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Clinical Trial Protocol

Short Title

Comparison of Centurion® Vision System with Balanced Tip and Infiniti® Vision System with the MFK tip during cataract extraction surgery of Hard Lenses.

Long Title

Comparison of Cumulative Dissipated Energy (CDE) and BSS Fluid used with the Centurion® with the 45° Balanced U/S tip vs the Centurion® with Mini Flared Kelman U/S tip vs the Infiniti® with Mini Flared Kelman U/S tip on Hard Lenses

Protocol Number:	CTU424-P001 / NCT02502526
Version Number	02
Sponsor Name & Address:	Alcon Research, Ltd. and its affiliates ("Alcon") 6201 South Freeway Fort Worth, Texas 76134-2099
Project Name / Number:	Centurion® Hard Lenses Study ([redacted]
Test Article(s) / Product(s):	Centurion® Vision System – version 2.04 45° Balanced Tip* *Used with INTREPID® Ultra Sleeve
Release Date:	Refer to electronic signature date

Principal Investigator: _____
Signature Date

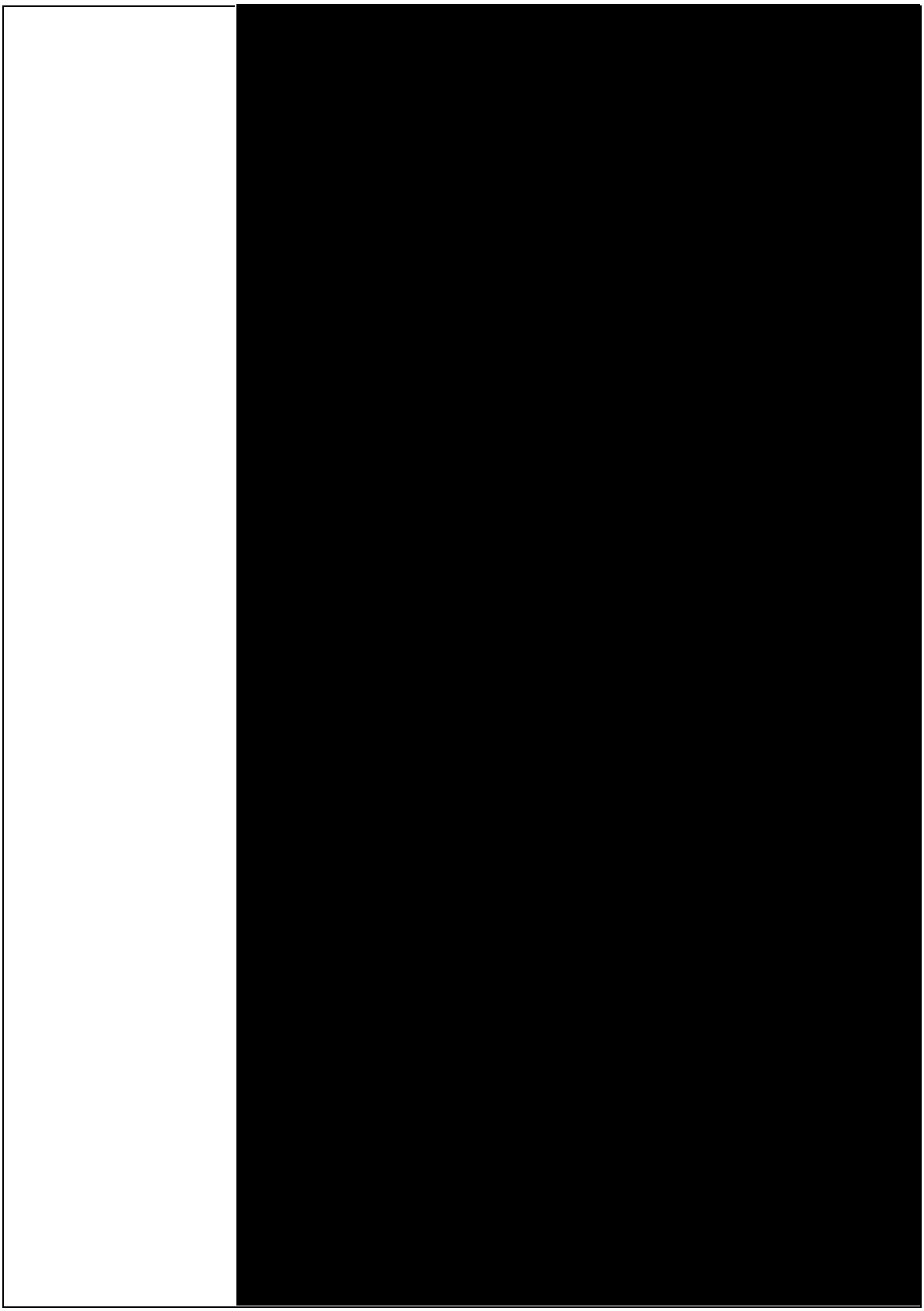
Principal Investigator Name: _____

Principal Investigator Address: _____

_____

1 PROTOCOL SYNOPSIS

Financial Disclosure for US FDA Submission Required?	☐ Yes ☒ No
Test Article(s) / Product(s):	Centurion® Vision System – version 2.04 45° Balanced Tip* *Used with INTREPID® Ultra Sleeve
Objective(s):	Primary objective is to demonstrate that the Centurion® Vision System used with the 45° Balanced Tip will result in less Cumulative Dissipated Energy (CDE) than the Infiniti® Vision System used with the 45° Mini-Flared Kelman (MFK) tip during cataract extraction surgery via phacoemulsification of cataract grades NII- NIV (LOCSII). The Secondary objectives for this study are as follows; 1. Demonstrate that the Centurion® Vision System used with the 45° Balanced Tip will result in less CDE than the Centurion® Vision System used with the 45° MFK tip during cataract extraction surgery via phacoemulsification of cataract grades NII-NIV (LOCSII). 2. Demonstrate that the Centurion® Vision System used with the 45° Balanced Tip will result in less BSS Fluid Used than the Infiniti® Vision System used with the 45° MFK tip during cataract extraction surgery via phacoemulsification of cataract grades NII-NIV (LOCSII). 3. Demonstrate that the Centurion® Vision System used with the 45° MFK tip will result in less BSS Fluid Used than the Infiniti® Vision System used with the 45° MFK tip during cataract extraction surgery via phacoemulsification of cataract grades NII-NIV (LOCSII). 4. Demonstrate that the Centurion® Vision System used with the 45° MFK tip will result in less CDE than the Infiniti® Vision System used with the 45° MFK tip during cataract extraction surgery via phacoemulsification of cataract grades NII- NIV (LOCSII).



	[redacted]
Clinical Trial Design:	Prospective, parallel, randomized, patient-masked, 3-arm, multi-center clinical study following subjects with surgery done with: • Centurion® Vision System, 45°Balanced Tip1 • Centurion® Vision System, 45°Mini Flared Kelman Tip1 • Infiniti® Vision System, 45°Mini Flared Kelman Tip2 1Used with INTREPID® Ultra Infusion Sleeve 2 Used with Ultra infusion Sleeve Phaco-emulsification of a harder lens requires more CDE and more BSS fluid. For this study, the softest lenses (LOCSII Opacities N0 and NI) will be excluded, leaving all lenses with LOCSII Opacities NII-NIV. For each group, cataract surgery will be performed on subjects who will be randomized with an equal number having their surgery performed with each configuration. Clear Cornea Incision: 2.2mm-2.4mm
No. of Subjects:	Approximately 177 subjects (59 per group) randomized with an expectation to have at least 159 completed subjects (53 per group) for evaluability.
Region(s):	Approximately 5 investigational sites across the USA, LACAN, Asia-Pacific and EMEA
Clinical Trial Duration:	a) Total expected duration of clinical investigation: approximately 12 months b) Expected duration of each subject participation: up to 5 months c) Planned follow-up duration for each subject: up to 3 months postoperative d) Estimated subject recruitment period (time needed to select the number of patients): approximately 6 months

Clinical Trial Population:	Adult subjects of 21 years of age and above requiring cataract extraction followed by IOL implantation. Nuclear Opalescence II to IV using LOCS II.	
Treatments:	***Test Article***:	Centurion® Vision System - version 2.04 45°Balanced Tip[1] [1]Used with INTREPID® Ultra Infusion Sleeve
	Administration:	Surgical instrumentation
	General Description:	Centurion® Vision System (v2.04) will be used with the 45° Balanced Tip (coupled with the INTREPID® Ultra Infusion sleeve) for phaco-emulsification procedure.
	Duration of Treatment:	One time routine surgical procedure followed by 3 months (+/- 14 days) of postoperative follow-up.
	Control Article:	Centurion® Vision System (version 2.04) with 45° Mini Flared Kelman u/s Tip[1] (with INTREPID® Ultra infusion sleeve) Infiniti® Vision System (version 3.01) with 45° Mini Flared Kelman u/s Tip[2] [1]Used with INTREPID® Ultra Infusion Sleeve [2]Used with Ultra infusion Sleeve
	Administration:	Surgical instrumentation
	General Description:	Centurion® Vision System (version 2.04) will be used with the 45° Mini Flared u/s Tip coupled with INTREPID® Ultra infusion sleeve) for phaco-emulsification procedure. Infiniti® Vision System (version 3.01) will be used with 45° Mini Flared Kelman u/s Tip (coupled with Ultra Infusion Sleeve) for phaco-emulsification procedure.
	Duration of Treatment:	One time routine surgical procedure followed by 3 months (+/- 14 days) of postoperative follow-up.
Inclusion & Exclusion Criteria:	Detailed information on inclusion and exclusion criteria can be found in *Section 10:Subject Population*	

Assessments:

Primary Variable	- Cumulative Dissipated Energy (CDE)

Secondary Variables	- CDE (depending on the objective) - Balanced Salt Solution (BSS) fluid used
Safety Variables	- Adverse Events (including SSIs) - Slit-lamp examination - Anterior chamber cells - Anterior chamber flare - Corneal oedema - Endothelial cell count - Dilated fundus examination - BCDVA - IOP - Problems during surgery - IOL placement - Device deficiencies
[redacted]	[redacted]

Statistical Analysis:

- **Safety Data Set**- Safety analyses will be conducted using the safety analysis set on a treatment- emergent basis. The Safety data set will include all subjects/ eyes exposed to any study procedures evaluated in this study.
- **Intent-to-Treat (ITT) Data Set** – will include all subjects who are randomized in the study and receive treatment. The ITT set will be the primary analysis set for efficacy.
- **Per Protocol Set (PPS)** - The PP set is a subset of ITT which excludes those who meet the critical deviation criteria as specified in the Deviations and Evaluability Plan. Supportive analyses of the primary and secondary endpoints will be conducted using the PP set if the number of subjects excluded from PP exceeds 5% of the ITT.

Safety summaries will be reported by treatment. For safety variables, all variables will be summarized descriptively by treatment group. No inferential testing will be performed for safety. If more than 5% of subjects are excluded due to deviations, the PPS will become the primary analysis set, and will be compared to the ITT to check for robustness of the results.

A sequential (closed) testing procedure will be used to control type I error rate due to multiplicity for primary and secondary endpoints at one- sided 0.05 significant level.

Primary:
The primary hypothesis is to demonstrate that the Centurion® Vision System used with the 45° Balanced Tip will result in less Cumulative Dissipated Energy (CDE) than the Infiniti® Vision System used with the 45° Mini Flared tip during cataract extraction surgery via phacoemulsification:

H_o: $\mu_{centurion\_Bal\ CDE} \geq \mu_{Infiniti\_MFK\ CDE}$

H_A: $\mu_{centurion\_Bal\ CDE} < \mu_{Infiniti\_MFK\ CDE}$

$\mu_{centurion\_Bal\ CDE}$ and $\mu_{Infiniti\_MFK\ CDE}$ are the true mean values of the primary performance endpoint, CDE under Centurion with the Balanced Tip, and Infiniti with the Mini Flared Kelman (MFK) tip, respectively.

The difference of CDE between two groups will be examined by using an analysis of covariance model (ANCOVA) adjusting for site and baseline opacity grade. Display of ANCOVA results in summary tables will contain difference between LS means, a one-sided p- value < 0.05 will conclude superiority of Centurion® over Infiniti® group.

Secondary:
The difference between two groups will be examined by using ANCOVA adjusting for site and baseline opacity grade. Display of ANCOVA results in summary tables will contain difference between LS Means, a one-sided p- value <0.05 will conclude superiority.

Safety:
Demographics and baseline characteristics will be summarized overall and by treatment arm. Other exploratory and safety variables will be summarized descriptively. Continuous measurements will be presented using n, mean, standard deviation, minimum, maximum and confidence intervals at each visit. Categorical measurements will be tabulated with the number and percent in each category at each visit.

Sample Size Justification:
Based on previous studies, a sample size of 53 in each group will have 80% power to detect a difference in means of -7.4 (the difference between a Group 1 mean, μ_1, of 38.5 and a Group 2 mean, μ_2, of 45.9) assuming that the common standard deviation is 15.2 using a two group t-test with a 0.05 one-sided significance level. Assuming a 10% dropout rate, approximately 59 subjects per group (177 in total) will be randomized.

