Pivotal Trial of WaveLight® EX500 Excimer Laser System for the Correction of Myopia with and without Astigmatism Using InnovEyes™ in Conjunction with InnovEyes™ sightmap

STUDY ID

RFP911-C001

PROTOCOL

NCT04219891

Device Protocol for RFP911-C001

Title: Pivotal Trial of WaveLight® EX500 Excimer Laser System for the Correction of Myopia with and without Astigmatism Using InnovEyes™ in Conjunction with InnovEyes™ sightmap

Protocol Number:	RFP911-C001
Development Stage of Project:	Development
Sponsor Name and Address:	Alcon Research, LLC and its affiliates ("Alcon") 6201 South Freeway Fort Worth, Texas 76134-2099
Test Product:	WaveLight® EX500 excimer laser system using InnovEyes™ in conjunction with InnovEyes™ sightmap

Investigator Agreement:

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

Have you ever been disqualified as an Investigator by any Regulatory Authority?

☐ No ☐Yes

Have you ever been involved in a study or other research that was terminated?

☐ No ☐Yes

If yes, please explain here:

Principal Investigator:

Signature Date

Name and Professional Position:

Address:

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1 GLOSSARY OF TERMS

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

Enrolled Subject	Any subject who signs an informed consent form for participation in the study.
Interventional Clinical Trial	A research trial that prospectively assigns, whether randomly or not, human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes, and/or a research trial in which diagnostic or monitoring procedures beyond standard of care are conducted and generate outcomes for use in analysis of data.
Investigational Product	Is defined as a preventative (vaccine), a therapeutic (drug or biologic), device, diagnostic, or palliative used as a test or control product in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form.
Malfunction	Failure of a medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or clinical investigation plan.
Non-Serious 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 that either resulted in: a. a life-threatening illness or injury. *Note: Life-threatening means that the individual was at immediate risk of death from the event as it occurred, ie, it does not include an event which hypothetically might have caused death had it occurred in a more severe form.*

	b. any potentially sight-threatening event or permanent impairment to a body structure or a body function. c. in-patient hospitalization or prolonged hospitalization. *Note: Planned hospitalization for a pre-existing condition, without serious deterioration in health, is not considered a serious adverse event. In general, hospitalization signifies that the individual remained at the hospital or emergency ward for observation and/or treatment (usually involving an overnight stay) that would not have been appropriate in the physician's office or an out-patient setting. Complications that occur during hospitalization are adverse events. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred, the event should be considered serious.* *d.* a medical or surgical intervention to prevent a) or b). *e.* any indirect harm as a consequence of incorrect diagnostic test results when used within manufacturer's instructions for use. • Fetal distress, fetal death, or a congenital abnormality or birth defect. *Refer to Section 11 for additional SAEs.*
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 management file.
Use Error	Act or omission of an act that results in a different medical device response than intended by manufacturer or expected by user. *Note: This definition includes slips, lapses, and mistakes. An unexpected physiological response of the subject does not in itself constitute a use error.*

2 LIST OF ACRONYMS AND ABBREVIATIONS

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

Abbreviation	Definition
ADE	Adverse device effect
AE	Adverse event
ANSI	American National Standards Institute
ASADE	Anticipated serious adverse device effect
BCDVA	Best corrected distance visual acuity
°C	Degrees Celsius
CC	Consistent cohort
cd/m^2	Candela per square meter
CFR	Code of Federal Regulations
cm	Centimeter
[redacted]	[redacted]
[redacted]	[redacted]
CTS	M&S Technologies' Clinical Trial Suite
CYL	Cylinder
D	Diopter
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ETDRS	Early Treatment of Diabetic Retinopathy Study
EX	Excimer
°F	Degrees Fahrenheit
FAS	Full analysis set
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
GmbH	Gesellschaft mit beschränkter Haftung - company with limited liability
hPa	hectopascal
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IOP	Intraocular Pressure
IP	Investigational product
IRB	Institutional review board
ISO	International Organization for Standardization
Kg	Kilogram
LASIK	Laser-assisted in situ keratomileusis
Lb	Pound
LED	Light emitting diode
logMAR	Logarithm of the minimum angle of resolution
m	Meter

Abbreviation	Definition
mm	Millimeter
mmHg	Millimeter of mercury
MOP	Manual of Procedures
MRC	Manifest Refraction Cylinder
MRSE	Manifest Refraction Spherical Equivalent
N	Number
N/A	Not applicable
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
SADE	Serious adverse device effect
SAE	Serious adverse event
SAF	Safety analysis set
SOP	Standard Operating Procedure
SPH	Sphere
µm	Micrometer
UCDVA	Uncorrected distance visual acuity
UCNVA	Uncorrected near visual acuity
US	United States
USADE	Unanticipated serious adverse device effect
USB	Universal Serial Bus
USV	Unscheduled Visit
VA	Visual Acuity
[redacted]	[redacted]

3 PROTOCOL SUMMARY

Investigational Product Type	Device
Study Type	Interventional
Investigational Products	Test Product: WaveLight® EX500 excimer laser system using InnovEyes in conjunction with InnovEyes sightmap
Purpose and Rationale	Current treatment planning for LASIK treatment, such as wavefront optimized, wavefront guided, and topography guided is based on simplified formulas and a standardized eye model and does not consider the multiple lens structure of the eye. InnovEyes takes the multi-lens nature of the eye into consideration. The purpose of this study is to evaluate the safety and effectiveness of the WaveLight EX500 excimer laser system for the correction of myopia with and without astigmatism using InnovEyes in conjunction with InnovEyes sightmap.
Objective(s)	To evaluate the safety and effectiveness of the WaveLight EX500 excimer laser system for the correction of myopia with and without astigmatism using InnovEyes in conjunction with InnovEyes sightmap. Details and additional information on objectives are provided in Section 6.
Endpoint(s)	Co-Primary Effectiveness Endpoint — Target Percentage of eyes with UCDVA of 20/40 or better (in eyes with preoperative BCDVA of 20/20 or better) at refractive stability — ≥ 85% Percentage of eyes with MRSE within 0.50 D at refractive stability — ≥ 50% Percentage of eyes with MRSE within 1.00 D at refractive stability — ≥ 75% Percentage of eyes that achieve refractive stability — ≥ 95%

	Co-Primary Safety Endpoint — Target at refractive stability Percentage of eyes with BCDVA worse than 20/40 (for eyes with BCDVA of 20/20 or better pre-op) — ≤ 1% Percentage of eyes that lose 2 lines or more of BCDVA — ≤5% Percentage of eyes that have an increase of manifest refractive astigmatism of greater than 2.00 D of absolute cylinder as compared to the preoperative refraction — ≤ 5% Percentage of eyes with a serious, non-flap related, ocular adverse event at the postoperative visits — ≤ 1%
Assessment(s)	Effectiveness • Mesopic pupil size • Keratometry with InnovEyes sightmap • Topography with InnovEyes sightmap • Biometry with InnovEyes sightmap • Uncorrected photopic distance visual acuity (UCDVA) • Manifest refraction • Cycloplegic refraction Safety • [redacted] • Slit lamp examination • Dilated fundus examination • Best corrected photopic distance visual acuity (BCDVA) • Aberrometry with InnovEyes sightmap • Pachymetry with InnovEyes sightmap • [redacted] • Intraocular Pressure (IOP)

Study Design	This is a prospective, single-arm, multi-center, interventional study with planned bilateral treatment. Qualified subjects will receive bilateral InnovEyes treatment and be followed for 1 year. Subjects will be asked to attend a total of 9 visits (screening, surgery, day 1, 1 week, 1 month, 3 month, 6 month, 9 month, and 1 year). Total expected duration of subject participation is approximately 1 year.
Subject Population	Subjects who desire to have LASIK will be consented and screened for meeting the inclusion and exclusion criteria. Subject enrollment will be monitored to ensure inclusion of required numbers of subjects in each one diopter interval based on the ranges of spherical and cylindrical refractive error (bin).
Key Inclusion Criteria (See Section 8.1 for a complete list of inclusion criteria)	Subjects must meet all inclusion criteria as listed in Section 8.1 Key Inclusion Criteria include: • Myopia up to and including -11.00 D with or without astigmatism up to -4.50 D, with spherical equivalent no more than -12.00 D as shown from InnovEyes sightmap Measured refraction • Best corrected photopic distance visual acuity of 20/20 or better (≤ 0.04 logMAR) • Uncorrected photopic distance visual acuity of 20/40 or worse (≥ 0.34 logMAR) • Stable refraction (within ± 0.50 D) as determined by MRSE for a minimum of 12 months prior to surgery
Key Exclusion Criteria (See Section 8.2 for a complete list of exclusion criteria)	Subjects must not meet exclusion criteria as listed in Section 8.2 Key Exclusion Criteria include: • History or evidence of active or inactive corneal disease or retinal vascular disease, keratoconus or glaucoma (or suspect) • Previous intraocular or corneal surgery • Intent to have monovision treatment
Data Analysis and Sample Size Justification	The safety analysis set (SAF) will contain all eyes that undergo surgery or attempted surgery (defined as eye drops given for flap treatment); the SAF will be the primary analysis set for the safety

	analyses. The full analysis set (FAS) will contain all eyes that successfully undergo surgery; the FAS will be the primary analysis set for the effectiveness analyses. The consistent cohort (CC) will contain all eyes in the FAS that have manifest refraction data at all post-operative visits. The CC will be the primary analysis set for the refractive stability analyses. Refractive stability is said to have been achieved at the latter of two postoperative manifest refractions performed at least 3 months apart (or at 3 months after surgery when compared with the 1-month visit) if all the requirements for stability listed in the endpoints section of the synopsis have been met. Stability will be confirmed by an adequate subgroup (at least 80% of the cohort) at the next scheduled visit interval. The number and percentage of eyes meeting each of the primary effectiveness endpoints will be calculated. The effectiveness criteria will be considered to have been met if the percentage meets or exceeds the target rate at the time of refractive stability for all primary effectiveness endpoints. The number and percentage of eyes experiencing each of the primary safety endpoints will also be calculated. The safety criteria will be considered to have been met if the percentage is less than the target rate at the time of refractive stability for all of the primary safety endpoints. [redacted] An analysis will be performed once refractive stability is achieved; a final analysis will be performed once the one-year follow-up is complete.

	Up to 374 eyes will be treated in this study. With 374 eyes treated, any ocular serious adverse event type that occurs in at least 1% of the population undergoing the procedure will be observed in this study at least one time, with approximately 95% probability. This is in accordance with ANSI Z80.11-2012(R2017).
Key Words	• LASIK • Ray Tracing • Myopia • Astigmatism
Associated Materials	• WaveLight® EX500 Laser System • WaveLight® FS200 Laser System • Patient Interface for WaveLight FS200 Laser System • WaveCard

Table 3–1 Schedule of Study Procedures and Assessments

		Screening[1]	Surgery	Postoperative							Other	
		Visit 0	Visit 00 / Visit 00A[2]	Visit 1 / Visit 1A	Visit 2 / Visit 2A	Visit 3 / Visit 3A	Visit 4 / Visit 4A	Visit 5 / Visit 5A	Visit 6 / Visit 6A	Visit 7 / Visit 7A	Early Exit	USV[3]
Procedure/ Assessment		**Day -30 to -1**	**Day 0**	**Day 1**	**Day 5 to 9**	**Day 21 to 35**	**Day 70 to 98**	**Day 147 to 182**	**Day 245 to 301**	**Day 330 to 420**		
Informed Consent		X										
Inclusion/Exclusion		X	X[4]									
Demographics		X										
Medical History		X										
Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X
Urine Pregnancy Test[5]*		X										
Cycloplegic Refraction		X						X				
Mesopic pupil size		X				X	X	X	X	X	X	
InnovEyes sightmap	Aberrometry	X[6]				X	X	X	X	X	X	
	Biometry	X[6]				X	X	X	X	X	X	
	Keratometry	X[6]				X	X	X	X	X	X	
	Pachymetry (Corneal Thickness)	X[6]				X	X	X	X	X	X	
	Topography*	X[6]				X	X	X	X	X	X	
	Wavefront Refraction	X[6]				X	X	X	X	X	X	
UCDVA		X		X	X	X	X	X	X	X	X	X
Manifest/Subjective Refraction[7]		X			X	X	X	X	X	X	X	

	Screening[1]	Surgery	Postoperative							Other	
	Visit 0	Visit 00 / Visit 00A[2]	Visit 1 / Visit 1A	Visit 2 / Visit 2A	Visit 3 / Visit 3A	Visit 4 / Visit 4A	Visit 5 / Visit 5A	Visit 6 / Visit 6A	Visit 7 / Visit 7A	Early Exit	USV[3]
Procedure/ Assessment	**Day -30 to -1**	**Day 0**	**Day 1**	**Day 5 to 9**	**Day 21 to 35**	**Day 70 to 98**	**Day 147 to 182**	**Day 245 to 301**	**Day 330 to 420**		
BCDVA	X			X	X	X	X	X	X	X	
UCNVA	X						X				
[redacted]	[redacted]				[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
IOP	X				X	X	X	X	X	X	X
Slit Lamp Examination	X		X	X	X	X	X	X	X	X	X
Dilated Fundus Examination	X						X			X	X
InnovEyes LASIK Planning	X										
InnovEyes LASIK		X									
[redacted]	[redacted]				[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse Events	X	X	X	X	X	X	X	X	X	X	X
Device Deficiencies	X	X	X	X	X	X	X	X	X	X	X

[1] Screening should cover evaluation of both eyes with intent for bilateral treatment on the same surgery day

[2] 'A' denotes visit for 2nd eye treated

[3] Unscheduled visit - other study assessments may be performed per the Investigator's discretion

[4] Confirm inclusion/exclusion criteria as needed

[5] Required only for women of child-bearing age, not postmenopausal or surgically sterile

[6] Measured twice, once with cycloplegia and once for treatment planning

[7] Subjective Refraction to assess for inclusion stability at Screening (Visit 0) should be performed on the site's chart; subjective refraction for VA testing will be refraction on Sponsor provided electronic chart

