Statistical Analysis Plan

A Post-Market Evaluation of LipiFlow Treatment in Cataract Surgery Practice

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STATISTICAL ANALYSIS PLAN

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SAP CHANGE HISTORY

Version	Section(s)	Page(s)	Description of Change(s)	Rationale for Change(s)
1.0	N/A	N/A	Original	N/A
2.0	Appendix II	11-12	Visual acuity conversion formula updated	M&S system will be used for all visual acuity measurements

1 INTRODUCTION

This document summarizes the statistical methods to be implemented during the analysis of data for the evaluation LipiFlow treatment in cataract surgery practice. This is a post-market, prospective, randomized, multi-center, bilateral, open-label, cross-over, comparative clinical study. Up to 140 subjects will be randomized and bilaterally implanted to achieve approximately 110 evaluable subjects (55 in the study arm and 55 in the control arm).

The purpose of this study is to evaluate the LipiFlow treatment in adult patients with mild to moderate Meibomian gland dysfunction (MGD) undergoing bilateral cataract surgery in terms of preoperative surgical planning and postoperative outcomes including refractive outcomes, visual outcomes and ocular comfort.

The key study endpoints are the comparisons between study group and control group for precision of biometric measurements preoperatively, mean change in total Meibomian gland score at 1 month postoperatively, mean monocular UCDVA at 3 months postoperatively, rate of refractive predictability at 3 months postoperatively and rate of bothersome ocular symptoms at 3 months postoperatively. Additional endpoints will be evaluated at 1 month and 3 months postoperatively for the both groups and 4 months postoperatively for crossover control group.

2 ANALYSIS POPULATIONS

2.1 ANALYSIS POPULATIONS

The primary analysis population will be all eyes that are randomized for the precision of biometric measurements, and all eyes that are randomized and implanted for all other analyses. Mean change in total Meibomian gland score will be compared between study group eyes and control group eyes at 1 month postoperatively. All other key study endpoints will be evaluated at 3 months postoperatively. Additional endpoints will be evaluated at 1 month and 3 months postoperatively for the study group and control group and 4 months postoperatively for crossover control group only. Missing data will not be imputed.

Since both eyes of the same subject will be randomized into the same group, eye-specific measurements of same subject are clustered and likely to be positively correlated. As a subset analysis, right and left eyes of subjects will be analyzed for the key eye-specific study endpoints separately to assess for any differences by eye. Demographics/enrollment/accountability data and binocular data will be reported for all randomized subjects with study IOLs successfully implanted.

2.2 VISIT WINDOWS

Each randomized group will have two preoperative visits, 1 month postoperative visit and 3 months postoperative visit. Subjects randomized to study group will receive LipiFlow treatment before the second preoperative visit. Subjects randomized to control group will receive crossover LipiFlow treatment after 3 months postoperative visit. There will be a 4 months postoperative visit for control group subjects. The exact number of days for each interval is described in the protocol. The number of eyes with missing visits or data outside of the visit intervals will be reported.

2.3 DATA CONVENTIONS

Descriptive statistics will typically include sample size (N), mean, standard deviation (SD), median, minimum (Min.), and maximum (Max.) as appropriate for continuous variables. 95% confidence interval around the mean will be reported where appropriate. For categorical data, the frequency and proportion will be computed.

For visual acuity data, letter scores will be converted to LogMAR prior to analysis. Formulas used for visual acuity analysis are included in Appendix II. For refractive data, all values will be converted to minus cylinder with sphere adjusted for infinity. Formulas used for refractive data are included in Appendix III.

3 ACCOUNTABILITY/DEMOGRAPHICS

3.1 ACCOUNTABILITY

The number of randomized subjects will be tabulated by site and by study group and control group. Subject accountability will be summarized as a frequency distribution by scheduled visits. The frequency and proportion of available subjects, including those outside of the interval, and the frequency and proportion of missing subjects (forms not yet completed, active, missed visit, lost to follow-up or discontinued) will be reported.

3.2 DEMOGRAPHICS

Subject demographic data including age, sex, race and ethnicity will be presented by study group and control group. Age will be summarized with descriptive statistics with mean, standard deviation, minimum and maximum. In addition, age will be categorized by less than 30, 30 to 39, 40 to 49, 50 to 59, 60 to 69, 70 and older group. The frequency distributions of sex, race, ethnicity and age group will be tabulated.

