SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: 2.5% Sodium Hyaluronate Ophthalmic Viscosurgical Device (OVD)

Device Trade Name: ClearVisc Ophthalmic Viscosurgical Device (OVD)

Device Procode: LZP

Applicant's Name and Address: Bausch Health
400 Somerset Corporate Boulevard
Bridgewater, NJ 08807

Date of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P200025

Date of FDA Notice of Approval: 3/23/2021

II. INDICATIONS FOR USE

ClearVisc is indicated for use as a surgical aid in ophthalmic anterior segment procedures including:

- Extraction of a cataract
- Implantation of an intraocular lens (IOL)

III. CONTRAINDICATIONS

There are no known contraindications to the use of ClearVisc as a surgical aid in ophthalmic anterior segment procedures.

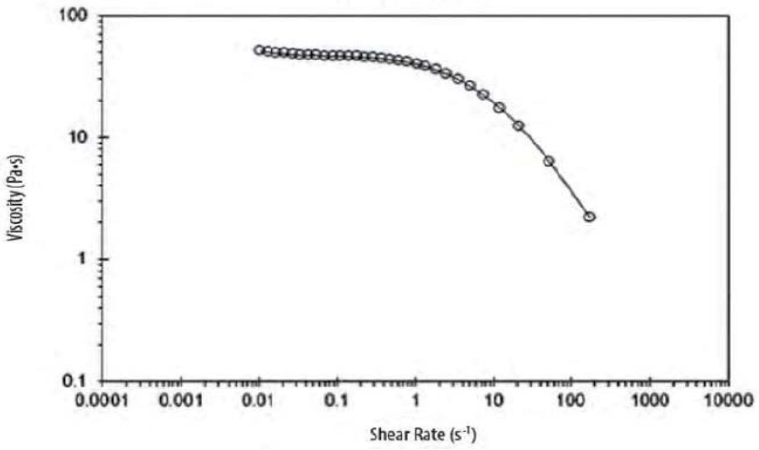
IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the ClearVisc OVD labeling.

V. DEVICE DESCRIPTION

Clearvisc OVD is a sterile, single-use formulation of sodium hyaluronate (NaHy) obtained from *Streptococcus pyogenes.* NaHy is a polysaccharide composed of repeating disaccharide units of sodium glucoronate and N-acetylglucosamine. ClearVisc OVD contains 25 mg/mL NaHy and 40 mg/ml of sorbitol, dissolved in physiological sodium chloride phosphate, tromethamine buffered solution with a pH of 6.8 to 7.6. The average molecular weight of the NaHy is 750,0000 Daltons (Da). The ClearVisc OVD has rheological dispersive properties.The viscosity of the ClearVisc OVD is 40 Pa.s at 25°C (77°F) and a shear rate of 1 s^{-1} (**Figure 1**). The osmolality is approximately 330 mOsm/Kg.

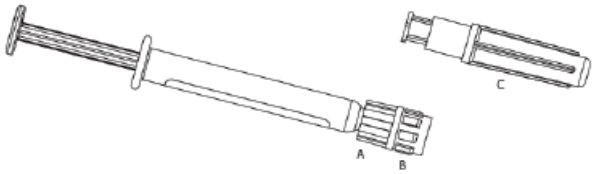
Figure 1: Rheological profile of the ClearVisc OVD



ClearVisc OVD is intended to protect intraocular tissues during surgery.

ClearVisc OVD is offered in a 1 mL glass syringe with a 25-gauge thin wall blunt canula. The cannula is attached to the syringe by a standard luer fitting and is used to inject the solution into the eye. In addition, ClearVisc OVD includes a polypropylene retention clip, which helps to maintain standard luer connection (preventing cannula detachment) between the syringe and cannula. The items are packaged in a custom polyethylene terephthalate, glycol-modified (PETG) tray with a Tyvek lid. The sealed trays are placed in a cardboard unit box along with the directions for use (DFU) and patient chart labels and secondarily sterilized with ethylene oxide (EO). **Figure 2** provides an illustration of syringe and canula.

Figure 2: Graphical representation of the syringe and cannula



Key: A - Luer Lock, B - Tip Cap, C - Cannula and Sheath

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several alternative OVDs available of varying formulations and properties. Each alternative has its own advantages and disadvantages.

VII. MARKETING HISTORY

ClearVisc OVD has not been marketed in the United States or any foreign country.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device. A known risk of OVDs is a transient postoperative increase in intraocular pressure (IOP) during the early postoperative period. Postoperative intraocular inflammation has been associated with the use of OVDs, including toxic anterior segment syndrome (TASS) due to high levels of endotoxin in the OVD resulting in product recall. Postoperative intraocular infection, i.e., endophthalmitis, has been reported due to contaminated OVD. These adverse effects can result in sequelae, such as corneal edema/decompensation and vision loss.

For the specific adverse events that occurred in the clinical study, please see Section X below.

IX. SUMMARY OF NONCLINICAL STUDIES

Characterization of the ClearVisc OVD

The characterization of the ClearVisc OVD had been conducted according to International Standard Organization (ISO) 15798, Ophthalmic implants- Ophthalmic Viscosurgical Devices. A summary of this characterization is provided in **Table 1**, below.

Table 1: **Characterization of the ClearVisc OVD**

Test	Purpose	Acceptance Criteria	Results
Absolute complex viscosity	Characterization of the physicochemical properties	Not applicable	The rheological profile was characterized at a controlled stress of 15 Pascal (Pa) over a frequency range of 0.001 to 100 Hz at a temperature of 25ºC ± 2ºC.
Chemical and biological contaminants	Evaluation of potential impurities (e.g., proteins, nucleic acids, solvents)	Not applicable	≤ 0.05% protein
Na Hy concentration	Characterization of the physicochemical properties	Not applicable	27 mg/ mL
Elasticity	Characterization of the physicochemical properties	Not applicable	The samples were analyzed at a controlled stress of 15 Pa over a frequency range of

			0.001 to 100 Hz at a temperature of 25°C ± 2°C.
Molecular mass distribution	Characterization of the physicochemical properties	Not applicable	Average molecular weight = 750,000 Da Polydispersity index = 1.30
Osmolality	Characterization of the physicochemical properties	Not applicable	342 mOsm / kg
Particulates	Evaluation of potential particulates	Not applicable	2.7 particles /g ≥ 10 µm 0.6 particles / g ≥ 25 µm
pH	Characterization of the physicochemical properties	pH= 6.8- 7.6	pH= 7.3
Refractive index	Characterization of the physicochemical properties	Not applicable	The refractive index was determined using a refractometer with 589 nm band pass filter. The refractive index is 1.3437.
Shear viscosity	Characterization of the physicochemical properties	Not applicable	The sample was analyzed at 25° ± 2°C over a range of shear rates from 0.001 to 1000 sec^{-1}. The Apparent Viscosity is 40 Pa.s at 25°C (77°F) and a shear rate of 1 s^{-1}.
Spectral transmittance	Characterization of the physicochemical properties	Not applicable	Spectral transmittance data was collected from 300 – 1100 nm using a calibrated

			spectrophotometer. Data was collected every 1 nm at 600 nm per minute. Samples were added directly to a quartz cuvette of 1 cm path length for analysis. Data was graphed as percent transmittance (%) vs. wavelength (nm).
Extrusion force	Evaluation of the extrusion force required to express the OVD from the syringe	Not applicable	2.90 lbf

Biocompatibility

Biocompatibility assessment was conducted on the finished sterile ClearVisc OVD or a similar OVD in accordance with ISO 15798 and ISO 10993-1, Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process, - Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity, - Part 5: Tests for in vitro cytotoxicity, - Part 10: Tests for irritation and sensitization, - Part 11: Tests for systemic toxicity. These assessments are summarized in **Table 2**.

All tests to evaluate the biocompatibility of the ClearVisc OVD were conducted in accordance with provisions of 21 CFR 58, Good Laboratory Practice (GLP) for Nonclinical Laboratory Studies.

