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Clinical Trial Protocol

Comparison of Topography Guided LASIK with WaveLight EX500 to SMILE with Zeiss VisuMax

Protocol Number:	RFL605-P001 / NCT02987660
Sponsor Name & Address:	Alcon Research, Ltd. and its affiliates ("Alcon") 6201 South Freeway Fort Worth, Texas 76134-2099
Project Name / Number:	A02827
Test Article(s) / Product(s):	WaveLight EX500 for Topography Guided LASIK
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), ISO 14155, the ethical principles within the Declaration of Helsinki, this protocol, and all applicable regulatory requirements. Additionally, I will comply with all procedures for data recording and reporting, will permit monitoring, auditing, and inspection of my research center, and will retain all records until notified by the Sponsor.
Principal Investigator:	
	Signature Date
Name and Investigator Number:	
Address:	
Telephone:	
Release Date:	<Refer to e-signature date>

1 PROTOCOL SYNOPSIS

Financial Disclosure for US FDA Submission Required?	☐ Yes ☒ No
Test Article(s) / Product(s):	Wavelight® EX500 for Topography Guided LASIK
Objective(s):	The primary objective of the study is to demonstrate that Topography Guided Laser in situ Keratomileusis (LASIK) is superior to Small Incision Lenticule Extraction (SMILE) in the percentage of eyes with manifest refraction cylinder ≤ 0.5 D at 3 months. The secondary objectives of the study are: • To demonstrate that Topography Guided LASIK is superior to SMILE in mean manifest refraction cylinder at 3 months. • To demonstrate that Topography Guided LASIK is superior to SMILE in mean uncorrected visual acuity (UCVA) at 3 months. [redacted]

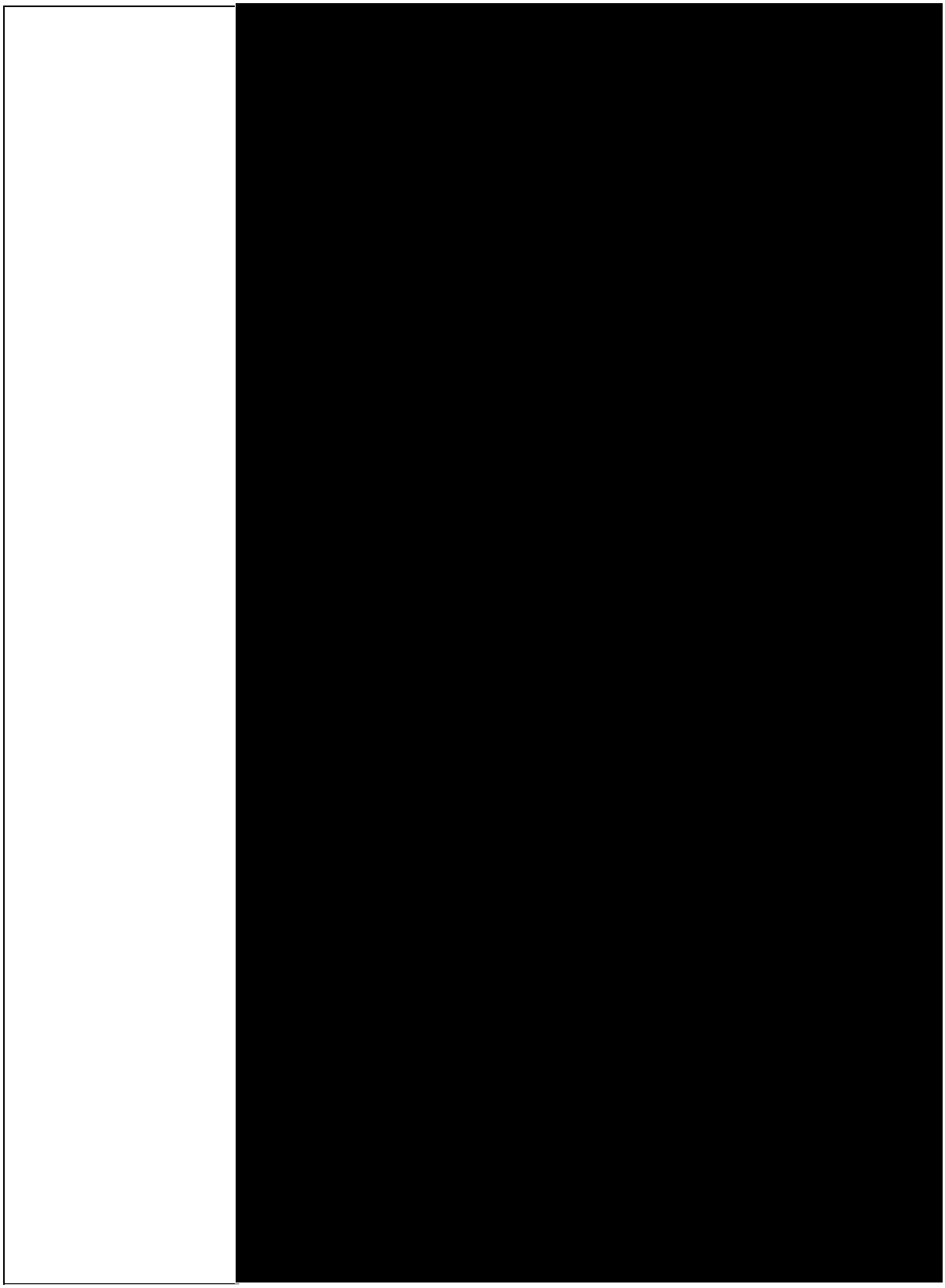
	The safety objectives of the study are: • To evaluate the adverse events (AEs) associated with Topography Guided LASIK and SMILE. • To evaluate post-surgery BCVA after Topography Guided LASIK and SMILE. • To evaluate mesopic uncorrected contrast sensitivity after Topography Guided LASIK and SMILE. • To evaluate quality of vision and vision related quality of life after Topography Guided LASIK and SMILE.
Clinical Study Design:	This is a prospective, parallel group, multi-center, group randomized (1:1 ratio), and observer masked study.
No. of Subjects:	Potential subjects will be screened, and approximately 450 subjects (225 subjects per treatment group) will be enrolled at approximately 8 study sites in order to allow approximately 400 subjects (200 subjects per treatment group) to be treated with bilateral laser refractive surgery (both eyes on same day), either Topography Guided LASIK or SMILE. This should result in at least 370 evaluable subjects (185 per treatment group).
Region(s):	EMEA, Asia, LACAR
Clinical Study Duration:	Subjects are required to attend a total of 7 visits over a period of up to 15 months as follows: Pre-Surgery Visit (Day -45 to Day -1), Surgery Visit (Day 0), and 5 Post-Surgery follow-up Visits (on Day 1, Week 1 [Day 5 to Day 9], Month 1 [Day 21 to Day 35], Month 3 [Day 70 to Day 98] and Month 12 [Day 330 to Day 375], respectively).
Clinical Study Population:	Subjects 18 years or older [subjects in Singapore must be 21 years of age or older and subjects in Korea must be upon completion of 19 years of age or older due to local regulations] with myopia requiring optical infinity adjusted manifest refraction spherical correction of -0.5 to -8.0 D and astigmatism correction of -0.75 to -5.0 D manifest refraction cylinder with at least 0.75 D of corneal astigmatism.

Treatments:	***Test Article***:	Wavelight EX500 for Topography Guided LASIK
	Administration:	The EX500 laser is used to ablate the corneal stroma which results in the refractive error correction. Prior to ablation, the corneal flap may be created with a femtosecond laser or microkeratome blade at the surgeon's discretion. Treatment planning will be based on topography.
	General Description:	Wavelight EX500 is a stationary scanning-spot excimer laser system used to perform the LASIK procedure. Ablation of the corneal tissue with the WaveLight EX500 results in the refractive error correction.
	Duration of Treatment:	The treatment is intended to last the subject's lifetime.
	Control Article:	Zeiss VisuMax for SMILE
	Administration:	The VisuMax Laser keratome is used to create a lenticule in the corneal stroma and a channel for the removal of the lenticule. Removal of the lenticule results in the refractive error correction.
	General Description:	Zeiss VisuMax Laser keratome, a femtosecond laser, generates a beam of ultra-short laser pulses used to perform the SMILE procedure, for refractive error correction.
	Duration of Treatment :	The treatment is intended to last the subject's lifetime.
Inclusion & Exclusion Criteria:	Inclusion criteria: Ocular criteria must be met in both eyes. 1. Subjects 18 years of age or older at the time of informed consent [subjects in Singapore must be 21 years of age or older and subjects in Korea must be upon completion of 19 years of age or	

	older due to local regulations]. 2. Able to comprehend and sign an informed consent form (ICF). 3. Willing and able to complete all post-surgery visits. 4. Myopia requiring (a) refractive error correction of -0.5 to -8.0 D optical infinity adjusted manifest refraction sphere with (b) astigmatism correction of -0.75 to -5.0 D manifest refraction cylinder and (c) at least 0.75 D of corneal astigmatism. 5. Intended treatment is targeted for emmetropia. 6. Pre-surgery BCVA of 0 logarithm of the minimum angle of resolution (logMAR) (20/20) or better. 7. Spherical equivalent difference of ≤ 0.5 D between the optical infinity adjusted manifest and optical infinity adjusted cycloplegic refraction outcomes. 8. Spherical equivalent difference of ≤ 0.5 D between refractive error corrections for a minimum of 12 months prior to surgery verified by consecutive optical infinity adjusted refractions and/or medical records or prescription history. 9. For contact lens wearers - Spherical equivalent difference of ≤ 0.5 D between outcomes from consecutive optical infinity adjusted manifest refraction outcomes performed at least 7 days apart after the contact lens wear has been stopped for the appropriate period of time as follows: • Soft (extended and daily wear) = 3 days • Rigid Gas Permeable (RGP) or Toric = 2 weeks • Hard polymethyl methacrylate (PMMA) = 3 weeks Exclusion Criteria: Ocular criteria must not be met in either eye. 1. Pregnancy or lactation, current or planned, during the course of the study. 2. Manifest refraction astigmatism that is more than 1.00 D than the topolyzer astigmatism assessed by Contoura software. 3. Mixed astigmatism refractive error. 4. Degenerations of structure of the cornea including diagnosed keratoconus, forme fruste kerataconus or pellucid marginal degeneration. 5. Dry eye as identified by the short questionnaire for dry eye syndrome (SQDES). 6. A calculated residual stromal bed thickness that is less than

<table>
<tr><td></td><td colspan="2">250 µm.
7. History or evidence of active or inactive corneal or other anterior segment disease (e.g, herpes simplex keratitis, recurrent erosion syndrome).
8. Diagnosed advanced glaucoma.
9. Uncontrolled diabetes.
10. Nystagmus or any other condition that would prevent a steady gaze during the treatment.
11. Previous intraocular or corneal surgery.
12. Weakened immune system, including diagnosed collagen vascular, autoimmune or immunodeficiency disease.
13. Systemic medications that may affect corneal healing including, but not limited to steroids, antimetabolites, immune response modifying drugs, etc.
14. Presence or history of any condition or finding that makes the subject unsuitable as a candidate for refractive surgery or study participation or may confound the outcome of the study, in the opinion of the Investigator.
15. Any subject currently participating in another investigational drug or device study that may confound the results of this investigation.
16. A known sensitivity to medications used during the study.</td></tr>
<tr><td rowspan="4">Effectiveness Endpoints and Assessments</td><td>Endpoints</td><td>Assessments</td></tr>
<tr><td colspan="2">Primary</td></tr>
<tr><td>Percentage of eyes with manifest refraction cylinder ≤ 0.5 D at 3 months</td><td>Manifest refraction</td></tr>
<tr><td colspan="2">Secondary</td></tr>
</table>

	Mean manifest refraction cylinder at 3 months	Manifest refraction
	Mean UCVA at 3 months	Photopic distance UCVA
	[redacted]	



	[redacted]	
Safety Endpoints and Assessments	**Endpoints**	**Assessments**
	Mean intraocular pressure (IOP) at Screening, 1 month, 3 months, and 12 months	Tonometry
	Frequency of treatment-emergent adverse events	Document adverse events
	Frequency of device deficiencies at day of surgery	Document device deficiencies
	• **Uncorrected contrast sensitivity:**	
	Mean mesopic uncorrected contrast sensitivity at each contrast level at Screening, 1 month, 3 months, and 12 months.	Mesopic uncorrected contrast sensitivity
	• **BCVA:**	

	Mean BCVA at Screening, 1 week, 1 month, 3 months, and 12 months	Photopic distance BCVA
	Percentage of eyes with post-surgery BCVA more than two lines better that is two lines better, one line better, less than one line better and greater than one line worse, one line worse, two lines worse, more than two lines worse than pre-surgery BCVA at Screening, 1 week, 1 month, 3 months, and 12 months.	Photopic distance BCVA
	• **Quality of vision and quality of life (for both RSVP and SQDES):**	
	Frequency of dry eye syndrome at Screening, 1 month, 3 months, and 12 months.	Short questionnaire for dry eye syndrome (SQDES)
	Mean overall and subscale vision related quality of life score at Screening, 1 month, 3 months, and 12 months	Refractive Status and Vision Profile (RSVP) questionnaire

Planned Analysis	The main analyses for effectiveness and safety will be conducted when the last subject completes the 3 months post-surgery follow-up visit. Subjects will be followed-up for an additional 9 months (Day 330 to Day 375) for safety [redacted] assessments. The primary endpoint is the percentage of eyes with manifest refraction cylinder less than or equal to 0.5 D at 3 months. The following superiority hypothesis for the primary effectiveness objective will be tested at the 5% significance level (α= 0.05) (two-sided): H_0: $p_L = p_S$ vs H_1: $p_L \neq p_S$ where p_L and p_s refer to the percentage of eyes with manifest refraction cylinder within ($\leq$) 0.5 D in the Topography Guided LASIK arm and SMILE arm, respectively. It will be analyzed using the chi-square test, accounting for the correlation between eyes within subjects. The secondary effectiveness hypotheses will be relevant only if the primary effectiveness null hypothesis is rejected at the 5% significance level (two-sided). If the aforementioned null hypothesis is rejected, then the familywise Type I error rate for the secondary effectiveness endpoints will be controlled at the 5% significance level by using the Hochberg testing procedure. The superiority hypothesis for the first secondary effectiveness objective will be tested (two-sided): H_0: $\mu_L = \mu_S$ vs H_1: $\mu_L \neq \mu_S$ where μ_L and μ_s denote the mean manifest refraction cylinder in the Topography Guided LASIK arm and SMILE arm, respectively.

