Short Title:

Statistical Analysis Plan
DEG723-P001 / NCT03956225

Full Title:

Statistical Analysis Plan
DEG723-P001

Protocol Title:	Comparison between iLux and LipiFlow in the treatment of Meibomian Gland Dysfunction (MGD): A 12-month, Multicenter study
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
	[redacted]
[redacted]	[redacted]
Approvals:	See last page for electronic approvals

Job Notes:

This is the second revision (Version 3.0) of the Statistical Analysis Plan for this study. This version of the Statistical Analysis Plan is based on Version 3.0 of the study protocol.

Executive Summary:

Key Objectives:

The primary objective is to demonstrate noninferiority in change from baseline in Meibomian Gland Score (MGS) with iLux Device (iLux) when compared to LipiFlow Thermal Pulsation System (LipiFlow) at the 12-Month Follow-up visit.

Decision Criteria for Study Success:

Success of this study will be based on demonstration of noninferiority in change from baseline in MGS at 12 months post single treatment with iLux when compared to LipiFlow, using a margin of 5.

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[redacted]

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1 Study Objectives and Design

1.1 Study Objectives

PRIMARY OBJECTIVE

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 Meibomian Gland Dysfunction (MGD) subjects with evaporative dry eye disease (EDE).

[redacted]

1.2 Study Description

Key components of the study are summarized in Table 1-1.

Table 1-1 Study Description Summary

Study Design	Prospective, randomized, parallel group, assessor-masked, controlled
Study 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. Target to complete: 188 Planned to enroll: ~278
Number of Sites	~15 (US)
Test Product	iLux Device (iLux)
Control Product	LipiFlow Thermal Pulsation System (LipiFlow)
Duration of Treatment	Approximately 12 months
Visits	Visit 1: Screening/Baseline

	Visit 2: Treatment [1-7 days from Visit 1]* Visit 3: 2-Week Follow-up [14 days (± 3 days) from Visit 2] Visit 4: 1-Month Follow-up [30 days (± 3 days) from Visit 2] Visit 5: 3-Month Follow-up [90 days (± 7 days) from Visit 2] Visit 6: 6-Month Follow-up [180 days (± 14 days) from Visit 2] Visit 7: 9-Month Follow-up [270 days (± 25 days) from Visit 2] Visit 8: 12-Month Follow-up [365 days (± 45 days) from Visit 2] *Randomization will occur at Visit 2

1.3 Randomization

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

1.4 Masking

This study is assessor-masked.

[redacted]

2 Analysis Sets

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 evaluated in this study. For treatment-emergent safety analyses, subjects/eyes will be categorized under the actual study treatment exposed.

Adverse events occurring from the time of informed consent but prior to first exposure to study treatment will be summarized in subject listings.

2.2 Full Analysis Set

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

[redacted]

3 Subject Characteristics and Study Conduct Summaries

The following tables will be presented:

- Subject Disposition

- Analysis Sets
- Subject Accounting
- Demographics Characteristics
- Baseline Characteristics [redacted]

Demographic characteristics and subject accounting tables will be summarized by study treatment group and overall [redacted] Baseline characteristics will be summarized by study treatment group and over all [redacted]

In addition, the following subject listings will be provided:

- Listing of Subjects Excluded from Protocol Defined Analysis Sets
- Listing of Treatment Assignment by Investigator
- Listing of Subjects Discontinued from Study

4 Effectiveness Analysis Strategy

This study defines 1 primary [redacted] endpoint. [redacted] FAS as the primary analysis set. [redacted]

Continuous variables will be summarized using the number of observations, mean, standard deviation, median, minimum and maximum, as well as confidence intervals/limits as applicable. Categorical variables will be summarized with counts and percentages from each category. In addition, change from baseline data will be summarized, for selected endpoints. For each subject and for each eye (if applicable) with available data, change from baseline will be computed at a particular visit, Visit *i*, as follows:

$$\text{change from baseline}_i = (\text{post-baseline value}_i - \text{baseline value}),$$

where

post-baseline value = data at Visit *i*, *i* = applicable post-baseline visit

baseline value = data at Visit 1

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

[redacted]

