site standard of care, documented in the subject's chart, confirmed as used by subject, and be listed as required in the EDC for each subject.

Surgical procedural steps that may impact treatment and related precautions, actions to be taken, or recommendations that result in discontinuation of study treatment are listed in Table 9–2. The table includes, but is not limited to, the most common or likely complications.

Table 9–2 Procedural Complications

Treatment/Procedure Complication	Precaution(s) and Action(s) to be taken	Subject Status
Flap Creation incomplete or irregular	If flap creation is unsuccessful or irregular, THEN the flap should not be lifted and/or subject should not be treated	Subject should be followed as per Section 10.4.2.
Partial or incomplete LASIK ablation	IF LASIK ablation is not successfully completed, retreatment is not allowed.	Subject should be followed as per Section 10.4.2.

10 STUDY PROCEDURES AND ASSESSMENTS

Study specific assessments will be obtained, including baseline prior to WaveLight EX500 excimer laser system LASIK and postoperatively at the study visits outlined below (where "A" denotes the visit for the 2nd eye treated):

- Screening - Visit 0 [-45 to -1 day prior to treatment]
- Visit 00 / Visit 00A [Day 0 – surgery]
- Visit 1 / Visit 1A [Day 1]
- Visit 2 / Visit 2A [Day 5 to 9]
- Visit 3 / Visit 3A [Day 21 to 35]
- Visit 4 / Visit 4A [Day 70 to 98]
- Visit 5 / Visit 5A [Day 147 to 182]
- Visit 6 / Visit 6A [Day 245 to 301]
- Visit 7 / Visit 7A [Day 330 to 420]

In addition to the scheduled visits listed above, the following visits may apply as needed:

- Early Exit [completed when a treated subject reports they wish to discontinue study participation, if subject is willing]
- Unscheduled Visit [completed when a treated subject reports for additional follow-up]

Clinical assessments to be obtained at study visits are outlined in Table 3–1 and are defined in the sections below.

[redacted]

10.1 Informed Consent and Screening

Visit 0 / Screening

The Investigator or delegate must explain the purpose and nature of the study, and have the subject read, sign, and date the IRB/IEC-approved informed consent document. The subject must sign the ICF BEFORE any study-specific procedures or assessments can be performed, including study-specific screening procedures. Additionally, have the individual obtaining consent from the subject and a witness, if applicable, sign and date the informed consent document.

The Investigator or delegate must provide a copy of the signed document to the subject and place the original signed document in the subject's chart, or provide documentation as required by local regulations.

IF a patient has reported for routine LASIK screening, THEN data obtained from the routine evaluation can be used for screening data as long as protocol requirements for timeframe (within 45 days of surgery) and required details have been met. (Examples of this data include, but are not limited to IOP, subjective manifest refraction for stability, and Cycloplegic refraction).

IF a screening phone script is used, THEN the subject should be pre-screened via phone and if interested in participating and a potential candidate for treatment, should be scheduled for an in-person visit as schedules allow, and consented prior to any study-specific testing.

10.2 Description of Study Procedures and Assessments

Detailed descriptions of assessments and procedures are provided in the MOP. The Investigator is responsible for ensuring responsibilities for all procedures and assessments are delegated to appropriately qualified site personnel.

10.2.1 Aberrometry

Visit 0

Measure aberrometry using standard of care method. The magnitude of the following aberrations will be collected in the database: astigmatism, coma, sphere/focus, spherical aberration, tilt, trefoil, and root mean square height (RMSh). The same type of instrument should be used throughout the study.

10.2.2 Adverse Event Collection: Safety Assessment

All Study Visits

Assess and record any adverse events that are observed or reported, including those associated with changes in concomitant medication dosing since the previous visit.

Note: AEs and device deficiencies must be recorded for all enrolled subjects from the time of signature of informed consent until their exit from the study, regardless of subject enrollment status (screen failure or received treatment).

10.2.3 Best Corrected Distance Visual Acuity: [redacted] Safety Assessment

Visit 0, Visit 2/2A – 7/7A, Early Exit

Perform best corrected visual acuity testing with the Sponsor provided electronic visual acuity system for both eyes prior to any assessment requiring administration of eye drops to dilate the eyes, or any assessment requiring contact with the eye. [redacted] The testing distance for this assessment is 4 m. Visual acuity must be obtained by study personnel who have successfully completed required training to conduct the assessment.

10.2.4 Concomitant Medications

All Study Visits

Collect all ocular medications and systemic medications that the investigator has determined will affect the evaluation of this trial used by the subject within the past 30 days or ongoing at

time of screening. Include herbal therapies, vitamins, and all over-the-counter as well as prescription medications. Throughout the subject's participation, obtain information on any changes in concomitant medications. Follow the MOP and Case Report Form Completion Guidelines for additional information on documentation and EDC entry for routine LASIK medications and take home and non-routine medications.

10.2.5 Cycloplegic Refraction

Visit 0, Visit 5/5A, Visit 7/7A, Early Exit

Perform the cycloplegic refraction after instilling cycloplegic drops using standard of care method.

10.2.6 Demographics

Visit 0

Obtain demographic information including age, race, ethnicity, and sex.