Table 2: **Biocompatibility assessment of the ClearVisc OVD**

Test	Purpose	Acceptance Criteria	Results
Cytotoxicity (ISO 10993-5)	Evaluates the cellular toxicity potential of the device in vitro	Non-cytotoxic	Pass
Guinea pig maximization (ISO 10993-10)	Evaluates the sensitization potential of the device	Non-sensitizer	Pass
Bacterial reverse mutation test (Ames test)	Evaluates the mutagenic potential of the implant	Non-mutagenic	Pass

(ISO 10993-3)			
In vitro chromosome aberration test (ISO 10993-3)	Evaluates the clastogenic (large scale genetic damage) potential of the implant in Chinese hamster ovary cells	Non-clastogenic	Pass
Mammalian erythrocyte micronucleus test (ISO 10993-3)	Evaluates the potential of the implant to induce micronuclei in mice	The device did not lead to micronuclei formation	Pass
Acute systemic toxicity (ISO 10993-11)	Evaluates the systemic toxicity potential of the device in mice	Non-toxic	Pass
Implantation (intraocular)	Evaluates the ocular tissue responses to the device in rabbits	No significant biological local response	Pass
Clearance of residual OVD from the anterior chamber (ISO 15789)	Evaluates the clearance of the radio-labeled OVD from the anterior chamber of the eye in rabbits	The radio-labeled OVD is cleared from the anterior chamber in < 100 hours	Pass
Degradation and toxicokinetic (ISO 15789)	Evaluates the degradation and toxicokinetic profile of the device	Low systemic exposure	Pass

The primary packaging of the ClearVisc OVD comprises of a 1 mL borosilicate glass syringe with a stopper/plunger tip, an integrated tip cap, and a 25 gauge thin wall blunt cannula. The assessment of the syringe, stopper/plunger tip and the cannula included biocompatibility (**Table 3**) and chemical characterization (**Table 4**).

Table 3: **Biocompatibility assessment of the primary packaging**

Test	Purpose	Acceptance Criteria	Results
Cytotoxicity (ISO 10993-5)	Evaluates the cellular toxicity potential of the glass syringe, stopper/plunger, and cannula in vitro	Non-cytotoxic	Pass

Intracutaneous reactivity	Evaluates the irritation potential of the glass syringe extract and cannula extract in rabbits	Non-irritant	Pass
Ocular irritation	Evaluates the irritation potential of the cannula extract after intracameral injection in rabbits	Non-irritant	Pass
Guinea pig maximization (ISO 10993-10)	Evaluates the sensitization potential of the glass syringe extract and cannula extract	Non-sensitizer	Pass
Acute systemic toxicity (ISO 10993-11)	Evaluates the systemic toxicity potential of the glass syringe extract and cannula extract in mice	Non-toxic	Pass
Material mediated pyrogenicity	Evaluates the potential of the glass syringe extract to induce febrile response in rabbits	Did not induce increase in temperature	Pass
Hemolysis	Evaluates the potential of the glass syringe and cannula to induce hemolysis in the rabbit blood	Non-hemolytic	Pass

Table 4: **Chemical characterization of the primary packaging**

Test	Purpose	Acceptance Criteria	Results
Elemental impurity assessment	Evaluates the presence of heavy metals in the glass syringe	Not applicable	<0.01 parts per million (ppm)
Chemical characterization	Evaluates the presence of volatile compounds in the plunger/stopper material	Not applicable	The toxicological risk assessment conducted on the identified chemicals did not identify safety concerns

Leachability	Evaluates the presence of leachable compounds from the primary packaging	Not applicable	The leachable chemical profile was compared to a control device

Sterilization, stability and shipping studies

A summary of these tests is included in **Table 5**.

Table 5: **Sterilization and stability studies**

Test	Purpose	Acceptance Criteria	Results
Sterile filtration validation	Validate that the sterile filtration process is capable of sterilizing the ClearVisc OVD	No Growth of Assay Filter	Pass
Aseptic fill validation	Validates that the syringe filling process can be completed aseptically, per EN ISO 13408-1:2015, EU GMP Annex 1 and FDA guidance "Sterile drug products produced by aseptic processing."	No Growth of Media filled units	Pass
EO sterilization qualification	Validates that the EO sterilization cycle is effective per EN ISO 11135:2014	Sterility Assurance Level of 10^{-6}	Pass
Ethylene Oxide (EO) and Ethylene Chlorohydrin (ECH) Sterilant Residuals	Evaluates sterilant residues in product after EO sterilization	EO - <9µg/device ECH - <15µg/device Specification based on risk assessment	Pass
Endotoxin Testing	Confirms product is non-pyrogenic	≤0.2 EU/ml	Pass
Package Evaluation – Internal Pressurization	Confirms Tray/Tyvek package configuration maintains sterility of product as per ASTM F2096-11	All samples with known defect fail at site of defect.	Pass

Sterility Testing	Confirms Syringe configuration maintains sterility of product	No Growth	Pass
Stability study	Assesses the stability of ClearVisc OVD over time stored at 2-8ºC	All specifications met at all evaluation time points	Pass
Shipping study	Demonstrates compliance with ISO 11607-1. Evaluates the product per ISO 11607-1 which included environmental conditioning and a simulated distribution cycle followed by sterile barrier seal strength testing, and a review of labeling legibility and product requirements.	No visible damage to device or labeling, no leaks of OVD, sterile barrier seal strength minimum 1.12 lbf/in (peak value) and functional performance verification.	Pass

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of ClearVisc OVD for use as a surgical aid in patients undergoing ophthalmic anterior segment procedures in the US under IDE # G170265. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

Subjects were treated between April 25, 2018 and December 28, 2018. The database for this PMA reflected data collected through the last postoperative visit on April 1, 2019 and the database lock on April 30, 2019 and included 372 subjects. There were 16 investigational sites.

The study was a prospective, multi-center, active control, two-armed, randomized, partially masked, comparative clinical trial. Eligible subjects were randomized 1:1 at the time of planned cataract surgery with posterior chamber intraocular lens (IOL) implantation to receive either the investigational device (ClearVisc OVD) or the control OVD (VISCOAT® OVD). Randomization was stratified by site, age group, and cataract severity. Only one eye of each subject was included in the study. Subjects were followed for 90 days postoperatively (Visit 5).

VISCOAT® OVD is a legally marketed alternative with similar indications for use and similar properties (i.e. dispersive) as the ClearVisc OVD. Although the investigators were not masked at the time of surgery as to which OVD was used, a

delegated examiner at each site who was masked to the randomized assignment of each patient performed all postoperative assessments.

Non-inferiority statistical hypothesis testing for safety and effectiveness endpoints were pre-specified.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the ClearVisc OVD study was limited to subjects who met the following inclusion criteria:

   - The subject must have been at least 45 years old and had a clinically documented diagnosis of age-related non-complicated cataract that was considered amenable to treatment with standard phacoemulsification cataract extraction and IOL implantation.
   - The subject must have had the capability to provide written informed consent on the Institutional Review Board (IRB) approved Informed Consent Form (ICF) and provide authorization as appropriate for local privacy regulations.
   - The subject must have been willing and able to return for all scheduled follow-up examinations through 90 days following surgery.
   - The subject must have had clear intraocular media other than the cataract in the operative eye.

   Patients were not permitted to enroll in the ClearVisc OVD study if they met any of the following exclusion criteria:

   - The subject had participated in any drug or device clinical investigation within 30 days prior to entry into this study and/or during the period of study participation.
   - The subject had any corneal pathology (e.g., significant scarring, guttata, inflammation, edema, dystrophy, etc.) in the operative eye.
   - The subject had anterior segment pathology likely to increase the risk of an adverse outcome for phacoemulsification cataract surgery (e.g., pseudoexfoliation syndrome, synechiae, iris atrophy, inadequate dilation, shallow anterior chamber, traumatic cataract, lens subluxation) in the operative eye.
   - The subject had any condition which prevented reliable specular microscopy in the operative eye.
   - The subject had a congenital ocular anomaly (e.g., aniridia, congenital cataract) in the operative eye.
   - The subject had a baseline ECD < 1500 cells/mm^2 in the operative eye.
   - The subject had a Grade 4+ nuclear cataract density in the planned operative eye.
   - The subject had glaucoma or ocular hypertension (IOP > 24 mmHg) in the operative eye.
   - The subject had any abnormality that prevented reliable Goldmann applanation tonometry in the operative eye.

