a Novartis company

Clinical Trial Protocol

A prospective, multicenter, randomized evaluation of refractive predictability in patients with or without corneal astigmatism (maximum allowable up to 1.25 D) when using the Cataract Refractive Suite and standard manual techniques

Protocol Number:	CTK246-P001 / NCT02974140
Sponsor Name & Address:	Alcon Research, Ltd. and its affiliates ("Alcon") 6201 South Freeway Fort Worth, Texas 76134-2099
Project Name / Number:	Cataract Refractive Suite/A02835
Test Articles / Products:	Cataract Refractive Suite (CRS) composed of the following: 1. VERION™ Image Guided System 2. LenSx® Femtosecond Laser 3. ORA™ (Optiwave Refractive Analysis) with VerifEye+™ (with or without the VerifEye Lynk)
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?	Q es E] No
Test Article/ Product:	Cataract Refractive Suite (CRS) composed of the following: 1. Verion Image Guided System 2. LenSx Femtosecond laser 3. Optiwave Refractive Analysis (ORA) with VerifEye+ (with or without the VerifEye Lynk)
Objectives:	**Effectiveness Objectives** *rimary:* • To compare the refractive predictability (prediction enor) between the CRS and standard manual technique at 1 month postoperative. *econdary:* • To compare the amount of cumulative dissipated energy (CDE) expended in the eye between the CRS and standard manual technique. • To assess the average estimated aspiration fluid used during surgely between the CRS and standard manual technique. • To assess the average aspiration time spent during surgely between the CRS and standard manual technique.
	[redacted]

	[redacted]	
Clinical Study Design:	This is a prospective, multi-center, observer masked, randomized, active control (standard manual technique), contralateral design study.	
No. of Subjects:	This study will enroll approximately 350 subjects to initially randomize and treat 300 subjects (that could potentially increase to approximately 580 subjects enrolled and 500 subjects randomized). An interim analysis will be performed once 200 subjects have been randomized, treated and completed 1-month follow-up visits. An additional 200 subjects may be randomized and treated beyond the initially planned 300 subjects. It is planned that the study will randomize and treat between 300 and 500 subjects.	
Regions:	US and EU	
Clinical Study Duration:	Total expected duration of the clinical investigation: a) Total expected duration of the clinical investigation- up to 11 months b) Expected duration of each subject's participation – up to 154 days c) Planned follow-up duration – 3.5 months d) Estimated time needed to select the number of subjects (enrollment period) - 6 months	
Clinical Study Population:	Adult subjects with bilateral cataracts who are candidates to receive ReSTOR +2.5 D multifocal IOL	
Treatments:	***Test Article***:	The CRS is composed of the following: 1. Verion Image Guided System 2. LenSx Femtosecond laser 3. ORA with VerifEye+ (with or without the VerifEye Lynk)
	Administration:	Intervention during preoperative planning and during cataract surgery.
	General Description:	The CRS is composed of a series of devices that address the pre-planning stages of IOL calculation and integrates this information into the operative stage up to postoperative follow-up.

	Control Article:	Active: Standard manual technique
	Administration:	Intervention during surgery
	General Description:	Standard phacoemulsification technique
Inclusion & Exclusion Criteria:	Inclusion Criteria: 1. Adults (≥ 22 years of age at the time of surgery), diagnosed with bilateral cataracts. 2. Planned cataract surgery and implantation of ReSTOR +2.5 D multifocal IOL in both eyes. 3. Target is emmetropia (+0.50 to -0.50). 4. Clear intraocular media other than cataract in study eye(s). 5. Willing and able to complete all required postoperative visits. 6. Able to comprehend and sign a statement of informed consent. 7. Potential postoperative visual acuity of 0.2 logarithm of the minimum angle of resolution (LogMAR) or better. 8. Preoperative keratometry reading between 40.0 D to 49.0 D in the primary meridians. 9. Preoperative axial length between 21.5 mm to 27.0 mm. 10. Preoperative/Baseline corneal with-the-rule (WTR), against-the-rule (ATR) or oblique astigmatism ≤ 1.25 D. Exclusion Criteria: 1. Significant irregular corneal astigmatism as assessed by the index relevant to the corneal topographer and investigator judgement of the topography maps 2. History of or current severe dry eyes. 3. Tear breakup time (TBUT) < 10 secs prior to randomization. 4. Retinal/uveal pathology or concurrent ocular disease including age-related macular degeneration (AMD), choroidal neovascularization (CNV), glaucoma, diabetic retinopathy, retinitis pigmentosa, optic nerve pathology. 5. Previous intraocular or corneal refractive surgery. 6. Any inflammation or edema (swelling) of the cornea, including but not limited to the following: keratitis, keratoconjunctivitis, and keratouveitis. 7. Amblyopia. 8. Previous corneal transplant.	

	9. Previous retinal detachment. 10. Recunent severe anterior or posterior segment inflammation of unknown etiology. 11. Pregnancy at time of Screening. 12. Participation in another concmTent clinical study. 13. Any other ocular condition or systemic co-morbidity that the Investigator determines would confound the results of this study or would prohibit completion of the study assessments.
Effectiveness EndpointsNariables	**Primary**
	• Percentageof eyes in which the MRSE at 1 month is :S 0 .5 0 D relative to predicted MRSE.
	Secondary
	• Cumulative dissipated energy (CDE) • Estimated aspiration fluid used • Phacoemulsification aspiration time
	[redacted]
Safety Variables	• Adverse events • Slit-lamp examination • lntraocular pressure (IOP) • Surgical problems • Dilated fundus examination • Device deficiencies

Planned Analyses	The primary effectiveness objective is to demonstrate superiority of the Cataract Refractive Suite (CRS) compared to standard manual techniques with respect to refractive predictability (predictive error) at 1 month. The null and alternative hypotheses for the primruy analysis are: Ho: Pc≤ Ps **Hi:** Pc> Ps where Pc and Psare the percentage of eyes with manifest refraction spherical equivalentwithin 0.5 D of predicted postoperative spherical equivalent at 1 month in the CRS and standard manual technique aims respectively. The primaryeffectiveness analysis will be analyzed using a one-sided McNemar's test at the $\alpha=0.05$ level.
	The secondruy endpoints ruve: • The mean CDE expended in the eye during surgery. • The mean estimated aspiration fluid used during surgery. • The mean aspiration time spent during surgery. The null and alternative hypotheses are the same for all secondary analysis and can be presented as: Ho: $\mu_c = \mu_s$ Hi: $\mu_c < \mu_s$ where μ_c denotes the mean value in the CRS group and μ_s denotes the mean value in the standard manual technique group for each of the respective secondruy endpoints. The secondary hypotheses will only be tested if the primary objective is met and each of the null hypotheses will be tested using a one-sided paired t-test. [redacted]
	The safety outcomes will be summruized with appropriate summarystatistics and also listed. The study will employ an adaptive design with potential sample size adjustment based on the proportion of discordance in the primary effectiveness outcome between the study eyes. An interim analysis to assess the need for sample size re-estimationwill be performed when the first 200 subjects who are randomized, treated and completed their assessment for the primruy effectiveness at Month 1.

Sample Size Justification	Based on recent clinical experience, the rates of success for the primary endpoint are assumed to be 83% and 75% for the CRS and standard manual technique arms, respectively. An estimate of the discordance in outcome between eyes is not known; however, based on the assumed rates of 83% and 75% for the primary endpoint, the rate of discordance must be between 8% and 33%. For an initial sample size calculation, the midpoint value of this range, 21%, is assumed. Based on these assumptions, 267 subjects, treated contralaterally, are required to provide 90% power to reject the null hypothesis. If the proportion of discordance is 33% and all other assumptions stay the same a sample of 433 subjects is needed to provide 90% power. The two samples (267 and 433) are inflated to account for up to 10% subject drop-out in the full analysis set (FAS) so the subject range increases to 300 to 500.

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3 ABBREVIATIONS

Abbreviation	Definition
ADE	Adverse device effect
AE	Adverse event
AMD	Age-related macular degeneration
ATR	Against-the-rule
[redacted]	[redacted]
CDE	Cumulative dissipated energy
CFR	Code of Federal Regulations
CIM	Corneal irregularity measurements
CJD	Creutzfeldt-Jacob Disease
cm	Centimeter
CNV	Choroidal neovascularization
CRS	Cataract Refractive Suite
CSM	Clinical site manager
CTM	Clinical Trial Management
D	Diopter
EBMD	Epithelial basement membrane dystrophy
eCRF	Electronic case report form
EDC	Electronic data capture
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
FAS	Full analysis set
FDA	US Food and Drug Administration
GCP	Good clinical practice
GPCMS	Global Product Complaint Management System
h	Hour
HIV	Human immunodeficiency virus
ICF	Informed consent form
IEC	Independent ethics committee
IOL	Intraocular lens
IOP	Intraocular pressure
IRB	Institutional review board
ISO	International Organization for Standardization
LCD	Liquid crystal displays
LCSM	Lead clinical site manager
LogMAR	Logarithm of the minimum angle of resolution
LRI	Limbal relaxing incision
[redacted]	[redacted]
[redacted]	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
mm	Millimeter
MOP	Manual of procedures
MRSE	Manifest refractive spherical equivalent

