Next Generation Cataract Surgery Study

STUDY ID

CTV678-E002

PROTOCOL

NCT06071104

Device Protocol for CTV678-E002

Title: Next Generation Cataract Surgery Study

Protocol Number:	CTV678-E002
Clinical Investigation Type:	Traditional Feasibility
Test Product:	UNITY™ Vitreoretinal Cataract System (VCS)
Sponsor Name and Address:	Alcon Research, LLC, and its affiliates (“Alcon”) 6201 South Freeway Fort Worth, Texas 76134-2099

Investigator Agreement:

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

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

Principal investigator:

Signature Date

Name and professional position:

Address:

Phone Number:

Off-hours Emergency Phone Number:

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1 GLOSSARY OF TERMS

Names of Test Product(s)	Throughout this document, test product(s) will be referred to as the UNITY Vitreoretinal Cataract System (VCS).
Name of Comparator Product(s)	N/A
Adverse Device Effect (ADE)	Adverse event related to the use of an investigational medical device or comparator. *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.*
Adverse Event (AE)	Untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device or comparator and whether anticipated or unanticipated. *Note: For subjects, this definition includes events related to the investigational medical device, comparator, or the procedures involved. For users or other persons, this definition is restricted to the use of the investigational medical device or comparator.* Requirements for reporting Adverse Events in the study can be found in Section 11.
Anticipated Serious Adverse Device Effect (ASADE)	An effect which by its nature, incidence, severity, or outcome has been identified in the risk assessment.

Clinical Investigation Plan (CIP)	The document(s) stating the rationale, objectives, design, and prespecified analysis, methodology, organization, monitoring, conduct, and record-keeping of the clinical investigation. *Note: The protocol and other documents referenced in the protocol (for example, the Statistical Analysis Plan, the Manual of Procedures, the Deviations and Evaluability Plan, and the Protocol Monitoring Plan) comprise the CIP.*
Clinical Investigation Report (CIR) / Clinical Study Report	The document describing the design, execution, statistical analysis, and results of a clinical investigation. The Clinical Investigation Report is synonymous with the Clinical Study Report.
Device Deficiency	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety, or performance. *Note: This definition includes malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling related to the investigational medical device or the comparator.* Requirements for reporting Device Deficiencies in the study can be found in Section 11.
Enrolled Subject	Any subject who signs an informed consent form for participation in the study.
Point of Enrollment	The time at which, following recruitment and before any clinical investigation-related procedures are undertaken, a subject signs and dates the informed consent form.

Interventional Clinical Trial	A pre- or post-market clinical investigation where the assignment of a subject to a particular medical device is decided in advance by a clinical investigation plan, or diagnostic or monitoring procedures requested in the CIP are in addition to those available as normal clinical practice and burden the subject.
Investigational Product	A preventative (vaccine), a therapeutic (drug or biologic), device, diagnostic, or palliative used as a test or comparator product in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form.
Malfunction	Failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or clinical investigation plan (CIP), or investigator's brochure (IB).
Nonserious Adverse Event	Adverse event that does not meet the criteria for a serious adverse event.
Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Serious Adverse Event (SAE)	Adverse event that led to any of the following: • Death. • A serious deterioration in the health of the subject, users or other persons as defined by one or more of the following: a) a life-threatening illness or injury *Note: Life-threatening means that the individual was at immediate risk of death from the event as it occurred, i.e., it does not include an event which hypothetically might have caused death had it occurred in a more severe form.* b) any potentially sight-threatening event or permanent impairment to a body structure or a body function including chronic diseases. c) inpatient hospitalization or prolonged hospitalization. d) a medical or surgical intervention to prevent a) or b). This includes any ocular secondary surgical intervention excluding posterior capsulotomy. e) any indirect harm as a consequence of incorrect diagnostic test results when used within manufacturer's instructions for use. • Fetal distress, fetal death, congenital abnormality or birth defect including physical or mental impairment. *Note: Planned hospitalization for a preexisting condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.* *Refer to Section 11 for additional SAEs.*

Serious Health Threat	Signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in subjects, users, or other persons, and that requires prompt remedial action for other subjects, users, or other persons. *Note: This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.*
Study Start	The start of the study is considered to coincide with the enrollment of the first patient.
Study Completion	The completion of the study is considered to coincide with the study-level last subject last visit or the decision to terminate the trial, whichever is later.
Unanticipated Serious Adverse Device Effect (USADE)	Serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the risk assessment.
Use Error	User action or lack of user action while using the medical device that leads to a different result than that intended by the manufacturer or expected by the user. *Note:* *a) Use error includes the inability of the user to complete a task.* *b) Use errors can result from a mismatch between the characteristics of the user, user interface, task, or use environment.* *c) Users might be aware or unaware that a use error has occurred.* *d) An unexpected physiological response of the patient is not by itself considered a use error.* e) *A malfunction of a medical device that causes an unexpected result is not considered a use error."*

Vulnerable Subject	An individual who is unable to fully understand all aspects of the investigation that are relevant to the decision to participate, or who could be manipulated or unduly influenced as a result of a compromised position, expectation of benefits or fear of retaliatory response.

2 LIST OF ACRONYMS AND ABBREVIATIONS

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

Abbreviation	Definition
ACD	Anterior chamber depth
AL	Axial length
ADE	Adverse device effect
AE	Adverse event
ASADE	Anticipated serious adverse device effect
AUS	Australia
BSS	Balanced salt solution
BCDVA	Best corrected distance visual acuity
C	Celsius
cc	Cubic centimeter
CDE	Cumulative dissipated energy
CFR	Code of Federal Regulations
CIP	Clinical investigation plan
CIR	Clinical investigation report
CRF	Case report form
D	Diopter
DFU	Directions for use
ECCE	Extracapsular cataract extraction
eCRF	Electronic case report form
EDC	Electronic data capture
EU	European Union
EUREQUO	European Registry of Quality Outcomes for Cataract and Refractive Surgery
F	Fahrenheit
FLACS	Femtosecond laser-assisted cataract surgery
FMS	Fluidics Management System
GCP	Good clinical practice
GPCMS	Global Product Complaint Management System
HP	Hand piece
I/A	Irrigation/Aspiration
IB	Investigator’s brochure

Abbreviation	Definition
ICF	Informed consent form
IEC	Independent ethics committee
IOL	Intraocular lens
IOP	Intraocular pressure
IP	Investigational product
IRB	Institutional review board
ISO	International Organization for Standardization
mm	Millimeter
mmHg	Millimeters of mercury
MOP	Manual of procedures
MSICS	Manual small incision cataract surgery
N/A	Not applicable
N	Sample size
Nd:YAG	Neodymium-doped yttrium aluminum garnet
NEI	National Eye Institute
PCO	Posterior capsule opacification
Phaco	Phacoemulsification
SADE	Serious adverse device effect
SAE	Serious adverse event
SICS	Manual small incision cataract surgery
SLE	Slit lamp examination
SOC	Standard of Care
SOP	Standard operating procedure
SSI	Secondary surgical intervention
TASS	Toxic anterior segment syndrome
UCDVA	Uncorrected distance visual acuity
USA	United States of America
U/S	Ultrasound
USADE	Unanticipated serious adverse device effect
USV	Unscheduled visit
VA	Visual acuity
VCS	Vitreoretinal Cataract System
WHO	World Health Organization

