

Statistical Analysis Plan

Clinical Investigation of the TECNIS® Next-Generation
Intraocular Lens, Model DEN00V

PROTOCOL NUMBER: PCOL107AHNG

NCT Number: NCT05574959

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STATISTICAL ANALYSIS PLAN

**Clinical Investigation of the TECNIS® Next-Generation Intraocular Lens, Model
DEN00V**

PROTOCOL NUMBER: PCOL107AHNG

SPONSOR

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SAP CHANGE HISTORY

Version	Section(s)	Description of Change(s)	Rationale for Change(s)
1.0	N/A	Original	N/A
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Version	Section(s)	Description of Change(s)	Rationale for Change(s)
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	[REDACTED] [REDACTED]	[REDACTED] [REDACTED]	[REDACTED] [REDACTED]
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1.0 INTRODUCTION

This document summarizes the statistical methods for the analyses of effectiveness and safety data of the TECNIS® Next-Generation Intraocular Lens, Model DEN00V in the clinical study protocol PCOL107AHNG. This study is a 6-month, prospective, multicenter, bilateral, two-arm, randomized, sponsor-, subject- and evaluator-masked clinical trial conducted at up to 10 sites in the USA. Subjects will be randomly assigned to receive the study investigational DEN00V IOL or the control monofocal ZCB00 IOL. The original planned sample size is to enroll up to 250 subjects [REDACTED]

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1.1 STUDY OBJECTIVES

The purpose of this clinical study is to compare the clinical outcomes for subjects bilaterally implanted with the TECNIS DEN00V lenses to those bilaterally implanted with TECNIS 1-piece IOL Model ZCB00 lenses. The first eyes are the primary eyes and the second eyes are the fellow eyes. The key study timeframe for all effectiveness and safety endpoints is 6 months.

1.2 STUDY ENDPOINTS

Primary effectiveness Endpoints

1. Monocular (first-eyes) photopic distance-corrected intermediate visual acuity (DCIVA) at 66 cm at 6 months
2. Monocular (first-eyes) distance-corrected depth of defocus at 6 months

3. Monocular (first-eyes) photopic best-corrected distance visual acuity (BCDVA) at 4 meters at 6 months

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1.3 RANDOMIZATION AND MASKING

Randomization will be first stratified by site. Within each site, the random assignment will be further stratified based on age group (< 70 years vs. ≥ 70 years), sex (male vs. female), and cataract severity (trace/mild vs. moderate/severe) of the first eye. The randomization list will be created by a JJSV biostatistician who is independent and not involved in the study activities. Using computer-generated randomization code stratified by site and age group, subjects will be randomized in ratio 1:1 to bilaterally receive the investigational IOL Model DEN00V or control IOL Model ZCB00. [REDACTED]

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2.0 ANALYSIS POPULATIONS AND GENERAL STATISTICS

2.1 ANALYSIS POPULATIONS

- ITT: Intent-to-treat (ITT) population will consist of all subjects randomized. Subjects will be analyzed per planned randomization schema.

- Safety: Safety Population (SP) will consist of all subjects for whom a study IOL touched the eye. Subjects will be analyzed per treatment received or attempted.
- Per-Protocol: First-eye Per-Protocol Population (first-eye PP) will include eyes with an investigational or control lens implanted, evaluated within the proper study interval and without clinically relevant protocol deviations (deviations that could potentially impact the primary or secondary endpoints at the key timeframe of the 6-month visit) as determined prior to database lock.
- Best-case population will consist of eyes in the safety population with no pre-operative ocular pathology, no macular degeneration detected at any time, and no previous surgery for the correction of refractive error.

2.2 MISSING DATA HANDLING RULES

2.2.1 MISSING DATA ANALYSIS METHODS

The primary and secondary effectiveness endpoints analyses are based on the first-eye data. Missing values for the primary (DCIVA and BCDVA) and secondary (DCNVA) effectiveness endpoints, regardless of being collected from bilateral subjects or unilateral subjects, will be handled as described below. [REDACTED]

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Observed case data: an additional analysis based on available observed case data will be performed for completeness ignoring missing values.

2.3 VISIT WINDOWS

All subjects will undergo the following visits: Preoperative for both eyes, 1st eye operative, 2nd eye operative, postoperative 1-day, 1-week and 1-month visits for each eye, and 6-month visit. 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 analysis⁴. Formulas used for visual acuity analysis are included in Appendix II. For refractive data,

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all values will be converted to plus cylinder with sphere adjusted for infinity⁵. Formulas used for refractive data are also included in Appendix II.