Abbreviation	Definition
N/A	Not applicable
nm	Nanometer
ORA	Optiwave Refractive Analysis
[redacted]	[redacted]
PMMA	Polymethyl methacrylate
PT	Preferred term
RGP	Rigid gas permeable
SADE	Serious adverse device effect
SAE	Serious adverse event
SE	Spherical equivalent
SOC	System organ class
SOP	Standard Operating Procedure
TBUT	Tear break up time
[redacted]	[redacted]
US/USA	United States of America
USV	Unscheduled study visit
WHO	World Health Organization
WTR	With-the-rule

4 GLOSSARY OF TERMS

Adverse Event (AE)	Any untoward medical occunence, unintended disease or injmy, or untoward clinical signs (including abnonnal laboratmy findings) in subjects, users or other persons, whether or not related to the investigational medical device (test ariicle). *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 ariicle) or control article. *Note: This definition includes adverse events resulting/ram 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 mar·keted produ ct, 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 occmTed.
Non-serious Adverse Event	AE that does not meet the criteria for a serious adverse event (SAE).
Serious Adverse Event	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 injmy. *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 fon n.* b) any potentially sight-threatening event or pe1manent impai1ment to a body stmcture 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 considereda serious adverse event. In general, hospitalizationsignifies 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) orb). e) any indirectha1m as a consequence of incon ect diagno stic test results when used within manufacturer's instmctions for use. • Fetal distress, fetal death, or a congenital abnmmality or bitih 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 ala1ming as a potential public health hazard, eg, human immunodeficiency vitus (HIV) or Creutzfeldt-Jacob Disease (CJD).
Use Enor	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 Institutional Review Board / Independent Ethics Committee (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 2

Purpose of Amendment: To revise an inclusion criterion, address omissions from the text and remove text about secondary surgical interventions

Rationale: The corneal irregularity inclusion criterion is too specific. Additionally, the other items are needed for clarification

Current Study Status: Enrolling

4 subjects have been enrolled in the study at 1 site

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

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

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

Itemized Changes:

Section	Item	Rationale
Sections 1 and 10	Changed the exclusion criterion 1: **From** Significant irregular corneal astigmatism where the corneal irregularity measurements (CIM) index is above 1.0 as measured by the corneal topographer.	To align the criterion with how corneal irregularity is evaluated in a standard clinic setting

	To Significant irregular corneal astigmatism as assessed by the index relevant to the corneal topographer and investigator judgement of the topography maps	
Sections 1 and 10	Added *condition* to the exclusion criterion 13: Any other ocular ***condition*** or systemic co-morbidity that the Investigator determines would confound the results of this study or would prohibit completion of the study assessments.	To clarify the text
Sections 3, 4 and 15	Removed any reference to secondary surgical intervention	Collection of secondary surgical intervention is not applicable since this is not a registration trial
Section 6	Added an "X" under the Screening Visit Column of the Schedule of Visits table for Keratometric measurements	To address an omission
Section 12	Revised text **from:** Perform Verion (measurement module and vision planner). **To** Use the Verion Vision Planner for IOL power calculation.	To clarify that only the vision planner portion is to be used and that it's used for IOL power calculation
Section 6	Revised text **from:** Verion (Measurement Module and Vision Planner) IOL calculation will only be used on the test eyes.	To clarify that only the vision planner portion is to be used and that it will be used on both eyes

	To Verion Vision Planner IOL calculation will only be used on both eyes.	
Section 12	Added *LenStar* Perform Keratometry with *LenStar*	To clarify that the LenStar will be used for keratometry
Section 12	Added below text: *Assess for irregular corneal astigmatism by evaluating the relevant irregularity index and the appearance of the topography maps. Document on the printed maps whether or not there is significant irregular corneal astigmatism and provide a justification for the assessment.*	To elaborate on the corneal topography assessment that will be used for the relevant exclusion criterion

5.2 Amendment 1

Purpose of Amendment: To implement revisions based on the change in IOL platform from monofocal to multifocal (ReSTOR +2.5 IOL)

Rationale: To align with business/reimbursement strategy

Current Study Status: Planning

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

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

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

Itemized Changes:

Objectives (Protocol Section 1 and Section 8)

[redacted]

[redacted]

Eligibility Criteria (Protocol Section 1 and Section 10)

Criterion	**Rationale**
Added an inclusion criterion, "target is emmetropia (+0.50 to -0.50)	To ensure no monovision treatments are planned
Changed minimum age from 21 to 22	To be consistent with age defined as adult for other trials executed in US
Replaced monofocal IOL implantation with ReSTOR +2.5 D IOL	To align with business/reimbursement strategy

Added Exclusion criterion: TBUT < 10 secs prior to randomization *NOTE*: If either eye has a TBUT < 10 secs at the Screening Visit, start treatment with warm compresses if all other eligibility criteria are met. The TBUT must be checked prior to randomization and if the TBUT is < 10 secs in either eye, the subject must be discontinued from the study	To exclude eyes with an unstable tear film which could impact visual acuity and manifest refraction outcomes. TBUT may improve with warm compresses and this treatment will be initiated in those subjects with TBUT < 10 secs at the screening visit and the TBUT will be checked prior to randomization to determine if it is ≥ 10 secs prior to randomization. Relevant changes made in Section 12 as well.

Statistics (Protocol Section 1 and Section 15)

Item	**Rationale**
Changed assumptions for control vs test rates from *70% vs 80%* **to** *75% vs 83%* Changed the range of required sample size from *202 - 318* to *267 – 433* Changed the range of the number of eyes to be randomized from *225 – 375* **to** *300 – 500*	New assumptions for control and test rates based on recently available data from the AnalyzOR Retrospective Data Exploration Study
[redacted]	[redacted]

Other

Added the following:

Item	**Rationale**
Create a 4.8 to 5.5 mm anterior capsulotomy centered on the line of sight using the manual technique (Section 12.1.2)	For consistency between eyes, subjects and sites
LenSx arcuate incisions may be refined based on ORA recommendations (Table 6-1	To maximize the value of ORA and

footnote)	consequently the CRS
Added note 'o' as 'If subject did not meet TBUT at screening visit and waim compress therapy is staiied. TBUT must be reassessed prior to ensure subject meets criteria prior to randomization' (Table 6-1 footnote)	For evaluation of the teaT fi hn
Added details of manufacturer for Test article: CRS (Table 11-1)	To comply with ISO14155:2011 guidance

Updated the following:

Updated screening visit From: Day -30 to 0 Screening for both eyes To: Day -30 to -1 Screening for both eyes (Table 6-1)	To ensure randomization 1 day prior to surgely.
Randomization was shifted From Visit 00 To Visit 0 (Table 6-1)	To ensure randomization 1 day prior to surgely.
Clinical study duration (Protocol Section 1): • Total expected duration of the clinical investigation- up to 5 months updated to 11 months. • Estimated time needed to select the number of subjects (emollment period) - 5 months updated to 6 months.	To clarify study timing

6 SCHEDULE OF VISITS

Table 6–1 Schedule of Visits

Nominal Time ± Visit Window Limits									
Procedure/Assessment	**Visit 0** **Both eyes assessed** Day -30 to -1 Screening for both eyes	**Visit 00** Day 0 Implant for Eye 1	**Visit 1** Day 1 for Eye 1	**Visit 00A** Day 7-14 Implant for Eye 2 (7-14 days after V00)	**Visit 1A** **Both eyes assessed** Day 1 for Eye 2; Days 8-15 for Eye 1	**Visit 2A** Day 7-10 post 2nd eye surgery	**Visit 3A** **Both eyes assessed** Month 1 (Days 20-40 post 2nd eye surgery)	**Visit 4A** **Both eyes assessed** Month 3 (Days 70-110 post 2nd eye surgery)	**USV[n]** N/A
Informed consent[a]	X								
Demographics	X								
Medical history	X								
Concomitant medications	X	X	X	X	X	X	X	X	X
Inclusion/exclusion criteria	X								
Pregnancy test[b]	X								
Randomization[c]	X								
IOP[d]	X		X		X			X	X
Corneal topography	X								
[redacted]									
Manifest refraction	X				X	X	X	X	X
[redacted]									
Predicted post-op spherical equivalent (SE)	X								
Slit-lamp examination	X		X		X	X	X	X	X

Nominal Time ± Visit Window Limits									
Procedure/Assessment	**Visit 0 Both eyes assessed**	**Visit 00**	**Visit 1**	**Visit 00A**	**Visit 1A Both eyes assessed**	**Visit 2A**	**Visit 3A Both eyes assessed**	**Visit 4A Both eyes assessed**	**USV[n]**
	Day -30 to -1 Screening for both eyes	Day 0 Implant for Eye 1	Day 1 for Eye 1	Day 7-14 Implant for Eye 2 (7-14 days after V00)	Day 1 for Eye 2; Days 8-15 for Eye 1	Day 7-10 post 2nd eye surgery	Month 1 (Days 20-40 post 2nd eye surgery)	Month 3 (Days 70-110 post 2nd eye surgery)	N/A
Tear Break Up Time (TBUT)	X[o]								
[redacted]									
Dilated fundus examination	X							X	
Biometry (LenStar)	X								
Keratometric measurements	X						X	X	
Use Verion Vision Planner for IOL power calculation)[f]	X								
Verion (digital marker L, digital marker M)[g]		X		X					
LenSx arcuate incisions[h]		X		X					
CDE		X		X					
Estimated aspiration fluid		X		X					
Phaco aspiration time		X		X					
VerifyEye+ measurement with or without VerifyEye Lynk[g, i]		X		X					
Problems during surgery[j]		X		X					
Manual LRI[k]		X		X					
Device deficiencies	X	X	X	X	X	X	X	X	X

Nominal Time ± Visit Window Limits									
Procedure/Assessment	**Visit 0 Both eyes assessed**	**Visit 00**	**Visit 1**	**Visit 00A**	**Visit 1A Both eyes assessed**	**Visit 2A**	**Visit 3A Both eyes assessed**	**Visit 4A Both eyes assessed**	**USV[n]**
	Day -30 to -1 Screening for both eyes	Day 0 Implant for Eye 1	Day 1 for Eye 1	Day 7-14 Implant for Eye 2 (7-14 days after V00)	Day 1 for Eye 2; Days 8-15 for Eye 1	Day 7-10 post 2nd eye surgery	Month 1 (Days 20-40 post 2nd eye surgery)	Month 3 (Days 70-110 post 2nd eye surgery)	N/A
Adverse events (both volunteered and elicited)[l]	X	X	X	X	X	X	X	X	X
Exit								X	X

[a]All subjects must consent to bilateral treatment; both eyes are to be treated.