4 STUDY ENDPOINTS

4.1 KEY STUDY ENDPOINTS

4.1.1 MEAN MONOCULAR UCDVA AT 3 MONTHS POSTOPERATIVE

The mean LogMAR monocular UCDVA will be reported for study group eyes and control group eyes. Note that a lower LogMAR value is a better acuity. The success criterion is a statistically significantly lower mean LogMAR monocular UCDVA for study group eyes compared to control group eyes ($p \leq 0.05$) at 3 months postoperative visit. The right eyes and left eyes data from each group will also be presented.

4.1.2 PRECISION (STANDARD DEVIATION) OF PREOPERATIVE AXIAL LENGTH (AL), ANTERIOR CHAMBER DEPTH (ACD) AND KERATOMETRIC MEASUREMENTS (K)

AL, ACD and K values will have three sets of measurements at the preoperative visit #1 and three sets of measurements at the preoperative visit #2. The standard deviation of each set of AL, ACD and K values will be computed at both preoperative visits and the average of the three computed standard deviations from each preoperative visit is defined as the precision. The difference in precision between the two preoperative visits will be calculated for AL, ACD and K values. The summary statistics of the difference in precision of AL, ACD and K values will be reported for study group eyes and control group eyes. The precisions of the AL, ACD and K values are expected to be better (smaller standard deviation) for study group eyes than the ones for control group eyes. The right eyes and left eyes data from each group will also be presented.

4.1.3 RATE OF REFRACTIVE PREDICTABILITY AT 3 MONTHS POSTOPERATIVE

The achieved MRSE is defined as “Postop MRSE – Targeted MRSE”. The frequency, proportion and 95% confidence intervals of eyes with achieved MRSE within 0.50 D and 1.00 D of targeted MRSE will be summarized at 3 months postoperatively. The proportion of study group eyes with achieved MRSE within 0.50D and within 1.00D of targeted MRSE is expected to be greater compared to control group eyes. The right eyes and left eyes data from each group will also be presented.

4.1.4 RATE OF BOTHERSOME OCULAR SYMPTOMS AT 3 MONTHS POSTOPERATIVE

The frequency and proportion of subjects who experienced moderate or severe ocular symptoms (halos, night glare, starburst, and night vision difficulties) will be reported. The rate of bothersome ocular symptoms at 3 months postoperatively is expected to be lower for study group subjects than that for control group subjects.

4.1.5 MEAN CHANGE IN TOTAL MEIBOMIAN GLAND SCORE FROM BASELINE TO 1 MONTH POSTOPERATIVE

The total Meibomian gland score is the sum of the grades for all 15 glands with a range of 0 to 45. Total Meibomian gland score will be presented by study group eyes and

control group eyes. Change in total Meibomian gland score is defined as total Meibomian gland score at 1 month postoperative visit minus the score at Baseline (before the LipiFlow treatment). A higher total Meibomian gland score reflects better Meibomian gland function. Greater mean change in total Meibomian gland score is expected for study group eyes than that for control group eyes. The right eyes and left eyes data from each group will also be presented.

4.2 OTHER ENDPOINTS

4.2.1 ENDPOINTS EVALUATED AT 1-MONTH POSTOPERATIVELY

Mean change in number of Meibomian Gland Yielding Liquid Secretion (MGYLS) from Baseline visit will be compared between study group eyes and control group eyes. The number of MGYLS (i.e., cloudy or clear liquid with a grade of 2 or 3) will be counted out of the 15 glands assessed with a range of 0 to 15. Mean number of MGYLS will be reported at Baseline visit and 1 month postoperatively. A higher number of MGYLS indicates better Meibomian gland function. Change in number of MGYLS is defined as number of MGYLS at 1 month visit minus number of MGYLS at Baseline visit. Mean change in number of MGYLS from baseline to 1 month postoperative visit is expected to be greater for study group eyes than that for control group eyes.

