Title

Comparison between iLux and LipiFlow in the treatment of Meibomian Gland Dysfunction (MGD): A 12-month, Multicenter study

Protocol Number:	DEG723-P001 / NCT03956225
[redacted]	[redacted]
Sponsor Name and Address:	Alcon Research, LLC and its affiliates ("Alcon") 6201 South Freeway Fort Worth, Texas 76134-2099
Test Product:	iLux® Device

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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[redacted]

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1 GLOSSARY OF TERMS

Names of test product(s)	Throughout this document, test product(s) will be referred to as iLux
Name of Control Product(s)	LipiFlow® Thermal Pulsation System (LipiFlow)
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	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.
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.
Postmarketing/Post-authorization study	Any study conducted within the conditions laid down in product labelling and other conditions laid down for the marketing of the product or under normal conditions of use. A postmarketing study falls either within the definitions of an interventional or a non- interventional study and may also fall within the definition of a post-approval study.
Product Complaints	Any oral, electronic, or written communication that alleges deficiencies related to the identity (labeling), quality, durability, reliability, safety, effectiveness, or performance of a marketed product, including failure of the product, labeling or packaging to meet specifications, whether or not the product is related to or caused the alleged deficiency. A complaint may allege that an adverse event or medical device malfunction has occurred.
Randomized Subjects	Any subject who is assigned a randomized treatment.
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.*
Serious Public Health Threat	Any event type which results in imminent risk of death, serious deterioration in state of health, or serious illness that requires prompt remedial action. This would include: Events that are of significant and unexpected nature such that they become alarming as a potential public health hazard, eg, human immunodeficiency virus (HIV) or Bird Flu.
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
°C	Degrees Celsius
[redacted]	[redacted]
CFR	Code of Federal Regulations
CI	Confidence interval
COL	Clinical Operations Lead
CRF	Case report form
CSM	Clinical Site Manager
DEP	Deviations and evaluability plan
DFU	Directions for use
ECP	Eye Care Professionals
eCRF	Electronic case report form
EDC	Electronic data capture
EDE	Evaporative dry eye
°F	Degrees Fahrenheit
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
[redacted]	[redacted]
IEC	Independent ethics committee
iLux	iLux System
IP	Investigational product
IRB	Institutional review board
IRT	Interactive response technology
ISO	International Organization for Standardization
LCL	Lower confidence limit
LED	Light emitting diode
LipiFlow	LipiFlow Thermal Pulsation System
MG	Meibomian gland
MGD	Meibomian Gland Dysfunction
MGE	Meibomian Gland Evaluator
MGS	Meibomian Gland Score
MOP	Manual of procedures
n	Number
N/A	Not applicable

Abbreviation	Definition
NI	Noninferiority
[redacted]	[redacted]
OD	Right eye
OS	Left eye
[redacted]	[redacted]
OU	Both eyes
[redacted]	[redacted]
SADE	Serious adverse device effect
SAE	Serious adverse event
SD	Standard deviation
SOP	Standard operating procedure
SP	Statistical Programmer
[redacted]	[redacted]
US	United States
USADE	Unanticipated serious adverse device effect
USV	Unscheduled visit
[redacted]	[redacted]

3 PROTOCOL SUMMARY

Investigational product type	Device
Study type	Interventional
Investigational products	Test Product: iLux Device (iLux) Control Product: LipiFlow Thermal Pulsation System (LipiFlow)
Purpose and rationale	The purpose of this study is to demonstrate that iLux MGD treatment is comparable to LipiFlow MGD treatment at 12 months post single treatment.
Objective(s)	The primary objective of this study is to demonstrate noninferiority of iLux when compared to LipiFlow in change from baseline in Meibomian Gland Score (MGS) at 12 months post single treatment in MGD subjects with evaporative dry eye disease (EDE).

	[redacted]
Endpoint(s)	Primary Effectiveness • Mean change from baseline in MGS [redacted]

	[redacted] Safety • AEs • Biomicroscopy findings • Device deficiencies
Assessment(s)	Effectiveness • Meibomian gland functionality assessment [redacted] Safety • AEs • Biomicroscopy • Device deficiencies
Study Design	This is a prospective, randomized, assessor-masked, parallel group study comparing the iLux to LipiFlow in subjects with EDE. Subjects will be randomized for bilateral treatment in a 1:1 ratio to receive a single treatment with either iLux or LipiFlow. Subjects will be expected to attend a total of 8 visits (Screening/Baseline, Treatment, 2-Week Follow-up, 1-Month Follow-up, 3-Month Follow-up, 6-Month Follow-up, 9-Month Follow-up and 12 - Month Follow-up/Exit).

Subject population	The study population will consist of adult male and female subjects ≥ 18 years old at the time of informed consent. Subjects must have signs and symptoms of EDE in both eyes. Planned number of subjects enrolled/consented: ~278 Required number of completed subjects: 188
Key inclusion criteria (See Section 8.1 for a complete list of inclusion criteria)	Adult male and female subjects ≥ 18 years of age who have signs and symptoms of EDE in both eyes.
Key exclusion criteria (See Section 8.2 for a complete list of exclusion criteria)	Subjects with uncontrolled systemic diseases that cause dry eye or those who are uncontrolled on medical therapy. Subjects who are unwilling and/or unable to complete the study visits as outlined in the protocol. Subjects who have received either the iLux or the LipiFlow treatment in the past 12 months.
Data analysis and sample size justification	**Planned Analysis** To address the primary [redacted] effectiveness objectives, planned analyses are summarized below:

Endpoint	**Comparison**	**Statistical Method**
Primary		
Change from baseline in MGS	iLux vs LipiFlow Noninferiority (NI margin = 5)	Mixed effects repeated measures
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

Sample Size Justification

Sample size calculations for primary [redacted] summarized below:

Endpoint	Assumptions	Type I error	N per group
Primary			
Change from baseline in MGS	Common SD = 0.068 NI margin = 7	One-sided 0.05	94
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]

Key words	Evaporative dry eye disease, Meibomian gland dysfunction

Associated materials	• The Johnson & Johnson Vision Meibomian Gland Evaluator (MGE)
	• iLux
	  o iLux instrument with protective cap
	  o Charging Stand with Power Supply
	  o Smart Tip Patient Interface
	  o Laptop computer for data download
	• LipiFlow
	  o LipiFlow disposable patient interface

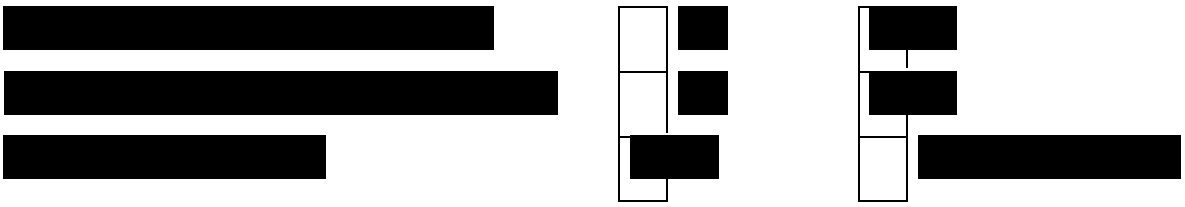
Table 3–1 Schedule of Study Procedures and Assessments