[b]Women of child-bearing potential only.

[c]Randomization must be completed following all Screening procedures and confirmation of subject eligibility at least 1 day prior to surgery

[d]IOP should be measured only after all biometric and topographic measurements are performed.

[redacted]

[f]Verion Vision Planner IOL calculation will only be used on both eyes.

[g]Verion (Digital Marker L, Digital Marker M) VerifEye+ with or without VerifEye Lynk will only be performed on the test eyes.

[h]LenSx arcuate incisions will only be performed according to the Verion plan on the test eye as described in the MOP. Incisions may be refined based on ORA recommendation

[i]IOL power recommended by ORA with VerifEye+ will only be used on the test eyes.

[j]Includes intraoperative complications.

[k]Manual LRI will only be performed on astigmatism of > 0.50 D, including any known surgically induced astigmatism.

[l]AEs should be collected from time of consent

[m]Assessments will be performed at the Week 1 visit for eye 1 only.

[n]The assessments captured at the USV are dictated by the Investigator per his/her medical judgment. Dilated fundus examination may also be performed, based on Investigator's judgment.

[o]If subject did not meet TBUT at screening visit and warm compress therapy is started, TBUT must be reassessed to ensure subject meets criteria prior to randomization.

[redacted] CDE=cumulative dissipated energy, IOP=intraocular pressure, LRI=limbal relaxing incision, USV=unscheduled study visit.

7 INTRODUCTION

7.1 Background

Cataract is the leading cause of blindness in the world, and cataract surgery is one of the most commonly performed operations in the Western world. Preferred surgical techniques have changed dramatically over the past half century with associated improvements in outcomes and safety. Femtosecond laser platforms that can accurately and reproducibly perform key steps in cataract surgery, including corneal incisions, capsulotomy and lens fragmentation, are now available (Day 2016). According to the World Health Organization (WHO), an estimated 20 million people worldwide are blind due to bilateral cataracts (Baltussen 2004).

Over the past decades, the safety and effectiveness of cataract surgery has improved, but cataract patients continue to have high expectations when it comes to their postoperative refractive outcomes. Modern cataract surgery is becoming a refractive procedure, and surgeons not only aim to remove the cataractous lens successfully but also to reduce or eliminate pre-existing refractive errors. Published literature reports 71% and 47% of post cataract removal patients are within ±0.5 D and ±0.25 D respectively of the biometry prediction error. It is interesting to note that only two thirds of the study population planned for emmetropia became emmetropic (Behndig 2012). Although there are reports on preoperative biometry prediction and astigmatism management (Behndig 2012, Hatch 2015), it is necessary to address the role of other variables such as posterior corneal curvature to total astigmatism and standard intraocular lens (IOL) calculation.

Although there are published results regarding the individual devices of the Cataract Refractive Suite (CRS) (Hatch 2015, Nemeth 2015, Woodcock 2016, and Ianchulev 2014) and retrospective study of the use of the major components of the CRS (AnalyzOR Retrospective Data Exploration Study, data on file), there is no prospective study that reports the refractive outcomes produced by using the major components of the CRS together.

The aim of this study is to assess the refractive accuracy when using the combined CRS for surgical planning and lens removal and to compare these results with those obtained using the standard manual technique.

The CRS is composed of a series of devices that address the pre-planning stages of IOL calculation and integrates this information into the operative stage up to postoperative follow-up. In this study, the major components of the CRS are identified as Verion Image Guided System, LenSx femtosecond laser and Optiwave Refractive Analysis (ORA) with VerifEye+ with or without VerifEye Lynk. Verion takes a preoperative image of the eye and

the information captured is automatically transferred and used for IOL calculation. This information is then linked to LenSx laser where the customized treatment is automatically integrated. Intraoperatively, phacoemulsification is performed to remove the cataractous lens. After which, the ORA with VerifEye+ refracts the eye in the aphakic state and can confirm the IOL power selected or recommend a different IOL power and IOL positioning if using a toric IOL. All of this information is stored in the system and can be used to track postoperative results and eventually help the surgeon personalize and optimize their surgeries to achieve reproducible and consistent refractive outcomes.

7.2 Clinical Study Design

This is a prospective, multi-center, observer-masked, randomized, active control (standard manual technique), contralateral design study to evaluate refractive predictability between CRS and standard manual technique. All products under investigation are commercially available in the countries where the study is being conducted.

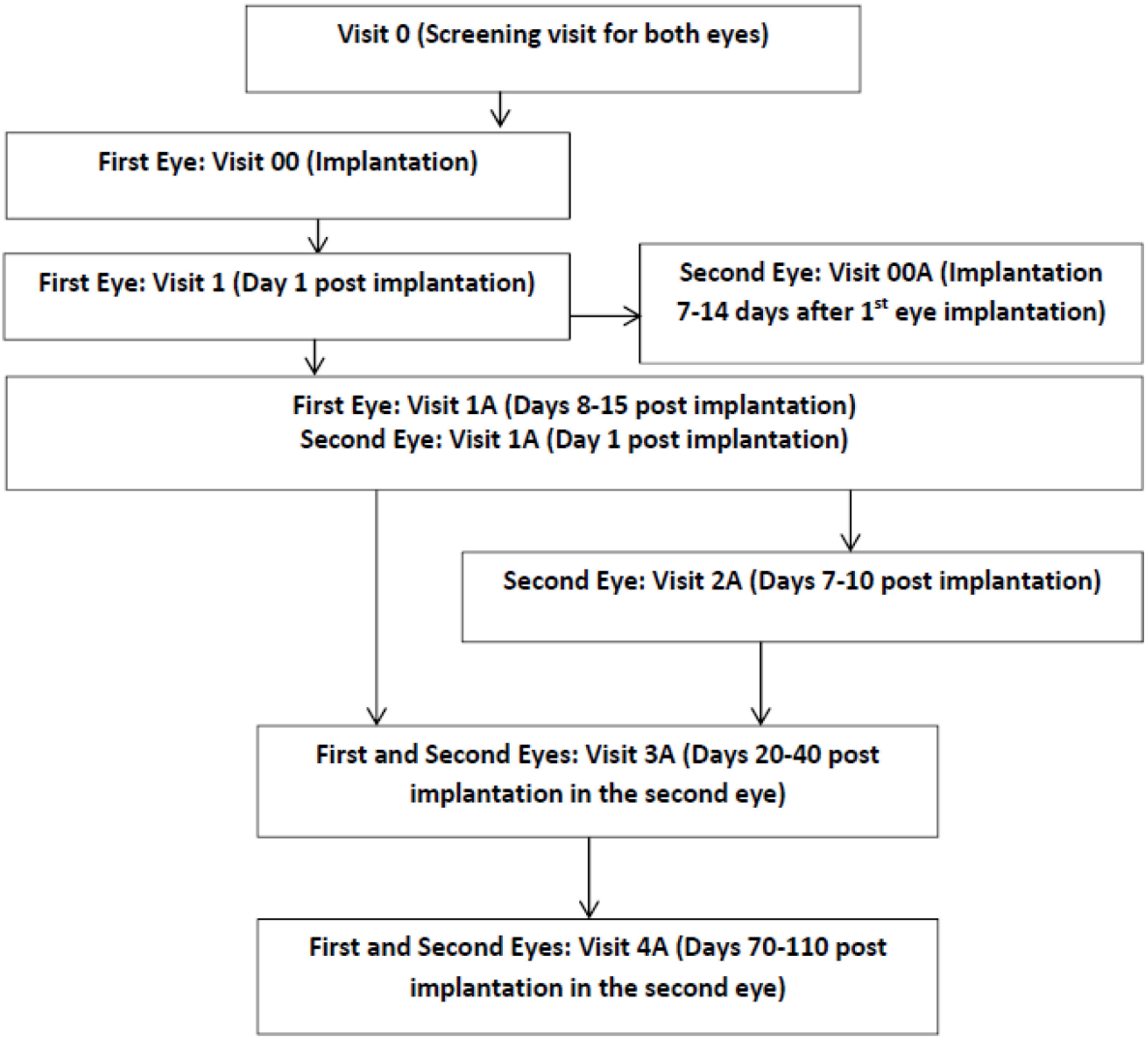
The eye with the worse preoperative best-corrected distance visual acuity (BCDVA) will undergo cataract surgery with IOL implantation first. If the preoperative BCDVA is equal in both eyes, then the right eye will undergo the surgery and IOL implantation first. The first eye will be randomized to receive the test or control treatment; the fellow eye will receive the opposite assignment. Subjects are required to attend 8 study visits, during which assessments will be scheduled separately for the first study eye, the second study eye and both study eyes.