3 PROTOCOL SUMMARY

Investigational product type	Device
Study type	Interventional, traditional feasibility
Investigational products	Test Product: UNITY VCS (including the console, remote control, foot controller, UNITY Cataract FMS Pack, and UNITY Anterior Vitrectomy Kit). Comparator Product: N/A
Purpose and Scientific Rationale for the Study	The purpose of this study is to obtain device-specific safety and performance clinical data to support marketability in Europe, and to collect user preference data. The study is not being conducted to mitigate any risk as the risk assessment did not find any new harms or increases in likelihood of any harms when compared to predecessor devices having the same intended use and indications for use.
Brief Summary of the Protocol	The aim of this study is to obtain device-specific clinical data and user preference data. This is a prospective, single-arm, non-randomized, multi-center clinical study of adults with a clinically documented diagnosis of age-related, non-complicated cataract who meet the inclusion/exclusion criteria.
Objective(s)	The objective is to obtain device-specific safety and performance clinical data to support marketability in Europe, and to collect user preference data.
Endpoint(s)	Primary Performance Endpoint • Percent of 'yes' responses to the question: ***Did UNITY VCS using anterior segment surgical functionality perform per the intended use as defined in Protocol Section 5.1?*** Secondary Performance Endpoint • Time from incision entry to incision closure

	Safety Endpoints • Adverse events (ocular and nonocular; serious and nonserious) • Secondary surgical interventions • Unplanned intraoperative surgical procedures • Device deficiencies
Assessment(s)	Effectiveness • User preference questionnaires • Overall procedure time from incision entry to incision closure (via stopwatch) Safety • UCDVA • BCDVA by manifest refraction • Tonometry/IOP • Slit lamp examination • Dilated fundus examination • Adverse events • Secondary surgical interventions • Device deficiencies [redacted]

Study Design	This is a prospective, interventional, open-label, single-arm, nonrandomized, multicenter clinical trial study of adults with a clinically documented diagnosis of age-related, noncomplicated cataract who meet the inclusion/exclusion criteria.
Subject population	Adult patients presenting for routine cataract surgery. Planned number of subjects enrolled/consented: Approximately 120 subjects/120 eyes (unilateral subjects) Planned number of completed subjects: Approximately 100 subjects/100 eyes (unilateral subjects)
Sites and Locations	Planned number of clinical sites: up to 5 sites Planned locations (initial list of locations, which may change during start up or conduct according to study needs): United States and/or Australia
Key inclusion criteria (See Section 8.1 for a complete list of inclusion criteria)	• Adults (>18 years of age) with a clinically documented diagnosis of age-related noncomplicated cataract • Eligible to undergo primary hydrophobic acrylic intraocular lens implantation into the capsular bag • Keratometry: 41 to 46 D, anterior chamber depth: 2.5 to 4 mm and axial length: 22 to 25 mm
Key exclusion criteria (See Section 8.2 for a complete list of exclusion criteria)	• Laser assisted fragmentation in the operative eye • More than 1+ guttata in the operative eye • A history of chronic or recurrent inflammatory eye disease or trauma (e.g., iritis, scleritis, uveitis, iridocyclitis, rubeosis iridis, herpes simplex keratitis) in the operative eye • Any ocular comorbidity (other than cataract) that may confound the results (e.g., zonular instability or zonular dehiscence or pseudoexfoliation, ocular surface disease, synechiae, iris atrophy, shallow anterior chamber, lens subluxation) in the operative eye • Diagnosis of glaucoma or ocular hypertension (IOP > 21 mmHg) in the operative eye

	• Diagnosed with severe systemic (e.g., history of cerebral vascular accident) or retinal disorders (e.g., macular degeneration, diabetic retinopathy, or other retinal pathology that might limit postoperative visual acuity or predispose the subject to postoperative retinal complications) in the operative eye • A poorly dilating pupil or other pupil defect that prevents the iris from retracting peripherally to at least 6 mm diameter dilation in the operative eye
Data analysis and sample size justification	The primary analysis set for effectiveness outcomes will be the all-implanted analysis set. The all-implanted analysis set includes all eyes with successful completion of the cataract surgery including IOL implantation. The safety analysis set will include all eyes with attempted use of the UNITY VCS (successful or aborted after contact with the eye) and will be used for the safety outcomes. Attempted use of the UNITY VCS is defined as any time the device makes contact with the eye. There will be no hypothesis testing for any study outcome. All study outcomes will be presented as data listings or with summary statistics that are appropriate to the scale of the endpoint (continuous, dichotomous, etc.). Based on a sample of 100 subjects, the expected half-width of the 95 % confidence interval for the percentage of surgeons reporting 'yes' to the question "***Did UNITY VCS using anterior segment surgical functionality perform per the intended use as defined in Protocol Section 5.1?***" will be $1.96 \cdot \sqrt{(p(1-p)/100)}$. This half-width is widest at p = 50%. Under this conservative assumption, the expected half-width is <10% given the sample size of 100. Allow enrollment for an additional 10% for screen failure and 10% for lost to follow-up to ensure 100 completed subjects.

Table 3–1 Schedule of Study Procedures and Assessments

Visit	**Visit 0 Screening**	**Visit 00 Surgery**	**Visit 1 1 Day**	**Visit 2 1 Week**	**Visit 3 1 Month / Exit**	**Early Exit**	**Unscheduled Visit** [7]
Day Number	**Day -60 to 0**	**Day 0**	**Day 1 to 3**	**Day 4 to 10**	**Day 28 to 42**	**N/A**	**N/A**
Eye	Both Eyes	Study eye	Study eye	Study eye	Study eye	Study eye	Study eye
Informed Consent	X						
Demographics	X						
Medical and Ocular History	X						
Concomitant Medications	X	X	X	X	X	X	X
Inclusion/Exclusion	X						
Urine Pregnancy Test [1]*	X						
Dilated Pupil Size	X						
Keratometry	X						
Biometry (ACD, AL)	X						
Slit Lamp Examination	X		X	X	X	X	(✓)
UCDVA[2]			X				

Visit	Visit 0 Screening	Visit 00 Surgery	Visit 1 1 Day	Visit 2 1 Week	Visit 3 1 Month / Exit	Early Exit	Unscheduled Visit [7]
Day Number	**Day -60 to 0**	**Day 0**	**Day 1 to 3**	**Day 4 to 10**	**Day 28 to 42**	**N/A**	**N/A**
Eye	Both Eyes	Study eye	Study eye	Study eye	Study eye	Study eye	Study eye
BCDVA[3]	X			X	X	X	(✓)
Intraocular Pressure	X		X	X	X	X	(✓)
Dilated Fundus Exam[4]	X				X	X	(✓)
Treatment (cataract surgery)		X					
[redacted]							
Time from incision entry to incision closure		X					
[redacted]							

Visit	Visit 0 Screening	Visit 00 Surgery[redacted]	Visit 1 1 Day	Visit 2 1 Week	Visit 3 1 Month / Exit	Early Exit	Unscheduled Visit [7]
Day Number	**Day -60 to 0**	**Day 0**	**Day 1 to 3**	**Day 4 to 10**	**Day 28 to 42**	**N/A**	**N/A**
Eye	Both Eyes	Study eye	Study eye	Study eye	Study eye	Study eye	Study eye
User Preference Questionnaire[redacted]		X					
Adverse Events	X	X	X	X	X	X	X
Device Deficiencies	X	X	X	X	X	X	X
Exit Form	(✓)	(✓)	(✓)	(✓)	X	X	(✓)

(✓) Assessment performed as necessary

[1] Women of child-bearing potential only

[2] VA to be conducted per site's SOC using Snellen chart

[3] VA to be conducted per site's SOC using manifest refraction and Snellen chart

[4] Assessment must be performed dilated

[redacted]

[redacted]

[7] Unscheduled Visit – additional study assessments may be performed per investigator's discretion

* Source only entries

[redacted]

4 PROTOCOL AMENDMENTS

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

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

[redacted]

5 INTRODUCTION

5.1 Rationale and Background

To meet the demands of increasing number of cataract surgeries coupled with high patient expectations, cataract surgeons desire the safest and most efficient device to remove the crystalline lens. The investigational device was developed to meet these needs by improving occlusion break surge responses and intraocular pressure control as well as reducing phacoemulsification time and energy.