Visit	Visit 1 Screening / Baseline	Visit 2 Treatment	Visit 3 2-Week Follow-up	Visit 4 1-Month Follow-up	Visit 5 3-Month Follow-up	Visit 6 6-Month Follow-up	Visit 7 9-Month Follow-up	Visit 8 12-Month Follow-up/ Exit	Unscheduled Visit / Early Exit
Day Number	Day 0	1 – 7 days after screening	14 days (post treatment) ± 3 days	30 days (post treatment) ± 3 days	90 days (post treatment) ± 7 days	180 days (post treatment) ± 14 days	270 days (post treatment) ± 25 days	365 days (post treatment) ± 45 days	N/A
Informed Consent	✓	-	-	-	-	-	-	-	-
Demographics	✓	-	-	-	-	-	-	-	-
Medical History	✓	-	-	-	-	-	-	-	-
Concomitant Medications	✓	✓	✓	✓	✓	✓	✓	✓	✓
Inclusion/Exclusion	✓	-	-	-	-	-	-	-	-
[redacted]									
[redacted]									
[redacted]									
[redacted]									
[redacted]									
Biomicroscopy †	✓	✓∞	✓	✓	✓	✓	✓	✓	✓

Visit	Visit 1 Screening / Baseline	Visit 2 Treatment	Visit 3 2-Week Follow-up	Visit 4 1-Month Follow-up	Visit 5 3-Month Follow-up	Visit 6 6-Month Follow-up	Visit 7 9-Month Follow-up	Visit 8 12-Month Follow-up/ Exit	Unscheduled Visit / Early Exit
Day Number	Day 0	1 – 7 days after screening	14 days (post treatment) ± 3 days	30 days (post treatment) ± 3 days	90 days (post treatment) ± 7 days	180 days (post treatment) ± 14 days	270 days (post treatment) ± 25 days	365 days (post treatment) ± 45 days	N/A
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Meibomian gland functionality assessment †	✓	-	✓	✓	✓	✓	✓	✓	-
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Randomization	-	✓	-	-	-	-	-	-	-
Treatment	-	✓	-	-	-	-	-	-	-
AEs	✓	✓	✓	✓	✓	✓	✓	✓	✓
Device deficiencies	-	✓	-	-	-	-	-	-	-
Exit form	(✓)	(✓)	(✓)	(✓)	(✓)	(✓)	(✓)	✓	(✓)

[redacted] (✓) As applicable

[redacted]



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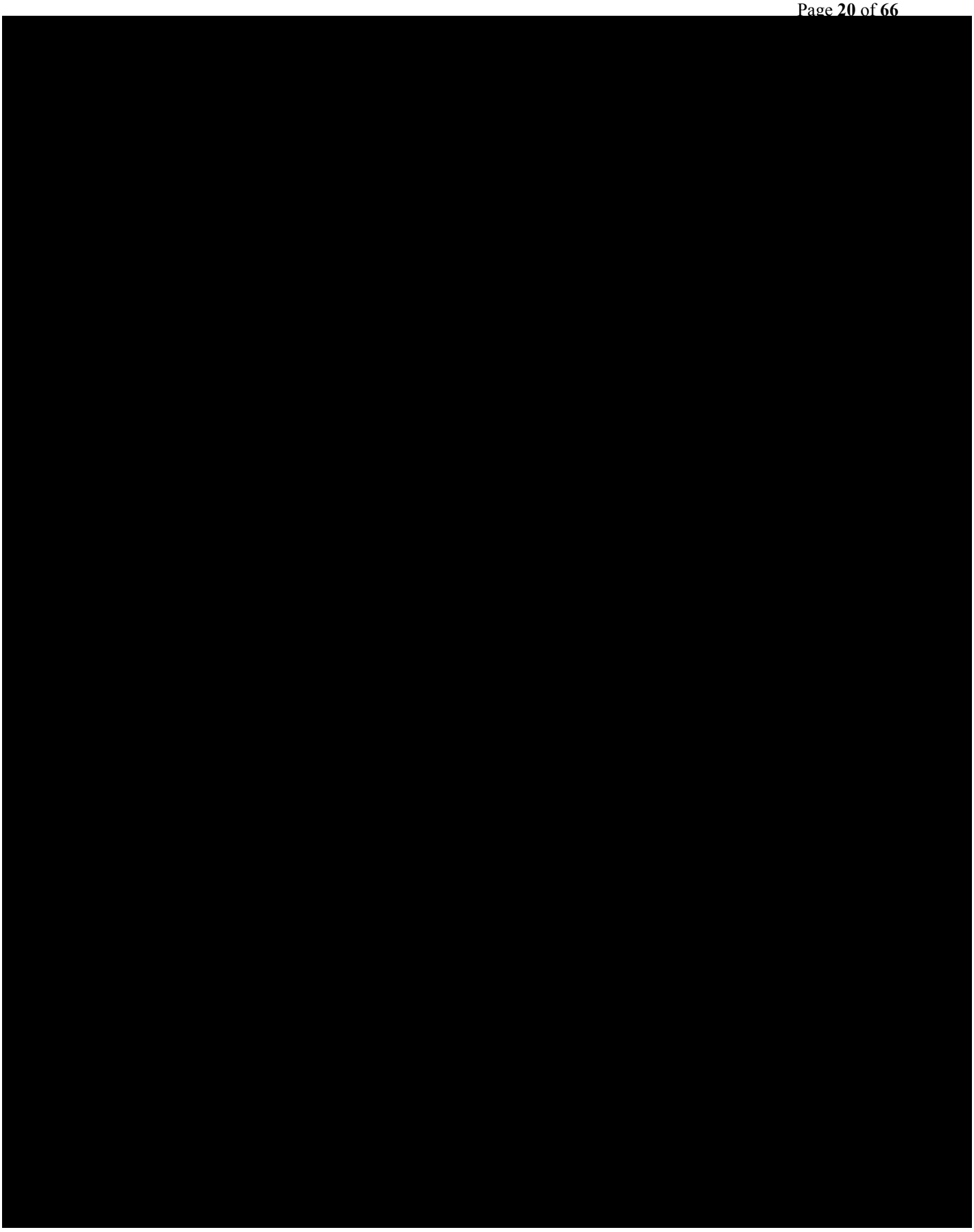