Subjects will attend the Screening visit from Day -30 to Day -1 (Surgery Eye 1, Visit 00), followed by Visit 1 (Day 1 post surgery for Eye 1), Visit 00A (Surgery Eye 2 [7-14 days after that for Eye 1]), Visit 1A for both eyes (Day 1 for Eye 2; Day 8-15 for Eye 1), Visit 2A (Day 7-10 post Eye 2 surgery), Visit 3A (Month 1 [Day 20-40 post Eye 2 surgery]), Visit 4A (Month 3 [Day 70-110 post Eye 2 surgery]). Total expected clinical study duration will be approximately 5 months after being screened for study eligibility.

This study will employ an adaptive design with a potential sample size adjustment based on interim analysis (Section 15.8). It is planned that the study will enroll approximately 350 subjects to initially randomize and treat 300 subjects (that could potentially increase to approximately 580 subjects enrolled and 500 subjects randomized). An interim analysis will be performed once 200 subjects have been randomized, treated and completed 1-month follow-up visits. An additional 200 subjects may be randomized and treated beyond the initially planned 300 subjects. Thus the study will randomize and treat between 300 and 500 subjects.

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

Figure 7–1 Study Design



In order to reduce bias, the observer (ie, study technician assessing primary endpoint data) will remain masked to the treatment assignment. The masked observer will be collecting and recording the required data at all the follow up visits. Alcon and other site personnel [eg, surgeons, 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] must not reveal the treatment assignment to masked site personnel at any time during the study.

8 CLINICAL STUDY OBJECTIVES

8.1 Primary Objective

The primary objective of the study is:

- To compare the refractive predictability(prediction enor) between the CRS and standard manual technique at 1 month postoperative.

8.2 Secondary Objectives

The secondary objectives of the study are:

- To compare the amount of cumulative dissipated energy expended in the eye between the CRS and standard manual technique.
- To assess the average estimated aspiration fluid used during surgelybetween the CRS and standard manual technique.
- To assess the average aspiration time spent during surgely between the CRS and standard manual technique.

[redacted]

8.4 Study Endpoints

8.4.1 Effectiveness Endpoints

The prima1y effectiveness endpoint is:

- Percentage of eyes in which the MRSE at 1 month is 0.50 D relative to predicted MRSE.

Seconda1y effectiveness endpoints are as follows:

- Mean cumulative dissipated energy (CDE) expended in the eye duringsurge1y.
- Mean estimated aspiration fluid used during surgery.
- Mean aspiration time spent during surge1y.

[redacted]

[redacted]

8.4.2 Safety Endpoints

Safety endpoints are as follows:

- Adverse events
- Slit-lamp examination
- Intraocular pressure (IOP)
- Surgical problems
- Dilated fundus examination
- Device deficiencies

9 INVESTIGATIONAL PLAN

9.1 Outline of Clinical Study

In this prospective, multi-center, observer masked, randomized, active control, post market clinical study, approximate ly 350 to 580 subjects with bilateral cataracts will be emolled at approximately 12 investigational sites and undergo cataract surgery. An estimated 300 to 500 subjects will be randomly assigned to receive either CRS or standard manual technique first, and the other eye will undergo opposite technique. Subjects participating in this study will attend a total of 8 study visits over a period of up to 154 days: a Screening visit (Visit 0), a surgery/implantation visit (Eye I-Visit 00; Eye 2-Visit 00A), and up to Visit 4A(124 days from first eye implantation) as post-surgery follow-up visits. Refer to Figure 7- 1 for a study outline diagram. Additional subjects may be emolled based on the interim analys is.

9 . 2 Rationale for Study Design

The study is being perform ed to assess the refractive predictability when using CRS and to compare the results with those assessed using standard manual technique. There are several factors that can affect accuracy to target such as variability in keratometiy readings, IOL calculation, surgeon factors, pre-existing and induced astigmatism and type of IOL implanted among others. This study is designed to mitigate these factors by ensuring appropriate target population with the inclusion/exclusion criteria; and using standard integrated measurement devices in order to implant and confirm the IOL that will be closest to target refraction.

9.3 Procedures Conducted at each Study Visit

Procedures required by the protocol to be conducted at each study visit are listed in the Table 6-1 and detailed in Section 12 and in the manual of procedures (MOP) that accompanies this protocol. A brief summa1yof the main procedures perfo1med by visit is provided here.

- At the Screening visit (Visit 0) the subject will sign infmmed consent. Standard procedures will be perfo1med to deternline subject eligibility.
- Following confam ation of eligibility, the surge1y visit will be scheduled for the first study eye. The subject will be randomized (via the Medidata RAVE) prior to the first surge1y visit to a technique sequence. The technique sequence will be randomly assigned as either: CRS then standard manual technique or standard manual technique then CRS.
- At the surge1yvisit (Visit 00), if subjects are randomized to CRS, the test devices to be used on the first eye during surge1y will be: Verion (digital marker L, digital marker M), LenSx device, VerifyEye+ measurement with or without VerifyEye Lynk. The estimated aspiration fluid, phacoemulsification aspiration time, and CDE will be recorded for both arms of the study. The subject will then undergo surge1y in the other eye using a standard manual technique and perfo1m manual LRI as needed as indicated on the MOP (Visit 00A).
- At the post-surge1y follow-up visits, ie, Visit 1 (for the first study eye), Visit l A (for both study eyes), Visit 2A (for the second study eye), Visit 3A and Visit 4A (for both eyes), the following assessments will be perfmmed: concomitantmedications, [redacted] manifest refract ion, slit-lamp examination, AEs and device deficiencies will be recorded in all post-surge1y follow-up visits.
    - IOP measurements will be perfmmed at Visit lA and Visit 4A.
    - Dilated fundus examination will be perfmmed at Visit 4A.
    - Keratometric measurements will be perfmmed at Visit 3A and Visit 4A.

9.4 Risk Benefit Assessment

9.4.1 Potential Risks

VERION® Image Guided System: The following conditions may affect the accuracy of surgical plans prepared with the Verion reference unit: a pseudophakic eye, eye fixation problems, a non-intact cornea or an ilTegular cornea and severe diy eyes. In addition, subjects should refrain from wearing contact lenses during the reference measurement as this may

interfere with the accuracy of the measurements (refer to Table 12-1 for details). The following conditions may affect the proper functioning of the Verion digital marker: changes in a subject's eye between preoperative measurement and surgely, an inegular elliptic limbus (eg, due to eye fixation during surgely, and bleeding or bloated conjunctiva due to anesthesia). In addition, the use of eye drops that constrict sclera vessels before or during surgely should be avoided.

LenSx® laser : The following complications may occur with the use of LenSx laser:

- Incomplete or intenupted capsulotomy
- Capsular tear
- Corneal abrasion or defect
- Infection
- Damage to intraocular structures
- Anterior chamber fluid leakage
- Anterior chamber collapse
- Suction failure
- Elevated pressure to the eye

The following conditions may affect the functioning of LenSx laser: corneal disease that precludes applanation of the cornea or transmission of laser light at 1030 nm wavelength, descemetocele with impending corneal rupture, presence of blood or other material in the anterior chamber, poorly dilating pupil, such that the iris is not peripheral to the intended diameter for the capsulotomy, conditio ns which would cause inadequate clearance between the intended capsulotomy depth and the endothelium (applicable to capsulotomy only), previous corneal incisions that might provide a potential space into which the gas produced by the procedure can escape, corneal thickness requirements that are beyond the range of the system, corneal opacity that would interfere with the laser beam, hypotony or the presence of a corneal implant, residual, recun ent, active ocular or eyelid disease, including any corneal abno1mality (for example, recun ent corneal erosion, severe basement membrane disease), hist01y of lens or zonular instability and any other contraindication to cataract or keratoplasty.

VeritEye+: The following cond itions may affect the accuracy of measurements taken by VerifEye+. Progressive retinal pathology such as diabetic retinopathy, macular degeneration, or any other pathology that the physician deems would interfere with patient fixation. Corneal pathology such as Fuchs', epithelial basement membrane dystrophy (EBMD), keratoconus, advanced pte1ygium impairing the cornea, or any other pathology that the physician deems would interfere with the measurement process. Residual viscous substances left on the corneal surface such as lidocaine gel or viscoelastics. Visually significant media opacity, such as prominent floaters or asteroid hyalosis. Retro or peribulbar block, or any other treatment that impairs a patient's ability to visualize the fixation light. Utilization of iris hooks during surge1y.Pupil dilation less than 4.5 mm.

Stand31'd manual technique: The following complications may occur with the standard manual technique.