The intended purpose of UNITY VCS, in general, is to facilitate management of fluid and gases, as well as removal, grasping, cutting, illumination, and coagulation of ocular materials.

For this study, UNITY VCS will only be used during anterior segment ophthalmic surgery. As such, the intended purpose of UNITY VCS, in this study, is ***to facilitate management of fluid as well as removal, cutting, and coagulation of ocular materials.***

The target patient population for this study are those undergoing anterior segment ophthalmic surgery.

Modern cataract procedures usually involve the use of an ultrasonic device that breaks up the crystalline lens (often cloudy) into small pieces, which are then gently removed from the eye with suction; this procedure is called phacoemulsification. Standard extracapsular cataract extraction (ECCE) and manual small incision cataract surgery (SICS or MSICS) are other surgical methods that remove the cataract without an ultrasonic device. Phacoemulsification, or "phaco", is the surgical technique most often employed based on the European Registry of

Quality Outcomes for Cataract and Refractive Surgery (EUREQUO) (Lundström 2012). Phacoemulsification is also the standard of care based on guidelines from the American Academy of Ophthalmology (AAO 2016). Femtosecond laser-assisted cataract surgery (FLACS) uses a femtosecond laser to create incisions, capsulotomies, and/or fragmentation patterns where only the laser fragmentation step assists in breaking up the cloudy lens into small pieces before removal, but the phacoemulsification machine would still be required to remove the lens. The intended clinical benefit of UNITY VCS, as used in the study, is to aid in the execution of anterior segment ophthalmic surgery.

According to the World Health Organization (WHO), cataracts is one of the leading causes of visual impairment and blindness, impacting 94 million globally (WHO 2022). Visual impairment is expected to continue to increase due to population growth and ageing (WHO 2022). The number of cases with cataracts in the United States was 24.4 million in 2010 and expected to be 50 million by 2050 (NEI 2017). Cataract surgery is the only way to treat cataracts (NEI 2023). The most performed ophthalmic procedure is cataract surgery (AAO 2023). This study is relevant as it aims to enhance equipment used to perform cataract surgery with the potential to benefit a very large patient population in the United States and globally.

Available alternative treatment options to UNITY VCS anterior segment functionality include other phacoemulsification machines that utilize ultrasound energy. While manual cataract surgery that does not utilize ultrasound energy may be used, phacoemulsification is considered standard of care (AAO 2016) and the preferred surgical technique in majority of cases (Lundström 2012). The Centurion Vision System, a predecessor to UNITY VCS anterior segment functionality, is the most utilized phacoemulsification machine in the world (2022 Cataract Surgical Equipment Market Report). The Centurion Vision System is Alcon's premium phacoemulsification system launched in 2013, with the addition of Active Sentry in 2019. The UNITY VCS's anterior segment functionality was designed to improve upon the latest iteration of the Centurion Vision System currently used successfully in the market. As such, the UNITY VCS is intended to provide greater benefits than the current standard of care.

5.2 Purpose of the Study

The study aims to:

(1) Obtain device-specific safety and performance clinical data to support marketability in Europe.

AND

(2) Collect user preference data

At the end of the study, a clinical study report and lay summary, if applicable, will be prepared in accordance with applicable regulatory requirements and standards. The Informed Consent will specify that a lay summary, if applicable, will be made available after the study is completed.

There are no immediate plans to submit the results of this traditional feasibility study for publication; however, the results may be offered for publication if they are of scientific interest, or if the results relate to a product that is subsequently approved or cleared for marketing. Alcon reserves the right of prior review of any publication or presentation of information related to the study. The author(s) of the publication will be the individual with substantial contribution to the conception or design of the work, OR the acquisition, analysis, or interpretation of data. Additionally, the author will draft the work or revise it critically for important intellectual content; provide final approval of the version to be published; and agree to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

5.3 Risks and Benefits

The benefit of cataract surgery is the removal of the opacified, cloudy crystalline lens. In comparison with predecessor phacoemulsification systems, the UNITY VCS anterior segment functionality provides enhancements that are designed to benefit patients. The two most used enhancements of UNITY VCS during cataract surgery will relate to fluidics and ultrasound. The fluidics enhancement was designed with the intent to allow surgeons to operate at lower IOP and higher vacuum while maintaining anterior chamber stability. In specific, operating at lower, more physiological IOP may be associated with greater reported patient comfort during surgery (Hou 2012), improved visual recovery due to better preservation of corneal endothelial health, and less macular edema postoperatively (Suzuki 2009, Chen 2012) as well as reduced complications due to less impact on retinal blood flow/reduction of ischemia (Findl 1997, Takhtaev 2019). The ultrasound enhancement was

designed to improve crystalline lens cutting efficiency and reduce energy. The overall potential benefit would be a safer and more efficient procedure.

Risk management principles have been applied to both the planning and the intended conduct of the clinical investigation, to ensure the reliability of the clinical data generated and the safety of the subjects.

The clinical investigation risks are managed through appropriate training and monitoring according to the protocol-specific monitoring plan. [redacted].

Participation in the clinical study will require the subject to undergo cataract surgery and implantation of a hydrophobic acrylic intraocular lens into the capsular bag. The use of femtosecond laser-assisted incisions and capsulotomies per product label is optional at the discretion of patient and surgeon; use of femtosecond laser-assisted procedures is not required for this study.

Complications may occur on the surgery day or throughout the postoperative period. As with any type of intraocular surgery, there is a possibility of complications due to anesthesia, drug reactions, and/or surgical problems. The surgical procedure can exacerbate a pre-existing ocular condition. [redacted]

[redacted].

In addition, a secondary surgical intervention (SSI) may be required following the initial cataract removal and subsequent IOL implantation. An IOL replacement may be appropriate in some cases of biometry error, incorrect IOL power, operating room error, residual refractive error, refractive shift, ocular infection, patient dissatisfaction, or visual symptoms. Other SSIs include, but are not limited to, removal of residual crystalline lens fragments, refractive laser treatment, paracentesis, vitreous aspirations, iridectomy for pupillary block, wound leak repair, intracameral and intravitreal antibiotic injections, and retinal detachment repair.

Postoperatively, the subject may experience transient ocular discomfort or pain, visual dysfunction and inflammation. Additionally, intraocular lens related complications can include decreased contrast sensitivity, decreased color perception, or clinically significant PCO that may require a Nd:YAG capsulotomy to improve vision and resolve subjective symptoms. Pigment precipitates on the IOL or in the anterior chamber may occur. Excessive pigment accumulation in the anterior chamber angle may contribute to a raised IOP, requiring treatment.

