BAUSCH + LOMB

ClearVisc™
2.5% sodium hyaluronate

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**For Intraocular Use**

**PLEASE READ CAREFULLY AND KEEP THIS PACKAGE INSERT FOR FUTURE REFERENCE.**

**DEVICE DESCRIPTION AND PHYSICAL CHARACTERISTICS**

ClearVisc™, an ophthalmic viscosurgical device (OVD), is a sterile solution of highly purified, medium molecular weight sodium hyaluronate. The sodium hyaluronate in ClearVisc is prepared from the culture of Streptococcus pyogenes. ClearVisc contains 25 mg/mL of sodium hyaluronate 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 viscosity is 40 Pa.s at 25°C (77°F) and a shear rate of 1 s-1 (**FIG. 1**). The average molecular weight of the sodium hyaluronate is 750, 000 Daltons. The osmolality is approximately 330 mOsm/Kg.

ClearVisc 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. It also includes a polypropylene retention clip, which helps to maintain standard luer connection between the syringe and cannula.

**INTENDED PURPOSE**

ClearVisc protects intraocular tissues during anterior segment surgery.

**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)

**CONTRAINDICATIONS**

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

**APPLICATIONS**

**Cataract Surgery and IOL Implantation**

The required amount of ClearVisc is infused through a needle or cannula into the anterior chamber. The protective effect of ClearVisc as an aid is optimized when the injection is performed prior to cataract extraction and insertion of the IOL and is effective for phacoemulsification cataract procedures. Additional ClearVisc can be injected as required to facilitate surgical procedures (see **PRECAUTIONS**).

**DIRECTIONS FOR USE**

- Using sterile opening technique, open tray and transfer sterile syringe onto sterile field.
- Remove the tip cap (**FIG. 2**) and attach the sterile 25 gauge or smaller angled cannula. Make sure the cannula is tightly connected with the Luer Lock tip of the syringe (**FIG. 3**).
- After the cannula is attached to the syringe (**FIG. 4** and **FIG. 5**), insert the syringe/cannula assembly through the rounded end of the retention clip (**FIG. 6**) until the retention clip is fully seated against the cannula hub. The syringe flange snaps into the "wings" of the retention clip (**FIG. 7**).

**PRECAUTIONS**

Precautions normally considered during anterior segment procedures are recommended. Pre-existing glaucoma may place patients at risk for increases in intraocular pressure from the OVD during the early postoperative period. The following warnings should be considered when using ClearVisc:

**WARNINGS**

- Do not use if the sterile barrier has been breached. Sterility cannot be guaranteed, and the patient will be at increased risk for infection.
- An excess quantity of ClearVisc should not be used. Excess OVD can cause increased intraocular pressure.
- ClearVisc should be removed from the anterior chamber at the end of surgery to prevent or minimize postoperative intraocular pressure increases (spikes). OVD remaining in the eye can cause increased intraocular pressure.
- If the postoperative intraocular pressure increases above expected values, corrective therapy should be administered. Increased intraocular pressure may lead to inflammation or vision loss.

- Do not re-use the cannula. Even after cleaning and rinsing, resterilized cannula could release particulate matter as ClearVisc is injected. It is recommended that a single-use disposable cannula be used when administering ClearVisc. Reuse may cause eye inflammation.
- If any particulate matter is observed, it should be removed by irrigation and/or aspiration. Particulate matter left in the eye may cause increased IOP or Light scattering /obstruction.
- Store at 2° to 8°C (36° to 46°F). Protect from freezing. The shelf life of ClearVisc is not guaranteed if it is not properly stored.

**ADVERSE REACTIONS**

Sodium hyaluronate is a natural component of tissues within the body and is generally well tolerated in human eyes. Transient postoperative inflammatory reactions and increases in intraocular pressure have been reported. Inflammation may result from increased intraocular pressure caused by use of the OVD. Intraocular inflammation, i.e., toxic anterior segment syndrome (TASS), has been attributed to OVDs. Furthermore, vision loss may be possible as a result of increased intraocular pressure and inflammation.

**ADVERSE REACTION REPORTING**

Adverse reactions and/or potentially sight-threatening complications that may be reasonably regarded as ClearVisc related should be reported to Bausch & Lomb Incorporated at 1-800-338-2020.