10.2.7 Device Deficiencies: Safety Assessment

All Study Visits

Assess and record any device deficiencies that are reported or observed. Requirements for reporting device deficiencies in the study can be found in Section 11.

Note: AEs and device deficiencies must be recorded for all enrolled subjects from the time of signature of informed consent, regardless of subject enrollment status (screen failure or received treatment).

10.2.8 Dilated Fundus Examination: Safety Assessment

Visit 0, 5/5A, 7/7A, Early Exit, USV

Dilated fundus examination includes ophthalmoscopic assessments of the vitreous, retina, macula, choroid, and optic nerve of both eyes.

10.2.9 Intraocular Pressure: Safety Assessment

Visit 0, 3/3A – 7/7A, Early Exit, USV

Intraocular pressure must be measured in both eyes using a Goldmann tonometer or any other instrument. The same type of instrument should be used throughout the study.

10.2.10 Keratometry

Visit 0

Measure keratometry (K1 and K2 with axis) using standard of care method. The same type of instrument should be used throughout the study.

10.2.11 LASIK Surgery

Visit 00/00A

Use the FS200 to create corneal flap, then use the EX500 to perform WFO LASIK. Treatment must be performed by a qualified surgeon (no more than 2 per site). Record flap diameter, flap thickness, optical zone and residual stroma thickness. Additional details are listed in the MOP.

10.2.12 Manifest / Subjective Refraction: Efficacy and Safety Assessment

Visit 0, 2/2A – 7/7A, Early Exit

Perform manifest refraction under photopic lighting conditions and measure vertex distance using a phoropter.

Note: The chart used for subjective manifest refraction depends on intended use of the data:

- For Inclusion stability at Screening (Visit 0) – performed on site chart
- For VA testing - performed on Sponsor provided electronic chart
- See MOP for more details.

Note: Refraction for Inclusion Criteria 4 for hyperopic and astigmatic range must come from the manifest refraction.

10.2.13 Medical History

Visit 0

Collect all ocular medical history and systemic medical history that the Investigator has determined will affect the evaluation of this trial. Throughout the subject's participation, obtain information on any changes in medical health and record in subject source documents. Follow the MOP and Case Report Form Completion Guidelines for additional information on documentation and EDC entry.

10.2.14 Mesopic Pupil Size

Visit 0

Measure mesopic pupil size using an infrared-based pupilometer.

[redacted]

[redacted]

10.2.17 Slit Lamp Examination: Safety Assessment

Visit 0, Visit 1/1A – 7/7A, Early Exit, USV

Slit Lamp Exam of the cornea, iris/anterior chamber, and lens must be performed in both eyes before instillation of any diagnostic eye drops. Follow the MOP for specific areas of detailed assessment according to required grading scales for Corneal Haze, Diffuse Lamellar Keratitis, and Epithelium Ingrowth.

10.2.18 Topography

Visit 0

Measure corneal topography using standard of care method. The same type of instrument should be used throughout the study. Record the presence or absence of irregular astigmatism. The Investigator's best judgement should be used for postoperative care.

10.2.19 Uncorrected Distance Visual Acuity: [redacted] Safety Assessment

Visit 0, Visit 1/1A – 7/7A, Early Exit, USV

Perform uncorrected visual acuity testing with the Sponsor provided electronic visual acuity system for both eyes prior to any assessment requiring administration of eye drops to dilate the eyes, or any assessment requiring contact with the eye. [redacted] Visual acuity must be obtained by study personnel who have successfully completed required training to conduct the assessment.

10.2.20 Urine Pregnancy Test

Visit 0

Collect a urine pregnancy test on female subjects of childbearing potential who are not postmenopausal or surgically sterile.

Note: The results from the urine pregnancy test will not be recorded in EDC.

10.3 Unscheduled Visits

After LASIK is performed, if a subject visit occurs between any regularly scheduled visits, then this visit must be documented as an Unscheduled Visit. During all unscheduled visits, the Investigator must conduct the USV procedures according to Table 3-1.

The Investigator may perform additional procedures for proper diagnosis and treatment of the subject. The Investigator must document this information in the subject's case history source documents.

If during an USV the subject is discontinuing from the study, the Investigator must conduct Early Exit procedures according to Table 3-1, Schedule of Study Procedures and Assessments and Section 10.4.3, as possible.

10.4 Discontinued Subjects

10.4.1 Screen Failures

Subjects who were excluded from the study after signing the informed consent and prior to surgical procedures beginning (prior to eye drops for flap creation), are considered a screen failure. The Investigator must document the reason for screen failure in the subject's chart.

Subject numbers must not be re-used.

10.4.2 Incomplete Treatments

If a subject's surgical treatment is started but discontinued due to complications or other reasons, every effort must be made to keep the subject in the study and to continue with the study required visits. For these subjects, appropriate follow-up assessments as per standard of care (including at minimum, AEs, slit lamp examination, UCDVA, manifest refraction, and BCDVA) should be conducted and collected. If the subject is not willing to complete all required follow-up visits, then document in the chart and exit the subject according to Section 10.4.3. See Section 11.6 for additional instructions for any adverse events.

Note: If drops are given for surgical treatment, but no laser procedure started and the surgery needs to be rescheduled, then reschedule surgery within the protocol defined visit window or follow rescreening instructions in Section 8.3.