	The superiority hypothesis for the second secondary effectiveness objective will be tested (two-sided): H_0: $\mu_L = \mu_S$ vs H_1: $\mu_L \neq \mu_S$ where μ_L and μ_S denotes the mean UCVA in the Topography Guided LASIK arm and SMILE arm, respectively. The secondary effectiveness endpoints will be analyzed using the statistic of Donner, which accounts for the intraclass correlation between eyes within subjects. [redacted]. Descriptive statistics will be presented for [redacted] safety endpoints.
Sample Size Justification	Based on the assumed rates of 90% vs 80% of eyes with manifest refraction cylinder less than or equal to 0.5 D at 3 months for Topography Guided LASIK and SMILE, respectively, and a correlation between eyes within subject of 0.39, a sample size of 185 subjects (treated bilaterally) per treatment group will provide 90% power to reject the hypothesis for the primary effectiveness objective (based on the two sided 5% significance level). In total, 740 eyes from approximately 370 subjects are required for this study.

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3 ABBREVIATIONS

Abbreviation	Definition
ADE	Adverse device effect
AE	Adverse event
BCVA	Best corrective visual acuity
CFR	Code of Federal Regulations
CJD	Creutzfeldt-Jacob Disease
CRO	Clinical research organization
CSM	Clinical site manager
CTM	Clinical trial management
DBL	Database lock
eCRF	Electronic case report form
EDC	Electronic data capture
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	US Food and Drug Administration
FWHM	Full width at half maximum
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent ethics committee
IOP	Intraocular pressure
IRB	Institutional review board
ITT	Intent to treat
LASIK	Laser in situ keratomileusis
LCSM	Lead clinical site manager
LogMAR	Logarithm of the minimum angle of resolution
MedDRA	Medical dictionary for regulatory activities
MOP	Manual of procedures
MRSE	Manifest refraction spherical equivalent
PMMA	Polymethyl methacrylate
PRK	Photorefractive keratectomy
PRO	Patient-reported outcomes
RGP	Rigid gas permeable
RSVP	Refractive Status and Vision Profile
PT	Preferred term
SADE	Serious adverse device effect
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SMILE	Small incision lenticule extraction
SOC	System organ class
SOPs	Standard operating procedures
SQDES	Short questionnaire for dry eye syndrome

TEAE	Treatment emergent adverse events
UCVA	Uncorrected visual acuity
UNSV	Unscheduled visit
US	United states
VA	Visual acuity

4 GLOSSARY OF TERMS

Adverse Event (AE)	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 article). *Note: For subjects, this definition includes events related to the test article, the control article, or the procedures involved. For users or other persons, this definition is restricted to events related to the test article.*
Adverse Device Effect (ADE)	Adverse event related to the use of an investigational medical device (test article) or control article. *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 test article or control article.*
Device Deficiency	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. *Note: This definition includes malfunctions, use errors, and inadequate labeling.*
Malfunction	Failure of a medical device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling of the device. The intended performance of the device refers to the intended use for which the device is labeled or marketed.
Product Complaint	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.
Non-serious Adverse Event	Adverse event that does not meet the criteria for 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 that either resulted in: 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.

	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, or a congenital abnormality or birth defect. *Refer to Section 13 for additional SAEs.*
Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Serious Public Health Threat	Any event type which results in imminent risk of death, serious deterioration in state of health, or serious illness that requires prompt remedial action. This would include: Events that are of significant and unexpected nature such that they become alarming as a potential public health hazard, e.g., human immunodeficiency virus (HIV) or Creutzfeldt-Jacob Disease (CJD).
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: This definition includes slips, lapses, and mistakes. An unexpected physiological response of the subject does not in itself constitute a use error.*

5 AMENDMENTS

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

5.1 Amendment 1

Purpose of Amendment: To implement clarifications and revisions learned during the planning of the study.

Rationale: Ensures proper documentation for processes and procedures that will be executed during the study.

Current Study Status: This study is recruiting with 2 patients enrolled at one site in France at this point in time.

Case Report Form Revision Required: [ ] Yes [X] No

Informed Consent Modifications Required: [X] Yes [ ] No

Changes made to the Informed Consent are only applicable to Dr. Sanchez site in Mexico.

Applicable Investigators: [X] All [ ] Selected (list below)

Itemized Changes:

Sections	**Revisions**		**Rationale**
Protocol synopsis, Section 7.2 Section 10 Inclusion/ Exclusion	Text updated from: Subjects 18 years or older with myopia requiring manifest refraction spherical correction of -0.5 to -8.0 D and astigmatism correction of -0.75 to -5.0 D manifest refraction cylinder with at least 0.75	Text updated to: Subjects 18 years or older [subjects in Singapore must be 21 years of age or older and subjects in Korea must be upon completion of 19 years of age or older due to local regulations] with myopia	To be consistent with legal adult age for other participating countries such as Singapore and Korea.

Sections	Revisions		Rationale
criteria	D of corneal astigmatism.	requiring optical infinity adjusted manifest refraction spherical correction of -0.5 to -8.0 D and astigmatism correction of -0.75 to -5.0 D manifest refraction cylinder with at least 0.75 D of corneal astigmatism.	
Protocol synopsis Table 11.1 and section 11.2 Section 12.1.2	Text updated from: Microkeratome laser.	Text updated to: Microkeratome blade.	For accuracy; microkeratome is not a laser.
Protocol synopsis Section 7.2 Section 10	Text updated from: Myopia requiring (a) refractive error correction of -0.5 to -8.0 D manifest refraction sphere with (b) astigmatism correction of -0.75 to -5.0 D manifest refraction cylinder and (c) at least 0.75 D of corneal astigmatism.	Text updated to: Myopia requiring (a) refractive error correction of -0.5 to -8.0 D optical infinity adjusted manifest refraction sphere with (b) astigmatism correction of -0.75 to -5.0 D manifest refraction cylinder and (c) at least 0.75 D of corneal astigmatism.	To emphasize that the inclusion criterion is based on the optical infinity adjusted manifest refraction.
Protocol synopsis, Section 10.1	Text updated from: Spherical equivalent difference of ≤ 0.5 D between the manifest and cycloplegic refraction outcomes.	Text updated to: Spherical equivalent difference of ≤ 0.5 D between the optical infinity adjusted manifest and optical infinity adjusted cycloplegic refraction outcomes.	To emphasize that the inclusion criterion is based on the optical infinity adjusted refraction.
Protocol synopsis, Section	Text updated from: Spherical equivalent difference of ≤ 0.5 D	Text updated to: Spherical equivalent difference of ≤ 0.5 D between	To emphasize that the inclusion criterion is based on the optical

Sections	Revisions		Rationale
10.1	between refractive error corrections for a minimum of 12 months prior to surgery verified by consecutive refractions and/or medical records or prescription history.	refractive error corrections for a minimum of 12 months prior to surgery verified by consecutive optical infinity adjusted refractions and/or medical records or prescription history.	infinity adjusted manifest refraction.
Protocol synopsis, Section 10.1	Text updated from: For contact lens wearers - Spherical equivalent difference of ≤ 0.5 D between outcomes from consecutive manifest refraction outcomes performed at least 7 days apart after the contact lens wear has been stopped for the appropriate period of time as follows.	Text updated to: For contact lens wearers - Spherical equivalent difference of ≤ 0.5 D between outcomes from consecutive optical infinity adjusted manifest refraction outcomes performed at least 7 days apart after the contact lens wear has been stopped for the appropriate period of time as follows.	To emphasize that the inclusion criterion is based on the optical infinity adjusted refraction.
Protocol synopsis, Section 10.2	Text updated from: Manifest refraction astigmatism that is more than 1.00 D than the topolyzer astigmatism assessed by Topolyzer Vario.	Text updated to: Manifest refraction astigmatism that is more than 1.00 D than the topolyzer astigmatism assessed by Contoura software.	The data from the Topolyzer Vario is used to derive the data provided by the Contoura Software, but data from the Contoura software is more relevant to this criterion.
[redacted]			

Sections	Revisions	Rationale
[redacted]		

Sections	Revisions	Rationale
[redacted]		

Sections	Revisions	Rationale
[redacted]		

Sections	Revisions		Rationale
[redacted]			
Protocol synopsis, Section 8.5.2	Text updated from: Mean intraocular pressure (IOP).	Text updated to:: Mean intraocular pressure (IOP) at Screening, 1 month, 3 months, and 12 months.	To specify the relevant time points.
Protocol synopsis, Section 8.5.2	Below text was deleted: • ~~Frequency of slit lamp findings~~ • ~~Frequency of dilated fundus findings~~		Deleted as no descriptive statistics will be performed for either assessment, only listings provided.
Protocol synopsis, Section 8.5.2	Text updated from: Frequency of adverse events.	Text updated to: Frequency of treatment-emergent adverse events.	To clarify that the analysis will be around AEs which occur after surgery.
Protocol synopsis, Section 8.5.2	Text updated from: Mean mesopic uncorrected contrast sensitivity at each contrast level at each study visit.	Text updated to: Mean mesopic uncorrected contrast sensitivity at each contrast level at Screening, 1 month, 3 months, and 12 months.	To specify the relevant time points.
Protocol synopsis, Section 8.5.2	Text updated from: Mean BCVA at each study visit.	Text updated to: Mean BCVA at Screening, 1 week, 1 month, 3 months, and 12 months.	To specify the relevant time points.
Protocol synopsis, Section 8.5.2	Text updated from: Percentage of eyes with post-surgery BCVA that is two lines better, one line better, one line worse, two lines worse than pre-surgery	Text updated to: Percentage of eyes with post-surgery BCVA more than two lines better that is two lines better, one line better, less than one line	To specify the relevant time points and added more categories for completeness.

Sections	Revisions		Rationale
	BCVA at each study visit.	better and greater than one line worse, one line worse, two lines worse, more than two lines worse than pre surgery BCVA at Screening, 1 week, 1 month, 3 months, and 12 months.	
Protocol synopsis, Section 8.5.2	Text updated from: Frequency of dry eye syndrome at each study visit.	Text updated to: Frequency of dry eye syndrome at Screening, 1 month, 3 months, and 12 months.	To specify the relevant time points.
Protocol synopsis, Section 8.5.2	Text updated from: Mean overall and subscale vision related quality of life score at each study visit.	Text updated to: Mean overall and subscale vision related quality of life score at Screening, 1 month, 3 months, and 12 months.	To specify the relevant time points.
Protocol synopsis, Section 15.4.1.1	Text updated from: H_0: $p_L \leq p_S$ H_1: $p_L > p_S$	Text updated to: H_0: $p_L = p_S$ H_1: $p_L \neq p_S$	To be consistent with the objectives of the study.
Protocol synopsis, Section 15.4.2.1	Text updated from: H_0: $\mu_L \geq \mu_S$ H_1: $\mu_L < \mu_S$ where μ_L and μs denote the mean UCVA in the Topography Guided LASIK arm and SMILE arm, respectively.	Text updated to: H_0: $\mu_L = \mu_S$ H_1: $\mu_L \neq \mu_S$ where μ_L and μs denote the mean manifest refraction cylinder in the Topography Guided LASIK arm and SMILE arm, respectively.	To be consistent with the study objectives.
Protocol synopsis, Section 15.4.2.1	Text updated from: H_0: $\mu_L \geq \mu_S$ H_1: $\mu_L < \mu_S$	Text updated to: H_0: $\mu_L = \mu_S$ H_1: $\mu_L \neq \mu_S$	To be consistent with the study objectives.

