# STATISTICAL ANALYSIS PLAN

# PROTOCOL NUMBER IOPCL AMD-20

## Early Feasibility Study to Evaluate the Safety and Effectiveness of the IOPCL AMD MAG for Secondary Implantation in the Capsular Bag to Improve Near Vision in Subjects with Age-Related Macular Degeneration after Cataract Surgery

NCT: 04984590

December 6, 2022

**APPENDIX 6: STATISTICAL ANALYSIS PLAN**

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| **Protocol Number:** | IOPCL AMD-020 |
| **Version:** | 1.3; December 6, 2022 |
| **Protocol Title:** | Early Feasibility Study to Evaluate the Safety and Effectiveness of the IOPCL AMD-MAG for Secondary Implantation in the Capsular Bag to Improve Near Vision in Subjects with Age-Related Macular Degeneration after Cataract Surgery |
| **Sponsor:** | OnPoint Vision Inc.<br>6A Liberty, Suite 100<br>Aliso Viejo, CA 92656<br>U.S.A. |

## APPROVAL SIGNATURES

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|---|---|
| **Product:** | AMD-MAG Intraocular Pseudophakic Contact Lens |
| **Protocol Number/Amendment:** | IOPCL AMD-020 |
| **SAP Version:** | 1.3 |
| **Version Date:** | December 6, 2022 |

The individuals signing below have reviewed and approve this statistical analysis plan.

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## TABLE OF CONTENTS

## LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | Adverse event |
| ANOVA | Analysis of variance |
| BCDVA | Best corrected distance visual acuity |
| BCNVA | Best corrected near visual acuity |
| CI | Confidence interval |
| CS | Contrast sensitivity |
| CSR | Clinical study report |
| EFS | Early feasibility study |
| ETDRS | Early Treatment Diabetic Retinopathy Study |
| IOP | Intraocular pressure |
| IOPCL | Intraocular pseudophakic contact lens |
| MRSE | Manifest refraction spherical equivalent |
| OCT | Optical Coherence Tomography |
| PCIOL | Pseudophakic intraocular lens |
| SAP | Statistical Analysis Plan |
| UBM | Ultrasound biomicroscopy |
| UCDVA | Uncorrected distance visual acuity |
| UCNVA | Uncorrected near visual acuity |
| VFQ-25 | Visual Function Questionnaire-25 |

# 1 INTRODUCTION

This Statistical Analysis Plan (SAP) outlines the statistical methods to be implemented within the scope of Protocol IOPCL AMD-20, entitled "Early Feasibility Study to Evaluate the Safety and Effectiveness of the IOPCL AMD-MAG for Secondary Implantation in the Capsular Bag to Improve Near Vision in Subjects with Age-Related Macular Degeneration after Cataract Surgery." Results of the proposed analyses will become the basis of the clinical study report for this protocol.

The purpose of this plan is to provide specific guidelines from which the analysis will proceed. All planned analyses specified in this document will be performed. Any changes to this plan, in the form of "post hoc" or "data driven" analyses will be identified as such in the final clinical study report. Any changes will either be reflected in amendments to this plan before the database lock or specifically documented in the clinical study report.

# 2 STUDY OBJECTIVE

The primary objective of this study is to determine the stability of the IOPCL AMD-MAG to successfully adhere to a pseudophakic intraocular lens without rotation or slippage.

The secondary objective of this study is to determine if the IOPCL-AMD-MAG can improve uncorrected near visual acuity in subjects previously implanted with an Alcon SN60WF, SA60AT or SA60WF monofocal intraocular lens.

# 3 STUDY ENDPOINTS

## 3.1 Effectiveness Endpoint

### 3.1.1 Primary Effectiveness Endpoint

The primary effectiveness endpoint identified for this Early Feasibility Study for IOPCL AMD-MAG is:

- Proportion of eyes (≥ 75%) able to achieve 10 letters or more of uncorrected near visual acuity (at 14 cm) at 12 months from baseline.

