Statistical Analysis Plan

CLINICAL EVALUATION OF THE VISION PERFORMANCE OF TECNIS EYHANCE™ INTRAOCULAR LENSES WITH TECNIS SIMPLICITY™ AS COMPARED TO TECNIS® 1-PIECE INTRAOCULAR

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STATISTICAL ANALYSIS PLAN

CLINICAL EVALUATION OF THE VISION PERFORMANCE OF TECNIS EYHANCE™ INTRAOCULAR LENSES WITH TECNIS SIMPLICITY™ AS COMPARED TO TECNIS® 1-PIECE INTRAOCULAR

PROTOCOL NUMBER: EMON-101-EHCE

SPONSOR
Johnson & Johnson Surgical Vision, Inc. ("JJSV")
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Irvine, CA 92618

SAP CHANGE HISTORY

Version	Section(s)	Description of Change(s)	Rationale for Change(s)
1.0	N/A	Original	N/A

1 INTRODUCTION

This document summarizes the statistical methods for analyses of effectiveness and safety data for the TECNIS Eyhance Intraocular Lenses in clinical study (protocol EMON-101-EHCE). This study is a 6-month, prospective, multicenter, bilateral, randomized, subject- and evaluator-masked clinical trial conducted at up to 15 sites in the USA. Subjects will be randomly assigned to receive the study Eyhance IOL or the control monofocal IOL. Up to 220 (110 test, 110 control) subjects will be enrolled in order to achieve 200 treated subjects at 6 months. No site may enroll more than 25% of the total sample size.

1.1 STUDY OBJECTIVES

The purpose of this clinical study is to compare the clinical outcomes for subjects bilaterally implanted with the TECNIS Eyhance Intraocular Lenses to those bilaterally implanted with TECNIS 1-piece Intraocular Lenses. All study endpoints will be evaluated at 6-months postoperative.

1.2 STUDY ENDPOINTS

PRIMARY EFFECTIVENESS ENDPOINT

The primary safety endpoint is the mean monocular first-eye best-corrected distance visual acuity (BCDVA) at 6 months.

SECONDARY EFFECTIVENESS ENDPOINTS

The secondary effectiveness endpoints are:

1. The mean monocular first-eye distance corrected intermediate visual acuity (DCIVA) at 66 cm at 6 months.
2. [redacted]

SAFETY ENDPOINTS

- Rate of secondary surgical interventions related to optical properties of the lens
- Rate of SPE-type adverse events (first-eye) vs. ISO SPE rates
- Rate of monocular (first-eye) BCDVA [redacted] vs. ISO SPE rates

OTHER ENDPOINTS

- [redacted]

- [redacted]

1.3 RANDOMIZATION AND MASKING

A randomization list stratified by investigational sites was created by a JJSV biostatistician who is independent and not involved in the study activities. Subjects will be randomized to TECNIS Eyhance IOL or the control IOL in 1:1 ratio. Unmasked study personnel at the site will be trained to the randomization process through the EDC system and will randomize subjects after the subject has signed the informed consent form, has met all eligibility criteria and the investigator has documented which eye will be the first implanted.

[redacted]

[redacted] Recommended steps to maintain masking include ensuring that all items pertaining to lens group assignment and lens implantation records are kept separately from all other study documents and subject medical records until after completion of the final study visit. [redacted]

[redacted]

2 ANALYSIS POPULATIONS AND GENERAL STATISTICS

2.1 ANALYSIS POPULATIONS

- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

- [redacted]

[redacted]

- [redacted]

[redacted]

Appendix I lists the planned analysis tables including the endpoints, the populations and missing data handling rules used.

2.3 VISIT WINDOWS

All subjects will undergo a minimum of 5 visits: Preoperative for both eyes, 1st eye operative, 2nd eye operative, postoperative for [redacted] at 1 month and 6 months. The exact number of days allowed for each interval is described in the protocol. The number of eyes with missing visits or data outside of the visit interval will be reported.

2.4 DATA CONVENTIONS

For visual acuity data, Snellen acuity will be converted to LogMAR prior to analysis[4]. Formulas used for visual acuity analysis are included in Appendix II. For refractive data, all values will be converted to plus cylinder [redacted]. Formulas used for refractive data are also included in Appendix II.