Sections	Revisions		Rationale
	where μ_L and μs denote the mean manifest refraction cylinder in the Topography Guided LASIK arm and SMILE arm, respectively.	where μ_L and μs denote the mean UCVA in the Topography Guided LASIK arm and SMILE arm, respectively.	
Section 7.2	Text updated from: Subjects are randomized 1:1 by investigational site on day of Pre-Surgery Visit to undergo bilateral surgery with either Topography Guided LASIK or SMILE scheduled on Day 0.	Text updated to: Subjects are randomized 1:1 by investigational site during the Pre-Surgery period to undergo bilateral surgery with either Topography Guided LASIK or SMILE scheduled on Day 0.	To clarify randomization may be over a period versus on a single day.
Section 12.1.1	Text updated from: Measure manifest refraction.	Text updated to: Measure manifest refraction at 4 meters and adjust for optical infinity.	To emphasize that the manifest refraction at 4 meters needs to be converted to optical infinity.
Section 12.1.1	Text updated from: Perform pupillometry under mesopic conditions using an infrared pupilometer or any other instrument.	Text updated to: Perform pupillometry under mesopic conditions using an infrared pupilometer.	For consistency of measurement.
Section 12.1.1	Text updated from: Perform cycloplegic refraction using a phoropter or trial lenses.	Text updated to: Perform cycloplegic refraction using a phoropter and adjust for optical infinity.	Trial frame refraction could be unreliable.
Section 12.1.1	Below text was added: *NOTE: A contact lens wearer is defined as someone who has worn contact lenses within 3 months prior to the Pre-Surgery Visit.*		To clarify the definition of a contact lens wearer.

Sections	Revisions		Rationale
Section 12.1.1	Below text was deleted: ~~A subject reschedules surgery and this rescheduling result in the pre-surgery/ screening assessments falling outside of the 45 day screening window (Day-45 to Day -1). The subject must not be re-randomized and must not be assigned a new subject number.~~		Not applicable.
Section 12.1.2	Below text was added: *Record the surgeon who performed the surgery. No more than two surgeons per site should perform a type of surgery.*		To minimize variability in outcomes from having too many surgeons performing a procedure.
Section 12.1.2	Text updated from: *NOTE*: Although the surgery is planned to be bilateral, in the case where the Investigator decides to not perform the surgery on the second eye on the same day the first eye is treated, the Investigator may treat the second eye at a later date while the subject is still in the study. In this case, AEs will also be collected for this eye.	Text updated to: *NOTE*: Although the surgery is planned to be bilateral, in the case where the Investigator decides to not perform the surgery on the second eye on the same day the first eye is treated, the Investigator may treat the second eye at a later date while the subject is still in the study. In this case, effectiveness and safety assessments will be conducted as per post-surgery follow up visits if the fellow eye is treated with the study treatment. If the fellow eye is not treated at all or treated with a non-study treatment, AEs will only be collected for this eye. Refer to the MOP Table 4-1 for further details.	To comprehensively outline data to be collected if both eyes do not have surgery on the same day or a non-study treatment is performed.
Section 12.1.3	Text updated from: Measure manifest refraction	Text updated to: Measure manifest refraction	To emphasize that the manifest refraction at 4

Sections	Revisions		Rationale
	at the Week 1, Month 1, 3 and 12 visits.	at 4 meters and adjust for optical infinity at the Week 1, Month 1, 3 and 12 visits.	meters needs to be converted to optical infinity.
Section 13.3	Text updated from: The completed form will be then faxed or emailed to the Study Sponsor at [redacted] according to the timelines outlined above; however, the reported information must be entered into the EDC system once it becomes operational.	Text updated to: The completed form will be then emailed to the Study Sponsor at [redacted] according to the timelines outlined above; however, the reported information must be entered into the EDC system once it becomes operational.	The safety fax number is no longer operational.
Section 15.6	Text updated from: The next largest p-value ($p_{[1]}$) will then be checked to see if it is less than the critical value (α=0.025).	Text updated to: The next largest p-value ($p_{[1]}$) will then be checked to see if it is less than the critical value ($\alpha/2$=0.025).	To clarify the alpha value for the next largest p-value (i.e. $p_{[1]} < \alpha/2$).
Section 15.7	Text updated from: Ocular and non-ocular treatment emergent AEs will be summarized separately by SOC and PT.	Text updated to: Ocular treatment emergent AEs will be summarized separately by SOC and PT.	Non-ocular treatment emergent AEs will not be summarized.
Section 15.7	Text updated from: Although the surgery is planned to be bilateral, in the case where the Investigator decides to not perform the surgery on the second eye, AEs will be collected for this eye.	Text updated to: Although the surgery is planned to be bilateral, the investigator may decide to not perform the surgery on the second eye on the same day as the first eye. In the following scenarios, if during the 12-month post-surgery study period:	To comprehensively outline data to be collected if both eyes do not have surgery on the same day or a non-study treatment is performed.

Sections	Revisions		Rationale
		• no surgery is performed on the second eye • surgery is performed on the second eye using a non-study surgery only AEs will be collected for the second eye	
Section 15.7	Text updated from: Other safety evaluations include slit lamp findings IOP, dilated fundus findings and PRO Questionnaires (RSVP, SQDES).	Text updated to: Other safety evaluations include slit lamp findings, IOP, surgical problems, dilated fundus findings and PRO Questionnaires (RSVP, SQDES).	To take care of an omission (surgical problems).
Section 15.7	Below text was deleted: ~~All other information collected (e.g., severity or relationship to study treatment) will be summarized and listed as appropriate. Summary tables will also be presented for the subset of AEs suspected to be treatment related~~.		The analysis for adverse events has been revised to make it more concise (e.g. removal of analysis for severity or relationship to study treatment).
Section 15.7	Below text was added: *For SQDES, a subject is defined as having dry eye syndrome if there was occurrence of both dryness and irritation of the eyes either constantly or often (that is, severe symptoms) or a report of a previous clinical diagnosis of dry eye syndrome.*		To outline how dry eye is defined from the SQDES.
Section 15.7	Below text was added: *Information from the nomogram, if one is used, and surgical report will also be provided.*		To specify that data from nomogram use will be provided.

6 SCHEDULE OF VISITS

Table 6–1 Schedule of Assessments

	Level	Pre-surgery	Surgery[h]	Post-Surgery					UNSV[j]
Procedure	**Subject/Eye**	**Screening (Day -45 to Day -1)**	**Day 0[a]**	**Day 1**	**Week 1 (Day 5 to Day 9)**	**Month 1 (Day 21 to Day 35)**	**Month 3 (Day 70 to Day 98)**	**Month 12[k] (Day 330 to Day 375)**	**N/A**
Informed consent[b]	S	X							
Demographics	S	X							
Medical/ocular history/concomitant medications	S/E	X	X	X	X	X	X	X	X
Inclusion/exclusion criteria	S/E	X	X						
Pregnancy test[c, f]	S	X							
RSVP questionnaire[f]	S	X				X	X	X	
SQDES[f]	S	X				X	X	X	
Photopic Distance UCVA[e, f]	E	X		X	X	X	X	X	X
Mesopic Uncorrected contrast sensitivity[f]	E	X				X	X	X	
Manifest refraction[f]	E	X			X	X	X	X	X
Photopic Distance BCVA[e, f]	E	X			X	X	X	X	
Pupillometry[f]	E	X							
Keratometry[d, f]	E	X							
Topography[d, f]	E	X				X	X	X	
Pachymetry[f]	E	X							
Axial length[f]	E	X							
Slit lamp examination[f]	E	X	X	X	X	X	X	X	X
IOP[f]	E	X				X	X	X	X
Cycloplegic refraction	E	X							

	Level	Pre-surgery	Surgery[h]	Post-Surgery					UNSV[j]
Procedure	**Subject/Eye**	**Screening (Day -45 to Day -1)**	**Day 0[a]**	**Day 1**	**Week 1 (Day 5 to Day 9)**	**Month 1 (Day 21 to Day 35)**	**Month 3 (Day 70 to Day 98)**	**Month 12[k] (Day 330 to Day 375)**	**N/A**
Dilated fundus examination	E	X						X	X
Randomization[g]	S	X							
LASIK or SMILE	E		X						
Adverse events[i]	S/E	X	X	X	X	X	X	X	X
Device deficiencies	NA		X						
Problems during surgery[l]	S/E		X						
Other procedures during surgery	S/E		X						

a. Relevant measurements from the Pre Surgery Visit should be repeated prior to surgery if needed to provide accurate Baseline measurements pre-surgery. This includes the second optical infinity adjusted manifest refraction to demonstrate refractive stability in contact lens wearers as outlined in Inclusion Criteria 9.
b. All subjects must consent to bilateral treatment; both eyes are to be treated on the day of surgery.
c. Women of child-bearing potential only.
d. Keratometry and corneal topography must be done prior to IOP and pachymetry.
e. Distance UCVA and BCVA will be measured at each visit using an ETDRS chart at 3 meters (10 feet) or 4 meters (13 feet). For subjects who cannot read English letters, a numerical, Tumbling E or a Landolt C logMAR chart can be used.
f. These tests must be done prior to the instillation of dilating or cylcoplegic agents. [redacted]
g. Randomization must be completed following all screening procedures and confirmation of subject eligibility during the Pre-Surgery visit.
h. Surgery must occur within 45 calendar days from the Pre Surgery Visit. Pre Surgery Visit and Surgery Visit cannot occur on the same day.
i. AEs should be collected from time of consent.
j. At an unscheduled visit, safety assessments and other assessments needed as per investigator's discretion may be performed.
k. If a subject discontinues early, these procedures should be performed before exiting the subject. Month 12 (Final Visit) procedures should be performed at the last available visit, if at all possible.
l. Includes intraoperative complications.

RSVP=Refractive Status and Vision Profile, SQDES=short questionnaire for dry eye syndrome, UCVA=uncorrected visual acuity, BCVA=best corrective visual acuity, IOP=intraocular pressure, LASIK=Laser in situ keratomileusis, SMILE=Small incision lenticule extraction, ETDRS=Early Treatment Diabetic Retinopathy Study, LogMAR=Logarithm of the Minimum Angle of Resolution, UNSV= unscheduled visit.

7 INTRODUCTION

7.1 Background

Laser in situ keratomileusis (LASIK), a refractive surgery procedure, has been in use for over 20 years for the correction of refractive error. The refractive error correction is achieved by the ablation of the required amount of corneal stromal tissue by an excimer laser. The WaveLight® EX500 excimer laser system is the most recent Alcon excimer laser (Sugar 2002).

Treatment planning for LASIK is done with the refractive error correction data and with or without other patient specific pre-surgical data. The use of patient specific pre-surgical data offers customization of LASIK. For example, with Topography Guided LASIK, corneal height data is used to plan the LASIK surgery. Topography Guided LASIK has been available outside the US since 2003 and had been used primarily for the treatment of irregular or diseased corneas that either had never been treated or had been previously treated (Knorz 2000, Kymionis 2004, Holland 2013). More recently, Topography Guided LASIK is being used as a primary treatment for regular corneas. A study by Stulting et. al showed that Topography Guided LASIK as a primary treatment for myopia with or without astigmatism was safe and effective in subjects who had regular corneas (Stulting 2016).

Small incision lenticular extraction (SMILE) is the newest refractive surgery procedure that is being used for the correction of myopia with or without astigmatism. The Zeiss VisuMax laser keratome ophthalmic surgical laser, a femtosecond laser, is the only marketed laser for the SMILE procedure. The VisuMax creates a lenticule of corneal tissue and a small (<4mm) channel through which the lenticule is removed. The removal of the lenticule results in correction of the refractive error. Refractive error correction data but not corneal height data is used in the treatment planning of SMILE. Data in the literature for SMILE is showing good outcomes for safety and effectiveness (Ivarsen 2014, Moshirfar 2015).

Fundamental difference between the EX500 and VisuMax are that the EX500 provides centration and cyclotorsion control, and the VisuMax does not. Centration and cyclotorsion control allow for better correction of astigmatism. Additionally, use of the topography data for treatment planning of Topography Guided data should allow for better correction of astigmatism compared to SMILE for which topography data is not used for treatment planning.

Myopia with astigmatism is a common refractive error (MarketScope 2015), and this study is designed to determine if the Topography Guided LASIK with the EX500 is superior to

SMILE with the VisuMax for the correction of astigmatism in subjects with myopia and astigmatism.

7.2 Clinical Study Design

This is a prospective, parallel group, multi-center, randomized, observer masked study comparing topography guided LASIK vs. SMILE, both of which are commercially available in the countries where the study is being conducted.

Potential subjects are screened and up to 450 subjects (225 subjects per treatment group) are enrolled at approximately 8 study sites in order to achieve about 185 evaluable subjects per treatment group. In total, 740 eyes from approximately 370 subjects are required for this study.

Subjects (18 years or older [subjects in Singapore must be 21 years of age or older and subjects in Korea must be upon completion of 19 years of age or older due to local regulations]) with myopia requiring refractive error correction of -0.5 to -8.0 D optical infinity adjusted manifest refraction sphere and astigmatism correction of -0.75 to -5.0 D manifest refraction cylinder and at least 0.75 D of corneal astigmatism in both eyes, and fulfilling all other eligibility criteria, are enrolled into the study and undergo pre-surgery screening. Among other exclusion criteria, subjects are excluded if they have a history or evidence of active or inactive corneal disease, and systemic disease and medications that may confound wound healing.