4.1 Effectiveness Endpoints

Primary Endpoint

The primary endpoint is change from baseline in MGS, which is derived from MGS, calculated separately for each eye (total from 15 glands), where baseline is defined as Visit 1. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4.2 Effectiveness Hypotheses

Primary Effectiveness

The null and alternative hypotheses for the primary analysis 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.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4.3 Statistical Methods for Effectiveness Analyses

4.3.1 Primary Effectiveness Analyses

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. Site and site by treatment interaction terms will be included as random effects to account for potential effect of sites on treatment difference. 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]
- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

5 Safety Analysis Strategy

5.1 Safety Endpoints

The safety endpoints are:

- Adverse events (AE)
- Biomicroscopy findings
    - Cornea findings
    - Conjunctiva findings
    - Other findings
- Device deficiencies

5.2 Safety Hypotheses

There are no formal safety hypotheses in this study. The focus of the safety analysis will be a comprehensive descriptive assessment of safety endpoints listed in Section 5.1.

5.3 Statistical Methods for Safety Analyses

The analysis set for all safety analyses is defined in Section 2.1. Baseline will be defined as the last measurement prior to exposure to study treatment on Visit 2. Safety variables will be summarized descriptively.

5.3.1 Adverse Events

The applicable definition of an AE is in the study protocol. All AEs occurring from when a subject signs informed consent to when a subject exits the study will be accounted for in the reporting.

Analysis and presentation of pre-treatment AEs and between-treatment AEs will be separated from treatment-emergent AEs occurring during the study periods. A pre-treatment AE is an event that occurs after signing informed consent but prior to exposure to study treatment. The period for treatment-emergent AE analysis starts from exposure to study treatment until the subject completes or is discontinued from the study.

The following tables and supportive listings will be provided:

- Incidence of All Ocular Treatment-Emergent Adverse Events

- Incidence of Ocular Serious Treatment-Emergent Adverse Events
- Incidence of All Nonocular Treatment-Emergent Adverse Events
- Incidence of Nonocular Serious Treatment-Emergent Adverse Events
- Listing of All Ocular Treatment-Emergent Adverse Events
- Listing of All Nonocular Treatment-Emergent Adverse Events
- Listing of All Ocular Pre-Treatment Adverse Events
- Listing of All Nonocular Pre-Treatment Adverse Events

5.3.2 Biomicroscopy Findings

The following tables and supportive listings will be provided:

- Frequency and Percentage for Biomicroscopy Findings by Visit
- Incidence of Increased Severity by 1 Grade in Biomicroscopy Findings
- Listing of Subjects With Other Biomicroscopy Findings
- Listing of Subjects with Clinically Significant Biomicroscopy Findings
- Listing of Subjects With Increased Severity by 1 Grade in Biomicroscopy Findings

5.3.3 Device Deficiencies

The following tables and supportive listings will be provided:

- Frequency of Treatment-Emergent Device Deficiencies
- Listing of Treatment-Emergent Device Deficiencies
- Listing of Device Deficiencies Prior To Treatment Exposure

6 Analysis Strategy for Other Endpoints

Not applicable

7 Sample Size and Power Calculations

The sample size calculation for the primary endpoin [redacted] is based on a prior clinical study that assessed performance of the LipiFlow and iLux devices.

[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]

[redacted]

[redacted]

[redacted]

[redacted] [redacted]

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

- [redacted]

[redacted]

9 References

Not Applicable

10 Revision History

This is the second revision (Version 3.0) of the Statistical Analysis Plan for this study. This version of the Statistical Analysis Plan is based on Version 3.0 of the study protocol. The purpose of this revision is to clarify specific reporting considerations and analysis strategies.

