Short Title: Statistical Analysis Plan CTU424-P001

Full Title:

Statistical Analysis Plan CTU424-P001 / NCT02502526

Protocol Title:	Comparison of Cumulative Dissipated Energy (CDE) and BSS Fluid used with the Centurion® with the 45° Balanced U/S tip vs the Centurion® with Mini Flared Kelman U/S tip vs the Infiniti® with Mini Flared Kelman U/S tip on Hard Lenses
Project Number:	CTU424-P001
Reference Number:	
Protocol TDOC Number:	TDOC-0050176
Author:	[redacted]
Approvals:	See last page for electronic approvals.
Job Notes:	This is the second revision (Version 3.0) of the Statistical Analysis Plan. Revisions were made to correct the calculation for [redacted] and to provide clarification on how endothelial cell density data would be analyzed.

Executive Summary:

Key Objective:

The key objective is to demonstrate that the Centurion® Vision System used with the 45° Balanced tip will result in less Cumulative Dissipated Energy (CDE) than the lnfiniti® Vision System used with the 45° Mini-Flared Kelman (MFK) tip during cataract extraction surgery via phacoemulsification of cataract grades NII- NIV (LOCSII).

Decision Criteria for Study Success:

The primary performance endpoint is CDE, compared between Centurion® with the 45° Balanced tip and lnfiniti® with the MFK tip.

The difference in CDE between these two groups will be examined via an analysis of covariance (ANCOVA) model adjusting for site and baseline opacity grade. The difference in least squares (LS) means will be calculated, along with a one-sided p-value. If this p-value is less than 0.05, it will be concluded that the CDE for Centurion® with the 45° Balanced MFK tip is statistically significantly less than the CDE for lnfiniti® with the MFK tip.

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1 Study Objectives and Design

1.1 Study Objectives

PRIMARY OBJECTIVE

Demonstrate that the Centurion® Vision System used with the 45° Balanced tip will result in less Cumulative Dissipated Energy (CDE) than the lnfiniti® Vision System used with the 45° Mini-Flared Kelman (MFK) tip during cataract extraction surgery via phacoemulsification of cataract grades NII- NIV (LOCSII).

SECONDARY OBJECTIVES

1). Demonstrate that the Centurion® Vision System used with the 45° Balanced tip will result in less CDE than the Centurion® Vision System used with the 45° MFK tip during cataract extraction surgery via phacoemulsification of cataract grades NII-NIV (LOCSII).

2). Demonstrate that the Centurion® Vision System used with the 45° Balanced tip will result in less BSS Fluid Used than the lnfiniti® Vision System used with the 45° MFK tip during cataract extraction surgery via phacoemulsification of cataract grades NII-NIV (LOCSII).

3). Demonstrate that the Centurion® Vision System used with the 45° MFK tip will result in less BSS Fluid Used than the lnfiniti® Vision System used with the 45° MFK tip during cataract extraction surgery via phacoemulsification of cataract grades NII-NIV (LOCSII).

4). Demonstrate that the Centurion® Vision System used with the 45° MFK tip will result in less CDE than the lnfiniti® Vision System used with the 45° MFK tip during cataract extraction surgery via phacoemulsification of cataract grades NII- NIV (LOCSII).

[redacted]

1.2 Study Description

This is a prospective, parallel, randomized, multi-center, 3-arm, patient-masked clinical study to evaluate the Centurion® Vision System during cataract extraction surgery followed by posterior chamber IOL implantation in adult patients (≥ 21 years of age).

For this study, the softest lenses (LOCSII Opacities N0 and NI) will be excluded, leaving all lenses with LOCSII Opacities NII-NIV.

For each group, cataract surgery will be performed on eligible subjects randomized with an equal number in the following three arms, having their surgery performed with each configuration.

