SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	1.0% Sodium Hyaluronate Ophthalmic Viscosurgical Device (OVD)
Device Trade Name:	StableVisc™ Ophthalmic Viscoelastic Device (OVD); TotalVisc™ Ophthalmic Viscoelastic Device (OVD)
Device Procode:	LZP
Applicants Name and Address:	Bausch Health 400 Somerset Corporate Boulevard Bridgewater, New Jersey 08807
Date of Panel Recommendation:	None
Premarket Approval Number:	P220009
Date of FDA Notice of Approval:	February 22, 2023

Approval is for StableVisc™ OVD in standalone packaging, and when co-packaged with previously approved ClearVisc™ OVD (as TotalVisc™ OVD). Only StableVisc™ OVD was studied under this Premarketing application. ClearVisc™ OVD was approved under P200025 on 03/23/2021. The SSED to support the ClearVisc™ indications is available on the CDRH website.

II. INDICATIONS FOR USE

StableVisc™ 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 contraindications to the use of StableVisc™ as a surgical aid in ophthalmic anterior segment procedures.

IV. WARNINGS AND PRECAUTIONS

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

V. DEVICE DESCRIPTION

StableVisc™ 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.

StableVisc™ OVD contains 10 mg/mL of sodium hyaluronate and 40 mg/mL of sorbitol, dissolved in physiological sodium chloride phosphate, tromethamine buffered solution with a pH 6.8 to 7.6. The average molecular weight of the sodium hyaluronate is 2,100,000 Daltons (Da). StableVisc™ OVD has rheological cohesive properties. The viscosity is 50 ± 15 Pa.s at 25°C (77°F) and a shear rate of 1 s^{-1} (**Figure 1**). The osmolality is approximately 340 mOsm/Kg.

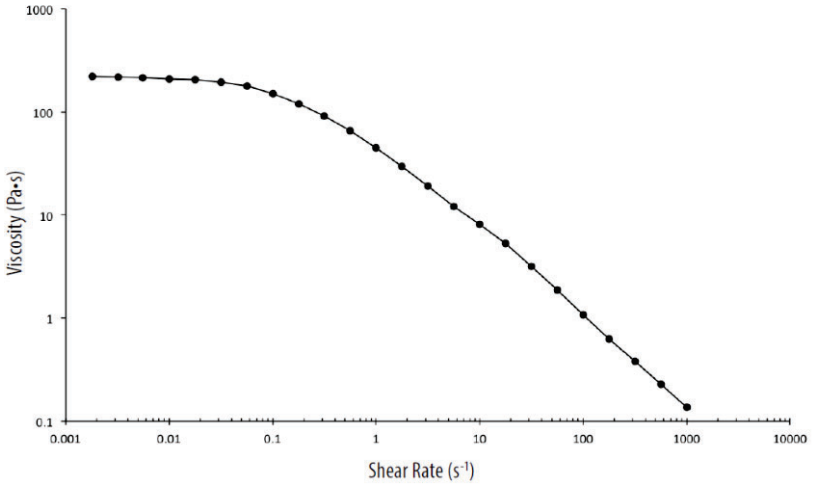
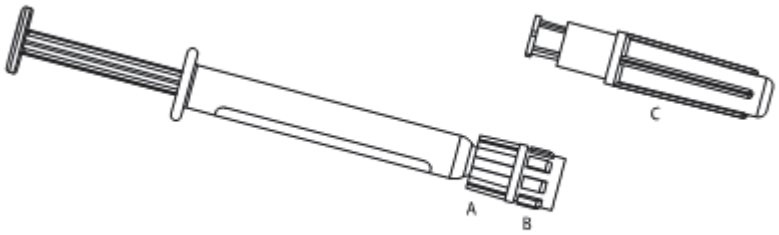


Figure 1: Rheological profile of the StableVisc™ OVD

StableVisc™ OVD is intended to protect intraocular tissues during surgery.

StableVisc™ OVD is offered in a 1 mL glass syringe with a 27-gauge 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, StableVisc™ 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 PETG (polyethylene terephthalate, glycol-modified) 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. **Figure 2** provides an illustration of the syringe and cannula.

Figure 2: Graphical representation of the syringe and cannula



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

StableVisc™ OVD is offered as a standalone product, or co-packaged with ClearVisc™ OVD (e.g., in individual syringes) as TotalVisc™ OVD. TotalVisc™ OVD is designed to provide two viscoelastic products with different physicochemical characteristics (i.e., StableVisc is a cohesive OVD, ClearVisc is a dispersive OVD) that can be used to perform specific tasks during cataract procedures.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several alternative OVDs available of varying formulations and properties. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

StableVisc™ 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 StableVisc™ OVD

The characterization of the StableVisc™ OVD was conducted according to International Standard Organization (ISO) 15798, Ophthalmic implants- Ophthalmic Viscosurgical Devices. A summary of the characterization is provided for StableVisc™ in **Table 1**, below.

Table 1: **Characterization of the StableVisc™ 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	12 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	Molecular weight = 2.1 x 106 Da Polydispersity index = 1.04
Osmolality	Characterization of the physicochemical properties	Not applicable	332 mOsm / kg
Particulates	Evaluation of potential particulates	Not applicable	3.1 particles /g ≥ 10 µm 1.7 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 was 1.3413 for StableVisc™.
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}.