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

2.5 TYPE I ERROR RATE AND MULTIPLICITY ADJUSTMENT

To control the overall study Type I error rate at 0.05 level, all the hypothesis tests on the primary endpoints must show statistical significance simultaneously (statistical success) before testing the secondary effectiveness endpoint (DCNVA) at full one-sided alpha level of 0.025.

No multiplicity adjustment is planned for the primary safety endpoints or other endpoints.

2.6 SITE POOLABILITY AND TREATMENT PAUSE

For the primary endpoints at 6 months, the site poolability and the impact of the treatment pause analyses will be performed using the first eyes observed case data in the ITT population.

2.6.1 SITE HETEROGENEITY

██████████ will be used to evaluate site heterogeneity by investigation of site effect and site-by-lens group interaction, separately for each of the primary endpoints (DCIVA and BCDVA) at 6 months. ██████████

Since there is no inferential statistics for the defocus curve primary effectiveness endpoint, only graphs of the defocus curve will be presented by site.

3.0 ACCOUNTABILITY/ENROLLMENT

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. Subject accountability table will present number of available eyes (those in interval and outside of the interval) and the number of missing and active subjects.

4.0 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. [REDACTED]

[REDACTED]

[REDACTED]

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Preoperative and operative parameters for first and second eyes will be reported for each IOL group. The frequency counts and proportions of eyes with selected responses will be tabulated for categorical data with descriptive statistics used for continuous data.

Baseline demographic data will be reported by site for completeness.

5.0 PRIMARY/SECONDARY EFFECTIVENESS ENDPOINTS

The ITT population will be the primary analysis set for the primary endpoints (DCIVA and defocus) and the secondary effectiveness endpoint. Both the ITT and PP populations will be the primary analysis sets for the primary BCDVA (non-inferiority) endpoint.

Effectiveness of the lens and study success will be demonstrated if all success criteria for the following 3 primary endpoints are simultaneously met based on the ITT multiple imputation analysis for DCIVA and BCDVA and ITT observed case for defocus curve.

5.1 PRIMARY EFFECTIVENESS ENDPOINTS

The primary effectiveness endpoints at 6 months will be summarized descriptively by IOL group.

5.1.1 MONOCULAR PHOTOPIC DCIVA AT 66 CM

The first primary endpoint is the mean (logMAR), monocular (first eye) DCIVA (66 cm) under photopic conditions at 6 months. The mean, SD, median, minimum, maximum and two-sided 95% C.I. will be reported by IOL group. The comparison between lens groups will be performed using a one-sided, two-sample t-test with an alpha level of 0.025.

Note that a lower or more negative logMAR value denotes a better visual acuity and a higher or more positive logMAR value denotes a poorer visual acuity. The null hypothesis is that the mean monocular DCIVA logMAR value for eyes in the investigational group is worse than or equal to that for control eyes. The alternate hypothesis is that the mean monocular DCIVA logMAR value for eyes in the investigational lens group is better than that for control eyes.

$H_0: \mu_c - \mu_t \leq 0$ (DEN00V is worse than (higher logMAR) or equal to control)

$H_1: \mu_c - \mu_t > 0$ (DEN00V is better (lower logMAR) than control)

where

μ_t = the mean logMAR DCIVA for investigational (DEN00V)

μ_c = the mean logMAR DCIVA for control (ZCB00)

Statistically significant superiority of the investigational lens will be achieved if pvalue $\leq$ 0.025. [REDACTED]

5.1.2 MONOCULAR DEPTH OF FOCUS

The second primary endpoint is mean monocular depth of defocus where visual acuity is 0.20 logMAR or better at 6 months (measured only negative direction from zero) for first eyes in investigational vs. control groups at 6 months. The mean visual acuity at each diopter of defocus will be plotted to obtain a defocus curve for both lens groups. The diopter of defocus where mean visual acuity crossing 0.20 logMAR will be calculated for each IOL group by the following method:

[REDACTED]

Clinical performance criterion: The diopter intercepts 0.20 logMAR on defocus curve is at least 0.50 D or more for the investigational lens vs. the control.