Eligible subjects will be assigned in 1:1:1 ratio in either of the three study arms:

• Arm 1: Centurion® Vision System, 45°Balanced tip[1]
• Arm 2: Centurion® Vision System, 45°MFK tip[1]
• Arm 3: lnfiniti® Vision System, 45°MFK tip[2]

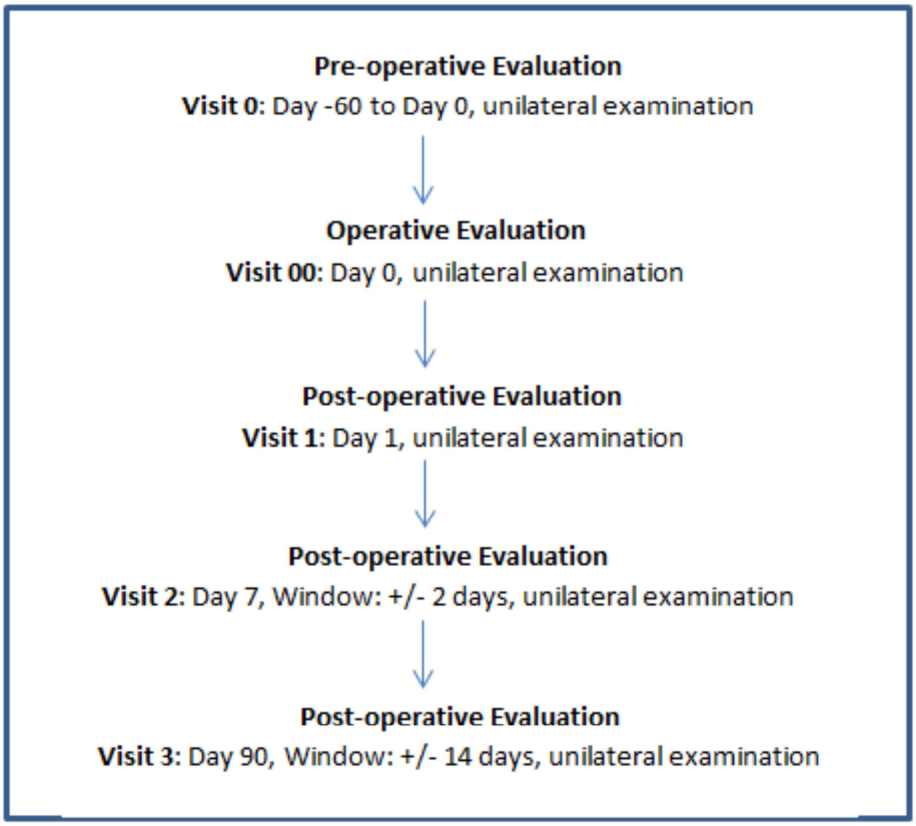
[1]Used with INTREPID® Ultra Infusion Sleeve
[2] Used with Ultra infusion Sleeve

Approximately 177 subjects (59 in each group) will undergo unilateral cataract surgery in the study to reach a minimum of 159 evaluable subjects (53 in each group) at the conclusion of the 3-month post-operative visit. Subjects will be enrolled sequentially in consent date and time order. The expected duration of subject participation is approximately five months. The study includes 5 visits as outlined below.

Table 1 – 1 Visit Schedule

Examination	Visit	Time for Procedure
Pre-operative (Screening)	Visit 0	-60 to 0 days from study eye surgery
Operative (Day of Surgery)	Visit 00	Day 0
1-Day post-operative follow-up	Visit 1	Day 1
1-Week post-operative follow-up	Visit 2	Day 7 (+/- 2 days)
3-months post-operative follow-up	Visit 3	Day 90 (+/- 14 days)

Figure 1 – 1 Study Design



1.3 Randomization

A randomization list will be generated by Sponsor personnel who is not involved in the day-to-day conduct of the study, and who does not have contact with the study subjects, the site, or the Alcon employees who do have site contact.

[redacted] Randomization should be completed within 2 working days prior to the date of surgery.