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3 ABBREVIATIONS

Abbreviation	Definition
ADE	Adverse Device Effect
AE	Adverse event
ASADE	Anticipated Serious Adverse Effect
Asp	Aspiration
BCDVA	Best Corrected Distance Visual Acuity
BSS	Balanced Salt Solution
[redacted]	[redacted]
CDE	Cumulative Dissipated Energy
CRF	Case report form
CV	Coefficient of Variance
CVS	Centurion® Vision System
CS	Clinically significant
DD	Device Deficiency
EC	Ethics Committee
ECD	Endothelial Cell Density
EMEA	Europe, Middle-east and Africa
[redacted]	[redacted]
ESCRS	European Society of Cataract and Refractive Surgeons
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator brochure
IEC	Independent ethics committee
ICD	Informed Consent Documentation
ICH	International Conference on Harmonization
ITT	Intent-to-Treat
IRB	Institutional review board
IRT	Interactive randomization technology
IOL	Intraocular lens
IOP	Itnraocular Pressure
ISO	International Organization for Standardization
ITT	Intent-to-Treat
IVS	Infiniti® Vision System
JCRS	Journal of Cataract and Refractive Surgery
LACAN	Latin America and Canada
LASIK	Laser-Assisted in situ Keratomileusis
LOCSII	Lens opacities classification system II
LogMAR	Logarithm of the Minimum Angle of Resolution
LRI	Limbal Relaxing Incision
MOP	Manual of Procedure
MedDRA®	Medical Dictionary for Regulatory Activities

Abbreviation	Definition
MFK tip	Mini-Flared Kelman tip
NSAID	Non-steroidal anti-inflammatory drug
NCS	Not clinically significant
PI	Principal Investigator
PPS	Per-Protocol Set
PP	Per protocol
POD	Post-Operative Day
POW	Post-Operative Week
SAE	Serious adverse event
SADE	Serious Adverse Device Effect
SAS®	SAS statistical software, SAS Institute Inc., Cary, NC
SSI	Secondary Surgical Intervention
TDOC	Technical document (Alcon numbering system for internal documents)
u/s	Ultra-sound
µ	Mean
UCDVA	Uncorrected Distance Visual Acuity
USA	United States of America

4 GLOSSARY OF TERMS

Adverse Device Effect (ADE)	Adverse event related to the use of an investigational medical device or comparator, if applicable. *Note: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation; any malfunction; and use error or intentional misuse of the investigational medical device or comparator, if applicable.*
Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device. *Note: For subjects, this definition includes events related to the investigational medical device, the comparator, or the procedures involved. For users or other persons, this definition is restricted to events related to investigational medical devices.*
Anticipated Serious Adverse Device Effect (ASADE)	Serious adverse device effect which by its nature, incidence, severity, or outcome has been identified in the risk analysis.
Assessment	A procedure used to generate data required by the study.
Device Deficiency	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. *Note: This definition includes malfunctions, misuse or use errors, and inadequate labeling.*
Performance (Clinical)	Behavior of a medical device or response of the subject to that medical device in relation to its intended use, when correctly applied to appropriate subjects.
Malfunction	Failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or clinical investigation plan.
Nonserious Adverse Event	Adverse event that does not meet the criteria for a serious adverse event.
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, operative, postoperative, etc.
Randomization Number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment.
Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Serious Adverse Event (SAE)	Adverse event that led to any of the following: • Death. • A serious deterioration in health that either resulted in: a) a life-threatening illness or injury. *Note: Life-threatening means that the individual was at immediate risk of death from the event as it occurred, ie, it does not include an event which hypothetically might have caused death had it occurred in a more severe form.* b) permanent impairment to a body structure or a body function. c) in-patient hospitalization or prolonged hospitalization. *Note: Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigation plan, without serious deterioration in health, is not considered a serious adverse event. In general, hospitalization signifies that the individual remained at the hospital or emergency ward for observation and/or treatment (usually involving an overnight stay) that would not have been appropriate in the physician's office or an out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred, the event should be considered serious.* d) a medical or surgical intervention to prevent a) or b). e) any indirect harm as a consequence of incorrect diagnostic test results when used within manufacturer's instructions for use. • Fetal distress, fetal death, or a congenital abnormality or birth defect.
Subject Number	A number assigned to each subject who enrolls in the study. When combined with the site number, a unique identifier is created for each subject in the study.
Unanticipated Serious Adverse Device Effect (USADE)	Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the risk analysis.

5 AMENDMENTS

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

5.1 Amendment 1

This protocol has been amended to include an additional 6-Month Safety Follow-up Visit for subjects meeting a specified criteria for a decrease in endothelial cell density (ECD) following cataract surgery. Subjects who have completed the 3 month visit with an ECD count of less than 1500 cells/mm^2 and/or a decrease in ECD of 20% or more (in comparison to the screening visit value), must return 3 months later for a 6 month safety follow up visit. Subject data from the additional safety assessments at this visit will be captured in the electronic database, accordingly. For subjects who meet the criteria for the 6 month visit, an adverse event will be reported for the decrease in ECD.

In addition, the protocol now requires the application and use of VisCoat® during the surgical procedure.

A diagram for Control article 2 was added.

Table 9-2-1 was titled Study Visit Plan.

Numbering for some tables and formatting of the document has changed to comply with the new document management system template.

6 SCHEDULE OF VISITS

Activity	**Visit 0** **(-60 to 0 d)** *Unilateral examination*	**Visit 00** **(0 d)** *Unilateral examination*	**Visit 1** **(1 d)** *Unilateral examination*	**Visit 2** **(7 +/- 2 d)** *Unilateral examination*	**Visit 3** **(90 +/- 14d)** *Unilateral examination*	**6-Month Safety Follow-up Visit****
Informed Consent	X					
Demographics	X					
Medical History	X	X				
Concomitant Medications	X	X	X	X	X	
Inclusion/Exclusion	X	X				
Surgery		X				
Problems During Surgery		X				
Other Procedures at Surgery		X				
Lens Information		X				
IOL Placement		X				
Programmable Phacoemulsification Settings		X				
Phacoemulsification Metrics *(Including CDE, BSS Fluid Use,* [redacted]		X				
Visual Acuity (UCDVA & BCDVA)	X			X	X	X[2]
Intraocular Pressure	X		X	X	X	
Specular Microscopy	X				X	X
[redacted]	[redacted]		[redacted]	[redacted]		[redacted]
Slit-Lamp Examination	X		X	X	X	X
Crystalline Lens Assessment	X					
Anterior chamber cells and flare	X		X	X	X	
Dilated Fundus Examination	X				X	
Randomization*	X					
Adverse Events *(Including Secondary Surgical Intervention)*	X	X	X	X	X	X
Device Deficiencies		X				
Complete Exit Form[1]					X	X

[1] If a subject exits early, the Visit 3 procedures should be performed at the last available visit, if at all possible
[2] Only BCDVA Visual Acuity to be completed at 6-Month Safety Follow-up visit
*Randomization should be completed within 2 working days prior to the date of surgery
**6-Month Safety Follow-up Visit (if required). See section 12.1.6 Additional 6-month Safety Follow-up Visit

7 INTRODUCTION

7.1 Background

Cataract surgery is a commonly performed procedure with over 5.0 million cases performed annually worldwide. Modern cataract surgery utilizes small incision and phacoemulsification surgical techniques to emulsify and aspirate the cataractous lens for implantation of a foldable intraocular lens (IOL).

The Centurion® Vision System [510(k) Number: CVS K121555, US-FDA approved in December 2012] is a new phaco-emulsifier aspirator manufactured by Alcon. The system incorporates Active Fluidics™ control system that maintains a stable surgical IOP despite variations in aspiration flow rate. A more stable surgical IOP allows the surgeon to experience less movement of ocular structures, as well as the option to lower the IOP setting. This coupled with the higher resistive aspiration tubing coupled with lower compliant aspiration tubing and Active Fluidics™ minimize occlusion break surge. The system is capable of creating significantly higher vacuum levels which creates higher tip holding forces. Previous studies have indicated that higher vacuum correlates to a lower Cumulative Dissipative Energy (CDE), which is a measure of the amount of energy dissipated at the incision. The metric also correlates to how much energy is required to perform the surgery. This study will be assessing the CDE as well as measuring the total BBS fluid used during the surgical procedure.

INTREPID® Balanced Ultrasound (u/s) Tip

The INTREPID® Balanced u/s tip [510(K) Number K911808] minimizes energy along the shaft area that interfaces with the incision while maximizing energy at the cutting edge. Since the u/s tip creates up to 190 microns of tip movement at 100% amplitude as compared to 130 micron of movement of the Mini Flared Kelman (MFK) tip, the amplitude is normally lowered to 60% amplitude to achieve equivalent cutting. The Balanced tip cuts in a superior fashion to the Mini Flared Kelman tip. Coupled with the INTREPID® Ultra Infusion sleeve, less energy is dissipated in the incision.

A previous Alcon-sponsored study (Clinicaltrials.gov identifier: NCT01848288) showed lower Cumulative Dissipated Energy (CDE), Aspiration Time and Aspiration Fluid Used for the Centurion® (K121555) with the Balanced tip vs the Infiniti® with a Mini Flared Kelman tip.

This study is designed to determine if Centurion® Vision System enhancements translate to a more efficient cataract procedure as defined by CDE and BSS fluid use.

Both the Centurion® (K121555) and Infiniti® (K112425, K120912) Vision Systems and the INTREPID® Balanced Tips and the MFK Tips are US FDA cleared and CE marked, and will be used as per the label indications. No new risks are introduced with the use of the either the Centurion® or the Infiniti®. As with any type of cataract surgery with intraocular lens implantation, there is a possibility of complications due to anesthesia, drug reactions, and surgical problems. Potential risks /surgical complications associated specifically to the phacoemulsification cataract procedure include the following:

- capsular injury
- thermal burns
- vitreous loss
- persistent corneal edema

A summary of known and potential risks and benefits to humans, as identified in the literature or through preclinical testing and/or prior clinical evaluations, for each investigational product can be found in the Directions for Use and Operator's Manual for the Centurion® Vison System and the Infiniti® Vision System.

7.2 Clinical Trial Design

Prospective, parallel, randomized, patient-masked, 3-arm, multi-center clinical study following subjects with surgery done with:

- Centurion® Vision System, 45°Balanced Tip[1]
- Centurion® Vision System, 45°Mini Flared Kelman Tip[1]
- Infiniti® Vision System, 45°Mini Flared Kelman Tip[2]

[1]Used with INTREPID® Ultra Infusion Sleeve
[2]Used with Ultra infusion Sleeve

Phaco-emulsification of a harder lens requires more CDE and more BSS fluid for this study, the softest lenses (LOCSII Opacities NO and N1) will be excluded, leaving all lenses with LOCSII Opacities NII-NIV.

The clear cornea incision will be between 2.2mm and 2.4mm.

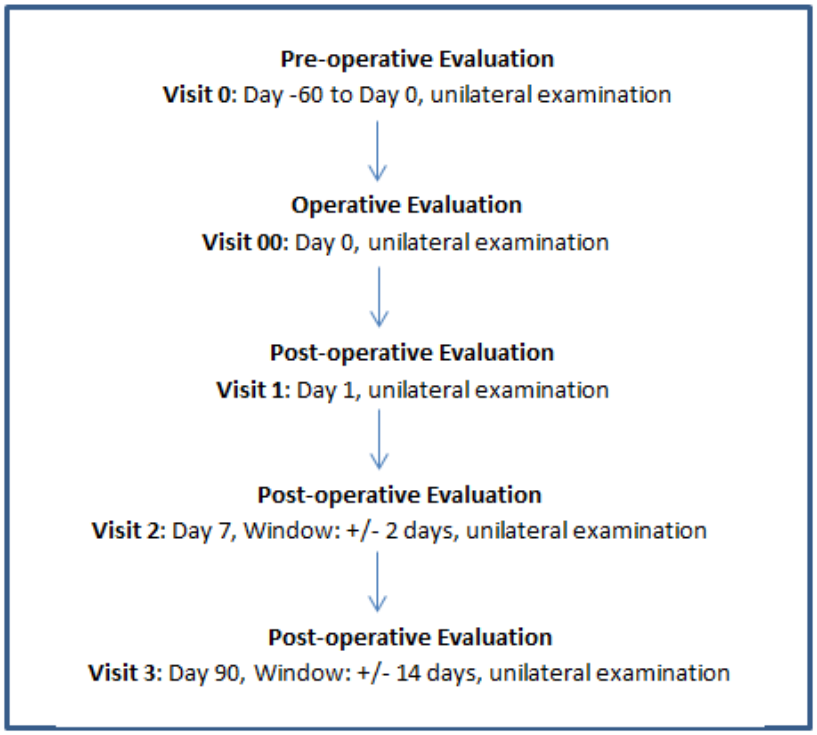
A randomization list will be generated by Sponsor personnel who is not involved in the day-to-day conduct of the study, and who does not have contact with the study subjects, the site, or the Alcon employees who do have site contact.

Randomized treatment assignment will be provided via Interactive Randomization Technology (IRT).

This is a subject-masked study and not observer-masked. Subjects will be masked to the treatment for the study eye. The surgeon (Investigator) is not masked to treatment as this is an impossibility with the medical devices studied here. Site personnel not participating in surgery and not requiring knowledge of randomization will be masked to the extent possible. Investigative sites will take all precautions necessary to ensure the subjects remain masked for the duration of the trial. It is encouraged that the Investigator take the opportunity to remind the subject that he/she will be masked for the duration of the trial.

Post-operatively (day 0), the subject will be required to attend follow-up visits at day 1, day 7 (+/- 2 days) and month 3 (+/- 14 days).

Figure 7–1 Study Design



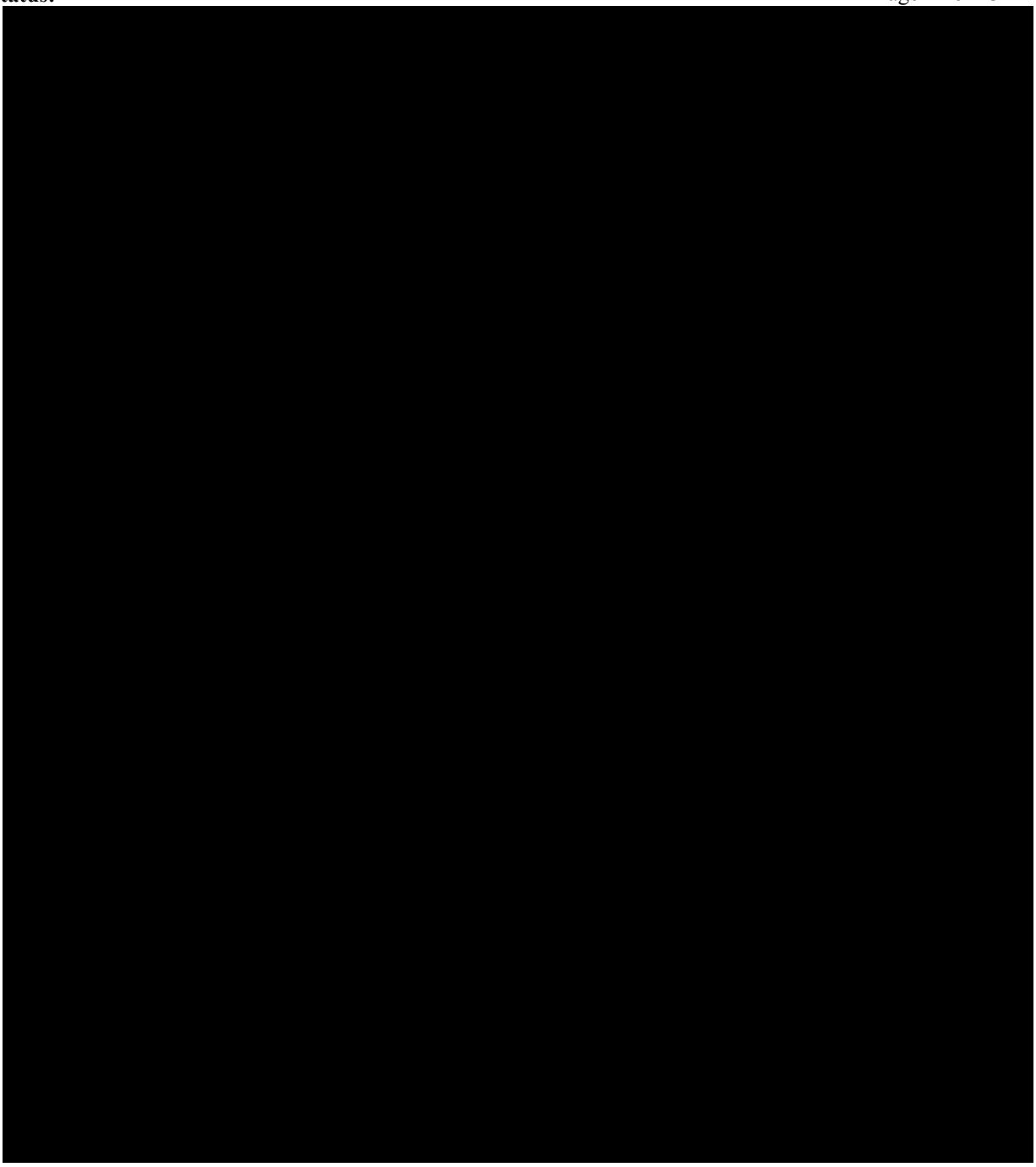
8 CLINICAL TRIAL OBJECTIVES

8.1 Primary Objective

Primary objective is to demonstrate that the Centurion® Vision System used with the 45° Balanced Tip will result in less Cumulative Dissipated Energy (CDE) than the Infiniti® Vision System used with the 45° MFK tip during cataract extraction surgery via phacoemulsification of cataract grades NII- NIV (LOCSII).