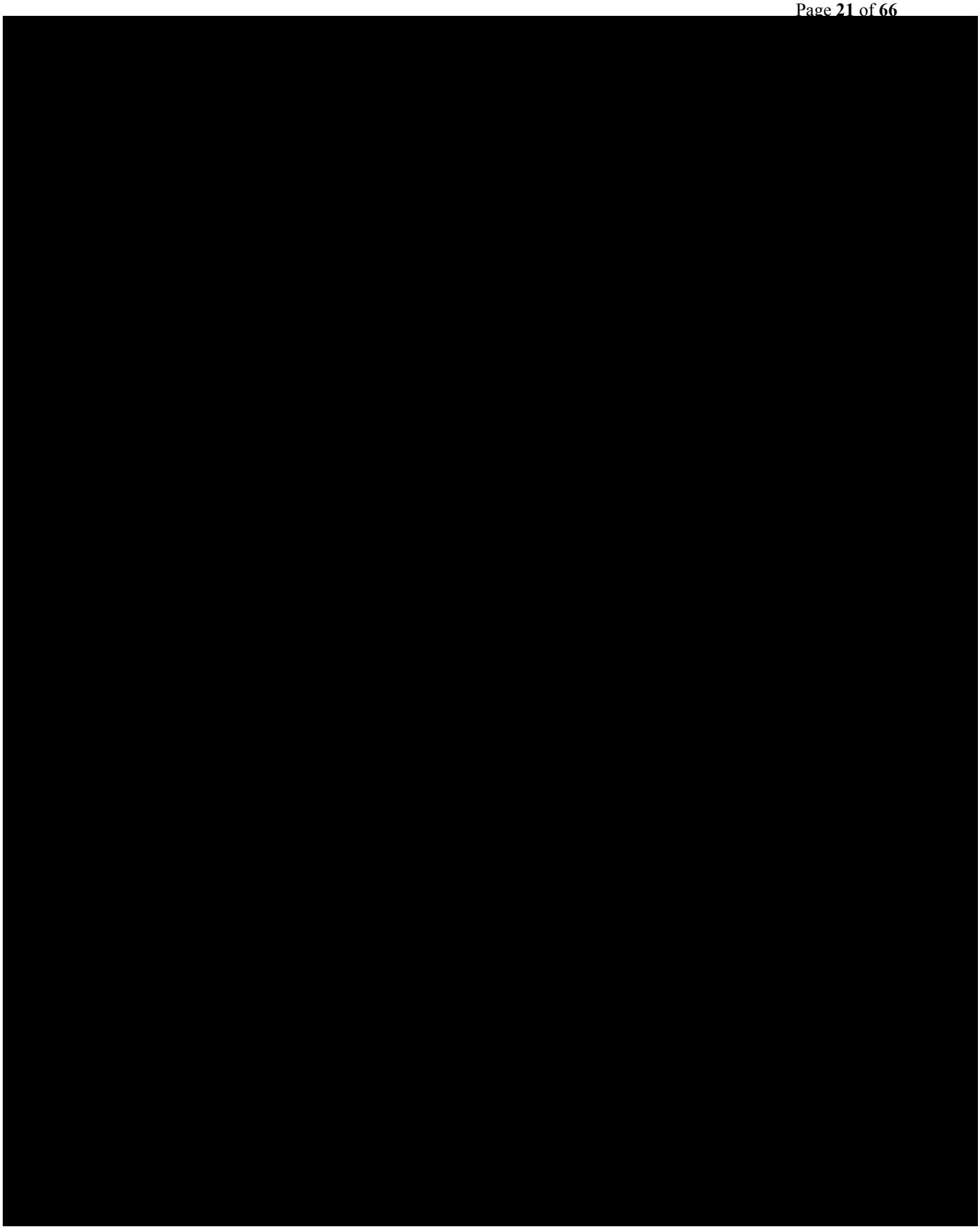

[redacted]

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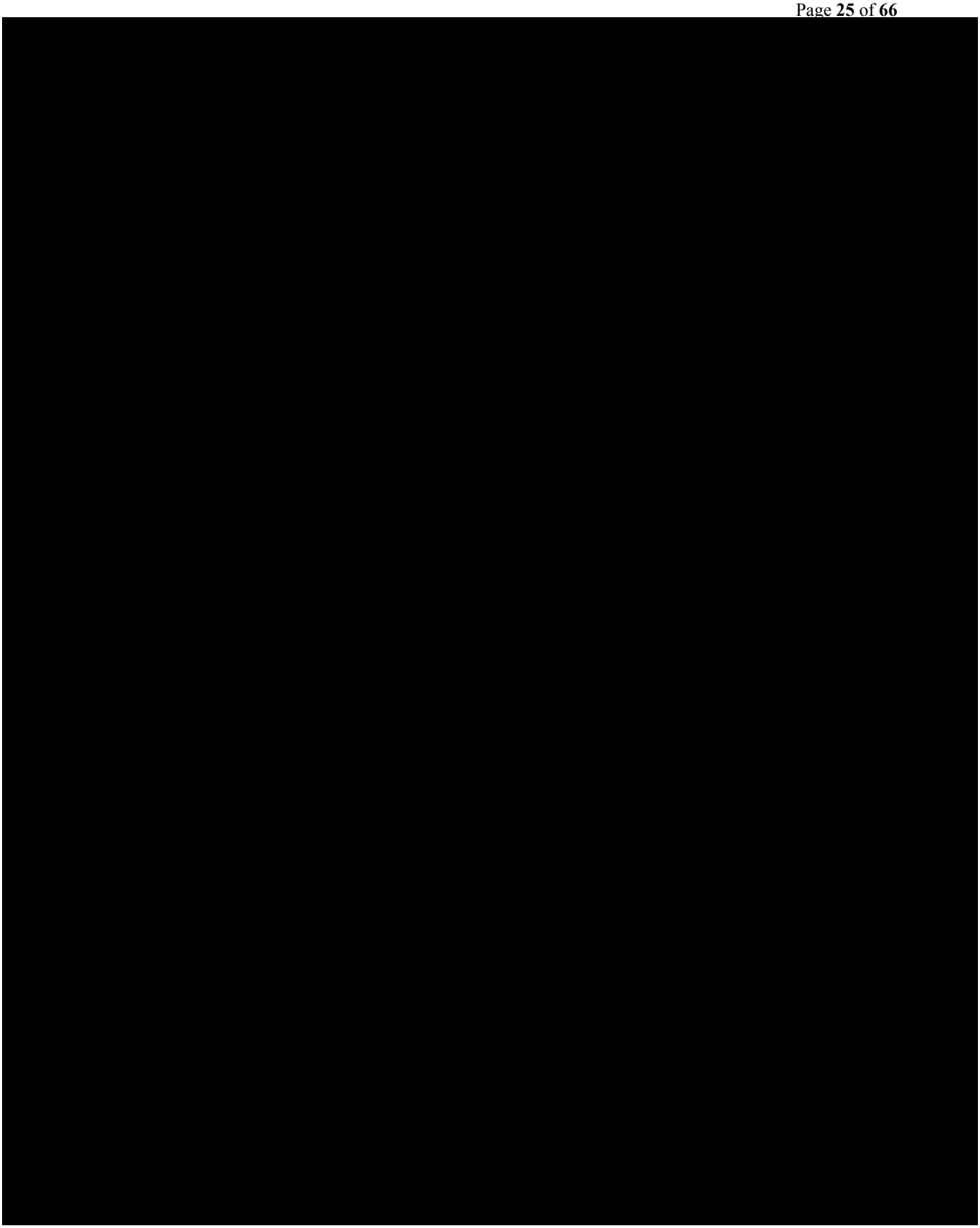

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[redacted]

[redacted]

[redacted]

5 INTRODUCTION

5.1 Rationale and Background

Meibomian glands are located in the tarsal plate of the upper and lower eyelids, where they terminate along the interior rim (or margin) of the eyelids. These glands secrete meibum, which is a lipid-rich essential component of a healthy tear film. When sufficient meibum is not present in the tear film matrix, the aqueous layer of the tear film is disrupted and readily evaporates resulting in irritation, redness, and inflammation of the lid margin and ocular surface. MGD is associated with a failure of these glands to produce adequate quality and quantity of meibum due to atrophy, inflammation, or obstruction, and is thought to be the most common cause of evaporative dry eye disease (Schaumberg 2011).