[redacted]

[4] [redacted]

[redacted]

3 ACCOUNTABILITY/ENROLLMENT

Descriptive statistics will typically include sample size (N), mean, standard deviation (SD), median, minimum (Min.), and maximum (Max.) as appropriate for continuous variables. For categorical data, the counts and percentages will be computed.

3.1 ACCOUNTABILITY

All summaries will be by OVD group. The number of enrolled subjects will be tabulated by site. Subject accountability will be summarized as a frequency distribution (counts and percentages) by scheduled visits. A frequency table will be generated, showing the number of available eyes (those in interval and outside of the interval) and the number of missing and active subjects.

4 DEMOGRAPHICS AND PREOPERATIVE/OPERATIVE PARAMETERS

Subject demographic data including age, sex, race, iris color and ethnicity will be presented by IOL group. Age will be categorized by less than 60, 60-69, 70-79 and ≥ 80 years old. In addition, age will be summarized with descriptive statistics. The frequency distribution of sex, race, iris color and ethnicity will also be tabulated. To ensure comparable demographic characteristics between groups, statistical testing will be performed. [redacted]Deviations from the proposed statistical guidelines will be substantiated by sound statistical rationale. In this study, unless otherwise indicated, two-sample t-tests will be used for continuous data, Wilcoxon rank sum test for ordinal data and Fisher's Exact test for categorical data.

5 POSTOPERATIVE ANALYSES – PRIMARY/SECONDARY ENDPOINTS

[redacted]

5.1 PRIMARY EFFECTIVENESS ENDPOINT

The primary effectiveness endpoint is the mean monocular first-eye best-corrected distance visual acuity at 4 m under photopic conditions at 6 months. The non-inferiority comparison between the IOL groups will be conducted using the two-sided 90% confidence interval on the mean BCDVA difference based on a t-distribution. The mean, SD, median, minimum, maximum and two-sided 90% C.I. will be presented by IOL

group. Note that lower logMAR value is a better acuity and a higher logMAR value is a poorer acuity. The null hypothesis is that the mean difference between the test and control IOLs is less than or equal to -0.1 logMAR, with the alternative hypothesis being that the mean difference is greater than -0.1 logMAR. A lower bound of the two-sided 90% confidence interval will be used for evaluation based on a two-sample t-test statistic. The success criterion is that the lower limit of the two-sided 90% confidence interval is above -0.1 logMAR.

H_o: $\mu_c - \mu_t \leq -0.10$ (test is inferior (higher logMAR value) to control)
H_1: $\mu_c - \mu_t > -0.10$ (test is not inferior (lower logMAR value) to control)

where

μ_t = the mean logMAR BCDVA for test group
μ_c = the mean logMAR BCDVA for control group

5.2 SECONDARY EFFECTIVENESS ENDPOINTS

MEAN DISTANCE-CORRECTED INTERMEDIATE VISUAL ACUITY AT 66 CM (DCVA66)

The first secondary effectiveness endpoint is the mean monocular first-eye distance-corrected intermediate visual acuity at 66 cm under photopic conditions at 6 months. The DCVA66 will be summarized (n, mean, SD, median, minimum, maximum) with the two-sided 95% CI by IOL group. Comparisons of mean DCVA66 between the test and control groups at 6 months will be performed using a two-sample t-test with a one-sided alpha level of 0.025.

The null hypothesis is that the mean monocular DCVA66 logMAR value for eyes in the test group is worse than or equal to that for the control group. The alternate hypothesis is that the mean monocular DCVA66 logMAR value for the test group is better than that for the control group.

H_o: $\mu_c - \mu_t \leq 0$ (test is worse than (higher LogMAR value) or equal to control)
H_1: $\mu_c - \mu_t > 0$ (test is better (lower LogMAR value) than control)

where

μ_t = the mean LogMAR DCVA66 for test group
μ_c = the mean LogMAR DCVA66 for control group

The success criterion is a statistically significantly better mean DCVA66 (lower LogMAR value) for test lens compared to the control lens group ($p \leq 0.025$).