Test	Purpose	Acceptance Criteria	Results
			The Apparent Viscosity is 50 ± 15 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	6.00 lbf

Biocompatibility

Biocompatibility assessment was conducted on the finished sterile StableVisc™ 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 were conducted in accordance with provisions of 21 CFR 58, Good Laboratory Practice (GLP) for Nonclinical Laboratory Studies.

Table 2: **Biocompatibility assessment of the StableVisc™ 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) (ISO 10993-3)	Evaluates the mutagenic potential of the implant	Non-mutagenic	Pass
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 StableVisc™ OVD comprises of a 1 mL borosilicate glass syringe with a stopper/plunger tip, an integrated tip cap, and a cannula. The assessment of the syringes, stopper/plunger tips and the cannulas 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 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 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	Evaluates sterilant residues in product after EO sterilization	EO - <9µg/device ECH - <15µg/device	Pass

Test	Purpose	Acceptance Criteria	Results
(ECH) Sterilant Residuals		Specification based on risk assessment	
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 OVD over time stored at 2-8ºC	All specifications met at all evaluation time points	Pass
Shipping study	Demonstrates compliance with ISO 11607-1:2019. Evaluates the product per ISO 11607-1:2019 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 – STABLEVISC OVD

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of StableVisc™ OVD for use as a surgical aid in patients undergoing ophthalmic anterior segment procedures in the US under IDE # G190194. 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 December 12, 2019 and January 31, 2022. The database for this PMA reflected data collected through the last postoperative visit on January 31, 2022 and the database lock on March 25, 2022 and included 390 subjects. There were 22 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 (StableVisc™ OVD) or the control OVD (ProVisc® 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).

ProVisc® OVD is a legally marketed alternative with similar indications for use and similar properties (i.e. cohesive) as the StableVisc™ 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 StableVisc™ 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 StableVisc™ 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. <u>Follow-up Schedule</u>

   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.

Preoperative and postoperative visit schedules and a summary of the parameters measured during the study are summarized in **Table 6** below. Adverse events and complications were recorded at all visits.

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					
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. <u>Clinical Endpoints</u>

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. 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. 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.

The secondary safety endpoints were as follows.

- Mean change from baseline in IOP at the six-hour post-operative visit
- Mean change from baseline in IOP at the 24-hour post-operative visit
- Proportion of subjects with summed score for anterior chamber cells and flare greater than zero at the six-hour and 24-hour post-operative visits

With regard to effectiveness, the primary effectiveness endpoint was a test for noninferiority of the test OVD (StableVisc™ OVD) when compared to the control OVD (ProVisc®) in mean percent change in endothelial cell density (ECD) from baseline to Postoperative Visit 5 (90 Days ± 14 days) in the study eye. Following Markov chain Monte Carlo (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.

The secondary effectiveness endpoint was a secondary superiority test of the primary effectiveness endpoint: endothelial cell density loss.

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 390 subjects randomized to treatment in the PMA trial, 97.4% (380/390) subjects were available for analysis at the completion of the study, the 3-month postoperative visit (Visit 5; **Table 7**). Of the 380 subjects that completed the study, 187 subjects and 193 subjects were in the StableVisc™ and ProVisc® groups, respectively (**Table 8**).

Table 7: Subject Accountability (All Enrolled Subjects)

	Preop Visit (N=388)	Op Visit Day 0 (N=388)	Postop Visit 1 (N=388)	Postop Visit 2 (N=388)	Postop Visit 3 (N=388)	Postop Visit 4 (N=388)	Postop Visit 5 (N=388)
Available for Analysis	388/388 (100%)	388/388 (100%)	387/388 (99.7%)	388/388 (100%)	385/388 (99.2%)	380/388 (97.9%)	381/388 (98.2%)
Discontinued	0	0	0	0	0	2/388 (0.5%)	3/388 (0.8%)
Lost to Follow-up	0	0	0	0	1/388 (0.3%)	1/388 (0.3%)	4/388 (1.0%)
Missing[a]	0	0	1/388 (0.3%)	0	2/388 (0.5%)	5/388 (1.3%)	0
Percent Accountability[b]	100%	100%	99.7%	100%	99.2%	98.4%	99.0%

Abbreviations: N = number of subjects in total, Op = operative, Preop = preoperative, Postop = postoperative
[a] Missing subjects were those who were not available for analysis, not active, discontinued, or lost to follow-up.
[b] 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
StableVisc™ (N=192; n, %)	Available for analysis	192/192 (100%)	192/192 (100%)	192/192 (100%)	192/192 (100%)	192/192 (100%)	189/192 (98.4%)	187/192 (97.4%)
	Active[1]	0	0	0	0	0	0	0
	Discontinued	0	0	0	0	0	2/192 (1.0%)	3/192 (1.6%)
	Lost to Follow-up	0	0	0	0	0	0	2/192 (1.0%)
	Missing[2]	0	0	0	0	0	1/192 (0.5%)	0
	Percent Accountability[3]	100%	100%	100%	100%	100%	99.5%	98.9%
ProVisc® (N=196; n, %)	Available for analysis	196/196 (100%)	196/196 (100%)	195/196 (99.5%)	196/196 (100%)	193/196 (98.5%)	191/196 (97.4%)	194/196 (99.0%)
	Active[1]	0	0	0	0	0	0	0
	Discontinued	0	0	0	0	0	0	0
	Lost to Follow-up	0	0	0	0	1/196 (0.5%)	1/196 (0.5%)	2/196 (1.0%)
	Missing[2]	0	0	1/196 (0.5%)	0	2/196 (1.0%)	4/196 (2.0%)	0
	Percent Accountability[3]	100%	100%	99.5%	100%	98.5%	97.4%	99.0%