- Incomplete or intenupted capsulotomy
- Capsular tear
- Corneal abrasion or defect
- Infection
- Damage to intraocular strnctures
- Anterior chamber fluid leakage
- Anterior chamber collapse

Another risk associated with phacoemulsification is rise in IOP. The response in IOP to phacoemulsification is biphasic, with a transient immediate rise followed by a modest long-te1mdecrease. Postoperative IOP usually peaks 5- 7 h after surge1y and returns to n01mal levels in 1- 3 days. Although transient, the elevated IOP can cause ocular pain, may increase the risk of sight threateningcomplications such as retinal vascular occlusion, progressive field loss in advanced glaucoma, and anterior ischemic optic neuropathy in susceptible patients (Karatas 2013).

9.4.2 Potential Benefits

VERION® Ima ge Guid ed Sys tem : The Verion reference unit is a preoperative measurement device that captures and utilizes a high-resolution reference image of a subject's eye. It provides preoperative surgical planning functions to assist the surgeon with planning cataract surgical procedures that takes into account variables not typically considered when doing standard IOL calculation such as rotational eye movementsand surgical induced astigmatism.

The Verion reference unit also suppmis the expmi of captured images of the eye (ie, scleral vessels, undilated pupil), preoperative measurement data, and surgical plans for use with the Verion digital marker and other compatible devices. These features enable automatic positioning and cent:ration of the capsulotomy and IOL as well as placement of corneal incisions in the right location taking into account cyclorotation of the eye which would othe1wise be unidentifiable without physically marking the eye pre-op.

LenSx laser: The LenSx laser is indicated for use in subjects undergoing cataract surgery for removal of the c1ystalline lens. It pre-cuts the anterior capsule, lens and creates the corneal incisions for easier removal of the cataractous lens in the operating room. The LenSx femtosecond laser can create corneal incisions that are single plane or multi-plane allowing for customization of the cuts. Since the LenSx device pre-cuts the eye prior to surge1y, this will require less phacoemulsification power and time to remove the cataractous lens. Reduced time in the eye has been associated with less risk for potential complications such as corneal bums and others.

With the integrationof the Verion to the LenSx femtosecond laser, the pre-op data collected from the Ve1ion refe rence unit is transfeITed to the Verion Digital Marker L allowing automatic positioning and placement of the cuts. This automatic feature can decrease any e1rnr that may come from manual transcription.

ORA with Verifeye+: The ORA$_{TM}$ System is designed to be used during ophthalmic surge1y. Wavefront data is obtained, analyzed, and presented to the user via a ca1i mounted liquid c1ystal displays (LCD) touchscreen, within a period that does not impede the surgical procedure. The ORA System is intended for use in the measurement and analysis of the refractive power of the eye (ie, sphere, cylinder, and axis measurements) and can obtain measurements in the phakic, aphakic and pseudophakic state. It uses proprieta1y IOL power calculations that aim to assist the surgeon in IOL power (sphere, and in the case of toric IOLs, cylinder power and axis of placement) selection intraoperatively. The predicted IOL power is calculated at the reference unit po1iion of the Verion, but then confiimed or an alternate plan suggested by ORA following the aphakic measurements. In this study, due to the type of IOL specified SV25T0, only the aphakic application will be used. The pseudophakic function of the system is typically only used in toric IOL cases to refine axis of placement.

Standardmanual technique: The poten tial benefits of standard manual techniques include:

- Removal of the cataractous lens.
- No additional equipment required and therefore has less associated cost.

- No extra learning curve for the surgeon that comes with using a new device.

9.4.3 Risk benefit Assessment

Surgical devices for both the techniques are commercially available and the safety and effectiveness of these surgeries have been established in clinical trials prior to approval of these devices.

Overall, the benefits of the CRS and manual technique are considered to outweigh the risks.

Phacoemulsification cataract surgery is considered a safe procedure; however, introduction of new technologies allows the surgeon to improve preoperative planning and optimize refractive outcomes (Solomon 2016).

10 SUBJECT POPULATION

Subjects 2 22 years age, diagnosed with bilateral cataracts and fulfilling all other eligibility criteria in Section 10.1 and Section 10.2, will be emolled into the study. This study will emoll approximately 350 subjects to initially randomize and treat 300 subjects (that could potentially increase to approximately 580 subjects emolled and 500 subjects randomized) to be emolled at approximately 12 sites.

10.1 Inclusion Criteria

Subjects should fulfill the below criteria to be eligible for this study.

1. Adults (2 22 years of age at the time of surge1y), diagnosedwith bilateral cataracts.
2. Planned cataract surge1y and implantation of of ReSTOR +2.5 D multifocal IOL in both eyes.
3. Target is emmetropia (+0.50 to -0.50).
4. Clear intraocular media other than cataract in study eye(s).
5. Willing and able to complete all required postoperative visits.
6. Able to comprehend and sign a statement of info1med consent.
7. Potential postoperative visual acuity of 0.2 logarithm of the minimum angle of resolution (LogMAR) or better.
8. Preoperative keratometiy reading between 40.0 D to 49.0 Din the prima1ymeridians.
9. Preoperative axial length between 21.5 mm to 27.0 mm.

10. Preoperative/Baseline corneal with-the-rule (WTR), against-the-rule (ATR) or oblique astigmatism ≤ 1.25 D.

10.2 Exclusion Criteria

1. Significant irregular corneal astigmatism as assessed by the index relevant to the corneal topographer and investigator judgement of the topography maps
2. History of or current severe dry eyes.
3. Tear breakup time (TBUT) < 10 secs prior to randomization.
4. Retinal/uveal pathology or concurrent ocular disease including age-related macular degeneration (AMD), choroidal neovascularization (CNV), glaucoma, diabetic retinopathy, retinitis pigmentosa, and optic nerve pathology.
5. Previous intraocular or corneal refractive surgery.
6. Any inflammation or edema (swelling) of the cornea, including but not limited to the following: keratitis, keratoconjunctivitis, and keratouveitis.
7. Amblyopia.
8. Previous corneal transplant.
9. Previous retinal detachment.
10. Recurrent severe anterior or posterior segment inflammation of unknown etiology.
11. Pregnancy at time of Screening.
12. Participation in another concurrent clinical study.
13. Any other ocular condition or systemic co-morbidity that the Investigator determines would confound the results of this study or would prohibit completion of the study assessments.

11 TREATMENT

Throughout the clinical study, the Investigator will be responsible for the ensuring that the clinical study products are not used in any unauthorized manner.

Table 11-1 Treatments

	Test article: CRS	**Control articles: Standa1·d m a nu al tec hniqu e**
Ad ministration	Intervention during preope rative planning and during cataract surge1y	Intervention during surge1y
Man ufacturer	Alcon Laboratories, Ft. Worth, TX, USA	--

11.1 Investigational Products

Test Article: CRS composed of the following:

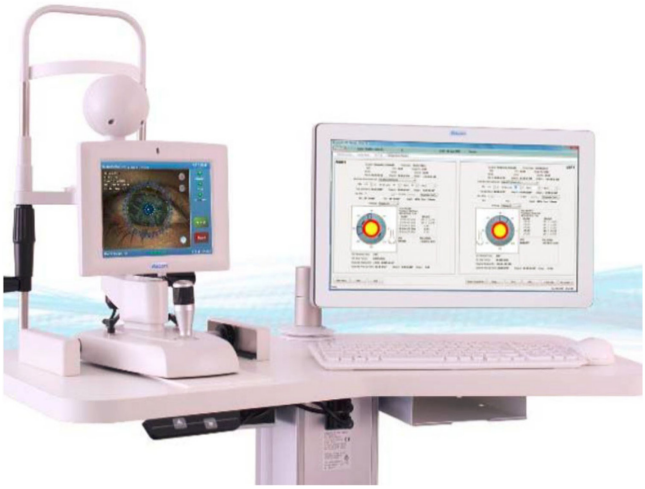
1. Verion Image Guided System which comprises of the following:
    - Verion measurement module
    - Verion visionplanner
    - Verion digital marker
2. LenSx femtosecond laser
3. ORA with VerifEye+ (with or without the VerifEye Lynk)

The CRS is a collection of advanced technologies that is designed to guide inf01med surgical decisions, minimize potential sources of en or, and may allow surgeons to be more consistent in delivering the desired refractive outcomes. The cmTent focus in cataract surge1y is toward achieving better refractive outcomes, and the CRS helps to achieve this goal because each component enhances accuracy in the many steps of the surgical procedure. The CRS may improve refractive outcomes by integrating the different technologies that is used from the planning stage to surge1y to postoperative follow-up. It gives the surgeon the capability to access, review and analyze their postoperative data all in one location and personalize surgeon factors to fmther optimize their results.

The Verion Image Guided system performs 3 functions: diagnostic imaging, surgical planning, and surgical guidance. The Verion Reference Unit is comprised of the Verion measurement module and the vision planner. The measurement module obtains a digital image of the eye and performs keratometry and pupillometry measurements. The Verion vision planner—performs IOL power selection and astigmatism management—uses the data from the measurement module. The reference image and the surgical plan are then exported to the Verion digital marker L and digital marker M that creates a computer-generated tracking overlay for the LenSx laser and the surgical microscope respectively. The image and overlay support eye tracking and registration while providing a real-time guide for accurate capsulotomy creation, corneal incisions, and IOL positioning.