**HOW SUPPLIED**

ClearVisc is a sterile viscoelastic preparation supplied in a disposable glass syringe delivering 1.0 mL of sodium hyaluronate, sorbitol and dual buffering system dissolved in USP water for injection (WFI). ClearVisc is sterile filtered and aseptically transferred to syringes. The filled syringes are sealed and the final package sterilized using ethylene oxide (EO). Contents of unopened and undamaged pouches are sterile. Do not use if package is opened or damaged. Refrigerated ClearVisc should be allowed to reach room temperature (approximately 20 to 45 minutes) prior to use.

**DISPOSAL**

Dispose of the unused or contaminated equipment, and/or packaging, by following applicable safe disposal procedures and in accordance with applicable laws and regulations regarding the disposal of biohazardous materials.

**RETURN GOODS POLICY**

All product returned to Bausch & Lomb Incorporated must be accompanied by a Returned Goods Authorization Number. Call 1-800-338-2020 for a Returned Goods Authorization Number and full policy information.

**STORAGE CONDITIONS**

Store at 2° to 8°C (36° to 46°F). Protect from freezing.

**MEDICAL DEVICE RE-USE STATEMENT**

If this product is reprocessed and/or re-used, Bausch + Lomb cannot guarantee the functionality, material structure, cleanliness or sterility of the product. Re-use could lead to illness, infection and/or injury, to the patient or user and, in extreme incidents, death. This product is labeled as “single-use” which is defined as a device intended to be used once only for a single patient.

**CLINICAL TRIAL**

A clinical study was performed 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 United States under IDE # G170265. 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/mm2 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 1** includes the parameters measured preoperatively and postoperatively. Adverse events and complications were recorded at all visits.

**Table 1: 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. 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 2**). 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 3**).

**Table 2: 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 3: 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 4**) 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 4: 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 5**. Baseline ocular characteristics were fairly similar between treatment groups.

**Table 5: 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 6** to **11**. Adverse effects are reported in **Table 12**.

The results of the analysis of the primary safety endpoint are presented in **Table 6**. 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 6: 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 7**). 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 7: 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 8**).

**Table 8: 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 9** 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 9: 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 10** 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 10: 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 |
| 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 11**.

**Table 11: Categorical Change from Baseline in IOP Measurement (mmHg) by Visit through Visit 2 - Safety Population**

| Visit<br>Change from Baseline Category (n, %) | ClearVisc<br>(Total N=184) | VISCOAT®<br>(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%) |
| 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 12**.

**Table 12**: **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 13** to **15**.

The results of the analysis of the primary effectiveness endpoint are presented in **Table 13**. 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 13: 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 14**).

**Table 14: Endothelial Cell Density (cells/mm²) 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 15**. 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 15: Categorical Percent Loss in Endothelial Cell Density (cells/mm$^2$) at Visit 5: Complete Case – Intent to Treat Population**

| Visit<br>Percent Loss | ClearVisc<br>(N=184) | VISCOAT®<br>(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%) |
| > 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 16** below, it is reasonable to assume that there is minimal site effect on device safety performance.

**Table 16: Proportion of Subjects with Postoperative Intraocular Pressure ≥30 mmHg at Any Follow-Up Visit by Study Center - Safety Population**

| | ClearVisc<br>(N=184) | VISCOAT®<br>(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 |

| | ClearVisc (N=184) | VISCOAT® (N=188) |
|---|---|---|
| IOP ≥ 30 mmHg at any follow-up visit | 4/21 = 0.190 | 10/23 = 0.435 |
| Site 6 | n = 25 | n = 25 |
| 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 | |
| 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 17 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 17: Endothelial Cell Density (cells/mm²) 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 18** below.

**Table 18: 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

Bausch & Lomb 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.