Mean change in ocular surface stain grade from Baseline visit will be compared between study group eyes and control group eyes. Corneal staining will be evaluated in five corneal regions on a scale of 0 (none), 1 (mild), 2 (moderate) and 3 (severe). The total corneal staining grade will be calculated as the sum of the grades for each of the five corneal regions on a scale from 0 to 15. A lower grade indicates less corneal surface desiccation. Conjunctival staining will be evaluated in six conjunctival regions on a scale of 0 (none), 1 (mild), 2 (moderate) and 3 (severe). The total conjunctival staining grade will be calculated as the sum of the grades for each of the six conjunctival regions on a scale from 0 to 18. A lower grade indicates less conjunctival surface desiccation. Mean ocular surface stain grade score will be reported at Baseline visit and 1 month postoperatively. Change in ocular surface stain grade score is defined as the score at 1 month visit minus the score at Baseline visit.

Mean change in Tear Break-up Time (TBUT) from Baseline will be compared between study group eyes and control group eyes. Three separate measurements of TBUT will be taken on each eye and the average of the three measurements will be calculated for analysis. Mean TBUT will be reported at Baseline visit and 1 month postoperatively. Change in TBUT is defined as TBUT at 1 month visit minus TBUT at Baseline visit. A higher tear break-up time indicates greater tear film stability. Mean change in TBUT from baseline to 1 month postoperative is expected to be greater for study group eyes than that for control group eyes.

Change in Eyelid Margin Evaluation from Baseline visit will be compared between study group eyes and control group eyes. The eyelid appearance will be graded as 'Obvious lid changes', 'Minimal lid changes' or 'Normal lid appearance'. In addition, the eyelids for the presence of MGD will be graded as either 'Obvious MGD' or 'Non-obvious MGD'. The frequency and percent of eyelid assessment and MGD presence assessment will be presented at Baseline visit and 1 month postoperatively.

4.2.2 ENDPOINTS EVALUATED AT 3-MONTH POSTOPERATIVELY

Mean LogMAR monocular BCDVA, mean LogMAR binocular UCDVA, UCIVA, UCNVA, BCDVA and contrast acuity will be reported for study group eyes/subjects and control group eyes/subjects at 3 months postoperatively. Better visual acuity outcomes (lower mean LogMAR scores) for study group eyes are expected compared to control group eyes.

Summary statistics (mean, standard deviation, median, minimum and maximum) will be reported for MRSE at 3 months postoperative visit for study group eyes and control group eyes. The difference between MRSE at 3 months postoperative visit and the target MRSE will be calculated. The difference is expected to be smaller (closer to zero) for study group eyes than that for control group eyes.

Mean change in total Standard Patient Evaluation of Eye Dryness (SPEED) score from Baseline visit to 3 months postoperative in the study group subjects will be compared to the control group subjects. The SPEED score is the sum of frequency and severity scores with a range from 0 to 28. A lower SPEED score represents less frequent and/or less severe dry eye symptoms. The mean SPEED score will be reported at Baseline and 3 months postoperative visit. Greater mean change in SPEED score from Baseline to 3 months for study group subjects is expected.

Mean change in total Meibomian gland score from Baseline visit in the study group eyes will be compared to the control group eyes. Greater mean change in total Meibomian gland score is expected for study group eyes than that for control group eyes.

4.2.3 ENDPOINTS EVALUATED AT 4-MONTH POSTOPERATIVE FOR CONTROL GROUP SUBJECTS ONLY

Mean change in LogMAR monocular BCDVA and UCDVA and mean change in LogMAR binocular UCDVA, UCIVA, UCNVA, BCDVA and contrast acuity will be reported for control group eyes from 3 months to 4 months postoperative visit. Better visual acuity outcomes (lower mean LogMAR scores) at 4 months visit are expected.

Mean MRSE at 4 months postoperative will be compared to target MRSE. Frequency and percent of eyes with MRSE within 0.50 D and within 1.00 D of target MRSE at 4 months postoperative will be reported.

Mean change in total Meibomian gland score and mean change in total SPEED score from 3 months to 4 months postoperative will be reported. An increase in both mean total Meibomian gland score and mean total SPEED are expected.

4.2.4 RATE OF ADVERSE EVENTS/MEDICAL AND/OR LENS FINDINGS

The frequency and proportion of eyes with optical/visual, medical and lens complications will be reported over time. The type and rates of adverse events will be summarized for both study group eyes and control group eyes.

5 SAMPLE SIZE CALCULATIONS

The sample size determination is based on the primary endpoint of uncorrected distance visual acuity (UCDVA). There is over 90% power to detect a 1-line or greater difference in mean UCDVA between the treatment and control groups with 55 subjects in each group. This assumes one-sided two-sample t-test with an alpha of 0.05 and standard deviation of 1.6 lines. Adding 20% screen failure/drop-out rate will require enrolling 69 subjects per group.