Abbreviations: N = number of subjects in total, n = number of subjects per treatment group, Op = operative, Preop = preoperative, Postop = postoperative
[1] Active subjects are those still ongoing in the study.
[2] Missing subjects are those who are not available for analysis, not active, discontinued, or lost to follow-up.
[3] Percent Accountability by Visit = [(# Available for Analysis) / (# Enrolled - # Discontinued - # Active)]*100

C. Demographics of PMA Cohort

The demographics of the trial population (**Table 9**) are representative of the US intended use population for an OVD. Demographics were similar between the treatment groups, with the exceptions of a higher percentage of Hispanic or Latino subjects in the StableVisc™ group compared with the ProVisc® group.

Table 9: Demographics - Safety Population

	StableVisc™ (N=192)	ProVisc® (N=196)	Total (N=388)
Age[1]			
n	192	196	388
Mean (SD)	68.7 (7.78)	67.9 (8.24)	68.3 (8.01)
Median	70.0	68.0	69.0
Min, Max	46, 93	45, 88	45, 93
≤ 65 years	59 (30.7%)	65 (33.2%)	124 (32.0%)
> 65 years	133 (69.3%)	131 (66.8%)	264 (68.0%)
Sex			
Male	77 (40.1%)	69 (35.2%)	146 (37.6%)
Female	115 (59.9%)	127 (64.8%)	242 (62.4%)
Ethnicity			
Hispanic or Latino	33 (17.2%)	21 (10.7%)	54 (13.9%)
Not Hispanic or Latino	159 (82.8%)	175 (89.3%)	334 (86.1%)
Race			
American Indian / Alaska Native	0	0	0
Asian	26 (13.5%)	26 (13.3%)	52 (13.4%)
Black / African American	11 (5.7%)	19 (9.7%)	30 (7.7%)
Native Hawaiian / Other Pacific Islander	1 (0.5%)	2 (1.0%)	3 (0.8%)
White	154 (80.2%)	149 (76.0%)	303 (78.1%)

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

[1] Age is calculated relative to the date of informed consent as described in the Statistical Analysis Plan

The baseline ocular characteristics are summarized in **Table 10**. Baseline ocular characteristics were similar between treatment groups, with the exception of the percentage of subjects with OD as the study eye (60.4% [116/192] vs 52.6% [103/196]) and the percentage of subjects with a cataract classification of nuclear or combination (35.9% [69/192] vs 42.3% [83/196] for nuclear and 63.5% [122/192] vs 55.1% [108/196] for combination) for the StableVisc™ group compared with the ProVisc® group, respectively.

Table 10: Baseline Ocular Characteristics - Safety Population

	StableVisc™ (N=192)	ProVisc® (N=196)	Total (N=388)
Study Eye			
OD	116 (60.4%)	103 (52.6%)	219 (56.4%)
OS	76 (39.6%)	93 (47.4%)	169 (43.6%)
Cataract Classification			
Type			
Nuclear	69 (35.9%)	83 (42.3%)	152 (39.2%)
Cortical	1 (0.5%)	2 (1.0%)	3 (0.8%)
Posterior Subcapsular	0	3 (1.5%)	3 (0.8%)
Combination	122 (63.5%)	108 (55.1%)	230 (59.3%)
Density			
Slight (1+)	17 (8.9%)	18 (9.2%)	35 (9.0%)
Moderate (2+)	119 (62.0%)	125 (63.8%)	244 (62.9%)
Dense (3+)	56 (29.2%)	53 (27.0%)	109 (28.1%)
Very Dense (4+)	0	0	0
Fellow Eye Status			
Normal	1 (0.5%)	2 (1.0%)	3 (0.8%)
Cataract	93 (48.4%)	87 (44.4%)	180 (46.4%)
Aphakic	0	0	0
Pseudophakic	98 (51.0%)	107 (54.6%)	205 (52.8%)

Abbreviations: N = number of subjects per treatment group, OD = oculus dexter (right eye), OS = oculus sinister (left eye)

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the Safety Population of all 388 eyes that were exposed to either the StableVisc™ OVD or ProVisc® 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, the proportion of subjects with postoperative IOP ≥ 30 mmHg at any Follow-Up Visit was 0.052 for the StableVisc™ group and 0.082 for the ProVisc® group (difference estimate [test – control] = -0.030; 90% CI = -0.0711 to 0.0121). These results demonstrated that the study met its endpoint for noninferiority for StableVisc™ when compared with ProVisc® (p=0.0027). In this analysis, the null hypothesis was that the test was inferior to the control; therefore, a p-value of < 0.05 determines that this null hypothesis can be rejected and StableVisc™ can be considered noninferior to ProVisc®. This analysis as presented here does not evaluate, nor was it intended to evaluate, whether StableVisc™ was superior to ProVisc®.