[redacted]

6 SAFETY ENDPOINTS

The safety population will be the primary analysis set for the safety endpoints. Best-case population will also be used in the analysis of BCDVA [redacted] vs. ISO SPE rate. First-eye data will be the primary analysis for safety endpoints. [redacted]

SECONDARY SURGICAL INTERVENTION RELATED OPTICAL PROPERTIES OF THE LENS

The counts and percentages of secondary surgical interventions (SSIs) related to optical properties of the lens will be reported by IOL group.

SPE RELATED ADVERSE EVENT VS. ISO SPE RATES

The counts and percentages of SPE-type adverse events will be reported by IOL group. The rate in the test lens group will be compared to the ISO Safety and Performance Endpoints (SPE) rates listed in ISO 11979-7 using two-sided 90% Clopper Pearson Exact confidence interval with no CIs multiplicity adjustment.

Success criteria is that the SPE grid that the lower two-sided 90% confidence limit of the test group is lower than the SPE rate.

MONOCULAR BCDVA VS. ISO SPE RATES

The counts and percentages of monocular BCDVA [redacted] will be presented by IOL group. The rate in the test lens group will be compared to the ISO SPE grid using two-sided 90% Clopper Pearson Exact confidence interval with no CIs multiplicity adjustment.

Success criteria is that the upper two-sided 90% confidence limit of the test group is higher than the SPE rate.

7 POSTOPERATIVE ANALYSES – OTHER ENDPOINTS

The safety population will be used for the analyses of all other endpoints.

7.1 OTHER VISUAL ACUITY ENDPOINTS

For other visual acuity endpoints, descriptive statistics will be reported for each IOL group and the difference between IOL groups. In addition, the counts and percentages

of eyes/subjects achieving each line will be reported over time by IOL group for all visual acuity endpoints.

[redacted]

7.3 MANIFEST REFRACTION

For manifest refraction, descriptive analysis of refractive sphere, cylinder, spherical equivalent (SEQ) and postoperatively SEQ minus intended SEQ will be reported by IOL groups and the difference between IOL groups for both eyes. In addition, the counts and percentages of each eye within certain diopter categories will be tabulated for refractive cylinder, SEQ and postoperatively SEQ minus intended SEQ by IOL groups for first and second eyes.

7.4 MEDICAL FINDINGS/ADVERSE EVENTS (NON-SERIOUS, NON-DEVICE RELATED)

Rates of medical findings/adverse events will be tabulated with counts and percentages of eyes with these events reported over time by OVD group.

Reporting of cumulative complications and cumulative adverse events (occurring at any time postoperative or at standard visits) will include data from all study eyes implanted.

[redacted]

[redacted]

8 SAMPLE SIZE CALCULATIONS

Study sample sizes are based on the minimum of 100 evaluable subjects per study group for visual acuity. [redacted].