- The subject had a known allergy to any of the components of the test or control OVDs.
- The subject was using any topical or systemic medications known to interfere with visual performance or complicate cataract surgery within 30 days of enrollment or during the study.
- The subject was scheduled to undergo other combined intraocular procedures during the cataract/IOL implantation surgery in the operative eye.
  NOTE: A relaxing keratotomy was allowed.
- The subject had diabetic retinopathy, wet age-related macular degeneration, or other retinal pathology that might limit postoperative visual acuity or predisposed the subject to postoperative retinal complications in the operative eye.
- The subject's fellow eye was already participating in this study.
- The subject had a history of chronic or recurrent inflammatory eye disease (e.g., iritis, scleritis, uveitis, iridocyclitis, rubeosis iridis) in the operative eye.
- The subject had a best corrected distance visual acuity of logarithm of the minimum angle of resolution (LogMAR) 1.0 (20/200, 6/60) or worse in the fellow eye.
- The subject had had previous corneal surgery in the planned operative eye.
- The subject had a previous retinal detachment in the operative eye.
- Females of childbearing potential (those who were not surgically sterilized or not postmenopausal for at least 12 months) were excluded from participation in the study if they met any one of the following conditions:
  - they were currently pregnant;
  - they planned to become pregnant during the study; and/or
  - they were breast-feeding.

2. Follow-up Schedule

   All subjects were scheduled for follow-up examinations at 6 hours ± 2 hours, 24 hours ± 4 hours, 7 days ± 2 days, 30 days ± 7 days, and 90 days ± 14 days postoperatively.

   Table 6 includes the parameters measured preoperatively and postoperatively. Adverse events and complications were recorded at all visits.

Table 6: **Study visit schedule and parameters evaluated at each study visit**

PROCEDURE/ ASSESSMENTS	Preop Visit Day -60 to Day -1	Op Visit Day 0	Postop Visit 6 Hours ± 2 hours Postop	Postop Visit 2 24 Hours ± 4 hours Postop	Postop Visit 3 7 Days ± 2 days Postop	Postop Visit 4 30 Days ± 7 days Postop	Postop Visit 5 90 Days ± 14 days Postop
Informed Consent	X						
Demographic Data	X						
Medical History	X						
Urine Pregnancy Test	X	X			X	X	X
Eligibility Criteria	X	X					
Randomization		X					

PROCEDURE/ ASSESSMENTS	Preop Visit Day -60 to Day -1	Op Visit Day 0	Postop Visit 6 Hours ± 2 hours Postop	Postop Visit 2 24 Hours ± 4 hours Postop	Postop Visit 3 7 Days ± 2 days Postop	Postop Visit 4 30 Days ± 7 days Postop	Postop Visit 5 90 Days ± 14 days Postop
Fellow Eye Status	X						
Surgical Procedure		X					
Manifest Subjective Refraction	X						X
Uncorrected Distance VA	X		X	X	X	X	X
Best Corrected Distance VA	X						X
Cataract Classification	X						
Slit Lamp Examination	X		X	X	X	X	X
IOP (Goldmann tonometry)	X		X	X	X	X	X
Dilated Fundus Examination	X						X
Ultrasound Pachymetry	X			X			X
ECD via specular microscopy of the central cornea	X						X
Concomitant Medications	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X

Abbreviations: ECD = endothelial cell density; IOP = intraocular pressure;VA = visual acuity

The key timepoints are shown below in the tables summarizing safety and effectiveness.

3. Clinical Endpoints

With regard to safety, the primary safety endpoint was evaluated by a non-inferiority test of the proportion of subjects who experienced at least one IOP measurement ≥ 30 mmHg in the study eye at any follow-up visit. Following Markov chain Monte Carlo (MCMC) imputation of missing IOP data, a one-sided upper 95% confidence interval (CI) for the difference between the test and control groups (i.e., test – control) in the proportion of subjects with at least one IOP measurement ≥ 30 mmHg in the study eye at any follow-up visit was constructed using the normal approximation to test the null hypothesis for the primary safety endpoint that the upper confidence limit of the 95% CI for the difference was ≥ 0.117. If the upper confidence limit was less than 0.117, then the null hypothesis of inferiority was rejected in favor of the alternative hypothesis of noninferiority.

With regard to effectiveness, the primary effectiveness endpoint was a test for noninferiority of the test OVD (ClearVisc OVD) when compared to the control OVD (VISCOAT®) in mean percent change in endothelial cell density (ECD) from baseline to Postoperative Visit 5 (90 Days ± 14 days) in the study eye. Following MCMC imputation of missing cell density data, a one-sided upper 95% confidence limit for the mean difference (test – control) in percent change between the test and comparator OVDs was constructed. If the upper confidence limit was less than 5%, then the null hypothesis of inferiority for the primary

effectiveness endpoint was rejected in favor of the alternative hypothesis of noninferiority.

Therefore, both the primary safety endpoint and the primary effectiveness endpoint needed to be met in order for the trial to be considered a success.

B. Accountability of PMA Cohort

At the time of database lock, of 372 subjects randomized to treatment in the PMA trial, 99.2 % (n=369) subjects were available for analysis at the completion of the study, the 3-month postoperative visit (Visit 5; **Table 7**). Of the 369 subjects that completed the study, 182 subjects (98.9%) and 187 subjects (99.5%) were in the ClearVisc and VISCOAT® groups, respectively (**Table 8**).

Table 7: Subject Accountability - All Treated Subjects

Subject Status (n, %)	Preop Visit (N=372)	Op Visit Day 0 (N=372)	Postop Visit 1 (N=372)	Postop Visit 2 (N=372)	Postop Visit 3 (N=372)	Postop Visit 4 (N=372)	Postop Visit 5 (N=372)
Available for analysis	372 (100%)	372 (100%)	367 (98.7%)	368 (98.9%)	368 (98.9%)	370 (99.5%)	369 (99.2%)
Discontinued	0	0	0	1 (0.3%)	2 (0.5%)	2 (0.5%)	2 (0.5%)
Lost to follow up	0	0	0	0	0	0	1 (0.3%)
Missing	0	0	5 (1.3%)	3 (0.8%)	2 (0.5%)	0	0
Percent Accountability[1]	100%	100%	98.7%	99.2%	99.5%	100%	99.7%

Abbreviations: N = number of subjects in total, Op = operative, Preop = preoperative, Postop = postoperative
[1] Percent Accountability by Visit = [(# Available for Analysis) / (# Enrolled - # Discontinued - # Active)]*100

Table 8: Subject Accountability by Treatment Assignment - All Treated Subjects

Treatment Group		Preop Visit	Op Visit Day 0	Postop Visit 1	Postop Visit 2	Postop Visit 3	Postop Visit 4	Postop Visit 5
ClearVisc (N = 184; n, %)	Available for analysis	184 (100%)	184 (100%)	180 (97.8%)	181 (98.4%)	183 (99.5%)	183 (99.5%)	182 (98.9%)
	Discontinued	0	0	0	0	1 (0.5%)	1 (0.5%)	1 (0.5%)
	Lost to follow up	0	0	0	0	0	0	1 (0.5%)
	Missing	0	0	4 (2.2%)	3 (1.6%)	0	0	0
	Percent Accountability[1]	100%	100%	97.8%	98.4%	100%	100%	99.5%
VISCOAT® (N = 188; n, %)	Available for analysis	188 (100%)	188 (100%)	187 (99.5%)	187 (99.5%)	185 (98.4%)	187 (99.5%)	187 (99.5%)
	Discontinued	0	0	0	1 (0.5%)	1 (0.5%)	1 (0.5%)	1 (0.5%)
	Lost to follow up	0	0	0	0	0	0	0
	Missing	0	0	1 (0.5%)	0	2 (1.1%)	0	0
	Percent Accountability[1]	100%	100%	99.5%	100%	98.9%	100%	100%

Abbreviations: N = number of subjects in total, n = number of subjects per treatment group, Op = operative, Preop = preoperative, Postop = postoperative
[1] Percent Accountability by Visit = [(# Available for Analysis) / (# Enrolled - # Discontinued - # Active)]*100

The demographics of the trial population (**Table 9**) are slightly atypical for a cataract study performed in the US, since there is a slightly higher proportion of Asian subjects. However, the demographics of this population are reasonably representative of the US intended use population for an OVD.