6 STUDY INTERIM REPORTS

An interim database lock will be performed for preoperative data after completion of the second preoperative visit.

APPENDIX I: TABLE LISTING

Variable	All Subjects	Study/control group	Note
ENROLLMENT/PREOP/OP			
Accountability/Enrollment			
Subjects/eyes by investigational site (n)	x	x	**Subjects and eyes**
Accountability table over time – (Available for analysis, Missing data –Forms not yet completed, Active, Missed visit, Lost to follow-up, Discontinued) (n and %)	x	x	**Subjects and eyes**
Out of Interval listing	x	x	**Subjects and eyes**
Demographics			
Demographic – Age in years (N, Mean, SD, Min, Max), race, sex, ethnicity (n and %) Age in groups (<30, 30-39, 40-49, 50-59, 60-69, ≥70) (n, %)	x	x	**Subjects**
Preoperative Characteristics			
Target refraction (MRSE) - (N, Mean, SD, Min, Max)		x	**eyes**
BSCVA in groups (≤20/30, 20/40, 20/50-20/80, 20/100, >20/100) – (n, %)		x	**eyes**
Total Meibomian gland score at 1st preop visit (baseline)- (N, Mean, SD, Min, Max, 95% CI)		x	**eyes**
Number of MGYLS at 1st preop visit (baseline) – (N, Mean, SD, Min, Max, 95% CI)		x	**eyes**
TBUT at 1st preop visit (baseline) – (N, Mean, SD, Min, Max, 95% CI)		x	**eyes**
SPEED score at 1st preop visit (baseline) – (N, Mean, SD, Min, Max, 95% CI)		x	**eyes**
Eyelid margin evaluation assessment (obvious/minimal changes/normal appearance; Obvious/Non-obvious MGD) at 1st preop visit (baseline) – (n, %)		x	**eyes**
KEY STUDY ENDPOINTS			
Mean monocular UCDVA at 3-month (N, Mean, SD, Min, Max, 95% CI of LogMAR)		x	**Eyes, also by right eye and left eye**

Precision (avg. of SD from 3 sets of measurements) of preop (2nd visit) AL, ACD and Ks		x	**Eyes, also by right eye and left eye**
Rate of MRSE predictability at 3-month (achieved MRSE within 0.5D/1.0D of target MRSE) – (n, %)		x	**Eyes, also by right eye and left eye**
Rate of bothersome ocular symptoms at 3-month – (n, %)		x	**subjects**
Mean change in total Meibomian gland score from baseline to 1-month – (N, Mean, SD, Min, Max, 95% CI)		x	**Eyes, also by right eye and left eye**
ENDPOINTS EVALUTED AT 1-MONTH POSTOP			
Mean change in number of MGYLS from baseline – (N, Mean, SD, Min, Max, 95% CI)		x	**eyes**
Mean change in ocular surface stain grade from baseline– (N, Mean, SD, Min, Max, 95% CI)		x	**eyes**
Mean change in TBUT from baseline– (N, Mean, SD, Min, Max, 95% CI)		x	**eyes**
Eyelid margin evaluation assessment (obvious/minimal changes/normal appearance; Obvious/Non-obvious MGD) at 1-month – (n, %)		x	**eyes**
ENDPOINTS EVALUTED AT 3-MONTH POSTOP			
Mean monocular BCDVA - (N, Mean, SD, Min, Max, 95% CI of LogMAR) Monocular BCDVA by acuity line over time (n and % within each category)		x	**eyes**
Mean binocular UCDVA, UCIVA, UCNVA, BCDVA - (N, Mean, SD, Min, Max, 95% CI of LogMAR) Binocular UCDVA, UCIVA, UCNVA, BCDVA by acuity line over time (n and % within each category)		x	**Subjects**
MRSE at 3M – (N, Mean, SD, Min, Max, 95% CI) Difference between 3M MRSE and target MRSE – (N, Mean, SD, Min, Max, 95% CI)		x	**eyes**
Contrast acuity at 3M - (N, Mean, SD, Min, Max, 95% CI of LogMAR)		x	**Subjects**
Mean change in SPEED score from baseline- (N, Mean, SD, Min, Max, 95% CI)		x	**eyes**
Mean change in total Meibomian gland score from baseline- (N, Mean, SD, Min, Max, 95% CI)		x	**eyes**