All the above-mentioned complications, adverse events, SSIs, and postoperative reported events have been reported as a result of the phacoemulsification surgical procedure with use of an anterior segment surgical system. The UNITY VCS, the investigational device, is not expected to increase any harms or the likelihood of those harms when compared to predecessor devices. [redacted]

The UNITY VCS's anterior segment functionality is expected to provide greater benefits and no changes in the harms or likelihood of harms when compared to the widely and successfully marketed predecessor device, the Centurion Vision System. As such, the expected benefits of using the UNITY VCS anterior segment functions are expected to outweigh the risks of adverse device effects for subjects that qualify for cataract surgery in this study.

Refer to the IB for additional information.

6 STUDY OBJECTIVES

6.1 Primary Objective(s)

Table 6–1 Primary Objective

Objective(s)	Endpoint(s)
Performance: To obtain device-specific performance clinical data	Performance: Percent of 'yes' responses to the question of: ***Did UNITY VCS using anterior segment surgical functionality perform per the intended use as defined in Protocol Section 5.1?***

6.2 Secondary Objective(s)

Table 6–2 Secondary Objective(s)

Objective(s)	Endpoint(s)
Performance: To obtain device-specific performance clinical data	Performance: Time from incision entry to incision closure

[redacted]

6.4 Safety Objective(s)

Table 6–3 Safety Objective(s)

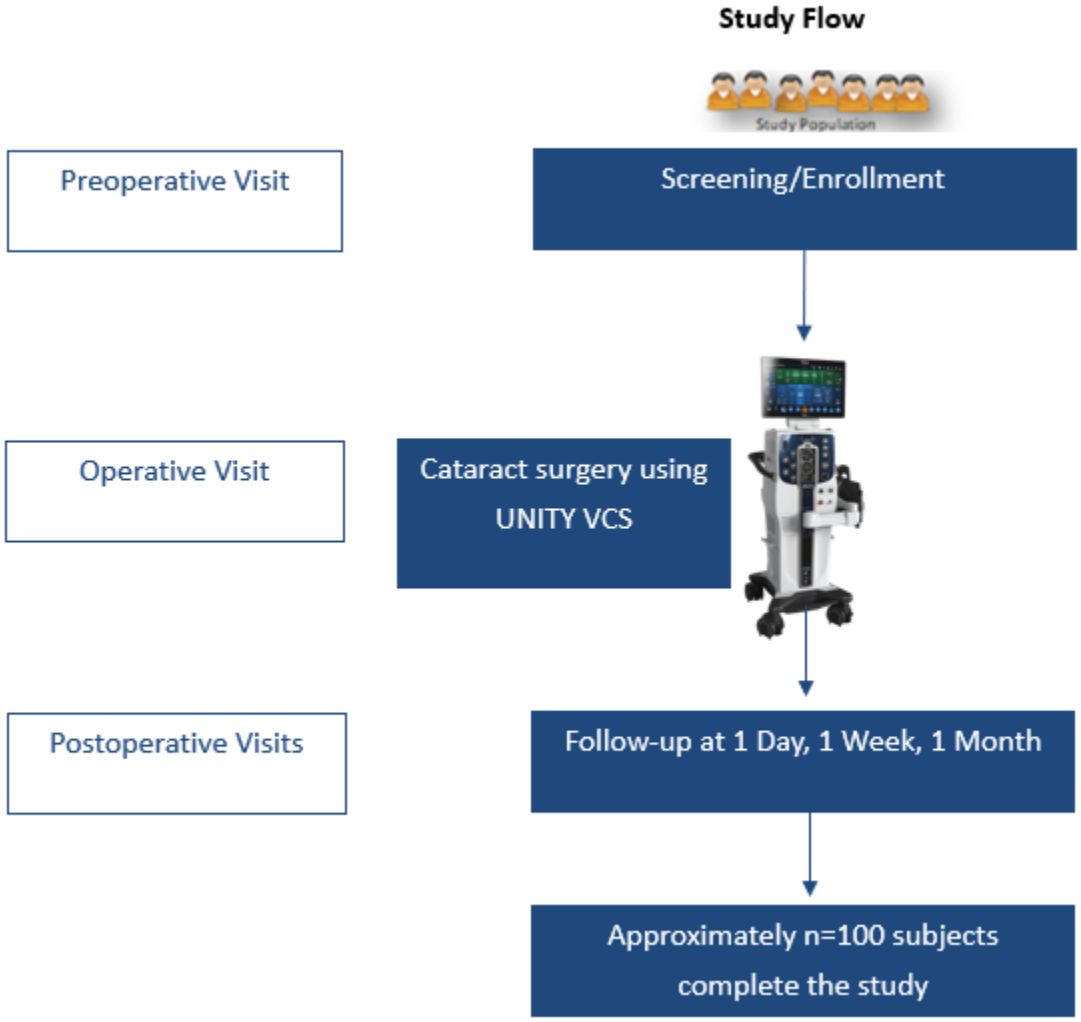
Objective(s)	Endpoint(s)
To obtain device-specific safety clinical data	Adverse events (ocular and nonocular; serious and nonserious) Device deficiencies Secondary surgical interventions Unplanned intraoperative surgical procedures

7 INVESTIGATIONAL PLAN

7.1 Study Design

This is a prospective, interventional, open-label, single-arm, nonrandomized and multicenter clinical study in the United States of America (USA) and/or Australia with approximately a 1-month follow-up.

Figure 7-1 Study Design Flow Chart



7.2 Rationale for Study Design

The UNITY VCS is a Class II nonimplantable medical device in the USA and a Class IIb nonimplantable medical device in the EU and AUS. For this class category, there are no currently well-established study designs governed by health authorities or international standards. The prospective design of this traditional feasibility study will reduce sources of bias and confounding variables. The intended patient population represents the majority of patients that will require use of the investigational device for cataract removal surgery where inclusion/exclusion criteria were carefully selected to reduce confounding variables.

The study design was also carefully thought out to allow it to represent a real world setting to ensure minimal intervention to the site's standard of care; this ensures the study gains the most realistic response with regard to device performance and safety. [redacted]

A potential weakness of the current study design is the fact that it is a single-arm study. However, this single-arm design is justified given that there are well established data regarding safety and performance of cataract surgery. As such, the safety and performance results from this study can be compared against this rich body of evidence to ensure the device meets state of the art standards.

7.2.1 Purpose and Timing of Interim Analyses and Resulting Design Adaptations

Not applicable. There are currently no planned interim analyses.

7.3 Rationale for Duration of Treatment/Follow-Up

The follow-up schedule was designed to allow collection of data at key time points that yield relevant performance and safety outcomes. The follow-up period will allow for adequate safety monitoring of adverse events; if patients develop complications, those will typically be present within approximately 1 month of cataract surgery.

7.4 Rationale for Choice of Comparator Product

There is no comparator in this study.

7.5 Data Monitoring Committee

Not applicable

8 STUDY POPULATION

The study population will consist of male and female subjects (over the age of 18 years) with a diagnosis of age-related noncomplicated cataract (unilaterally). It is aimed to enroll (consent) approximately 120 subjects in up to 5 sites in the United States and/or Australia with a target of 100 subjects treated, with 10 to 40 subjects per site. Site-specific targets may vary based upon individual site capabilities and each site may include more than one surgeon. Each surgeon will perform at least 10 surgeries, but no more than 33% of the total subjects treated. Estimated time needed to recruit subjects for the study is approximately 5 months; however, unanticipated circumstances may shorten or lengthen this time and would not require amendment of this protocol. Because a 10% screening failure rate is expected and 10% for lost to follow-up, approximately 120 subjects are expected to be enrolled to ensure 100 completed subjects.