Note: Please inform the Sponsor as soon as possible when an incomplete treatment occurs in order to discuss and confirm proper reporting and follow-up.

10.4.3 Discontinuations

Discontinued subjects are individuals who voluntarily withdraw or are withdrawn from the study by the Investigator after the surgical procedure (eye drops given for flap creation), has begun.

Subjects may discontinue from study or study treatment at any time for any reason. Subjects may also be discontinued from study treatment at any time if, in the opinion of the Investigator, continued treatment poses a risk to their health.

For subjects discontinuing from the study after treatment, the Investigator must complete all Early Exit procedures according to Table 3-1, Schedule of Study Procedures and Assessments, if the subject is willing and able, and if in the opinion of the Investigator it is safe for the subject to do so.

The Investigator must document the reason for study or treatment discontinuation in the subject's chart.

To ensure the safety of all subjects who discontinue early, Investigators must assess each subject and, if necessary, advise them of any therapies and/or medical procedures that may be needed to maintain their health.

Subject numbers of discontinued subjects must not be re-used.

10.5 Clinical Study Termination

The Study Sponsor reserves the right to close the investigational site or terminate the study in its entirety at any time.

If the clinical study is prematurely terminated or suspended by the Study Sponsor:

- The Study Sponsor must:
    - Immediately notify the Investigator(s) and subsequently provide instructions for study termination.
    - Inform the Investigator and the regulatory authorities of the termination/suspension and the reason(s) for the termination/suspension.
- The Investigator must:
    - Promptly notify the IRB/IEC of the termination or suspension and of the reasons.
    - Provide subjects with recommendations for poststudy treatment options as needed.

The Investigator may terminate the site's participation in the study for reasonable cause.

10.5.1 Follow-Up of Subjects After Study Participation Has Ended

Following this study, the subject will return to their eye care professional for their routine eye care. In cases where a subject has a continuing adverse event at the time of study completion, see Section 11.6.

10.6 Contingency Measures

To overcome challenges that may arise during unexpected events which could interrupt the conduct of the trial as planned (eg, natural disasters or a public health emergency), contingency measures may be implemented. The intent of contingency measures would be to

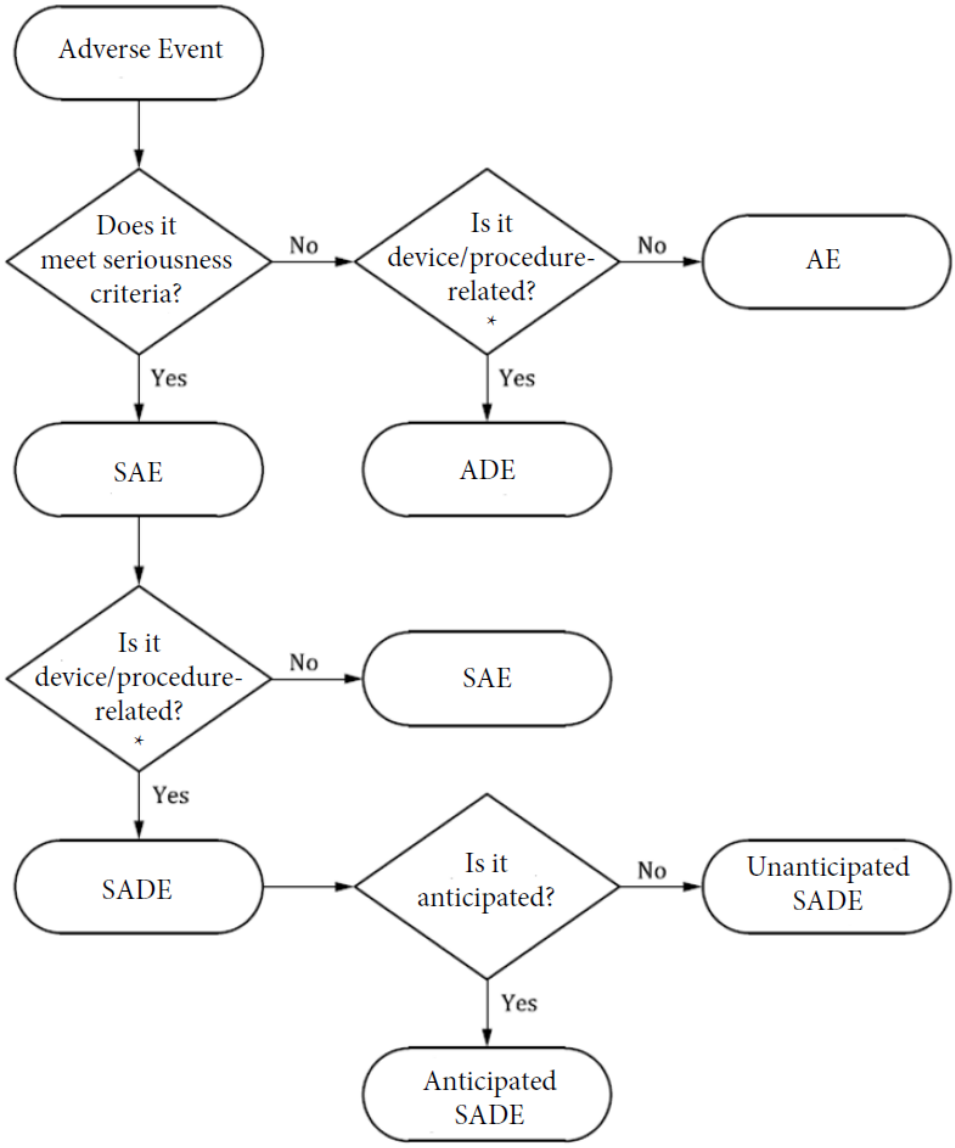
address the care of enrolled subjects during such unexpected events. It is not expected that contingency measures would affect study design; however, if necessary, the protocol would be amended accordingly. Written notification describing these contingency measures will be provided to the IRB and other regulatory agencies, as applicable. During such events, Investigators must continue to use medical judgement in the care of subjects and follow national and local guidance as well as IRB reporting requirements. Additional information can be found in the MOP.