Table 9: Demographics - Safety Population

	ClearVisc (N=184)	VISCOAT® (N=188)	Total (N=372)
Age (years), n	184	188	372
Mean (SD)	69.6 (6.76)	69.2 (7.37)	69.4 (7.07)
Median	70.0	69.0	70.0
Min, Max	47, 86	45, 86	45, 86
Sex, n (%)			
Male	73 (39.7%)	68 (36.2%)	141 (37.9%)
Female	111 (60.3%)	120 (63.8%)	231 (62.1%)
Ethnicity, n (%)			
Hispanic or Latino	20 (10.9%)	33 (17.6%)	53 (14.2%)
Not Hispanic or Latino	164 (89.1%)	155 (82.4%)	319 (85.8%)
Race, n (%)[1]			
American Indian/Alaska Native	2 (1.1%)	2 (1.1%)	4 (1.1%)
Asian	39 (21.2%)	43 (22.9%)	82 (22.0%)
Black/African American	20 (10.9%)	7 (3.7%)	27 (7.3%)
Native Hawaiian/Other Pacific Islander	0	0	0
White	124 (67.4%)	138 (73.4%)	262 (70.4%)
Other	1 (0.5%)	0	1 (0.3%)

Abbreviations: Max = maximum, Min = minimum, N = number of subjects per treatment group, n = number of subjects per category, SD = standard deviation

[1] Four subjects self-identified as two races: 1 White + Black/African American and 3 White + American Indian/Alaskan Native

The baseline ocular characteristics are summarized in **Table 10**. Baseline ocular characteristics were fairly similar between treatment groups.

Table 10: Baseline Ocular Characteristics - Safety Population

	ClearVisc (N=184)	VISCOAT® (N=188)	Total (N=372)
Study Eye, n (%)			
OD	91 (49.5%)	110 (58.5%)	201 (54.0%)
OS	93 (50.5%)	78 (41.5%)	171 (46.0%)
Cataract Classification, n (%)			
Type			
Nuclear	75 (40.8%)	72 (38.3%)	147 (39.5%)
Cortical	4 (2.2%)	4 (2.1%)	8 (2.2%)
Posterior Subcapsular	1 (0.5%)	2 (1.1%)	3 (0.8%)
Combination	104 (56.5%)	110 (58.5%)	214 (57.5%)

Density			
Slight (1+)	9 (4.9%)	4 (2.1%)	13 (3.5%)
Moderate (2+)	86 (46.7%)	102 (54.3%)	188 (50.5%)
Dense (3+)	88 (47.8%)	82 (43.6%)	170 (45.7%)
Very Dense (4+)	1 (0.5%)	0	1 (0.3%)
Fellow Eye Status, n (%)			
Normal	0	0	0
Cataract	97 (52.7%)	89 (47.3%)	186 (50.0%)
Aphakic	0	0	0
Pseudophakic	87 (47.3%)	99 (52.7%)	186 (50.0%)

Abbreviations: OD = oculus dexter (right eye), OS = oculus sinister (left eye)

C. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the Safety Population of all 372 eyes that were exposed to either the ClearVisc OVD or VISCOAT® OVD (control). The key safety outcomes for this study are presented below in **Tables 11** to **16**. Adverse effects are reported in **Table 17**.

The results of the analysis of the primary safety endpoint are presented in **Table 11**. For this analysis, missing data for eight subjects in the ClearVisc arm and four subjects in the control arm were imputed by the MCMC method and the calculated proportion was based on the average of 20 imputed datasets. By this method, the proportion of subjects with postoperative IOP ≥ 30 mmHg (IOP spike) at any follow-up visit was 0.174 for the ClearVisc group and 0.203 for the VISCOAT® group. The upper confidence limit of the estimated difference in proportions was 0.038, which is less than the non-inferiority margin of 0.117 (p=0.0002). Therefore, the primary safety endpoint of non-inferiority of the proportion of subjects who experienced at least one IOP spike at any follow-up visit in the ClearVisc group when compared with the VISCOAT® group was met.

Table 11: Proportion of Subjects with Postoperative Intraocular Pressure ≥30 mmHg at Any Follow-Up Visit - Safety Population

	ClearVisc (N=184)	VISCOAT® (N=188)	Difference in Proportions (ClearVisc - VISCOAT®)[1]	
			Estimate (90% CI)	P-value
IOP ≥ 30 mmHg at any follow-up visit	32.05/184 = 0.174	38.25/188 = 0.203	-0.029 (-0.096, 0.038)	0.0002

Abbreviations: CI = confidence interval, IOP = intraocular pressure, mmHg = millimeters of mercury, N = number of subjects per treatment group

Notes:
- Missing IOP values at follow-up visits are imputed using Markov chain Monte Carlo methods. The calculated proportion is based on the average of twenty imputed datasets.

- Subjects experiencing one or more IOP spikes are counted only once.
- In the ClearVisc treatment arm, 8 subjects have imputed data for this table. In the VISCOAT treatment arm, 4 subjects have imputed data for this table.

[1] The estimated difference in proportions between the treatment groups and the 90% confidence interval is constructed using the normal approximation. An upper confidence limit less than 0.117 favors the hypothesis of noninferiority of ClearVisc as compared to VISCOAT and the one-sided p-value at a 0.050 significance level is presented for this noninferiority test.

Similar proportions were seen using only observed data (**Table 12**). Thirty-one (31) of 184 subjects (0.168) in the ClearVisc arm and 38 of 187 subjects in the VISCOAT® arm (0.203) had at least one postoperative IOP spike; one subject in the control group had no postoperative IOP data.

Table 12: Proportion of Subjects with Postoperative Intraocular Pressure ≥30 mmHg at Any Follow-Up Visit (Observed Data) – Safety Population

	ClearVisc N=184	VISCOAT® N=188	Difference in Proportions (90% CI)
IOP ≥ 30 mmHg at any follow-up visit	31/184 = 0.168	38/187 = 0.203	-0.035 (-0.101, 0.032)

Abbreviations: IOP = intraocular pressure, N = number of subjects per treatment group

The timepoint of subjects' first IOP spikes were similar for the two groups with the majority of spikes occurring at < 6 hours postoperatively (**Table 13**).

Table 13: Percentage of Subjects Who Had Their First IOP ≥30 mmHg by Visit - Safety Population

Subjects with First IOP Spike Occurring at Each Visit Timing of Measurement	ClearVisc (N=184)	VISCOAT® (N=187)
Visit 1 (n/N, %)	25/180 (13.9%)	34/186 (18.3%)
Measurement Obtained <6 hours postoperatively	19	25
Measurement Obtained ≥6 hours postoperatively	6	9
Visit 2 (n/N, %)	6/181 (3.3%)	4/187 (2.1%)

Abbreviations: IOP = intraocular pressure, N = number of subjects per treatment group
Note: The denominator consists of all subjects that had an IOP measurement at that visit.
Note: There were no subjects who had their first IOP spike at Visits 3, 4, or 5.

The proportion of subjects in each group at each postoperative visit with a first IOP increase in the study eye of ≥ 10 mmHg from baseline is presented in Table 14 stratified by whether this degree of increase raised the IOP to ≥ 30 mmHg (qualified as an "IOP spike"). The proportions of subjects at each postoperative visit with their first IOP increase of ≥ 10 mmHg from baseline are fairly similar between groups with the proportions of these increases at each visit that qualifed as IOP spikes also being fairly similar between groups.