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

	StableVisc™ (N=192)	ProVisc® (N=196)	Difference in Proportion (StableVisc™ – ProVisc®)[a] Estimate (90% CI)	P-value
IOP ≥ 30 mmHg at any follow-up visit	10/192 = 0.052	16/196 = 0.082	-0.030 (-0.0711, 0.0121)	0.0027

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

Notes: Subjects experiencing one or more IOP spikes were counted only once. No subjects had imputed data for this table. Only observed data were used.

[a] The estimated difference in proportions between the treatment groups and the 90% CI was constructed using the normal approximation z-test. An upper confidence limit less than 0.1 favored the hypothesis of noninferiority of StableVisc™ as compared to ProVisc® and the one-sided p-value at a 0.050 significance level was presented for this noninferiority test.

The timepoint of subjects' first IOP spikes were similar for the two groups with the majority of spikes occurring at < 6 hours postoperatively (**Table 12**).

Table 12: 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	StableVisc™ (N=192)	ProVisc® (N=196)
Visit 1	7/191 (3.7%)	13/195 (6.7%)
Measurement Obtained <6 hours postoperatively	6	11
Measurement Obtained ≥6 hours postoperatively	1	2
Interim between Visit 1 and Visit 2	1/13 (7.7%)	0
Measurement Obtained <6 hours postoperatively	1	0
Measurement Obtained ≥6 hours postoperatively	0	0
Visit 2	2/192 (1.0%)	2/195 (1.0%)
Visit 3	1/192 (0.5%)	1/193 (0.5%)

Abbreviations: IOP = intraocular pressure, mmHg = millimeters of mercury, 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 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 13** 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 qualified as IOP spikes also being fairly similar between groups.

Table 13: 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	StableVisc™ (N=192)	ProVisc® (N=196)
Visit 1	25/191 (13.1%)	29/195 (14.9%)
IOP measurement <30 mmHg	18	17
IOP measurement ≥30 mmHg	7	12
Visit 2	12/192 (6.3%)	7/195 (3.6%)
IOP measurement <30 mmHg	10	5
IOP measurement ≥30 mmHg	2	2
Interim between Visit 2 and Visit 3	1/9 (11.1%)	0
IOP measurement <30 mmHg	1	0
IOP measurement ≥30 mmHg	0	0
Visit 3	2/192 (1.0%)	2/193 (1.0%)
IOP measurement <30 mmHg	1	1
IOP measurement ≥30 mmHg	1	1

Abbreviations: IOP = intraocular pressure, mmHg = millimeters of mercury, 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 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 14** 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 14: Intraocular Pressure - Summary by Visit - Safety Population

	StableVisc™ (N=192)		ProVisc® (N=196)	
Visit	Observed Value	Change from Baseline	Observed Value	Change from Baseline
Baseline[1]				
n	192		196	
Mean (SD)	15.7 (2.80)		15.8 (3.04)	
Median	16.0		16.0	
Min, Max	8, 22		8, 24	
Postop Visit 1 (6 ± 2 hours)				
n	191	191	195	195
Mean (SD)	19.5 (6.53)	3.8 (6.29)	20.0 (6.75)	4.2 (6.87)
Median	19.0	4.0	20.0	4.0
Min, Max	8, 48	-12, 31	6, 60	-11, 48
Postop Visit 2 (24 ± 4 hours)				
n	192	192	195	195
Mean (SD)	18.0 (4.70)	2.3 (4.57)	18.4 (4.78)	2.6 (4.73)
Median	18.0	2.0	18.0	2.0
Min, Max	10, 38	-7, 20	10, 36	-9, 19
Postop Visit 3 (7 ± 2 days)				
n	192	192	193	193
Mean (SD)	15.6 (3.76)	-0.1 (3.92)	15.7 (3.39)	-0.0 (3.49)
Median	15.0	0.0	16.0	0.0
Min, Max	9, 35	-8, 22	4, 30	-15, 11
Postop Visit 4 (30 ± 7 days)				
n	181	181	184	184
Mean (SD)	14.5 (3.05)	-1.2 (3.10)	15.0 (3.14)	-0.7 (3.32)
Median	14.0	-1.0	15.0	-1.0
Min, Max	8, 22	-10, 7	9, 26	-7, 9
Postop Visit 5 (90 ± 14 days)				
n	184	184	192	192
Mean (SD)	14.0 (2.85)	-1.7 (3.06)	14.1 (3.15)	-1.7 (3.11)
Median	14.0	-1.0	14.0	-1.0
Min, Max	8, 25	-11, 9	8, 24	-9, 6

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 15**.