11 ADVERSE EVENTS AND DEVICE DEFICIENCIES

11.1 General Information

An AE is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users, or other persons, whether or not related to the investigational medical device (test product). Refer to the Glossary of Terms and figures below for categories of AEs and SAEs.

Figure 11–1 Categorization of All Adverse Events



*In this study, only AE related to the investigational product/device (ie, WaveLight EX500 excimer laser system) is considered as device related ADE.

Specific Events Relevant to this Protocol

In addition to reporting all AEs (serious and non-serious) meeting the definitions, the Investigator must report any occurrence of the following as an ocular SAE:

- Diffuse lamellar keratitis (Grade 3 or above)
- Corneal infiltrate or ulcer

- Any persistent corneal epithelial defect at one month or later
- Corneal edema at 1 month or later (specify flap or bed)
- Epithelium in the interface with loss of 2 lines (10 letters) or more BCDVA
- Miscreated flap (lost, incomplete, too thin)
- Melting of the flap
- IOP with increase of > 10 mmHg above baseline on two consecutive examinations or an IOP greater than 30 mmHg on two consecutive examinations
- Haze beyond 6 months with loss of 2 lines or greater (≥ 10 letters ETDRS) of BCDVA
- Decrease in BCDVA of greater than or equal to 2 lines (≥ 10 letters ETDRS) not due to irregular astigmatism as shown by rigid contact lens refraction at 3 months or later
- Retinal detachment
- Retinal vascular accidents
- Ocular penetration
- Any other vision-threatening event

The Investigator must also report the following ocular AEs:

- Diffuse lamellar keratitis (Grade 2 or less)
- Corneal edema between one week and 1 month after the procedure
- Peripheral corneal epithelial defect at 1 month or later (location of the defect to be identified as on, off, or across the flap)
- Epithelium in the interface
- Foreign body sensation at 1 month or later
- Pain at 1 month or later
- Ghost/double images in the operative eye
- Flap is not of the size and shape as initially intended or resultant flap is misaligned

AEs that occur in association with a device that is used in conjunction with FS200 will be reported separately from those occurring with EX500.

This list is consistent with the categories provided in ANSI Z80.11 2012(R2017). Any other potentially sight-threatening event may also be considered serious based on the judgment of the Investigator and should be reported appropriately as delineated in Section 11.3.

Device Deficiencies

A device deficiency may or may not be associated with subject harm (ie, ADE or SADE); however, not all ADEs or SADEs are due to a device deficiency. The Investigator should determine the applicable category for the identified or suspect device deficiency and report any patient harm separately. Examples of device deficiencies include the following:

- Calibration issue: Error in or Unable to calibrate laser
- Computer software issue or system error message
- Defective component
- Detachment of device or device component
- Device breakage (eg, joystick)
- Device emits odor (eg, gas leak, and smoke)
- Failure of laser firing
- Failure to meet product specifications (eg, incorrect laser assembly)
- Failure to transmit record
- Foreign material present in device
- Image display error or failure to display
- Incorrect laser output energy
- Instructions difficult to understand/follow
- Mechanical issues (eg, failure to focus, align, track, position, or unintended system motion)
- Power issue: Equipment will not power on; power loss; or intermittent connection
- Other events that may meet the definition of device deficiency

11.2 Monitoring for Adverse Events

At each visit, after the subject has had the opportunity to spontaneously mention any problems, the Investigator should inquire about AEs by asking the standard questions shown below and report as applicable:

- "Have you had any health problems since your last study visit?"
- "Have there been any changes in the medicines you take since your last study visit?"

In addition, changes in *any protocol-specific parameters and/or questionnaires* evaluated during the study are to be reviewed by the Investigator. Any untoward (unfavorable and unintended) change in *a protocol-specific parameter or questionnaire response* that is clinically relevant, in the opinion of the Investigator, is to be reported as an AE. These clinically relevant changes will be reported regardless of causality.

11.3 Procedures for Recording and Reporting

AEs are collected from the time of informed consent. Any pre-existing medical conditions or signs/symptoms present in a subject prior to the start of the study (ie, before informed consent is signed) are not considered AEs in the study and should be recorded in the Medical History section of the eCRF.