Table 14: Percentage of Subjects Who Had Their First IOP Change from Baseline of ≥10 mmHg by Visit and IOP Measurement Level - Safety Population

Percentage of Subjects with First IOP Change from Baseline of ≥10 mmHg at Each Visit	ClearVisc (N=184)	VISCOAT® (N=187)
Visit 1 (n/N, %)	84/180 (46.7%)	85/186 (45.7%)
IOP measurement <30 mmHg	59/84 (70.2%)	51/85 (60.0%)
IOP measurement ≥30 mmHg	25/84 (29.8%)	34/85 (40.0%)
Visit 2 (n/N, %)	11/181 (6.1%)	7/187 (3.7%)
IOP measurement <30 mmHg	8/11 (72.7%)	5/7 (71.4%)
IOP measurement ≥30 mmHg	3/11 (27.3%)	2/7 (28.6%)
Visit 3 (n/N, %)	0/183 (0.0%)	1/185 (0.5%)
IOP measurement <30 mmHg	0	1/1 (100.0%)
IOP measurement ≥30 mmHg	0	0

Abbreviations: IOP = intraocular pressure, N = number of subjects per treatment group
Note: There were no subjects who had their first IOP change from baseline ≥ 10 mmHg at Visits 4 or 5.

The mean, median, minimum, and maximum of observed IOP measurements at each specified study visit and change from baseline at each specified postoperative study visit are presented in **Table 15** stratified by treatment arm. The mean changes in IOP from baseline were similar between the two groups at each of the specified postoperative visits.

Table 15: Intraocular Pressure - Summary by Visit - Safety Population

	ClearVisc (N=184)		VISCOAT® (N=188)	
Visit	Observed Value	Change from Baseline	Observed Value	Change from Baseline
Baseline[1]				
n	184		188	
Mean (SD)	15.3 (2.84)		15.2 (2.73)	
Median	16.0		15.0	
Min, Max	9, 22		9, 24	
Postop Visit 1 (6 ± 2 hours)				
n	180	180	186	186
Mean (SD)	24.7 (7.97)	9.4 (7.60)	25.2 (9.00)	10.0 (8.92)
Median	24.0	9.0	24.0	9.0
Min, Max	10, 62	-10, 43	5, 65	-12, 53
Postop Visit 2 (24 ± 4 hours)				
n	181	181	187	187
Mean (SD)	19.4 (5.81)	4.1 (5.72)	19.0 (5.18)	3.8 (4.98)
Median	19.0	3.0	19.0	4.0
Min, Max	10, 42	-10, 25	8, 37	-10, 19
Postop Visit 3 (7 ± 2 days)				
n	183	183	185	185
Mean (SD)	15.2 (3.42)	-0.1 (3.50)	15.6 (3.43)	0.5 (3.89)
Median	15.0	0.0	15.0	0.0
Min, Max	8, 28	-9, 14	8, 26	-11, 17
Postop Visit 4 (30 ± 7 days)				
n	183	183	187	187

Visit	ClearVisc (N=184)		VISCOAT® (N=188)	
	Observed Value	Change from Baseline	Observed Value	Change from Baseline
Mean (SD)	14.6 (3.17)	-0.7 (3.25)	15.0 (3.01)	-0.1 (3.30)
Median	14.0	-1.0	15.0	0.0
Min, Max	8, 27	-10, 9	10, 24	-14, 11
Postop Visit 5 (90 ± 14 days)				
n	182	182	187	187
Mean (SD)	13.9 (2.95)	-1.3 (3.22)	14.2 (2.76)	-0.9 (2.87)
Median	14.0	-1.0	14.0	-1.0
Min, Max	6, 27	-10, 7	6, 23	-16, 9

Abbreviations: IOP= intraocular pressure, Max = maximum, Min = minimum, N = number of subjects per treatment group, n = number of subjects per category, OVD = ophthalmic viscosurgical device, SD = standard deviation;

Note: No subjects have imputed data for this table. Only observed data is used.

[1] Baseline is defined as the last available measurement prior to OVD exposure.

In addition, the distributions of the changes in IOP from baseline were fairly similar between the two groups at each postoperative visit. These results are shown through Visit 2 (the 24-hour postoperative visit) in **Table 16**.

Table 16: Categorical Change from Baseline in IOP Measurement (mmHg) by Visit through Visit 2 - Safety Population

Visit Change from Baseline Category (n, %)	ClearVisc (Total N=184)	VISCOAT® (Total N=187)
Number of subjects with both Baseline[1] and Interim between operative and Visit 1 IOP Measurements	N=0	N=0
Number of subjects with both Baseline[1] and Visit 1 IOP Measurements	N=180	N=186
Visit 1		
-15 to -11	0 (0.0%)	1 (0.5%)
-10 to -6	3 (1.7%)	1 (0.5%)
-5 to -1	8 (4.4%)	12 (6.5%)
0 to 4	32 (17.8%)	39 (21.0%)
5 to 9	53 (29.4%)	48 (25.8%)
10 to 14	55 (30.6%)	41 (22.0%)
15 to 19	13 (7.2%)	21 (11.3%)
20 to 24	6 (3.3%)	10 (5.4%)
25 to 29	8 (4.4%)	7 (3.8%)
30 to 34	1 (0.6%)	3 (1.6%)
35 to 39	0 (0.0%)	2 (1.1%)
40 to 44	1 (0.6%)	0 (0.0%)
50 to 54	0 (0.0%)	1 (0.5%)
Number of subjects with both Baseline[1] and Interim between Visit 1 and Visit 2 IOP Measurements	N=24	N=33
Interim between Visit 1 and Visit 2		
-10 to -6	2 (8.3%)	2 (6.1%)
-5 to -1	1 (4.2%)	0 (0.0%)
0 to 4	2 (8.3%)	5 (15.2%)
5 to 9	5 (20.8%)	8 (24.2%)
10 to 14	9 (37.5%)	11 (33.3%)

Visit Change from Baseline Category (n, %)	ClearVisc (Total N=184)	VISCOAT® (Total N=187)
15 to 19	4 (16.7%)	6 (18.2%)
20 to 24	0 (0.0%)	1 (3.0%)
30 to 34	1 (4.2%)	0 (0.0%)
Number of subjects with both Baseline[1] and Visit 2 IOP Measurements	N=181	N=187
Visit 2		
-10 to -6	7 (3.9%)	6 (3.2%)
-5 to -1	30 (16.6%)	27 (14.4%)
0 to 4	71 (39.2%)	72 (38.5%)
5 to 9	40 (22.1%)	64 (34.2%)
10 to 14	27 (14.9%)	13 (7.0%)
15 to 19	4 (2.2%)	5 (2.7%)
20 to 24	1 (0.6%)	0 (0.0%)
25 to 29	1 (0.6%)	0 (0.0%)

Abbreviations: IOP = intraocular pressure, N = number of subjects per treatment group, n = number of subjects per category, OVD = ophthalmic viscosurgical device

Note: For multiple interim visits that occurred within the same interim time period, the largest (most positive) change from baseline is summarized.

[1] Baseline is defined as the last available measurement prior to OVD exposure.

Adverse effects that occurred in the PMA pivotal clinical trial:

Intraoperative:

Two of 184 (1.1%) treated subjects in the ClearVisc group and five of 188 (2.7%) treated subjects in the VISCOAT® control group had intraoperative complications in the study eye. A torn posterior capsule was reported for one ClearVisc group subject and five VISCOAT® group subjects. Two of these events in the control group were considered serious; both resulted in vitreous loss and retained lens material and one required pars plana vitrectomy with lensectomy and membrane stripping. Hyphema was reported as an intraoperative adverse event (AE) for another subject in the ClearVisc group.

Postoperative:

There was one non-ocular postoperative adverse event (AE) considered related to the device. This was headache, which occurred in a ClearVisc group subject. There were a total of 96 ocular postoperative AEs that occurred in the study eyes of 63 (34.2%) of the 184 treated ClearVisc subjects and 110 ocular postoperative AEs that occurred in the study eyes of 80 (42.6%) of the 188 treated VISCOAT® subjects. The ocular postoperative AEs that occurred in each arm are summarized in **Table 17**.