Table 15: Categorical Change from Baseline in IOP Measurement (mmHg) by Visit through Visit 2 - Safety Population

Visit Change from Baseline Category (n, %)	StableVisc™ (N=192)	ProVisc® (N=196)
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=191	n=195
Visit 1		
-15 to -11	3 (1.6%)	1 (0.5%)
-10 to -6	7 (3.7%)	7 (3.6%)
-5 to -1	28 (14.7%)	34 (17.4%)
0 to 4	75 (39.3%)	71 (36.4%)
5 to 9	53 (27.7%)	53 (27.2%)
10 to 14	19 (9.9%)	18 (9.2%)
15 to 19	3 (1.6%)	7 (3.6%)
20 to 24	1 (0.5%)	2 (1.0%)
25 to 29	0	1 (0.5%)
30 to 34	2 (1.0%)	0
45 to 49	0	1 (0.5%)
Number of subjects with both Baseline[1] and Interim between Visit 1 and Visit 2 IOP Measurements	n=8	n=11
Interim between Visit 1 and Visit 2		
-15 to -11	3 (37.5%)	1 (9.1%)
-10 to -6	1 (12.5%)	3 (27.3%)
-5 to -1	0	1 (9.1%)
5 to 9	1 (12.5%)	0
10 to 14	1 (12.5%)	4 (36.4%)
15 to 19	1 (12.5%)	2 (18.2%)
20 to 24	1 (12.5%)	0
Number of subjects with both Baseline[1] and Visit 2 IOP Measurements	n=192	n=195
Visit 2		
-10 to -6	3 (1.6%)	7 (3.6%)
-5 to -1	52 (27.1%)	35 (17.9%)
0 to 4	85 (44.3%)	95 (48.7%)
5 to 9	35 (18.2%)	41 (21.0%)
10 to 14	15 (7.8%)	15 (7.7%)
15 to 19	1 (0.5%)	2 (1.0%)
20 to 24	1 (0.5%)	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.

The secondary statistical comparisons of summed cells and flare were evaluated hierarchically after the ECD loss superiority test, which was unsuccessful. Consequently, these tests were not eligible for statistical success. For the Safety Population with observed data only, at the 6-hour Postoperative Visit, the incidence of summed cells and flare greater than zero units was 0.927 for the StableVisc™ group and 0.959 for the ProVisc® group

(difference estimate [test – control] = -0.032; 90% CI= -0.079 to 0.014). At the 24 hour Postoperative Visit, the incidence was 0.953 for the StableVisc™ group and 0.939 for the ProVisc® group (difference estimate [test – control] = 0.014; 90% CI = 0.031 to 0.059).

These results demonstrated that the study did not meet its endpoint for noninferiority for StableVisc™ when compared with ProVisc® at the 6-hour (p=0.0857; p=0.1715 when adjusted for multiplicity) or 24-hour Postoperative Visit (p=0.2661; p=0.2661 when adjusted for multiplicity). In this analysis, the null hypothesis was that the test was equivalent to the control; therefore, a p-value of > 0.05 determines that this null hypothesis cannot be rejected and StableVisc™ cannot be considered different from ProVisc®. These results are shown in **Table 16**.

Table 16: Incidence of Summed Cells and Flare Greater than Zero Units by 6- and 24-hour Visits, Observed Data Only: Secondary Safety Analysis (Safety Population)

			Difference in Proportion (StableVisc™ – ProVisc®)		
	StableVisc™ (N=192)	**ProVisc® (N=196)**	**Estimate (90% CI)[a]**	**P-value[b]**	**Adjusted P-value[c]**
6-hour Postoperative Visit	191	195	-	-	-
Summed cells and flare grades > 0 units	177/191 = 0.927	187/195 = 0.959	-0.032 (-0.079, 0.014)	0.0857	0.1715
24-hour Postoperative Visit	192	196	-	-	-
Summed cells and flare grades > 0 units	183/192 = 0.953	184/196 = 0.939	0.014 (-0.031, 0.059)	0.2661	0.2661

Abbreviations: CI = confidence interval, IOP = intraocular pressure, LSM = least square mean, LSMD = least square mean difference, Max = maximum, Min = minimum, N = number of subjects per treatment group, n = number of subjects per category, OVD = ophthalmic viscosurgical device, SD = standard deviation, SE = standard error

[a] The estimated difference in proportions between the treatment groups and the 95% CI was constructed using the normal approximation.

[b] The p-value for a chi-square test of the difference in proportions at a one-sided significance level of 0.025 was presented.

[c] If the primary endpoints and the secondary effectiveness and safety hypotheses were met, the type I error rate for the secondary cells and flare hypothesis was controlled using the Holm stepwise procedure. The null hypothesis of equal summed cells and flare grades > 0 units between treatments were rejected if the adjusted p-value is < 0.05.

Adverse effects that occurred in the PMA pivotal clinical trial:

Intraoperative:

The only intraoperative complications reported for more than two subjects in either treatment group were the placement of a suture to seal the corneal incision (3 subjects [1.6%, 3/192] in the StableVisc™ group and 5 subjects [2.6%, 5/196] in the ProVisc® group) and the use of standard of care surgical medication with prophylactic IOP lowering treatments (7 subjects [3.6%, 7/192] in the StableVisc™ group and 8 subjects [4.1%, 8/196] in the ProVisc® group).

Postoperative:

There were no non-ocular postoperative adverse event (AE) considered related to the device. The ocular postoperative AEs that occurred in each arm are summarized in **Table 17**.