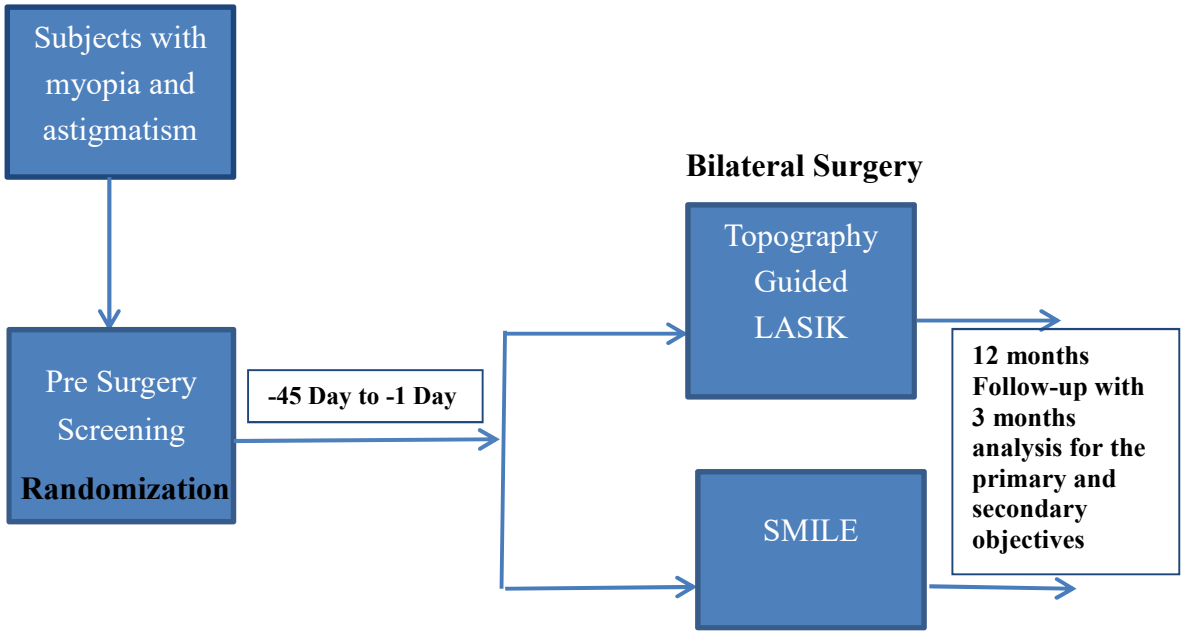
Qualifying subjects are required to attend a total of 7 visits over a period of up to 15 months (See Section 9.1).

Subjects are randomized 1:1 by investigational site during the Pre-Surgery period to undergo bilateral surgery with either Topography Guided LASIK or SMILE scheduled on Day 0.

The main analyses for effectiveness and safety are conducted when the last subject completes the 3 months Post-Surgery follow-up Visit. Subjects are followed-up for an additional 9 months (Day 330 to Day 375) for safety and [redacted] assessments. Final data analyses are conducted at study completion.

An overview of the study design is presented in Figure 7–1.

Figure 7–1 Study Design



Site personnel performing the manifest refraction subjective assessment and all uncorrected visual acuity (UCVA) testing after randomization are to remain masked with regard to treatment assignment until after the final database lock (DBL). Alcon and other site personnel [e.g., nurses and technicians involved with the surgery, site personnel entering data in the electronic case report forms (eCRF), site personnel administering other study related procedures, e.g. Refractive Status and Vision Profile (RSVP) and short questionnaire for dry eye syndrome (SQDES) questionnaires] must not reveal the treatment assignment to masked site personnel at any time during the study. Refer to Section 13.5 for unmasking of study information.

8 CLINICAL STUDY OBJECTIVES

8.1 Primary Objective

The primary objective of the study is to demonstrate that Topography Guided LASIK is superior to SMILE in the percentage of eyes with manifest refraction cylinder ≤ 0.5 D at 3 months.

8.2 Secondary Objectives

The secondary objectives of the study are:

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

8.4 Safety Objectives

The safety objectives of the study are:

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

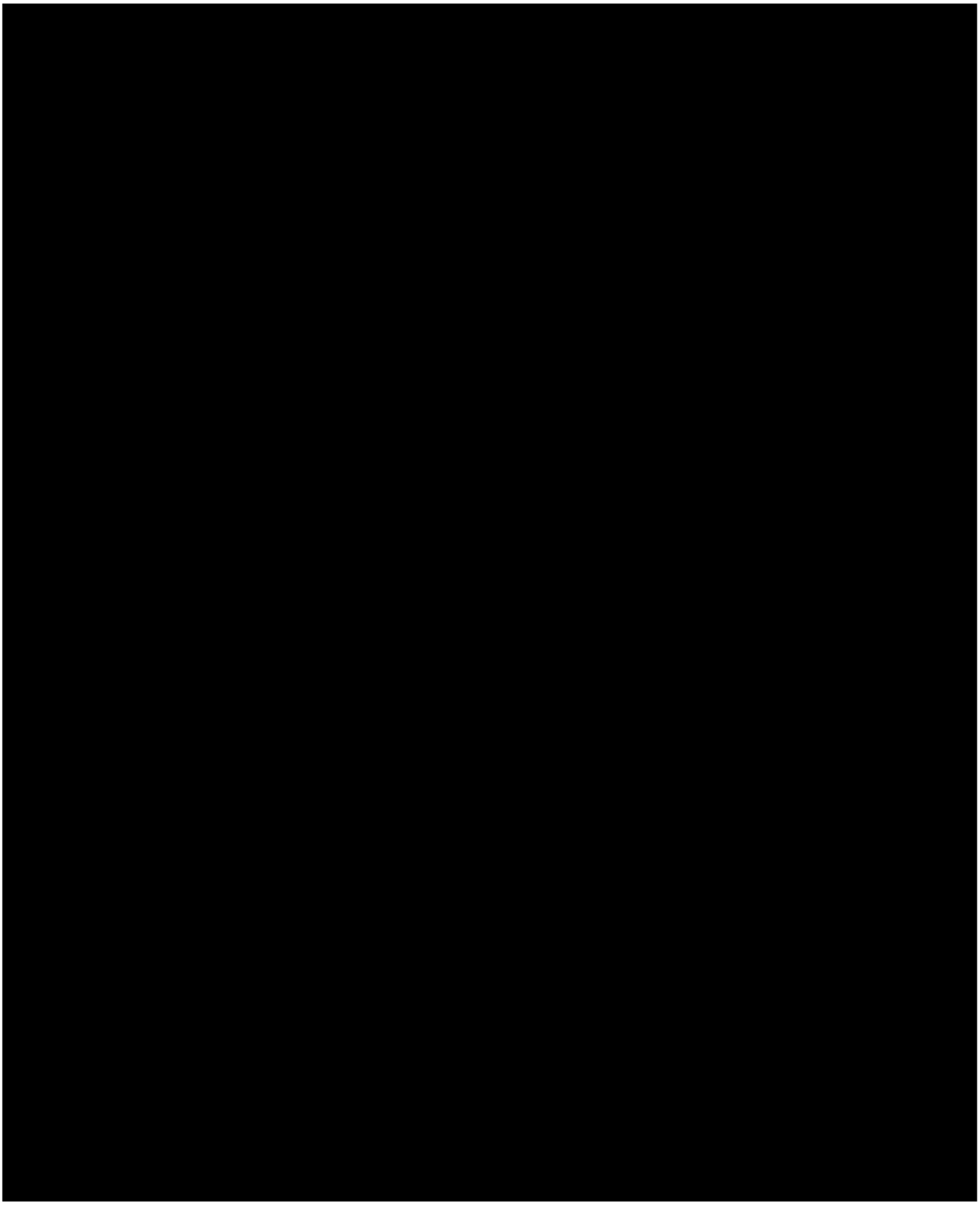
8.5 Study Endpoints

8.5.1 Effectiveness Endpoints

The primary effectiveness endpoint is the percentage of eyes with manifest refraction cylinder $\leq$ 0.5 D at 3 months.

Secondary effectiveness endpoints are as follows:

- Mean manifest refraction cylinder at 3 months.
- Mean UCVA at 3 months.



[redacted]

8.5.2 Safety Endpoints

The secondary safety endpoints are as follows:

- Frequency of treatment-emergent AEs.
- Mean intraocular pressure (IOP) at Screening, 1 month, 3 months, and 12 months.
- Frequency of device deficiencies
- BCVA:
  - Mean BCVA at Screening, 1 week, 1 month, 3 months, and 12 months.
  - Percentage of eyes with post-surgery BCVA more than two lines better, two lines better, one line better, less than one line better and greater than one line

worse, one line worse, two lines worse, more than two lines worse than pre-surgery BCVA at Screening, 1 week, 1 month, 3 months, and 12 months.

- Uncorrected contrast sensitivity:
  - Mean mesopic uncorrected contrast sensitivity at each contrast level at Screening, 1 month, 3 months, and 12 months.
- Quality of vision and quality of life (for both RSVP and SQDES):
  - RSVP: Mean overall and subscale vision related quality of life score at Screening, 1 month, 3 months, and 12 months.
  - SQDES: Frequency of dry eye syndrome at Screening, 1 month, 3 months, and 12 months.

9 INVESTIGATIONAL PLAN

9.1 Outline of Clinical Study

In this prospective, parallel group, multi-center, group randomized, observer masked study, subjects requiring refractive correction of myopia and astigmatism will be screened. If the protocol inclusion and exclusion criteria are met, subjects will be invited to participate. An institutional review board (IRB) or independent ethics committee (IEC) approved Informed Consent Document will be signed prior to initiation of any study related procedures.

The intended treatment is bilateral (i.e. surgery in both eyes) Topography Guided LASIK or SMILE. It is planned that each subject will have surgery on both eyes on the same day. Subjects participating in this study will attend a total of 7 visits for both eyes as follows : Pre-Surgery Visit (Day -45 to Day -1), Surgery Visit (Day 0), and 5 Post-Surgery follow-up Visits (on Day 1, Week 1, Month 1, Month 3, and Month 12, respectively). Each subject is expected to complete the study in approximately 12 months (Day 330 to Day 375) after the Surgery Visit (Day 0). The total expected duration of each subject's participation is up to 15 months (Pre-surgery to Month 12 post-surgery). Refer to Figure 7–1 Study Design for a study outline diagram.

Re-treatment procedures are not allowed for any enrolled study eye. Unscheduled visits may occur as needed.

9.2 Rationale for Study Design

This study is designed to test the differences in astigmatism treatment between Topography Guided LASIK and SMILE. The difference in astigmatism treatment between the two refractive surgeries is hypothesized to be related to the differences in the lasers and treatment planning. With Topography Guided LASIK, the cyclotorsion control and the centration features of the EX500 laser and the use of topography data for treatment planning should enhance the accuracy of astigmatism treatment. In contrast, with SMILE, the VisuMax Laser keratome does not have cyclotorsion control or centration nor is topography data used for treatment planning. The study population includes subjects with myopia and astigmatism because this is a prevalent refractive error (Market Scope 2015) and is an approved indication for both lasers. (refer to Procedure's and Operator's or User's manual).

9.2.1 Procedures Per Study Visit

The clinical study procedures to be conducted at each study visit are listed in Table 6–1 and detailed in Section 12. Further details on the actual assessments are provided in full in the Manual of Procedures (MOP) for this study. A brief summary of the procedures performed by visit is provided here.

NOTE: All assessments performed at the eye level as listed in Table 6–1 will be done monocularly.

At the Pre-Surgery Visit (Day -45 to Day -1) the subject will sign the informed consent form (ICF). Standard procedures will be performed to determine subject eligibility. The subject will be evaluated against all entry criteria. The subject status (e.g, continuing or screen failure) will be documented and the subject's data will be entered into electronic data capture (EDC) at the time of consent to assign subject number. For continuing subjects:

1. The subject will be randomized to Topography Guided LASIK or SMILE in the EDC system.
2. The subject will be provided with pre-surgery information and medications in accordance with investigational site's standard of care.
3. The Investigator will consider any unresolved complications or events in either eye prior to surgery.
4. The Surgery Visit (Day 0) will be scheduled to occur within 45 calendar days of the Pre-Surgery Visit (Screening).

a. Inclusion/ exclusion criteria will be reviewed prior to surgery to ensure subjects are still eligible for the study (see Section 10.1 and 10.2). Subjects failing to pass entry criteria will not be re-screened. If a subject is excluded post-randomization and prior to the laser touching the eye (defined as once flap creation is initiated for LASIK and once laser touches the eye for SMILE), the subject should be discontinued from participation in the study.

b. The surgery will be performed on both eyes. The subject will be prepared for surgery in accordance with site specific operating procedures.

5. After surgery, the ocular and/or non-ocular concomitant medication will be administered as per Investigator's standard procedures.

6. The subject will return to the investigative site to complete post-surgery follow-up assessments. At all Post-Surgery follow-up Visits (Day 1, Week 1, Month 1, Month 3, Month 12), effectiveness and safety assessments will be performed. No secondary surgical intervention or re-treatment procedures are allowed in this study.

NOTES:

- AEs will be recorded at each visit and reported from the time of informed consent for all subjects in the study.