MGD is one of the most common ophthalmic conditions found in clinical practice. Yet, MGD is often under-diagnosed. Clearing meibomian gland (MG) obstruction may also mitigate the chronic pathologic progression of MGD, including atrophy of the glands. Population-based studies have reported a prevalence of MGD ranging from 3.5% to 69.3% with differences among studies by race/ethnicity and parameters used to define presence of MGD. Furthermore, studies have shown that 61.7% to 86% of those with dry eye symptoms have clinical signs of MGD (Lekhanont 2006, Lin 2003, Lemp 2012). According to the International Workshop on MGD Report published in 2011, "*MGD may well be the leading cause of dry eye disease throughout the world"* (Nichols 2011).

A common clinical treatment to improve meibomian gland function in patients with obstructive MGD involves the application of heat and pressure therapy to the eyelids to express the meibum and other material from the gland (Lekhanont 2006). Warming the eyelid tissue softens or melts the meibum, which is known to facilitate expression using pressure.

The iLux System is a commercially available medical device designed for use by the Eye Care Professional (ECP) to apply localized heat and pressure therapy to a patient's eyelids.

Warming is accomplished using light energy emitted from LED in this instrument. A mechanism in this device allows the operator to apply pressure to the eyelid by controlling the movement of the outer pad using finger pressure applied to the compression control button.

The LipiFlow Thermal Pulsation System is a commercially available medical device for use by the ECP to provide localized heat and pressure therapy to adult patients with chronic conditions of the eyelids, including MGD.

Additional information on both devices can be found in their respective DFUs.

5.2 Purpose of the Study

The purpose of this post-approval study is to demonstrate that iLux MGD treatment offers comparable treatment effectiveness to LipiFlow MGD treatment at 12 months post single treatment.

The primary objective of this study is to demonstrate noninferiority of iLux when compared to LipiFlow in change from baseline in (MGS at 12 months post single treatment in MGD subjects with EDE.

[redacted]

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

[redacted]

5.3 Risks and Benefits

The iLux and LipiFlow devices are non-significant risk devices because they do not meet FDA's criteria for a significant risk device in that the product poses no significant risk to the subject. Potential benefit of iLux treatment is unblocking the inspissated and/or obstructed meibomian glands and expression of the contents of the MG via heating and expression.

Known potential risks may include:

- Eyelid/eye pain requiring discontinuation of the treatment procedure

- Eyelid irritation or inflammation
- Temporary reddening of the skin
- Ocular surface irritation or inflammation (eg, corneal abrasion, conjunctive edema or conjunctival injection (hyperemia))
- Ocular symptoms (eg, burning, stinging, tearing, itching, discharge, redness, foreign body sensation, visual disturbance, sensitivity to light)

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

Risks associated with the LipiFlow can be found in the DFU.

6 STUDY OBJECTIVES

6.1 Primary Objective(s)

Table 6–1 Primary Objective(s)

Objective(s)	Endpoint(s)
The primary objective of this study is to demonstrate noninferiority of iLux when compared to LipiFlow in change from baseline MGS at 12 months post single treatment in MGD subjects with EDE.	Change from baseline in MGS at the 12-Month Follow-up Visit

6.2 Secondary Objective(s)

Table 6–2 Secondary Objective(s)

Not applicable.

[redacted]

[redacted]

6.4 Safety Objective(s)

Table 6–4 Safety Objective(s)

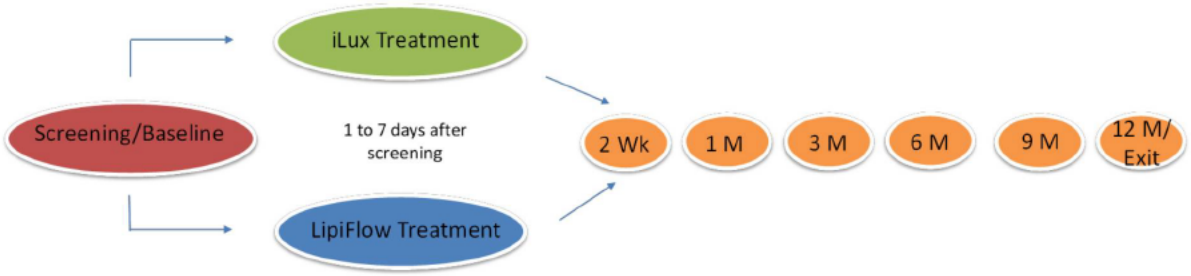
Objective(s)	Endpoint(s)
Describe the safety profile of the investigational products	• AEs • Biomicroscopy findings • Device deficiencies

7 INVESTIGATIONAL PLAN

7.1 Study Design

This is a prospective, randomized, assessor-masked, parallel group study comparing the iLux to the LipiFlow in subjects with EDE.

Subjects will be randomized for bilateral treatment in a 1:1 ratio to receive a single treatment with either the iLux or LipiFlow. Subjects will be expected to attend a total of 8 visits (Screening / Baseline, Treatment, 2-Week Follow-up, 1-Month Follow-up, 3-Month Follow-up, 6-Month Follow-up, 9-Month Follow-up, and 12-Month Follow-up/Exit).


iLux Treatment
Screening/Baseline
1 to 7 days after screening
LipiFlow Treatment
2 Wk
1 M
3 M
6 M
9 M
12 M/ Exit

[redacted]

[redacted]

[redacted]

[redacted]

[redacted].

7.4 Rationale for Choice of Control Product

The LipiFlow is a commercially available device used in the treatment of MGD. It is cleared to be marketed by the United States Food and Drug Administration and will be used as the control device in this study.

There are several reusable warm compresses available for at home management of MGD; however, the LipiFlow is the only commercially available in office device that uses localized heat and pressure (thermal pulsation) therapy for the treatment of MGD similar to the test device. Hence, LipiFlow will serve as a control product in this study.

7.5 Data Monitoring Committee

Not applicable.