### 3.1.2 Secondary Effectiveness Endpoints

The secondary effectiveness endpoints identified for this Early Feasibility Study for IOPCL AMD-MAG are:

- Proportion of eyes (≥ 50%) able to achieve 20 letters or more of uncorrected near visual acuity (at 14 cm) at 12 months from baseline.
- Proportion of eyes (≥75%) able to achieve improvement of 10 letters or more when comparing uncorrected near visual acuity (UCNVA) (at 14 cm) at 12 months from baseline BCNVA (at 30 cm, wearing the appropriate preoperative distance refractive correction in addition to +3.0D add).

- Proportion of eyes (≥50%) able to achieve improvement of 20 letters or more when comparing uncorrected near visual acuity (UCNVA) (at 14 cm) at 12 months from baseline BCNVA (at 30 cm, wearing the appropriate preoperative refractive distance correction addition to +3.0D add).
- Proportion of eyes (≥ 75%) able to achieve improvement of 10 letters or more when comparing best corrected near visual acuity (BCNVA) (at 14 cm) at 12 months from baseline BCNVA (at 30 cm, wearing the appropriate preoperative distance refractive correction in addition to +3.0D add).
- Proportion of eyes (≥ 50%) able to achieve improvement of 20 letters or more when comparing best corrected near visual acuity (BCNVA) (at 14 cm) at 12 months from baseline BCNVA (at 30 cm, wearing the appropriate preoperative distance refractive correction in addition to +3.0D add).

### 3.1.3 Exploratory Effectiveness Endpoints

The following exploratory effectiveness endpoints evaluated for eyes that achieve ≥ 20 letters of improvement in UCNVA during preoperative simulation testing.

- Proportion of eyes (≥ 75%) achieving improved reading speed (at 40 cm) at 12 months from baseline defined as ≥ 2 lines/blocks of gain with a decrease in reading speed ≥ 1 minute and with overall improvement in critical point size
- Proportion of eyes (≥ 75%) achieving independence from external magnifier usage at 12 months postoperatively

## 3.2 Safety Endpoints

- Preservation of Best Corrected Distance Visual Acuity (BCDVA)

The preservation of BCDVA is defined as proportion of eyes (< 5%) that lose two or more lines (≥10 letters) of BCDVA at 12 months from baseline.

- Preservation of Best Corrected Near Visual Acuity (BCNVA)

Proportion of eyes (<5%) that lose two or more lines of BCNVA (≥10 letters on the Sloan Near Vision Chart at 14 cm) at 12 months from baseline.

- Incidence of secondary surgical intervention (SSI)
- Successful Delivery of the IOPCL as determined as all postoperative scheduled visits starting at 7-14 days postoperative.

The successful delivery of the IOPCL is defined as no capsular tear, no visible damage to either the IOL or IOPCL, and uniform leaflet coverage of all IOPCL haptic tabs.

- Long-term Adherence and Positional Stability

The long-term adherence and positional stability is defined as 1) minimal change in uniformity of the gap between consecutive scheduled visits at 1-2 months and later as determined by UBM imaging (where minimal change is defined as +/- 10 microns between visits established and maintained using UBM imaging).

- Tilt
    - Tilt of the PCIOL as determined at all post-operative scheduled visits starting at 30-60 days post-operative. Minimal tilt of the PCIOL confirmed via penlight examination and defined as ≤ 10 degrees between the postoperative tilt of the PCIOL and the pre-operative tilt of the PCIOL.
    - Tilt of the IOPCL AMD-MAG as determined at all post-operative scheduled visits starting at 30-60 days post-operative. Minimal tilt of the IOPCL AMD-MAG (using the PCIOL as a reference point) confirmed via penlight examination and defined as ≤ 10 degrees between the post-operative tilt of the PCIOL and the postoperative tilt of the IOPCL AMD-MAG.
- Decentration
    - Decentration as determined at all post-operative scheduled visits starting at 7-14 days post-operative. Centration of the IOPCL AMD-MAG (using the PCIOL as a reference point) confirmed during slit lamp examination and defined as uniform exposed area of the PCIOL outside of the IOPCL AMD-MAG at the vertical and horizontal meridians between ≥ 0.25 mm and ≤ 0.75 mm.
- Adverse Events

Counts and percentages for incidence of cumulative and persistent intraoperative and postoperative adverse events.