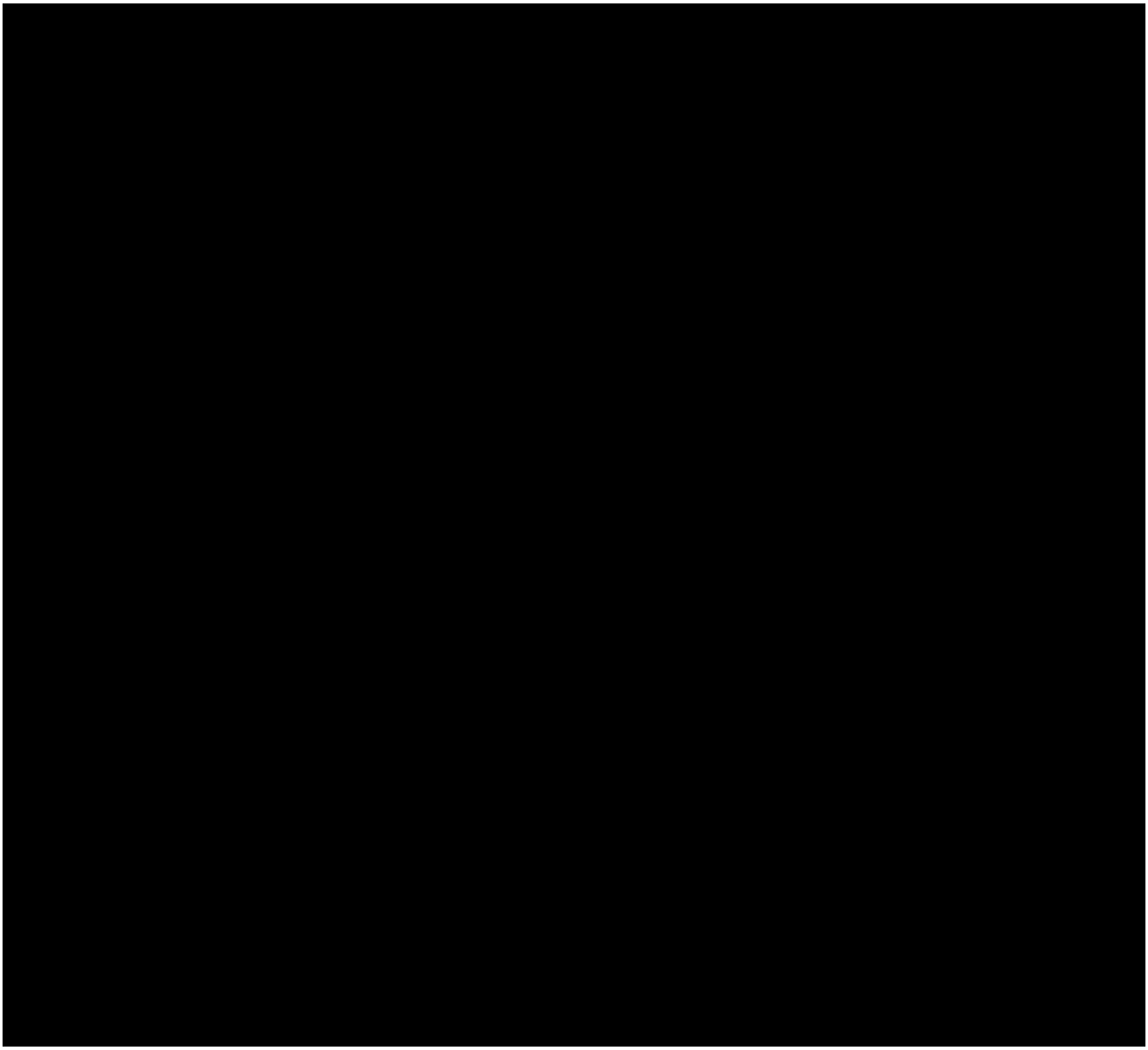
[redacted]

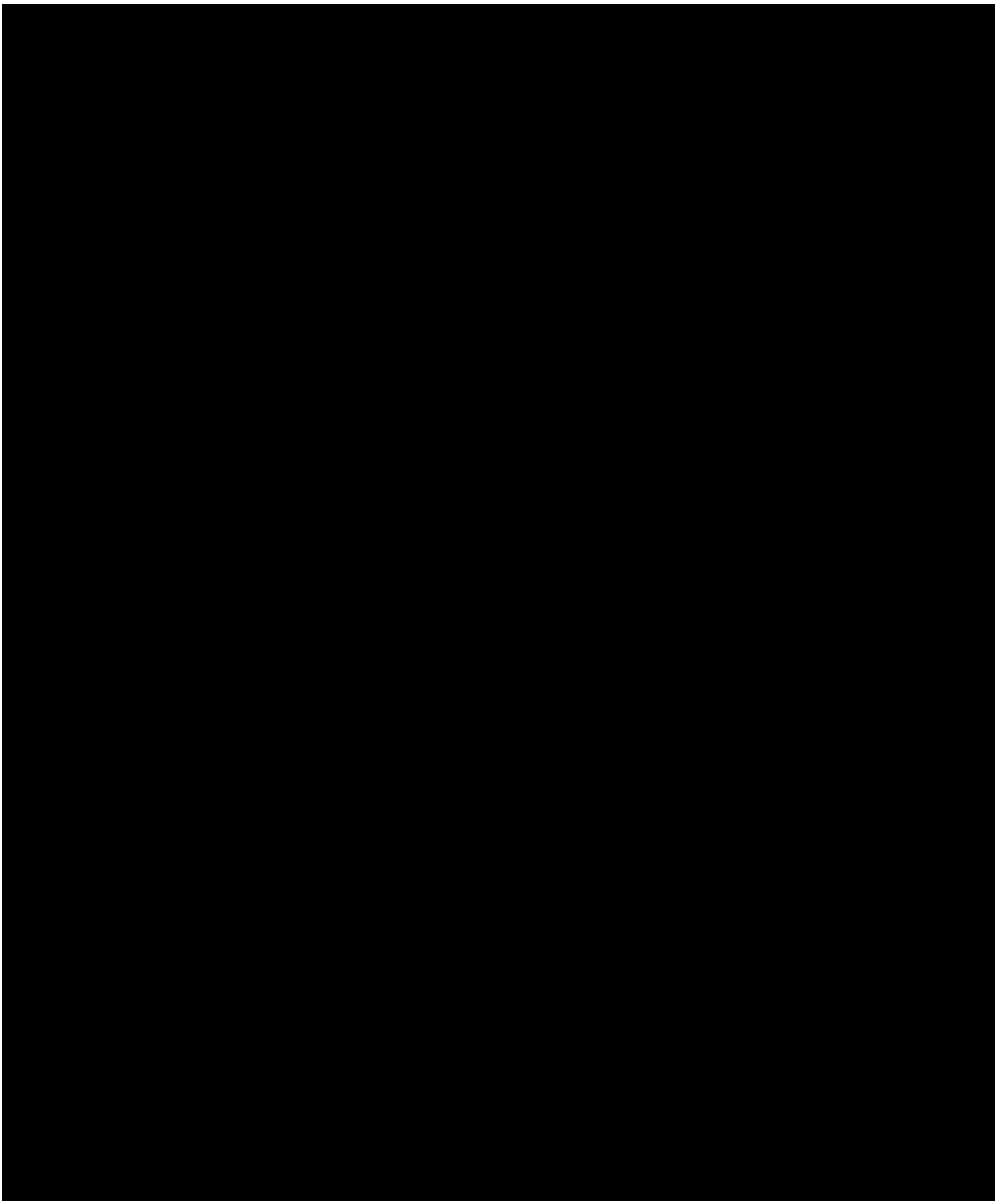
* Data collected in source only

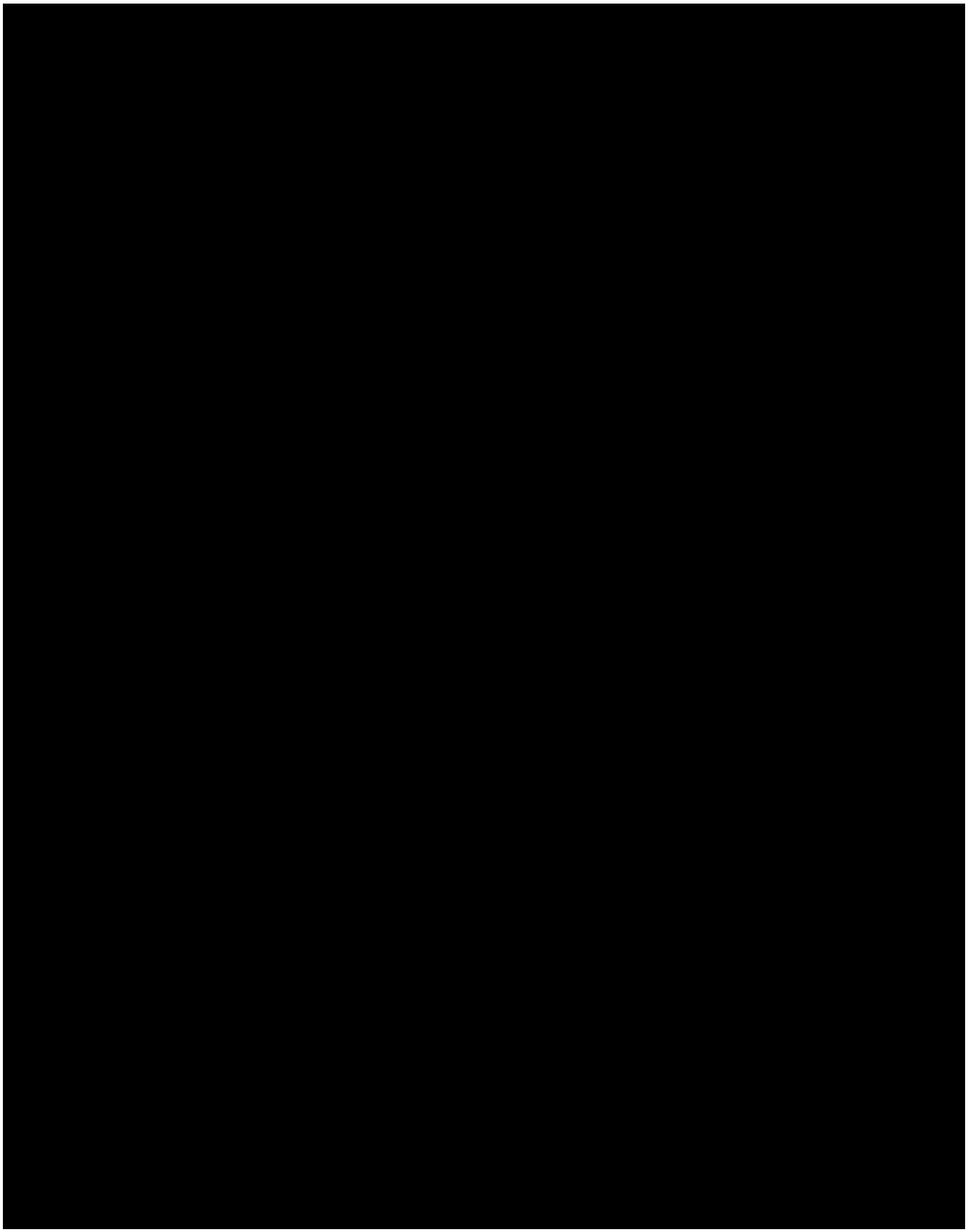
4 PROTOCOL AMENDMENTS

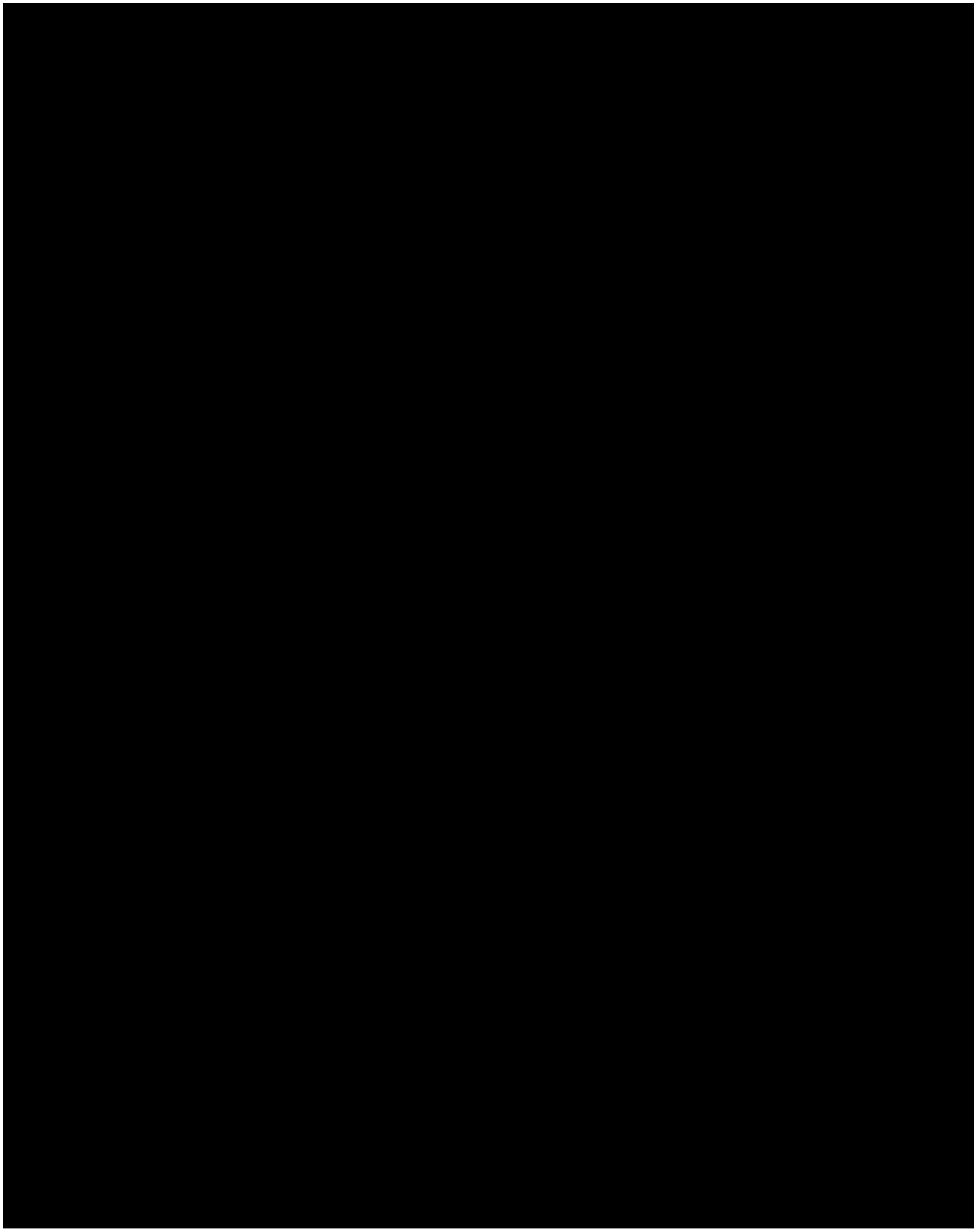
Modification of the protocol is prohibited without prior written agreement in the form of a protocol amendment. All amendments must be created by the Study Sponsor and must be approved by the IRB/IEC and global and regional Health Authorities, as applicable, prior to implementation except when required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