5.1.3 MONOCULAR PHOTOPIC BCDVA AT 4 M

The third primary effectiveness endpoint is mean (logMAR) first-eye, monocular BCDVA (4 m) at 6 months postoperative. The mean, SD, median, minimum, maximum and two-sided 90% CI for BCDVA will be reported by IOL group. The hypothesis is that the investigational lens is non-inferior to the control lens. This is demonstrated by the lower limit of the 90% two-sided confidence interval (CI) of the difference in mean (logMAR) first-eye monocular BCDVA (4 m) at 6 months not exceeding the non-inferiority margin of -0.10 logMAR. The two-sided 90% confidence interval will be calculated using the two-sample t-test statistic.

$H_0: \mu_c - \mu_t \leq -0.10$ (DEN00V is inferior to control)

$H_1: \mu_c - \mu_t > -0.10$ (DEN00V is not inferior to control)

where

μ_t = mean logMAR BCDVA for investigational (DEN00V)

μ_c = mean logMAR BCDVA for control (ZCB00)

The statistical criterion requires the lower bound of the 2-sided 90% confidence interval for the difference between the IOLs to be greater than -0.10 logMAR.

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8.0 SAMPLE SIZE CALCULATIONS

The study sample size satisfies the requirements for a Level B modification of a parent lens per ISO/TR 22979:2017 (E) and ANSI Z80.35-2018 which requires a minimum of 100 bilaterally implanted evaluable subjects in each IOL group. The screen failure rate is assumed to be around 10%, and the dropout rate up to 6 months is assumed to be approximately 10%. Accounting for the screen failure rate and the dropout rate, the study will enroll approximately 250 subjects [REDACTED]

[REDACTED]

In addition to satisfying the ISO sample size requirement, a total of 200 bilateral subjects evaluable at 6 months (the same original total sample size for powering the study) provide the following statistical power levels for comparing the IOL groups on the primary effectiveness endpoints while controlling for the study Type I error rate of 0.05.

Monocular Photopic Distance Corrected Intermediate Visual Acuity (66 cm)

For monocular (first-eye), distance corrected intermediate visual acuity (DCIVA), with 100 subjects in each lens group there is over 90% power to detect a 0.10 logMAR or greater difference in mean visual acuity between the investigational and control lens groups using a one-sided two-sample t-test at a one-sided alpha of 0.025 and assuming a standard deviation of 0.16 logMAR.

Monocular Depth of Focus

There is no statistical comparison for this endpoint; therefore, no formal sample size calculation was performed.

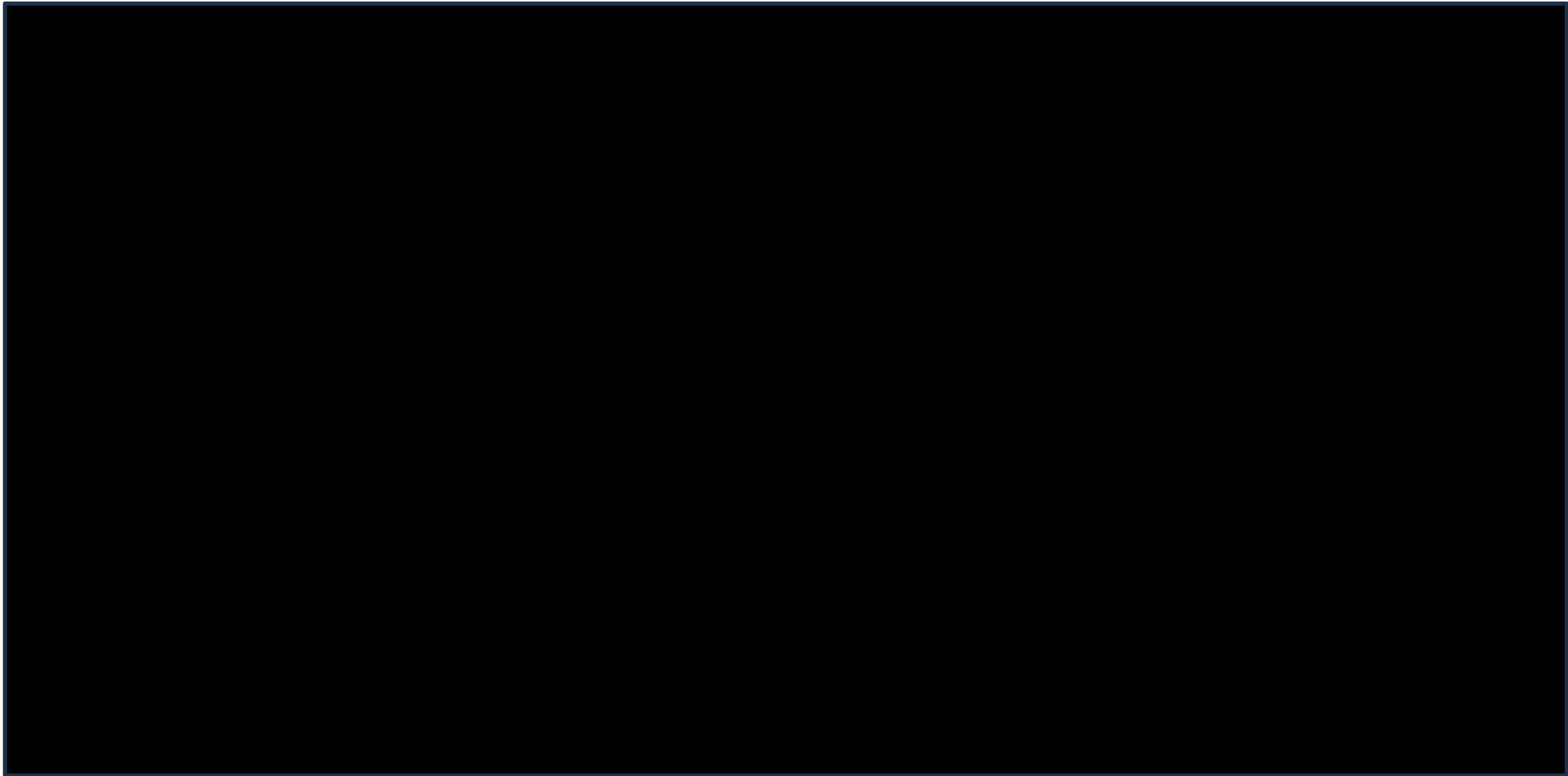
Monocular Photopic Best-Corrected Distance Visual Acuity (4 m)