- Secondary Surgical Interventions

Counts and percentages for incidence of secondary surgical interventions (e.g., removal of interlenticular opacity, repositioning of IOPCL, explant of IOPCL, repositioning of PCIOL) (excluding Nd:YAG treatments for PCO).

### 3.3 Other Clinical Outcomes

- Visual acuity parameters (BCDVA, BCNVA, UCDVA, UCNVA)
- MRSE stability
- Add power
- Slit lamp examination including assessment capsular stability, decentration and tilt
- Gonioscopy
- Reading speed
- Contrast sensitivity (mesopic)
- Applanation intraocular pressure (IOP) using Goldmann

- Dilated fundus examination
- Optical coherence tomography (OCT)
- Spatial visualization between PCIOL and IOPCL using ultrasound biomicroscopy (UBM)
- Specular microscopy
- Visual symptoms (VFQ-25)
- External magnifier usage

# 4 STUDY DESIGN

This will be a three (3) center US clinical trial, in which a maximum of 10 subjects will be implanted unilaterally with the IOPCL AMD-MAG and followed for 12 months.

The subjects who might be eligible are potentially interested in participating and have provided their informed consent will be examined preoperatively to obtain a medical history and to establish a baseline for their ocular condition. Qualified subjects who provide written consent will be enrolled into the study.

Subjects will undergo IOPCL implantation. Postoperatively, subjects will undergo a complete ophthalmic evaluation at regularly scheduled intervals in accordance with study protocol.

An Investigational Device Exemption (IDE) application will be submitted on clinical outcomes when all enrolled eyes have a chance of reaching the 4-6-month post-operative visit (Postop Form 4).

This study is being conducted in accordance with 21CFR, Parts 50, 54, 56 and 812.42 (U.S.C 282(j)). ISO 14155 Clinical investigation of Medical Devices for Human Subjects, ISO 11979-7, and the ethical principles laid down in the Declaration of Helsinki.

# 5 ANALYSIS POPULATIONS

The analyses will include the data of all study eyes where implantation of IOPCL was attempted and/or successful.

# 6 STATISTICAL CONSIDERATIONS

## 6.1 General Considerations

Descriptive statistics (mean, median, standard deviation, minimum, and maximum) will be used to summarize continuous variables. Frequencies and percentages will be used to summarize categorical variables.

Any analysis not described in this plan will be considered exploratory, and will be documented in the clinical study report (CSR) as a post hoc analysis or a change to the planned analysis.

### 6.2 Sample Size

Sample size is limited to maximum of 10 subjects (eyes) for this Early Feasibility Study (EFS).

### 6.3 Randomization and Masking

This study will not be randomized or masked.

### 6.4 Data Transformations and Derivations

- Age in years (round down) will be calculated using informed consent date and birth date.
- Time variables based on two dates (e.g., Start Date and End Date), will be calculated as (End Date – Start Date) (in days) unless otherwise specified in the planned analysis section. For example, the postoperative day = postoperative visit date – lens implantation date (i.e. surgical date).
- The following unit conversion will be implemented unless otherwise specified:
    - Months = Days / 30.4375
    - Years =Days / 365.25

### 6.5 Handling of Dropouts and Missing Data

All data analyses will be conducted based on available data. No imputation will be performed.

### 6.6 Examination of Subgroups

Due to the small sample size, no subgroup analyses will be conducted.

