Short Title:

Statistical Analysis Plan CTB258-P001

Full Title:

Statistical Analysis Plan CTB258-P001

Protocol Title:	Clinical Evaluation of FLACS (Femtosecond Laser Assisted Cataract Surgery) with Combination of LenSx and Centurion
Project Number:	[redacted]
Protocol TDOC Number:	TDOC-0054960
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Approvals:	See last page for electronic approvals.
Job Notes:	

This is the first revision (Version 2.0) Statistical Analysis Plan for this study. The primary purpose of this revision was to add Modified Full Analysis Set to Efficacy Analysis Sets in Section 2.1. See Section 10, Revision History, for more detail and the other changes.

Executive Summary:

Key Objectives:

The primary objective of this study is to demonstrate less Cumulative Dissipated Energy (CDE), lower endothelial cell loss and lower average torsional amplitude with combination of LenSx® and Centurion® (LenSx) than conventional cataract surgery (Conventional).

Decision Criteria for Study Success:

Primary Efficacy

Superiority of LenSx to Conventional surgery for Cumulative Dissipated Energy (CDE) at Visit 00 will be demonstrated when a treatment difference is statistically significant (one-sided alpha = 0.025, t-test).

Secondary Efficacy

If and only if superiority of CDE is demonstrated, hypothesis testing of superiority for Endothelial Cell Density (ECD) followed by average torsional amplitude will be conducted sequentially.

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1 Study Objectives and Design

1.1 Study Objectives

The objective of this study is to demonstrate less Cumulative Dissipated Energy (CDE), lower endothelial cell loss and lower average torsional amplitude with combination of LenSx® and Centurion® (LenSx) than conventional cataract surgery (Conventional).

1.2 Study Description

This is a prospective, observer-masked (specular microscope only), randomized, within-subject control, single-center study. The population is patients undergoing cataract surgery by phacoemulsification whose cataract grade is diagnosed as grade 2, 3 or 4 (Emery-Little classification). One eye will be assigned to Cataract surgery with LenSx and the other eye to conventional cataract surgery randomly according to the randomization list. The randomization information will be masked only to the specular microscope observer. Examinations and observations will be performed prospectively from preoperative visit until around 6 months after surgery. As 50 subjects are required for the effectiveness assessment in this study, 55 subjects will be enrolled assuming around ten percent discontinuation.

1.3 Randomization

Cataract surgery with LenSx (LenSx) or conventional cataract surgery (Conventional) will be allocated to either eye within a subject according to the randomization list. The eye with more aggravated cataract will be operated first. If both eyes are the same, then always pick the right eye.

1.4 Masking

This is an observer-masked study, and the only specular microscope observer will be masked with regard to treatment assignment while the study is in progress. A person different from the surgeon will be assigned as the specular microscope observer before the start of the study.

1.5 Interim Analysis

No interim analyses are planned for this study.

2 Analysis Sets

2.1 Efficacy Analysis Sets

Full Analysis Set (FAS)

The FAS will include eyes with successful cataract surgery for which anterior capsulotomy and lens fragmentation have been completed using the assigned surgical techniques.

Modified Full Analysis Set (MFAS)

The MFAS will include eyes with successful cataract surgery for which anterior capsulotomy and lens fragmentation have been completed. Eyes will be analyzed according to the actually assigned surgical techniques. This dataset is used only for sensitivity analysis of primary and secondary endpoints.

Per Protocol Set (PPS)

The PPS will include all eyes with successful cataract surgery for which anterior capsulotomy and lens fragmentation have been completed using the assigned surgical techniques and meeting the following conditions;

- at least 1 postoperative visit; and
- no major protocol violation.

The PPS might exclude visits by individual subjects or observed data that do not meet the clinical study protocol criteria.

The FAS will be used for primary effectiveness analysis, secondary effectiveness analysis [redacted] The MFAS and PPS will be used only for sensitivity analysis of primary and secondary endpoints.

2.2 Safety Analysis Set

The Pre-Treatment Safety Analysis Set will be the set that will be used to summarize occurrence of adverse experiences prior to exposure to cataract surgery using test device. The Treatment-Emergent Safety Analysis Set will be used for safety analysis after cataract surgery using test device.

2.3 Pharmacokinetic Analysis Set

Not Applicable.

3 Subject Characteristics and Study Conduct Summaries

For all analysis datasets (Safety Analysis Set, FAS and PPS), demographics (sex, age, cataract grade) will be summarized. For sex and cataract grade, the N and percentage will be summarized. For age (<60, 60-69, 70-79, ≥ 80), the N and percentage, and descriptive statistics (arithmetic mean, standard deviation, N, median, minimum and maximum) will be summarized. Study conduct summaries will be presented in a subject disposition table for all enrolled subjects.