- Patient-reported outcomes (PROs) will be measured in the study to assess the incidence of symptoms and/or post-surgery change in symptoms from pre-surgery status via subjective ratings. These will consist of the RSVP questionnaire (Vitale 2000), a validated instrument for the measurement of vision related quality of life, and SQDES for the diagnosis of dry eye (Gulati 2006).

9.3 Risk Benefit Assessment

9.3.1 Potential Risks

LASIK and SMILE

The risks of LASIK are well known, however, the risks of SMILE are still being investigated because it is a newer procedure (Sekundo 2011, Solomon 2009).

Some risks are similar for LASIK and SMILE. First, the laser could malfunction and the procedure would need to be stopped before completion. If this happens, a second surgical procedure may be needed. Second, LASIK and SMILE may not fully correct, or may overcorrect the refractive error, leaving the subject with some residual refractive error.

Undercorrection or overcorrection may be treatable by performing a second refractive surgery. Additionally, decentration of the treatment as a result of off-center placement of the laser may occur, which could affect the outcome and consequently the subject's vision.

LASIK

LASIK involves the creation of a corneal flap, and the following complications may infrequently occur: decentered or dislocated flap, debris under the flap, flap tears, completely dissected flap (free flap), and flap that's too thin (Shortt 2013). These complications are managed during the surgery which may include switching to another surgical procedure such as photorefractive keratectomy (PRK).

Serious complications leading to significant permanent visual loss such as infections and corneal ectasia occur rarely with LASIK; however, complications such as chronic dry eye, starbursts, glare, halos and reduced contrast sensitivity occur more frequently (Sugar 2002). Some of these complications, such as corneal ectasia and dry eyes, may be minimized by selecting suitable subjects for LASIK. To minimize the risk of corneal ectasia, subjects with suspicious pre-surgery topographies and thin corneas should not be treated with LASIK. To minimize the risk of chronic dry eye, existing dry eye should be treated prior to the LASIK. It is more challenging to minimize the visual symptoms risks such as glare, halos, starbursts, and reduced contrast sensitivity because these complications are inherent to how refractive surgery works. Subject education of the possibility of having these types of complications is key.

The risks of Topography Guided LASIK are not known to be different than the risks of other methods of LASIK.

SMILE

Ivarsen et al (Ivarsen 2014) performed a study to evaluate the safety of SMILE. A total of 1574 eyes were treated with SMILE and followed for 3 months. In this study, the pre-surgery complications reported in at least one eye were as follows:

- Abrasion at the incision
- Lenticule extraction difficulties
- Minor tear at the incision
- Suction loss
- Central abrasion
- Cap perforation
- Major tear

- Impossible lenticule extraction

The post-surgery complications reported in at least one eye were as follows:

- Haze
- Dry surface
- Epithelial islands at incision
- Fiber in the interface
- Infiltrates/keratitis
- Monocular ghost images
- Interface inflammation

In general, these complications may be minimized by sufficient proficiency in performing the SMILE procedure, and laser setting optimization.

9.3.2 Potential Benefits

LASIK and SMILE

A key benefit of LASIK and SMILE is the correction of the subject's refractive error resulting in the elimination or reduction of the need for glasses or contact lenses. Subjects who have spent most of their lives dependent on glasses really enjoy reducing or eliminating this dependence. Contact lens wearers who have LASIK or SMILE benefit from the convenience of not having to maintain a contact lens regimen. One study showed that contact lens wearers who had LASIK were very satisfied after the surgery (Price 2016).

9.3.3 Risk Benefit Assessment

Overall, the benefits of LASIK and SMILE outweigh the risks. Several strategies are employed to minimize the risks associated with either surgery. Stringent inclusion/exclusion criteria are utilized during the subject screening process to assure that potential subjects are acceptable candidates. Post-Surgery follow-up Visits are scheduled at regular intervals to monitor improvement in vision, as well as to monitor subject safety. Subjects are given detailed post-surgery instructions to minimize discomfort and post-surgery complications and are instructed to call their doctor immediately if any problems occur. In addition, extensive technical training of surgeons and clinical staff in the proper use of surgical equipment and techniques used with these procedures is employed to reduce the risks of user error.

10 SUBJECT POPULATION

Subjects ≥ 18 years of age [subjects in Singapore must be 21 years of age or older and subjects in Korea must be upon completion of 19 years of age or older due to local regulations] with myopia requiring refractive error correction of -0.5 to -8.0 D optical infinity adjusted manifest sphere and astigmatism correction of -0.75 to -5.0 D manifest refraction cylinder and at least 0.75 D of corneal astigmatism in both eyes, and fulfilling all other eligibility criteria in Section 10.1 and Section 10.2, will be enrolled into the study.

Within a 45 calendar day window prior to surgery, subjects will be screened and randomized in a 1:1 manner to receive EX500 for Topography Guided LASIK or VisuMax for SMILE.

All ocular related inclusion and exclusion criteria apply to both eyes. It is estimated that approximately 6 months will be required to complete enrollment for this study.

NOTE: No one site will randomize more than 25% of the total subject cohort and enrolment will be competitive in order to complete enrolment on time.

10.1 Inclusion Criteria

Below is a list of inclusion criteria. Ocular criteria must be met in both eyes.

1. Subjects 18 years of age or older at the time of informed consent [subjects in Singapore must be 21 years of age or older and subjects in Korea must be upon completion of 19 years of age or older due to local regulations]
2. Able to comprehend and sign an informed consent form (ICF).
3. Willing and able to complete all post-surgery visits.
4. Myopia requiring (a) refractive error correction of -0.5 to -8.0 D optical infinity adjusted manifest refraction sphere with (b) astigmatism correction of -0.75 to -5.0 D manifest refraction cylinder and (c) at least 0.75 D of corneal astigmatism.
5. Intended treatment is targeted for emmetropia.
6. Pre-surgery BCVA of 0 logarithm of the minimum angle of resolution (logMAR) (20/20) or better.

7. Spherical equivalent difference of ≤ 0.5 D between the optical infinity adjusted manifest and optical infinity adjusted cycloplegic refraction outcomes.

8. Spherical equivalent difference of ≤ 0.5 D between refractive error corrections for a minimum of 12 months prior to surgery verified by consecutive optical infinity adjusted refractions and/or medical records or prescription history.

9. For contact lens wearers - Spherical equivalent difference of ≤ 0.5 D between outcomes from consecutive optical infinity adjusted manifest refraction outcomes performed at least 7 days apart after the contact lens wear has been stopped for the appropriate period of time as follows:

   - Soft (extended and daily wear) = 3 days
   - Rigid Gas Permeable (RGP) or Toric = 2 weeks
   - Hard polymethyl methacrylate (PMMA) = 3 weeks

10.2 Exclusion Criteria

Below is a list of exclusion criteria. Ocular criteria must not be met in either eye.

1. Pregnancy or lactation, current or planned, during the course of the study.

2. Manifest refraction astigmatism that is more than 1.00 D than the topolyzer astigmatism assessed by Contoura software.

3. Mixed astigmatism refractive error.

4. Degenerations of structure of the cornea including diagnosed keratoconus, forme fruste kerataconus or pellucid marginal degeneration.

5. Dry eye as identified by the SQDES.

6. A calculated residual stromal bed thickness that is less than 250 µm.

7. History or evidence of active or inactive corneal or other anterior segment disease (e.g, herpes simplex keratitis, recurrent erosion syndrome).

8. Diagnosed advanced glaucoma.

9. Uncontrolled diabetes.

10. Nystagmus or any other condition that would prevent a steady gaze during the treatment.

11. Previous intraocular or corneal surgery.

12. Weakened immune system, including diagnosed collagen vascular, autoimmune or immunodeficiency disease.

13. Systemic medications that may affect corneal healing including, but not limited to steroids, antimetabolites, immune response modifying drugs, etc.

14. Presence or history of any condition or finding that makes the subject unsuitable as a candidate for refractive surgery or study participation or may confound the outcome of the study, in the opinion of the Investigator.

15. Any subject currently participating in another investigational drug or device study that may confound the results of this investigation.

16. A known sensitivity to medications used during the study.

11 TREATMENT

The treatment in this study involves the use of either the EX500 for Topography Guided LASIK or the VisuMax for SMILE as described in Table 11–1.

For the purposes of this study, treatment will be considered to have begun once the flap creation is initiated for LASIK and once the laser touches the eye for SMILE.

Table 11–1 Treatments

	Test Article: Wavelight EX500 for Topography Guided LASIK	**Control Article:** Zeiss VisuMax for SMILE
Administration	The EX500 laser is used to ablate the corneal stroma which results in the refractive error correction. Prior to ablation, the corneal flap may be created with a femtosecond laser or microkeratome blade at the surgeon's discretion. Treatment planning will be based on topography.	The VisuMax Laser keratome is used to create a lenticule in the corneal stroma and a channel for the removal of the lenticule. Removal of the lenticule results in the refractive error correction.
Duration of treatment	The treatment is intended to last the subject's lifetime.	The treatment is intended to last the subject's lifetime.

The Investigator will be responsible for ensuring that the EX500 and VisuMax Laser Systems are used in accordance with their indications and procedural guidance provided in their respective Operator's (or User's) and Procedure's Manuals by a licensed ophthalmologist with LASIK and/or SMILE surgery experience. A summary of the necessary training and experience needed to use the investigational device must be recorded at the site.

11.1 Investigational Products

Test Article: Wavelight EX500 Laser System for Topography Guided LASIK

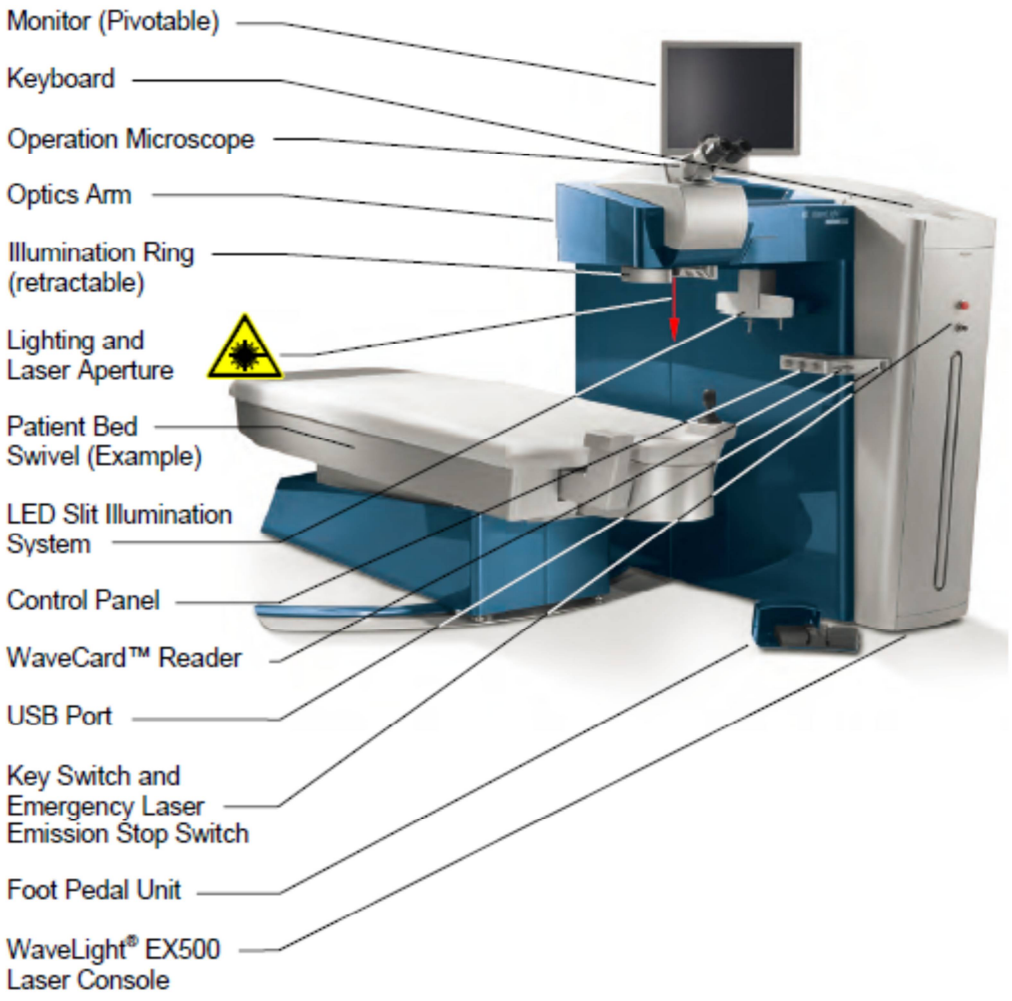
EX500 is a stationary scanning-spot excimer laser system used in refractive surgery for the treatment of myopia, myopia with astigmatism, hyperopia, hyperopia with astigmatism and mixed astigmatism. The system consists of technologically refined features, including a compact excimer laser with leading edge high pulse frequency, a galvanometer scanner for positioning the laser spot and a fast eye tracker for determining eye position and laser-beam direction. The Gaussian shaped beam profile of the individual pulses and an ablation diameter of approximately 0.95 mm (0.68 mm Full Width at Half Maximum [FWHM]) assure the desired contour and minimize surface irregularities during ablation.