8 STUDY POPULATION

The study population will consist of adult male and female subjects ≥ 18 years old at the time of informed consent who have signs and symptoms of EDE in both eyes. The aim is to enroll

(consent) approximately 278 subjects, with a target to randomize 236 subjects, and complete 188 subjects at approximately 15 sites in the US. Site-specific targets may vary based upon individual site capabilities. [redacted]

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.

8.1 Inclusion Criteria

Subjects eligible for inclusion in this study must fulfill **all** of the following criteria. When criteria are ocular, both eyes must meet criteria.

1. Subject must be 18 years of age or older at the time of informed consent
2. Subject must be able to understand and must sign an ICF that has been approved by an IRB
3. Subject must be willing and able to attend all study visits

[redacted]

7. Subject agreement to not wear contact lenses for the duration of the study

8.2 Exclusion Criteria

Subjects fulfilling **any** of the following criteria are not eligible for participation in this study. When criteria are ocular, the subject is not eligible if either eye meets criteria.

1. History of (laser) refractive surgery or vitreo-retinal surgery

[redacted]

7. Active ocular infection or active ocular inflammation (including allergic conjunctivitis, vernal or giant papillary conjunctivitis) or history of chronic, recurrent severe ocular inflammation within the 3 months prior to Screening

8. Lid surface abnormalities that affect lid function in either eye

[redacted]

[redacted]

14. Eyelid tattoos, including permanent eyeliner makeup
15. Individuals who were treated with LipiFlow or iLux in either eye in the last 12 months
16. Contact lens wear within the 1 month prior to Screening

Women of childbearing potential or women who are pregnant at the time of study entry are not excluded from participation. [redacted]

9 TREATMENTS ADMINISTERED

9.1 Investigational Product(s)

Test Product(s): iLux Device

Control Product(s) (If applicable): LipiFlow Thermal Pulsation System

Table 9–1 Test Product

Test Product	iLux (Gen 1.5)
Manufacturer	TearFilm Innovations, Inc. 12625 High Bluff Drive, Suite 107 San Diego, CA 92130
Indication for use and intended purpose in the current study	The iLux is indicated for the application of localized heat and pressure therapy in adult patients with MGD, also known as EDE. The iLux includes the following: o iLux instrument with protective cap o Charging Stand with Power Supply o Smart Tip Patient Interface o Laptop computer for data download
Product description and parameters available for this study	The iLux instrument records data during operation that is useful for evaluating performance and usage. The software application, associated computer, and data docking station provides the capability to download this data. Refer to the DFU for product description and parameters.
Formulation	N/A
Usage	The iLux is a commercially available, FDA cleared medical device intended for use by qualified ECPs to apply localized heat and pressure therapy to adult patients' lower or upper eyelids.
Packaging description	The Carrying Case holds the Instrument, Charging Stand, Power Supply, User Manual and Protective Cap.

	The study laptop will be provided separately from the Carrying Case. The Smart Tip Patient Interface is provided in separate sterile packaging.
Labeling description	Refer to the DFU/User Manual
Storage conditions	Test product must be stored in a safe, secure location with limited access separated from general stock. Avoid exposing the iLux or Smart Tip Patient Interface to temperatures above 40°C (104°F) or below 10°C (50°F). Refer to the DFU/User Manual for additional instructions.
Supply	Alcon will provide the iLux and associated consumables.

Table 9–2 Control Product

Control Product(s)	LipiFlow Thermal Pulsation System
Manufacturer	Johnson & Johnson Vision
Indication for Use	The LipiFlow is intended for the application of localized heat and pressure therapy in adult patients with chronic cystic conditions of the eyelids, including MGD, also known as EDE or lipid deficiency dry eye.
Product description and parameters available for this study	Console, Model LFTP-1000 Activator, Model LFD – 1000, LFD -1100, (disposable) for single patient use and Activator II (Model LFD-2000) with the new semi-permanent Cable (Model CBL-2000) Refer to the DFU for product description and parameters.
Formulation	N/A
Usage	The LipiFlow is a commercially available device used in the treatment of MGD. It is cleared to be marketed by the US FDA and will be used as the control device in this study.

Number/Amount of Product to be Provided to the subject	Sites will utilize their own LipiFlow and associated consumables.
Packaging description	Refer to the DFU
Labeling description	Refer to the DFU/User Manual
Storage conditions	Refer to the DFU/User Manual for instructions
Supply	Sites will utilize their own LipiFlow and associated consumables.

The iLux and LipiFlow must be maintained within specified environmental conditions, as described in their respective DFUs.

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

Anesthetic eye drops shall be instilled in both eyes prior to treatment.

No other medical devices or medications are required to be used in conjunction with the treatments during the clinical study.

9.3 Treatment Assignment / Randomization

Subjects will be randomized in a 1:1 ratio to receive bilateral treatment with either iLux or LipiFlow, respectively.

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

A randomization list will be generated using a validated system that automates the random assignment of treatment arms to randomization numbers in the specified ratio. Subjects will be assigned treatment according to the randomization list uploaded in the IRT system. The randomization list will be generated and maintained by the Study Sponsor.