### 6.7 Covariates

Covariates are not considered for adjustment in the analyses.

### 6.8 Timing of Analyses

An interim analysis will be performed when all enrolled subjects either have been seen for their 4-6 month visit, or have earlier exited from the study before the 4-6 month visit, or the visit window has closed for the 4-6 month visit (i.e., missed visit).

Interim safety summaries will be provided for annual reports based on regulatory requirement. Postoperative follow-up through 12 months on all implanted subjects will be completed as per protocol at which the final report analysis will be performed.

## 7 PLANNED METHODS OF ANALYSES

### 7.1 Accountability and Disposition

Accountability of the eyes by visit will be provided based on ISO 11979-7:2018 for all eyes. Reasons for discontinuation of study will be summarized. The number and percentage of eyes and subjects in each analysis population will be summarized.

## 7.2 Demographic and Baseline Characteristics

Demographics, preoperative parameters, and operative parameters will be summarized descriptively by mean, standard deviation, median, minimum, and maximum for the continuous outcomes and by count and percentage for the categorical outcomes.

## 7.3 Protocol Deviations

Major protocol deviations are those that represent a divergence from the protocol that could have a significant effect on the integrity of the study data, or on the subject's rights, safety, or welfare. Major protocol deviations also include exemptions to the study inclusion/exclusion criteria and will be summarized by category. A list of subjects with major protocol deviations will be presented.

## 7.4 Effectiveness Analysis

### 7.4.1 Primary Analyses of the Primary Effectiveness Endpoint

The proportion of eyes able to achieve 10 letters or more of uncorrected near visual acuity (at 14 cm) at 12 months from baseline will be summarized.

### 7.4.2 Primary Analyses of the Secondary Effectiveness Endpoints

The proportion of eyes able to achieve 20 letters or more of uncorrected near visual acuity (at 14 cm) at 12 months from baseline will be summarized.

- Change in UCNVA from baseline will be reported in lines including the following bins: loss of 15 or more letters, loss of 10 or more letters, loss of more than 5 letters, no change (within +/- 5 letters), gain of more than 5 letters, gain of 10 or more letters, gain of 15 or more letters, gain of 20 or more letters.
- The UCNVA value of the implanted eyes will be summarized descriptively by mean, standard deviation, median, minimum, and maximum at 1 month or later.

The proportion of eyes able to achieve 10 letters or more of uncorrected near visual acuity (at 14 cm) at 12 months from baseline BCNVA (at 30 cm, wearing the appropriate preoperative distance refractive correction in addition to +3.0D add).

- Change in UCNVA from baseline BCNVA will be reported in lines including the following bins: loss of 15 or more letters, loss of 10 or more letters, loss of more than 5 letters, no change (within +/- 5 letters), gain of more than 5 letters, gain of 10 or more letters, gain of 15 or more letters, gain of 20 or more letters.

The proportion of eyes able to achieve 20 letters or more of uncorrected near visual acuity (at 14 cm) at 12 months from baseline BCNVA (at 30 cm, wearing the appropriate preoperative distance refractive correction in addition to +3.0D add).

- Change in UCNVA from baseline BCNVA will be reported in lines including the following bins: loss of 15 or more letters, loss of 10 or more letters, loss of more than 5 letters, no

change (within +/- 5 letters), gain of more than 5 letters, gain of 10 or more letters, gain of 15 or more letters, gain of 20 or more letters.

The proportion of eyes able to achieve 10 letters or more of best corrected near visual acuity (at 14 cm) at 12 months from baseline BCNVA (at 30 cm, wearing the appropriate preoperative distance refractive correction in addition to +3.0D add).

- Change in BCNVA from baseline will be reported in lines including the following bins: loss of 15 or more letters, loss of 10 or more letters, loss of more than 5 letters, no change (within +/- 5 letters), gain of more than 5 letters, gain of 10 or more letters, gain of 15 or more letters, gain of 20 or more letters.