8.2 Secondary Objectives

1. Demonstrate that the Centurion® Vision System used with the 45° Balanced Tip will result in less CDE than the Centurion® Vision System used with the 45° MFK tip during cataract extraction surgery via phacoemulsification of cataract grades NII- NIV (LOCSII).
2. Demonstrate that the Centurion® Vision System used with the 45° Balanced Tip will result in less BSS Fluid Used than the Infiniti® Vision System used with the 45° MFK tip during cataract extraction surgery via phacoemulsification of cataract grades NII- NIV (LOCSII).
3. Demonstrate that the Centurion® Vision System used with the 45° MFK tip will result in less BSS Fluid Used than the Infiniti® Vision System used with the 45° MFK tip during cataract extraction surgery via phacoemulsification of cataract grades NII- NIV (LOCSII).
4. Demonstrate that the Centurion® Vision System used with the 45° MFK tip will result in less CDE than the Infiniti® Vision System used with the 45° MFK tip during cataract extraction surgery via phacoemulsification of cataract grades NII- NIV (LOCSII).



8.4 Study Endpoints

8.4.1 Effectiveness Endpoints

Cumulative Dissipated Energy (CDE) - CDE is a metric displayed on the system user interface of both the Centurion® and Infiniti® systems. CDE represents the energy dissipated of the u/s tip and infusion sleeve at the 'incision point' defined as 5.6mm behind the cutting edge. It reflects the total of CDE (ie, CDE longitudinal + CDE torsional).

CDE = CDE_{long} + CDE_{Tor} = (Longitudinal Time x Average Longitudinal Power) + (Torsional Time x 0.4 x Average Torsional Amplitude)

CDE will be used as both a *primary or secondary endpoint*, depending on the objective.

BSS Fluid Used - BSS Fluid will be measured by weighing the BSS bag after priming. The BSS bag will then be re-inserted and the system will then require a re-prime. A clamp will be temporarily used on the administration tubing to prevent fluid from being pulled from the bag. The BSS bag will be weighed after the case.

BSS fluid used corresponds to the total fluid through the anterior chamber.

[redacted] is a function of [redacted], Aspiration Flow Rate, and Pump modulation. The Pump modulation varies as tissue is occluded and unclouded against the tip.

Incision Leakage is a function of surgical IOP, incision size, incision construction, and how the phaco hand-piece and 2nd instrument is used.

A reduction in BSS Fluid Used implies less induced trauma to tissues. BSS Fluid Used will be used as [redacted] a *secondary* [redacted] *endpoint* [redacted].

[redacted]

[redacted]

8.4.2 Safety Endpoints

- BCDVA - Best correction using the 100% contrast ETDRS charts at 3 meters (Monocular)
- Intraocular Pressure (IOP)
- Problems during surgery
- Other procedures at surgery
- IOL placement
- Slit-lamp examination
- Dilated fundus examination
- Adverse Events (including SSIs)
- Device deficiencies

9 INVESTIGATIONAL PLAN

9.1 Outline of Clinical Trial

The purpose of this study is to evaluate the Centurion® Vision System during cataract extraction surgery followed by posterior chamber IOL implantation in adult patients (≥ 21 years of age) with nuclear opalescence grading of NII – NIV (using LOCSII grading scale).

For this study, the softest lenses (LOCSII Opacities N0 and NI) will be excluded, leaving all lenses with LOCSII Opacities NII-NIV.

For each group, cataract surgery will be performed on eligible subjects randomized with an equal number in the following three arms, having their surgery performed with each configuration.

- Arm 1: Centurion® Vision System, 45°Balanced Tip[1]
- Arm 2: Centurion® Vision System, 45°Mini Flared Kelman Tip[1]
- Arm 3: Infiniti® Vision System, 45°Mini Flared Kelman Tip[2]

[1]Used with INTREPID® Ultra Infusion Sleeve
[2]Used with Ultra infusion Sleeve

Approximately 177 subjects (59 in each group) will undergo unilateral cataract surgery in the study to reach a minimum of 159 evaluable subjects (53 in each group) at the conclusion of the 3-month postoperative visit. Subjects will be enrolled sequentially in consent date and time order. The expected duration of subject participation is approximately five months. The study includes 5 visits as outlined below.

Table 9–1 Visit Schedule

Examination	Visit	Time for Procedure
Pre-operative (Screening)	Visit 0	-60 to 0 days from study eye surgery
Operative (Day of Surgery)	Visit 00	Day 0
1-Day postoperative follow-up	Visit 1	Day 1
1-Week postoperative follow-up	Visit 2	Day 7 (+/- 2 days)
3-months postoperative follow-up	Visit 3	Day 90 (+/- 14 days)

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

Adverse events (including SSIs) and any DDs will be assessed and reported at all scheduled and unscheduled visits for each subject beginning at the time of informed consent.

NOTE: At the time of study close, unresolved AEs/SAEs related to the device will be followed to conclusion, or for six months following close, whichever comes first. The Sponsor will be updated accordingly. A 6-Month Safety Follow-up Visit will be conducted (if required). See section 12.1.6 Additional 6-Month Safety Follow-up Visit.

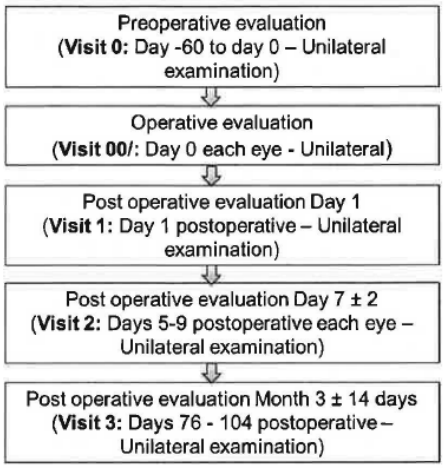
External Evaluation Group

External Reading Center to be used to measure the Endothelial Cell Density (ECD), Coefficient of Variance (ΔCV), morphology and hexagonality preoperatively and postoperatively at month 3 using Konan microscope. This will help us to determine the degree of cell loss following cataract extraction surgery.

9.2 Study Design

Detailed in Section 9.1 of this protocol. The schematic representation of the study visit plan is given in the below table.

Table 9-2-1 Study Visit Plan



9.3 Rationale for Study Design

The Centurion® Vision System incorporates Active Fluidics™ control system that maintains a stable surgical IOP despite variations in aspiration flow rate. A more stable surgical IOP allows the surgeon to experience less movement of ocular structures, as well as safely lower the surgical IOP. This coupled with the higher resistive aspiration tubing coupled with lower compliant aspiration tubing and Active Fluidics™ minimize occlusion break surge. The

system is capable of creating significantly higher vacuum levels (~20% higher than the Infiniti® Vision system) which creates higher tip holding forces.

Previous Alcon-sponsored study (M-13-006, Data on File) have also shown that the Centurion® with the 45° Balanced u/s tip used significantly less CDE than the Infiniti® with the 45° MFK tip. At 100% amplitude, the Balanced tip creates 190 µm stroke vs 130 µm stroke for the MFK tip. The Centurion amplitude is normally set at 60% max and the Infiniti at ~90% max. CDE is therefore reduced by 33%.

This study has been designed to obtain a better understanding of how both the Centurion® and the Balanced Tip affect CDE and BSS fluid used, as well as assess the correlation to ΔCCT and ΔECD.

9.4 Procedures Per Study Visit

Refer to Section 12 (Clinical Trial Procedures) for information on study-specific assessments and procedures.

9.5 Risk Benefit Assessment

Both the Centurion® (K121555) and Infiniti® (K112425, K120912) Vision Systems and the INTREPID® Balanced Tips and the MFK Tips are US FDA cleared and CE marked, and will be used as per the label indications. No new risks are introduced with the use of the either the CVS or the IVS. As with any type of intraocular surgery, there is a possibility of complications due to anesthesia, drug reactions, and surgical problems. Potential risks / surgical complications associated specifically to the phacoemulsification cataract procedure include the following:

- capsular injury;
- thermal burns;
- vitreous loss; and
- persistent corneal edema.

Additional subject discomforts may include pupil dilation and the use of numbing eye drops. There is an additional subject burden of one non-standard postoperative visit (Visit 3).

10 SUBJECT POPULATION

The study population will include approximately 177 (59 per group) subjects screened and randomized, with an expectation to have at least 159 evaluable subjects (53 per group). The study will be conducted globally at approximately 5 sites with about 35 subjects enrolled per site.

To participate in this clinical trial, subjects must be of 21 years of age and above requiring cataract extraction followed by IOL implantation. Subjects should have a Nuclear Opalescence grading of NII to NIV (using LOCS II grading scale) to be eligible for this study.

10.1 Inclusion Criteria

1. Adult patients 21 years of age or older of either gender or any race.
2. Willing and able to consent for participation.
3. Willing and able to attend postoperative examinations per protocol schedule.
4. Patients must have a cataract in at least one eye with a Nuclear Opalescence of II-IV (via LOCS II) followed by posterior chamber IOL implantation

10.2 Exclusion Criteria

1. Subjects whose postoperative best corrected visual potential is expected to be worse than 20/60 Snellen (0.5 effects logMAR) at the final study visit.
2. Planned multiple procedures, including Laser Phaco, LASIK, LRI's etc during surgery or the course of this study.
3. Clinically significant corneal endothelial dystrophy (eg, Fuch's dystrophy, ECD < 1500 cells/mm^2)
4. Patients who have severe conditions of acute or chronic diseases or illnesses that, per Investigator's clinical judgment, would increase the operative risk or confound the result of this investigation.
5. Small pupil size that will require mechanical dilation using iris hooks, Malyugin ring or similar devices effects.
6. Weaken /Broken zonules
7. Subjects who were enrolled in the study may not be re-enrolled for the second eye.
8. Untreated or uncontrolled Glaucoma

9. Previous intraocular or corneal surgery of any kind, including any type of surgery for either refractive or therapeutic purposes.
10. A poorly dilating pupil or other pupil defect that prevents the iris from retracting peripherally to at least 5 mm dilation.
11. Current or previous usage of an alpha-1-selective adrenoceptor blocking agent or an antagonist of alpha 1A adrenoceptor (eg, Flomax® (tamsulosin hydrochloride), Hyntrin® (terazosin hydrochloride), or Cardura® (doxazosin mesylate).
12. Diagnosed with severe retinal disorders (eg, macular degeneration, proliferative diabetic retinopathy).
13. History of corneal disease (eg, herpes simplex, herpes zoster, etc).
14. History of retinal detachment.
15. Known zonular instability or zonular dehiscence (eg, Marfan's syndrome, pseudoexfoliation syndrome, etc).
16. Any patient currently participating in another drug or device study

11 TREATMENT

Upon signing informed consent, subjects will be considered enrolled in the study and a subject ID number will be assigned by entering the subject into the EDC system. The qualified subjects will be randomized in a 1:1:1 manner to receive treatment with Centurion® Vision System/ 45°Balanced Tip1 or Centurion® Vision System/ 45°Mini Flared Tip[1] or Infiniti® Vision System/ 45°Mini Flared Tip[2].

Throughout the clinical trial, the Investigator will be responsible for the accounting of all investigational products and will ensure that the clinical trial products are not used in any unauthorized manner.

[1]Used with INTREPID® Ultra Infusion Sleeve
[2]Used with Ultra infusion Sleeve

11.1 Investigational Products

The Centurion® Vision System and Infiniti® Vision System, including accessories approved by Alcon (ie, tips, sleeves and packs, etc), constitute complete surgical systems. These systems are intended for use by licensed ophthalmic surgeons and their surgical teams. The Vision System devices utilized in this postmarket trial are CE Marked and 510k cleared. Approved labeling will be applied and devices provided in standard manufacturer's packaging (where applicable).

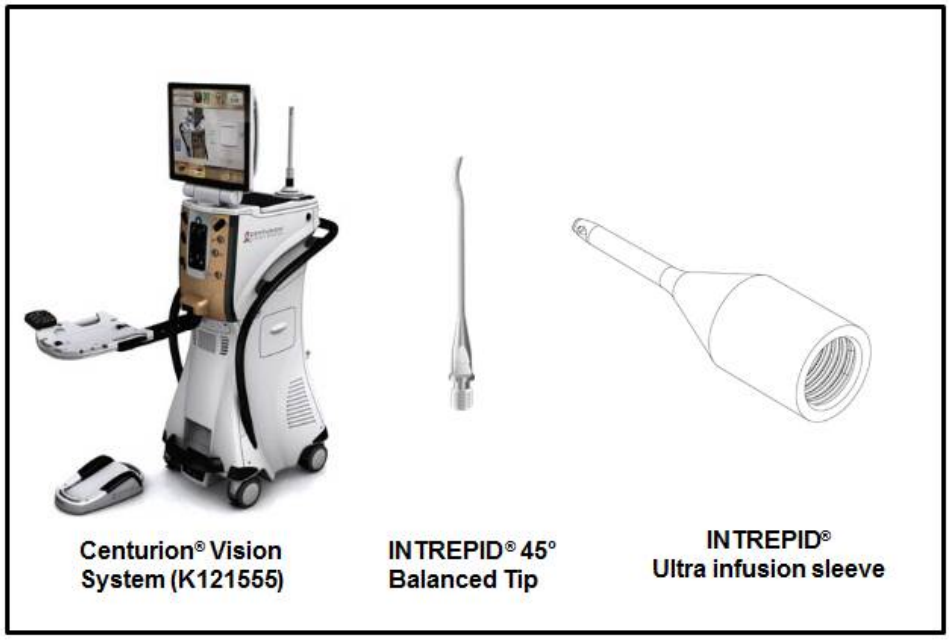
Test Article: Centurion® Vision System (v2.04) will be used with the 45° Balanced Tip (coupled with the INTREPID® Ultra Infusion sleeve).