For monocular (first-eye), best-corrected distance visual acuity (BCDVA), with 100 subjects in each lens group there is over 90% power to conclude non-inferiority in visual acuity between the investigational and control lens groups at one-sided alpha of 0.05 with non-inferiority margin of 0.10 logMAR, assuming no difference between the IOLs and a standard deviation of 0.12 logMAR. The two-sided 90% confidence interval will be calculated using the two-sample t-test statistic.

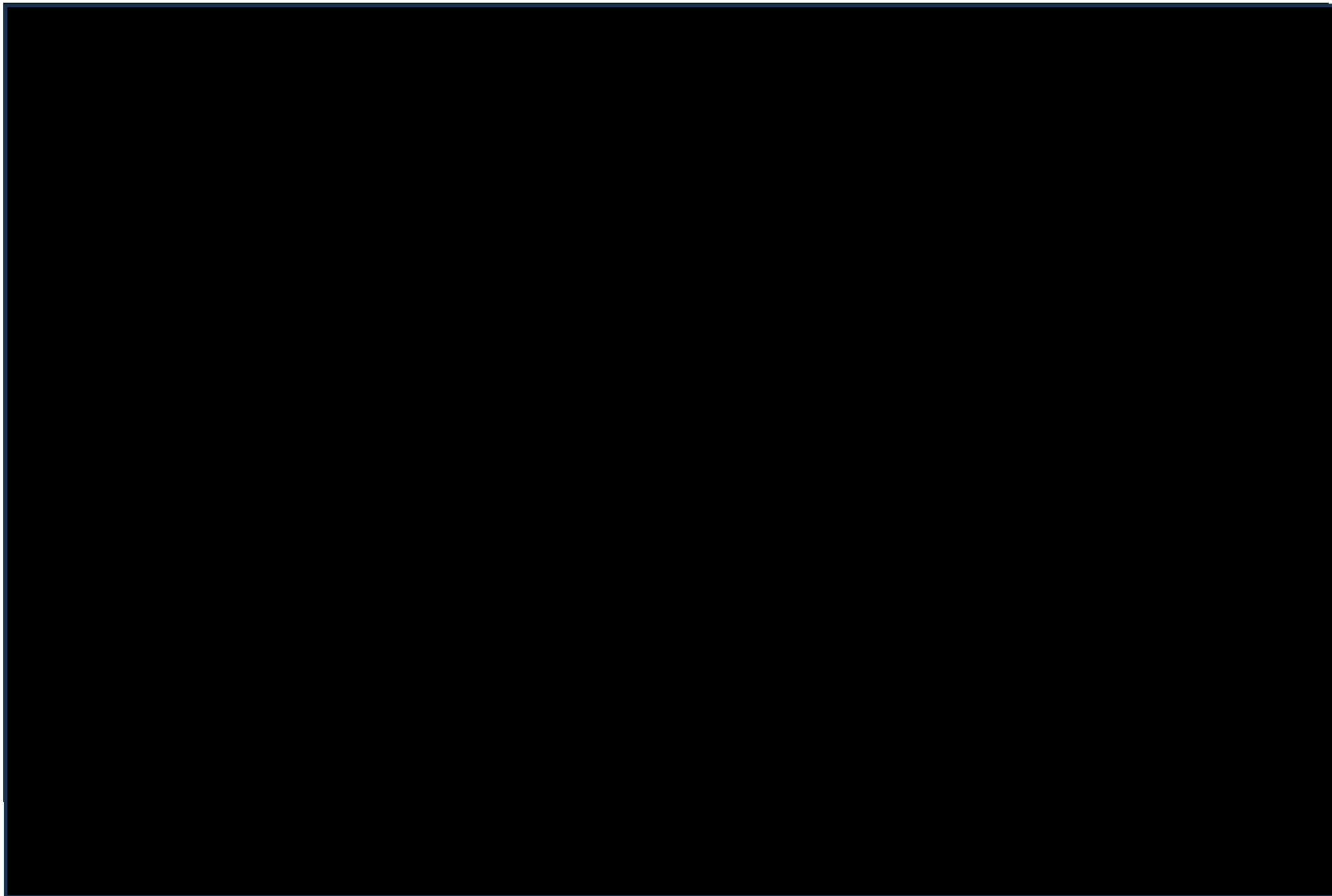
Monocular Photopic Distance Corrected Near Visual Acuity (40 cm)