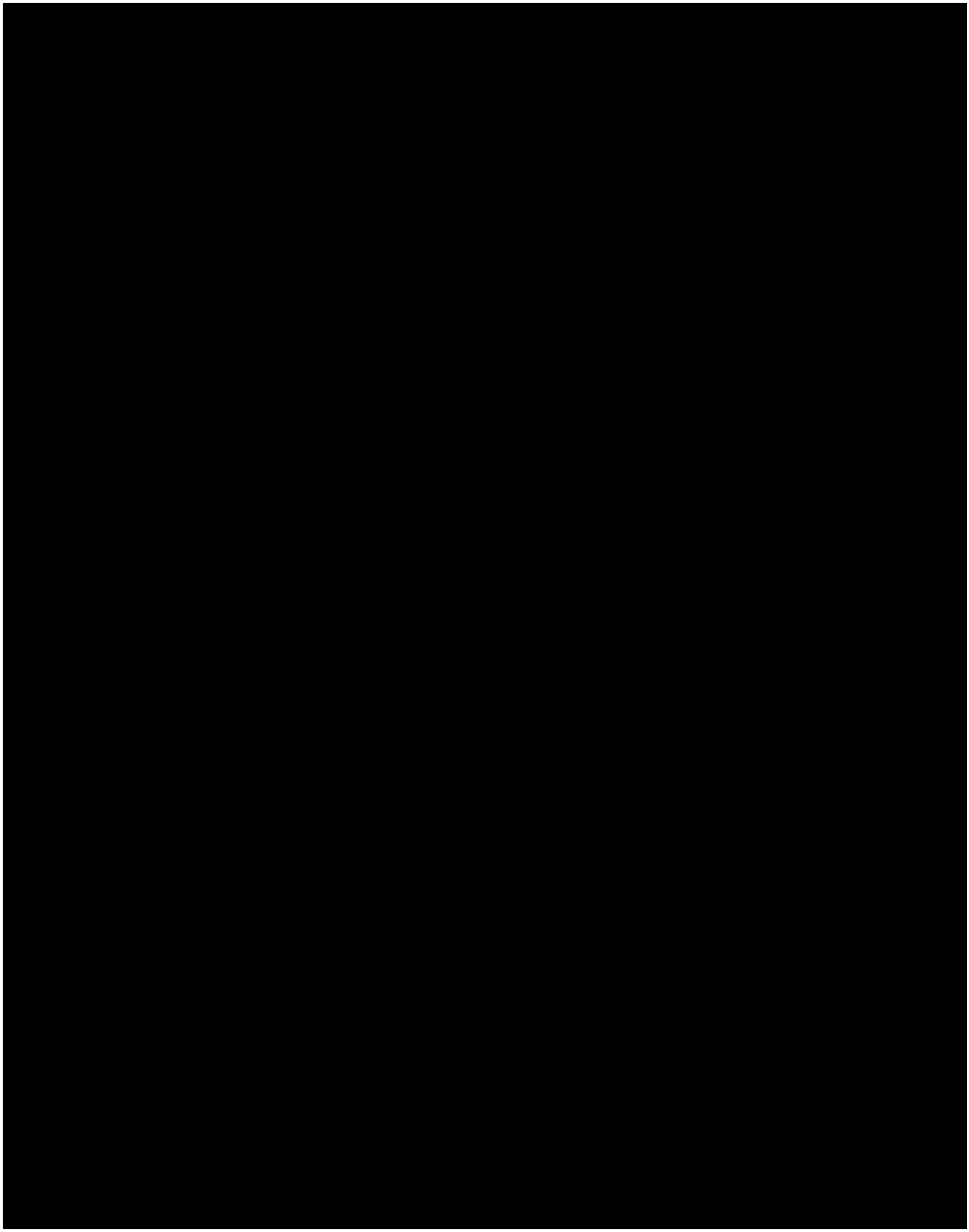
Amendments may necessitate that the informed consent and other study-related material be revised. If the consent form is revised, all subjects currently enrolled in the study must sign the approved, revised informed consent (re-consent), as required by the IRB/IEC.

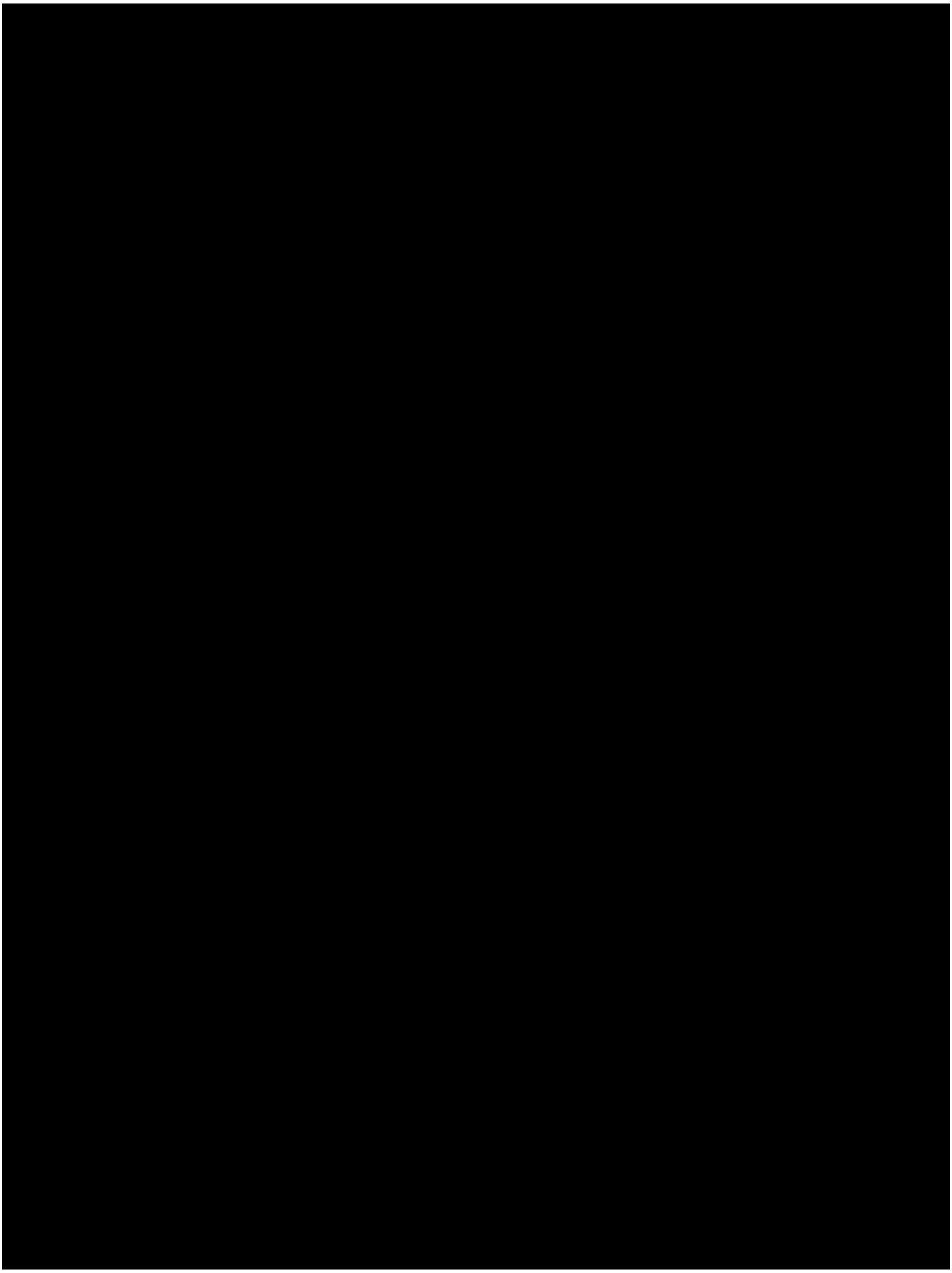












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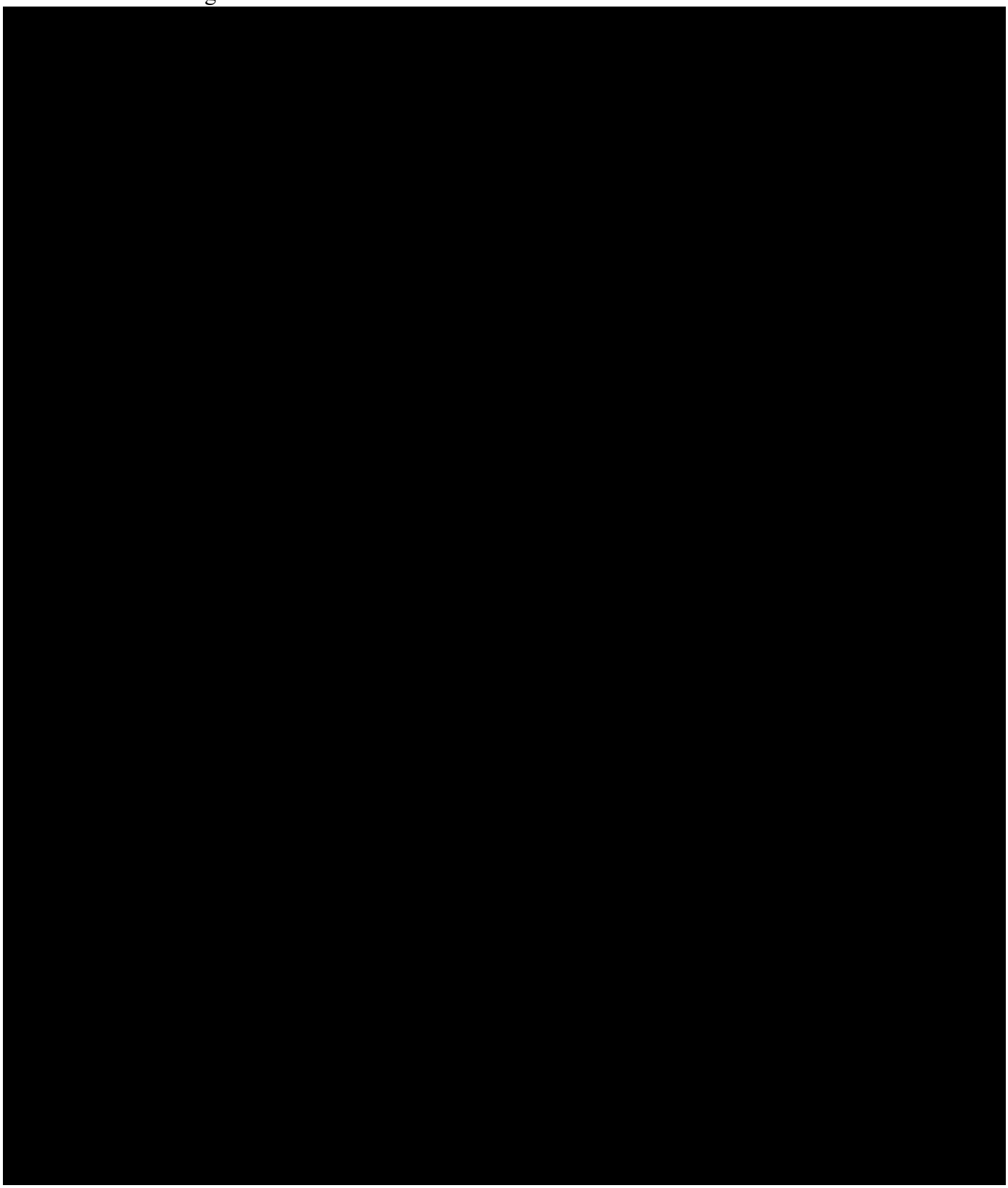