Table 17: Postoperative Ocular Adverse Events (AEs) – Safety Population

Event	ClearVisc N=184		VISCOAT® N=188	
	# of Events	# (%) of Subjects, n	# of Events	# (%) of Subjects, n
TOTAL	**96**	**63 (34.2%)**	**110**	**80 (42.6%)**
Increased IOP	**34**	**31 (16.8%)**	**38**	**38 (20.2%)**
Intraocular Inflammation	**13**	**11 (6.0%)**	**7**	**7 (3.7%)**
Iritis	6	6 (3.3%)	5	5 (2.7%)
Rebound Inflammation	3	3 (1.6%)	2	2(1.1%)
Macular edema/ Cystoid macular edema	3	3 (1.6%)	0	0
Macrophage deposits	1	1 (0.5%)	0	0
Corneal Edema Related AEs	**6**	**5 (2.7%)**	**5**	**5 (2.7%)**
Corneal edema	2	2 (1.1%)	1	1 (0.5%)
Corneal wound edema/inflammation	0	0	3	3(1.6%)
Descemet's folds	3	3 (1.6%)	0	0
Decrease in endothelial cell density from baseline (of 55% to 922 cells/mm^2 at Visit 5)	0	0	1	1 (0.5%)
Increase of pachymetry from baseline (of 429 µ at Visit 2)	1	1 (0.5%)	0	0
Other Corneal AEs	**20**	**19 (10.3%)**	**18**	**17 (9.0%)**
Punctate keratitis	17	17 (9.2%)	13	13 (6.9%)
Corneal abrasion	2	2 (1.1%)	3	3 (1.6%)
Herpes simplex keratitis	1	1 (0.5%)	1	1 (0.5%)
Foreign body - metallic at wound	0	0	1	1 (0.5%)
Conjunctiva	**5**	**5 (2.7%)**	**8**	**8 (4.3%)**
Conjunctival/ subconjunctival hemorrhage	4	4 (2.2%)	4	4 (2.1%)
Ocular hyperemia	1	1 (0.5%)	0	0
Conjunctivitis bacterial	0	0	1	1 (0.5%)
Conjunctivitis allergic	0	0	3	3 (1.6%)
Other Ocular Surface Disorders/ Lids & Lashes	**7**	**7 (3.8%)**	**9**	**8 (4.3%)**
Eye irritation	1	1 (0.5%)	2	2 (1.1%)
Foreign body sensation	2	2 (1.1%)	3	2 (1.1%)
Dry eye/Meibomian gland dysfunction/ Blepharitis/ Chalazion	4	4 (2.2%)	3	3 (1.6%)
Upper lid tenderness	0	0	1	1 (0.5%)

Lens	**7**	**7 (3.8%)**	**8**	**8 (4.3%)**
Posterior capsule opacification	**7**	**7** (3.8%)	6	6 (3.2%)
Halo vision	0	0	1	1 (0.5%)
Negative dysphotopsia	0	0	1	1 (0.5%)
Retina	**3**	**3 (1.6%)**	**8**	**7 (3.7%)**
Epiretinal membrane (ERM)	1	1 (0.5%)	2	2 (1.1%)
Retinal hemorrhage	1	1 (0.5%)	1	1 (0.5%)
Chorioretinal scar	1	1 (0.5%)	0	0
Age-related macular degeneration	0	0	1	1 (0.5%)
Macular drusen	0	0	1	1 (0.5%)
Retinal pigment epithelial changes	0	0	1	1 (0.5%)
Paramacular pigmentary changes – around arcade	0	0	1	1 (0.5%)
Retinal tear	0	0	1	1 (0.5%)
Vitreous	**1**	**1 (0.5%)**	**7**	**7 (3.7%)**
Floaters/ degeneration/ detachment	1	1 (0.5%)	6	6 (3.2%)
Flashes	0	0	1	1 (0.5%)
Decrease in Vision - indeterminate	**0**	**0**	**2**	**1** (0.5%)

The most frequently reported AE was IOP increase (16.8% and 20.2% of eyes for ClearVisc and VISCOAT® groups, respectively). None of the ocular postoperative AEs were reported as serious AEs (SAEs).

2. Effectiveness Results

The analysis of effectiveness was based on the Intent-to-Treat (ITT) Population of all 372 study eyes randomized to treatment and was performed at the 3-month postoperative timepoint (Visit 5). Key effectiveness outcomes are presented in **Tables 18** to **20**.

The results of the analysis of the primary effectiveness endpoint are presented in **Table 18**. For the ITT Population with missing data imputed using MCMC methods, mean percent change in ECD from baseline to Visit 5 was 8.4% loss for the ClearVisc group and 6.8% loss for the VISCOAT® control group. The upper confidence limit for the least square mean difference (LSMD) in the percent change in ECD between groups was 3.6%, which is less than the pre-specified non-inferiority margin of 5% ($p = 0.0032$). Therefore, the primary effectiveness endpoint of non-inferiority of mean percent change in ECD from baseline to postoperative Visit 5 (90 days ± 14 days) in the study eye for the ClearVisc group when compared to the control group was considered met.

Table 18: Change from baseline in Endothelial Cell Density (ECD; cells/mm^2) at 90 days – Intent to Treat Population

	ClearVisc (N=184)		VISCOAT® (N=188)	
Time Point	Observed Value	Percent Loss[1]	Observed Value	Percent Loss[1]
Baseline[2]				
n	183		188	
Mean (SD)	2508.8 (363.68)		2487.4 (373.14)	
Median	2498.0		2492.0	
Min, Max	1238, 3404		1242, 3396	
Postop Visit 5 (90 ± 14 days)				
n	168	168	178	178
Mean (SD)	2280.2 (443.03)	8.4 (12.19)	2309.4 (467.84)	6.8 (12.54)
Median	2313.5	3.8	2375.5	2.4
Min, Max	1102, 3574	-10, 55	777, 3467	-11, 63
LSM (SE)[2]	2291.6 (48.49)	8.3 (1.26)	2311.9 (48.94)	6.7 (1.26)
LSMD (ClearVisc - VISCOAT®) (SE)[3]		1.6 (1.25)		
90% CI of LSMD[3]		-0.5, 3.6		
P-value[3]		0.0032		
Superiority Test:				
95% CI of LSMD[4]		-0.9, 4.0		
P-value[4]		0.1021		

Abbreviations: CI = confidence interval, ECD = endothelial cell density, ITT = Intent-to-Treat, LSM = least square mean change from baseline, LSMD = least square mean difference between treatment groups, Max = maximum, Min = minimum, N = number of subjects per treatment group, n = number of subjects per category, OVD = ophthalmic viscosurgical device, Postop = postoperative, SD = standard deviation, SE = standard error

Note: Missing ECD values are imputed using Markov chain Monte Carlo methods. Descriptive statistics are presented with observed data only.

[1] Percent loss is calculated as [(Baseline value - Visit 5 value)/Baseline value]*100.
[2] Baseline is defined as the last available measurement prior to OVD exposure.
[3] Estimates of the LSM and LSMD between treatment groups are based on a statistical model with percent loss as the dependent variable, and treatment group and investigator as fixed factors. An upper confidence limit less than 5% favors the hypothesis of noninferiority of ClearVisc as compared to VISCOAT and the one-sided p-value at a 0.050 significance level is presented for this noninferiority test of difference in percent loss.
[4] A two-sided 95% confidence interval is constructed around the LSMD in percent loss between treatment groups and a one-sided p-value is presented. A p-value < 0.025 favors the secondary effectiveness hypothesis of superiority of ClearVisc as compared to VISCOAT if the primary endpoints are met.

Similar results were obtained for the Complete-Case analysis that included only those study eyes from the ITT Population which had both observed preoperative and postoperative Visit 5 ECD measurements available (**Table 19**).