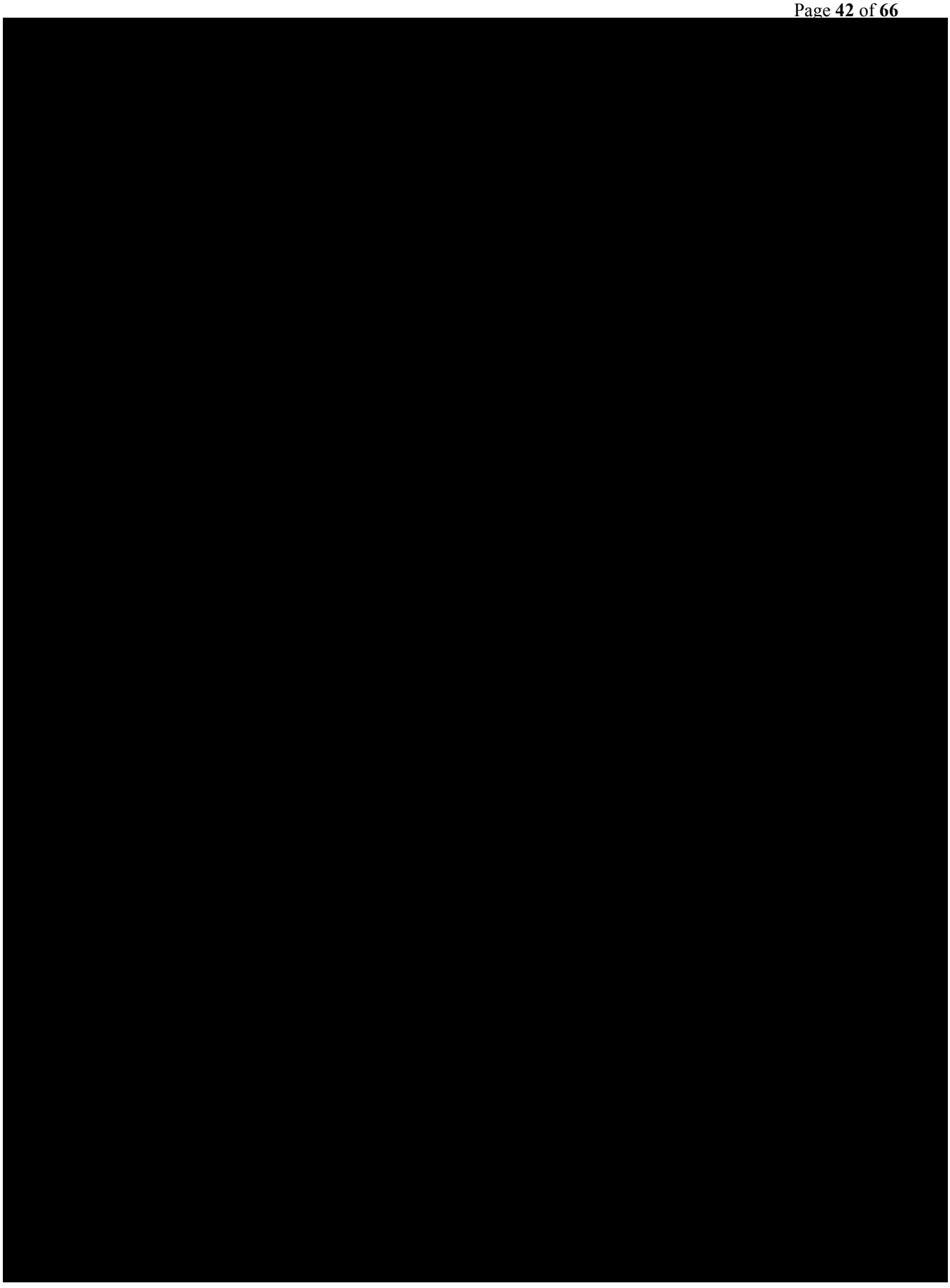
IRT

At Visit 2, all eligible subjects will be randomized via the EDC/IRT integration system to one of the treatment arms. The Investigator or delegate will access the respective system after confirming that the subject meets all the eligibility criteria. A randomization number will be automatically assigned to the subject according to the subject randomization list but will not be communicated to the site user. The EDC/IRT integration system will inform the site user of the treatment assignment to be assigned to the subject.

9.4 Treatment masking

This study is assessor-masked with subjects randomized to receive bilateral treatment with either iLux or LipiFlow at Visit 2 with follow-up up at various timepoints during a 12-month study period. Masked assessors will remain masked to the subject's study treatment assignment throughout the duration of the study. [redacted]

[redacted]



[redacted]

9.5 Accountability Procedures

Upon receipt, the Investigator or delegate must conduct an inventory of all IP, and IP-related accessories by serial number and/or lot number, complete study-specific confirmation of receipt procedures as described in the MOP, and retain any required documentation in the Investigator's clinical study records. Throughout the study, the Investigator or delegate must maintain records of IP use for each subject. This record must be made available to the study monitor for the purposes of verifying the accounting of IP supplies. 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 to the Study Sponsor study-related Alcon products associated with a device deficiency. 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 reconciliation and return of the iLux and all used and unused accessory items 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.

The use of systemic medications known to cause dry eye is allowed, as long as the subject is on a stable dosage regimen for at least 1 month prior to the Screening Visit and must be on the same regimen for the duration of their participation in the study (see Exclusion Criteria 10). Subjects who are not on a stable regimen for at least 1 month prior to the Screening Visit should not be enrolled in the study. If there is a change in a subject's medication regimen while participating in the study, the subject should notify the Site immediately.

10 STUDY PROCEDURES AND ASSESSMENTS

10.1 Informed Consent and Screening

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

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

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 responsibilities for all procedures and assessments are delegated to appropriately qualified site personnel.

10.2.1 Demographics

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

10.2.2 Medical History

Medical History includes both ocular and nonocular conditions, which are ongoing or resolved within 3 months of the Informed Consent date.

Collect information on all medications taken within the 30 days prior to the Informed Consent date. Include herbal therapies, vitamins, and all over-the-counter as well as prescription medications.

Throughout the subject's participation, obtain information on any changes in medical health and/or the use of concomitant medications.

10.2.3 Adverse Event Collection: Safety Assessment

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

10.2.4 Slit-Lamp Biomicroscopy: Safety Assessment

A slit-lamp exam must be performed on both eyes at every visit. Any significant changes to the cornea and conjunctiva will be recorded.

10.2.5 Device Deficiencies: Safety Assessment

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

Examples of device deficiencies include the following:

- Excessive or unintended exposure
- Incorrect temperature displayed
- Rapid heating
- Excessive pressure
- Unretractable instrument
- Damaged disposable tip
- Error message displayed
- Suspect product contamination
- Unsealed device packaging

Additional information can be found in the DFU/User manual.

10.3 Unscheduled Visits

An unscheduled visit (USV) is defined as follows:

- Ocular examination that is not standard of care and is not required by the protocol,
- Examination conducted by the study staff, and
- New clinically significant ocular health findings, or a change to a previous finding was discovered

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

During all unscheduled visits, the Investigator must conduct the following procedures:

- Collect AE information
- Record changes in medical condition or concomitant medication
- Biomicroscopy

The Investigator may perform additional procedures for proper diagnosis and treatment of the subject. The Investigator must document this information in the subject's case history source documents.

If during an Unscheduled Visit the subject is discontinuing from the study, the Investigator must conduct Early Exit procedures according to Table 3-1 Schedule of Study Procedures and Assessments, as possible.

10.4 Discontinued Subjects

10.4.1 Screen Failures

Subjects who discontinue from the study after signing the informed consent and prior to randomization will be categorized as screen failures.

The Investigator must document the reason for screen failure in the subject's case history source documents and enter the subject in the EDC.

[redacted]

10.4.2 Discontinuations

Discontinued subjects are individuals who have signed an ICF and who voluntarily withdraw or are withdrawn from the study by the Investigator post-randomization. Any subject receiving a subsequent treatment with the iLux or LipiFlow during the study period at any time will be exited from the study.

Discontinued subjects will not be replaced; subject numbers of discontinued subjects must not be re-used.

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

For subjects discontinuing from the study, the Investigator must complete all Early Exit procedures according to Table 3-1 Schedule of Study Procedures and Assessments, if the subject is willing and able, and if in the opinion of the Investigator it is safe for the subject to do so.

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

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

Subjects discontinuing from the trial for any reason will continue to follow up with their eye care provider as applicable.

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

Not Applicable

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 which may include completion of exit visit procedures.
- 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.