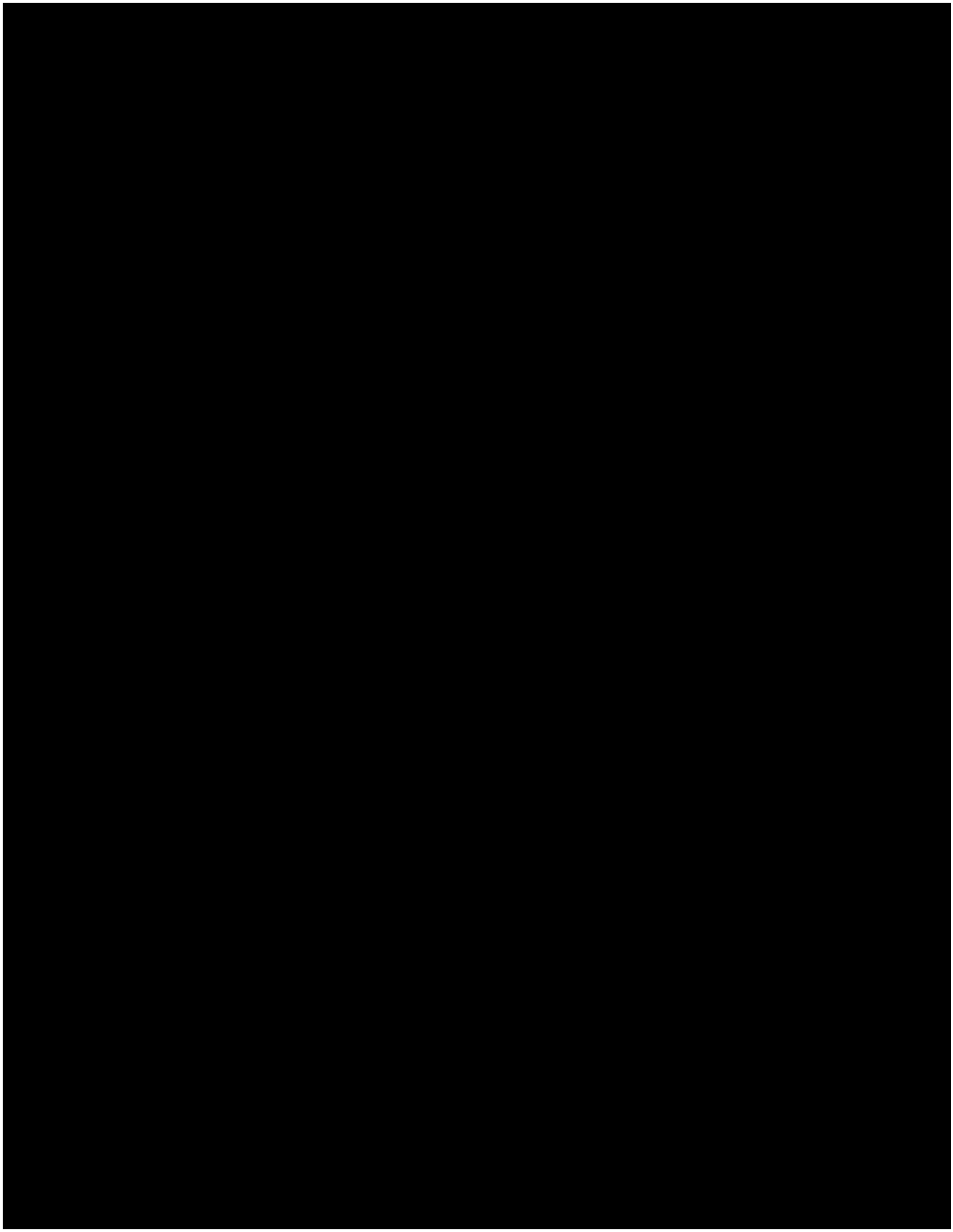

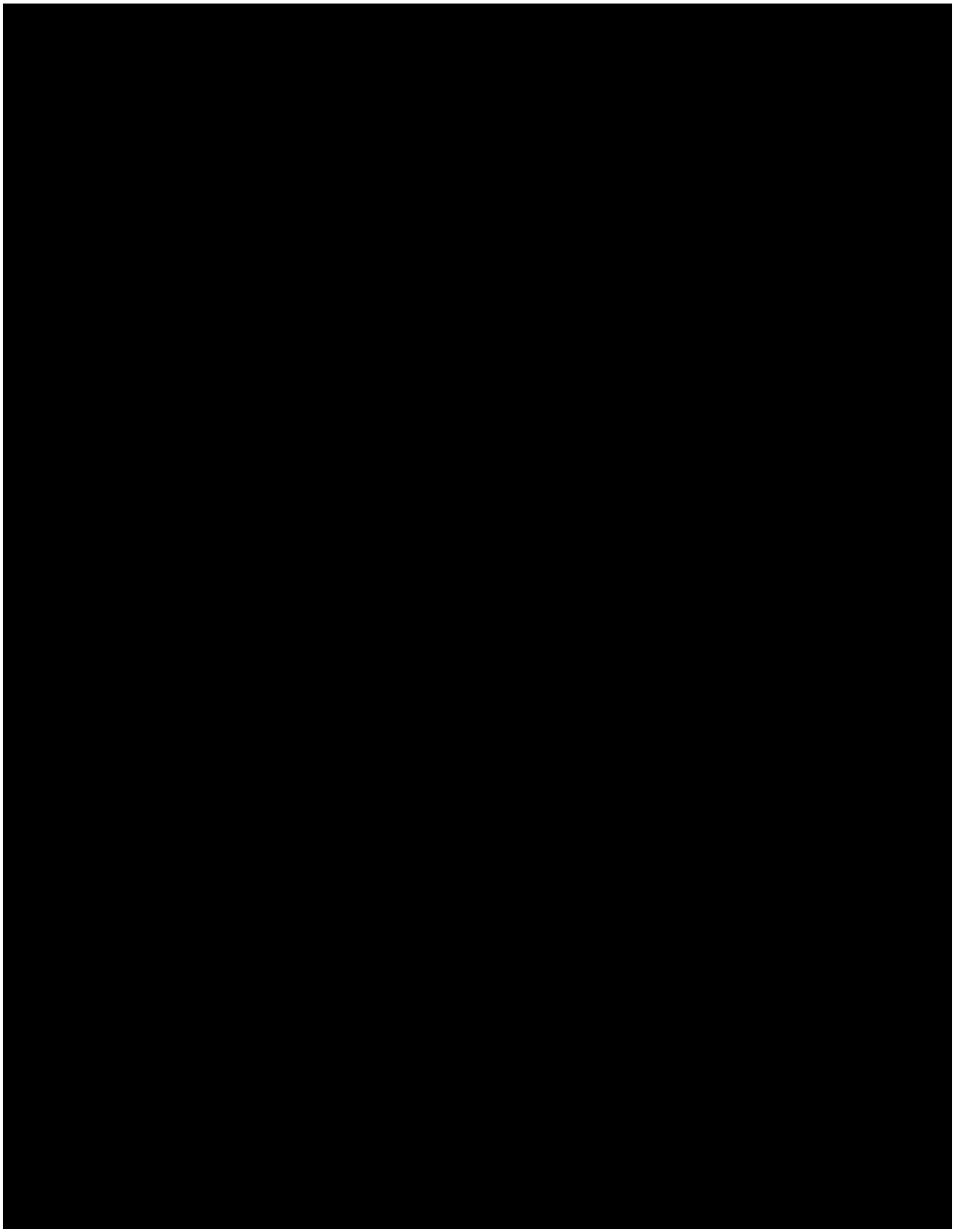

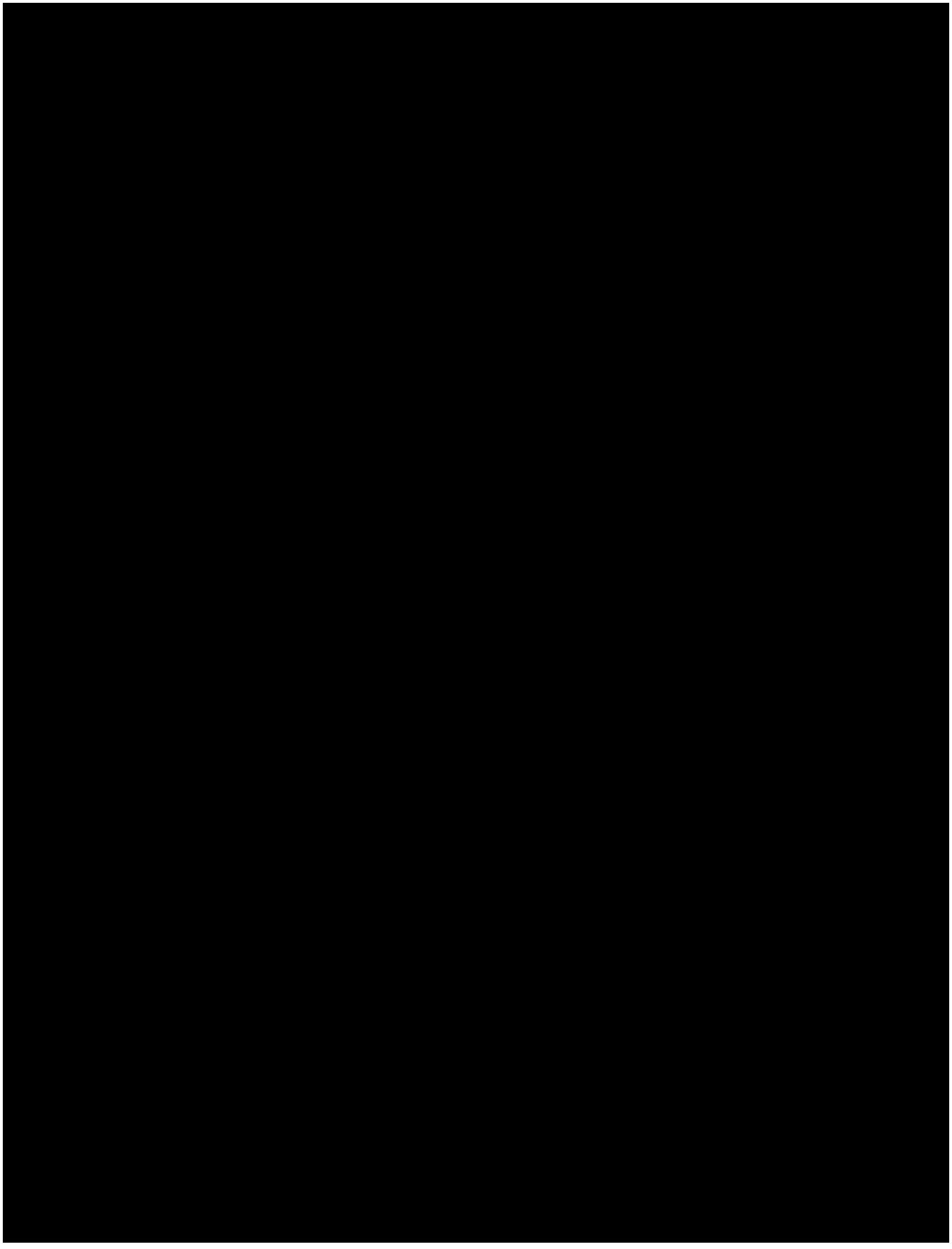

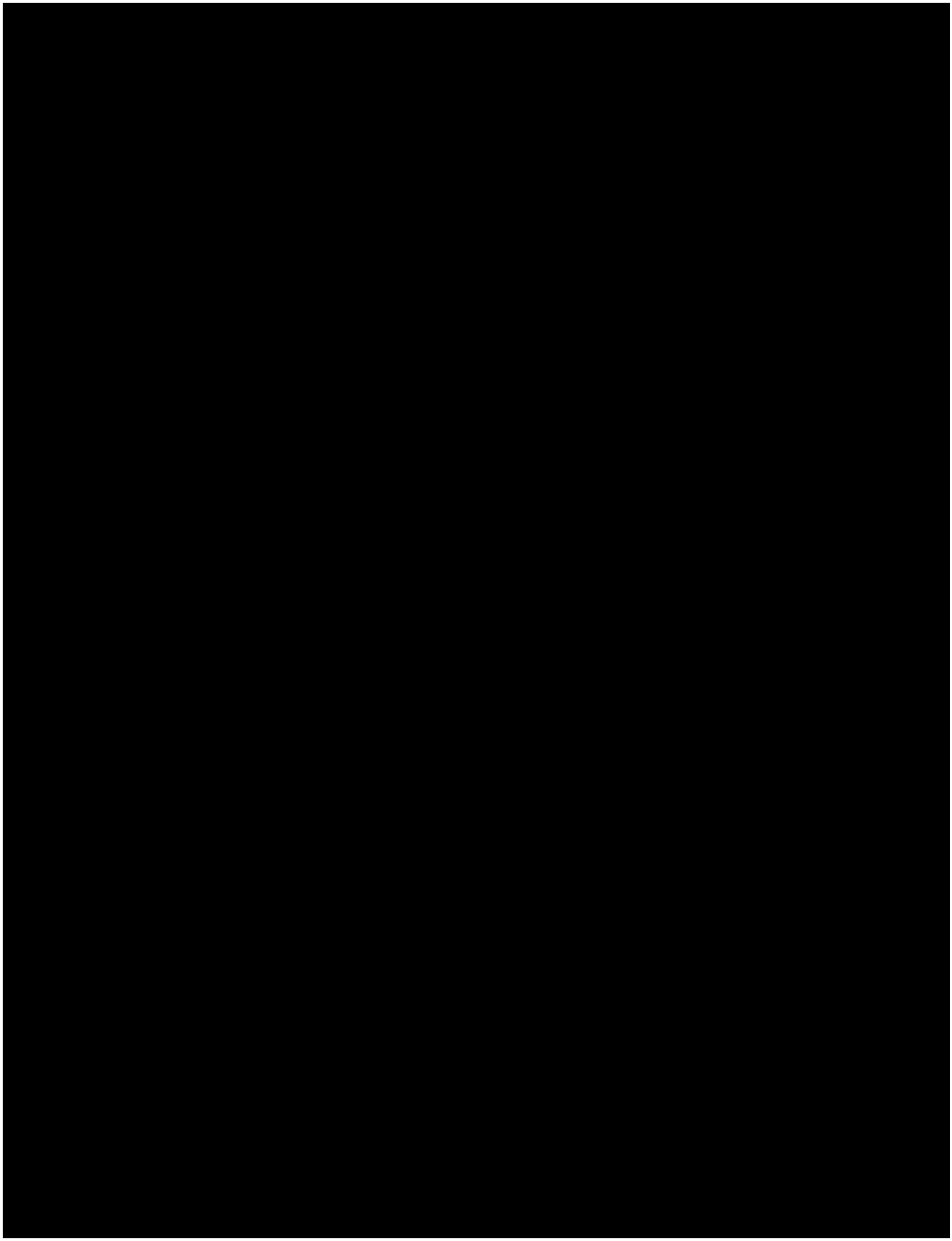

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5 INTRODUCTION

5.1 Rationale and Background

The goal of refractive surgery is to provide the patient with his or her best possible visual performance. Accurate methods of calculation are required to achieve satisfactory surgical outcomes. In order to improve the clinical outcome from LASIK treatment, a new treatment option named “InnovEyes” has been developed. Current treatment planning for LASIK procedures, such as wavefront optimized, wavefront guided and topography guided is based on simplified formulas and a standardized eye model and does not consider the multiple lens structure of the eye. The InnovEyes software for the WaveLight EX500 uses a new, computer-based method to calculate ablation profiles based on a ray tracing algorithm and also takes the multi-lens nature of the eye into consideration. For the InnovEyes procedure, the model data of the eye are replaced by measured diagnostic data of the individual patient from the subject’s eye such as topography, aberrometry, wavefront, and eye length. By combining these data, a patient-specific ablation profile is then generated from the calculated individual eye model based on an iterative “Ray Tracing” calculation. By considering all optical elements of the eye, such as the back and front surfaces of the cornea and the crystalline lens, as well as the corresponding distances in the eye model, ray tracing offers currently the highest possible accuracy to improve the refractive predictability of corneal laser surgery (Simon 2011).