Table 19: Endothelial Cell Density (cells/mm^2) and Percent Loss Sensitivity Analysis: Complete Case - Intent to Treat Population

	ClearVisc (N=184)		VISCOAT® (N=188)	
Time Point	Observed Value	Percent Loss[1]	Observed Value	Percent Loss[1]
Baseline[2]				
n	168		178	
Mean (SD)	2490.5 (357.20)		2476.4 (375.88)	
Median	2483.0		2479.0	
Min, Max	1238, 3404		1242, 3396	
Postop Visit 5 (90 ± 14 days)				
n	168	168	178	178
Mean (SD)	2280.2 (443.03)	8.4 (12.19)	2309.4 (467.84)	6.8 (12.54)
Median	2313.5	3.8	2375.5	2.4
Min, Max	1102, 3574	-10, 55	777, 3467	-11, 63
LSM (SE)[3]	2272.4 (48.99)	8.5 (1.26)	2301.9 (49.23)	6.8 (1.26)
LSMD (ClearVisc - VISCOAT®) (SE)[3]		1.7 (1.25)		
90% CI of LSMD[3]		-0.3, 3.8		
P-value[4]		0.0046		

Abbreviations: CI = confidence interval, ECD = endothelial cell density, ITT = Intent-to-Treat, LSM = least square mean change from baseline, LSMD = least square mean difference between treatment groups, Max = maximum, Min = minimum, N = number of subjects per treatment group, n = number of subjects per category, OVD = ophthalmic viscosurgical device, Postop = postoperative, SD = standard deviation, SE = standard error

Note: Complete case analysis includes only subjects with both Preoperative and Postoperative Visit 5 ECD measurements.

[1] Percent loss is calculated as [(Baseline value - Visit 5 value)/Baseline value]*100.
[2] Baseline is defined as the last available measurement prior to OVD exposure.
[3] Estimates of the LSM and LSMD between treatment groups are based on a statistical model with percent loss as the dependent variable, and treatment group and investigator as fixed factors. An upper confidence limit less than 5% favors the hypothesis of noninferiority of ClearVisc as compared to VISCOAT.
[4] The one-sided p-value at a 0.050 significance level is presented for the noninferiority test of difference in percent loss.

The distribution of the percent loss in ECD from baseline at Visit 5 (with negative (-) values indicating gain) in each arm is shown in **Table 20**. The distributions are fairly similar between groups, although there is a trend for slightly higher frequencies of percent losses at higher ECD percent levels with the ClearVisc OVD than the control.

Table 20: Categorical Percent Loss in Endothelial Cell Density (cells/mm^2) at Visit 5: Complete Case – Intent to Treat Population

Visit Percent Loss	ClearVisc (N=184)	VISCOAT® (N=188)
Number of subjects with both Baseline[1] and Postoperative Visit 5 ECD Measurements	n=168	n=178
Postoperative Visit 5 (90 days +/- 14 days)		
> -15 to -10%	1 (0.6%)	1 (0.6%)
> -10 to -5%	4 (2.4%)	4 (2.2%)
> -5 to 0%	34 (20.2%)	50 (28.1%)
> 0 to 5%	56 (33.3%)	51 (28.7%)
> 5 to 10%	24 (14.3%)	31 (17.4%)
> 10 to 15%	13 (7.7%)	16 (9.0%)
> 15 to 20%	6 (3.6%)	5 (2.8%)

Visit Percent Loss	ClearVisc (N=184)	VISCOAT® (N=188)
> 20 to 25%	11 (6.5%)	4 (2.2%)
> 25 to 30%	5 (3.0%)	5 (2.8%)
> 30 to 35%	7 (4.2%)	3 (1.7%)
> 35 to 40%	2 (1.2%)	3 (1.7%)
> 40 to 45%	1 (0.6%)	0
> 45 to 50%	2 (1.2%)	0
> 50 to 55%	2 (1.2%)	1 (0.6%)
> 55 to 60%	0	3 (1.7%)
> 60 to 65%	0	1 (0.6%)

Abbreviations: ECD = endothelial cell density, ITT = intent-to-treat, N = number of subjects per treatment group, n = number of subjects per category, OVD = ophthalmic viscosurgical device

[1] Baseline is defined as the last available measurement prior to OVD exposure.

3. Subgroup Analyses

The following characteristics were evaluated for potential association with outcomes:

Subgroup analyses concerning study sites:

Subgroup analysis concerning study sites was conducted as an assessment of data poolability across sites for both primary safety and effectiveness endpoints.

For the primary safety endpoint, poolability of results (observed data only) across study sites was assessed by performing a Cochran-Mantel-Haenszel test between the treatment groups stratified by study site. The p-value for the Breslow-Day test for homogeneity of odds ratios across study sites was compared to a critical value of 0.15. The resulting p-value is 0.4866. Based on these results summarized in **Table 21** below, it is reasonable to assume that there is minimal site effect on device safety performance.

Table 21: Proportion of Subjects with Postoperative Intraocular Pressure ≥30 mmHg at Any Follow-Up Visit by Study Center - Safety Population

	ClearVisc (N=184)	VISCOAT® (N=188)
Site 1	n = 24	n = 25
IOP ≥ 30 mmHg at any follow-up visit	0	0
Site 2	n = 11	n = 12
IOP ≥ 30 mmHg at any follow-up visit	0	0
Site 3	n = 27	n = 28
IOP ≥ 30 mmHg at any follow-up visit	4/27 = 0.148	4/28 = 0.143
Site 4	n = 14	n = 16
IOP ≥ 30 mmHg at any follow-up visit	6/14 = 0.429	10/16 = 0.625
Site 5	n = 21	n = 23
IOP ≥ 30 mmHg at any follow-up visit	4/21 = 0.190	10/23 = 0.435
Site 6	n = 25	n = 25

	ClearVisc (N=184)	VISCOAT® (N=188)
IOP ≥ 30 mmHg at any follow-up visit	5/25 = 0.200	2/25 = 0.080
Site 7	n = 6	n = 7
IOP ≥ 30 mmHg at any follow-up visit	2/6 = 0.333	3/7 = 0.429
Site 8	n = 7	n = 7
IOP ≥ 30 mmHg at any follow-up visit	1/7 = 0.143	1/7 = 0.143
Site 9	n = 17	n = 15
IOP ≥ 30 mmHg at any follow-up visit	4/17 = 0.235	3/15 = 0.200
Site 10	n = 2	n = 3
IOP ≥ 30 mmHg at any follow-up visit	1/2 = 0.500	1/3 = 0.333
Site 11	n = 12	n = 12
IOP ≥ 30 mmHg at any follow-up visit	2/12 = 0.167	2/12 = 0.167
Site 12	n = 1	n = 0
IOP ≥ 30 mmHg at any follow-up visit	0	0
Site 13	n = 6	n = 4
IOP ≥ 30 mmHg at any follow-up visit	1/6 = 0.167	0
Site 15	n = 7	n = 6
IOP ≥ 30 mmHg at any follow-up visit	0	1/6 = 0.167
Site 16	n = 3	n = 3
IOP ≥ 30 mmHg at any follow-up visit	1/3 = 0.333	0
Site 17	n = 1	n = 2
IOP ≥ 30 mmHg at any follow-up visit	0	1/2 = 0.500
P-value[1]	0.4866	
P-value[2]	0.6610	

Abbreviations: CMH = Cochran-Mantel-Haenszel, IOP = intraocular pressure, mmHg = millimeters of mercury

Notes:
- Subjects experiencing one or more IOP spikes are counted only once.
- No subjects have imputed data for this table. Only observed data is used.

[1] The p-value comparing treatment groups is based on a CMH test stratified by study center.
[2] The p-value for the Breslow-Day test for homogeneity of odds ratios across study sites is compared to a critical value of 0.15.

For the primary effectiveness endpoint, poolability across study sites was evaluated by modeling ECD loss (%) as a function of the fixed class variables of treatment and Investigator including their interaction using the available data for the ITT Set. Poolability is assessed by comparing the p-value for the interaction to a critical value of 0.15. Based on the results summarized in **Table 22**, below, the p-value for the interaction term is 0.3984. Therefore, it is believed that a possible site effect on device effectiveness is reasonably low.