8.1 Inclusion Criteria

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

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

1. Subject must be able to understand and sign an IRB/IEC approved Informed Consent form.
2. Willing and able to attend all scheduled study visits as required per protocol.
3. Adults (>18 years of age) with a clinically documented diagnosis of age-related noncomplicated cataract
4. Eligible to undergo primary hydrophobic acrylic intraocular lens implantation into the capsular bag.
5. Subject has clear intraocular media (including clear corneas) other than the cataract in the operative eye
6. Keratometry: 41 to 46 D, anterior chamber depth: 2.5 to 4 mm and axial length: 22 to 25 mm

8.2 Exclusion Criteria

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

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

    a. they are currently pregnant,

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

    c. intend to become pregnant during the study period,

    d. are breastfeeding.

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

2. Laser assisted fragmentation in the operative eye.

3. Planned postoperative procedures during the course of the study (e.g., corneal refractive surgery) in the operative eye.

4. More than 1+ guttata in the operative eye.

5. A history of chronic or recurrent inflammatory eye disease or trauma (e.g., iritis, scleritis, uveitis, iridocyclitis, rubeosis iridis, herpes simplex keratitis) in the operative eye.

6. Previous intraocular or corneal surgery in the operative eye.

7. Any ocular comorbidity (other than cataract) that may confound the results (e.g., zonular instability or zonular dehiscence or pseudoexfoliation, ocular surface disease, synechiae, iris atrophy, shallow anterior chamber, lens subluxation) in the operative eye.

8. Diagnosis of glaucoma or ocular hypertension (IOP > 21 mmHg) in the operative eye.

9. Any topical or systemic medications known to interfere with visual performance or complicate cataract surgery.

10. Diagnosed with severe systemic (e.g., history of cerebral vascular accident) or retinal disorders (e.g., macular degeneration, diabetic retinopathy, or other retinal pathology that might limit postoperative visual acuity or predispose the subject to postoperative retinal complications) in the operative eye.

11. A poorly dilating pupil or other pupil defect that prevents the iris from retracting peripherally to at least 6 mm diameter dilation in the operative eye.

12. Mechanical or surgical manipulation required to enlarge the pupil at time of surgery.

13. Conditions that, per investigator's clinical judgment, would confound the results of this investigation.

14. Currently participating in another drug or device clinical trial or having participated in another drug or device clinical trial within 30 days of enrolment into this study.

8.3 Rescreening of Subjects

Rescreening of subjects is not allowed in this study.

If subjects initially met all inclusion/exclusion criteria but surgery cannot be completed within 60 days of initial screening, then the investigator per their SOC should verify that subject continues to meet all inclusion/exclusion criteria at the time of surgery.

9 TREATMENTS ADMINISTERED

9.1 Investigational Product(s)

Test Product(s):	UNITY Vitreoretinal Cataract System (VCS)
Comparator Product(s) (If applicable):	Not applicable

Table 9–1 Test Product

Test Product	UNITY VCS (including the console, remote control, foot controller, UNITY Cataract FMS Pack, and UNITY Anterior Vitrectomy Kit)*

[redacted]

Manufacturer	Alcon Laboratories, Inc. 6201 South Freeway Fort Worth, TX 76134 USA

[redacted]

Indication for use and intended purpose in the study	Intended Use: The UNITY VCS, consisting of the console and compatible devices, is intended to facilitate management of fluid and gases, as well as removal, grasping, cutting, illumination and coagulation of ocular materials. Indications For Use: The UNITY VCS, consisting of the console and compatible devices, is indicated for use during anterior and posterior segment ophthalmic surgery. While the UNITY VCS is able to perform anterior and posterior segment functionalities, only the anterior segment functionalities will be enabled during this study. All posterior segment functionalities will be disabled in this study.
Product description and parameters available for this study	The UNITY VCS in this study is a surgical instrument for use in anterior segment ophthalmic surgeries. The product's capabilities include driving a variety of handpieces that provide the ability to emulsify and remove the crystalline lens, cut and remove vitreous as well as coagulation to stop bleeding. While UNITY VCS is able to perform anterior and posterior segment functionalities, only the anterior segment functionalities will be enabled during this study. All posterior segment functionalities will be disabled in this study.
Formulation	N/A
Usage	The UNITY VCS anterior segment functionalities will be used as directed in the user manual.

Packaging description	Each UNITY VCS console and all compatible anterior segment devices will be packaged individually and have an investigational product specific serial or lot number [redacted]
Labeling description	Investigational labeling regulations apply for UNITY VCS console, remote control, foot controller, UNITY Cataract FMS Pack and UNITY Anterior Vitrectomy Kit. These devices will be labeled appropriately (e.g., "CAUTION – Investigational device. Limited by Federal [or United States] law to investigational use" or "Exclusively for Clinical Investigation" or "For Clinical Trial Use Only"). Each unit will be identifiable via a serial or lot number.
Training and/or experience requirements for device	The UNITY VCS should only be used by authorized study personnel. It should only be operated according to the operating instructions as listed in the associated user manual and DFUs. [redacted]
Storage conditions	Temperature and relative humidity listed below apply to room environmental conditions preceding and during device use. Temperature: 50 to 95 °F (10 to 35 °C) Operating; 14 to 131 °F (-10 to 35 °C) Nonoperating Relative Humidity: 10 to 95% without condensation See User Manual for complete requirements and instructions.
Additional information	Not applicable
Supply	UNITY VCS which includes the console and all compatible anterior segment devices will be shipped to the site by the sponsor. Refer to the MOP for a detailed description.

More information on the test product be found in the Investigator's Brochure and Directions for Use for the UNITY VCS.

9.3 Treatment Assignment / Randomization

Only after signing the ICF will a subject be assigned a subject number by the electronic data capture system.

All subjects who meet the inclusion/exclusion criteria and sign informed consent will undergo cataract surgery with the UNITY VCS. Bias will be minimized as this is a single-arm study.

If both eyes qualify for the study, the study eye will be determined per investigator's discretion.

There will be no randomization of subjects.

9.4 Treatment masking

Not applicable as this is an open-label, single-arm study.

9.5 Accountability Procedures

Upon receipt of IP, the investigator or delegate must conduct an inventory of equipment and accessories by serial or lot number, complete study-specific confirmation of receipt

procedures as described in the MOP, and retain any required documentation in the investigator's clinical study records.

- All IPs sent to the investigator must be accounted for by study sponsor personnel, and in no case be used in an unauthorized manner.
- Refer to Section 11 of this protocol for additional information on the reporting of device deficiencies and to the MOP for information on return of investigational products associated with these events.

The investigator is responsible for allowing de-installation of the provided UNITY VCS and to return (or destroy) all unused sponsor-provided accessories and supplies as directed at the conclusion of the study or according to the instructions provided in the MOP.