An initial clinical trial in which the ray tracing algorithm was used was conducted by WaveLight GmbH in 2009-2010. The purpose of the study was to assess the efficacy, safety, and predictability of an individualized laser-assisted in situ keratomileusis (LASIK) ablation profile based on an optical ray tracing algorithm to treat moderate to high myopic astigmatism (Schumacher 2012). For this initial Ray tracing (now called InnovEyes) treatment, calculation was performed with a Mathlab program installed on a separate computer and treatment was implemented by the WaveLight Concerto or Allegretto laser. In addition, in this initial clinical trial, the diagnostic data were collected from three different WaveLight diagnostic devices. This trial provided evidence of the safety, efficacy, and predictability of laser-assisted in situ keratomileusis outcomes using an optical ray tracing algorithm to treat moderate to high myopic astigmatism and shows that good results are sustained through 1 year (Cummings 2013).

Since the past study using the InnovEyes software and ray tracing algorithm was completed, a new diagnostic device named “InnovEyes™ sightmap” has been developed. Historically needed data for LASIK treatment has been gathered from different diagnostic devices, but for improved usability and a defined common coordinate system, the InnovEyes sightmap combines the necessary measurements for InnovEyes treatment within one device.

The InnovEyes sightmap is designed to perform measurements (Scheimpflug Camera principle, Hartmann-Shack principle, and interferometry) which includes the cornea, pupil, anterior chamber, lens, and length of the eye. Furthermore, it provides the axial dimensions of the eye. It is also indicated to analyze the optical aberrations of the eye by using wavefront technology.

In detail, the InnovEyes sightmap provides data to evaluate the:

- Corneal shape including corneal thickness, anterior, and posterior corneal surface
- Anterior chamber angle, depth, and volume
- White-to-white distance
- Pupil diameter
- Conditions of the lens (eg, opaque crystalline lens)
- Location of cataracts (eg, nuclear, sub-capsular, and/or cortical)
- Axial length
- Optical aberrations of the eye

This device has been developed for ophthalmic diagnosis and for use in hospitals, in eye doctor medical practices and at optometrists/opticians. The examination data get stored electronically and can be exported and used in combination with the WaveLight GmbH laser systems (ie, EX500) to perform InnovEyes treatment for qualified subjects.

5.2 Purpose of the Study

The purpose of this clinical study is to determine the safety and effectiveness of the WaveLight EX500 excimer laser system for the correction of myopia with and without astigmatism using InnovEyes in conjunction with InnovEyes sightmap.

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

Results of the study may be used for publication if they are of scientific interest and for marketing after approval or clearance for marketing.

5.3 Risks and Benefits

As with any refractive surgical procedure or diagnostic device, there are potentials risks with the use of the InnovEyes sightmap and InnovEyes treatment. However, there are no additional warnings or precautions associated with these outside of the risks identified for the use of other similar diagnostic devices or other LASIK procedures performed on the EX500.

There may also be unknown risks to use of the InnovEyes sightmap and InnovEyes treatment. Any risk to subjects in this clinical study will be minimized by compliance with the eligibility criteria and study procedures, clinical oversight, and monitoring.

The medical benefit of the InnovEyes sightmap is in its collection of diagnostic data and data of the optical properties of the whole eye in order to facilitate treatment planning for refractive surgery. The diagnostic data may be used to screen out patients that are not eligible for surgery or for planning treatment with the intent of improving outcomes with InnovEyes LASIK.

The medical benefit of the InnovEyes software is in the accuracy of determining an individual eye's ablation profile.

More information on summary of the literature, description of the investigational device, guidance for the Investigator, as well as known and potential risks and benefits can be found in the Investigator's Brochure (IB) [IB-0171] Investigator Brochure for InnovEyes and InnovEyes sightmap and the InnovEyes sightmap user manual.

6 STUDY OBJECTIVES

6.1 Primary Objective(s)

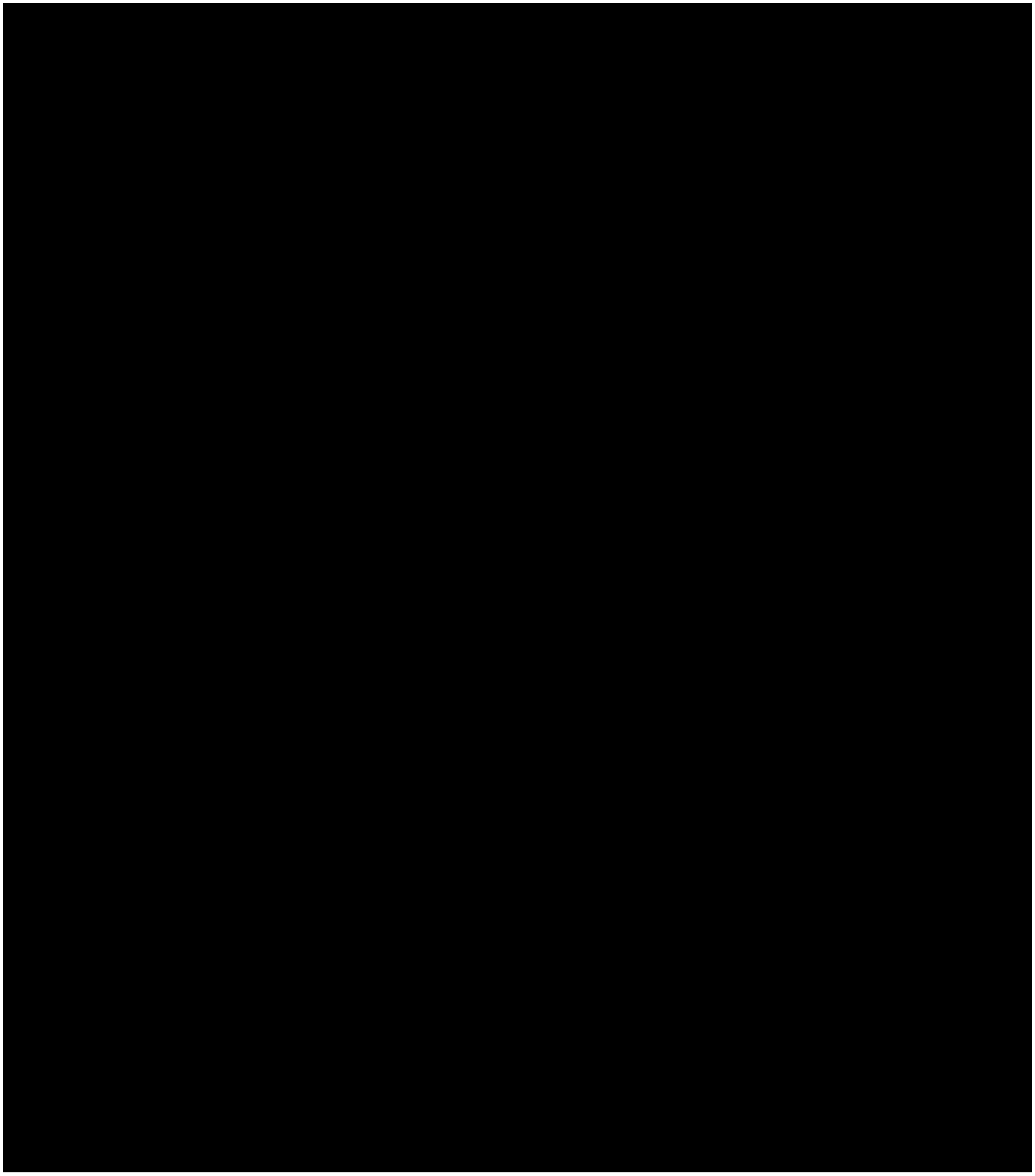
The primary objective of this study is to evaluate the effectiveness of the WaveLight EX500 excimer laser system for the correction of myopia with and without astigmatism using InnovEyes in conjunction with InnovEyes sightmap.

6.1.1 Primary Endpoints

- Percentage of eyes with UCDVA of 20/40 or better (in eyes with preoperative BCDVA of 20/20 or better) at refractive stability (Target ≥ 85%)
- Percentage of eyes with MRSE within 0.50 D at refractive stability (Target ≥ 50%)

- Percentage of eyes with MRSE within 1.00 D at refractive stability (Target ≥ 75%)
- Percentage of eyes that achieve refractive stability (Target ≥ 95%)

Note: Refractive stability is defined in Section 6.4 and Section 12.4



6.3 Safety Objective(s)

The primary safety objective of this study is to evaluate the safety of the WaveLight EX500 excimer laser system for the correction of myopia with and without astigmatism using InnovEyes in conjunction with InnovEyes sightmap.

6.3.1 Primary Safety Endpoints

- Percentage of eyes that lose 2 lines or more of BCDVA (Target at refractive stability ≤ 5%)
- Percentage of eyes with BCDVA worse than 20/40 (for eyes with BCDVA of 20/20 or better pre-op) (Target at refractive stability ≤ 1%)
- Percentage of eyes that have an increase of manifest refractive astigmatism of greater than 2.00 D of absolute cylinder as compared to the preoperative refraction (Target at refractive stability ≤ 5%)
- Percentage of eyes with a serious, non-flap related, ocular adverse event at the postoperative visits (Target per event type at refractive stability ≤ 1%)

[redacted]

6.4 Refractive Stability

Stability analyses will be performed on eyes that have every follow-up exam from 1-month up to the stability time point (the Consistent Cohort), as well as on the eyes that have 2 consecutive exams, but not necessarily every follow-up exam. The following stability analyses will be performed for the time intervals between all consecutive pairs of scheduled postoperative refractions:

- Percentage of eyes that achieve:
    - a change of less than or equal to 1.00 D of MRSE between two refractions performed at 1 month and 3 months, and between subsequent refractions performed at least 3 months apart;

  - a change of less than or equal to 0.50 D of MRSE between two refractions performed at 1 month and 3 months, and between subsequent refractions performed at least 3 months apart;

- Mean overall change and change per month in MRSE between consecutive scheduled visits as determined by a paired analysis;
- Mean ± SD MRSE for the preoperative and each postoperative visit;
- Assessment of cylinder stability for correction of spherocylindrical refractive errors

Refractive stability is achieved at the latter of two postoperative manifest refractions performed at least 3 months apart or at 3 months after surgery when compared with the 1-month interval, when all of the following recommended criteria are met:

- At least 95% of the treated eyes have a change ≤ 1.00 D of MRSE between the 2 refractions;
- The mean rate of change in MRSE, as determined by a paired analysis, is ≤ 0.5 D per year (0.04 D/month) over the same time period;
- The mean rate of change of MRSE decreases monotonically over time, with a projected asymptote of zero or a rate of change attributable to normal aging;
- The 95% confidence interval for the mean rate of change in MRSE includes zero or a rate of change attributable to normal aging; and
- Stability is confirmed at least 3 months after the stability time point by a statistically adequate subgroup (at least 80% of the cohort).

7 INVESTIGATIONAL PLAN

7.1 Study Design

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

Subjects will be evaluated initially for suitability as candidates for bilateral LASIK. Potential subjects willing to participate will be consented and screened. Approximately 187 qualified subjects (up to 374 eyes) will receive bilateral InnovEyes LASIK and be followed for 1 year. Total duration of subject participation is approximately 1 year and includes 9 study visits consisting of Screening, Surgery, 1 day, 1 week, 1 month, 3 month, 6 months, 9 months, and

12 months. Subjects will be enrolled with intent to treat at least 20 eyes in each spherical diopter and each cylindrical diopter range (with only 10 eyes in the highest cylinder bin). Approximately 10 US study sites will participate in this clinical study. It is estimated that enrollment and follow-up of all subjects will take approximately 22 months. Additional information on the study population can be found in Section 8.

Assessments will be obtained at baseline and at appropriate times after InnovEyes LASIK to evaluate the safety and effectiveness of the treatment. [redacted]

The main analyses for effectiveness and safety will be conducted when refractive stability for the cohort has been determined and 80% of the eyes in the cohort have completed the next scheduled visit after refractive stability (Refractive Stability is defined in Section 6.4 and 12.4). The Sponsor may file a Pre-Market Approval application once this analysis is complete. Subjects are followed for at least 12 months (Day 330 to Day 420) for safety and supportive effectiveness assessments. Final data analyses will be conducted at study completion.

7.2 Rationale for Study Design

The prospective, single group study design, objectives, planned visits and assessments, and planned analysis at refractive stability are based on recommendations by ANSI Z80.11-2012(R2017) (American National Standard for Ophthalmics – Laser Systems for Corneal Reshaping, approved August 9, 2012 and Reaffirmed December 11, 2017) and ISO 14155:2011.