The small spot of the EX500 requires the use of only minimal pulse energy. The result is a compact excimer laser beam source with minimal gas volume and minimal gas consumption. As the excimer laser is operated at a high repetition frequency, short treatment times are

assured. The integrated eyetracker offers automatic centering of the ablation and tracking of even rapid eye movements.

Treatments by the EX500 may be planned at an auxillary laptop and the information is transferred by a network or may be planned at the EX500 itself.

Figure 11–1 Wavelight EX500 Laser System



The product is manufactured by WaveLight GmbH and manufactured for Alcon Laboratories, Inc. The product is a CE Marked device approved for use and commercially available in the countries with participating Investigators as well as other countries across the globe.

More information on the laser and accessories, auxiliary parts, and consumables can be found in the EX500 User Manual.

Control Article: VisuMax Laser keratome for SMILE

Figure 11–2 VisuMax

The VisuMax laser keratome generates a beam of ultra-short laser pulses which are guided to the aperture in the treatment objective by an optical system (including controllable laser beam deflectors). The optical system focuses the laser beam into the corneal tissue. At its focal point, each ultra-short laser pulse causes an optical breakdown, creating plasma with a diameter of only a few microns. Continuous movement of the laser beam by the optical system creates incision surfaces within the cornea. All desired incisions are created in one work sequence.

For the laser treatment, a contact glass (part of the treatment pack) adheres both to the subject's eye and to the laser aperture by vacuum applied to the laser aperture and the contact glass.

The laser keratome’s integrated viewing optics allows the surgeon the immediate examination and preparation of the eye as well as the observation of the ongoing operation through the surgical microscope. An integrated video camera records the sequence of treatment.

An integrated computer with special software enables easy control of the laser keratome and saves the treatment data; other computers control and monitor the internal sequences.

The product is manufactured by Carl Zeiss Meditec AG, Jena. The product is a CE Marked device approved for use and commercially available in the countries with participating Investigators as well as other countries across the globe.

More information on the laser and accessories, auxiliary parts, and consumables can be found in the VisuMax User Manual.

11.2 Usage

The EX500 is used with the LASIK procedure for the correction of refractive errors. The LASIK procedure involves the creation of corneal flap, with a femtosecond laser or microkeratome blade that is hinged and pulled back to expose the corneal stroma. Then, the EX500 is used to ablate the necessary amount of corneal stroma to correct the refractive error.

LASIK may be customized by using subject specific diagnostic data. With Topography Guided LASIK, corneal topography data from each subject is used to customize the LASIK treatment.

The VisuMax is used with the SMILE procedure for the correction of refractive errors. The SMILE procedure involves the creation of a refractive lenticule and small incision of less than 4 mm all in one step. The lenticule is removed through the incision which results in changing the shape of the cornea thereby achieving the desired refractive correction.

Any significant discrepancy and/or deficiency when using the lasers must be recorded in the source documents and reported to the Sponsor, with an explanation (for details Refer to Section 13).

11.3 Accountability Procedures

Throughout the study, the Investigator will be responsible for accounting of the use of the investigational devices and all ancillary supplies and will ensure that the study products are not used in any unauthorized manner.

Upon receipt of any clinical supplies and ancillary supplies, the Investigator will conduct an inventory audit, complete and sign the Receipt of Clinical Supplies form as directed by the Sponsor. A copy must be retained in the Investigator’s clinical trial records.

The Investigator/staff must not use any ancillary supply that is damaged (such as broken, or seal is broken, etc). Damaged and/or deficient supplies should be brought to the attention of the Sponsor as soon as discovered. Refer to Section 13 Device Deficiencies and Adverse

Events for more instructions on reporting. Please follow instructions from your Clinical Site Manager (CSM) to ensure return, destruction and or replacement as needed.

During laser use, a daily temperature, humidity and pressure log will be maintained and appropriate investigational devices room environmental conditions will be documented and will be made available for inspection.

12 CLINICAL STUDY PROCEDURES

12.1 Clinical Study Assessments

The following section outlines the assessments to be performed in this clinical study.

The study assessments are listed by study visit in Table 6–1 and full details of the assessments for this study are described in the RFL605-P001 MOP.

All assessments must be documented in source documentation and eCRFs (if applicable).

12.1.1 Pre-Surgery screening Visit (Day -45 to Day -1)

Below is a list of study procedures to be undertaken at Pre-Surgery Visit (Screening). The procedures must be performed in the order presented below unless otherwise stated. All ocular assessments must be done monocularly.

For applicable assessments, both eyes must qualify for the study, therefore the screening assessments will be performed in both eyes.

Upon signing the informed consent, subjects are considered enrolled. The subject is assigned a single subject identifier at the Pre-Surgery Visit. The subject identifier consists of a combination of a 4 digit investigator number and a 5 digit subject number. The number is automatically generated sequentially by the EDC system. As an example: “4584.00001” (The investigator number and subject number are separated by a “.” character).

This number is used throughout the clinical study. Within 45 business days of surgery, subjects will be screened and randomized based on 1:1 allocation to receive EX500 for Topography Guided LASIK or VisuMax for SMILE.

1. Upon identification of a possible study participant, carry out the informed consent process. Refer to Section 16.2 Informed Consent Procedures.

   NOTE: Subjects must formally consent to participate in the study prior to undergoing any study specific testing. Upon signing informed consent, subjects are considered enrolled in

the study.

2. Perform a urine pregnancy test if the subject is a woman of childbearing potential.
3. Document demographics, ocular and non-ocular medical history, ocular and non-ocular concomitant medications.
4. Administer the RSVP Questionnaire (a 52-item questionnaire) to assess quality of vision and vision related quality of life.
5. Administer the SQDES to evaluate dry eye symptom and severity.

   NOTE: Investigators and site staff must review both questionnaires results prior to subjects leaving the office to ensure completeness.
6. Conduct the following procedures in an order that is feasible for your site :

   NOTES:

   - Each subject must be refracted by an ophthalmologist, optometrist, or a skilled technician. For further details, refer to MOP.
   - To ensure the stability of refraction, eligible subjects who currently wear contact lenses must discontinue their use for the appropriate amount of time before undergoing refractive laser surgery in the study as indicated in Table 12–1.

     NOTE: A contact lens wearer is defined as someone who has worn contact lenses within 3 months prior to the Pre-Surgery Visit.

Table 12–1 Minimum time to stop wearing contact lens before Pre-Surgery Visit

Type of Contact Lens	Minimum Time to Stop Wearing Contact Lens before Pre-Surgery Visit
Hard (PMMA) lenses	3 weeks
RGP lenses	2 weeks
Soft (extended and daily wear)	3 days

   - Perform lighting measurements for VA and contrast sensitivity testing.
   - Measure distance UCVA in photopic conditions using an Early Treatment Diabetic Retinopathy Study (ETDRS) chart at 3 meters (10 feet) or 4 meters (13 feet) recorded in logMAR. For subjects who cannot read English letters, a numerical, Tumbling E or a Landolt C logMAR chart can be used.
   - Measure uncorrected contrast sensitivity in mesopic conditions using a Vector

Vision Chart, recorded in logCS.

- Measure manifest refraction at 4 meters and adjust for optical infinity.
- Measure distance BCVA in photopic conditions using Early Treatment ETDRS chart at 3 meters (10 feet) or 4 meters (13 feet) recorded in logMAR. For subjects who cannot read English letters, a numerical, Tumbling E or a Landolt C logMAR chart can be used.

7. Conduct the following procedures in an order that is feasible for your site:
   - Perform keratometry using a Topolyzer Vario.
   - Perform topography using a Topolyzer Vario. Verify that the corneal astigmatism is regular (bow-tie shape).
   - Perform pupillometry under mesopic conditions using an infrared pupilometer. The same instrument should be used throughout the study.
   - Perform axial length measurement using an optical biometer or any other instrument. The same instrument should be used throughout the study.
   - Perform pachymetry using an ultrasonic contact pachymeter device or any other instrument. The same instrument should be used throughout the study.

8. Perform slit lamp examination.
9. Measure IOP using a Goldmann tonometer or any other instrument. The same instrument will be used throughout the study.
10. Perform cycloplegic refraction using a phoropter and adjust for optical infinity. The same equipment should be used throughout the study.
11. Perform dilated fundus examination.
12. Record any AEs. Refer to Section 13 for further details.

    NOTE: SAEs must be entered into EDC within 24 hours of the Investigator's knowledge.

13. Evaluate subject against all entry criteria. Document the subject status.
14. Randomize the subject and schedule the Surgery Visit to occur within 45 days of the Pre-

Surgery Visit (Screening).

NOTE: The subject should be discontinued from participation in the study if:

- Any complication occurred prior to any laser coming in contact with the eye.

12.1.2 Surgery Visit (Day 0)

Prior to surgery, the Investigator must ensure that the treatment planning has been completed and that the subject is still qualified.

If a subject is excluded post-randomization and prior to the Surgery Visit (i.e. the laser does not come in contact with the eye), the subject must be discontinued from participation in the study. Refer to Section 12.4 for further details.

During the day of surgery, the Investigator must record information regarding the surgery and related conditions and also details regarding medication used during the surgery, any problems or complications or other procedures that occur during the surgery.

Below is a list of procedures to be undertaken at Surgery Visit. Procedures must be performed in the order presented below unless otherwise stated. All ocular assessments will be done monocularly.

Activities involving multiple delegated staff members may be performed in parallel if this aligns with the study specified sequence.

Preparation for surgery :

1. Prior to surgery, review inclusion/exclusion criteria and ensure subject has been properly consented for participation in the study. Refer to Sections 10.1 and 10.2. Also, document any changes to ocular and non-ocular concomitant medications.
2. Perform slit lamp examination prior to surgery.
3. Prepare subject/eyes for surgery in accordance with site specific operating procedures.
4. Ensure the investigational device to which the subject is randomized is utilized for the surgery.

Procedures related to laser surgeries :

Laser systems and surgeries should be performed according to the Operator's (or User's) and Procedure's manuals. Refer to the manuals for specific instructions for device set up and

maintenance to ensure proper function prior to treatment.

1. Ensure the Laser System is calibrated per manufacturer's instructions prior to the procedure.
2. Ensure that treatment parameters are precisely transferred from the files to the laser system.

   NOTE: Treatment target is emmetropia for all eyes.
3. Perform surgery under topical anesthesia as per the normal routine of the surgeon.

   NOTE: Although the surgery is planned to be bilateral, in the case where the Investigator decides to not perform the surgery on the second eye on the same day the first eye is treated, the Investigator may treat the second eye at a later date while the subject is still in the study. In this case, effectiveness and safety assessments will be conducted as per post-surgery follow up visits if the fellow eye is treated with the study treatment. If the fellow eye is not treated at all or treated with a non-study treatment, AEs will only be collected for this eye. Refer to the MOP Table 4-1 for further details.
4. Record any AEs and device deficiencies. Refer to Section 13 for further details.

   NOTE: SAEs must be entered into EDC within 24 hours of the Investigator's knowledge.

   OTHER NOTES:

- Record the method of flap creation for the Topography guided LASIK surgery (microkeratome blade or femtosecond laser) in source document.
- Record operating room temperature and environmental conditions control in source document.
- Record all surgical medications used during the procedure in source document.
- Record surgical problems or complications that occur during surgery in source document.
- Record any other procedures during surgery in source document.
- Record the surgeon who performed the surgery. No more than two surgeons per site should perform a type of surgery.

12.1.3 Post-Surgery follow-up Visits (Day 1, Week 1, Months 1, 3 and 12)

Below is a list of study procedures to be undertaken at the Post-Surgery follow-up Visits (Day 1, Week 1 [Day 5 to Day 9], Months 1 [Day 21 to Day 35], 3 [Day 70 to Day 98] and 12

[Day 330 to Day 375]). Procedures must be performed in the order presented below unless otherwise stated. All ocular assessments must be done monocularly.

1. Record any changes to subjects' ocular and non-ocular medical history or concomitant medications at all visits.
2. Administer the RSVP Questionnaire at the Month 1, 3, and 12 visits.
3. Administer the SQDES Questionnaire at the Month 1, 3, and 12 visits.

   NOTE: Investigators and site staff must review both questionnaires results prior to subjects leaving the office to ensure completeness.
4. Conduct the following procedures in an order that is feasible for your site :
   - Perform lighting measurements for VA and contrast sensitivity testing at all visits.
   - Measure distance UCVA in photopic conditions at all visits.
   - Measure uncorrected contrast sensitivity in mesopic conditions at the Month 1, 3, and 12 visits.
   - Measure manifest refraction at 4 meters and adjust for optical infinity at the Week 1, Month 1, 3, and 12 visits.
   - Measure distance BCVA in photopic conditions at the Week 1, Month 1, 3, and 12 visits.
5. Conduct the following procedures in an order that is feasible for your site :
   - Perform topography at the Month 1, 3, and 12 visits.

   
6. Perform slit lamp examination at all visits.
7. Measure IOP at the Month 1, 3, and 12 visits.
8. Perform dilated fundus examination at Month 12.
9. Record any AEs at all visits. Refer to Section 13 for further details.

NOTE: SAEs must be entered into EDC within 24 hours of the Investigator's knowledge.