In addition, dry eye, superficial punctate keratitis, and optical visual disturbances (eg, glare, halo, and starburst) are examples of early postoperative findings that are typically observed following kerato-refractive surgery. These are not considered AEs if they can be reasonably expected to resolve within 6 months and not result in any untoward long term visual outcome impact. However, based on the Investigator's medical judgment, signs and symptoms of dry eye and ocular visual disturbances prior to 6 months, or persisting beyond 6 months post kerato-refractive surgery, may be considered an AE.

For each recorded event, the ADEs and SAEs documentation must include: date of occurrence, severity, treatment (if applicable), outcome, and assessments of the seriousness and causality. In addition, the Investigator must document all device deficiencies reported or observed with test and control products on the Device Deficiency eCRF. The site must submit all available information on ADEs, SAEs, and device deficiencies to the Study Sponsor immediately as follows:

- ADEs or SAEs are documented on the *Serious Adverse Event and Adverse Device Effect* eCRF within 24 hours of the Investigator's or site's awareness.

- Device deficiencies are documented on the *Device Deficiency* eCRF within 24 hours of the Investigator's or site's awareness.
- A printed copy of the completed *Serious Adverse Event and Adverse Device Effect* and/or *Device Deficiency* eCRF must be included with product returns.
- Additional relevant information after initial reporting must be entered into the eCRF as soon as the data become available.
- Document any changes to concomitant medications on the appropriate eCRFs.
- Document all relevant information from Discharge Summary, Autopsy Report, Certificate of Death, etc., if applicable, in narrative section of the *Serious Adverse Event and Adverse Device Effect* eCRF.

  Note: Should the EDC system become non-operational, the site must complete the appropriate paper *Serious Adverse Event and Adverse Device Effect* and/or *Device Deficienc*y Form. The completed form is emailed to the Study Sponsor at MSUS.Safety@Alcon.com according to the timelines outlined above; however, the reported information must be entered into the EDC system once it becomes operational.

Any AEs and device deficiencies for non-study marketed devices/products (eg, FS200, Custom Paks) will be considered and processed as spontaneous (following the postmarket vigilance procedures) and should be communicated to the device's/product's manufacturer as per local requirements.

Study Sponsor representatives may be contacted for any protocol related question and their contact information is provided in the Manual of Procedures that accompanies this protocol.

Further, depending upon the nature of the AE or device deficiency being reported, the Study Sponsor may request copies of applicable portions of the subject's medical records. The Investigator must also report all AEs and device deficiencies that could have led to a SADE according to the requirements of regulatory authorities or IRB/IEC.

Intensity and Causality Assessments

Where appropriate, the Investigator must assess the intensity (severity) of the AE based on medical judgment with consideration of any subjective symptom(s), as defined below:

Intensity (Severity)

Mild	An AE is mild if the subject is aware of but can easily tolerate the sign or symptom.
Moderate	An AE is moderate if the sign or symptom results in discomfort significant enough to cause interference with the subject's usual activities.
Severe	An AE is severe if the sign or symptom is incapacitating and results in the subject's inability to work or engage in their usual activities.

For every AE in the study, the Investigator must assess the causality (Related or Not Related to the medical device or study procedure). An assessment of causality will also be performed by Study Sponsor utilizing the same definitions, as shown below:

Causality

Related	An AE classified as related may be either definitely related or possibly related where a direct cause and effect relationship with the medical device or study procedure has not been demonstrated, but there is a reasonable possibility that the AE was caused by the medical device or study procedure.
Not Related	An AE classified as not related may either be definitely unrelated or simply unlikely to be related (ie, there are other more likely causes for the AE).

The Study Sponsor will assess the AEs and may upgrade the Investigator's assessment of seriousness and/or causality. The Study Sponsor will notify the Investigator of any AEs that is upgraded from non-serious to serious or from unrelated to related.

Furthermore, the Study Sponsor shall promptly conduct an evaluation of any unanticipated adverse device effect, including anticipated adverse events that occur in unanticipated severity or frequency. The results of this evaluation will be reported to the FDA, the IRB, and participating Investigators within 10 working days upon receiving notification of the effect.

[redacted]

[redacted]

11.5 Unmasking of the Study Treatment

Not applicable; this study is open-label.

11.6 Follow-Up of Subjects with Adverse Events

The Investigator is responsible for adequate and safe medical care of subjects during the study and for ensuring that appropriate medical care and relevant follow-up procedures are maintained after the study.

The Investigator should provide the Study Sponsor with any new safety information (which includes new AEs and changes to previously reported AEs) that may affect the safety evaluation of the device. For AEs that are unresolved/ ongoing at time of subject exit from study, any additional information received at follow-up should be documented in the eCRFs up to study completion (ie, database lock).

Any additional data received up to 6 months after subject discontinuation or exit must be documented and available upon the Study Sponsor's request. All complaints received after this time period will be considered and processed as spontaneous (following the postmarket vigilance procedures) and should be communicated to the medical device's manufacturer as per local requirements.

The Investigator should also report complaints on non-Alcon products directly to the manufacturer as per the manufacturer's instructions or local regulatory requirements.

11.7 Pregnancy in the Clinical Study

Pregnancy is not reportable as an AE; however, complications may be reportable and will be decided on a case–by-case basis. An Alcon form will be utilized to capture all pregnancy-related information until birth of the child.

12 ANALYSIS PLAN

This information will also be contained within a separate biostatistical analysis plan which will be prepared and finalized prior to database lock.