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

Bilateral treatments of subjects will be implemented in this study based on past clinical study results that provide initial safety, effectiveness, and stability data (Schumacher 2012; Cummings 2013).

7.2.1 Purpose and Timing of Interim Analyses and Resulting Design Adaptations

Analysis will occur for review of refractive stability as specified by ANSI Z80.11-2012(R2017), which includes 1 additional visit beyond stability completed by at least 80% of the cohort.

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

7.3 Rationale for Duration of Treatment/Follow-Up

One year follow-up (Day 330 to 420) of subjects will be implemented in this study based on past clinical study results using the ray tracing algorithm that provided initial safety, effectiveness, and stability data through one year follow-up. (Schumacher 2012; Cummings 2013).

7.4 Data Monitoring Committee

Not applicable.

8 STUDY POPULATION

The study population consists of subjects who desire to have and qualify for LASIK treatment, are 18 years of age or older, and have myopia up to -11.00 D with or without astigmatism up to -4.50 D. This study is aimed to enroll (consent) approximately 374 subjects at up to 10 sites in the United States with a target of up to 374 eyes treated. Because about 50% screening failure rate and up to 10% lost to follow-up rate is expected, these numbers will allow for treatment and follow-up of at least 300 eyes and account for overlap or over-enrollment in certain ranges to achieve the required number of 20 eyes per diopter over the intended refractive range. Allocation of study bins will be closely monitored through the use of listings generated from the InnovEyes sightmap Measured refraction entered in EDC. Investigative sites will be trained on the importance of timely entry of data in EDC to ensure enrollment bin allocation is up to date. When enrollment in a refractive bin is complete, sites will be instructed to refrain from enrolling eyes in that bin. Site-specific targets may vary based upon individual site capabilities, but each site is expected to treat a minimum of 20 eyes and no more than 92 eyes per site.

Enrollment will be monitored to aim for 20 or more eyes treated and followed to refractive stability in each diopter interval based on the ranges of spherical and cylindrical refractive error (bin). Therefore at least 220 eyes will be treated for the sphere range (20 eyes/diopter interval of 0 to -11.00) and at least 110 eyes will be treated for the cylinder range (20 eyes for 0 to ≤ -0.50 and > -0.50 to ≤ -1.00 cylinder and 20 eyes/diopter for intervals from > -1.00 to

-4.00 and 10 eyes in > -4.00 to -4.50). For a diagram showing the study bins, refer to the Manual of Procedures (MOP). All bin assignments are made based on the InnovEyes sightmap Measured refraction entered in EDC. Estimated time needed to recruit subjects for the study is approximately 10 months; however, unanticipated circumstances may shorten or lengthen this time and would not require amendment of this protocol.

8.1 Inclusion Criteria

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

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

1. Subject must be able to understand and sign an IRB/IEC approved Informed Consent form
2. Willing and able to attend all scheduled study visits as required per protocol
3. Minimum of 18 years of age, or age of adulthood as determined by local regulations
4. Myopia up to -11.00 D with or without astigmatism up to -4.50 D, with spherical equivalent no more than -12.00 D as shown from InnovEyes sightmap Measured refraction
5. Best corrected photopic distance visual acuity of 20/20 or better (≤ 0.04 logMAR)
6. Uncorrected photopic distance visual acuity of 20/40 or worse (≥ 0.34 logMAR)
7. Less than 0.75 D MRSE difference between cycloplegic and subjective manifest refractions
8. Less than 0.75 D MRSE difference between InnovEyes sightmap Measured refraction and subjective manifest refractions
9. Stable refraction (within ± 0.50 D) as determined by MRSE for a minimum of 12 months prior to surgery, verified by consecutive subjective refractions and/or medical records or prescription history
10. Demonstrated stable refraction for contact lens wearers: within ± 0.5 D MRSE on two consecutive exam dates under the following conditions

a. Lenses are not worn for at least 3 weeks (rigid or toric contact lenses) or 1 week (soft contact lenses) prior to the first refraction used to establish stability and through the day of surgery

b. the two subjective refractions are performed at least 7 days apart

8.2 Exclusion Criteria

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

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

   a. they are currently pregnant,

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

   c. intend to become pregnant during the study period,

   d. are breast-feeding

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

2. Acute or chronic disease or illness that would increase the operative risk or confound the outcomes of the study

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

4. Ocular condition (other than high myopia) that may predispose the subject to future complications, for example:
   - history or evidence of active or inactive corneal disease (eg, herpes simplex keratitis, herpes zoster keratitis, recurrent corneal erosion syndrome, corneal dystrophy, etc)
   - evidence of retinal vascular disease
   - keratoconus or keratoconus suspect
   - glaucoma or glaucoma suspect by exam findings and/or family history

5. Previous intraocular or corneal surgery

6. Predicted residual stromal bed thickness < 250 µm
7. Intended to have monovision treatment
8. Participation in other clinical trials during the course of the study that may confound study results
9. Other condition or assessment that causes subject to not be an acceptable candidate for treatment or study participation as clinically assessed and documented by the Investigator

8.3 Rescreening of Subjects

Rescreening of subjects is allowed for the conditions listed below:

Rescheduling of surgery: If a subject reschedules surgery or surgery is rescheduled due to other reasons, and this rescheduling results in preoperative/screening assessments (Visit 0) falling outside of the -30 to -1 day window, assessments should be repeated and inclusion/exclusion criteria re-verified to ensure the subject still qualifies to proceed with study surgery.

Criteria not met: Rescreening of subjects who did not meet inclusion/exclusion criteria is allowed one time per subject. Rescreening is allowed only if criteria previously not met could reasonably have changed since the prior screening. Criteria that could change and rescreening would be allowed include: Inclusion 3, 6, or if changes in refractive stability or receipt of additional past records can show stability for criteria 7 – 10.

NOTE: IF a subject is rescreened, THEN use the same subject number. Update the screening data in EDC with date and results of the rescreening. Keep the original consent date captured in EDC. Document the rescreening, and keep results from both screening visits in the subject's chart.

9 TREATMENTS ADMINISTERED

In this study, the WaveLight EX500 excimer laser will be used to perform InnovEyes LASIK treatment using preoperative data from the InnovEyes sightmap. Subjects who qualify for inclusion into the study will undergo treatment in both eyes. All treated eyes will be targeted for emmetropia.

An outline of key LASIK treatment steps after confirming subject qualification, including obtaining data from the InnovEyes sightmap, include:

- Prepare subject for treatment using standard of care methods for LASIK treatment
- Create corneal flap using the WaveLight FS200 using standard of care methods for LASIK treatment
- Perform InnovEyes LASIK using the WaveLight EX500
    - Target should be emmetropia
    - Treatment must be performed by trained and delegated Investigator (no more than 2 Investigators per site allowed)
- Use standard of care methods for post-LASIK treatment
- Follow subject according to Table 3–1

Note: Additional procedure information is listed in the MOP and User Manuals.

Note: Retreatment of the eye is not allowed in the study.

9.1 Investigational Product(s)

Test Product(s):	• WaveLight EX500 excimer laser system • InnovEyes Software • InnovEyes sightmap [See Table 9–1 to Table 9–3 for details on each product]
Control Product(s) (If applicable):	Not applicable

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

Test Product	WaveLight EX500 excimer laser system
Manufacturer	WaveLight GmbH Am Wolfsmantel 5 91058 Erlangen, Germany
Indication for Use and Intended Purpose in the Current Study	The WaveLight EX500 is an FDA approved stationary scanning-spot excimer laser system used in refractive surgery for the treatment of myopia, myopic astigmatism, hyperopia, hyperopic astigmatism, and mixed astigmatism, including customized refractive surgery based on data delivered by WaveLight's diagnostic devices.

	For this clinical study, the WaveLight EX500 software will be upgraded to include the ray tracing treatment (InnovEyes). This treatment option on the EX500 can only be activated by use of the WaveCard supplied by the Sponsor and will be used for treatment of myopia, with or without astigmatism.
Product Description and Parameters Available for this Study	For treatments, at least the following components of the system have to be operated: • Laser Console - containing operating elements, laser head, optical transmission system, energy, and system controls; ○ Eyetracker, scanner motors, gas supply, plume evacuator, headup display, video system, N2 generator focusing and fixation lights, system software and ablation profiles with scanning spot patterns, operating microscope with illumination, LED slit illumination system, and test systems • Patient Bed - with moving motors and bed control • System Notebook (WaveNet Planning System) – containing software for programming treatment parameters
Formulation	N/A
Usage	In this study, the WaveLight EX500 excimer laser will be used to perform InnovEyes LASIK treatment. Prior to usage for the laser portion of the treatment, a corneal flap must be created. For this study, the WaveLight FS200 femtosecond laser unit will be utilized to create the flap. The WaveLight EX500 laser system is intended for use solely by the physicians trained in the use of this laser system and its accessories. During its operation, it does not come into contact with the eye, and treatment usually lasts 1.3 seconds per diopter. The WaveLight EX500 can be used in combination with a class B network (WaveNet) as a data exchange medium for importing treatment data from the WaveLight GmbH diagnostic devices, such as InnovEyes sightmap in this study, see Table 9–3.
Operating Conditions	Temperature: + 64°F (+ 18°C) to + 86°F (+ 30°C) above dew point Humidity: 20% to 70% at + 77°F (+ 25°C), not condensing

	Air pressure (recommended): 800 hPa to 1060 hPa (Barometric)
Supply	Each selected investigational site must have an EX500.

Table 9–2 Test Product - InnovEyes Software

Test Product	InnovEyes software for WaveLight EX500 excimer laser system
Manufacturer	WaveLight GmbH Am Wolfsmantel 5 91058 Erlangen, Germany
Indication for Use and Intended Purpose in the Current Study	InnovEyes is the tradename of a software which uses the ray tracing algorithm and is intended for the treatment of myopia, with and without astigmatism. It uses ocular data from the InnovEyes sightmap to calculate a subject specific ablation profile for refractive correction using the EX500. Treatment ranges for Ray Tracing: • Myopia -11.00 to 0.00 D • Myopic Astigmatism -4.50 to 0.00 D • Optical zones Between 6.0 and 7.0 mm
Product Description and Parameters Available for this Study	InnovEyes software is loaded onto the WaveLight EX500 excimer laser to perform customized InnovEyes treatments, and can be activated only by use of a specific Platinum WaveCard in combination with a data set transferred from the InnovEyes sightmap. The Workflow and graphical user interface for the InnovEyes planning and treatment shall be similar to existing workflows and graphical user interfaces.
Formulation	N/A
Usage	InnovEyes software will display as an InnovEyes treatment option on the EX500 for selection by the user. A Sponsor supplied Wavecard is required to activate this treatment option. InnovEyes treatment is permitted only with a complete set of valid diagnostic data from the InnovEyes sightmap. InnovEyes software is intended for use solely by the physicians trained in the use of the EX500 laser system and its accessories.

Operating Conditions	N/A
Supply	WaveLight/Alcon representatives will install the InnovEyes software onto the site's EX500 laser.

Table 9–3 Test Product – InnovEyes sightmap

Test Product	InnovEyes sightmap
Manufacturer	WaveLight GmbH Am Wolfsmantel 5 91058 Erlangen, Germany
Indication for Use and Intended Purpose in the Current Study	The InnovEyes™ sightmap is a non-contact ophthalmic diagnostic device designed to capture images of the anterior segment of the eye, which includes the cornea, pupil, anterior chamber, and lens of the eye. Furthermore, it provides the axial dimensions of the eye. It is also indicated to analyze the optical aberrations of the eye by using wavefront technology. This device has been developed for ophthalmic diagnosis and for use in hospitals, in eye doctor medical practices including use by optometrists/opticians. The examination data get stored electronically and can be exported and used in combination with the WaveLight GmbH laser systems in the field of refractive surgery. Data transfer can be done via a network interface or via USB stick.
Product Description and Parameters Available for this Study	The InnovEyes sightmap is a non-contact ophthalmic diagnostic device. The InnovEyes sightmap contains the following components: • InnovEyes sightmap detector head mounted on a cross table (adjustable platform) • Head Rest • Panel Personal Computer • Electronics unit including power supply • Set of connecting cables • Test Object • Black Cloth

	• Dust protection cap The following components are optional: • Operator chair • Patient chair • Lift Table Diagnostic System
Formulation	N/A
Usage	The InnovEyes sightmap will be used to collect subject ocular data to be used in InnovEyes LASIK treatment on the EX500. In this study, the InnovEyes sightmap will provides data to evaluate the following areas in planning InnovEyes LASIK: • Corneal shape including corneal thickness, anterior, and posterior corneal surface • Anterior chamber angle, depth, and volume • White-to-white distance • Pupil diameter • Conditions of the lens (eg, opaque crystalline lens) • Location of cataracts (eg, nuclear, sub-capsular, and/or cortical) • Axial length • Optical aberrations of the eye The InnovEyes sightmap should only be used by specially trained physicians, medical staff, and optometrists who are well versed in its diagnostics abilities and possible dangers. It should only be operated according to the operating instructions as listed in the user manual.
Operating Conditions	Temperature (recommended) + 10°C (+ 50°F) to + 40°C (+ 104°F) Humidity (recommended) 30% to 75% at + 25°C (+ 77°F) Air pressure (Barometric) 700 hPa to 1060 hPa
Supply	The InnovEyes sightmap will be delivered in appropriate packaging to cover and protect the 16 kg (35.7 lb) device that measures approximately 275 x 320 to 400 x 500 to 535 mm (10.8 x 12.6 to 15.7 x 19.7 to 20.0 in). WaveLight/Alcon representatives will install the device at the clinical site prior to study startup.

The Investigator will be responsible for ensuring that the products are used in accordance with their respective indications and procedural guidance provided in the appropriate User and Procedure Manuals. The EX500 and the InnovEyes sightmap operating conditions fall within routine ambient conditions for a medical/ophthalmic office; therefore, a daily log will not be required to document environmental conditions. Clinical sites should ensure conditions are met as they do in standard clinical practice. IF conditions occur outside of the accepted ranges, THEN do not operate the device and contact the study Sponsor.