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

System Organ Class[1] / Preferred Term[1]	StableVisc™ (N=192)	ProVisc® (N=196)
Total Number of TEAEs	75	90
Subjects Reporting at Least One TEAE	62 (32.3%)	63 (32.1%)
Eye disorders	34 (17.7%)	33 (16.8%)
Corneal oedema	14 (7.3%)	10 (5.1%)
Dry eye	3 (1.6%)	3 (1.5%)
Punctate keratitis	1 (0.5%)	3 (1.5%)
Anterior chamber inflammation	3 (1.6%)	0
Conjunctival haemorrhage	1 (0.5%)	2 (1.0%)
Cystoid macular oedema	1 (0.5%)	2 (1.0%)
Foreign body sensation in eyes	2 (1.0%)	1 (0.5%)
Iritis	2 (1.0%)	1 (0.5%)
Photophobia	2 (1.0%)	1 (0.5%)
Posterior capsule opacification	1 (0.5%)	2 (1.0%)
Vitreous detachment	2 (1.0%)	1 (0.5%)
Vitreous floaters	2 (1.0%)	1 (0.5%)
Conjunctival hyperaemia	0	2 (1.0%)
Anterior chamber cell	0	1 (0.5%)
Astigmatism	1 (0.5%)	0
Blepharospasm	0	1 (0.5%)
Diabetic retinopathy	1 (0.5%)	0
Diplopia	0	1 (0.5%)
Eye disorder	0	1 (0.5%)
Eye inflammation	1 (0.5%)	0
Eye pain	0	1 (0.5%)
Hypotony of eye	0	1 (0.5%)
Macular fibrosis	0	1 (0.5%)
Meibomian gland dysfunction	1 (0.5%)	0
Neovascular age-related macular degeneration	0	1 (0.5%)
Photopsia	0	1 (0.5%)
Refraction disorder	0	1 (0.5%)
Retinal haemorrhage	0	1 (0.5%)
Scleral discolouration	1 (0.5%)	0
Uveitis	0	1 (0.5%)
Visual acuity reduced	0	1 (0.5%)
Investigations	14 (7.3%)	16 (8.2%)
Intraocular pressure increased	14 (7.3%)	16 (8.2%)
Surgical and medical procedures	12 (6.3%)	9 (4.6%)
Cataract operation	11 (5.7%)	7 (3.6%)
Intra-ocular injection	0	1 (0.5%)
Intraocular lens repositioning	1 (0.5%)	0
Ptosis repair	0	1 (0.5%)
Injury, poisoning and procedural complications	5 (2.6%)	7 (3.6%)
Corneal abrasion	1 (0.5%)	3 (1.5%)
Posterior capsule rupture	2 (1.0%)	1 (0.5%)
Anterior capsular rupture	0	1 (0.5%)
Cataract operation complication	0	1 (0.5%)

System Organ Class[1] / Preferred Term[1]	StableVisc™ (N=192)	ProVisc® (N=196)
Fall	0	1 (0.5%)
Femur fracture	0	1 (0.5%)
Joint dislocation	0	1 (0.5%)
Post procedural inflammation	1 (0.5%)	0
Procedural nausea	1 (0.5%)	0
Immune system disorders	2 (1.0%)	1 (0.5%)
Hypersensitivity	1 (0.5%)	1 (0.5%)
Seasonal allergy	1 (0.5%)	0
Infections and infestations	2 (1.0%)	1 (0.5%)
Conjunctivitis	1 (0.5%)	0
Endophthalmitis	1 (0.5%)	0
Hordeolum	0	1 (0.5%)
Metabolism and nutrition disorders	0	2 (1.0%)
Dehydration	0	1 (0.5%)
Hypokalaemia	0	1 (0.5%)
Hyponatraemia	0	1 (0.5%)
Congenital, familial and genetic disorders	0	1 (0.5%)
Corneal dystrophy	0	1 (0.5%)
Gastrointestinal disorders	0	1 (0.5%)
Abdominal pain	0	1 (0.5%)
Diarrhoea	0	1 (0.5%)
Nervous system disorders	0	1 (0.5%)
Visual field defect	0	1 (0.5%)
Renal and urinary disorders	0	1 (0.5%)
Acute kidney injury	0	1 (0.5%)
Vascular disorders	0	1 (0.5%)
Hypotension	0	1 (0.5%)

Abbreviations: N = number of subjects per treatment group, TEAE = treatment-emergent adverse event
Note: At each level of summarization (any event, system organ class, and preferred term), subjects reporting more than one adverse event are counted only once.
[1] Adverse events not related to a device are coded to System Organ Class and Preferred Term using the Medical Dictionary for Regulatory Activities (MedDRA), version 22.1.

The proportion of subjects reporting a TEAE at least once was similar across groups. Of the most common TEAEs, the most frequently reported (≥ 5% of subjects in either group) were corneal oedema (7.3% [14/192] and 5.1% [10/196] for StableVisc™ and ProVisc®, respectively), intraocular pressure increased (7.3% [14/192] and 8.2% [16/196] for StableVisc™ and ProVisc®, respectively), and cataract operation (5.7% [11/192] and 3.6% [7/196] for StableVisc™ and ProVisc®, respectively).

One Serious Adverse Event (SAE) was reported. One patient in the StableVisc™ group developed acute postoperative bacterial endophthalmitis which was severe, considered not related to StableVisc™ according to the surgeon, and was ongoing when the patient discontinued from the study.