1.4 Masking

This is a subject-masked study and not observer-masked. Subjects will be masked to the treatment for the study eye. The surgeon (Investigator) is not masked to treatment as this is impossible with the medical devices studied here. Site personnel not participating in surgery and not requiring knowledge of randomization will be masked to the extent possible. Investigative sites will take all precautions necessary to ensure the subjects remain masked

for the duration of the trial. It is encouraged that the Investigator take the opportunity to remind the subject that he/she will be masked for the duration of the trial.

1.5 Interim Analysis

No interim analyses are planned for this study.

2 Analysis Sets

Three analysis sets are defined: Safety, Intention-to-Treat (ITT) and Per-Protocol Set (PPS).

2.1 Performance Analysis Sets

The ITT set will include all subjects who are randomized in the study and receive procedure. The ITT set will be the primary analysis set for performance.

The PPS is a subset of ITT which excludes those who meet the critical deviation criteria as specified in the Deviations and Evaluability Plan. Supportive analysis of the primary and secondary endpoints will be conducted using PPS if the number of subjects excluded from PPS exceeds 5% of the ITT.

2.2 Safety Analysis Set

The safety analysis set will include all subjects exposed to any study procedures evaluated in this study. Safety data is to be collected for each subject beginning at the time of informed consent.

2.3 Pharmacokinetic Analysis Set

Not Applicable.

3 Subject Characteristics and Study Conduct Summaries

Demographic information (age, sex, ethnicity, and race) and baseline characteristics will be summarized overall and by procedure group on the ITT set.

Descriptive statistics for the crystalline lens assessment LOCS II scores, as well as ECD and [redacted] will be presented by procedure group and overall. In addition, frequency and percentage of subjects randomized at each investigational site will be presented by procedure group and overall. A listing showing the baseline crystalline lens assessment LOCS II scores will be provided.

4 Performance Analysis Strategy

4.1 Performance Endpoints

Primary Endpoint

- Cumulative Dissipated Energy (CDE)

Secondary Endpoints

- CDE and BSS fluid use

BSS Used = Incision Leakage Fluid + Aspiration Fluid Used

Up to three specular microscopy images will be taken of the study eye at Visit 0 and Visit 3. The mean of the up to three values for endothelial cell density, coefficient of variation and percent hexagonal cells, rounded to one decimal place, will be used in the analyses.

4.2 Performance Hypotheses

4.2.1 Hypothesis for the Primary Endpoint

The null and alternative hypotheses for the primary endpoint are:

$$H_0: \mu_{\text{centurion\_Bal CDE}} \geq \mu_{\text{Infiniti\_MFK CDE}}$$

$$H_A: \mu_{\text{centurion\_Bal CDE}} < \mu_{\text{Infiniti\_MFK CDE}}$$

$\mu_{\text{centurion\_Bal CDE}}$ and $\mu_{\text{Infiniti\_MFK CDE}}$ are the true mean values of the primary endpoint, CDE under Centurion® with the Balanced tip, and Infiniti® with the MFK tip, respectively.

4.2.2 Hypothesis for the Secondary Endpoints

The null and alternative hypotheses for the secondary analyses are:

Secondary hypotheses 1

$$H_0: \mu_{centurion\_Bal\ CDE} \geq \mu_{centurion\ \_MFK\ CDE}$$

$$H_A: \mu_{centurion\_Bal\ CDE} < \mu_{centurion\ \_MFK\ CDE}$$

Where $\mu_{centurion\_Bal\ CDE}$ and $\mu_{centurion\_MFK\ CDE}$ are the true mean values of the secondary endpoint, CDE under Centurion® with the Balanced tip, and Centurion® with the MFK tip, respectively.

Secondary hypotheses 2

$$H_0: \mu_{centurion\_Bal\ BSS} \geq \mu_{lnfiniti\ \_MFK\ BSS}$$

$$H_A: \mu_{centurion\_Bal\ BSS} < \mu_{lnfiniti\ \_MFK\ BSS}$$

Where $\mu_{centurion\_Bal\ BSS}$ and $\mu_{lnfiniti\ \_MFK\ BSS}$ are the true mean values of the secondary endpoint, BSS under Centurion® with the Balanced tip, and lnfiniti® with the MFK tip, respectively.