NOTE: Secondary Surgical Intervention: Retreatments will not be allowed in this study.

12.2 Unscheduled Visits

If a subject is examined more than once during any of the scheduled follow-up periods, or between scheduled follow-up periods, an unscheduled visit (UNSV) form should be completed reporting any study parameters or any relevant data collected at this visit.

An UNSV is defined as one that meets all of the following:

- Examination that is not standard of care and not required by the protocol
- Examination conducted by the study staff
- New finding, continuation of an existing finding, or a change to a previous finding is noted

An UNSV may or may not result in the capture of an AE. Likewise, an AE may be captured without the report of an UNSV (e.g, AE identified subsequent to study eye examination by non-study personnel).

The assessments captured at the UNSV are dictated by the Investigator per his/her medical judgment. The following assessments/documentation are recommended.

- Changes to subjects' ocular and non-ocular medical history or concomitant medications
- Slit lamp examination
- Manifest refraction
- Distance UCVA
- Fundus examination
- IOP
- AEs

NOTE: Assessments/ documentation are not limited to the above list.

If the subject is discontinued at the UNSV, then all early exit procedures must be performed (refer to Table 6–1).

For safety purposes, if an UNSV is required after the final study visit (Month 12), then the visit will be documented in the source documents.

12.3 Missed Visits

If a subject misses a scheduled visit, the subject should be rescheduled within allowed window for the same visit. Diligence should be shown in trying to schedule the subject for all visits, and all attempts to contact the subject documented in the subject's chart. In documentation, include dates, times, method of contact, etc. If attempts to contact the subject are unsuccessful, the date the subject is considered lost to follow-up must be documented. If a subject is unable to return for the final study visit, the Exit eCRF with the appropriate reason for discontinuation indicating the subject is lost to follow-up will be completed.

12.4 Discontinued Subjects

Discontinued subjects are those who withdraw, or are withdrawn from the study after signing the ICF and prior to completing all study visits. Subjects signing consent, but withdraw or are withdrawn prior to randomization will be considered discontinued due to screen failure, and the failed entry criterion must documented in source document and EDC (refer to Section 10).

Subjects may discontinue study participation at any time and for any reason. Subjects who complete the laser treatment in either eye will not be discontinued by the Investigator.

Subject numbers from discontinued subjects will not be reissued. Discontinued subjects will not be replaced.

It is the Investigator's responsibility to select only those subjects who are likely to be both willing and able to complete the required follow-up for participation in this study.

12.5 Clinical Study Termination

The Sponsor reserves the right to close the investigational site or terminate the study in its entirety at any time, for reasonable cause. The Investigator also may terminate the study at his/her site for reasonable cause. Reasons for the closure of an investigational site or termination of a study may include:

- The Investigator fails to comply with the protocol or Good Clinical Practice (GCP) guidelines.
- Safety concerns.
- Inadequate recruitment of subjects by the Investigator.

If the clinical study is prematurely terminated or suspended, the Sponsor will inform the Investigator and the regulatory authorities (where applicable) of the termination/suspension and the reason for the termination/suspension. The Investigator must promptly notify the IRB/IEC of the termination or suspension and of the reasons. If the Sponsor terminates the study for safety reasons, it will immediately notify the Investigator(s), and provide written instructions for study termination and applicable subject follow-up.

13 DEVICE DEFICIENCIES AND ADVERSE EVENTS

13.1 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 article). Refer to the Section 4 Glossary of Terms for categories of AEs and SAEs.

Figure 13-1 Categorization of All Adverse Events

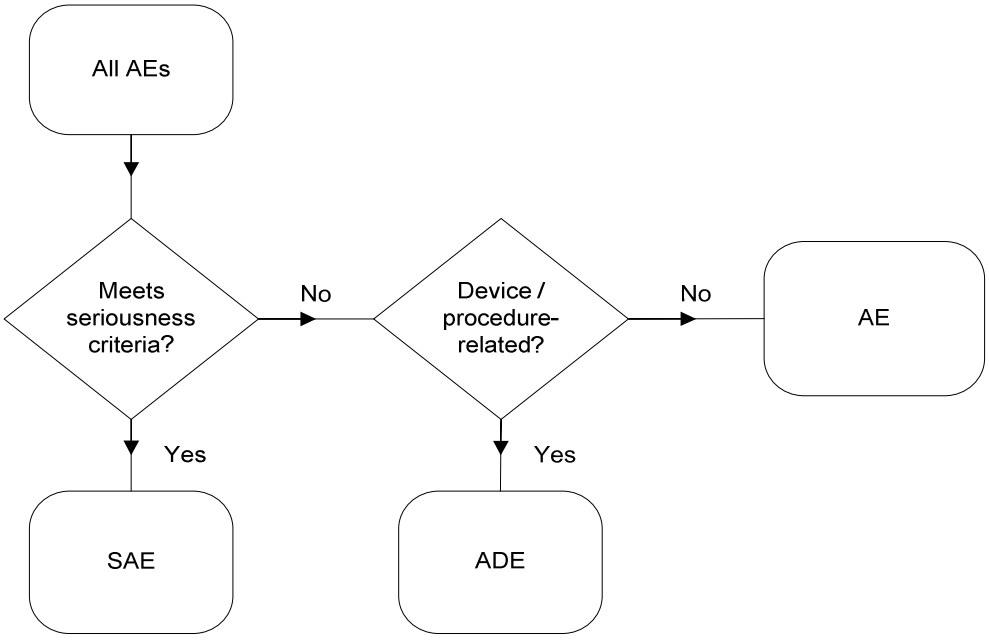
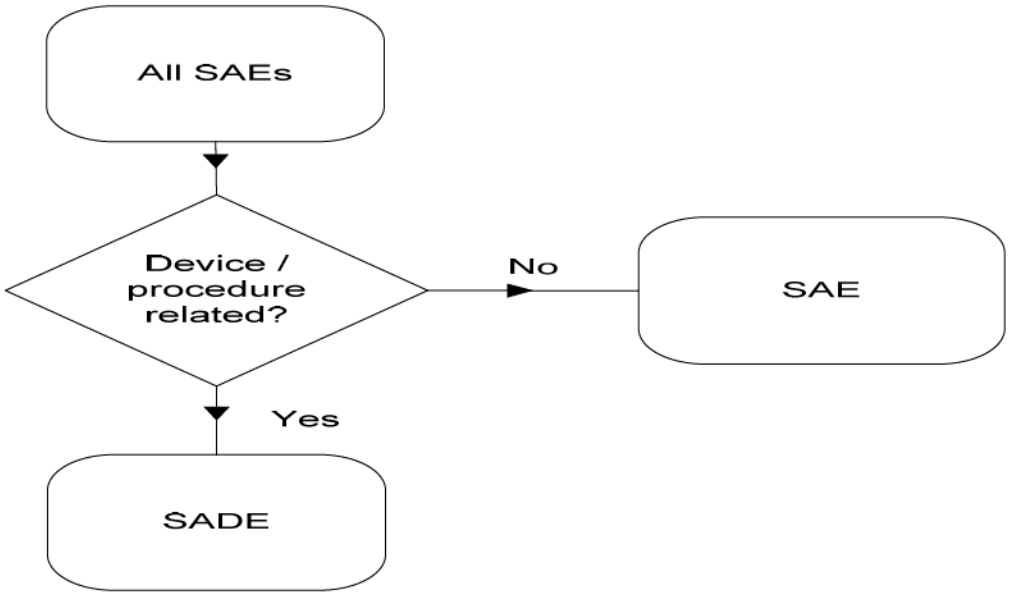


Figure 13–2 Categorization of All Serious Adverse Events



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 ocular events as a serious adverse event (SAE):

- Diffuse lamellar keratitis moderate or worse.
- Corneal infiltrate or ulcer.
- Any persistent corneal epithelial defect at one month or later.
- Moderate or severe (as defined in Section 13.3) corneal edema at 1 month or later (for LASIK, specify flap or bed).
- Melting of the flap (LASIK only).
- Decrease in BCVA of greater than or equal to 2 lines (≥ 10 letters ETDRS).
- Retinal detachment.
- Ocular perforation.

Any other potentially sight-threatening event may also be considered serious based on the judgment of the Investigator and should be reported appropriately.

Device Deficiencies

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

- Incorrect laser output energy
- Failure to meet product specifications (e.g, incorrect laser assembly)
- Unable to calibrate laser
- Suspect disposable product contamination or defect (subject interface)
- Computer software issue or system error message
- Failure of eye tracker
- Failure of laser firing

13.2 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:

- "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?"

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.

13.3 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 (i.e., before the ICF is signed) are not considered AEs in the study and should be recorded in the Medical History section of the eCRF.

In addition, corneal edema and superficial punctate keratitis are examples of early post-operative findings that are typically observed following ocular refractive surgery. These

are not considered AEs if they can be reasonably expected to resolve within a week and not result in any untoward long term visual outcome impact.

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 the Wavelight EX 500 Laser system and the VisuMax Laser keratome system 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:

- All SAEs must be reported immediately (within 24 hours) of the Investigator's or site's awareness.
- ADEs that do not meet seriousness criteria and device deficiencies must be reported within 10 calendar days 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 (refer to Section 11.3 Accountability Procedures).
- 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 Adverse Device Effect (for related AEs) and Serious Adverse Event eCRF.

NOTE: In the case of the EDC system becoming non-operational, the site must complete the appropriate paper ***Serious Adverse Event and Adverse Device Effect*** and/or ***Device Deficiency*** Form. The completed form will be then emailed to the Study Sponsor at [redacted] 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 devices other than the test and control devices (i.e. Topolyzer Vario, Pupillometer and Analyzer I or II) will be considered and processed as spontaneous (following the post-market 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 MOP 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 (i.e, 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 AE that is upgraded from non-serious to serious or from unrelated to related.

13.4 Return product analysis

Study Sponsor representatives and their contact information are provided in the MOP that accompanies this protocol.

Alcon products associated with device deficiencies and/or product-related AEs should be returned as specified in the MOP and must include the Complaint number which will be provided by the study Sponsor after the case is entered in the Study Sponsor's Global Product Complaint Management System (GPCMS).

13.5 Unmasking of the Study Information

Site personnel performing the manifest refraction subjective assessment and all UCVA testing after randomization are to remain masked with regard to treatment assignment until after the final DBL. Alcon and other site personnel (nurses and technicians involved with the surgery, site personnel entering data in eCRF, site personnel administering other study related procedures, e.g. RSVP and SQDES questionnaires) must not reveal the treatment assignment to masked site personnel at any time during the study.

13.6 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 (i.e, DBL).

All complaints received after this time period will be considered and processed as spontaneous (following the post-market 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.

13.7 Pregnancy in the Clinical Study

If a woman becomes pregnant during the study this should be noted within the source documentation and Sponsor notified. 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.

14 DATA REVIEW AND HANDLING

14.1 Completion of Source Documents and Case Report Forms

The nature and location of all source documents must be identified to ensure that original data required to complete the eCRFs exist and are accessible for verification by the monitor. If electronic source records are maintained, these records will be reviewed for 21 Code of Federal Regulations (CFR) Part 11 compliance and the method of verification will be determined in advance of starting the study. Data reported on the eCRFs must be derived from source documentation and be consistent with source documentation, and any discrepancies must be explained in writing. At a minimum, source documentation must include the following information for each subject:

- Subject identification (name, sex)
- Documentation of subject eligibility
- Date of informed consent, and a copy of the signed ICF
- Dates of visits
- Documentation that protocol-specific procedures were performed
- Results of study assessments, as required by the protocol
- Documentation of AEs and other safety parameters (as 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 each entry in the source documents be identifiable (eg, initials or signature and date). Any change or correction to data reported in the source, or on a eCRF, must be dated, initialed, and explained if necessary. Changes must not obscure the original entry (ie, an audit trail must be maintained). Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded on the eCRF are consistent with the original source data.

EDC is designated for data collection and should be completed by designated individuals only. Required examinations must be recorded on the eCRFs. All data reported must have corresponding entries in the source documents. The Investigator will review the reported data and certify that the eCRFs are accurate and complete as indicated by signature. Subject identifiers must not be recorded on the eCRFs beyond subject number, demographics information, and/or other study identifiers.

Deviations from this protocol, regulatory requirements, and GCP must be recorded in the study records. An explanation of the deviation should be included, as applicable. In addition, corrective and preventive action should be identified, implemented, and documented within the study records.

14.2 Data Review and Clarifications

Upon completion of the eCRFs, the data will be reviewed by Alcon study personnel for accuracy and completeness. If corrections and/ or any additions to the data are deemed necessary, queries will be generated by Alcon data management or the site management (study monitor) team and forwarded to the investigative site. Staff at each site are expected to respond to data queries in a timely manner and ensure that the corrections and changes made to the data in the EDC system are reflected in the subjects' source documentation. In addition, prior to study start (first subject first visit) a plan for data validation will be completed by Alcon Clinical Data Management and agreed upon by members of the Clinical Trial Management (CTM) team.

Concomitant medications entered into the database will be coded using the current version of the WHO (World Health Organization) Drug Reference List. Medical history and AEs will be coded using the current version of the medical dictionary for regulatory activities (MedDRA) terminology.