9.6 Changes to concomitant medications, treatments/ procedures

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

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

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

10 STUDY PROCEDURES AND ASSESSMENTS

Study assessments will be obtained prior to cataract surgery with the UNITY VCS and postoperatively at the study visits outlined below:

- Screening – Visit 0 (Day -60 to 0 prior to treatment)
- Surgery – Visit 00 (Day 0)
- 1 Day – Visit 1 (Day 1 to 3)
- 1 Week – Visit 2 (Day 4 to 10)
- 1 Month/Exit – Visit 3 (Day 28 to 42)

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

- Unscheduled Visit (completed when a treated subject reports for additional follow-up)

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

10.1 Informed Consent and Screening

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

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

If a patient has reported for routine cataract screening, then data obtained from the routine evaluation can be used for screening data as long as protocol requirements for timeframe (within 60 days of surgery) and required details have been met. Routine cataract screening data include, but are not limited to slit lamp exam, IOP, dilated pupil size, keratometry, biometry (ACD, AL), Snellen BCDVA with manifest refraction, and dilated fundus exam.

10.2 Description of Study Procedures and Assessments

Study-specific procedures and assessments described here may include SOC; other SOC procedures performed in the clinical management of the subject are not excluded.

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

10.2.1 Demographics

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

10.2.2 Medical and Ocular History

Collect medical history information, including information on all medications used within the past 30 days of signing the informed consent form. Include herbal therapies, vitamins, and all over-the-counter as well as prescription medications. Throughout the subject's participation,

obtain information on any changes in medical health and/or the use of concomitant medications.

Medical History and Concomitant Medications will be collected in the eCRF as outlined in the MOP.

10.2.3 Adverse Event Collection: Safety Assessment

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

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

10.2.4 Slit Lamp Biomicroscopy: Safety Assessment

SLE of the cornea, iris/anterior chamber, and lens must be performed before instillation of any diagnostic eye drops at the screening visit.

Refer to the MOP for grading scales for study specific assessments.

10.2.5 Device Deficiencies: Safety Assessment

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

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

10.2.6 Dilated Fundus: Safety Assessment

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

10.2.7 Uncorrected Distance Visual Acuity: Safety Assessment

Snellen visual acuity testing without manifest refraction must be performed prior to any assessment requiring administration of eye drops to dilate the eye, or any assessment requiring contact with the eye.

10.2.8 Best Corrected Distance Visual Acuity: Safety Assessment

Snellen visual acuity testing with manifest refraction must be performed prior to any assessment requiring administration of eye drops to dilate the eye, or any assessment requiring contact with the eye.

10.2.9 Intraocular Pressure: Safety Assessment

Intraocular pressure must be measured using SOC.

10.2.10 Urine Pregnancy Test: Other Assessment

A urine pregnancy test is required for female subjects of childbearing potential that are not postmenopausal or surgically sterile.

10.2.11 Keratometry: Eligibility Assessment

Capture keratometry measurements of the central cornea using SOC.

10.2.12 Pupil Size: Eligibility Assessment

Measure dilated pupil size under photopic condition using SOC.

10.2.13 Biometry: Eligibility Assessment

Perform biometry using SOC. Document the following: ACD, AL.

10.2.14 Assessment through the operating microscope: Other Assessment

If femtosecond laser is used then perform an assessment of the cornea and conjunctiva, and other femtosecond laser related findings through the operating microscope after femtosecond laser-assisted incision and/or capsulotomy but before entry into the eye for cataract removal surgery.

10.2.15 Time from incision entry to incision closure: Secondary Performance Assessment

Obtain time from incision entry into the eye to incision closure using a stopwatch.

[redacted]

[redacted]

10.3 Unscheduled Visits

An Unscheduled Visit (USV) is defined as follows:

- Ocular examination that is not SOC and not required by the protocol
- Examination conducted by the study staff
- New findings, or change to a previous finding was discovered

A USV may or may not result in the capture of an adverse event. Likewise, an adverse event may be captured without the report of a USV (e.g., AE identified subsequent to study eye examination by nonstudy personnel).

If a subject visit occurs between any regularly scheduled visit and the visit is conducted by study personnel, this visit must be documented as an USV. If the subject seeks medical attention outside the clinic (for example, at an Emergency Room) or at the clinic but is seen by nonstudy personnel, the investigator is to capture adverse event-related information on the adverse event form upon becoming aware.

During all USVs, the investigator must conduct the following procedures:

- Collect adverse event information, if applicable
- Collect device deficiency information, if applicable
- Collect SSI information, if applicable
- Record changes in medical condition or concomitant medication

[redacted]

[redacted]

The investigator may perform additional procedures for proper diagnosis and treatment of the subject. These include but are not limited to those noted in Table 3–1 Schedule of Study Procedures and Assessments. The investigator must document this information in the subject's case history source documents.

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

10.4 Discontinued Subjects

10.4.1 Screen Failures

Subjects who were excluded from the study after signing the informed consent and prior to exposure.

The investigator must document the reason for the screen failure in the subject's case history source documents.

Subject numbers must not be re-used.

10.4.2 Discontinuations

Discontinued subjects are individuals who voluntarily withdraw or are withdrawn from the study by the investigator after signing informed consent, meeting eligibility criteria, and are exposed to IP.

Subject numbers of discontinued subjects must not be re-used (i.e., subject replacement is not allowed).

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

For subjects choosing to discontinue from the study after exposure to IP, the investigator must complete all Exit procedures according to Table 3–1 Schedule of Study Procedures and

Assessments, if the subject is willing and able, and if in the opinion of the investigator it is safe for the subject to do so.

The investigator must document the reason for study or treatment discontinuation in the subject's case history source documents.

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

10.4.3 Schedule of Procedures and Assessments for Subjects Discontinued from Investigational Product

If a subject discontinues from study treatment, every effort must be made to keep the subject in the study and to continue with the study assessments as specified in the schedule of study procedures and assessments until the final visit.

10.5 Clinical Study Termination

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

If the clinical study is prematurely terminated or suspended by the study sponsor:

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

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

10.5.1 Follow-up of subjects after study participation has ended

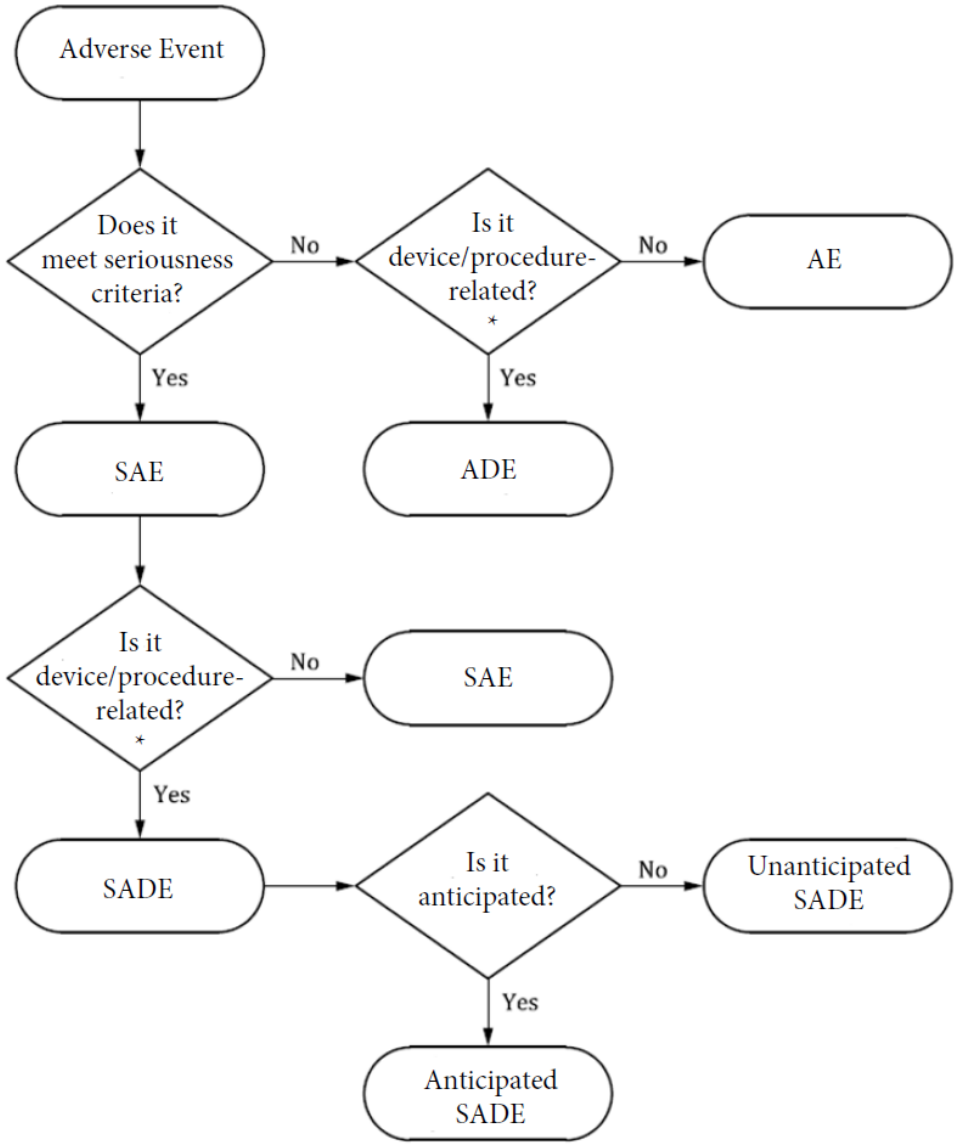
Following this study, the subject will return to their eye care professional for their routine eye care.