Secondary hypotheses 3

$$H_0: \mu_{centurion\_MFK\ BSS} \geq \mu_{lnfiniti\ \_MFK\ BSS}$$

$$H_A: \mu_{centurion\_MFK\ BSS} < \mu_{lnfiniti\ \_MFK\ BSS}$$

Where $\mu_{centurion\_MFK\ BSS}$ and $\mu_{lnfiniti\_MFK\ BSS}$ are the true mean values of the secondary endpoint, BSS under Centurion® with the MFK tip, and lnfiniti® with the MFK tip, respectively.

Secondary hypotheses 4

$$H_0: \mu_{centurion\_MFK\ CDE} \geq \mu_{lnfiniti\ \_MFK\ CDE}$$

$$H_A: \mu_{centurion\_MFK\ CDE} < \mu_{lnfiniti\ \_MFK\ CDE}$$

Where $\mu_{centurion\_MFK\ CDE}$ and $\mu_{lnfiniti\ \_MFK\ CDE}$ are the true mean values of the secondary endpoint, CDE under Centurion® with the MFK tip, and lnfiniti® with the MFK tip, respectively.

4.3 Statistical Methods for Performance Analyses

4.3.1 Primary Performance Endpoint

The difference of CDE between two groups will be examined by using an analysis of covariance model (ANCOVA) adjusting for site and baseline opacity grade. Display of ANCOVA results in summary tables will contain difference between LS means, a one-sided p-value < 0.05 will conclude superiority of Centurion over Infiniti group.

4.3.2 Secondary Performance Endpoints

The difference between two groups will be examined by using ANCOVA adjusting for site and baseline opacity grade. Display of ANCOVA results in summary tables will contain difference between LS Means, a one-sided p-value <0.05 will conclude superiority.

4.4 Multiplicity Strategy

A sequential (closed) testing procedure will be used to control type I error rate due to multiplicity for primary and secondary endpoints at one-sided 0.05 significance level.

4.5 Subgroup Analyses and Effect of Baseline Factors

Not applicable.

4.6 Interim Analysis for Performance

Not applicable.

4.7 Handling of Missing Data

No imputation technique will be performed on missing values.

5 Safety Analysis Strategy

5.1 Safety Endpoints

The safety endpoints are:

- Adverse events (including Secondary Surgical Interventions (SSIs))
- Slit-lamp examination findings (clinical observations)
- Anterior chamber cells
- Anterior chamber flare
- Corneal edema
- Endothelial cell count
- Dilated fundus examination findings (clinical observations)
- Best corrected distant visual acuity (BCDVA)
- Intraocular pressure (IOP)
- Problems during surgery
- IOL placement
- Device deficiencies

Analysis for the anterior chamber cells, anterior chamber flare and endothelial cell counts will be presented in the performance analysis section.

5.2 Safety Hypotheses

There are no formal safety hypotheses in this study.

5.3 Statistical Methods for Safety Analyses

Safety analyses will be conducted using the safety analysis set on a treatment-emergent basis. The safety analysis set will include all subjects exposed to the investigational procedure. For treatment-emergent safety analyses, subjects will be categorized under the actual treatment received. Subjects exposed to an incorrect study treatment for the entire treatment period will be included in the group corresponding to the treatment received. Subjects exposed to an incorrect study treatment for a portion of the treatment period will be accounted for under the actual treatment the subject was first exposed to in the study.

Analysis of the safety endpoints will include descriptive statistics for each parameter by procedure group. Descriptive statistics generated for safety parameters will be based upon the type of parameter (i.e., whether the data are categorical or continuous) being analyzed. For categorical parameters, the statistics used to summarize the data descriptively will include sample size, number in the category and percent in the category. For continuous parameters, sample size, mean, median, standard deviation, minimum and maximum, etc. will be presented.