8.1 MONOCULAR BEST-CORRECTED DISTANCE VISUAL ACUITY (BCDVA) AT 4 M

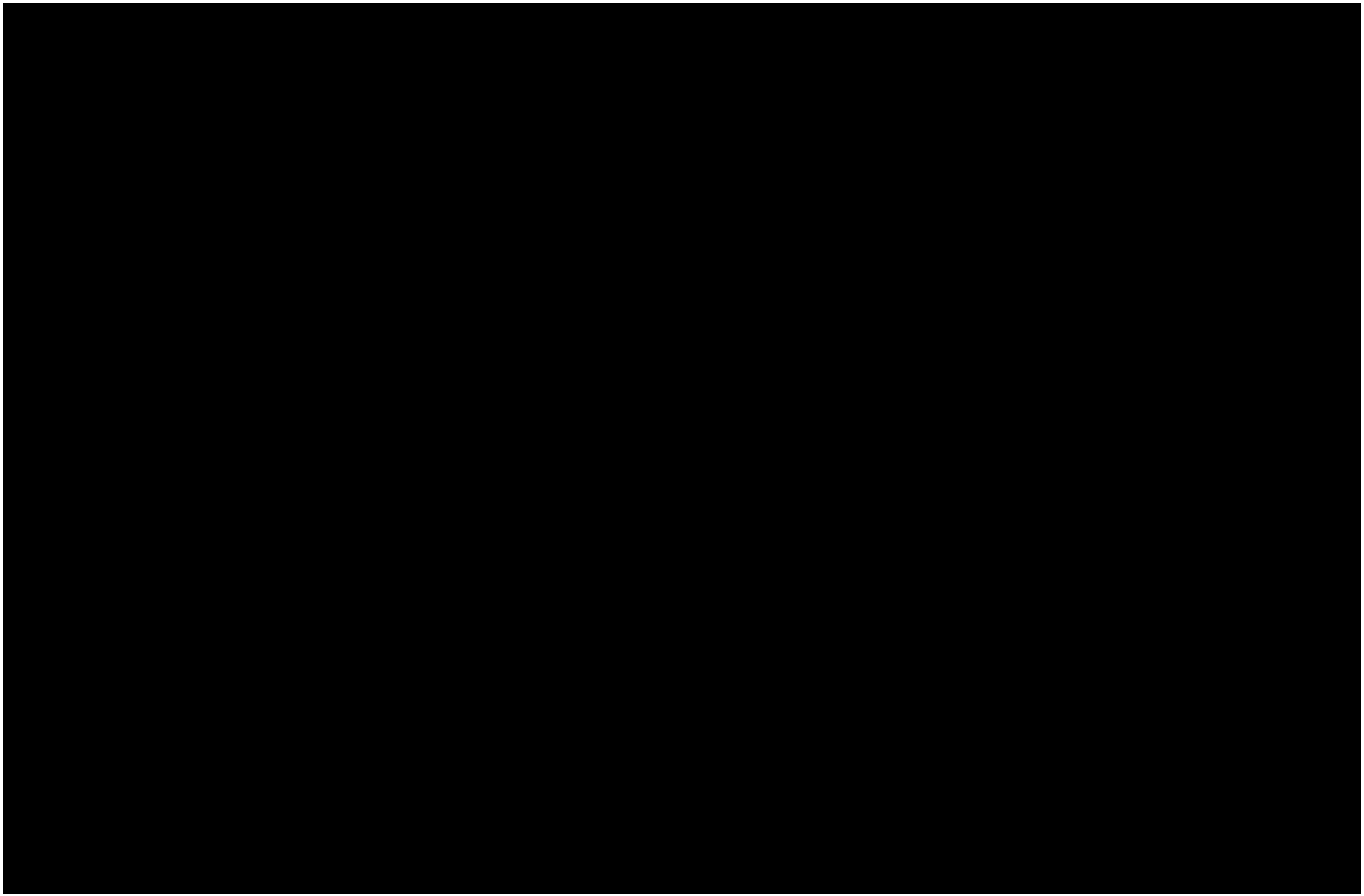
For monocular best-corrected near visual acuity at 4 m (BCDVA), with 100 subjects in each lens group there is over 90% power to conclude non-inferiority in visual acuity between the test and control lens group at two-sided alpha of 0.10 with a non-inferiority margin of 1 line, assuming there is no difference between the IOLs and a standard deviation of 1.2 lines.