The Centurion® Vision System is a phacoemulsification aspiration platform indicated for emulsification, separation, and aspiration of cataracts, residual cortical material and lens epithelial cells; vitreous aspiration and cutting associated with anterior vitrectomy; bipolar coagulation; and intraocular lens injection. The system employs similar functionality and technologies of its predecessor, the Infiniti® Vision System. In addition to the existing functions for irrigation/aspiration, phacoemulsification, vitreous aspiration cutting, and bipolar coagulation, the CVS also introduces new modalities for active irrigation, automated IOL injection, and advanced surgical display for viewing of biometry data and surgical operating parameters.

Standard, sterile, single-use pack of supplies and accessories necessary to perform one cataract removal procedure each will be locally procured by the investigational sites (Alcon will reimburse the costs).

See Figure 11-1 and Figure 11-2 for product and accessory diagrams.

Figure 11–1 Test Article Diagram



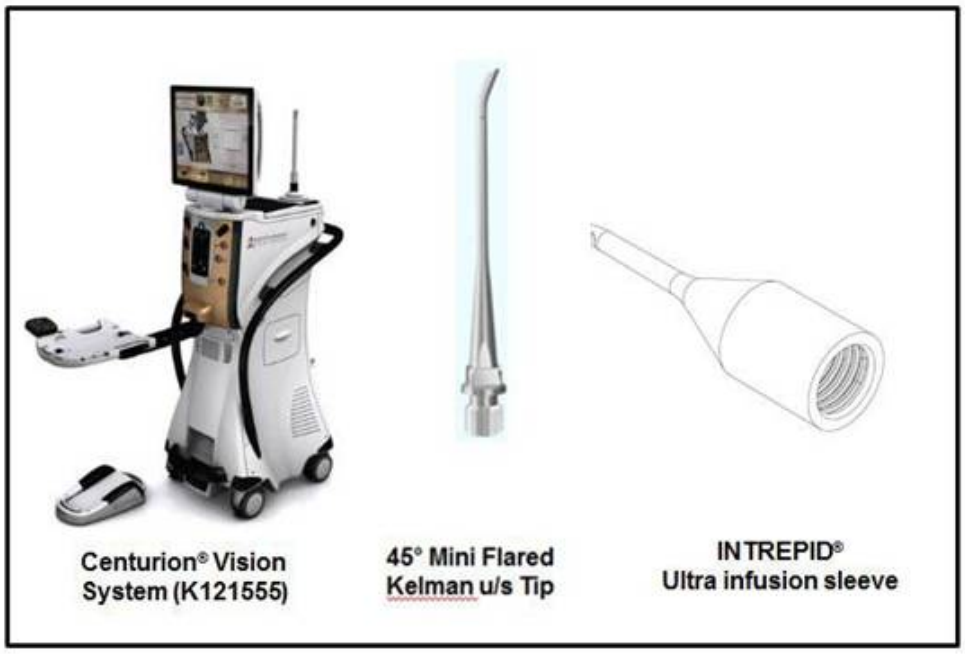
Control Articles:

1. Centurion® Vision System (v2.04) used with the 45° Mini Flared Kelman u/s Tip (coupled with INTREPID® Ultra Infusion Sleeve)
2. Infiniti® Vision System (version 3.01) used with 45° Mini Flared u/s Tip (coupled with Ultra Infusion Sleeve) for phaco-emulsification procedure.

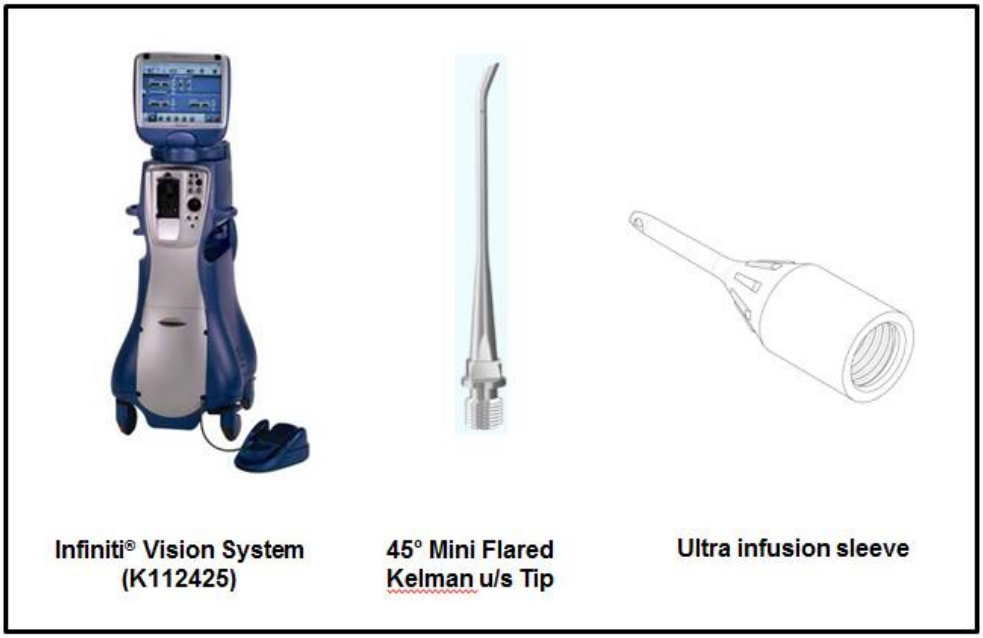
The Infiniti® Vision System is a phacoemulsification aspiration platform indicated for emulsification, separation, and aspiration of cataracts, residual cortical material and lens epithelial cells; vitreous aspiration and cutting associated with anterior vitrectomy; and bipolar coagulation. Standard, sterile, single-use packs of supplies and accessories necessary to perform one lens removal procedure each will be procured by the investigational sites (Sponsor will reimburse the costs). Protocol defined accessories will include the Mini-Flared tip and Ultra infusion sleeve. These products represent the standard of care for the Infiniti® Vision System.

Figure 11–2 Control Article Diagrams

Control Article 1



Control Article 2



11.2 Usage

The approved surgical products employed in this study will be utilized in accordance with approved indication(s). Refer to the system operator manuals and consumable surgical pack DFUs for in-depth instructions.

11.3 Accountability Procedures

The Investigator or the designee will order/ procure the clinical supplies (surgery packs, BSS Bags and other surgery-related ancillary supplies) and Alcon will reimburse the costs on an actual basis (if available, copies of the invoices and/ or order forms should be filed in the Investigator's clinical trial records for the Clinical Site Manager or any other Sponsor-personnel to review during the monitoring visits).

Upon receipt of study products, the Investigator or designee will conduct an inventory. Alcon will provide the site with accountability logs which will can be used to capture information on the subject ID, pack lot/ batch number, expiry date, date of dispensation, name of dispenser and will also have a column for 'sticking' the labels from the surgery packs. The Clinical Site Manager will train the site on appropriately completing this log.

The Investigator or the designee should follow the manufacturer's instruction on the storage-specifications of the supplies.

During the study, the site must maintain records (either in the Alcon provided log or site-specific logs) of study article dispensation and collection for each subject. The accountability log or any similar record must be made available to the study monitor for the purposes of verifying the accounting of clinical supplies.

Any discrepancies and/or deficiencies between the observed disposition and the written account must be recorded in the source notes along with a detailed explanation.

At the conclusion of the study, the Clinical Site Manager will perform a final reconciliation of the accountability records. The Investigator will be responsible for the collection of all unused supplies unless otherwise instructed by the Sponsor.

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

NOTE: Over-labeling is not required as the site staff are all unmasked for this study.

12 CLINICAL TRIAL PROCEDURES

12.1 Clinical Trial Assessments

The following section describes in general the assessments to be performed in this clinical trial. Assessments are thoroughly described in the Manual of Procedures (hereto MOP). Refer to section 6 SCHEDULE OF VISITS for an overview of assessments by visit.

NOTE: All ocular assessments are to be performed on the study eye only. Refer to section 10 SUBJECT POPULATION for information on study eye selection.

12.1.1 Pre-operative visit (Visit 0; Day -60 to Day 0)

Conduct pre-screening, screening and assign patient screening number as follows:

12.1.1.1 Pre-Screen

Where permitted by national and local laws and regulations, pre-screen all potential cataract patients via chart review. Additionally prescreen patients spontaneously presenting for cataract evaluation and/or annual examinations. In both cases, prescreen inclusion/exclusion criteria based upon routine testing conducted for all cataract patients.

NOTE: Prior to undertaking study specific testing, informed consent is required.

12.1.1.2 Informed Consent

Refer to Section 16.2: Informed Consent Procedures for specifics regarding informed consent process. For patients that pass pre-screening, explain the nature of the study. If the patient is willing to participate, appropriately consent the potential study subject and have him/her sign and date the Institutional Review Board (IRB) or Ethics Committee (EC) approved Informed Consent Document (ICD). **If the patient is unable to comprehend and sign the ICD, he/she is not eligible for the study.** Assign the potential subject a screening number (refer to *Section 12.1.1.3* below) prior to any study specific testing.

NOTE: The subject's medical record must indicate participation in this study and desire to continue participation in the study.

12.1.1.3 Subject Number Assignment

Once the patient has been formally consented, the relevant patient information should be entered in the EDC system (Medidata® Rave) and the system will assign the subject number sequentially starting with [redacted] etc.

12.1.1.4 Demographics, Medical History and Concomitant Medications

Document demographics, ocular and non-ocular medical history, ocular and non-ocular concomitant medications and pregnancy status (where applicable). Refer to MOP for further instruction.

Ensure pregnancy status is documented for all women of child-bearing potential. Compare with Inclusion/Exclusion criteria (refer to *Section 10: Subject Population*). Identify potential safety issues for subject if enrolled in the study.

Record all concomitant medications for ocular and non-ocular conditions used by the subject at the time of the examination. No study specific medications are required for this study. The medications used during the trial are those that the Investigator deems necessary for cataract surgery procedures and treatment.

NOTE: Routine preoperative and intra-operative medications do not require capture.

12.1.1.5 Inclusion/Exclusion Criteria

Refer to the list of Inclusion/Exclusion criteria in *Section 10: Subject Population*. Ensure the subject meets all requirements for participation and eligibility; ie meets all the inclusion and none of the exclusion criteria.

12.1.1.6 Selection of Study Eye

The study eye should be the eye with the worse cataract as indicated by LOCS II assessment. Where cataract grade is the same in both eyes, the right eye should be chosen as the study eye. Record the assigned study eye in the medical notes.

12.1.1.7 Visual Acuity (UCDVA and BCDVA) Testing

Perform Uncorrected Distance Visual Acuity (UCDVA) testing and Best Corrected Distance Visual Acuity (BCDVA) testing with study specified equipment. Refer to MOP for further instruction.

Ensure UCDVA and BCDVA testing precedes IOP measurement, the administration of eye drops to dilate or anesthetize the eyes, or any examination requiring contact with the eye.

NOTE: Lighting conditions must be measured and recorded prior to VA testing.

12.1.1.8 Intraocular pressure (IOP)

Measure IOP using Goldmann or other applanation method. For each subject, the same instrument type should be used for all measurements in the study.

12.1.1.9 Specular Microscopy

Utilize a commercially available specular microscope (Konan microscope) to photograph the corneal endothelial cells as per the instructions provided by the Reading Center. Detailed information on transmission of the images to the reading Center for analysis is provided in the MOP.

NOTE: If the subject has been dismissed prior to assessment of image quality (not recommended) and images are of poor quality, the subject will be asked to return and the assessment will be repeated.

[redacted]

12.1.1.11 Slit-lamp Examination

Examine the anterior segment of the eye, including the eyelid, sclera, conjunctiva, cornea, iris, and natural crystalline lens. Record all preoperative baseline clinical observations and the clinical significance of each observation. Give consideration to Inclusion/Exclusion criteria (refer to *Section 10: Subject Population*).

NOTE: Certain pathologies may become apparent after cataract extraction and IOL implantation. In these instances, the preoperative pathology status should be updated.

12.1.1.12 Crystalline Lens Assessment

Assess cataract grade using LOCS II classifications (Chylack 1989). Refer to MOP (*LOCS II Instructions for Grading*) for detailed grading instructions.

12.1.1.13 Inflammatory Signs

Grade inflammatory signs including cells and flares, and corneal edema. Refer to MOP (*Inflammatory Signs Grading*) for details including grading scale.

12.1.1.14 Dilated Fundus Examination

Perform a dilated fundus examination (indirect and direct ophthalmoscopy). Record diameter of dilated pupil. Record all preoperative baseline clinical observations with consideration given to the inclusion and exclusion criteria (Refer to *Section 10. Subject Population*) and note clinical significance.

NOTE: Certain pathologies may become apparent after cataract extraction and IOL implantation. In these instances, the preoperative pathology status should be updated.

12.1.1.15 Randomization

Randomization should be undertaken within 2 business days of the operative visit. Ensure that all inclusion/exclusion criteria have been met and that all preoperative (Visit 0) assessments have been performed. Utilize the IRT system to randomize subject's study eye to the test or to the control group.

12.1.1.16 Adverse Events

Record AEs as described in *Section 13: Device Deficiencies and Adverse Events*.

12.1.2 Operative Visit (Visit 00 – Day 0, Unilateral)

12.1.2.1 Medical History

Update subject's ocular and non-ocular medical history.

12.1.2.2 Ocular and Non-ocular Concomitant Medication

Record changes in ocular and non-ocular concomitant medications.

NOTE: Routine preoperative and intra-operative medications do not require capture.

12.1.2.3 Inclusion/ Exclusion Criteria

Refer to the list of Inclusion/Exclusion criteria in *Section 10: Subject Population*. Ensure the subject still meets all requirements for participation and eligibility.

12.1.2.4 Surgery

NOTE: Prior to performing study surgeries, surgeons should have a minimum experience of 100 cases with the Infiniti® Vision System and 100 cases with the Centurion® Vision System.