The proportion of eyes able to achieve 20 letters or more of best corrected near visual acuity (at 14 cm) at 12 months from baseline BCNVA (at 30 cm, wearing the appropriate preoperative distance refractive correction in addition to +3.0D add).

- Change in BCNVA from baseline will be reported in lines including the following bins: loss of 15 or more letters, loss of 20 or more letters, loss of more than 5 letters, no change (within +/- 5 letters), gain of more than 5 letters, gain of 10 or more letters, gain of 15 or more letters, gain of 20 or more letters.

### 7.4.3 Exploratory Effectiveness Endpoints

The following exploratory effectiveness endpoints will be evaluated for eyes that achieve ≥ 20 letters of improvement in UCNVA during preoperative simulation testing.

- Proportion of eyes (≥ 75%) achieving improved reading speed (at 40 cm) at 12 months from baseline defined as ≥ 2 lines/blocks of gain with a decrease in reading speed ≥ 1 minute and with overall improvement in critical point size

  Change in reading speed will be reported as follows:

  - Change in lines/blocks using the following bins: loss of 3 or more blocks, loss of 2 or more blocks, loss of more than 1 block, no change (within 1 block), gain of more than 1 block, gain of 2 or more blocks, gain of 3 or more blocks, gain of 4 or more blocks.

  - Change in reading rate using the following bins: loss of 3 minutes or more, loss of 2 or more minutes, loss of more than 1 minute, no change (within 1 minute), gain of more than 1 minute, gain of 2 or more minutes, gain of 3 or more minutes, gain of 4 or more minutes.

  - Change in critical point size using the following bins: loss of 3 or more point sizes, loss of 2 or more point sizes, loss of 1 point size, no change in point size, gain of 1 point size, gain of 2 or more point sizes, gain of 3 or more point sizes, gain of 4 or more point sizes.

  Reading speed of the primary eyes will be summarized descriptively by mean, standard deviation, median, minimum, and maximum at 1 month or later.

- Proportion of eyes (≥ 75%) achieving independence from external magnifier usage at 12 months postoperatively

Independence from external magnifier usage will be reported using the following bins: continued usage of all external magnifier(s) used preoperatively (no change), deceased usage of 1 or more external magnifiers used preoperatively (partial independence); deceased usage of all external magnifiers used preoperatively (complete independence)

### 7.4.4 Additional Effectiveness Analyses

- All the available monocular uncorrected distance visual acuity and monocular uncorrected near visual acuity at each protocol specified scheduled visit will be presented for the primary eyes. The categorical presentations will include the visual acuity of 75 letters or better, 70 letters or better, 65 letters or better, 60 letters or better, 55 letters or better, 50 letters or better, 45 letters or better, 40 letters or better, and fewer than 40 letters.

## 7.5 Safety Analyses

The safety population will be used to summarize all safety endpoints. No imputation for the missing values will be performed.

### 7.5.1 Preservation of BCDVA

The analysis of this clinical outcome will be based on the observed data of IOPCL AMD-MAG. The number and percent of IOPCL implanted eyes with a BCDVA loss of 2 or more lines (≥10 letters) at 12 months from preoperative will be derived.

Additionally, if needed, data listing or summary will be provided for eyes with a BCDVA loss of ≥ 2 lines from the best BCDVA before the corresponding visits.

### 7.5.2 Preservation of BCNVA

The analysis of this clinical outcome will be based on the observed data of IOPCL AMD-MAG. The number and percent of IOPCL implanted eyes with a BCNVA loss of 2 or more lines (≥10 letters) at 12 months from preoperative will be derived.

Additionally, if needed, data listing or summary will be provided for eyes with a BCNVA loss of ≥ 2 lines from the best BCNVA before the corresponding visits.

### 7.5.3 Secondary Surgical Intervention (SSI)

For each SSI category, the cumulative number and percent of eyes reported with the SSI will be reported. A line listing will be reported for each SSI which will included subject ID, visit, visit date, SSI category, and clinical sequalae.