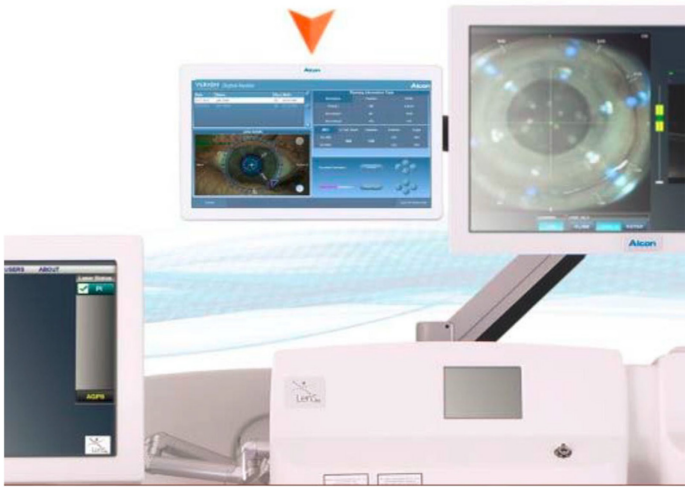
The Verion measurement module is used for performing pre- and post-op measurements and the Verion vision planner is used to plan the surgery steps (including lens calculation) and to record the surgery and postoperative measurement data (Figure 11–1).

Figure 11–1 Test Article1: Verion Image Guided System (Verion Reference Unit)



Verion digital marker is the link of the diagnostic and surgery context information to the eye coordinate system. It provides the integrated image guidance throughout the diagnostic and surgery process and the per-subject documentation of the surgery workflow (Figure 11-2 and Figure 11–4).

Figure 11-2 Test Article2: Verion digital marker L



The LenSx laser creates incisions through tightly focused femtosecond laser pulses that cut tissue with micron-scale precision. The incision is achieved by contiguously placed microphotodisruptions scanned by a computer-controlled delivery system. The LenSx laser is indicated for use in subjects undergoing cataract surgery for removal of the crystalline lens. Intended uses in cataract surgery include anterior capsulotomy, phacofragmentation, and the creation of single plane and multi-plane arc cuts/incisions in the cornea, each of which may be performed either individually or consecutively during the same procedure (Figure 11–3).

Figure 11–3 Test Article3: LenSx Femtosecond Laser

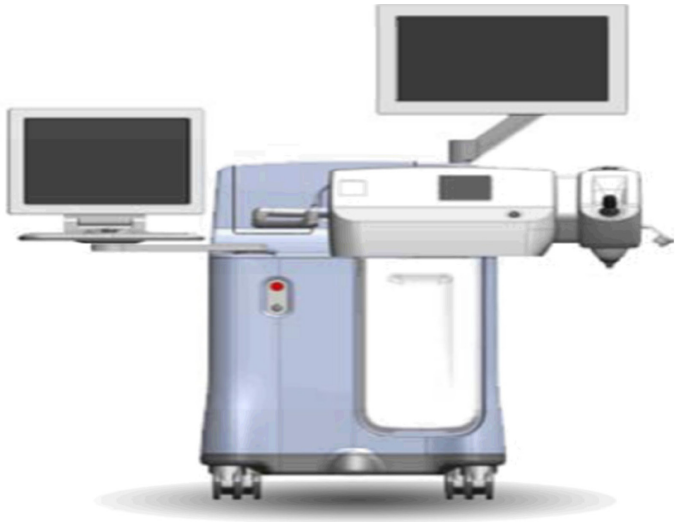


Figure 11–4 Test Article4: Verion Digital Marker M

ORA with VerifEye + is an intraoperative aberrometer that is capable of calculating the IOL power based on the aphakic refraction and the subject's preoperatively measured axial length and keratometry readings and white to white measurements. In this study, IOL power recommended by ORA with VerifEye+ will be used on the test eyes.

Figure 11–5 Test Article5: ORA with Verifeye+

ORA with VerifEye Lynk is an intraoperative aberrometer which contains a data interface with Verion. It is used in conjunction with Verion digital marker M (Version 3.0) to combine intraoperative refraction with integrated image guidance. ORA System AnalyzOR in the VerifEye Lynk system receives all required preoperative data from the Verion vision planner (Version 3.0).

Control Articles: Standard manual technique and manual limbal relaxing incisions as necessary. If a manual limbal relaxing incision is needed, the calculation will be based on the output of the Verion measurement module and Vision planner taken at Screening. The control procedure is standard biometry for IOL calculation and cataract removal using phacoemulsification technique.

11.2 Usage

Verion reference unit and Verion digital marker:

Plausibility of measurement: Ensure the cornea is in natural condition before performing a Verion measurement. Normal conditions might be violated after direct cornea contact. Do not perform more than 15 measurements per session per eye.

The user should check all measurement readings for plausibility. Ensure that the subject is not wearing contact lenses during the time of reference measurement. Dry eyes might impact the accuracy and robustness of the keratometry measurement. It may not be possible to carry out measurements on subjects with fixation problems. Reference measurements results for subjects with a non-intact cornea (eg, due to cornea implants, corneal transplants, corneal scarring, keratorefractive surgery, or irregular cornea) or pathologies that influence the appearance of limbus, pupil and/or iris may be incorrect. In such cases, a cross-check with other alternative diagnostic devices/methods is mandatory. Always check status for plausibility. Reference measurements on such subjects may be incorrect. Measurements of pseudophakic subjects may be incorrect or not possible due to the reflexes of the IOL.

The user should check all measurement readings for plausibility. This involves verifying the registration proposals of the Verion digital marker between reference and microscope image, as well as verifying limbus detection during live tracking. An irregular elliptic limbus may not be detected correctly during the surgery.

Refer to the user manuals for the Verion reference unit and the Verion digital marker for a complete description of proper use and maintenance of these devices, as well as a complete list of contraindications, warnings and precautions.

Refer to the LenSx laser operator’s manual for a complete listing of indications, warnings and precautions.

Refer to the ORA VerifEye+ operator’s manual for a complete description of proper use and maintenance of these devices, as well as a complete list of warnings and precautions.

The control procedure (standard manual technique) is standard biometry for IOL calculation and cataract removal using phacoemulsification technique.

12 CLINICAL STUDY PROCEDURES

12.1 Clinical Study Assessments

The following section outlines the assessments to be performed in this clinical study. Assessments are described in detail in the MOP, and are outlined in tabular format in Section 6 of this protocol.

NOTE: AEs are collected and reported for both the study eyes (refer to Section 13).

12.1.1 Screening Visit (Visit 0)

Visit 0: Day -30 to Day -1 (for both eyes)

Upon signing informed consent, subjects are considered enrolled. Subjects will be assigned a single subject identifier at the Screening 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 electronic data capture (EDC) system. As an example: "4584.00001" (the Investigator number and subject number are separated by a "." character).

Eligible subjects who currently wear contact lenses must discontinue their use before undergoing Screening procedures in the study for the appropriate amount of time as indicated in Table 12–1.

Table 12–1 Minimum time to stop wearing contact lens before Screening visit

Type of Contact Lens	Minimum Time to Stop Wearing before Preoperative Visit[a]
Hard (PMMA) lenses	3 weeks
RGP lenses	3 weeks
Soft Toric lenses	2 weeks
Soft lenses	3 days

[a]These guidelines are estimations only. Preoperative measurements should not be taken until stability of the keratometry reading has been established.

PMMA= polymethyl methacrylate, RGP=rigid gas permeable.

Below is a list of study procedures to be undertaken at Visit 0. Procedures should be performed in the order presented below unless otherwise stated. All assessments must be documented in the source documentation and eCRFs (if applicable).

1. For a potential subject meeting all entry criteria via pre-screening, invite him/her to participate in the study, and carry out the informed consent process if he/she is interested. 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.

2. Document demographics, ocular and nonocular medical history, ocular and nonocular concomitant medications.
3. Perform a urine pregnancy test, if the subject is a woman of childbearing potential.
4. [redacted]
5. Perform manifest refraction (refer to MOP for details).
6. [redacted]
7. Perform slit-lamp evaluation.
8. Measure the TBUT. Record time in source document.

NOTE: If either eye has a TBUT < 10 secs at the Screening Visit, start treatment with warm compresses if all other eligibility criteria are met.

9. Perform corneal topography. Assess for irregular corneal astigmatism by evaluating the relevant irregularity index and the appearance of the topography maps. Document on the printed maps whether or not there is significant irregular corneal astigmatism and provide a justification for the assessment.
10. Perform Keratometry measurement with LenStar
11. Use the Verion Vision Planner for IOL power calculation.(refer to MOP for details).
12. Perform biometry (LenStar) (refer to MOP for details).
13. Identify target refraction.
14. Perform intraocular pressure measurement. IOP should be measured only after all biometric and topographic measurements are performed (refer to MOP for details).
15. Conduct dilated fundus examination (refer to MOP for details).
16. Record any device deficiency and AEs.
17. Randomize the subject.

NOTE: Randomization must be completed following all Screening procedures and confirmation of subject eligibility prior to surgery (this includes TBUT*).