2. Effectiveness Results

The analysis of effectiveness was based on the Intent-to-Treat (ITT) Population of all 390 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 17.5% loss for the StableVisc™ group and 16.9% loss for the ProVisc® control group. The upper confidence limit for the least square mean difference (LSMD) in the percent change in ECD between groups was 2.9%, which is less than the pre-specified non-inferiority margin of 5% (p=0.0019). 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 StableVisc™ 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

	StableVisc™ (N=194)		ProVisc® (N=196)	
Time Point	Observed Value	Percent Loss[1]	Observed Value	Percent Loss[1]
Baseline[2]				
n	191		194	
Mean (SD)	2566.9 (344.77)		2511.3 (348.91)	
Median	2617.0		2520.0	
Min, Max	1644, 3381		1055, 3392	
Postop Visit 5 (90 ± 14 days)				
n	176	176	182	182
Mean (SD)	2121.7 (561.51)	17.5 (17.58)	2073.1 (533.61)	16.9 (18.73)
Median	2238.5	11.3	2159.5	9.6
Min, Max	660, 3166	-7, 71	546, 3103	-11, 81
LSM (SE)[2]	2117.1 (49.76)	18.2 (1.63)	2056.8 (49.16)	18.0 (1.60)
LSMD (StableVisc™ – ProVisc®) (SE)[3]		0.2 (1.65)		
90% CI of LSMD[3]		-2.5, 2.9		
P-value[3]		0.0019		

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 were based on a statistical model with percent loss as the dependent variable, and treatment group, baseline cataract severity, and Investigator as fixed factors, and age as a continuous covariate. An upper confidence limit less than 5% favored the hypothesis of noninferiority of StableVisc™ as compared to ProVisc® and the one-sided p-value at a 0.050 significance level was presented for this noninferiority test of difference in percent loss.

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

	StableVisc™ (N=194)		ProVisc® (N=196)	
Time Point	Observed Value	Percent Loss[1]	Time Point	Observed Value
Baseline[2]				
n	176		182	
Mean (SD)	2560.3 (349.97)		2505.5 (352.04)	
Median	2614.0		2514.0	
Min, Max	1644, 3381		1055, 3392	
Postop Visit 5 (90 ± 14 days)				
n	176	176	182	182
Mean (SD)	2121.7 (561.51)	17.5 (17.58)	2073.1 (533.61)	16.9 (18.73)
Median	2238.5	11.3	2159.5	9.6
Min, Max	660, 3166	-7, 71	546, 3103	-11, 81
LSM (SE)[3]	2103.2 (51.01)	18.6 (1.60)	2044.2 (49.84)	18.4 (1.56)
LSMD (StableVisc™ - ProVisc®) (SE)[3]		0.3 (1.59)		
90% CI of LSMD[3]		-2.3, 2.9		
P-value[4]		0.0016		

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 StableVisc™ as compared to ProVisc®.
[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.

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

Visit Percent Loss	StableVisc™ (N=194)	ProVisc® (N=196)
Number of subjects with both Baseline[1] and Postoperative Visit 5 ECD Measurements	n=176	n=182
Postoperative Visit 5 (90 days +/- 14 days)		
> -20 to -15%	0	0
> -15 to -10%	0	1 (0.5%)
> -10 to -5%	3 (1.7%)	2 (1.1%)
> -5 to 0%	11 (6.3%)	17 (9.3%)
> 0 to 5%	32 (18.2%)	41 (22.5%)
> 5 to 10%	34 (19.3%)	31 (17.0%)
> 10 to 15%	22 (12.5%)	18 (9.9%)
> 15 to 20%	14 (8.0%)	7 (3.8%)
> 20 to 25%	14 (8.0%)	17 (9.3%)
> 25 to 30%	12 (6.8%)	11 (6.0%)
> 30 to 35%	4 (2.3%)	6 (3.3%)
> 35 to 40%	8 (4.5%)	7 (3.8%)
> 40 to 45%	5 (2.8%)	7 (3.8%)
> 45 to 50%	2 (1.1%)	1 (0.5%)
> 50 to 55%	6 (3.4%)	5 (2.7%)
> 55 to 60%	4 (2.3%)	4 (2.2%)
> 60 to 65%	2 (1.1%)	2 (1.1%)
> 65 to 70%	2 (1.1%)	4 (2.2%)
> 70 to 75%	1 (0.6%)	0
> 75 to 80%	0	0
> 80 to 85%	0	1 (0.5%)

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 less than 0.4319. 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