### 7.5.4 Successful Delivery of the IOPCL

The analysis of this clinical outcome will be based on the observed data of IOPCL AMD-MAG IOPCL. The number and percent of eyes with successful delivery of the IOPCL will be reported.

### 7.5.5 Long-term Adherence and Positional Stability

The analysis of this clinical outcome will be based on the observed data of IOPCL AMD-MAG IOPCL. The number and percent of eyes with established and maintained central spacing as determined by UBM imaging between the IOPCL and IOL will be reported. The number and percent of eyes reporting decentration of the IOPCL or tilt of the PCIOL and/or IOPCL will be reported.

### 7.5.6 Adverse Events

For each adverse event, number and percent of eyes reported with the event will be summarized at each scheduled visit (including intraoperatively) and during the study (i.e. cumulative and persistent).

### 7.5.7 Other Safety Analyses

#### 7.5.7.1 Best-corrected Distance Visual Acuity

All the available monocular best-corrected distance visual acuity at each protocol specified scheduled visit will be presented for the implanted eyes. The categorical presentations will include the visual acuity of 20/16 or better, 20/20 or better, 20/25 or better, 20/32 or better, 20/40 or better, 20/50 or better, 20/63 or better, 20/80 or better, and worse than 20/80.

#### 7.5.7.2 Best-corrected Near Visual Acuity

All the available monocular best-corrected near visual acuity at each protocol specified scheduled visit will be presented for the implanted eyes. The categorical presentations will include the visual acuity of 75 letters or better, 70 letters or better, 65 letters or better, 60 letters or better, 55 letters or better, 50 letters or better, 45 letters or better, 40 letters or better, and fewer than 40 letters.

#### 7.5.7.3 MRSE Stability

The MRSE mean, standard deviation, median, minimum, and maximum will be calculated. The percentage of eyes will be calculated for MRSE within ± 0.50 D and ± 1.00 D.

#### 7.5.7.4 Tonometry

Goldmann measurements of IOP and its change from baseline will be summarized descriptively at each visit.

#### 7.5.7.5 Slit Lamp, Gonioscopic and Fundus Examination Findings

Numbers and percentages of eyes will be summarized for each of the findings at each visit.

#### 7.5.7.6 Contrast Sensitivity (Mesopic)

Mesopic contrast sensitivity and its change from baseline will be summarized descriptively at each visit.

#### 7.5.7.7 Optical Coherence Tomography (OCT)

Numbers and percentages of eyes will be summarized for each of the findings at each visit.

#### 7.5.7.8 Specular Microscopy

Endothelial cell count and its change from baseline will be summarized descriptively at each visit.

#### 7.5.7.9 Visual Symptoms

Each item of the Visual Function Questionnaire (VFQ-25) will re-coded and a score calculated according to the NEI VFQ-25 Scoring Algorithm, for each subject at each specified visit. These scores will be summarized based on mean, standard deviation, minimum, and maximum. Similar descriptive statistics will be prepared for the change in the VFQ-25 from preoperative.

#### 7.5.7.10 Surgical Difficulty

The distribution of responses to surgical difficulty and managing of the capsular tissue will be summarized at the operative visit by number and percentages of eyes.

## 8 CHANGES FROM PLANNED ANALYSES

### 8.1 Changes from the Original Protocol

Version 1.1 – Added safety analyses for surgical difficulty.

Version 1.2 – Updated endpoint analyses and clinical assessments to reflect revision 4 of the clinical protocol.

Version 1.3 – Added secondary effectiveness endpoints (UCNVA at 12 months compared to BCNVA at baseline and BCNVA at 12 months compared to baseline); added safety endpoint for SSIs.

## 9 REFERENCES

ISO 11979-7, Ophthalmic implants - Intraocular lenses - Part 7: Clinical investigations, 2018.