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4142500 Rev. 2021-01











**FIG. 1**

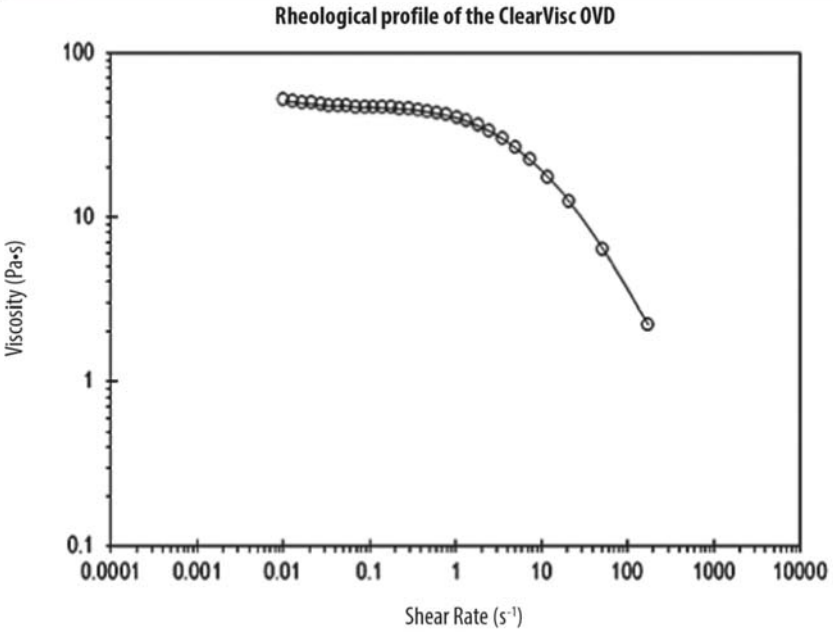
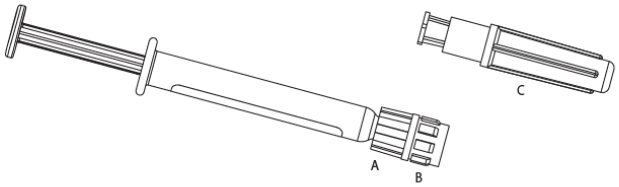
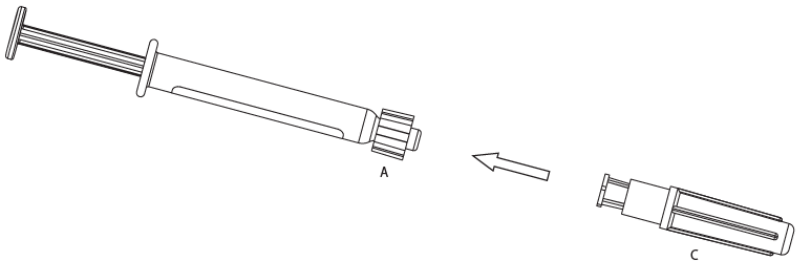



**FIG. 2**




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

**FIG. 3**




Key: A - Luer Lock, C - Cannula and Sheath

**FIG. 4**

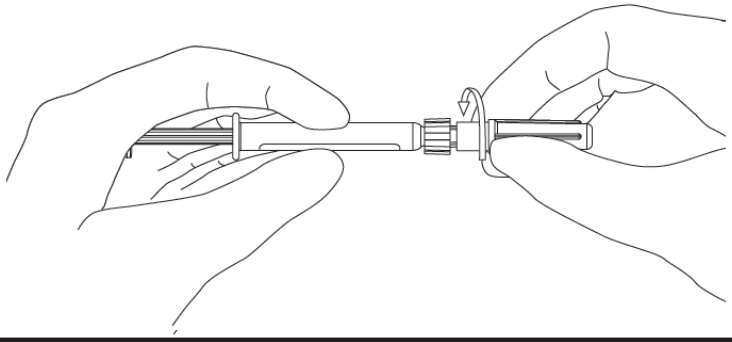


**FIG. 5**

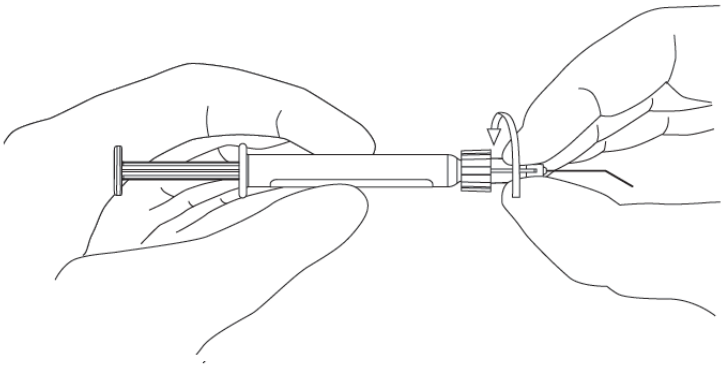


**FIG. 6**

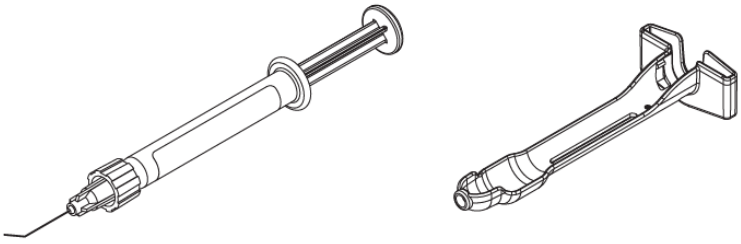


**FIG. 7**