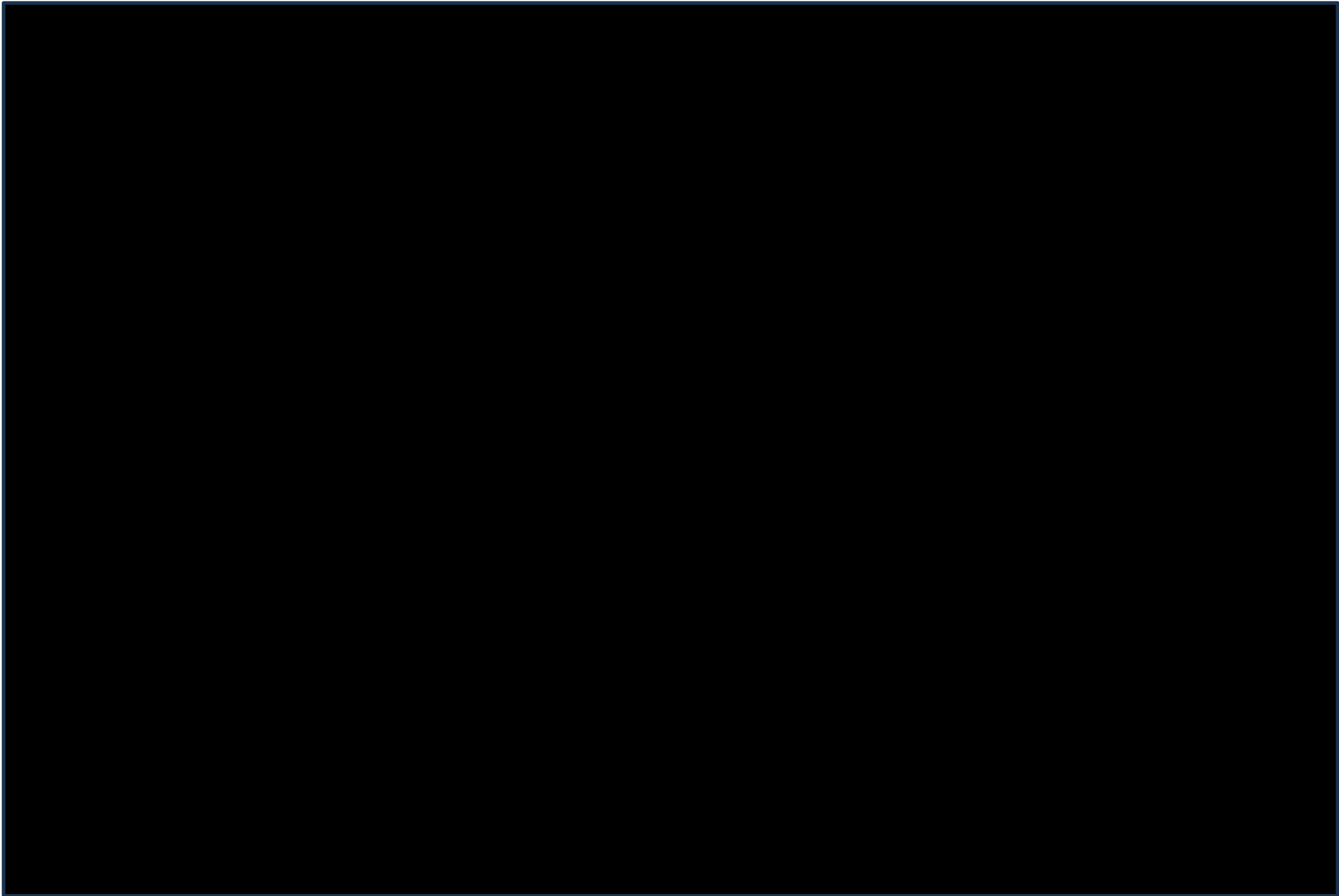
For monocular (first-eye), distance corrected near acuity (DCNVA), with 100 subjects in each lens group there is over 90% power to detect a 0.10 logMAR or greater difference in mean visual acuity between the investigational and control lens groups at a one-sided alpha of 0.025, using a two-sample t-test and assuming standard deviation of 0.16 logMAR.