Counts and percentages will be presented as categorical variables. N, mean, standard deviation, median, minimum, and maximum will be presented for continuous variables.

12.1 Subject Evaluability

Final subject evaluability must be determined prior to locking the database, based upon the Deviations and Evaluability Plan.

12.2 Analysis Sets

All eligible subjects will be screened to determine if they meet all inclusion and no exclusion criteria. Subjects who provide informed consent will be considered enrolled in the study.

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

12.2.1 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.

12.2.2 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.

12.3 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized for each subject. Appropriate summary statistics will be presented for each characteristic. These summaries will be based on the SAF and the FAS.

12.4 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.

12.5 Effectiveness Analyses

12.5.1 Analysis of Primary Effectiveness Endpoint(s)

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

12.5.1.1 Statistical 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%

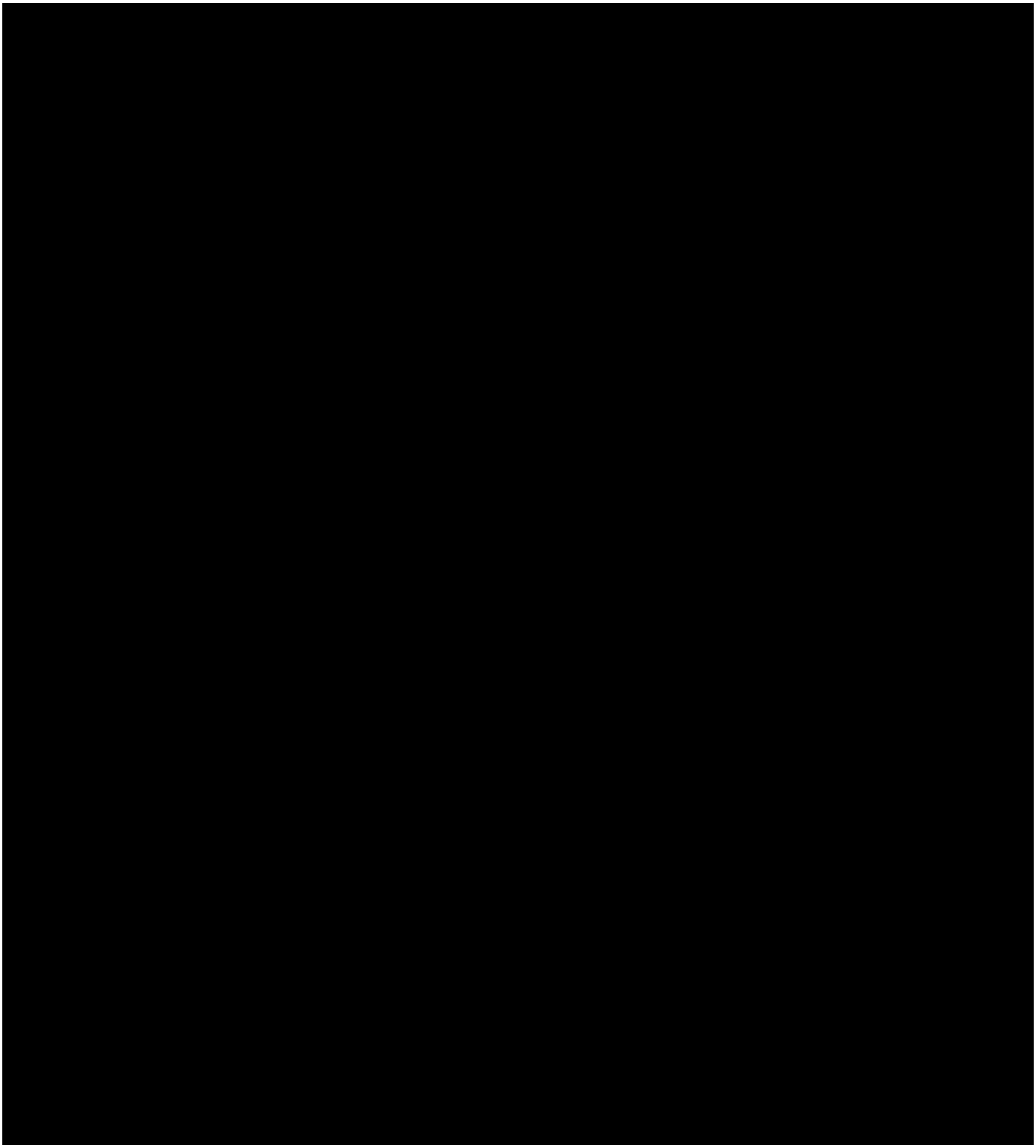
where π1(EX500) is the population proportion of eyes in the EX500 group with MRSE within ±0.50 D at refractive stability, and π2(EX500) is the population proportion of eyes in the EX500 group with MRSE within ± 1.00 D at refractive stability. The constants 50.0% in Test 1 and 75.0% in Test 2 are the 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]

12.5.1.2 Analysis Methods

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. These analyses will be performed for the whole FAS as well as stratified by preoperative MRSE subgroups. An analysis will be performed once refractive stability is achieved; a final summary of these endpoints will be performed once the one-year follow-up is complete.



[redacted]

12.6 Handling of Missing Data

No imputation of missing data is planned.