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

Figure 11–1 Categorization of All Adverse Events

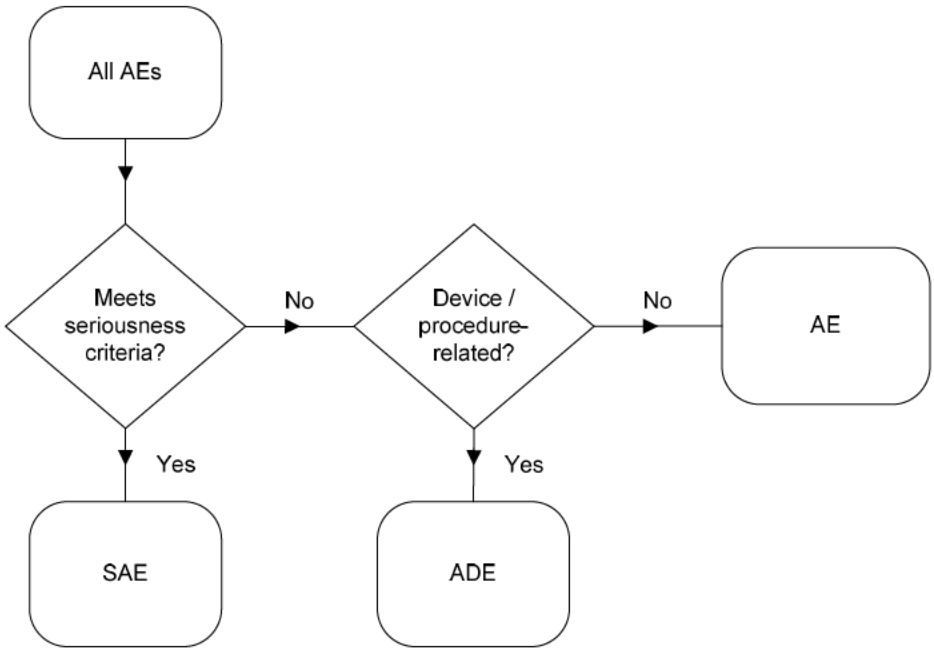
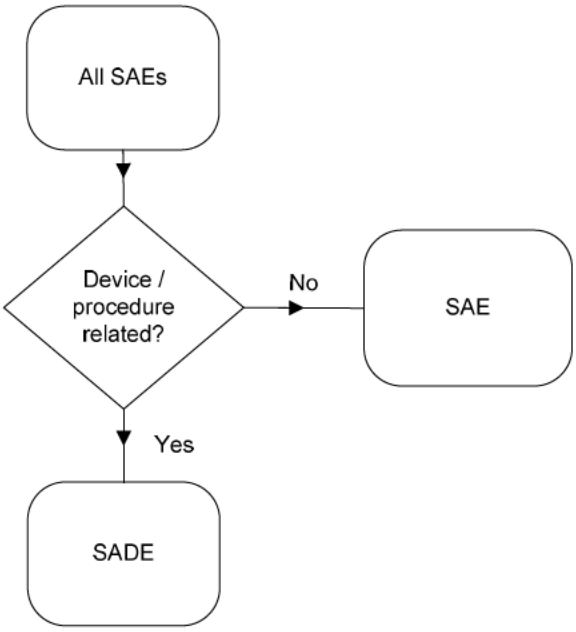


Figure 11-2 Categorization of All Serious Adverse Events



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 subject harm separately.

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:

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

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

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.

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 articles on the Device Deficiency eCRF. The site must submit all available information on ADEs, SAEs, and device deficiencies to the Study Sponsor immediately as follows:

- All SAEs must be reported immediately (within 24 hours) of the Investigator's or site's awareness.
- ADEs that do not meet seriousness criteria and device deficiencies must be reported within 10 calendar days of the Investigator's or site's awareness.

- A printed copy of the completed ***Serious Adverse Event and Adverse Device Effect*** and/or ***Device Deficiency*** eCRF must be included with product returns. Refer to the MOP for additional information on 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 Adverse Device Effect (for related AEs) and Serious Adverse Event eCRF.

  Note: Should the EDC system become non-operational, the site must complete the appropriate paper ***Serious Adverse Event and Adverse Device Effect*** and/or *Device Deficiency* 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 (ie, LipiFlow, Johnson & Johnson Vision) will be considered and processed as spontaneous (following the postmarket vigilance procedures) and should be communicated to the device's/product's manufacturer as per local requirements.

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

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

11.4 Return product analysis

Study Sponsor representatives and their contact information are provided in the Manual of Procedures 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.

All Alcon products used or unused, regardless of AE/Device Deficiency association will be returned at the end of the enrollment period as instructed by the Sponsor.

11.5 Unmasking of the Study Treatment

Masked information on the identity of the assigned medical device should not be disclosed during the study (see Section 9.4 of the protocol). If the treatment code needs to be broken in the interest of subject safety, the Investigator is encouraged to contact an appropriate Study

Sponsor representative prior to unmasking the information if there is sufficient time. Dependent upon the individual circumstances (ie, medical emergency), the code may be broken prior to contact with the Study Sponsor. The Study Sponsor must be informed of all cases in which the code was broken and of the circumstances involved. Additionally, the Study Sponsor may be required to unmask the information in order to fulfill expedited regulatory reporting requirements.

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).

All complaints received after this time period will be considered and processed as spontaneous (following the postmarket vigilance procedures) and should be communicated to the medical device's manufacturer as per local requirements.

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

11.7 Pregnancy in the Clinical Study

Women of childbearing potential or women who are pregnant at the time of study entry are not excluded from participation. Pregnancy is not reportable as an AE; however, complications may be reportable and will be decided on a case–by-case basis. [redacted]

12 ANALYSIS PLAN

Continuous variables will be summarized using the number of observations, mean, standard deviation (SD), median, minimum, and maximum, as well as confidence intervals or confidence limits where applicable. Categorical variables will be summarized with counts and percentages from each category. Any deviations to the analysis plan will be updated

during the course of the study as part of a protocol amendment or will be detailed in the clinical study report.

12.1 Subject Evaluability

Final subject evaluability must be determined prior to breaking the code for masked treatment assignment and locking the database, based upon the Deviations and Evaluability Plan (DEP).

12.2 Analysis Sets

12.2.1 Safety Analysis Set

Safety analyses will be conducted using the safety analysis set on a treatment-emergent basis. As such, the safety analysis set will include all subjects/eyes exposed to any study treatment. For treatment-emergent safety analyses, subjects/eyes will be categorized under the actual study treatment exposed.

12.2.2 Full Analysis Set

The full analysis set (FAS) is the set of all randomized subjects who are exposed to any study treatment.

[redacted]

12.3 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized by treatment group and overall. Counts and percentages will be presented for categorical variables such as sex, age group, race, and ethnicity. Number of observations, mean, SD, median, minimum, and maximum will be presented for continuous variables such as age.

12.4 Effectiveness Analyses

This study defines 1 primary, [redacted] endpoints, [redacted] will use the FAS as the primary analysis set. [redacted]

[redacted]

12.4.1 Analysis of Primary Effectiveness Endpoint(s)

The primary objective of this study is to demonstrate noninferiority in change from baseline in MGS with iLux compared to LipiFlow at 12 months following a single treatment. The primary endpoint, change from baseline in MGS, is derived from MGS, collected separately for each eye, where baseline is defined as Visit 1.