Confirm subject meets all inclusion/exclusion criteria (refer to *Section 10: Subject Population*), and has been randomized (refer to *Section 12.1.1.17. Randomization*) prior to proceeding with surgery.

Care should be taken to protect endothelium with the Ophthalmic Viscosurgical Device, VisCoat®. As the nuclear disassembly is performed, reapplication of the VisCoat® should be done throughout the procedure in order to protect the endothelium. The surgeon should create a working space each time before re-engaging the ultrasound.

NOTE: Prepare subject for surgery per site specific standard operating procedures. Manually create a 5.0 to 5.5 mm capsulorhexis and proceed with phacoemulsification as specified by randomization.

Femtosecond laser use at any point in the surgery (eg, incision, capsulotomy, lens fragmentation, etc) is prohibited. Additionally pre-chop nucleofracture technique is prohibited. The IOL implantation needs to be managed either with Alcon Monarch® IOL injector (or the INTREPID® AutoSert® IOL injector) and the same cartridge D (2.2-2.4 mm).

12.1.2.4.1 Problems During Surgery

Indicate what problems, if any, occurred during surgery.

12.1.2.4.2 Other Procedures at Surgery

Indicate other procedures, if any that occurred at the time of surgery. Other procedures include those performed outside of routine cataract surgery.

NOTE: Other planned procedures at the time of surgery are exclusionary (Refer to *Section 10: Subject Population*).

12.1.2.4.3 Lens Information

Document details of the IOL implanted including IOL model and brand in the medical notes.

12.1.2.4.4 Successful Placement of IOL in Capsular Bag

Indicate in the medical notes if IOL placement in the capsular bag was successful.

12.1.2.5 Programmable Phacoemulsification Settings

Document whether preferred pre-programmed phacoemulsification machine settings were altered prior to or during the surgical procedure. If settings were altered, indicate the setting(s) modified.

12.1.2.6 Phacoemulsification Metrics

12.1.2.6.1 Cumulative Dissipated Energy (CDE)

At the conclusion of the surgery, record CDE as reported on the Vision System interface.

12.1.2.6.2 BSS Fluid Use

Weigh the empty drain bag in preparation for the total BSS consumption calculation. Refer to the MOP for calculation details.

NOTE: It is preferable to use the same BSS Bags (BSS or BSS Plus) for all the case.

12.1.2.7 Adverse Events

Record all AEs including SSIs. Use the AE form as described in *Section 13: Device Deficiencies and Adverse Events*.

12.1.2.8 Device Deficiencies

Record device deficiencies if observed. Use the Device Deficiency Form as described in *Section 13: Device Deficiencies and Adverse Events*.

12.1.3 1-Day Postoperative Visit (Visit 1 – Day 1, Unilateral)

12.1.3.1 Ocular and Non-ocular Concomitant Medication

Record changes in ocular and non-ocular concomitant medications.

12.1.3.2 Intraocular Pressure (IOP)

Measure IOP using Goldmann or other applanation method. For each subject, the same instrument type should be used for all measurements in the study.

[redacted]

12.1.3.4 Slit-lamp Examination

Examine the anterior segment of the eye, including the eyelid, sclera, conjunctiva, cornea, iris, and natural crystalline lens. Record all new clinical observations and note the clinical significance of each observation.

NOTE: Certain pathologies may become apparent after cataract extraction and IOL implantation. In these instances, the preoperative pathology status should be updated.

12.1.3.5 Inflammatory Signs

Grade inflammatory signs including cells and flares, and corneal edema. Refer to MOP (*Inflammatory Signs Grading*) for details including grading scale.

12.1.3.6 Adverse Events

Record all AEs including SSIs. Use the AE form as described in *Section 13: Device Deficiencies and Adverse Events*.

12.1.4 1-Week Postoperative Visit (Visit 2 – 7 +/- 2 Days, Unilateral)

12.1.4.1 Ocular and Non-ocular Concomitant Medication

Record changes in ocular and non-ocular concomitant medications.

12.1.4.2 Visual Acuity (UCDVA and BCDVA) Testing

Perform Uncorrected Distance Visual Acuity (UCDVA) testing and Best Corrected Distance Visual Acuity (BCDVA) testing with study specified equipment. Refer to MOP for further instruction.

Ensure UCDVA and BCDVA testing precedes IOP measurement, the administration of eye drops to dilate or anesthetize the eyes, or any examination requiring contact with the eye.

NOTE: Lighting conditions must be measured and recorded prior to VA testing.

12.1.4.3 Intraocular Pressure (IOP)

Measure IOP using Goldmann or other applanation method. For each subject, the same instrument type should be used for all measurements in the study.

[redacted]

12.1.4.5 Slit-lamp Examination

Examine the anterior segment of the eye, including the eyelid, sclera, conjunctiva, cornea, iris, and natural crystalline lens. Record all new clinical observations and note the clinical significance of each observation.

NOTE: Certain pathologies may become apparent after cataract extraction and IOL implantation. In these instances, the preoperative pathology status should be updated.

12.1.4.6 Inflammatory Signs

Grade inflammatory signs including cells and flares, and corneal edema. Refer to MOP (*Inflammatory Signs Grading*) for details including grading scale.

12.1.4.7 Adverse Events

Record all AEs including SSIs. Use the AE form as described in *Section 13: Device Deficiencies and Adverse Events*.

12.1.5 3-Month Postoperative Visit (Visit 3 – 90 +/- 14 Days, Unilateral)

12.1.5.1 Ocular and Non-ocular Concomitant Medication

Record changes in ocular and non-ocular concomitant medications.

12.1.5.2 Visual Acuity (UCDVA and BCDVA) Testing

Perform Uncorrected Distance Visual Acuity (UCDVA) testing and Best Corrected Distance Visual Acuity (BCDVA) testing with study specified equipment. Refer to MOP for further instruction.

Ensure UCDVA and BCDVA testing precedes IOP measurement, the administration of eye drops to dilate or anesthetize the eyes, or any examination requiring contact with the eye.

NOTE: Lighting conditions must be measured and recorded prior to VA testing.

12.1.5.3 Intraocular Pressure (IOP)

Measure IOP using Goldmann or other applanation method. For each subject, the same instrument type should be used for all measurements in the study.

12.1.5.4 Specular Microscopy

Utilize a commercially available specular microscope (Konan microscope) to photograph the corneal endothelial cells as per the instructions provided by the Reading Center; the images will then be transferred to the Reading Center for analysis.

NOTE: If the subject has been dismissed prior to assessment of image quality (not recommended) and images are of poor quality, the subject will be asked to return and the assessment repeated.

12.1.5.5 Slit-lamp Examination

Examine the anterior segment of the eye, including the eyelid, sclera, conjunctiva, cornea, iris, and natural crystalline lens. Record all new clinical observations and note the clinical significance of each observation.

NOTE: Certain pathologies may become apparent after cataract extraction and IOL implantation. In these instances, the preoperative pathology status should be updated.

12.1.5.6 Inflammatory Signs

Grade inflammatory signs including cells and flares, and corneal edema. Refer to MOP (*Inflammatory Signs Grading*) for details including grading scale.

12.1.5.7 Dilated Fundus Examination

Perform a dilated fundus examination (indirect and direct ophthalmoscopy). Record diameter of dilated pupil. Record all preoperative baseline clinical observations with consideration given to the inclusion and exclusion criteria (Refer to *Section 10: Subject Population*) and note clinical significance.

NOTE: Certain pathologies may become apparent after cataract extraction and IOL implantation. In these instances, the preoperative pathology status should be updated.

12.1.5.8 Adverse Events

Record all AEs including SSIs. Use the AE form as described in *Section 13: Device Deficiencies and Adverse Events*.

12.1.6 Additional 6-Month Safety Follow-up Visit

Subjects who have completed the 3 month visit with an ECD count of less than 1500 cells/mm^2 and/or a decrease in ECD of 20% or more (in comparison to the screening visit value) at their 3 month visit, must return 3 months later for a 6 month safety follow-up visit.

The following safety assessments are to be performed at the 6-Month Safety Follow-up visit:

- A repeat ECD assessment
- Visual Acuity - BCDVA
- Slit lamp examination - corneal edema
- [redacted]
- Any other assessment performed as standard of care at the site

Subject data from the additional safety assessments will be captured in the electronic database, accordingly.

12.2 Discontinued Subjects

Discontinued subjects withdraw, or are withdrawn, from the study after 1) signing consent, 2) meeting the inclusion and exclusion criteria, and 3) having been randomized. Subjects signing consent, but withdrawing prior to randomization shall be considered a screen failure, and the failed entry criterion documented (eg, inclusion criterion 2, exclusion criterion 4). Refer to *Section 10 SUBJECT POPULATION*. Subjects randomized, but withdrawing prior to surgery shall be considered discontinued, and the reason for discontinuation documented (eg, discontinued due to withdrawal by subject).

Subjects may discontinue study participation at any time and for any reason. Subjects may be discontinued from the study at any time if in the opinion of the PI or designated, qualified medical personnel, continued participation poses a health risk. Subject numbers from discontinued subjects will not be reissued. Discontinued subjects will not be replaced.

12.3 Clinical Trial Termination

The study can be terminated at any time by the Sponsor. If the study is terminated, the Investigator and any regulatory authorities will be informed within 5 days of the decision. The Investigator will be responsible for informing the subjects and their Institutional Review Board (IRB) of the early termination of the trial. The Sponsor will be responsible for providing procedures to ensure protection of the subject interests.

12.4 Unscheduled Visit

After signing ICF, if a subject requires a study eye visit that is not specified in the protocol, the visit is considered an Unscheduled Visit (UNSV). For the 6-Month Safety Follow-up Visit please refer to Section 12.1.6.

Study eye ocular examinations conducted by non-study personnel are not considered an UNSV. Also, Pre-planned, routine postoperative visits (eg, 1-month postoperative visit) are not considered unscheduled visits unless an AE (serious or non-serious) is reported and study personnel are involved in the conduct of the visit.

NOTE: Any AE (serious or non-serious) arising from a pre-planned, routine postoperative visit must be captured and reported as in accordance with Section 13: Device Deficiencies and Adverse Events regardless of study personnel involvement.

During an unscheduled visit, it is recommended that the following information be collected:

- Concomitant medications
- Visual acuity (UCDVA, BCDVA)
- Slit-lamp exam
- Conjunctival edema grading
- Wound leakage
- Fundus exam
- IOP

- Adverse events and device deficiencies

Activities undertaken during an UNSV should be collected in accordance with this protocol and the MOP. Data collected will be entered into EDC.

If the subject is discontinued at the unscheduled visit, all Early Exit procedures should be performed. Refer to *Section 6 SCHEDULE OF VISITS*. If an UNSV is required after the final study visit for safety purposes, the data will not be captured in EDC. Refer to *Section 13.5 Follow-Up of Safety Information*.

12.5 Missed Visit

If a subject unavoidably misses a scheduled exam, he/she should be rescheduled within the same exam period. The Investigational site should show diligence in trying to schedule the subject for all exams. If a subject is unable to return for the final study visit, the Exit Form should be completed with the appropriate reason for discontinuation indicated.

12.6 Early Exit Visit

If a subject exits from the study early (ie, does not complete the scheduled or planned study visits) complete the early exit form including the following recommended activities:

- UCDVA and BCDVA
- IOP
- Specular microscopy
- Slit-lamp examination
- Inflammatory signs
- Dilated fundus exam
- Note AEs (including SSIs)
- Note changes to systemic and ocular concomitant medications

13 DEVICE DEFICIENCIES AND ADVERSE EVENTS

13.1 General Information

An adverse event (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 product (test or control article). 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.

Figure 13–1 Categorization of All Adverse Events

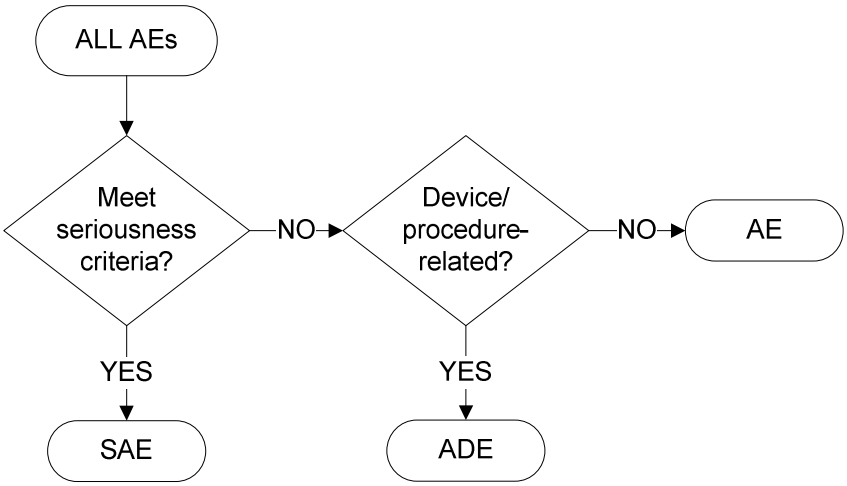
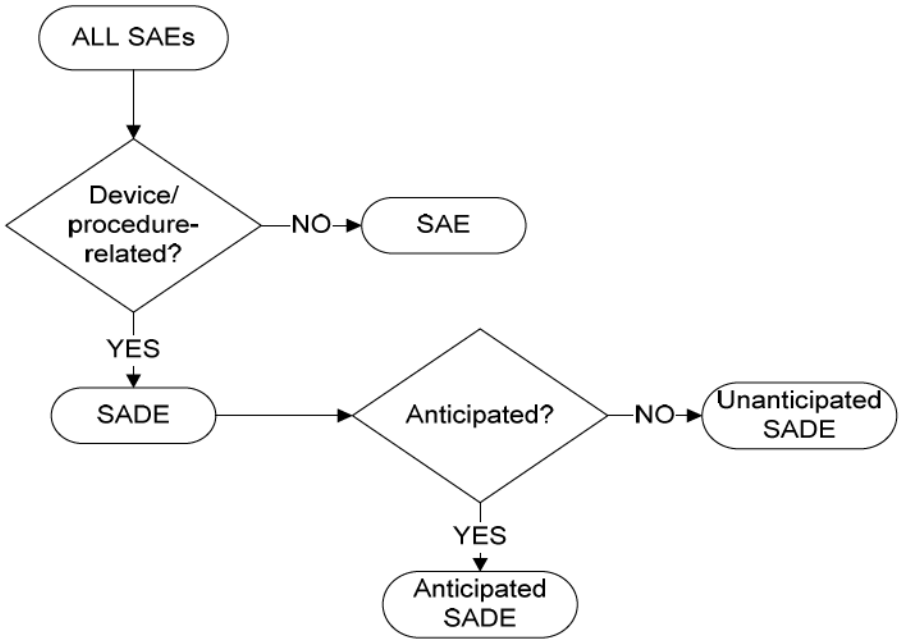


Figure 13-2 Categorization of All Serious Adverse Events



Serious Adverse Events

A serious adverse event is an AE that led to any of the following:

- Death.
- A serious deterioration in the health of the subject that either resulted in:
    a. a life-threatening illness or injury.
    Note: *Life-threatening means that the individual was at immediate risk of death from the event as it occurred, ie, it does not include an event which hypothetically might have caused death had it occurred in a more severe form.*
    b. any potentially sight-threatening event or permanent impairment to a body structure or a body function.

c. in-patient hospitalization or prolonged hospitalization.
Note: *Planned hospitalization for a pre-existing condition, without serious deterioration in health, is not considered a SAE. In general, hospitalization signifies that the individual remained at the hospital or emergency ward for observation and/or treatment (usually involving an overnight stay) that would not have been appropriate in the physician's office or an out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred, the event should be considered serious.*

d. a medical or surgical intervention to prevent a) or b)

e. any indirect harm as a consequence of incorrect diagnostic test results when used within manufacturer's instructions for use.