Upon completion of the study and once the database is declared complete and accurate, the database will be locked and data will be available for data analysis. Any changes to the database after lock will be implemented upon agreement between Alcon's and PLSS's CTM and biostatistics department, and will be completed following Alcon's procedures for changes to a database after DBL.

NOTE: Missing data can have a detrimental effect on the integrity and soundness of a clinical study. All efforts should be made by the clinical investigative site to prevent missing study visits and procedures during the study.

15 ANALYSIS PLAN

The main focus of the analyses is the eye (individual-level) rather than subject (group-level). However some data (e.g. demographics, non-ocular AEs) will only be available at the subject level.

At each study visit, quantitative variables will be presented based on descriptive statistics (the number of non-missing observations, mean, median, standard deviation [SD], minimum and maximum values) for the observed values and change from pre-surgery (if applicable). Qualitative variables will be presented by frequency tables.

The baseline value is the last available, non-missing, value collected prior to surgery (i.e. prior to the laser being in contact with the eye).

Further technical details and discussion of the following statistical considerations will be provided in the statistical analysis plan (SAP), which will be finalized before DBL.

15.1 Subject Evaluability

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

15.2 Analysis Data Sets

The following analysis sets will be defined for this study: intention to treat (ITT) and safety analysis set. Assignment of study eyes to the appropriate analysis set(s) will be determined prior to DBL.

The ITT analysis set will contain all study eyes for which study treatment has begun for the set of subjects that are randomized. For the purposes of this study, the treatment will be considered to have begun once the flap creation is initiated for LASIK and once laser touches the eye for SMILE.

All eyes in the ITT analysis set will be assigned to the treatment to which they are randomized.

The safety analysis set will contain all study eyes for which study treatment has begun; all eyes in the safety analysis set will be assigned to the treatment actually received.
In general, the ITT analysis set will be used to display subject disposition, demographics and baseline characteristics, medical history and the analysis of the effectiveness endpoints. The safety analysis set will be used for the analysis of the safety endpoints.

15.3 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized by treatment group and overall.

Relevant medical history (ocular and non-ocular) and current medical conditions will be tabulated by system organ class (SOC) and preferred term (PT) of the MedDRA dictionary. Other relevant baseline information will be listed and summarized as appropriate with descriptive statistics.

15.4 Effectiveness Analyses

All effectiveness endpoints are defined at the eye (as opposed to subject) level. As the measurements from the paired eyes of the same subject will have a tendency to be positively correlated, the main analyses will adjust for this correlation (i.e. intracluster correlation).

15.4.1 Primary Effectiveness

The primary effectiveness endpoint is stated in Section 8.5.1.

15.4.1.1 Statistical Hypotheses

The following superiority hypothesis for the primary effectiveness objective will be tested at the two-sided 5% significance level (α=0.05):

H_0: $p_{L=} p_S$

H_1: $p_L \neq p_S$

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

15.4.1.2 Analysis Methods

The primary effectiveness analysis will be analyzed using the chi-square test quoted in Fleiss et al (Fleiss 2003) at the two-sided 5% significance level (α=0.05). This statistic takes into account the intracluster correlation/ agreement between eyes within subject.

15.4.2 Secondary Effectiveness

The secondary effectiveness endpoints are stated in Section 8.5.1.

15.4.2.1 Statistical Hypotheses

The following superiority hypothesis for the first secondary effectiveness objective will be tested (two-sided):

H_0: $\mu_L = \mu_S$

H_1: $\mu_L \neq \mu_S$

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

The following superiority hypothesis for the second secondary effectiveness objective will be tested (two-sided):

H_0: $\mu_L = \mu_S$

H_1: $\mu_L \neq \mu_S$

where μ_L and μ_S denotes the mean UCVA in the Topography Guided LASIK arm and SMILE arm, respectively.

15.4.2.2 Analysis Methods

The secondary effectiveness analysis will be analyzed using the statistic of Donner, et al (Donner 1981), which accounts for the intraclass correlation between eyes within subjects, at the two-sided 5% significance level (α=0.05).

15.5 Handling of Missing Data

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

15.6 Multiplicity

In order to control the type 1 error at the 5% significance level (α=0.05) over the family of primary and secondary hypotheses, the secondary effectiveness hypotheses will be relevant only if the primary effectiveness null hypothesis is rejected at the 5% significance level (two-sided).

If the null hypothesis of the primary effectiveness endpoint is rejected, then the secondary effectiveness endpoints will be tested using the Hochberg testing procedure (Hochberg 1988). The Hochberg procedure is a step-up method for multiple testing controlling for the type I error rate.

First, the p-values obtained from the analysis of the secondary effectiveness endpoints will be ranked from smallest (1) to largest (2). Second, if the largest p-value ($p_{[2]}$) associated with the two secondary effectiveness endpoints is less than the critical value (α=0.05), then the two secondary effectiveness null hypotheses will be rejected and testing will stop. If the aforementioned p-value is greater than or equal to the critical value (α=0.05), then the associated secondary effectiveness null hypothesis will fail to be rejected. The next largest p-value ($p_{[1]}$) will then be checked to see if it is less than the critical value ($\alpha/2$=0.025).

[redacted]

15.7 Safety Analysis

[redacted]

No inferential testing will be performed on these parameters.

The eye-level safety analyses will be performed using the safety analysis set. For safety parameters collected on the subject-level (e.g. PRO questionnaires, non-ocular AEs), the population of interest will be the set of subjects with at least one eye for which treatment has begun (i.e. at least one eye in the safety analysis set).

Adverse Events

AEs will be assessed throughout the study period (from pre-surgery Day -45 up to post-surgery follow-up for Month 12). For more details, refer to Section 13.1.

AEs will be deemed treatment emergent if the onset date is on or after the date of surgery. Any AEs recorded prior to the start of surgery will be listed separately from the treatment emergent AEs. Only treatment emergent adverse events (TEAEs) will be summarized. Ocular treatment emergent adverse events will be summarized separately by SOC and PT.

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

All information obtained on AEs (including those which are collected pre-surgery as well as TEAEs) will be displayed by treatment and subject.

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

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

Then only AEs will be collected for the second eye.

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

Device Deficiencies

Device deficiency will be evaluated at day of surgery (Day 0). For more details, refer to Section 13.1.

The number and percentage of all device deficiencies will be tabulated by treatment. A listing of all device deficiencies will also be provided.

Other Safety Assessments

Other safety evaluations include slit lamp findings IOP, surgical problems, dilated fundus findings and PRO Questionnaires (RSVP, SQDES). For details refer to Section 12.1.

The mean overall and eight subscale vision related quality scores will be derived from the RSVP questionnaire.

For SQDES, a subject is defined as having dry eye syndrome if there was occurrence of both dryness and irritation of the eyes either constantly or often (that is, severe symptoms) or a report of a previous clinical diagnosis of dry eye syndrome.

Information from the nomogram, if one is used, and surgical report will also be provided.

15.8 Interim Analyses

There is no formal interim analysis planned. The main analysis will occur after the 3 months post-surgery follow-up. Subjects will be followed up for an additional 9 months post-surgery (i.e. in total 12 months [Day 330 to Day 375] after surgery) for safety [redacted].

15.9 Sample Size Justification

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

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

To ensure the required sample size is achieved, approximately 225 subjects (contributing 2 eyes each) will be enrolled per treatment arm. This will take into account drop-outs prior to surgery. It is expected that 400 subjects (200 subjects per treatment arm) will receive bilateral treatment. Of these subjects, it is expected that a further 7% may drop out during the 3 months post-surgery.

16 ADMINISTRATIVE PROCEDURES

16.1 Regulatory and Ethical Compliance

This clinical study will be conducted in accordance with the principles of the Declaration of Helsinki, and in compliance with ISO 14155:2011 Clinical investigation of medical devices for human subjects, GCP, the Code of Federal Regulations (CFR), and laws and regulations of foreign countries, whichever affords greater protection to subjects. The study will also be conducted in accordance with the Sponsor's Standard Operating Procedures (SOPs) and all other applicable regulations. The Investigator and all clinical study staff will conduct the clinical study in compliance with this protocol. The Investigator must ensure that all personnel involved in the conduct of the clinical study are qualified to perform their assigned duties through relevant education, training, and experience.

16.2 Informed Consent Procedures

Voluntary informed consent must be obtained from every subject prior to the initiation of any screening or other clinical study-related procedures. The Investigator must have a defined process for obtaining consent. Specifically, the Investigator, or designee, will explain the clinical study to each potential subject and the subject must indicate voluntary consent by signing and dating the approved ICF. 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 will provide subjects with information regarding the purpose, procedures, requirements, and restrictions of the clinical study, along with any known risks and potential benefits associated with the investigational product, 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 clinical study and will be provided with contact information for the appropriate individuals should questions or concerns arise during the clinical study. The subject also will 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 and must provide a duplicate copy to each subject.

16.3 Responsibilities of the Investigator and IRB/IEC

Before clinical study initiation, this protocol, the ICF (and assent form, if applicable), any other written information provided to subject, and any advertisements planned for subject recruitment must be approved by an IRB / Independent Ethics Committee (IEC). A master list

of IRBs/IECs for this clinical study can be found in the Trial Master File. The Investigator must provide documentation of IRB/IEC approval to the Sponsor. The approval must be dated and must identify the applicable protocol, amendments (if any), ICF, assent form (if any), all applicable recruiting materials, written information for subjects, and subject compensation programs. The IRB/IEC must be provided with a copy of the Directions for Use, any periodic safety updates, and all other information as required by local regulation and/or the IRB/IEC. At the end of the clinical study or in the case of early termination, the Investigator will notify the IRB/IEC of the clinical study's final status. Finally, the Investigator will report to the IRB/IEC on the progress of the clinical study at intervals stipulated by the IRB/IEC.

16.4 Sponsor and Monitoring Responsibilities

The Sponsor will designate a monitor to conduct the appropriate site visits at the appropriate intervals. The clinical investigation will be monitored to ensure that the rights and wellbeing of the subjects are protected; the reported data are accurate, complete, and verifiable from the source documents; the equipment used to assess variables in the clinical investigation is maintained and calibrated per manufacturer instructions and Sponsor requirements; and the study is conducted in compliance with the current approved protocol (and amendment[s], if applicable), with current GCP, and with applicable regulatory requirements. All investigative sites will have a site initiation. Monitoring will be conducted periodically while the clinical study is ongoing. Monitoring methods may include site visits, telephone, written, and fax correspondence. The assigned CSM will contact each site at appropriate intervals. The Lead Clinical Site Manager (LCSM) will determine the frequency of site visits. Close-out visits will take place after the last visit of the last subject. Enrollment will be tracked and reported at regular intervals. Details regarding enrollment (eg, number of subjects pre-screened, screened, reasons for screen failures, etc.) may be requested of the investigative site and must be provided within a reasonable time period. The Sponsor will be responsible for implementing and maintaining quality assurance and quality control systems to ensure the study is conducted and data are generated, documented and reported in compliance with the protocol, GCP and applicable regulatory requirements.

The 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 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 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.

16.5 Regulatory Documentation and Records Retention

The Investigator is accountable for the integrity, retention, and security of all study related data. The Investigator must maintain accurate, complete, and current records relating to the clinical study. The Investigator must maintain the required records during the investigation and for a period of time specified by local law or per the Clinical Study Agreement, whichever is longer. If the Investigator retires, relocates, of for any other reason withdraws from responsibility of keeping the study records, the Sponsor must be notified and suitable arrangements made for retention of study records and source documents needed to comply with national and international regulations.

16.6 Confidentiality and Publication of the Clinical Study

Any information other than that which is disclosed upon registration should not be discussed with persons outside the study. The protocol, study data, and information related to the study or to Alcon's products or research programs that is provided by Alcon (Confidential Information) is to be kept confidential, and not disclosed directly or indirectly to any third party other than those involved in the study who have a need to know. All data and discoveries arising out of the study, patentable or non-patentable, shall be the sole property of Alcon, Inc. Alcon reserves the right of prior review of any publication or presentation of information related to the study. Alcon may use these data now and in the future for presentation or publication at Alcon's discretion or for submission to government regulatory agencies.

The existence of this clinical study is confidential and should not be discussed with persons outside of the study. You shall hold confidential, and not disclose directly or indirectly to any third party other than those persons involved in the study who have a need to know, the protocol, the data arising out of the study, and any other information related to the study or to Alcon's products or a research program that is provided by Alcon to you (the "Confidential Information"). All such persons must be instructed not to further disseminate this information to others. You shall not use the Confidential Information for any purpose other than the study. The foregoing obligations of confidence and non-use assumed by you shall not apply to: (a) information which at the time of disclosure is in the public domain; (b) information which thereafter lawfully becomes part of the public domain other than through disclosure by or through you; (c) information which, as evidenced by your written records, was known by you prior to Alcon's disclosure; (d) information which is lawfully disclosed to you by a third

party not under any obligation of confidence to Alcon; or (e) information which is required to be disclosed by law or government regulatory agency, provided reasonable advance notice of such disclosure is given to Alcon. In signing this protocol, you agree to the release of the data from this study and acknowledge the above confidentiality and publication policy. The provisions of this Statement shall survive the completion of the study.

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18 APPENDICES

Not Applicable