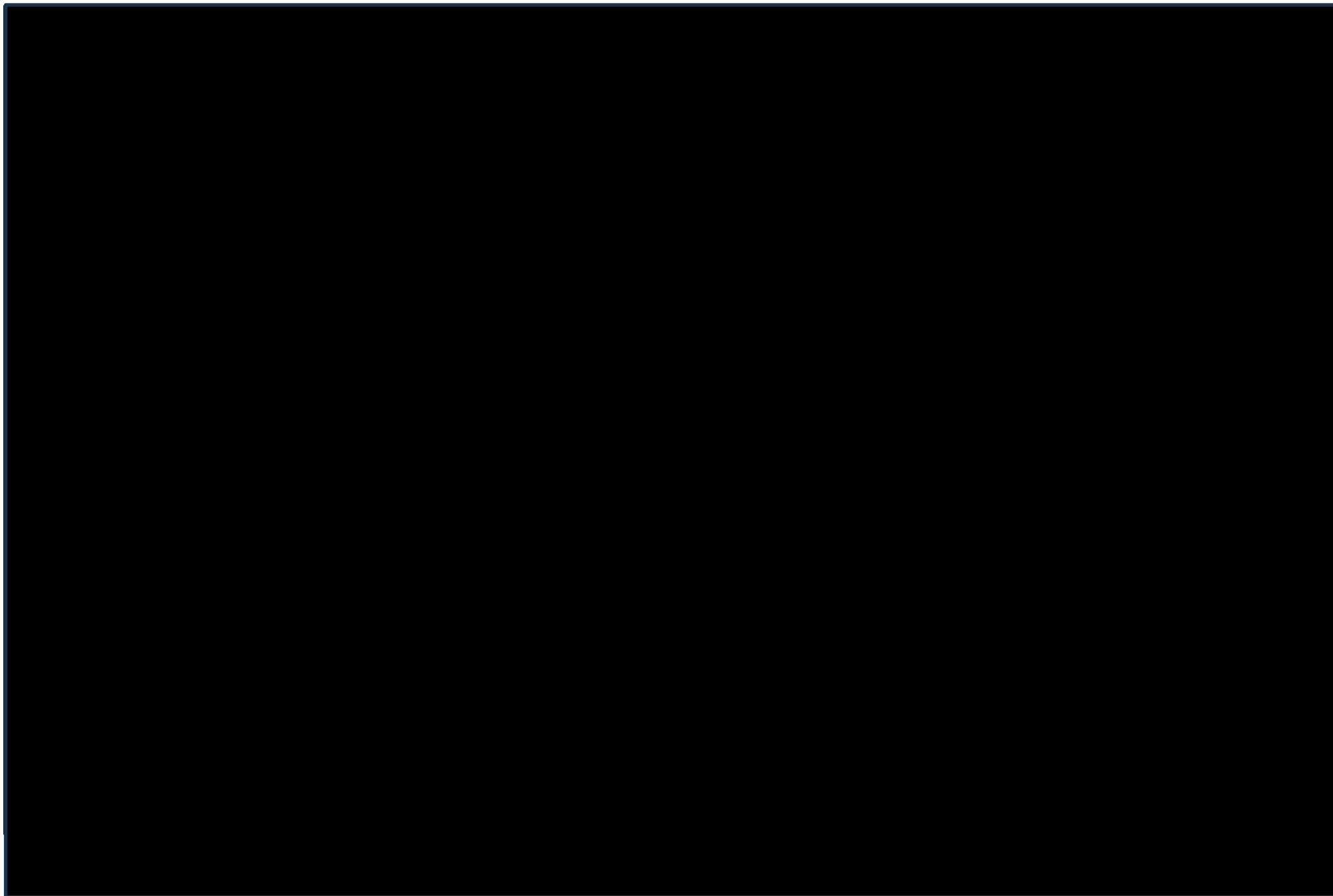
Because the gate keeping testing approach applies to testing the primary endpoints first, followed by the secondary endpoint, the sample size calculation for the secondary endpoint of DCNVA at 40 cm was performed at the nominal one-sided 0.025 alpha level.