- Fetal distress, fetal death, or a congenital abnormality or birth defect.

Specific Events Relevant to this Protocol

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

- Capsule injury
- Thermal burns of the eye
- Vitreous loss

A change in corneal endothelial cell count following phacoemulsification and posterior chamber IOL implantation in subjects with a more advanced cataract (ie, Grades NII-NIV via LOCSII scoring) is an event of special interest. A change in corneal endothelial cell count has been defined as an ECD count of less than 1500 cells/mm^2 and/or a decrease in ECD of 20% or more at the subjects 3 month visit. To further characterize changes in ECD from baseline, an AE must be reported for any subject who experiences a change as defined above. Adverse events for corneal endothelial cell loss may be considered serious based on the judgment of the investigator.

Any other potentially sight-threatening event may also be considered serious based on the judgment of the Investigator and should be reported appropriately as delineated in Section 13.2. In addition, postoperative high IOP or corneal edema (grade 3) presented

persistently from 1 day to 1 month postoperative should be considered as a serious adverse event.

An adverse device effect (ADE) is an AE related to the use of an investigational product (test or control article). This definition includes AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation; any malfunction; and use error or intentional misuse of the test article or control article.

Serious Adverse Device Effect

A serious adverse device effect (SADE) is an ADE that has resulted in any of the consequences characteristic of a SAE.

Anticipated Serious Adverse Device Effect

An anticipated serious adverse device effect (ASADE) is a SADE which by its nature, incidence, severity, or outcome has been identified in the risk analysis report.

Unanticipated Serious Adverse Device Effect

An unanticipated serious adverse device effect (USADE) is a SADE which by its nature, incidence, severity or outcome has not been identified in the risk analysis report.

Device Deficiencies

A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. This definition includes malfunctions, use errors, and inadequate labeling. Malfunction is defined as a failure of a medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or clinical investigation plan. Use error is defined as an act or omission of an act that results in a different medical device response than intended by manufacturer or expected by user; this includes slips, lapses, and mistakes. An unexpected physiological response of the subject does not in itself constitute a use error.

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

- Aspiration/Irrigation functionality failure

- Failure of pressure sensor
- Improper use of viscoelastic
- Footswitch non-functioning
- Unsealed device packaging
- Suspect product contamination
- Lack of efficacy

13.2 Monitoring of 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 trial visit?"
- "Have there been any changes in the medicines you take since your last trial visit?"

AEs should be reported for any clinically relevant change, in the opinion of the Investigator, in concomitant medication(s) that is the result of an untoward (unfavorable and unintended) change in a subject's medical health.

Changes in any protocol-specific ocular or systemic parameter evaluated during the trial are to be reviewed by the Investigator. In addition, the subject's responses to any questionnaire utilized during the trial are to be reviewed by the Investigator. Any untoward (unfavorable and unintended) change in a protocol-specific parameter or questionnaire response that is clinically relevant, in the opinion of the Investigator, is to be reported as an AE. These clinically relevant changes will be reported regardless of causality.

13.3 Procedures for Recording and Reporting

All AEs must be documented on the AE eCRF by the site and are monitored on a routine basis by the trial Sponsor.

AEs are collected from the time of informed consent. Any pre-existing medical conditions or symptoms present in a subject are not considered AEs in the trial.

Aqueous cells and flare, corneal edema, raised IOP and superficial punctate keratitis are examples of early postoperative findings that are typically observed following ocular surgery. These are not considered AEs if they can be reasonably expected to resolve within a week and not result in any untoward long term visual outcome impact.

The Investigator must promptly document all ADEs and SAEs with details including the date of occurrence, severity, treatment (if applicable), outcome, and assessments of the seriousness and causality. In addition, the Investigator must promptly document all device deficiencies on the *Device Deficiency* eCRF. The site must submit all available information on ADEs, SAEs, and device deficiencies to the trial Sponsor immediately as follows:

- ADEs or SAEs are documented on the *Adverse Device Effect and Serious Adverse Event* eCRF within 24 hours of the Investigator's or site's awareness.
- Device deficiencies are documented on the *Device Deficiency* eCRF within 24 hours of the Investigator's or site's awareness. Please include a printed copy of the completed Device Deficiency eCRF with product returns.
- Additional relevant information after initial reporting is to be entered into the eCRF as soon as the data become available.
- Document any changes to concomitant medications on the appropriate eCRFs.
- All relevant documentation such as Discharge Summary, Autopsy Report, Certificate of Death, etc, should be faxed to the trial Sponsor at [redacted].

Note: *Should the EDC system become non-operational, the site must complete the appropriate paper Adverse Device Effect and Serious Adverse Event Form or Device Deficiency Form. The completed form is faxed to the trial Sponsor at* [redacted] *within 24 hours of the Investigator's or site's awareness; however, the reported information must be entered into the EDC system once it becomes operational.*

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

Further, depending upon the nature of the AE or device deficiency being reported, the trial 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

For every AE in the trial, the Investigator must assess the causality (Related or Not Related to the medical device or test procedure). An assessment of causality will also be performed by a trial Sponsor physician 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 test procedure has not been demonstrated, but there is a reasonable possibility that the AE or device deficiency was caused by the medical device or test 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).

Where appropriate, the Investigator must assess the intensity (severity) of the AE as mild, moderate, or severe, 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.

13.4 Unmasking of the Trial Information

Subjects will be masked to the treatment for the study eye. The surgeon (Investigator) is not masked to the treatment. Site personnel not participating in surgery and not requiring knowledge of randomization will be masked to the extent possible (see section 7.2 Clinical trial design).

Masked information on the identity of the assigned medical device should not be disclosed during the trial. If the treatment code needs to be broken in the interest of subject safety, the Investigator is encouraged to contact an appropriate trial Sponsor representative prior to unmasking the information if there is sufficient time. Dependent upon the individual circumstances (ie, medical emergency), the code may be broken prior to contact with the trial Sponsor. The trial Sponsor must be informed of all cases in which the code was broken and

of the circumstances involved. Additionally, the trial Sponsor may be required to unmask the information in order to fulfill expedited regulatory reporting requirements.

13.5 Follow-Up of Safety Information

The Investigator is responsible for adequate and safe medical care of subjects during the trial and for ensuring that appropriate medical care and relevant follow-up procedures are maintained after the trial. The Investigator should provide the trial 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. Any additional data from these follow-up procedures must be documented and available upon the trial Sponsor's request.

Subjects with an ECD count of less than 1500 cells/mm^2 and/or a decrease in ECD of 20% or more (in comparison to the screening visit value) at their 3 month visit, must return for a safety follow-up visit approximately 6 months following the date of surgery. (Refer to Section 12.1.6). Subject data from the additional safety assessments at this visit will be captured in the electronic database, accordingly.

13.6 Pregnancy in the Clinical Trial

Women of childbearing potential or women who are pregnant at the time of trial entry are not excluded from participation. Pregnancy should be included in the Medical History section of the eCRF when a pregnant woman enters the trial. If a woman becomes pregnant during the trial, this information should be documented. Pregnancy is not reportable as an AE; however, complications may be reportable and will be decided on a case-by-case basis. An Alcon prepared 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 will 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 CFR Part 11 compliance and the method of verification will be determined in advance of starting the study. Data reported on the eCRFs shall be derived from source document and be consistent with source document, and any discrepancies shall be explained in writing. At a minimum, source documentation should include the following information for each subject:

- Subject identification (name, sex)
- Documentation of subject eligibility
- Date of informed consent, and copy of signed informed consent form
- Dates of visits
- Documentation that protocol-specific procedures were performed
- Results of study testing, as required by the protocol
- Documentation of AEs and other safety parameters (as applicable)
- Records regarding medical histories and the use of concomitant therapies prior to and during the study
- Date of study completion and reason for early discontinuation (if applicable)

It is required that the author of each entry in the source documents be identifiable (eg, initials or signature and date). Any change or correction to data reported in the source, or on an eCRF, shall be dated, initialed, and explained if necessary. Changes shall not obscure the original entry (ie, an audit trail shall be maintained). Direct access to source documentation (medical records) must be allowed for the purpose of verifying that the data recorded on the eCRF are consistent with the original source data.

EDC will be designated for data collection and should be completed by designated individuals only. Required examinations must be recorded on the eCRFs. All data reported will 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. No subject identifiers should be recorded on the eCRFs beyond subject number, demographics information, and/or other study identifiers.

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

14.2 Data Review and Clarifications

Upon completion of the eCRFs, the data will be reviewed by Alcon study personnel for accuracy and completeness. If corrections and/or any additions to the data are deemed necessary, queries will be generated by Alcon data management or the site management (study monitor) team and forwarded to the investigative site. Staff at each site is 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 adverse events will be coded using the medical dictionary for regulatory activities (MedDRA) terminology.

Upon completion of the study and once the database is declared completed 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

The final subject evaluability will be determined prior to locking the database.

15.2 Analysis Data Sets

Three analysis sets will be defined: Safety, Intention-to-Treat (ITT) and Per-Protocol (PP).

15.2.1 Safety analysis set

Safety analyses will be conducted using the safety analysis set on a treatment-emergent basis. The Safety data set will include all subjects/eyes exposed to any study procedures evaluated in this study.

Safety data is to be collected for each subject beginning at the time of informed consent. Should any AEs occur prior to any study procedures these AEs will be presented separately from those treatment-emergent AEs considered in the safety analysis.

15.2.2 Intention-to-Treat (ITT) Analysis Set

The ITT set will include all subjects will include all subjects who are randomized in the study and receive treatment. The ITT set will be the primary analysis set for efficacy.

15.2.3 Per-Protocol (PP) Analysis Set

The PP set is a subset of ITT which excludes those who meet the critical deviation criteria as specified in the Deviations and Evaluability Plan. Supportive analysis of the primary and secondary endpoints will be conducted using the PP set if the number of subjects excluded from PP exceeds 5% of the ITT.

15.3 Demographics and Baseline Characteristics

Demographic information (age, sex, ethnicity, and race) and baseline characteristics will be summarized overall and by procedure group, on both Safety and ITT datasets.

Baseline Characteristics descriptive statistics for the crystalline lens assessment LOCS II scores, ECD and [redacted] will be presented by procedure group and overall. A listing showing the baseline crystalline lens assessment LOCS II scores will be provided.

15.4 Performance Analyses

15.4.1 Primary Performance

The primary endpoint is Cumulative Dissipated Energy (CDE).

15.4.1.1 Statistical Hypotheses

The null and alternative hypotheses for the primary analysis are:

H_o: $\mu_{centurion\_Bal\ CDE} \geq \mu_{Infiniti\_MFK\ CDE}$

H_A: $\mu_{centurion\_Bal\ CDE} < \mu_{Infiniti\_MFK\ CDE}$

$\mu_{centurion\_Bal\ CDE}$ and $\mu_{Infiniti\_MFK\ CDE}$ are the true mean values of the primary endpoint, CDE under Centurion® with the Balanced Tip, and Infiniti® with the Mini Flared Kelman (MFK) tip, respectively.

15.4.1.2 Analysis Methods

The difference of CDE between two groups will be examined by using ANCOVA adjusting for site and baseline opacity grade. Display of ANCOVA results in summary tables will contain difference between LS means, a one- sided p- value < 0.05 will conclude superiority of Centurion® over Infiniti® group.

15.4.2 Secondary Performance

The secondary endpoints are CDE and BSS fluid used.

[redacted]

15.4.2.1 Statistical Hypotheses

The null and alternative hypotheses for the secondary analyses are:

<u>Secondary hypotheses 1</u>

H_o: $\mu_{centurion\_Bal\ CDE} \geq \mu_{centurion\ \_MFK\ CDE}$

H_A: $\mu_{centurion\_Bal\ CDE} < \mu_{centurion\ \_MFK\ CDE}$

Where $\mu_{centurion\_Bal\ CDE}$ and $\mu_{centurion\_MFK\ CDE}$ are the true mean values of the secondary endpoint, CDE under Centurion® with the Balanced Tip, and Centurion® with the Mini Flared Kelman (MFK) tip, respectively.

Secondary hypotheses 2

H_o: $\mu_{centurion\_Bal\ BSS} \geq \mu_{Infiniti\ \_MFK\ BSS}$

H_A: $\mu_{centurion\_Bal\ BSS} < \mu_{Infiniti\ \_MFK\ BSS}$

Where $\mu_{centurion\_Bal\ BSS}$ and $\mu_{Infiniti\ \_MFK\ BSS}$ are the true mean values of the secondary endpoint, BSS under Centurion® with the Balanced Tip, and Infiniti® with the Mini Flared Kelman (MFK) tip, respectively.

Secondary hypotheses 3

H_o: $\mu_{centurion\_MFK\ BSS} \geq \mu_{Infiniti\ \_MFK\ BSS}$

H_A: $\mu_{centurion\_MFK\ BSS} < \mu_{Infiniti\ \_MFK\ BSS}$

Where $\mu_{centurion\_MFK\ BSS}$ and $\mu_{Infiniti\ \_MFK\ BSS}$ are the true mean values of the secondary endpoint, BSS under Centurion® with the Mini Flared Kelman (MFK) Tip, and Infiniti® with the Mini Flared Kelman tip, respectively.

Secondary hypotheses 4

H_o: $\mu_{centurion\_MFK\ CDE} \geq \mu_{Infiniti\ \_MFK\ CDE}$

H_A: $\mu_{centurion\_MFK\ CDE} < \mu_{Infiniti\ \_MFK\ CDE}$

Where $\mu_{centurion\_MFK\ CDE}$ and $\mu_{Infiniti\ \_MFK\ CDE}$ are the true mean values of the secondary endpoint, CDE under Centurion® with the Mini Flared Kelman (MFK) Tip, and Infiniti® with the Mini Flared Kelman tip, respectively.