More information on the test product can be found in the Investigator's Brochure (IB) [IB-0171] *Investigator Brochure for InnovEyes and InnovEyes sightmap* and in the *InnovEyes sightmap user manual*. Information on the WaveLight EX500 can be found in the *EX500 User Manual* and *Quick User Manual EX500 InnovEyes*.

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

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

- WaveLight FS200: The FDA approved FS200 will be used for creation of the corneal flap according to MOP and associated user manuals, and is to be performed by a qualified ophthalmic surgeon.
- Patient Interface: The patient interface designed for use with the FS200 will be used according to the approved user guide.
- WaveCard: The clinical study treatment, InnovEyes, can be executed only by using a specific WaveCard that has not been available in the U.S. to date. This WaveCard is serial-number-specific for a particular laser and a defined number of treatments. This WaveCard will be provided to the site upon installation of the InnovEyes Software and will be labeled "*CAUTION--Investigational device. Limited by Federal (or United States) law to investigational use*."
- Medications given for InnovEyes LASIK will be per the Investigator's standard of care for LASIK.

9.3 Treatment Assignment/Randomization

After signing the ICF, a subject must be entered into the EDC system and will be assigned a subject number upon entry. This subject number will be used to identify the subject through the clinical study. Subjects that qualify based on inclusion and exclusion criteria should be

treated as schedules allow surgery to be performed. This is a single group study as recommended by ANSI Z80.11 2012(R2017) and all subjects will be planned for bilateral InnovEyes LASIK with a target of emmetropia; therefore, no randomization will be used.

9.4 Treatment Masking

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

9.5 Accountability Procedures

Upon receipt of the InnovEyes sightmap and InnovEyes software installation on the EX500, the Investigator or delegate must complete study-specific confirmation of receipt procedures as described in the MOP, and retain any required documentation in the Investigator's clinical study records. Throughout the study, the Investigator or delegate must maintain records of IP use for each subject (eg, dispensation log and WaveCard use documentation). These records must be made available to the study monitor for the purposes of verifying the accounting of IP use. Any discrepancies and/or deficiencies between the observed disposition and the written account must be recorded along with an explanation. All IPs sent to the Investigator must be accounted for by Study Sponsor personnel, and in no case be used in an unauthorized manner.

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

The Investigator is responsible for proper disposition/return of all unused IP (such as sightmap device and removal or inactivation of software) at the conclusion of the study, according to the instructions provided in the MOP.

9.6 Changes to Concomitant Medications, Treatments/Procedures

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

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

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

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

10 STUDY PROCEDURES AND ASSESSMENTS

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

- Screening - Visit 0 [-30 to -1 day prior to treatment]
- Visit 00 / Visit 00A [Day 0 – surgery]
- Visit 1 / Visit 1A [Day 1]
- Visit 2 / Visit 2A [Day 5 to 9]
- Visit 3 / Visit 3A [Day 21 to 35]
- Visit 4 / Visit 4A [Day 70 to 98]
- Visit 5 / Visit 5A [Day 147 to 182]
- Visit 6 / Visit 6A [Day 245 to 301]
- Visit 7 / Visit 7A [Day 330 to 420]

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

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

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

10.1 Informed Consent and Screening

Visit 0 / Screening

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

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

IF a patient has reported for routine LASIK screening, THEN data obtained from the routine evaluation can be used for screening data as long as protocol requirements for timeframe (within 30 days of surgery) and required details have been met. [Examples of this data include, but are not limited to IOP, Subjective Manifest Refraction for stability, and Cycloplegic refraction].

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

10.2 Description of Study Procedures and Assessments

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

10.2.1 Adverse Event Collection

All Study Visits

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

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

[redacted]

[redacted]

10.2.3 Best Corrected Distance Visual Acuity

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

Perform best corrected visual acuity testing with the Sponsor provided electronic visual acuity system for both eyes prior to any assessment requiring administration of eye drops to dilate the eyes, or any assessment requiring contact with the eye. The system for this study is M&S Technologies' Clinical Trial Suite (CTS). The CTS is comprised of a 13-inch laptop computer and a control tablet. Background luminance is standardized and automatically calibrates to study specifications (approximately 85 cd/m^2 for photopic lighting conditions). VA optotypes are calibrated for both distance-to-subject and pixels-per-inch. The testing distance for this assessment is 4m. Visual acuity must be obtained by study personnel who have successfully completed required training to conduct the assessment.

10.2.4 Concomitant Medication

All Study Visits

Collect all medications used by the subject within the past 30 days or ongoing at time of screening. Include herbal therapies, vitamins, and all over-the-counter as well as prescription medications. Throughout the subject's participation, obtain information on any changes in concomitant medications. Follow the MOP and Case Report Form Completion Guidelines for additional information on documentation and EDC entry for routine LASIK medications and take home and non-routine medications.

10.2.5 Cycloplegic Refraction

Visit 0, Visit 5/5A

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

10.2.6 Demographics

Visit 0

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

10.2.7 Device Deficiencies

All Study Visits

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

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

10.2.8 Dilated Fundus Examination

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

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

10.2.9 InnovEyes LASIK Planning

Visit 0

Treatment planning using the InnovEyes planning software can be completed on the WaveNet Planning Station or EX500 using the exported data from the InnovEyes sightmap. The InnovEyes treatment will be based on the InnovEyes sightmap Measured refraction. Ensure sphere is between 0 and -11.00 D and cylinder is between 0 and -4.50 D, with a spherical equivalent of no more than -12.00 D (Inclusion Criteria 4). Additional details are listed in the MOP.

10.2.10 InnovEyes LASIK

Visit 00 / Visit 00A

Using the FS200 to create corneal flap, then use the EX500 laser to perform the InnovEyes LASIK based on the subject data from InnovEyes sightmap. Treatment must be performed by a qualified surgeon (no more than 2 per site). Additional details are listed in Section 9 and in the MOP.

10.2.11 InnovEyes Sightmap Assessments

Perform InnovEyes sightmap measurements according to the user manual and additional details listed in the MOP. Measurements for treatment are obtained on undilated eyes, but a cycloplegic assessment will be obtained at screening also for evaluation purposes.

Note: InnovEyes sightmap may only be used by specially trained physicians, medical staff and optometrists who are well versed in its diagnostic abilities and possible dangers and who possess the necessary skills to use it in conformity with the operating instructions contained in the User Manual.

10.2.11.1 Aberrometry

Visit 0, Visit 3/3A – 7/7A, Early Exit

Measure wavefront aberrometry using the InnovEyes sightmap according to the user manual and MOP instructions. The magnitude of the following aberrations will be collected in the database: astigmatism, coma, sphere/focus, spherical aberration, tilt, trefoil, and root mean square height (RMSh).

10.2.11.2 Biometry

Visit 0, Visit 3/3A – 7/7A, Early Exit

Measure Axial Length and Anterior Chamber Depth using the InnovEyes sightmap according to the user manual and MOP instructions.

Note: Anterior Chamber Depth is collected as Biometry data, but instructions are under Tomography in the InnovEyes sightmap user manual.

10.2.11.3 Keratometry

Visit 0, Visit 3/3A – 7/7A, Early Exit

Measure Keratometry (K1 and K2 with axis) using the InnovEyes sightmap according to the user manual and MOP instructions.

Note: Keratometry is collected separately, but instructions are under Tomography in the InnovEyes sightmap user manual.

10.2.11.4 Pachymetry (Corneal Thickness)

Visit 0, Visit 3/3A – 7/7A, Early Exit

Measure central corneal thickness using the InnovEyes sightmap according to the user manual and MOP instructions. Ensure that at least a 250 µm residual stromal bed will remain with the planned InnovEyes LASIK (Exclusion Criteria 6).

Note: Pachymetry is collected separately, but instructions are under Tomography in the InnovEyes sightmap user manual.

10.2.11.5 Topography

Visit 0, Visit 3/3A – 7/7A, Early Exit

Measure corneal topography using the InnovEyes sightmap according to the user manual and MOP instructions.

Note: The results from the topography will not be recorded in EDC.

10.2.11.6 Wavefront Refraction

Visit 0, Visit 3/3A – 7/7A, Early Exit

Measure wavefront refraction using the InnovEyes sightmap according to the user manual and MOP instructions.

10.2.12 Intraocular Pressure

Visit 0, Visit 3/3A – 7/7A, Early Exit, USV

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

10.2.13 Manifest Refraction / Subjective Refraction

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

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

Note: The chart used for subjective Manifest Refractions can depend on use of the data:

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

Note: Refraction for Inclusion Criteria 4 for myopic and astigmatic range must come from the InnovEyes sightmap Measured refraction.

10.2.14 Medical History

Visit 0 / Screening

Collect subject medical history information. Throughout the subject's participation, update if a condition ends. Follow Case Report Form Completion Guidelines for additional information.

10.2.15 Mesopic Pupil Size

Visit 0, Visit 3/3A – 7/7A, Early Exit

Measure mesopic pupil size using an infrared-based pupilometer.

10.2.17 Slit Lamp Examination

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

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

10.2.18 Uncorrected Distance Visual Acuity

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

Perform uncorrected visual acuity testing with the Sponsor provided electronic visual acuity system for both eyes prior to any assessment requiring administration of eye drops to dilate the eyes, or any assessment requiring contact with the eye. The system for this study is M&S Technologies' Clinical Trial Suite (CTS). The CTS is comprised of a 13-inch laptop computer and a control tablet. Background luminance is standardized and automatically calibrates to study specifications (approximately 85 cd/m^2 for photopic lighting conditions). VA optotypes are calibrated for both distance-to-subject and pixels-per-inch. The testing distance for this assessment is 4m. Visual acuity must be obtained by study personnel who have successfully completed required training to conduct the assessment.

10.2.19 Uncorrected Near Visual Acuity

Visit 0, Visit 5/5A

Perform uncorrected near visual acuity testing with the Sponsor provided electronic visual acuity system for both eyes prior to any assessment requiring administration of eye drops to

dilate the eyes, or any assessment requiring contact with the eye. The system for this study is M&S Technologies' CTS. The CTS is comprised of a 13-inch laptop computer and a control tablet. Background luminance is standardized and automatically calibrates to study specifications (approximately 85 cd/m^2 for photopic lighting conditions). The testing distance for this assessment is 40 cm. Visual acuity must be obtained by study personnel who have successfully completed required training to conduct the assessment.

10.2.20 Urine Pregnancy Test

Visit 0

Collect a urine pregnancy test on female subjects of childbearing potential that are not post-menopausal or surgically sterile.

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

10.3 Unscheduled Visits

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

The Investigator may perform additional procedures for proper diagnosis and treatment of the subject as needed. The Investigator must document this information in the subject's chart.

IF during an Unscheduled Visit the subject is discontinuing from the study, THEN the Investigator must conduct Early Exit procedures and discontinue the subject as per Section 10.4.

10.4 Discontinued Subjects

10.4.1 Screen Failures

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

Subject numbers must not be re-used.

10.4.2 Incomplete Treatments

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

Note: IF drops are given for surgical treatment, but no laser procedure started and the surgery needs to be rescheduled, THEN ensure to reschedule InnovEyes Treatment within protocol window or following instructions in Section 8.3.

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

10.4.3 Discontinuations

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

Subjects may discontinue from study or study treatment at any time for any reason. Subjects may also be discontinued from study or 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 treatment, the Investigator must complete all Early Exit procedures according to Table 3–1 if the subject is willing and able, and if in the opinion of the Investigator it is safe for the subject to do so.

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

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

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

10.5 Clinical Study Termination

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

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

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

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

10.5.1 Follow-up of Subjects after Study Participation has Ended

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

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

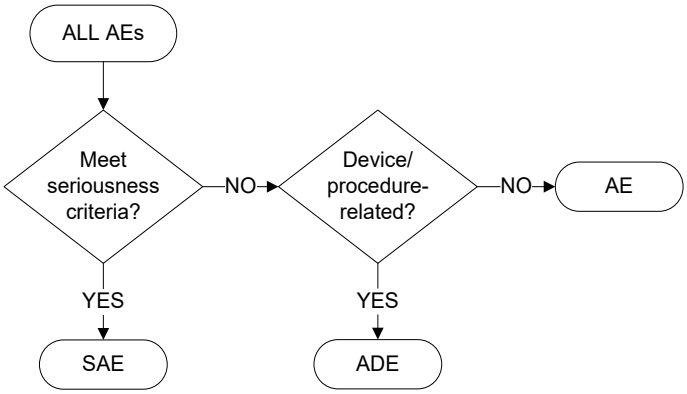
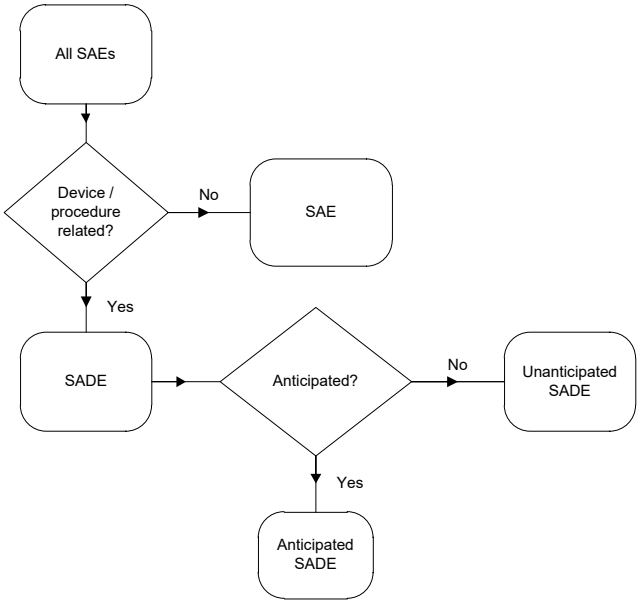


Figure 11–2 Categorization of All Serious Adverse Events



Specific Events Relevant to this Protocol

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

- Diffuse lamellar keratitis (Grade 3 or above)
- Corneal infiltrate or ulcer
- Any persistent corneal epithelial defect at one month or later
- Corneal edema at 1 month or later (specify flap or bed)
- Epithelium in the interface with loss of 2 lines (10 letters) or more BCDVA

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

The Investigator must also report the following ocular AEs:

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

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

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

Device Deficiencies

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

- Calibration issue: Error in or Unable to calibrate laser or diagnostic device
- Computer software issue or system error message
- Defective component
- Detachment of device or device component
- Device breakage (eg, headrest, chin rest, and joystick)
- Device emits odor (eg, gas leak, and smoke)
- Failure of laser firing
- Failure to meet product specifications (eg, incorrect laser assembly)
- Failure to transmit record
- Foreign material present in device
- Image display error
- Incorrect laser output energy
- Incorrect measurement
- Instructions difficult to understand/follow
- Lack of effectiveness
- Mechanical issues (e.g., failure to focus, align, track, position, or unintended system motion)
- No display or display failure
- Poor quality image
- Power issue: Equipment will not power on; power loss; or intermittent connection
- Suspect product contamination (patient interface)
- Unable to capture image
- Other events that may meet the definition of device deficiency

11.2 Monitoring for Adverse Events

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

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

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

11.3 Procedures for Recording and Reporting

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

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

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

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

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

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

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

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

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

Intensity and Causality Assessments

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

Intensity (Severity)

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

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

Causality

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

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

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

11.4 Return Product Analysis

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

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

11.5 Unmasking of the Study Treatment

Not applicable; this study is open-label.