ENDPOINTS EVALUATED at 4-MONTH POSTOP			
Mean monocular BCDVA and UCDVA and change from 3M to 4M - (N, Mean, SD, Min, Max, 95% CI of LogMAR) Monocular BCDVA and UCDVA by acuity line over time (n and % within each category)		x	Control group eyes only
Mean binocular UCDVA, UCIVA, UCNVA, BCDVA and change from 3M to 4M - (N, Mean, SD, Min, Max, 95% CI of LogMAR) Binocular UCDVA, UCIVA, UCNVA, BCDVA by acuity line over time (n and % within each category)		x	Control group subjects only
MRSE at 4M – (N, Mean, SD, Min, Max, 95% CI) Difference between 4M MRSE and target MRSE – (N, Mean, SD, Min, Max, 95% CI)		x	Control group eyes only
Contrast acuity at 4M and change from 3M to 4M - (N, Mean, SD, Min, Max, 95% CI of LogMAR)		x	Control group subjects only
Mean change in SPEED score from baseline- (N, Mean, SD, Min, Max, 95% CI)		x	Control group eyes only
Mean change in total Meibomian gland score from baseline- (N, Mean, SD, Min, Max, 95% CI)		x	Control group eyes only
RATE OF ADVERSE EVENTS/MEDICAL/LENS FINDINGS			
Type and rate of AE, medical and/or lens findings (n and %)		x	eyes

KEY: MGYLS=Meibomian gland yielding liquid secretion, TBUT=tear break-up time, SPEED=standard patient evaluation of eye dryness, MGD=Meibomian gland dysfunction, AC=axial length, ACD=anterior chamber depth, K=keratometric measurements, UCIVA=uncorrected intermediate VA at 66cm, UCNVA=uncorrected near VA at 40cm, UCDVA=uncorrected distance visual acuity, BCDVA=best-corrected distance visual acuity

APPENDIX II: FORMULAS USED FOR VISUAL ACUITY

LOGMAR CONVERSIONS AND LINE CHANGES

LogMAR score for UCVA and BCDV	
Category	LogMAR
20/16 or better	≤ -0.06
20/20 or better	≤ 0.04
20/25 or better	≤ 0.14
20/32 or better	≤ 0.24
20/40 or better	≤ 0.34
20/50 or better	≤ 0.44
20/63 or better	≤ 0.54
20/80 or better	≤ 0.64
20/100 or better	≤ 0.74
Worse than 20/100	>0.74

Formulas for Converting Near, Distance and Intermediate VA to LogMAR Values (M&S System):

LogMAR value = (85-letter score)/50

Example: A subject has distance letter score of 78
Converting to LogMAR: (85-78)/50 = 0.14 LogMAR

If the standard distance is not used for M&S system, no calculation adjustment will be needed since the M&S system already takes that into account.

Converting from LogMAR to Snellen and Decimal Equivalent:

Snellen denominator=20*(10**(LogMAR value))
Decimal VA= 20/(Snellen Denominator)

Example: A subject has a LogMAR score of 0.20
The Snellen denominator is: 20*(10**(0.20) = 20*(1.585) = 31.7=20/32
Decimal VA = 20/32=0.625

APPENDIX III: FORMULAS USED FOR REFRACTIVE DATA

Formulas for Manifest Refractive Data

Converting to Minus Cylinder Notation:

If the original cylinder value is positive then the following formulas are used:

1. New sphere value=original sphere value + original cylinder value
2. Final cylinder value=change the sign of original cylinder value
3. Final axis value: if the cylinder is equal to 0 then the axis will be set to 0; if the original axis is >0 and ≤90 then final axis=original axis +90; if the original axis >90 and ≤180 then final axis=original axis – 90

Adjusting for Infinity: Final sphere = new sphere (in minus cylinder notation) – 0.25

Spherical Equivalent: Spherical equivalent = final sphere + (0.5*final cylinder)

Examples:

Refraction on CRF: sphere: -3.25, cylinder: 0.50, axis: 80

In minus cylinder notation: sphere = -2.75, cylinder = -0.50, axis = 170
Adjusting for infinity: sphere = -3.00, cylinder = -0.50, axis = 170
Spherical equivalent = -3.00 + 0.5*(-0.50) = -3.25