15.4.2.2 Analysis Methods

The difference between two groups will be examined by using ANCOVA adjusting for site and baseline opacity grade. Display of ANCOVA results in summary tables will contain difference between LS Means, a one-sided p-value < 0.05 will conclude superiority.

15.4.3.1 Analysis Methods

Descriptive statistics will be displayed for the supportive endpoints. The variables will be summarized by procedure group, with n, mean, median, standard deviation [SD], minimum and maximum for continuous variables, and counts and percentages for categorical variables.

15.5 Handling of Missing Data

No imputation technique will be performed for missing values.

15.6 Multiplicity

A sequential (closed) testing procedure will be used to control type I error rate due to multiplicity for primary and secondary endpoints at one-sided 0.05 significance level.

15.7 Safety Analysis

The safety endpoints are:

- Adverse Events (including SSIs)
- Slit-lamp examination
- Anterior chamber cells
- Anterior chamber flare
- Corneal edema
- Endothelial cell count

- Dilated fundus examination
- BCDVA
- IOP
- Problems during surgery
- IOL placement
- Device deficiencies

Analysis of the safety endpoints will include descriptive statistics for each parameter by procedure group. Descriptive statistics generated for safety parameters will be based upon the type of parameter (ie, whether the data are categorical or continuous) being analyzed. For categorical parameters, the statistics used to summarize the data descriptively will include sample size, number in the category and percent in the category. For continuous parameters, sample size, mean, median, standard deviation, minimum and maximum will be presented.

Listings describing details of adverse events will be provided. Listings describing details of adverse events reported prior to the surgery will be presented separately from the safety analysis.

AEs will be coded by Medical Dictionary for Regulatory Activities (MedDRA). Counts and percentages of specific AEs will be presented by System Organ Class (SOC) and Preferred Term (PT). Relatedness and severity will be presented for each AE entry. AEs will be classified as ocular and non-ocular, treatment-emergent and non-treatment-emergent. All AEs and DDs will be listed.

15.8 Interim Analyses

Not applicable.

15.9 Adaptive Study Design

Not applicable.

15.10 Sample Size Justification

Based on previous studies, a sample size of 53 in each group will have 80% power to detect a difference in means of -7.4 (the difference between a Group 1 mean of 38.5 and a Group 2 mean of 45.9).

Assuming that the common standard deviation is 15.2 using a two group t-test with a 0.05 one-sided significance level.

Assuming a 10% dropout rate, 59 subjects per group (up to 177 in total) will be randomized.

16 ADMINISTRATIVE PROCEDURES

16.1 Regulatory and Ethical Compliance

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

16.2 Informed Consent Procedures

Voluntary informed consent will be obtained from every subject (and/or legal representative, as applicable) prior to the initiation of any screening or other clinical trial-related procedures. The Investigator must have a defined process for obtaining consent. Specifically, the Investigator, or designee, will explain the clinical trial 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 trial, 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 trial and will be provided with contact information for the appropriate individuals should questions or concerns arise during the clinical trial. The subject also will be told that their records may be accessed by appropriate authorities and Sponsor-designated personnel. The Investigator must keep the original, signed copy of the consent and must provide a duplicate copy to each subject.

16.3 Responsibilities of the Investigator and IRB/IEC

Before clinical trial initiation, this protocol, the informed consent form (and assent form, if applicable), any other written information provided to subject, and any advertisements

planned for subject recruitment must be approved by an Institutional Review Board / Independent Ethics Committee (IRB/IEC). A master list of IRBs/IECs for this clinical trial can be found in the Trial Mater 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 Investigator's Brochure, any periodic safety updates, and all other information as required by local regulation and/or the IRB/IEC. At the end of the clinical trial or in the case of early termination, the Investigator will notify the IRB/IEC of the clinical trial's final status. Finally, the Investigator will report to the IRB/IEC on the progress of the clinical trial at intervals stipulated by the IRB/IEC.

16.4 Sponsor and Monitoring Responsibilities

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

All 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 Global Clinical Site Management (GCSM) personnel and/or the assigned Clinical Monitor will contact each site at appropriate intervals. The GCSM representative will determine the frequency of site visits. Close-out visits will take place after the last visit of the last subject. The Sponsor reserves the right to attend surgeries and/or subject examinations where required for investigative site training and/or education.

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 should be 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 Publication of the Clinical Trial

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 has 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.

17 REFERENCES

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Wang Y, Xia Y, Zeng M, Liu X, Luo L, et al. Torsional ultrasound efficiency under different vacuum levels in different degrees of nuclear cataract. J Cataract Refract Surg. 2009;35(11):1941-5.

18 APPENDICES

Attachment follows.

CENTURION® VISION SYSTEM

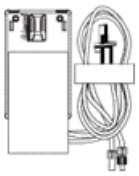
CENTURION® FMS Pack

DIRECTION FOR USE

CAUTION: The pack Directions-for-Use are not intended to substitute for the necessity of reading and understanding the CENTURION® Vision System Operator's Manual. The Operator's Manual, which is provided with the instrument, includes in-depth material intended to familiarize the Operating Room Staff with the controls and functions of the instrument.

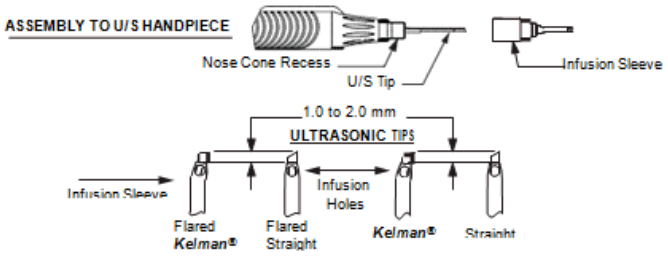
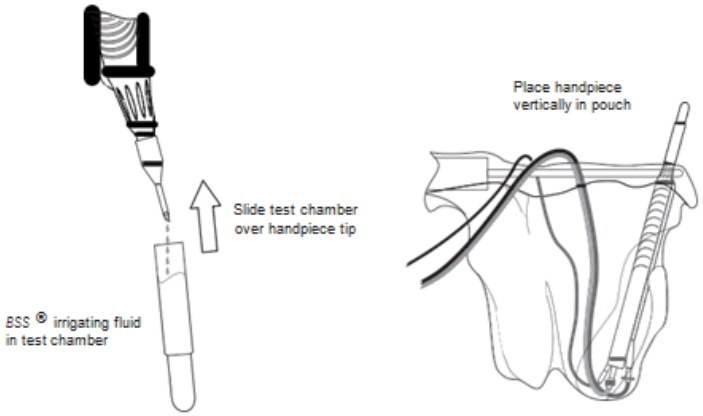
CAUTION: U.S. Federal Law restricts this device to sale by or on the order of a physician.

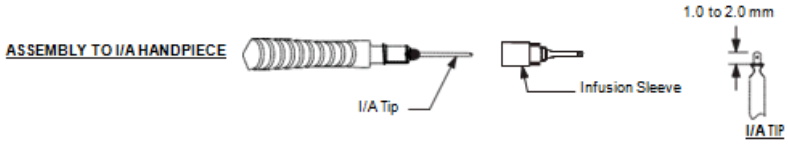
DESCRIPTION: Each pack contains the sterile single-use supplies necessary to perform one lens removal procedure using the CENTURION® Vision System. Following is a list of pack items and a brief explanation of their use. Individual component availability is dependent on pack configuration.

Fluidic Management System (FMS) 	Active FMS Spike 	Ultrasonic Tip 	Tip Holder/Wrench 	I/A Tip Wrench 
	Gravity FMS Spike 	Test Chamber 	Infusion Sleeve (2x) 	Tray Support Cover 

FMS PACK DIRECTIONS FOR USE:

FMS Setup Procedure	
1. Open pack and aseptically transfer contents to sterile field.	Circulator
2. Drape the Tray Support Cover over both the tray and support arm of the instrument. Extend the wire loop(s) from the tray and push drape down to form pouch.	Scrub Nurse
3. For Active Fluidics procedures, install approved Alcon irrigation bag and close the Active Fluidics compartment door. **Use of irrigation bags other than those approved by Alcon for use in the Active Fluidics system can result in a patient injury or system damage per section D in PRECAUTIONS and WARNINGS.**	Circulator
4. Install FMS by inserting the bottom of the FMS into the instrument fluidics module. Using the handle, push FMS into the module. Ensure that the tubing and drain bag hang freely. Place the tubing sets on the draped tray. **Note:** Do not spike the irrigation bottle or bag prior to FMS insertion.	Circulator or Scrub Nurse
5. Connect female luer fitting (Blue) on the aspiration line to the male luer fitting (Gray) on the irrigation line.	Scrub Nurse
6. Active and Gravity FMS spikes are different as shown above. For Active FMS, spike the irrigation bag secured within the Active Fluidics compartment. Ensure that the compartment door is fully closed. For Gravity FMS, spike the irrigation bottle or bag and attach to hanger on IV pole. Squeeze drip chamber to fill approximately 2/3 to 3/4 full.	Circulator or Scrub Circulator
7. Ensure correct Doctor and Procedure setting are selected. Press Prime FMS on the Setup screen to initiate priming/test sequence. After successful completion of the priming/test sequence, the prime status indicator will change from NOT PRIMED (red) to PRIMED (Green). If the priming/test sequence fails, an advisory message will be displayed. When prime is complete, Setup will automatically switch to Fill step but will not activate until the Fill button is pressed.	Circulator or Scrub Nurse

Ultrasound Handpiece Setup	
8. Thread U/S Tip onto U/S handpiece. Tighten firmly, using the Tip Holder/Wrench. Remove Tip Holder/Wrench and retain for future tip removal. **Match the proper color coding for the Ultrasonic Tip and the corresponding Infusion Sleeve per section D in PRECAUTIONS AND WARNINGS.**	Scrub Nurse
9. Thread Infusion Sleeve onto the handpiece, over the U/S Tip. Sleeve end should clear bevel on U/S Tip by 1-2 mm. Avoid twisting of the Sleeve. **NOTE:** Infusion Sleeves fit over both U/S and I/A tips. Orient port holes as shown: 	Scrub Nurse
10. Connect male irrigation line luer fitting (Gray) and female aspiration line luer fitting (Blue) to U/S handpiece. For U/S handpieces equipped with a locking irrigation port, turn the white luer lock clockwise to tighten and lock fitting to handpiece.	Scrub Nurse
11. Prepare handpiece for tuning and flow check. To allow irrigation fluid to flow from U/S tip, press Fill button on front panel or use the remote control to scroll to Fill and press Enter. Fill Test Chamber. Observe the stream of irrigating fluid from the irrigation and aspiration ports when the Fill button is depressed. If the stream of fluid is weak or absent, good fluidics response will be jeopardized. Good clinical practice dictates the testing for adequate irrigation and aspiration flow prior to entering the eye.	Scrub Nurse or Surgeon
12. Slide Test Chamber over Infusion Sleeve making sure that no air bubbles are present. Place handpiece vertically in the pouch created by the Tray Support Cover with Test Chamber pointing upwards. 	Scrub Nurse
13. To conduct handpiece tuning and flow check, press Test Handpiece button on front panel or use the remote control to scroll to Test Handpiece and press Enter. If the handpiece fails tuning or flow test, an advisory will be displayed. The handpiece tuning process can be aborted at any time by pressing Cancel (X).	Circulator or Scrub Nurse
14. Verify Patient Eye Level (PEL) with respect to the sensor reference indicator on the console. Press the Surgery button from the Setup screen to transition to the Surgery screen if PEL verification function is enabled. **Note:** With PEL verification disabled, after successful prime/ tune of the handpiece, the system will automatically transition to the Surgery screen.	Circulator or Scrub Nurse

Irrigation / Aspiration Handpiece Setup	
15. Thread I/A tip onto I/A handpiece if required. Tighten firmly, using the I/A Tip Wrench. Remove I/A tip wrench and retain for future tip removal. Thread Infusion Sleeve onto the handpiece, over the I/A Tip. Sleeve end should clear end of I/A Tip by 1-2 mm. Avoid twisting of the Sleeve. Orient port holes as shown below and ensure that I/A Tip aspiration hole is not obstructed.  	Scrub Nurse
16. Connect male irrigation line luer fitting (Gray) and female aspiration line luer fitting (Blue) to I/A handpiece. For I/A handpieces equipped with a locking irrigation port, turn the white luer lock clockwise to tighten and lock fitting to handpiece.	Scrub Nurse
17. Utilize the Fill button in the Setup screen or the optional Fill button, if added to the Surgery screen, to allow irrigation fluid to stream from the I/A tip to prime the handpiece. See the Operator's Manual for instructions to customize the Surgery screen. If the Fill button is not added, when in Surgery screen, depress footswitch to position 1 to stream irrigation fluid from the irrigation port and activate reflux function to stream fluid from the I/A tip's aspiration port. Observe the stream of irrigating fluid from the irrigation and aspiration ports. If the stream of irrigation fluid is weak or absent, good fluidics response will be jeopardized. Good clinical practice dictates the testing for adequate irrigation and aspiration flow prior to entering the eye.	Scrub Nurse or Surgeon
Removal of Ultrasonic Tip Or I/A Tip From Handpiece:	
18. Remove the infusion sleeve. Use the appropriate tip wrench for tip removal. Slide the tip through the opening of the wrench and engage the tip by turning the wrench slightly until the flat portions of the square nut engage the Tip Wrench. Then push Tip Holder/Wrench until it is fully seated and turn counterclockwise until tip is fully removed.	Circulator or Scrub Nurse

PRECAUTIONS AND WARNINGS:

A. Use of this product may require surgical setting adjustments. Ensure that appropriate system settings are used with the system packs. Prior to initial use, contact your Alcon Sales Representative for in service information. (Within the U.S. call 800-TO-ALCON, or 817-293-0450. Outside of the U.S., contact your local Alcon Sales Representative.)

B. If any item in the pack is received in a defective condition, Alcon is to be notified immediately. Do not use any of the contents if the sterile package is damaged or the seal is broken in any way. In these cases, please contact:

By Phone:
In USA (800) 757-9780
Ask for Medical Safety
International (817) 293-0450
Or contact local Alcon Representative

By Mail:
Alcon Research, Ltd
Attention: Medical Safety (AB2-6)
6201 South Freeway
Fort Worth, TX 76134-2099
USA

By E-mail:
MedicalSafetyHouston@alconlabs.com

Each pack is identified by a lot number which provides traceability and should be given to Consumer Affairs Department when discussing the pack.