11 ADVERSE EVENTS AND DEVICE DEFICIENCIES

11.1 General Information

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

Figure 11-1 Categorization of All Adverse Events



*In this study, only AEs related to the investigational product/device (i.e., UNITY VCS) are considered as device related ADE.

Specific Events Relevant to this Protocol

In addition to reporting all AEs (serious and nonserious) meeting the definitions, the investigator must report any occurrence of the following as an SAE including but not limited to:

Serious Adverse Events

- Postoperative corneal incision site wound leakage
- Hypopyon
- Hyphema
- Toxic anterior segment syndrome
- Posterior capsular tear
- Vitreous prolapse
- Iridodialysis
- Posterior lens dislocation
- Chronic corneal edema (corneal stromal or epithelial swelling resulting in BCDVA of ≤20/40 at ≥1 month)
- Clinically significant cystoid macular edema
- Uncontrolled increase in IOP ≥10 mmHg over baseline and at least 25 mmHg
- Endophthalmitis
- Retinal detachment
- Pupillary block
- Suprachoroidal hemorrhage
- Vitreous hemorrhage
- Vision-threatening surgical problems
- Secondary surgical intervention (excluding posterior capsulotomy)

NOTE: Wound burps during the first week postoperatively, suture removal, planned blepharoplasty, and Nd:YAG capsulotomy (for PCO) are not considered adverse events for this study.

Any other potentially sight-threatening event may also be considered serious based on the judgment of the investigator and should be reported appropriately as delineated in Section 11.3.

AEs occurring in association with a device that is used in conjunction with the UNITY VCS (e.g., femtosecond laser) will be classified separately from those associated with the investigational device itself.

Device Deficiencies

A device deficiency may or may not be associated with subject harm (i.e., 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. [redacted]

[redacted]

11.2 Monitoring for Adverse Events

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

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

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

11.3 Procedures for Recording and Reporting

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

In addition, aqueous cells and flare, corneal edema, eye redness, raised IOP, subconjunctival hemorrhage, 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 2 weeks and not result in any untoward long term visual outcome impact. Expected complications from use of femtosecond laser-assisted procedures as noted in Section 5.3 will not be considered device related AEs..

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

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

Note: Should the EDC system become nonoperational, the site must complete the appropriate paper *Serious Adverse Event and Adverse Device Effect* and/or *Device Deficiency* Form. The completed form is emailed to the Study Sponsor at msus.safety@Alcon.com for USA-based sites and at Australia.auff-complaints@alcon.com for AUS-based sites, according to the

timelines outlined above; however, the reported information must be entered into the EDC system once it becomes operational.

In addition to recording all AEs into the EDC system, any AEs and device deficiencies for nonstudy marketed devices/products (e.g., Alcon's or other manufacturers' products used concomitantly during the study will be considered and processed as spontaneous following the postmarket vigilance procedures) and should be communicated to the device's/product's manufacturer as per local requirements.

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

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

Intensity and Causality Assessments

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

Intensity (Severity)

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

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

Causality

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

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

11.4 Return Product Analysis

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

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

11.5 Unmasking of the Study Treatment

Not applicable; this study is open-label.

11.6 Follow-Up of Subjects with Adverse Events

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

The investigator should provide the Study Sponsor with any new safety information (which includes new AEs and changes to previously reported AEs) that may affect the safety evaluation of the device. For AEs that are unresolved/ongoing at time of discontinuation, any additional information received at follow-up should be documented in the eCRFs up to study completion (i.e., database lock). Any additional data received up to 6 months after a subject completed the study should be documented and available upon the Study Sponsor's request.

All complaints received after this time period will be considered and processed as spontaneous (following the postmarket vigilance procedures) and should be communicated to the medical device's manufacturer as per local requirements. The investigator should also report complaints on non-Alcon products directly to the manufacturer as per the manufacturer's instructions or local regulatory requirements.

11.7 Pregnancy in the Clinical Study

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

12 ANALYSIS PLAN

12.1 Subject Evaluability

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

12.2 Analysis Sets

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

12.2.1 All-Implanted Analysis Set

The primary analysis set for effectiveness outcomes will be the all-implanted analysis set. The all-implanted analysis set includes all eyes with successful completion of the cataract surgery, including IOL implantation.

12.2.2 Safety Analysis Set

The safety analysis set will include all eyes with attempted use of the UNITY VCS (successful or aborted after contact with the eye) and will be used for the safety outcomes. Attempted use of the UNITY VCS is defined as any time the device makes contact with the eye.

12.3 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized for each subject. Counts and percentages will be presented for categorical variables such as sex, age, race and ethnicity. Sample size (N), mean, standard deviation, median, minimum, and maximum will be presented for continuous variables such as age.

12.4 Effectiveness Analyses

12.4.1 Analysis of Primary Effectiveness Endpoint

The primary performance endpoint is the percent of 'yes' responses to the question: ***Did UNITY VCS using anterior segment surgical functionality perform per the intended use as defined in Protocol Section 5.1?***

12.4.1.1 Statistical Hypotheses

No hypothesis testing of the primary effectiveness endpoint is planned.

12.4.1.2 Analysis Methods

Standard descriptive statistics will be presented for the primary effectiveness endpoint based on the type. For categorical summaries, statistics will include sample size, number in category, and percentage in each category. For continuous summaries, number of subjects, mean, median, standard deviation, minimum, maximum, and two-sided 95% confidence intervals for both mean and median will be reported. Individual subject data listings will also be provided.

12.4.2 Analysis of Secondary Effectiveness Endpoints

The secondary performance endpoint is time from incision entry to incision closure.

12.4.2.1 Statistical Hypotheses

There are no hypothesis tests of the secondary effectiveness endpoints planned.