4 Efficacy Analysis Strategy

The objective of this study is to demonstrate superiority of less-invasiveness of cataract surgery with LenSx to conventional cataract surgery.

4.1 Efficacy Endpoints

The primary endpoint is Cumulative Dissipated Energy (CDE) at Visit 00 (surgery day).

The secondary endpoints are as follows.

- Percent change of corneal endothelial cell density (ECD) at Visit 5 (150-210 days after surgery) from Pre-Operative Visit
- Average torsional amplitude (%) at Visit 00 (surgery day)

[redacted]

[redacted]

n

4.2 Efficacy Hypotheses

The null hypothesis (H_0) and the alternative hypothesis (H_1) for the primary analysis are as follows.

$$H_0 : \mu_{(LenSx)} = \mu_{(Conv)}$$

$$H_1 : \mu_{(LenSx)} < \mu_{(Conv)}$$

, where each of $\mu_{(LenSx)}$ and $\mu_{(Conv)}$ denotes the population mean of CDE for LenSx and Conventional surgery.

The null hypothesis (H_0) and the alternative hypothesis (H_1) for the secondary analysis are as follows.

Percent ECD change at Visit 5	Average torsional amplitude at Visit 00
$H_0 : \mu_{(LenSx)} = \mu_{(Conv)}$	$H_0 : \mu_{(LenSx)} = \mu_{(Conv)}$
$H_1 : \mu_{(LenSx)} > \mu_{(Conv)}$	$H_1 : \mu_{(LenSx)} < \mu_{(Conv)}$

, where each $\mu_{(LenSx)}$ and $\mu_{(Conv)}$ denotes the means of the parameters for LenSx and Conventional surgery in population.

4.3 Statistical Methods for Efficacy Analyses

The superiority of LenSx to Conventional surgery will be tested if there is a significant difference in mean between the surgical techniques (MMRM-based t-test, significance level: one-sided 2.5%). The descriptive statistics of CDE at Visit 00 (surgery day) will be calculated by each surgical techniques (arithmetic mean, standard deviation, N, median, minimum and maximum) and the means will be estimated using 95% confidence intervals based on the MMRM (mixed model for repeated measures).

The hypothesis on percent ECD change from preoperative visit to Visit 5 (150-210 days after surgery) will be tested only if the superiority is demonstrated in the primary analysis. The

hypothesis on average torsional amplitude at Visit 00 (surgery day) will be tested only if there is a significant difference in percent ECD change (both MMRM-based t-test, significance level: one-sided 2.5%). The descriptive statistics of ECD, absolute and percent ECD change and average torsional amplitude will be calculated for each of the surgical techniques (arithmetic mean, standard deviation, N, median, minimum and maximum) and the means will be estimated using 95% confidence intervals based on the MMRM (mixed model for repeated measures). The following is the SAS psuedo code for the primary and secondary analyses.

```
PROC MIXED ;
  CLASS surgery subjid ;
  MODEL y = surgery / DDFM=KR ;
  RANDOM subjid ;
  LSMEANS surgery / CL DIFFS  ;
RUN ;
```

[redacted]

Table. 4–1 summarizes the key efficacy analyses.

Table. 4–1 Summary of Analysis Strategy for Key Efficacy Endpoints

Endpoint	Main vs. Sensitivity Approach[a]	Statistical Method[b]	Analysis Set	Missing Data Approach
Primary				
CDE at Visit 00	M	MMRM[c]	FAS	Observed data only
CDE at Visit 00	S	MMRM[c]	MFAS	Observed data only
CDE at Visit 00	S	MMRM[c]	PPS	Observed data only
Secondary				
Percent ECD change at Visit 5	M	MMRM[c]	FAS	Observed data only
Percent ECD change at Visit 5	S	MMRM[c]	MFAS	Observed data only
Percent ECD change at Visit 5	S	MMRM[c]	PPS	Observed data only

Average Torsional Amplitude at Visit 00	M	MMRM[c]	FAS	Observed data only
Average Torsional Amplitude at Visit 00	S	MMRM[c]	MFAS	Observed data only
Average Torsional Amplitude at Visit 00	S	MMRM[c]	PPS	Observed data only
[redacted]				

[a]M=Main analysis approach; S=Sensitivity analysis approach
[b]Further details on statistical models are:
[c] Mixed model for repeated measures

4.4 Multiplicity Strategy

In the primary analysis, multiplicity will not be an issue since there is only one primary endpoint. For the 2 secondary endpoints, the hypotheses will be tested in the pre-specified order only if the superiority is demonstrated in the primary analysis. Therefore, the type I family-wise error (FWE) for the total of 3 hypothesis tests (primary analysis (once) and secondary analysis (twice)) is controlled (one-sided 2.5%). No hypothesis test is planned for any of the other exploratory endpoints.