C. The pack components are intended for one lens removal procedure only.
- **Potential risk from reuse or reprocessing include: fluid path leaks or obstruction resulting in reduced fluidics performance, reduced tip cutting performance, presence of tip burrs and foreign particle introduction into the eye**.

D. Improper usage or assembly could result in a potentially hazardous condition for the patient:
- Mismatch of consumable components and/or use of settings not specially adjusted for a particular combination of consumable components may create potentially hazardous fluidics imbalance.
- Use of non-approved handpieces may create potentially hazardous fluidics imbalance.
- Use of incisions that are smaller than recommended can lead to mechanical and/or thermal damage to the eye tissues.
- Use of irrigation bags other than those approved by Alcon for use in the Active Irrigation can result in a patient injury or system damage.

Infusion Sleeves/Type	Sleeve Color	Recommended Incision Size	Recommended Tips
0.9 mm High Infusion Sleeve	Light Purple	3.2 mm	0.9 mm and 0.9 mm ABS® MicroTip 0.9 mm Tapered ABS® MicroTip 0.9 mm Flared ABS® MicroTip 0.9 mm MiniFlared ABS® Tip 0.9 mm ABS® Mini Tip, 0.9 mm ABS® INTREPID® Balanced Tip 0.9 mm ULTRACHOPPER® Tip Standard I/A, Silicone I/A, INTREPID® I/A Tip
0.9 mm Micro Sleeve	Dark Purple	2.75 mm	
0.9 mm Ultra Sleeve	Red	2.2 mm	0.9 mm Flared ABS® MicroTip, 0.9 mm MiniFlared ABS® Tip 0.9 mm ABS® Mini Tip, 0.9 mm ABS® INTREPID® Balanced Tip 0.9 mm ULTRACHOPPER® Tip Silicone I/A, INTREPID® I/A Tip
0.9 mm Nano Sleeve	Orange	1.8 mm	
0.7 mm Ultra Sleeves	Yellow	2.2 mm	0.7 mm ABS® Mini Tip 0.7 mm ABS® INTREPID® Balanced Tip
0.7 mm Nano Sleeves	Gray	1.8 mm	

E. The equipment used in conjunction with the ALCON® pack disposables constitutes a complete surgical system. Use of disposables other than those of Alcon may affect system performance and create potential hazards and if it is determined to have contributed to the malfunction of equipment under contract, could result in the voidance of the contract and or invoicing at prevailing hourly rates.

F. Do not exceed maximum capacity of drain bag (500 ml). Excessive pressure can result from exceeding drain bag maximum capacity and potentially result in a hazardous condition for the patient.

Definitions for symbols that may appear on product labels:

	SEE DIRECTIONS FOR USE		DO NOT USE IF PACKAGE IS DAMAGED		MANUFACTURER
REF	CATALOG NUMBER		SINGLE USE - DO NOT REUSE		DATE OF MANUFACTURER
LOT	BATCH CODE		USE BY : YEAR-MONTH	DEHP	CONTAINS DEHP
	DOES NOT CONTAIN LATEX OR DRY NATURAL RUBBER	One of the following sterilization symbols will apply to this package			
EC REP	AUTHORIZED REPRESENTATIVE IN THE EUROPEAN COMMUNITY	STERILE R	STERILE - STERILIZED BY IRRADIATION		
		STERILE EO	STERILE - STERILIZED BY ETHYLENE OXIDE		
Rx only	CAUTION: U.S. FEDERAL LAW RESTRICTS THIS DEVICE TO SALE BY OR ON THE ORDER OF A PHYSICIAN				PEEL POINT

EC REP
Alcon Laboratories (U.K.) Ltd.
Frimley Business Park
Frimley, Camberley
Surrey, GU16 7SR, United Kingdom

CE 0123

Alcon®
ALCON LABORATORIES, INC.
6201 SOUTH FREEWAY
FORT WORTH, TX 76134-2099 USA
a Novartis company
MADE IN USA

316-3193-001 REV. B

INFINITI ® *OZil* ® AND U/S HANDPIECE DIRECTIONS FOR USE

Refer to the driving console Operator's Manual (and Addendums) for handpiece compatibility.

CAUTION: The Handpiece Directions-for-Use are not intended to substitute for the necessity of reading and understanding the driving console Operator's Manual. The Operator's Manual, which is provided with the console, includes in-depth material intended to familiarize the Operating Room Staff with the controls and functions of the console.

CAUTION: U.S. Federal Law restricts this device to sale by or on the order of a physician.

WARNINGS:

1. If the handpiece is received in a defective condition, do not use and notify Alcon immediately:
   By Phone: Technical Services
   (In USA) (800) 832-7827
   (International) (800) 832-7827 or
   contact local Alcon representative
   By Mail: Alcon
   Technical Services
   15800 Alton Parkway
   Irvine, CA 92618 USA
   Each handpiece is identified by a Serial Number which provides traceability and should be given to Technical Services when discussing the handpiece.
2. Before each use, the handpiece and power cord should be inspected for damages (e.g. nicks, crimps, dents exposed wires). If the handpiece is damaged it should be immediately removed from service. Use of damaged Handpiece may result in serious permanent patient injury.
3. Each time the Handpiece is connected to the driving console, it performs a check cycle. If the Handpiece performs improperly and fails the check cycle, remove it from the driving console and return it to Alcon for evaluation.
4. Use care in handling the handpiece, particularly when cleaning. Extra attention to protecting the nosecone area should be taken. Always clean the handpiece over a surface cushioned with a pad or rubber mat.
5. This handpiece is to be used only with approved Alcon surgical systems. See the particular Operator's Manual of the surgical system for a list of appropriate handpieces for that system.
6. In the event of any difference between this document and the driving console Operator's Manual, please use the information in this Directions-For-Use. If you have questions, please contact Alcon.
7. Be sure the handpiece connector is dry before connecting it to the console.
8. Do not ultrasonically clean the handpiece. Ultrasonic cleaning of this handpiece will cause irreparable damage.
9. Never immerse the handpiece in liquid after autoclaving; allow it to air cool for at least 15 minutes.
10. During any phacoemulsification procedure, metal particles may result from inadvertent touching of the phacoemulsification tip with a second instrument. Another potential source of metal particles resulting from any ultrasonic handpiece may be the result of ultrasonic energy causing micro abrasions of the ultrasonic tip.
11. If in the medical opinion of the physician a patient with a prion related disease undergoes a high risk procedure, the instrument should be destroyed or be processed according to local requirements.

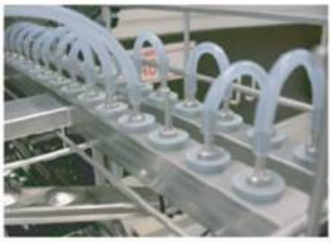
DESCRIPTION: Each package contains one ultrasonic handpiece.

DIRECTION FOR USE: The following cleaning and sterilization instructions provide a method for effectively cleaning and sterilizing the ***Infiniti*** ® *Ozil* ® and U/S Handpieces per EN ISO 17664[1]. Due to the potential for Toxic Anterior Segment Syndrome (TASS), Alcon does not recommend the use of enzymatic cleaners, detergents, or disinfectant solutions. If however, local jurisdictions mandate their use relative to ophthalmic instruments, the materials of construction are compatible with both, up to a pH of 11.3, when the enzymatic chemicals, detergents or disinfectant solutions are completely rinsed/neutralized immediately after cleaning/processing, per your facility's standard procedure.

1. Thoroughly clean the handpiece before initial use and IMMEDIATELY after each subsequent use. Do not store or allow the handpiece to dry after use until thoroughly cleaned. Both a manual cleaning process and a cleaning process using an automated washer are presented.
2. **Cleaning Procedure: Manual**
   Perform the following steps to thoroughly clean the handpiece.
   Step One: Remove the irrigation and aspiration tubing from the handpiece.
   Step Two: Unplug the handpiece connector from the console and install the protective cap.
   Step Three: Remove the infusion sleeve and tip from the handpiece using the tip wrench and discard according to surgical facility guidelines.
   Step Four: Wipe any residue from the handpiece with a soft, clean, lint free non-abrasive cloth and rinse the handpiece with room temperature sterile deionized water to remove any remaining debris. If necessary, wash the exterior of the handpiece using a soft bristled cleaning brush.
   Step Five: Submerge the nosecone (front part) of the handpiece in a container of room temperature sterile deionized water.
   Step Six: Using a syringe, draw or push a minimum of 120cc of sterile deionized water through both the irrigation and aspiration paths.
   Step Seven: Using the same syringe, flush both ports with a minimum of 60cc of air.
   Step Eight: Dry the exterior surfaces of the handpiece and cable with a soft clean, lint free non-abrasive cloth.
   Step Nine: Visually inspect to ensure the Handpiece is clean and dry. Repeat the process as needed.
   Step Ten: Place the cleaned handpiece and cable in an autoclavable tray to prevent damage to connector and handpiece during storage and autoclaving or wrap to prevent damage in preparation for autoclaving.
3. **Automated Washer Procedure**
   In the event use of an automated process is required, perform all of the following steps to process the handpiece.
   Note: a) Due to the potential for the accumulation of particulate and bioburden residues in the washer water reservoirs, it is the surgical facility's responsibility to properly maintain the equipment and their associated filters to ensure the introduction of contaminant- free solutions into the handpieces.
   b) This automated washing procedure provides a method for effectively processing up to three (3) handpieces at a time.
   c) The temperatures and cycle parameters below will not cause damage to the product.
   d) Do not wash the handpieces with non-ophthalmic instruments.
   Step One: Manually clean the handpiece immediately after each surgical procedure per the manual cleaning procedure above before using an automated washer.
   Step Two: Prepare the washer with multi-purpose injector per Operator's Manual. The circulation rate of the automated washer should be at least 106 gallons (401 liters) of water per minute. The use of a typical automated washer and wire basket is depicted below.
   Note: Use de-ionized water only.
   Required materials:
   - Detergent with pH range of 8.5 up to 9.5.
   - Organic acid neutralizer with pH range of 3.0-2.6.
   - Adaptors and silicone tubing, e.g. Customized Auto Wash Kit: Alcon REF 8065750456.

   Step Three: Set detergent and neutralizer dispensers as recommended by detergent and washer manufacturer.
   Step Four: Program washer a minimum of to have the following automated cycle:
   - Main wash at a minimum of 55° C for at least 10 minutes (dispense detergent as recommended by detergent and washer manufacturer)
   - Neutralize for a minimum of 1.5 minutes (dispense neutralizer as recommended by detergent and washer manufacturer)
   - Rinse for a minimum of 5 minutes at 22 - 27° C then drain
   - Repeat rinse for a minimum of 5 minutes at 22 - 27° C then drain
   - Final Rinse a minimum of 70° C for at least 1.5 minutes then drain
   - Dry at a minimum of 100° C for at least 5 minutes

   Note: Additional rinsing steps will not alter the effectiveness of the validated cycle.

		
Step Five: Using the Auto Wash Kit, secure the handpiece to the wire mesh basket using the small gauge wire and connect the handpiece with the "Y" adapter assembly as shown.	**Step Six:** Place wire basket with handpiece in multi-purpose injector rack and connect the "Y" adapter assembly to the 4 mm diameter injector nozzle as shown.	**Step Seven:** Plug off any unused injector nozzle with silicone tubing. **Pictured:** Miele* Labwasher, Model G7735 with injector Model # 0-177.

Step Eight: Start the wash program. When the wash program is completed, visually inspect to ensure the Handpiece is clean and dry. Repeat the process as needed. Place the processed handpiece and cable in an autoclavable tray to prevent damage to connector and handpiece during storage and autoclaving or wrap to prevent damage in preparation for autoclaving.

4. **Sterilization:**

Sterilize the handpiece using a steam sterilization cycle. The sterilization instructions provided in Table 1 below have been validated by Alcon Laboratories, Inc. as being CAPABLE of sterilizing the ***Infiniti®*** *Ozil* ® and U/S Handpieces for re-use. It remains the responsibility of the processor to ensure that the processing as actually performed using equipment, materials and personnel in the facility achieve the desired result. This requires verification and routine monitoring of the process. Likewise any deviation by the processor from the instructions provided should be properly evaluated for effectiveness and potential adverse consequences. Please refer to nationally recognized standards, or to your facility's standard procedures.

Note: Due to the potential for the accumulation of particulate and bioburden residues in the sterilizer water reservoirs, it is the surgical facility's responsibility to properly maintain the equipment and their associated filters to ensure the introduction of steam into the Handpiece is contaminant free at levels acceptable per the surgical facility's requirements.

Table 1 - STERILIZATION TEMPERATURES AND TIME SETTINGS

STERILIZER TYPE	PULSES	CONFIGURATION	MINIMUM TEMPERATURE	MINIMUM EXPOSURE TIME (MINUTES)
Gravity Displacement	N/A	Wrapped	132° C (270° F)	18
Gravity Displacement	N/A	Unwrapped	132° C (270° F)	8
Pulsing Prevacuum	4	Unwrapped	132° C (270° F)	4
Pulsing Prevacuum	4	Wrapped	134° C (273° F)	5
Pulsing Prevacuum (four negative and four positive pulses)	4	Wrapped	134-137° C (273-279° F)	3

Note: This product has been validated to perform reliably after steam sterilization at 134°C (273°F) for 18 minutes (prevacuum, wrapped).

5. After transport to the driving console for the next use, refer to your driving console Operator's Manual for proper surgical setup.
6. Refer to Alcon's Pack/Tip Directions for Use for proper assembly of the tip to the Handpiece.
7. There are not specific limits for the time or conditions of storage.
8. **References:**

[1]EN ISO 17664: Sterilization of medical devices - Information to be provided by the manufacturer for the processing of resterilizable medical devices.

Definitions for symbols that may appear on product labels:

	SEE DIRECTIONS FOR USE		MANUFACTURER	SN / SN	SERIAL NUMBER
	DOES NOT CONTAIN LATEX OR DRY NATURAL RUBBER		DATE OF MANUFACTURE	REF / REF	CATALOG NUMBER
EC REP	AUTHORIZED REPRESENTATIVE IN THE EUROPEAN COMMUNITY	℞ only	CAUTION: U.S. FEDERAL LAW RESTRICTS THIS DEVICE TO SALE BY OR ON THE ORDER OF A PHYSICIAN		

EC REP
Alcon Laboratories (U.K.) Ltd.
Frimley Business Park
Frimley, Camberley
Surrey, GU16 7SR, United Kingdom

CE 0123

Alcon®
ALCON LABORATORIES, INC.
6201 SOUTH FREEWAY
FORT WORTH, TX 76134-2099 USA
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210-1860-001 REV. T

Date/Time (mm/dd/yyyy GMT):	Signed by:	Justification:
[redacted]		