12.4.2.2 Analysis Methods

The number of subjects, mean, median, standard deviation, minimum, maximum, and two-sided 95% confidence intervals for both mean and median will be reported for the secondary endpoint. Individual subject data listings will also be provided.

12.5 Handling of Missing Data

No imputation of missing data is planned.

12.6 Safety Analyses

The safety endpoints are:

- Adverse events (ocular and nonocular; serious and nonserious)

- Secondary surgical interventions
- Unplanned intraoperative surgical procedures
- Device deficiencies

12.6.1 Analysis of Safety Endpoints

The focus of the safety analysis will be a comprehensive descriptive assessment of the occurrence of adverse events as well as the other listed parameters above.

12.6.1.1 Statistical Hypotheses

There are no safety hypotheses planned in this study.

12.6.1.2 Analysis Methods

For all safety measures, descriptive statistics will be presented based on the type. For categorical variables, summary statistics will include sample size (subjects/eyes), number in category, and percentage in each category. For continuous variables, number of subjects/eyes, mean, median, standard deviation, minimum, and maximum will be reported. Individual subject data listings will also be provided.

12.7 Interim Analyses and Reporting

No interim analyses are planned.

12.8 Sample Size Justification

Based on a sample of 100 surgeries, the expected half-width of the 95 % confidence interval for the percentage of surgeons reporting 'yes' to the question "***Did UNITY VCS using anterior segment surgical functionality perform per the intended use as defined in Protocol Section 5.1?***" will be $1.96 \cdot \sqrt{(p(1-p)/100)}$. This half-width is widest at p = 50%. Under this conservative assumption, the expected half-width is <10% given the sample size of 100.

Allow enrollment for an additional 10% for screen failure and 10% for lost to follow-up to ensure 100 completed subjects. (See also Section 8 of this protocol for more details.)

13 DATA HANDLING AND ADMINISTRATIVE REQUIREMENTS

13.1 Subject Confidentiality

The investigator must ensure that the subject's identity is kept confidential throughout the course of the study. In particular, the investigator must keep an enrollment log with

confidential identifying information that corresponds to the subject numbers and initials of each study participant. The study sponsor may collect a copy of the enrollment log ***without any directly identifying subject information***.

The study sponsor may share patient-level data collected in this trial with qualified researchers to help facilitate product development or enhancements in research that is not directly related to the study objectives. The Informed Consent explains this to the study subject.

13.2 Completion of Source Documents and Case Report Forms

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

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

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

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

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

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

13.3 Data Review and Clarifications

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

13.4 Sponsor and Monitoring Responsibilities

The study sponsor will select principal investigators that are qualified by education, training, and experience to assume responsibility for the proper conduct of this clinical trial. For this study, the principal investigator must be a health care professional licensed to perform cataract surgery.

The study sponsor is financially funding this clinical trial and will compensate the investigator and/or the Institution(s) at which the study is conducted in accordance with a signed clinical trial agreement.

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

The site may not screen subjects or perform the informed consent process on any subject until it receives a notification from an appropriate study sponsor representative that the site may commence conducting study activities. Monitoring will be conducted periodically while the clinical study is ongoing. Monitoring methods may include site visits, telephone, written, and fax correspondence. Close-out visits will take place after the last visit of the last subject at the site.

Videos of surgery should be maintained with subject records for verification as source data and sent to sponsor for review as requested. Such data will be coded with a subject number only and will not contain subject personal information.

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

13.5 Regulatory Documentation and Records Retention

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

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

13.6 Quality Assurance and Quality Control

The study sponsor will secure agreement from all involved parties to ensure direct access to all study related sites, source data and documents, and reports for the purpose of monitoring

and auditing by the study sponsor, and inspection by domestic and foreign regulatory authorities. Quality control will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. Agreements made by the study sponsor with the investigator/institution and any other parties involved in the clinical study will be provided in writing as part of the protocol or as a separate agreement.

14 ETHICS

Investigations are conducted in compliance with Good Clinical Practices; international and national regulations, laws and guidelines; ISO 14155; the conditions of approval imposed by reviewing IRBs/IECs or regulatory authorities; and in accordance with the ethical medical research principles outlined in the Declaration of Helsinki.

- The SOPs of the study sponsor and contract research organizations participating in the conduct of the clinical study and all other applicable regulations shall apply.
- Notifications and timelines for reporting protocol deviations should be based upon applicable IRB/Ethics Committee requirements.

The investigator must ensure that all personnel involved in the conduct of the study are qualified to perform their assigned responsibilities through relevant education, training, and experience. The investigator and all clinical study staff must conduct the clinical study in compliance with the protocol. The investigator is not allowed to deviate from the protocol except to protect the rights, safety, and well-being of human subjects under emergency circumstances. Emergency deviations may proceed without prior approval of the sponsor and the IRB/IEC but shall be documented and reported to the sponsor and the IRB/IEC as soon as possible. Deviations from this protocol, regulatory requirements, and/or GCP must be recorded and reported to the Sponsor prior to database lock. If needed, corrective and preventive action should be identified, implemented, and documented within the study records. Failure to implement identified corrective and preventative actions may result in site closure by the sponsor. Use of waivers to deviate from the clinical protocol is prohibited.

Before clinical study initiation, this protocol, the informed consent form, if applicable, any other written information given to subjects, and any advertisements planned for subject recruitment must be approved by an IRB/IEC. The investigator must provide documentation of the IRB/IEC approval to the study sponsor. The approval must be dated and must identify the applicable protocol, amendments (if any), informed consent form, assent form (if any), all applicable recruiting materials, written information for subject, and subject compensation programs. The IRB/IEC must be provided with a copy of the Investigator’s Brochure, any periodic safety updates, and all other information as required by local regulation and/or the

IRB/IEC. Any additional requirements imposed by the IRB/IEC or regulatory authority shall be followed. At the end of the study, the investigator must notify the IRB/IEC about the study's completion. The IRB/IEC also must be notified if the study is terminated prematurely. Finally, the investigator must report to the IRB/IEC on the progress of the study at intervals stipulated by the IRB/IEC.

Voluntary informed consent must be obtained in writing from every subject. The obtaining of consent shall be documented before any procedure specific to the clinical investigation is applied to the subject.

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

The investigator must have a defined process in case a subject would like to withdraw their consent(s). The investigator is the designated contact point for any such withdrawals.

The investigator must have a defined process in case a subject would like to exercise any of their rights under applicable Data Protection laws. The investigator is the designated contact point for any such requests.

The sponsor will secure a human clinical trial insurance certificate according to applicable country regulations when required.

The study sponsor assures that the key designs of this protocol will be registered on public databases where required by current regulations, and, as applicable, results will be posted.

15 REFERENCES

15.1 Regulations and Standards

The following references may be applicable in whole or in part for this clinical trial.

- EN ISO 14155:2020 - Clinical Investigation of Medical Devices for Human Subjects - Good Clinical Practice
- EU MDR: Regulation (EU) 2017/745 of the European Parliament and of the Council
- 21 CFR Part 11 - Electronic Records; Electronic Signatures
- 21 CFR Part 50 - Protection of Human Subjects
- 21 CFR Part 56 - Institutional Review Boards
- 21 CFR Part 812 - Investigational Device Exemptions
- 21 CFR Part 54 - Financial Disclosure by Clinical Investigators
- The California Bill of Rights, if applicable

15.2 Scientific and Other References

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