Table 22: Endothelial Cell Density (cells/mm^2) and Percent Loss by Study Center – Intent to Treat Population

	ClearVisc (N=184)		VISCOAT® (N=188)	
Time Point	Observed Value	Percent Loss[1]	Observed Value	Percent Loss[1]
Baseline[2]				
n	183		188	
Mean (SD)	2508.8 (363.68)		2487.4 (373.14)	
Median	2498.0		2492.0	
Min, Max	1238, 3404		1242, 3396	
Postop Visit 5 (90 ± 14 days)				
n	168	168	178	178
Mean (SD)	2280.2 (443.03)	8.4 (12.19)	2309.4 (467.84)	6.8 (12.54)
Median	2313.5	3.8	2375.5	2.4
Min, Max	1102, 3574	-10, 55	777, 3467	-11, 63
LSM (SE)[3]	2272.4 (34.20)	8.5 (0.88)	2301.9 (34.37)	6.8 (0.88)
LSMD (ClearVisc - VISCOAT® (SE)[3]		1.7 (0.87)		
90% CI of LSMD[3]		0.3, 3.2		
P-value[4]		0.3984		

Abbreviations: CI = confidence interval, ECD = endothelial cell density, ITT = Intent-to-Treat, LSM = least square mean change from baseline, LSMD = least square mean difference between treatment groups, Max = maximum, Min = minimum, N = number of subjects per treatment group, n = number of subjects per category, OVD = ophthalmic viscosurgical device, Postop = postoperative, SD = standard deviation, SE = standard error

[1] Percent loss is calculated as [(Baseline value - Visit 5 value)/Baseline value]*100.
[2] Baseline is defined as the last available measurement prior to OVD exposure.
[3] Estimates of the LSM and LSMD between treatment groups are based on a statistical model with difference in percent loss as the dependent variable, and treatment group, investigator, and the interaction term as fixed factors.
[4] A p-value for the interaction term (treatment*investigator) > 0.15 indicates poolability across sites.

Subgroup analyses concerning IOP-reducing intervention:
A subgroup analysis was conducted concerning the primary safety endpoint according to the following categorization:

- Subjects who received IOP-reducing intervention; and
- Subjects who did not receive IOP-reducing intervention.

The results are presented in **Table 23**, below.

Table 23: Proportion of Subjects with Postoperative Intraocular Pressure ≥30 mmHg at Any Follow-Up Visit by IOP Intervention - Safety Population

	ClearVisc (N=184)	VISCOAT® (N=188)	Difference in Proportion (ClearVisc - VISCOAT®)[1]	
			Estimate (95% CI)	P-value
Subjects who received IOP-reducing intervention	n = 34	n = 39		
IOP ≥ 30 mmHg at any follow-up visit	28/34 = 0.824	35/39 = 0.897	-0.074 (-0.208, 0.060)	0.0095
Subjects who did not receive IOP-reducing intervention	n = 150	n = 149		
IOP ≥ 30 mmHg at any follow-up visit	4.05/150 = 0.027	3.25/149 = 0.022	0.005 (-0.026, 0.036)	<0.0001

Abbreviation: CI = confidence interval, IOP = intraocular pressure, mmHg = millimeters of mercury, N = number of subjects per treatment group

Notes:

• Missing IOP values at follow-up visits are imputed using Markov chain Monte Carlo methods. The calculated proportion is based on the average of twenty imputed datasets.
• Subjects experiencing one or more IOP spikes are counted only once.
• In the ClearVisc treatment arm, 8 subjects have imputed data for this table. In the VISCOAT treatment arm, 4 subjects have imputed data for this table.

[1] The estimated difference in proportions between the treatment groups and the 90% confidence interval is constructed using the normal approximation. An upper confidence limit less than 0.117 favors the hypothesis of noninferiority of ClearVisc as compared to VISCOAT and the one-sided p-value at a 0.050 significance level is presented for this noninferiority test.

For both subgroups, the results demonstrated noninferiority for ClearVisc when compared with VISCOAT® ($p=0.0095$ for subjects who received IOP-reducing intervention and $p < 0.0001$ for subjects who did not receive IOP-reducing intervention).

4. Pediatric Extrapolation
   In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

D. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 16 investigators of which none were full-time or part-time employees of the sponsor and 1 had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0
- Significant payment of other sorts: 1
- Proprietary interest in the product tested held by the investigator: 0
- Significant equity interest held by investigator in sponsor of covered study: 0

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. The one investigator with a disclosable financial interest treated only 6 subjects out of 184 (3.3%) in the ClearVisc group and only 7 subjects out of 188 (3.7%) in the Viscoat group. Given the results of the primary analyses, there is little concern that the results of these subjects significantly affected the outcomes of the trial. Therefore, the information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

Not applicable.

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Ophthalmic Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The primary effectiveness endpoint of the pivotal clinical trial is the non-inferiority of the ClearVisc experimental device treatment group when compared with the VISCOAT® control device treatment group in mean percent corneal endothelial cell density (ECD) from baseline to Postoperative Visit 5 (90 Days ± 14 days) in the study eye. The ClearVisc group had a mean percent change of 8.4% loss in ECD from baseline to Postoperative Visit 5, whereas the VISCOAT® group had a mean percent change of 6.8% loss. Non-inferiority was demonstrated statistically. There is a trend for slightly higher frequencies of percent losses at higher ECD percent levels with the ClearVisc OVD than the control.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and animal studies as well as data collected in the pivotal clinical trial conducted to support PMA approval, as described above. The primary safety endpoint is the non-inferiority of the ClearVisc group when compared with the control group in the proportion of subjects who experience at least one intraocular pressure (IOP) measurement ≥ 30 mmHg in the study eye at any follow-up visit. The proportion of subjects with postoperative IOP ≥ 30 mmHg at any follow-up visit is 17% (31/184 subjects) for the ClearVisc group and 20% (38/187 subjects) for the control group. Non-inferiority was met statistically.

The mean change in IOP from baseline was similar between groups at each visit, and so were the distributions of IOP change from baseline. In addition, the proportion of subjects with their first episode of a clinically significant change in IOP from baseline at each visit was similar between the two groups.

There does not appear to be a clinically significant difference in the adverse events that occurred during the trial between the two groups. For the main risks of increased IOP and intraocular inflammation, rates were 16.8% (31/184 subjects) and 6% (11/184 subjects) respectively in the ClearVisc group and 20.2% (38/188 subjects) and 3.7% (7/188 subjects) respectively in the VISCOAT® group.

C. Benefit-Risk Determination

The probable benefits of the device are also based on data collected in the pivotal clinical trial conducted to support PMA approval, as described above. While there is a trend for slightly less benefit of protecting the corneal endothelial cells during cataract surgery with the dispersive ClearVisc OVD as compared to with the dispersive control OVD, as evidenced by the clinical effectiveness information summarized above, there is clinically meaningful benefit of the ClearVisc OVD.

The probable risks of the device are also based on data collected in the pivotal clinical trial conducted to support PMA approval, as described above. The risks of ClearVisc OVD include increase in IOP and intraocular inflammation, which both may secondarily cause corneal edema and loss of vision.

Additional factors considered in determining probable risks and benefits for the ClearVisc OVD device included the uncertainty surrounding the potential adverse effects of the OVD due to confounding by the effects of surgery and the other devices and medications used during surgery and potential bias introduced by lack of masking of investigators to subjects' treatment assignment.

1. Patient Perspective
   This submission either did not include specific information on patient perspectives or the information did not serve as part of the basis of the decision to approve or deny the PMA for this device.

In conclusion, given the available information above, the data support that for use as a surgical aid in the ophthalmic anterior segment procedures including extraction of a cataract and implantation of an intraocular lens, the probable benefits outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. The benefit of corneal endothelial protection outweighs the risk of IOP spikes and other less common risks.

XIV. CDRH DECISION

CDRH issued an approval order on 3/23/2021.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.