	StableVisc™ (N=192)	ProVisc® (N=196)
Site 1	n = 16	n = 15
IOP ≥30 mmHg at any follow-up visit	0	0
Site 2	n = 8	n = 10
IOP ≥30 mmHg at any follow-up visit	0	0
Site 3	n = 15	n = 14
IOP ≥30 mmHg at any follow-up visit	1/15 = 0.067	3/14 = 0.214
Site 4	n = 7	n = 8
IOP ≥30 mmHg at any follow-up visit	1/7 = 0.143	0
Site 5	n = 10	n = 12
IOP ≥30 mmHg at any follow-up visit	0	1/12 = 0.083
Site 6	n = 15	n = 17
IOP ≥30 mmHg at any follow-up visit	3/15 = 0.200	6/17 = 0.353
Site 7	n = 15	n = 17
IOP ≥30 mmHg at any follow-up visit	0	1/17 = 0.059
Site 8	n = 16	n = 16
IOP ≥30 mmHg at any follow-up visit	1/16 = 0.063	3/16 = 0.188
Site 9	n = 6	n = 3
IOP ≥30 mmHg at any follow-up visit	0	0
Site 10	n = 2	n = 2
IOP ≥30 mmHg at any follow-up visit	0	0
Site 12	n = 17	n = 17
IOP ≥30 mmHg at any follow-up visit	1/17 = 0.059	0
Site 13	n = 17	n = 15
IOP ≥30 mmHg at any follow-up visit	0	0
Site 14	n = 19	n = 15
IOP ≥30 mmHg at any follow-up visit	1/19 = 0.053	0
Site 16	n = 3	n = 4
IOP ≥30 mmHg at any follow-up visit	0	0
Site 17	n = 5	n = 6
IOP ≥30 mmHg at any follow-up visit	0	0
Site 18	n = 7	n = 8
IOP ≥30 mmHg at any follow-up visit	0	0
Site 19	n = 6	n = 6
IOP ≥30 mmHg at any follow-up visit	2/6 = 0.333	1/6 = 0.167
Site 20	n = 1	n = 2
IOP ≥30 mmHg at any follow-up visit	0	0
Site 21	n = 5	n = 7
IOP ≥30 mmHg at any follow-up visit	0	0
Site 22	n = 2	n = 2
IOP ≥30 mmHg at any follow-up visit	0	1/2 = 0.500
P-value[1]	<0.2460	
P-value[2]	<0.4319	

Abbreviations: CMH = Cochran-Mantel-Haenszel, IOP = intraocular pressure, mmHg = millimeters of mercury, N = number of subjects per treatment group, n = number of subjects per category

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 0.7861. 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

	StableVisc™ (N=194)		ProVisc® (N=196)	
Time Point	Observed Value	Percent Loss[1]	Observed Value	Percent Loss[1]
Baseline[2]				
n	191		194	
Mean (SD)	2566.9 (344.77)		2511.3 (348.91)	
Median	2617.0		2520.0	
Min, Max	1644, 3381		1055, 3392	
Postop Visit 5 (90 ± 14 days)				
n	176	176	182	182
Mean (SD)	2121.7 (561.51)	17.5 (17.58)	2073.1 (533.61)	16.9 (18.73)
Median	2238.5	11.3	2159.5	9.6
Min, Max	660, 3166	-7, 71	546, 3103	-11, 81
LSM (SE)[3]	2102.8 (44.56)	18.7 (1.41)	2056.5 (43.15)	18.0 (1.36)
LSMD (StableVisc™ - ProVisc®) (SE)[3]		0.8 (1.65)		
90% CI of LSMD[3]		-2.0, 3.5		
P-value[4]		0.7861		

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, mm2 = millimeters squared, 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

	StableVisc™ (N=192)	ProVisc® (N=196)	Difference in Proportion (StableVisc™ – ProVisc®)[a] Estimate (90% CI)[a]	P-value
Subjects who received IOP-reducing intervention, n	18	22	-	-
IOP ≥30 mmHg at any follow-up visit	8/18 = 0.444	13/22 = 0.591	-0.146 (-0.405, 0.112)	0.6162
Subjects who did not receive IOP-reducing intervention, n	174	174	-	-
IOP ≥30 mmHg at any follow-up visit	2/174 = 0.011	3/174 = 0.017	-0.006 (-0.027, 0.015)	<0.0001

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

Notes:

- No subjects had imputed data for this table. Only observed data were used. Subjects experiencing one or more IOP spikes were counted only once.
- Subjects experiencing one or more IOP spikes were counted only once.

[a] The estimated difference in proportions between the treatment groups and the 95% CI was constructed using the normal approximation z-test. An upper confidence limit less than 0.1 favored the hypothesis of noninferiority of StableVisc™ as compared to ProVisc® and the one-sided p-value at a 0.050 significance level was presented for this noninferiority test.

For subjects who did not receive IOP-reducing intervention, the results demonstrated noninferiority for StableVisc™ when compared with ProVisc® ($p < 0.0001$). For subjects who received IOP-reducing intervention, the results did not demonstrate noninferiority ($p=0.6162$) due to the small number of subjects receiving such intervention.

4. Pediatric Extrapolation

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

E. 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 22 investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XI. 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.

XII. 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 StableVisc™ experimental device treatment group when compared with the ProVisc® 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 StableVisc™ group had a mean percent change of 17.5% loss in ECD from baseline to Postoperative Visit 5, whereas the ProVisc® group had a mean percent change of 16.9% loss. Non-inferiority was demonstrated statistically. There is a trend for slightly higher frequencies of percent losses at higher ECD percent levels with the StableVisc™ 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 StableVisc™ 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 5.2% (10/192 subjects) for the StableVisc™ group and 8.2% (16/196 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. The most common adverse events of increased IOP and corneal edema, rates were 7.3% (14/192 subjects) and 7.3% (14/192 subjects) respectively in the StableVisc™ group and 8.2% (16/196 subjects) and 5.1% (10/196 subjects) respectively in the ProVisc® group.

C. Benefit-Risk Determination

The probable benefits of the device is 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 OVD as compared to with the control OVD, as evidenced by the clinical effectiveness information summarized above, there is clinically meaningful benefit of the 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 StableVisc™ OVD include increase in IOP and corneal edema.

Additional factors considered in determining probable risks and benefits for the StableVisc™ 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.

XIII. CDRH DECISION

CDRH issued an approval order on February 22, 2023.

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

XIV. 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.