Listings describing details of adverse events will be provided. Listings describing details of adverse events reported prior to the surgery will be presented separately from the safety analysis.

5.3.1 Adverse Events

AEs will be coded by Medical Dictionary for Regulatory Activities (MedDRA). All AEs occurring from when a subject signs informed consent to when a subject exits the study will be accounted for in the reporting. A treatment-emergent AE is an event not present prior to exposure to investigational product or any pre-existing event that worsens following exposure to investigational product.

Descriptive summaries (counts and percentages) for specific AEs will be presented by System Organ Class (SOC) and Preferred Term (PT). In addition to an overall presentation of all AEs, if applicable, reports will be generated for special classes of AEs such as most , ocular AEs, non-ocular AEs, investigational product-related AEs, serious AEs, and AEs resulting in treatment discontinuation. Relatedness and severity will be presented for each AE entry. These reports will be supported by individual subject's listings, as necessary.

Only subject listings will be provided for AEs that occur after signing informed consent but prior to exposure to investigational procedure. These listings will comprise all events occurring during this period in any subject who consented to participate in the study.

5.3.2 Slit Lamp Examination

Slit-lamp examination will be performed at all non-operative visits (pre-operative Visit 0 and post-operative Visit 1, Visit 2, Visit 3) and at any unscheduled visit.

Number and percentage of slit lamp findings will be summarized for each visit by procedure. A listing including all slit-lamp data will be provided for each visit by procedure.

5.3.3 Corneal Edema

[redacted]

Grade from 0 to 3 for signs of corneal edema are: 0-None, 1-Mild, 2-Moderate and 3-Severe.

Corneal edema grade will be summarized for each visit by procedure. A listing of corneal edema grade will be provided for each visit by procedure.

5.3.4 Dilated Fundus Examination

Fundus examination will be performed at pre-operative Visit 0 and post-operative Visit 3.

Number and percentage of fundus exam findings will be summarized for each visit by procedure. A listing of fundus exam findings will be provided for each visit by procedure.

5.3.5 Best Corrected Distance Visual Acuity (BCDVA)

Best corrected distance visual acuity (BCDVA) will be performed at Screening (Visit 0), Day 7 (Visit 2) and Day 90 (Visit 3) visits.

Observed and change from baseline BCDVA values will be presented descriptively. In addition, frequency and percentages of subjects who experience a pre-specified category of change in BCDVA from Baseline to last post-baseline assessment visit and maximum loss from Baseline to any post-baseline assessment visit will be presented according to the following mutually exclusive categories: <1 line loss or improvement, ≥1 line loss and ≥2 line loss.

A listing of all subjects with a ≥2 line in BCDVA from baseline to any post-baseline visit will be presented. For subjects who had ≥2 line loss at any study visit, BCDVA values at all visits will be presented. Subject listings will include the following variables: investigational procedure, subject, age, sex, race, visit, eye, baseline VA, VA at the visit and VA change from baseline.

5.3.6 Intraocular Pressure

IOP assessment is performed at all non-operative visits (pre-operative Visit 0 and post-operative Visit 1, Visit 2, Visit 3), and at any unscheduled visit.

Descriptive summaries (N, mean, median, and standard deviation, minimum and maximum, etc.) of observed values and change from baseline values will be presented at each study visit by procedure.

A listing will be provided by procedure which presents all the subjects with an increase or decrease in IOP of more than 10 mmHg at any visit compared to the same eye at baseline.

5.3.7 Problems during Surgery

Surgical problems are collected at operative Visit 00 (Day 0).

Numbers and percentages on operative eye with surgical problems will be presented by procedure. A listing of subjects with surgical problems will be provided by procedure.

5.3.8 IOL Placement

IOL placement data is collected at operative Visit 00 (Day 0).

Numbers and percentages on eye(s) with a change from baseline in IOL position category (Tilted, Decentered) will be presented by procedure. A listing of subjects with IOL position change will be provided by procedure. The listing will include the following variables: procedure, investigator, subject, age, sex, visit, eye and amount of tilting or decentration.