12.4.1.1 Statistical Hypotheses

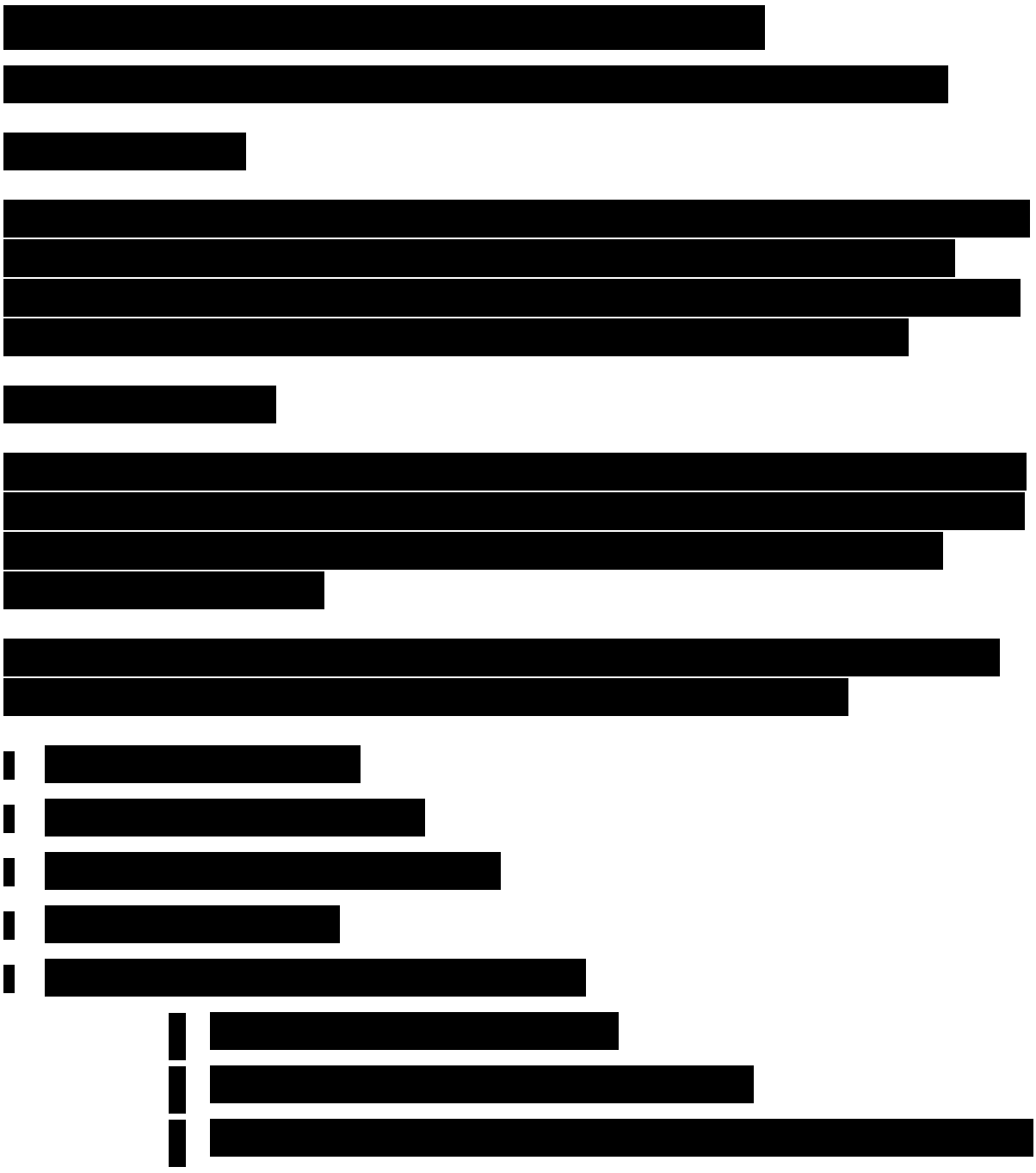
The null and alternative hypotheses are formulated in terms of the predefined margin of 5 for noninferiority:

$$H_0: \mu_{(iLux)} - \mu_{(Lipiflow)} \leq -5$$
$$H_a: \mu_{(iLux)} - \mu_{(Lipiflow)} > -5$$

where $\mu_{(iLux)}$ and $\mu_{(Lipiflow)}$ denote the mean change from baseline in MGS for iLux and LipiFlow, respectively.

12.4.1.2 Analysis Methods

A mixed effects repeated measures model will be utilized to test these hypotheses. The model will include terms for treatment, visit, treatment by visit interaction, and baseline MGS. Within-subject correlation due to eye will also be accounted for in the model. Treatment difference (iLux minus LipiFlow) and the corresponding one-sided 95% lower confidence limit (LCL) will be computed. Noninferiority in change from baseline in MGS will be declared if the LCL is greater than -5.



[redacted]

[redacted]

12.5 Handling of Missing Data

All data obtained in evaluable subjects/eyes will be included in the analysis. No imputation for missing values will be carried out f[redacted]

12.6 Safety Analyses

The safety endpoints are:

- AEs
- Biomicroscopy findings
- Device deficiencies

There are no safety hypotheses planned in this study. The focus of the safety analysis will be a comprehensive descriptive assessment of occurrence of AEs as well as the other listed parameters.

All AEs 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 safety analysis set on a treatment-emergent basis. Descriptive summaries (counts and percentages) for ocular and nonocular AEs will be presented by Medical Dictionary for Regulatory Activities Preferred Terms. AEs leading to study discontinuation, and SAEs will be identified. Individual subject listings will be provided, as necessary.

Individual subject listings will be provided for AEs that occur after signing informed consent but prior to exposure to IP.

Each biomicroscopy parameter will be tabulated by its grade. For select biomicroscopy parameters, counts and percentages of eyes that experience an increase of 1 grade from

baseline (last assessment prior to study treatment exposure) to any subsequent visit will be presented. A supportive listing will be generated which will include all biomicroscopy data from all visits for those eyes experiencing the increase.

Two listings for device deficiencies, prior to exposure of study treatment and treatment-emergent, will be provided. Additionally, each device deficiency category will be tabulated.

No inferential testing will be done for safety analysis.

[redacted]

12.8 Sample Size Justification

[redacted]

Primary Effectiveness

To demonstrate noninferiority (margin = 5) in change from baseline in MGS as a one-tailed hypothesis with α=0.05, and using a standard deviation of 11.661, 90% power can be attained with a sample size of 188 (94 per treatment group).

[redacted]

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.

13.3 Data Review and Clarifications

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

13.4 Sponsor and Monitoring Responsibilities

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

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

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.

Alcon may have an expert Sponsor Representative present during subject visits to offer training to the Investigator on proper operation of the device 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 DFU, 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.

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

[redacted]

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