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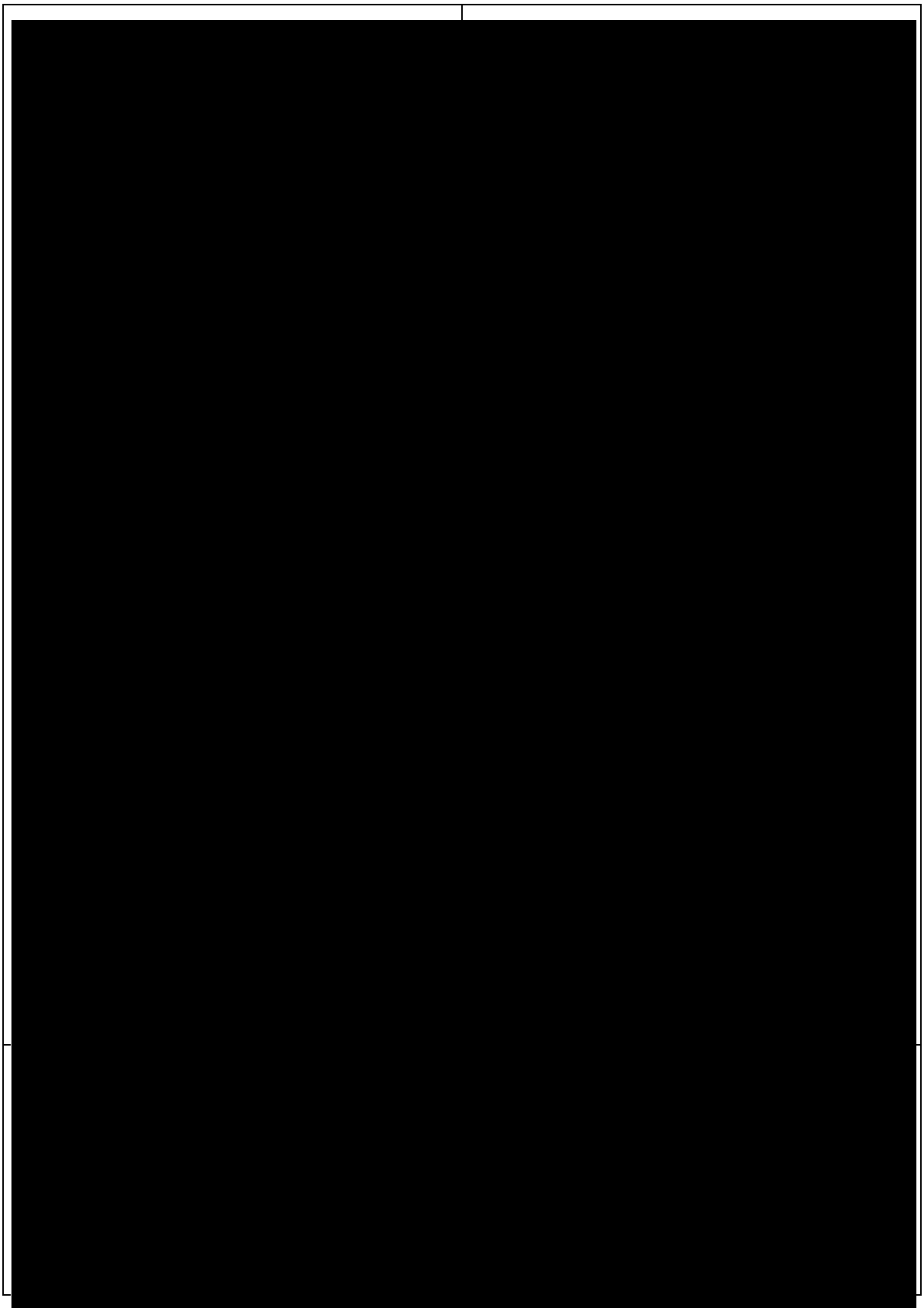
[redacted]

[redacted]	[redacted]
[redacted]	[redacted]



11 Appendix

Table 11-1 Overview of Study Plan

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]	[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]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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
Biomicroscopy †	✓	✓∞	✓	✓	✓	✓	✓	✓	✓
[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	(✓)	(✓)	(✓)	(✓)	(✓)	(✓)	(✓)	✓	(✓)

*Performed post treatment ∞ Performed pre and post treatment § Source only (✓) As applicable

† This test will be provided by an examiner not involved in treating the subjects and masked to the arm to which the subject is randomized

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