11.6 Follow-Up of Subjects with Adverse Events

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

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

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

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

11.7 Pregnancy in the Clinical Study

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

12 ANALYSIS PLAN

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

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

12.1 Subject Evaluability

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

12.2 Analysis Sets

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

12.2.1 Safety Analysis Set

The safety analysis set (SAF) will contain all eyes that undergo surgery or attempted surgery (defined as eye drops given for flap treatment); the SAF will be the primary analysis set for the safety analyses.

12.2.2 Full Analysis Set

The full analysis set (FAS) will contain all eyes that successfully undergo surgery; the FAS will be the primary analysis set for the effectiveness analyses.

12.2.3 Consistent Cohort Analysis Set

The consistent cohort (CC) will contain all eyes in the FAS that have manifest refraction data at all post-operative visits from one month up to and including the visit where refractive stability is established. The CC will be the primary analysis set for the refractive stability analyses.

12.3 Demographic and Baseline Characteristics

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

12.4 Refractive Stability

Stability analyses will be performed on eyes that have every follow-up exam from 1-month up to the stability time point (the CC), as well as on the eyes that have 2 consecutive exams, but not necessarily every follow-up exam. The following stability analyses will be performed for the time intervals between all consecutive pairs of scheduled postoperative refractions:

- Percentage of eyes that achieve:

  - a change of less than or equal to 1.00 D of MRSE between two refractions performed at 1 month and 3 months, and between subsequent refractions performed at least 3 months apart;
  - a change of less than or equal to 0.50 D of MRSE between two refractions performed at 1 month and 3 months, and between subsequent refractions performed at least 3 months apart;

- Mean overall change and change per month in MRSE between consecutive scheduled visits as determined by a paired analysis;
- Mean ± SD MRSE for the preoperative and each postoperative visit;
- Assessment of cylinder stability for correction of spherocylindrical refractive errors

Refractive stability is achieved at the latter of two postoperative manifest refractions performed at least 3 months apart or at 3 months after surgery when compared with the 1-month interval, when all of the following recommended criteria are met:

- At least 95% of the treated eyes have a change ≤ 1.00 D of MRSE between the 2 refractions;
- The mean rate of change in MRSE, as determined by a paired analysis, is ≤ 0.5 D per year (0.04 D/month) over the same time period;
- The mean rate of change of MRSE decreases monotonically over time, with a projected asymptote of zero or a rate of change attributable to normal aging;
- The 95% confidence interval for the mean rate of change in MRSE includes zero or a rate of change attributable to normal aging; and
- Stability is confirmed at least 3 months after the stability time point by a statistically adequate subgroup (at least 80% of the cohort).

The primary safety and effectiveness endpoints for the study can only be evaluated once refractive stability has been established within the CC, as well as on the eyes that had 2 consecutive exams, but not necessarily every follow-up exam.

12.5 Effectiveness Analyses

12.5.1 Analysis of Primary Effectiveness Endpoints

In order to establish effectiveness of the WaveLight EX500 excimer laser system for the correction of myopia with and without astigmatism using InnovEyes in conjunction with InnovEyes sightmap, the following four co-primary endpoints are defined:

- Percentage of eyes with UCDVA of 20/40 (in eyes with preoperative BCDVA of 20/20 or better) or better at refractive stability (Target: ≥ 85%)
- Percentage of eyes with MRSE within 0.50 D at refractive stability (Target: ≥ 50%)
- Percentage of eyes with MRSE within 1.00 D at refractive stability (Target: ≥ 75%)
- Percentage of eyes that achieve refractive stability (Target: ≥ 95%)

12.5.1.1 Statistical Hypotheses

No hypothesis testing of the primary effectiveness endpoints is planned.

12.5.1.2 Analysis Methods

The FAS will be used for this analysis. The number and percentage of eyes meeting each of the primary effectiveness endpoints will be calculated. The effectiveness criteria will be considered to have been met if the percentage meets or exceeds the target rate at the time of refractive stability for all primary effectiveness endpoints. These analyses will be performed for the whole FAS [redacted]. An analysis will be performed once refractive stability is achieved; a final summary of these endpoints will be performed once the one year follow-up is complete.

[redacted]

12.6 Handling of Missing Data

No imputation of missing data is planned.

12.7 Safety Analyses

All adverse events occurring from the time a subject signs informed consent to study exit will be accounted for in the reporting. Safety analyses will be conducted using the SAF through descriptive summaries (counts and percentages) and listings. In addition, separate subject listings will be provided for AEs that occur in subjects:

- after signing informed consent but prior to exposure to IP (InnovEyes sightmap)
- exposed to IP (InnovEyes sightmap) but do not proceed to InnovEyes treatment (and thus are not included in the SAF)

12.7.1 Analysis of Primary Safety Endpoints

In order to establish safety of the WaveLight EX500 excimer laser system for the correction of myopia with and without astigmatism using InnovEyes in conjunction with InnovEyes sightmap, the following four co-primary endpoints are defined:

- Percentage of eyes that lose 2 lines or more of BCDVA (Target at refractive stability ≤ 5%)
- Percentage of eyes with BCDVA worse than 20/40 (for eyes with BCDVA of 20/20 or better pre-op) (Target at refractive stability ≤ 1%)
- Percentage of eyes that have an increase of manifest refractive astigmatism of greater than 2.00 D of absolute cylinder as compared to the preoperative refraction (Target at refractive stability ≤ 5%)
- Percentage of eyes with a serious, non-flap related, ocular adverse event at the postoperative visits (Target per event type at refractive stability: ≤ 1%)

12.7.1.1 Statistical Hypotheses

No hypothesis testing of the primary safety endpoints is planned.

12.7.1.2 Analysis Methods

The SAF will be used for this analysis. The number and percentage of eyes experiencing each of the primary safety endpoints will also be calculated. The safety criteria will be considered to have been met if the percentage is less than the target rate at the time of refractive stability for all of the primary safety endpoints.

[redacted]

12.8 Interim Analyses and Reporting

An analysis will be performed once refractive stability is achieved; a final analysis will be performed once the one year follow-up is complete.

12.9 Sample Size Justification

Up to 374 eyes will be treated in this study. With 374 eyes treated, any ocular serious adverse event type that occurs in at least 1% of the population undergoing the procedure will be observed in this study at least one time, with approximately 95% probability. This is in accordance with ANSI Z80.11-2012(R2017).

13 DATA HANDLING AND ADMINISTRATIVE REQUIREMENTS

13.1 Subject Confidentiality

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

The Study Sponsor may release anonymized study data to external researchers for purposes of future research directly related to the study objectives, or future research that is beyond the

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

13.2 Completion of Source Documents and Case Report Forms

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

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

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

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

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

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

The Sponsor reserves the right to collect anonymized raw data from the InnovEyes sightmap or InnovEyes software at any point of the study and at the end of the study in order to use for further review of the treatment results and for future development of the procedure.

[redacted]

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.

[redacted]

13.4 Sponsor and Monitoring Responsibilities

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

The site may not screen subjects or perform the informed consent process on any subject until it receives a notification from an appropriate Study Sponsor representative that the site may commence conducting study activities. Monitoring will be conducted periodically while the clinical study is ongoing. Monitoring methods may include site visits, telephone, written, and

email correspondence. Close-out visits will take place after the last visit of the last subject at the site.

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

Additionally, Alcon may have an expert Sponsor Representative present during screening (eg, for the collection of InnovEyes sightmap measurements) or surgery to offer training to the Investigator on proper operation of the device and/ or to make technical observations during the study visit.

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

13.5 Regulatory Documentation and Records Retention

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

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

13.6 Quality Assurance and Quality Control

The Study Sponsor will secure agreement from all involved parties to ensure direct access to all study related sites, source data and documents, and reports for the purpose of monitoring and auditing by the Study Sponsor, and inspection by domestic and foreign regulatory authorities. Quality control will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. Agreements made by the Study Sponsor

with the Investigator/Institution and any other parties involved in the clinical study will be provided in writing as part of the protocol or as a separate agreement.

14 ETHICS

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

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

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

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

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

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

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

15 REFERENCES

15.1 References Applicable for All Clinical Studies

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

15.1.1 US References Applicable for Clinical Studies

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

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

15.2 References for This Clinical Study

- ANSI Z80.11-2012 (R2017) American National Standard for Ophthalmics – Laser Systems for Corneal Reshaping
- Cummings AB, Kelly GE. Optical ray tracing-guided myopic laser in situ kertomileusis: 1-year clinical outcomes. Clinical Ophthalmol 2013;7:1181-1191.
- Eydelman MB, Drum B, Holladay J, Hilmantel G, Kezirian G, Durrie D, et al. Standardized analyses of correction of astigmatism by laser systems that reshape the cornea. J Refract Surg 2006;22:81-95.

- Simon D, Schumacher S, Mrochen M. Ray Tracing: the Future of Refractive Surgery. Cataract & Refractive Surgery Today. August 2011(55-56).
- Schumacher S, Seiler T, Cummings A, Maus M, Mrochen M. Optical ray tracing-guided laser in situ keratomileusis for moderate to high myopic astigmatism. J Cataract Refract Surg. 2012;38(1):28–34.

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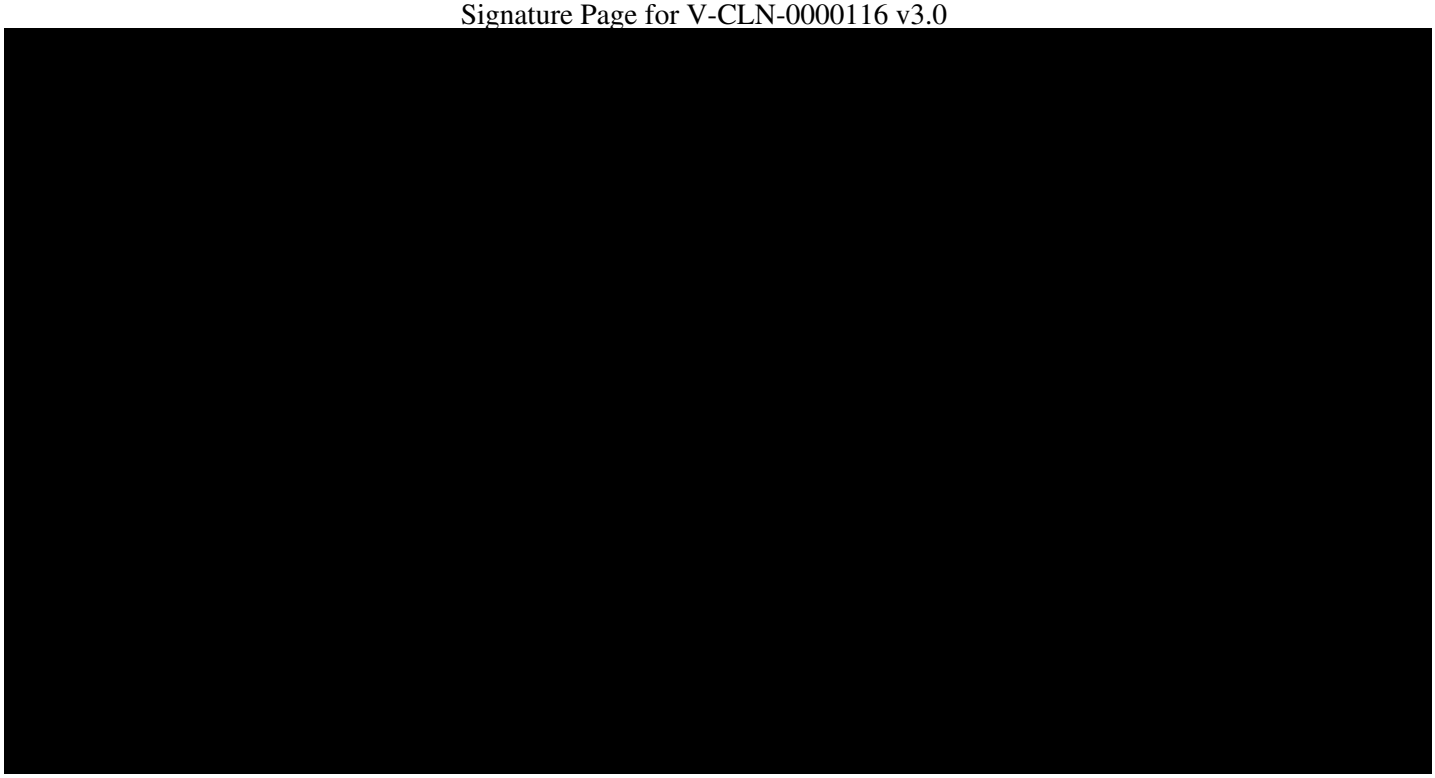

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