12.7 Safety Analyses

The safety analysis set will include all eyes for which refractive surgery is attempted with test device (regardless of success or failure). All adverse events occurring from the time a subject signs informed consent to study exit will be accounted for in the reporting. 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.

12.7.1 Analysis of Primary Safety Endpoint(s)

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

12.7.1.1 Statistical Hypotheses

No hypothesis testing of the primary safety endpoints is planned.

12.7.1.2 Analysis Methods

The SAF will be used for this analysis. The number and percentage of eyes experiencing each of the primary safety endpoints will also be calculated.

[redacted]

[redacted]

13 DATA HANDLING AND ADMINISTRATIVE REQUIREMENTS

13.1 Subject Confidentiality

The Investigator must ensure that the subject's anonymity is maintained throughout the course of the study. In particular, the Investigator must keep an enrollment log with confidential identifying information that corresponds to the subject numbers and initials of each study participant. At the end of the clinical study, the Study Sponsor will collect a copy of the enrollment log ***without any identifying subject information***. All documents submitted to the Study Sponsor will identify the subjects exclusively by number and demographic information. No other personally identifying information will be transmitted to the Study Sponsor.

The Study Sponsor may release anonymized study data to external researchers for purposes of future research directly related to the study objectives, or future research that is beyond the scope of the current study objectives. The Informed Consent Form explains this to study subjects. Anonymization means that all identifiable information will be removed from the dataset and all links to the subjects in the study will be removed. Anonymization of the data will maintain confidentiality of the subjects who participate in the study so that they cannot be identified by external researchers. The anonymized data set will contain records from all of the subjects in the current study, but the anonymization process might change the data set in some ways, so external researchers will be informed that they might not be able to duplicate some of the results from this study.

13.2 Completion of Source Documents and Case Report Forms

The nature and location of all source documents will be identified to ensure that original data required to complete the CRFs exist and are accessible for verification by the site monitor, and all discrepancies shall be appropriately documented via the query resolution process. Site monitors are appointed by the Study Sponsor and are independent of study site staff.

If electronic records are maintained, the method of verification must be determined in advance of starting the study.

At a minimum, source documents include the following information for each subject:

- Subject identification (name, sex, race/ethnicity)
- Documentation of subject eligibility
- Date of informed consent

- Dates of visits
- Documentation that protocol specific procedures were performed
- Results of study parameters, as required by the protocol
- IP accountability records
- Documentation of AEs and other safety parameters (if applicable)
- Records regarding medical histories and the use of concomitant therapies prior to and during the study
- Date of study completion and reason for early discontinuation, if applicable

It is required that the author of an entry in the source documents be identifiable. Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded on the CRF are consistent with the original source data.

Only designated individuals at the site will complete the CRFs. The CRFs must be completed at regular intervals following the clinical study visit schedule. It is expected that all data reported have corresponding entries in the source documents. The Principal Investigator is responsible for reviewing and certifying that the CRFs are accurate and complete. The only subject identifiers recorded on the CRFs will be subject number, and subject demographic information.

13.3 Data Review and Clarifications

A review of CRF data to the subject's source data will be completed by the site monitor to ensure completeness and accuracy. After the CRFs have been completed, additional data clarifications and/or additions may be needed as a result of the data cleaning process. Data clarifications are documented and are part of each subject's CRF.

13.4 Sponsor and Monitoring Responsibilities

The Study Sponsor will designate a monitor to conduct the appropriate site visits at the appropriate intervals according to the study monitoring plan. The clinical investigation will be monitored to ensure that the rights and well-being of the subjects are protected, the reported data are accurate, complete, and verifiable from the source documents, and the study is conducted in compliance with the current approved protocol (and amendments[s], if applicable), with current GCP, and with applicable regulatory requirements.

The site may not screen subjects or perform the informed consent process on any subject until it receives a notification from an appropriate Study Sponsor representative that the site may

commence conducting study activities. Monitoring will be conducted periodically while the clinical study is ongoing. Monitoring methods may include site visits, telephone, written and email correspondence. Close-out visits will take place after the last visit of the last subject at the site.

A Coordinating Investigator may be identified by the Study Sponsor to review and endorse the final study report. In cases where a Coordinating Investigator is engaged, the Study Sponsor will select the Coordinating Investigator based upon their experience, qualifications, active study participation, and their willingness and availability to take on this role.

Additionally, Alcon may have an expert Sponsor Observer or Representative present during screening or surgery to offer training to the Investigator on proper operation of the device and/ or to make technical observations during the study visit.

- The Sponsor Representative must be supervised by the Investigator or designee to ensure the Sponsor Representative's presence or activities do not bias the outcome of the study, affect the quality of the research data, and/or compromise the rights and welfare of the subject. The Sponsor Representative will not intervene with the standard of care provided to study subjects or make safety-related decisions or assessments. The activities of Sponsor Representatives will be described in the Informed Consent.

13.5 Regulatory Documentation and Records Retention

The Investigator is required to maintain up-to-date, complete regulatory documentation as indicated by the Study Sponsor and the Investigator's files will be reviewed as part of the ongoing study monitoring. Financial information is to be kept separately.