4.5 Subgroup Analyses and Effect of Baseline Factors

The consistency of the treatment effect on the primary endpoint will be assessed descriptively using summary statistics by categories of the following subgroup factors:

- Age category (<60, 60-69, 70-79, ≥ 80 years)
- Sex (Female, Male)
- Cataract Grade (Grade 2, Grade 3, Grade 4)

Also, percent ECD change from Visit 0, average torsional amplitude, [redacted] will be analyzed in summary statistics by subgroup of cataract grade (Grade 2, Grade 3, Grade 4).

4.6 Interim Analysis for Efficacy

No interim analyses are planned for this study.

5 Safety Analysis Strategy

5.1 Safety Endpoints

The safety endpoints are as below.

- Adverse events
- Device Deficiencies
- Slit Lamp Examination

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 2.2. Safety variables after exposure to the test device are listed in Section 5.1. Each safety variable will be summarized descriptively.

5.3.1 Adverse Events

The number and percentage of eyes with ocular adverse events will be presented by each surgical technique. Also, the number and percentage of subjects with non-ocular adverse events will be presented by investigational technique. An eye with multiple ocular AEs of the same preferred term is only counted once toward the total of this preferred term. Also, a subject with multiple non-ocular AEs of the same preferred term is only counted once toward the total of this preferred term.

Adverse events will be summarized in the following tables by system organ class and preferred level term:

- All Adverse Events (Serious and Non-Serious Combined)
  - Ocular
  - Non-Ocular
- All Adverse Device Effects
  - Ocular
  - Non-Ocular

- All Serious Adverse Events (including Serious Adverse Device Effects)
  - Ocular
  - Non-Ocular
- Any Deaths

Any frequent adverse event that was non-Serious and occurred >5% in one arm will be reported by investigational technique. Also, patient listings will be included for adverse experiences occurred prior to surgery with pre-treatment safety analysis set.

5.3.2 Device Deficiencies

A listing all device deficiencies, as recorded on the Device Deficiency Form will be provided.

5.3.3 Slit Lamp Examination

Number and percentage of presence or not presence of biomicroscopy finding will be tabulated by each surgical technique and by visit. A listing which includes abnormal slit-lamp observations will be provided. The listing will include all slit-lamp data from all visits with the following variables: surgical technique, subject, visit, eye, and slit-lamp observations at the visit.

5.4 Interim Analysis for Safety

No interim analyses are planned for this study.

6 Pharmacokinetic Analysis Strategy

Not Applicable.

7 Sample Size and Power Calculations

The 50 evaluable subjects will be enrolled for this study. For CDE, treatment difference was assumed 1.9% with common standard deviation of 1.2%. The sample size was simulated in Table. 7–1 varying correlation coefficient between both eyes because intra-subject positive correlation between both eyes is assumed for endpoints in this study.

Table. 7–1 Statistical Power for CDE (N=50)

Correlation between Both Eyes	Actual Power

Correlation between Both Eyes	Actual Power
0	>0.999
0.25	>0.999
0.50	>0.999
0.75	>0.999
0.99	>0.999

Also, for ECD, treatment difference and common standard deviation of ECD percent change from Baseline at Visit 5 was assumed 5.5% with common standard deviation of 11%. The sample size was simulated in Table. 7–2 in the same manner as CDE.

Table. 7–2 Statistical Power for ECD (N=50)

Correlation between Both Eyes	Actual Power
0	0.688
0.25	0.808
0.50	0.934
0.75	0.998
0.99	>.999

8 References

No references.

9 Revision History

This is the first revision (Version 2.0) of the Statistical Analysis Plan for this study. This version of the Statistical Analysis Plan is based on Version 2.0 of the study protocol.

The main purpose of this revision (Version 2.0) is to add Modified Full Analysis Set to Efficacy Analysis Sets in Section 2.1.

The other changes are follows;

- In Section 2.1, adding explanation of use of MFAS for sensitivity analysis of primary and secondary endpoints, and

- In Section 4.3, adding primary and secondary endpoints of MFAS to Table 4-1.

Date/Time (mm/dd/yyyy GMT):	Signed by:	Justification:
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]