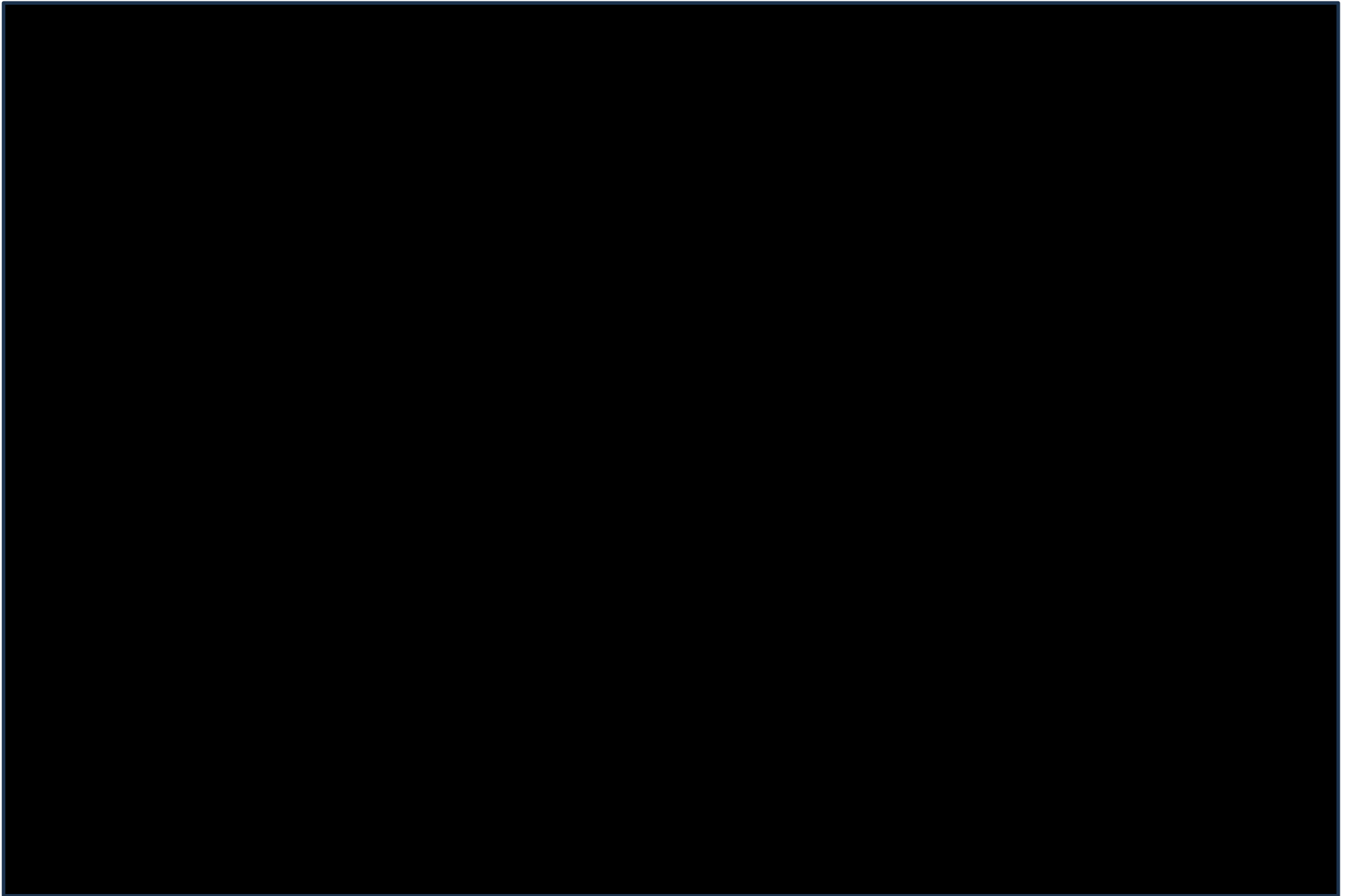


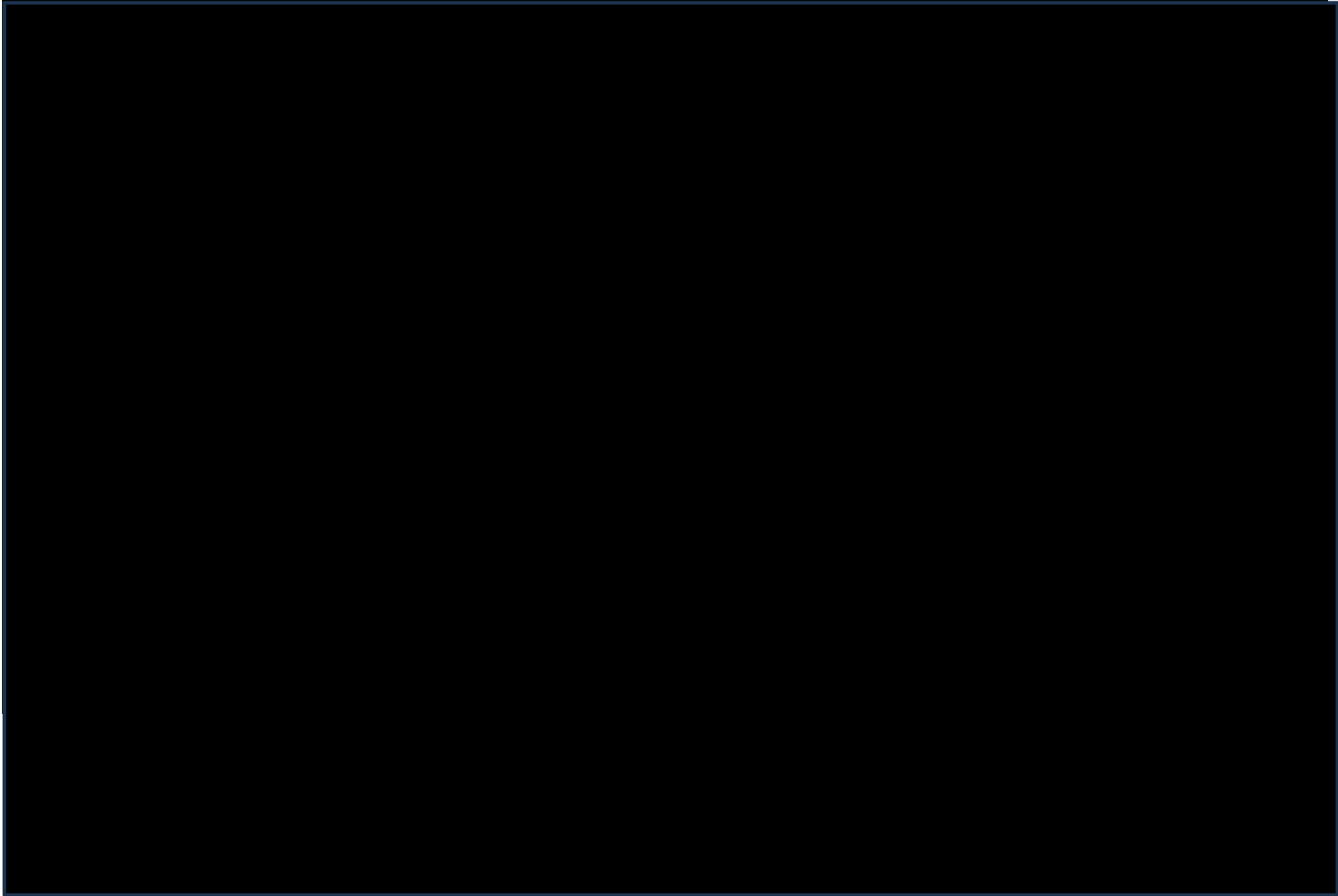












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