*If subject starts warm compresses after the screening visit, the subject must return prior to surgery day (Visit 00: Day 0) to have TBUT reassessed. If the TBUT is < 10 secs in either eye, the subject must be discontinued from the study as a screen fail. If the TBUT is ≥ 10 secs in each eye, the subject may be randomized and continue in the study. The warm compresses regimen must be maintained for the duration of the study. Record TBUT in source.

12.1.2 Surgery Visit (Visit 00 and Visit 00A)

Visit 00: Day 0 (implant for Eye 1)

Visit 00A: 7-14 days after surgery for Eye 1 (implant for Eye 2)

Below is a list of study procedures to be undertaken at surgery visit. Procedures should be performed in the order presented below. Activities involving multiple delegated staff members may be performed in parallel. All assessments must be recorded in source documentation and eCRFs (if applicable).

Procedures to be performed in the CRS eye:

1. Document any changes to ocular and nonocular concomitant medications.
2. Prepare subject /operative eye for surgery in accordance with site specific operating procedures.
3. Create a 4.8 to 5.5 mm anterior capsulotomy centered on the line of sight using the LenSx femtosecond laser.
4. Remove the cataract by phacoemulsification using Centurion.
5. Record use of CDE.
6. Record estimated aspiration fluid.
7. Record phacoemulsification aspiration time.
8. Record aphakic refraction and aphakic spherical equivalent (SE).
9. Record IOL power recommended by VerifEye+ (or Lynk) and predicted post-op SE.

10. Record implanted IOL power and predicted post-op SE.
11. Record surgical problems, complications, or other events that occur during surgery.
12. Record any device deficiencies and AEs. Refer to Section 13 for further detail.

Procedures to be performed in the Standard Manual Technique eye:

1. Ensure IOL power calculation was performed.
2. Document any changes to ocular and nonocular concomitant medications.
3. Prepare subject /operative eye for surgery in accordance with site specific operating procedures.
4. Create a 4.8 to 5.5 mm anterior capsulotomy centered on the line of sight using the manual technique.
5. Remove the cataract by phacoemulsification using the Centurion.
6. Record use of CDE.
7. Record estimated aspiration fluid.
8. Record phacoemulsification aspiration time.
9. Perform manual limbal relaxing incision (LRI). Manual LRI will only be performed on astigmatism of > 0.50 D, including any known surgically induced astigmatism, according to the Verion measurements obtained at Screening.
10. Record implanted IOL power and predicted post-op SE.
11. Record surgical problems, complications, or other events that occur during surgery.
12. Record any device deficiencies and AEs. Refer to Section 13 for further detail.

12.1.3 Visit 1 (Day 1 for Eye 1)

1. Document any changes to ocular and nonocular concomitant medications.
2. [redacted]
3. Perform slit-lamp examination.

4. Perform IOP measurement.

5. Record any device deficiencies and AEs. Refer to Section 13 for further detail.

12.1.4 Post-Surgery Visit (Visit 1A, 2A, 3A and Visit 4A)

Below is a list of study procedures to be undertaken at post-surgery visits. Procedures should be performed in the order presented below. All assessments must be recorded in source documents and eCRFs (if applicable).

Ocular assessments are to be performed in the study eye only.

1. Document changes in ocular and nonocular concomitant medications at Visit 1A, 2A, 3A, and Visit 4A.
2. [redacted]
3. [redacted]
4. [redacted]
5. [redacted]
6. Perform manifest refraction assessment at Visit 1A, 2A, 3A, and Visit 4A. However, at Visit 1A, assessments will be performed at the Week 1 visit for eye 1 only (Refer to MOP for details).
7. [redacted]
8. Perform slit-lamp examination at Visit 1A, 2A, 3A, and Visit 4A. Refer to MOP for details.
9. [redacted]
10. [redacted]
11. Perform Keratometric measurements at Visit 3A and Visit 4A.
12. Perform IOP at Visit 1A and 4A only. IOP should be measured after all VAs, corneal

measurements and refractive findings have been obtained. Refer to MOP for details.

13. Perform dilated fundus exam at Visit 4A only. Refer to MOP for details.
14. Record any device deficiencies and AEs. Refer to Section 13 for further detail.
15. Document subject exit from study at Visit 4A.

12.2 Unscheduled Visits

An unscheduled study visit (USV) 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 USV may or may not result in the caphire of an AE. Likewise, an AE may be captured without the report of an USV (eg, AE identified subsequent to study eye examination by non-study personnel).

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

- Concomitant medications
- IOP
- [redacted]
- [redacted]
- Manifest refraction
- Slit-lamp examination
- Dilated fundus examination, as necessary
- Device deficiencies
- AEs

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

For safety purposes, if an USV is required after the final study visit, the visit should be documented. Refer to Section 13.6 for further detail.

12.3 Missed Visit

If a subject misses a scheduled visit, reschedule the subject within the same visit period. 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 doc umentation, 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 should be documented.

If a subject is unable to return for the final study visit, complete the Exit case rep01i form with the appropriate reason for discontinuation indicating the subject is lost to follow-up.

12.4 Discontinued Subjects

Discontinued subjects withdraw, or are withdrawn from the study after signing informed consent and prior to completing all study visits. Subjects signing consent, but withdrawing or withdrawn prior to randomization will be considered discontinued due to screen failure and the failed entry criterion will be documented (refer to Section 10).

Subjects may discontinue study pariicipation at any time and for any reason. Subjects may be discontinued from the study at any tin1e if, in the medi ca l opinion of the Principal Investigator or designated, qualified medical personnel, continued pariicipation poses a health risk to the subject. Subject numbers from discontinued subjects will not bereissued. Discontinued subjects will not be replaced.

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 any reasonable cause. The Investigator may also terminate the study at his/her site for reasonable cause. Reasons for the closure of an investigational site or termi nation of a study may include:

- The Investigator fails to comply with the protocol or good clinical practice (GCP) guidelines.
- Safety concerns.
- Inadequate recrnitment of subjects by the Investigator.

If the clinical study is prematurely terminated or suspended, the Sponsor will inform the Investigator and the regulat01y authorities (where applicable) of the termination/suspension and the reason for the termination/suspension. The Investigator should promptly notify the IRB/IEC of the termination or suspension and of the reasons.

If the Sponsor terminates the study for safety reasons, the Sponsor 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 definitions of all categories of AEs and SAEs.

Figure 13–1 Categorization of All Adverse Events

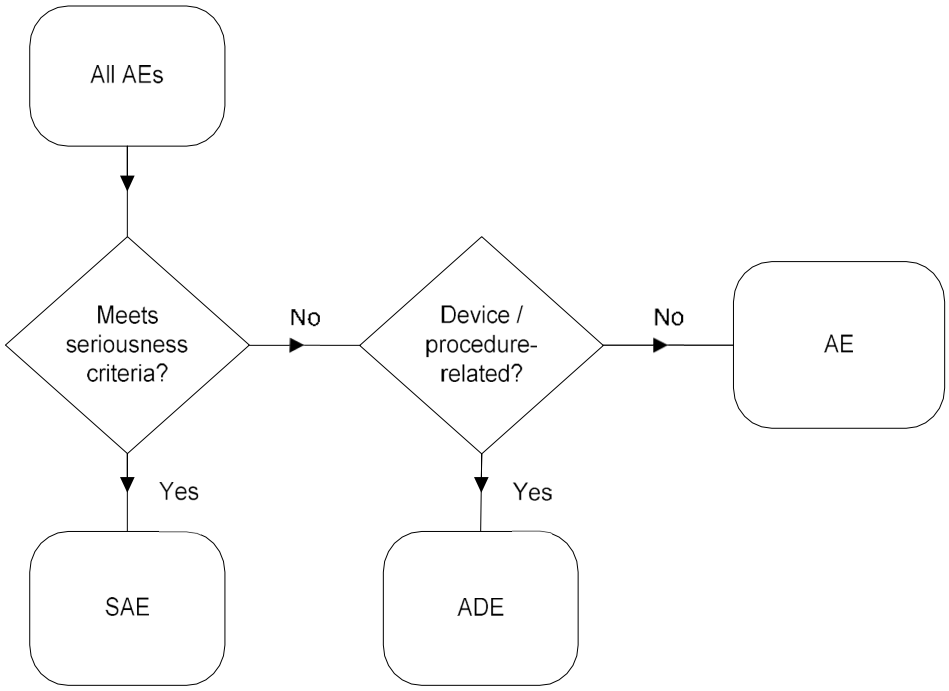
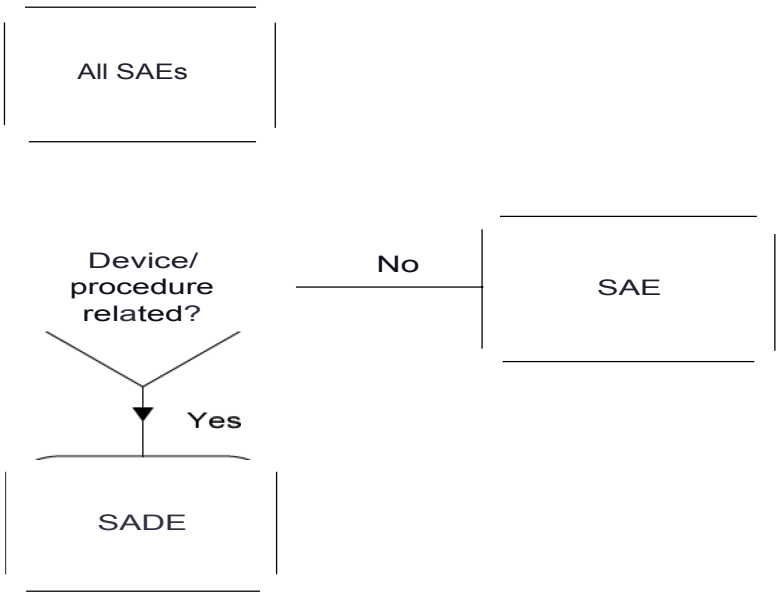


Figure 13-2 Categorization of All Serious Adverse Events



Device Deficiencies

A device deficiency may or may not be associated with subject haim (ie, ADE or SADE); however, not all ADEs or SADEs are due to a device deficiency. The Investigator should dete1mine the applicable category for the identified or suspect device deficiency and repmt any subject ha1m separa tely. For definitions of device deficiency, malfunction and use en or, refer to Section 4.