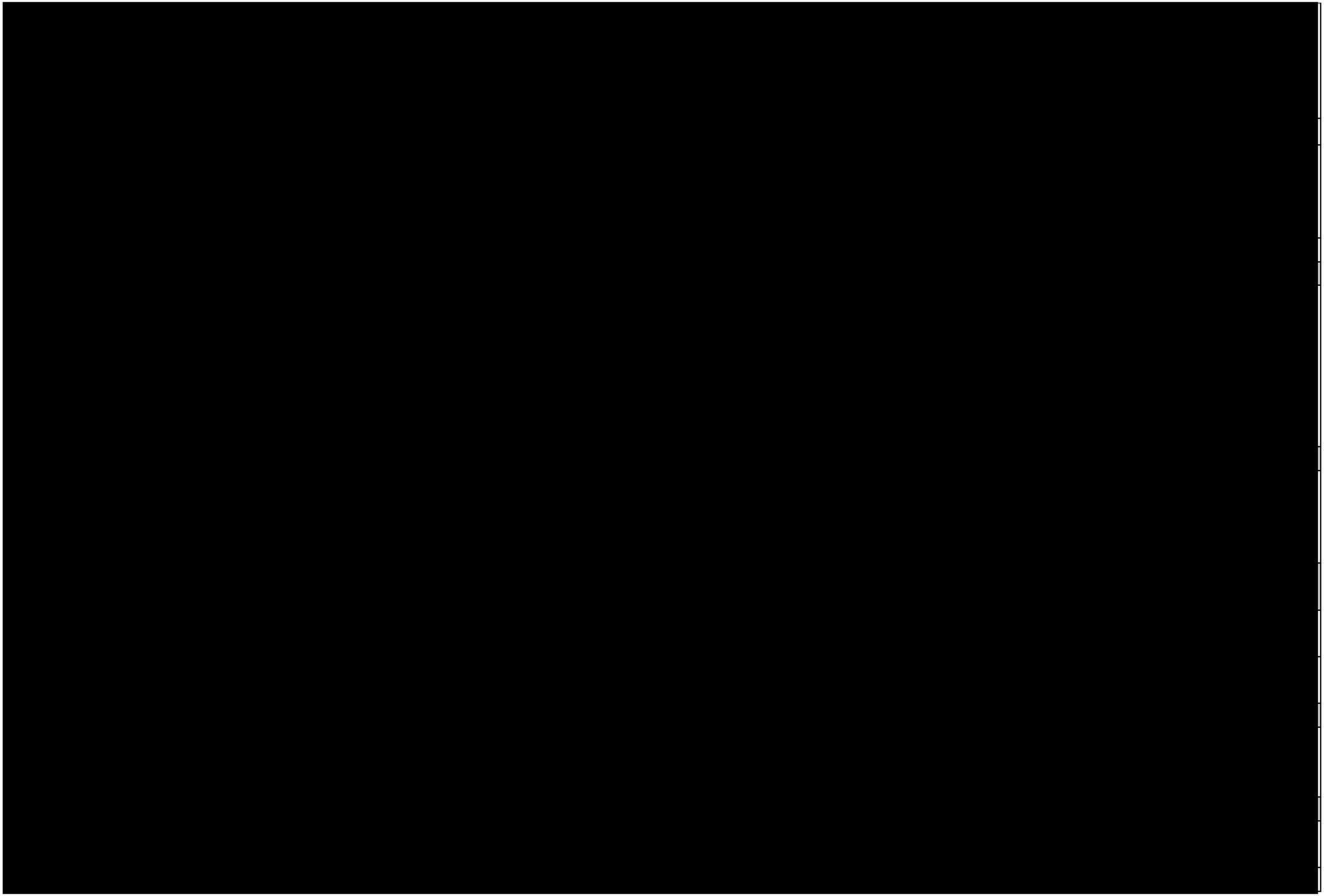
8.2 MONOCULAR DISTANCE-CORRECTED INTERMEDIATE VISUAL ACUITY AT 66 CM (DCVA66)

For monocular distance-corrected intermediate visual acuity at 66 cm, with 100 subjects in each lens group, there is over 90% power at one-sided 0.025 alpha to detect a 0.8-line or greater difference in mean visual acuity between the test lens and control lens groups, assuming a standard deviation of 1.6 lines.

[redacted]

APPENDIX I: TABLE LISTING





[redacted]

[redacted]

TIME FRAME: The 6-month postoperative visit is the key timeframe for reporting.
STATISTICS: See text portion of the statistical analysis plan for information on inferential statistics for comparisons between IOL groups

APPENDIX II: FORMULAS USED FOR VISUAL ACUITY, REFRACTIVE DATA, AND CONTRAST SENSITIVITY

[redacted]

Key: " * " = multiplication, " - " = subtraction, " / " = division, " ** " = exponent,
log10 = log in base 10, CRF = Case Report Form

Formulas for Converting Distance, Intermediate and Near VA to LogMAR Values [redacted]

[redacted]

[redacted]

[redacted]

Formulas for 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

Formulas for Refractive Data

[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

Spherical Equivalent (SEQ)

Signature Page for VTMF-17329976, V-TMF Version: 1.0
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[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Signature Meaning:
To verify that the content is accurate and true to the best of my knowledge.