Additionally, the Investigator must keep study records and source documents consistent with the terms of the clinical study agreement with the Study Sponsor. If the Investigator retires, relocates, or for any other reason withdraws from responsibility of keeping the study records, then the Study Sponsor must be notified and suitable arrangements made for retention of study records and source documents needed to comply with national and international regulations.

13.6 Quality Assurance and Quality Control

The Study Sponsor will secure agreement from all involved parties to ensure direct access to all study related sites, source data and documents, and reports for the purpose of monitoring and auditing by the Study Sponsor, and inspection by domestic and foreign regulatory

authorities. Quality control will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. Agreements made by the Study Sponsor with the Investigator/Institution and any other parties involved in the clinical study will be provided in writing as part of the protocol or as a separate agreement.

14 ETHICS

This clinical study must be conducted in accordance with the ethical principles contained within:

- The Declaration of Helsinki, and in compliance with the ICH E6 GCP Consolidated Guideline, ISO 14155:2011, and the applicable US FDA 21 CFR Regulations.
- SOPs of the Study Sponsor and contract research organizations participating in the conduct of the clinical study and all other applicable regulations.
- Notifications and timelines for reporting protocol deviations should be based upon applicable Ethics Committee requirements

The Investigator must ensure that all personnel involved in the conduct of the study are qualified to perform their assigned responsibilities through relevant education, training, and experience. The Investigator and all clinical study staff must conduct the clinical study in compliance with the protocol. Deviations from this protocol, regulatory requirements and/or GCP must be recorded and reported to the Sponsor prior to database lock. If needed, corrective and preventive action should be identified, implemented, and documented within the study records. Use of waivers to deviate from the clinical protocol is prohibited.

Before clinical study initiation, this protocol, the informed consent form, any other written information given to subjects, and any advertisements planned for subject recruitment must be approved by an IRB/IEC. The Investigator must provide documentation of the IRB/IEC approval to the Study Sponsor. The approval must be dated and must identify the applicable protocol, amendments (if any), informed consent form, assent form (if any), all applicable recruiting materials, written information for subject, and subject compensation programs. The IRB/IEC must be provided with a copy of the User Manual, any periodic safety updates, and all other information as required by local regulation and/or the IRB/IEC. At the end of the study, the Investigator must notify the IRB/IEC about the study's completion. The IRB/IEC also must be notified if the study is terminated prematurely. Finally, the Investigator must report to the IRB/IEC on the progress of the study at intervals stipulated by the IRB/IEC.

Voluntary informed consent must be obtained in writing from every subject and the process shall be documented before any procedure specific to the clinical investigation is applied to

the subject. The Investigator must have a defined process for obtaining consent. Specifically, the Investigator, or their delegate, must explain the clinical study to each potential subject and the subject must indicate voluntary consent by signing and dating the approved informed consent form. The subject must be provided an opportunity to ask questions of the Investigator, and if required by local regulation, other qualified personnel. The Investigator must provide the subject with a copy of the consent form written in a language the subject understands. The consent document must meet all applicable local laws and provide subjects with information regarding the purpose, procedures, requirements, and restrictions of the study, along with any known risks and potential benefits associated with the IP and the study, the available compensation, and the established provisions for maintaining confidentiality of personal, protected health information. Subjects will be told about the voluntary nature of participation in the study and must be provided with contact information for the appropriate individuals should questions or concerns arise during the study. The subject also must be told that their records may be accessed by appropriate authorities and Sponsor-designated personnel. The Investigator must keep the original, signed copy of the consent (file in subject's medical records) and must provide a duplicate copy to each subject according to local regulations.

The Study Sponsor assures that the key design elements of this protocol will be registered on www.clinicaltrials.gov as required by current regulations and, if applicable, other public databases as required by local country regulations. In addition, results of this study will be made publicly available on www.clinicaltrials.gov regardless of outcome as required by current regulations and, if applicable, in other public databases as required by local country regulations.

15 REFERENCES

15.1 References Applicable for All Clinical Studies

- ISO 14155:2011 Clinical investigation of medical devices for human subjects - Good clinical practice

15.1.1 US References Applicable for Clinical Studies

- 21 CFR Part 11 - Electronic Records; Electronic Signatures
- 21 CFR Part 50 - Protection of Human Subjects
- 21 CFR Part 56 - Institutional Review Boards
- 21 CFR Part 812 - Investigational Device Exemptions

- 21 CFR Part 54 - Financial Disclosure by Clinical Investigators
- The California Bill of Rights

15.2 References For This Clinical Study

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

US Food and Drug Administration (FDA). Checklist of Information Usually Submitted in an Investigational Device Exemptions (IDE) Application for Refractive Surgery Lasers. Issued October 10, 1996.

Durrie DS, Smith RT, Waring GO, Stahl JE, Schwendeman FJ. Comparing conventional and wavefront-optimized LASIK for the treatment of hyperopia. J Refract Surg. 2010;26:356-63.

El-Naggar MT, Hovaghimian DG. Assessment of refractive outcome of femtosecond-assisted LASIK for hyperopia correction. Electron Physician. 2017;9:3958-65.

Motwani M, Pei R. Treatment of moderate-to-high hyperopia with the wavelight allegretto 400 and EX500 excimer laser systems. Clin Ophthalmol. 2017;11:999-1007.