- Laser defect
- Laser optic
- Unable to calibrate laser
- Suspect product contamination (patient interface)
- Lack of effectiveness

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 evaluated during the study are to be reviewed by the Investigator. Any untoward (unfavorable and unintended) change in a protocol-specific parameter that is clinically relevant, in the opinion of the Investigator, is to be repmied as an AE. These clinically relevant changes will be repo1ied regardless of causality.

13.3 Procedures for Recording and Reporting

AEs are collected from the time of infmmed consent. Any pre-existing medical conditions or signs/symptoms present in a subject prior to the stali of the study (ie, before info1med consent is signed) are not considered AEs in the study and should be recorded in the Medical Histmy section of the eCRF.

For each recorded event, the ADEs and SAEs documentation must include: date of occmTence, seve rity, treatment (if applicable), outcome, and assessments of the seriousness and causality. In addition, the Investigator must document all device deficiencies reported or observed with test and control ruticles on the Device Deficiency eCRF. The site must submit all available info1mation on ADEs, SAEs, and device deficiencies to the Study Sponsor immediately as follows:

- All SAEs must be repmted immediately (within 24 hours) of the Investigator's or site's awru·eness.
- 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.
- Additional relevant infmmation after initial repo1ting 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 info1mation from Discharge Summa1y Autopsy Repo1i; Ce1tificate of Death etc, if applicable, in the nrurntive section of the ADE (for related AEs) and SAE eCRF.

NOTE: Should the EDC system become non-operational, the site must complete the appropriate paper ***Serious Adverse Event and Adverse Device Effect*** and/or *Device Deficiency* Fmm. The completed fo1m is faxed or emailed to the Study Sponsor at - [redacted] according to the timelines outlined above; however, the repmied information must be entered into the EDC system once it becomes operational.

Any AEs and device deficiencies for non-study marketed devices/products 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 (ie, there are other more likely causes for the AE).

The Study Sponsor will assess the AEs and may upgrade the Investigator's assessment of seriousness and/or causality. The Study Sponsor will notify the Investigator of any AEs that are 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/reported per manufacturer instructions and must include the Complaint # which will be provided by Study Sponsor after the case is entered in the Study Sponsor's Global Product Complaint Management System (GPCMS).

13.5 Protocol Masking Requirements

Masked information on the identity of the assigned medical device should not be disclosed to the observer during the study (see Section 7.2). The Study Sponsor must be informed of all cases in which unmasking of the observer occurs and of the circumstances involved.

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 (ie, database lock).

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

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 signed informed consent form
- 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 entiy in the source documents be identifiable (eg, initials or signature and date). Any change or correction to data reported in the source must be dated, initialed, and explained if necessaiy. 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.

The EDC system 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. Designated 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 Drug Reference List. Medical history and AEs will be coded using 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 clinical trial management and biostatistics department, and will be completed following Alcon's procedures for changes to a database after database lock.

15 ANALYSIS PLAN

15.1 Subject Evaluability

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

15.2 Analysis Data Sets

The full analysis set (FAS) will contain all eyes that are randomized and for which an IOL is successfully implanted; all eyes in the FAS will be assigned to the treatment actually received for analysis purposes. The FAS will be the primary analysis set for all effectiveness summaries and analyses, as well as all baseline and study summaries.

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

Assignment of study eyes to the appropriate analysis set(s) will be determined prior to database lock.

15.3 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized by treatment group and overall using frequency tables for qualitative variables and descriptive statistics for quantitative variables.

Relevant medical history (ocular and nonocular) 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

15.4.1 Primary Effectiveness

15.4.1.1 Statistical Hypotheses

The null and alternative hypotheses for the primary effectiveness analysis are:

$$H_0: p_c \leq p_s$$

$$H_1: p_c > p_s$$

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

15.4.1.2 Analysis Methods

The primary effectiveness analysis will be analyzed using a one-sided McNemar's test at the α=0.05 level.

15.4.2 Secondary Effectiveness

15.4.2.1 Statistical Hypotheses

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

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

$$H_1: \mu_c < \mu_s$$

where μ_c denotes the mean value in the CRS group and μ_s denotes the mean value in the standard manual technique group for each of the respective secondary endpoints.

15.4.2.2 Analysis Methods

Each of the null hypotheses will be tested using a paired *t*-test; the family-wise type-I-error of 5% will be controlled using the Hochberg testing procedure outlined in Section 15.6.

[redacted]

15.4.3.2 Analysis Methods

Continuous data will be presented using n, mean, standard deviation, median, minimum, and maximum values. Categorical data will be presented with the number and percent in each category. All other summaries will be outlined in the statistical analysis plan (SAP).

15.5 Handling of Missing Data

The FAS and safety analysis set will not include any imputed values. Although missing data will occur, the influence of missing data is expected to be minimal.

15.6 Multiplicity

In order to control the overall type I error rate, the secondary effectiveness hypotheses will only be tested if the primary effectiveness null hypothesis is rejected at the 5% significance level (one-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 at the 5% significance level.

15.7 Safety Analysis

Adverse Events

All information obtained on AEs will be summarized for ocular and nonocular AEs separately.

The number and percentage of all ocular AEs, including for either eye, will be tabulated by treatment and preferred term. An eye with multiple ocular AEs of the same preferred term is only counted once toward the total of this preferred term. A listing of nonocular AEs will be provided.

Device Deficiencies

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

All other safety assessments (IOP, slit-lamp examination and dilated fundus examination) will be summarized. Number and percentage will be presented for categorical variables and descriptive statistics for continuous variables.

15.8 Interim Analyses

An interim analysis for the purposes of sample size re-estimation will be performed when the first 200 subjects who are randomized and treated complete their assessment for the primary effectiveness endpoint at Month 1 (Visit 3A). Alcon staff not involved with the conduct of the trial will re-estimate the sample size based on the data from the first 200 subjects. These staff will provide the re-estimated sample size and the predicted conditional power of the final test statistic based on that sample size. If the conditional power of the study is < 50% for the largest allowable sample size (500 subjects), no additional sample size beyond the originally planned 300 subjects will be added, and termination of the study may be considered. Because additional sample size will not be added if the conditional power of the study is < 50% at the maximum allowable sample size, any effect of the sample size modification on the type 1 error should be minimal (Mehta 2011).

15.9 Adaptive Study Design

The study will employ an adaptive design with potential sample size adjustment based on the proportion of discordance from the interim analysis. This study will enroll approximately 350 subjects to initially randomize and treat 300 subjects (that could potentially increase to approximately 580 subjects enrolled and 500 subjects randomized). Based on the calculation from the interim analysis an additional 200 subjects may be randomized and treated thus the study will randomize and treat a total sample size in the range of 300 to 500 subjects. Any additional sample size will be added in blocks of 50 in order to prevent any back-calculation of the interim study results. For example in the event an additional 30 subjects are needed, a total of 50 will be added to the study.

15.10 Sample Size Justification

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

An estimate of the discordance in outcome between eyes is not known; however it's estimated that discordance will be in the range 8% to 33%. For an initial sample size calculation, the midpoint value of this range, 21%, will be assumed. Based on these assumptions 267 subjects, treated contralaterally, are required to provide 90% power to reject the null hypothesis for a one sided McNemars test at the 5% level using the approximation from Miettinen (Miettinen 1968). If the proportion of discordance is 33% and all other assumptions stay the same a sample of 433 subjects is needed.

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

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 International Organization for Standardization (ISO) 14155:2011 Clinical investigation of medical devices for human subjects – GCP, CFR, and laws and regulations of foreign countries, whichever affords greater protection to subjects. The study will also be conducted in accordance with the Standard Operating Procedures (SOPs) of Alcon and Contract Research Organizations participating in the conduct of the clinical study, and all other applicable regulations. The Investigator and all clinical study staff will conduct the clinical study in compliance with this protocol. The Investigator will 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, must explain the clinical study to each potential subject and the subject must indicate voluntary consent by signing and dating the approved informed consent form. The subject must be provided an opportunity to ask questions of the Investigator, and if required by local regulation, other qualified personnel. The Investigator must provide the subject with a copy of the consent form written in a language the subject understands. The consent document must meet all applicable local laws and 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 will also 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 informed consent form (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/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), informed consent form, 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 study 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 Clinical Site Manager (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) 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, or 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