5.3.9 Device Deficiencies

Device deficiencies data is collected at operative Visit 00 (Day 1). A frequency table showing counts and percentages for each device deficiency category will be provided by procedure. A listing of all device deficiencies will be provided by procedure.

5.4 Interim Analysis for Safety

Not Applicable.

6 Sample Size and Power Calculations

Based on previous studies, a sample size of 53 subjects in each procedure group will have a 80% power to detect a mean difference of -7.4 percent-seconds in CDE between the two procedure groups (Centurion® with the 45° Balanced tip minus lnfiniti® with the MFK tip) using a two-sample t-test with a one-sided 5% level of significance, assuming a common standard deviation of 15.2.. Assuming a 10% dropout rate, 59 subjects per procedure group (up to 177 in total) will be randomized.

7 References

See protocol Section 17 for details.

8 Revision History

8.1 Revisions for Version 2.0

The following revisions were made to Version 2.0 of the Statistical Analysis Plan to provide additional clarification to the analysis of performance and safety endpoints.

- Analysis of Anterior chamber cells, Anterior chamber flare and Endothelial cell counts were removed from the safety analysis section as it was already covered under the performance analysis section. In addition, some editorial changes were made to the safety endpoints.

- To be consistent with the protocol, changes were made to the reporting of BCDVA data using logMAR instead of number of letters read.

- Additional editorial changes.

8.2 Revisions for Version 3.0

The following revisions were made to Version 3.0 of the Statistical Analysis Plan to correct the calculation for Estimated Incision Leakage and to provide clarification on how endothelial cell density data would be analyzed.

In Section 1.1, the sentences:

[redacted]

*BSS Used for Centurion = (Bag Weight after Prime)-(Bag Weight after surgery) – 0.5ml
*BSS Used for Infiniti = (Bottle Weight after prime)-((Bottle weigh after Surgery)

[redacted]

were changed to

[redacted]

*BSS Used for Centurion = (Bag Weight after Prime) – (Bag Weight after Surgery) – 0.5ml
*BSS Used for Infiniti = (Bottle Weight after prime) – (Bottle Weight after Surgery)

[redacted]

In addition, the following sentences were added to Section 4.2:

Up to three specular microscopy images will be taken of the study eye at Visit 0 and Visit 3. The mean of the up to three values for endothelial cell density, coefficient of variation and percent hexagonal cells, rounded to one decimal place, will be used in the analyses.

9 Appendix

Table 11.-1 Schedule of Visits

Activity	Visit 0 (-60 to 0 d) *Unilateral examination*	Visit 00 (0 d) *Unilateral examination*	Visit 1 (1 d) *Unilateral examination*	Visit 2 (7 +/- 2 d) *Unilateral examination*	Visit 3 (90 +/- 14d) *Unilateral examination*
Informed Consent	X				
Demographics	X				
Medical History	X	X			
Concomitant Medications	X	X	X	X	X
Inclusion/Exclusion	X	X			
Surgery		X			
Problems During Surgery		X			
Other Procedures at Surgery		X			
Lens Information		X			
IOL Placement		X			
Programmable Phacoemulsification Settings		X			
Phacoemulsification Metrics *(Including CDE, BSS Fluid Use,* [redacted]		X			
Visual Acuity (UCDVA & BCDVA)	X			X	X
Intraocular Pressure	X		X	X	X
Specular Microscopy	X				X
[redacted]	X		X	X	
Slit Lamp Examination	X		X	X	X
Crystalline Lens Assessment	X				
Anterior chamber cells and flare	X		X	X	X
Dilated Fundus Examination	X				X
Randomization*	X				
Adverse Events *(Including Secondary Surgical Intervention)*	X	X	X	X	X
Device Deficiencies		X			
Complete Exit Form[1]					X

[1]If a subject exits early, the Visit 3 procedures should be performed at the last available visit, if at all possible.

*Randomization should be completed within 2 working days prior to the date of surgery.

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