**Table 6: Cumulative[a] Rates of Inflammation (Safety Population of All Treated Eyes)**

| | | Fermented N=211 | | Control N=210 | |
|---|---|---|---|---|---|
| **Category** | **Inflammation** | **n** | **%** | **n** | **%** |
| Epithelial Edema | None (0) | 131 | 62.1 | 134 | 63.8 |
| | Trace (+1) | 58 | 27.5 | 54 | 25.7 |
| | Mild (+2) | 26 | 12.3 | 22 | 10.5 |
| | Moderate (+3) | 7 | 3.3 | 7 | 3.3 |
| | Severe (+4) | 1 | 0.5 | 1 | 0.5 |
| Stromal Edema | None (0) | 161 | 76.3 | 160 | 76.2 |
| | Trace (+1) | 46 | 21.8 | 45 | 21.4 |
| | Mild (+2) | 8 | 3.8 | 11 | 5.2 |
| | Moderate (+3) | 1 | 0.5 | 2 | 1.0 |
| | Severe (+4) | 0 | 0.0 | 1 | 0.5 |
| Cells | None (0) | 12 | 5.7 | 8 | 3.8 |
| | Rare (0.5+) | 133 | 63.0 | 132 | 62.9 |
| | Trace (+1) | 155 | 73.5 | 147 | 70.0 |
| | Mild (+2) | 29 | 13.7 | 36 | 17.1 |
| | Moderate (+3) | 4 | 1.9 | 6 | 2.9 |
| | Severe (+4) | 1 | 0.5 | 0 | 0.0 |
| Flare | None (0) | 100 | 47.4 | 96 | 45.7 |
| | Faint/Trace/Mild (1+) | 111 | 52.6 | 111 | 52.9 |
| | Moderate (2+) | 2 | 0.9 | 8 | 3.8 |
| Anterior Synechiae | None (0) | 210 | 99.5 | 209 | 99.5 |
| | Trace (+1) | 1 | 0.5 | 0 | 0.0 |
| | Mild (+2) | 0 | 0.0 | 1 | 0.5 |
| Posterior Synechiae | None (0) | 210 | 99.5 | 210 | 100.0 |
| | Trace (+1) | 1 | 0.5 | 0 | 0.0 |
| Fibrin Presence | None (0) | 208 | 98.6 | 209 | 99.5 |
| | Trace (+1) | 2 | 0.9 | 1 | 0.5 |
| | Mild (+2) | 1 | 0.5 | 0 | 0.0 |

[a] Cumulative includes unscheduled visits

*Endothelial Cell Count*

The primary effectiveness endpoint of the mean percent endothelial cell (ECC) change preoperatively vs. 3 months was achieved in the study as the lower 95% CI of the mean percent difference between OVD groups was within the -5% non-inferiority margin for ECC loss in both the ITT and safety populations (**Table 7**). As such, the mean percent ECC change in the fermented group was statistically non-inferior to that of the control group.

**Table 7: Mean Percent Change Difference in Endothelial Cell Counts**

| Population | Mean Percent Change[a] | Lower 95% Confidence Limit | Upper 95% Confidence Limit |
|---|---|---|---|
| TT: All Randomized Subjects | 1.05 (0.80 SE) | -0.53 | 2.64 |
| Safety: All Paired-Eye Subjects | 1.11 (11.89 SD) | -0.52 | 2.74 |

[a] Percent Change=(Postop ECC Minus Preop ECC)/Preop ECC) with Difference= Fermented OVD Percent Change Minus Control OVD

As shown in **Table 8** between preop and 3 months postoperative, the mean percent ECC change was -5.55% (SD 9.99) in the fermented group and -6.66% (SD 10.23) in the control group, for a mean percent change difference between groups of 1.11% (SD 11.89).

**Table 8: Change in ECC from Baseline to 3 Months (Safety Population- Paired Eye Subjects)**

| Variable | Group | N[a] | Mean | Standard Deviation |
|---|---|---|---|---|
| Preoperative[b] | Fermented | 206 | 2552.96 | 361.65 |
| | Control | 206 | 2543.75 | 355.64 |
| | Difference | 206 | 9.21 | 131.54 |
| 3 Months | Fermented | 206 | 2410.82 | 420.16 |
| | Control | 206 | 2377.14 | 423.53 |
| | Difference | 206 | 33.68 | 313.36 |
| Percent Change[c] | Fermented | 206 | -5.55 | 9.99 |
| (Preoperative vs 3 months) | Control | 206 | -6.66 | 10.23 |
| | Difference | 206 | 1.11[d] | 11.89 |

[a] Two paired-eye subjects missing 3-month ECC data; therefore, N=206.
[b] The difference between OVD groups at preoperative visit was not statistically significant (p-value=0.3162)
[c] Percent Change=(Postop ECC Minus Preop ECC)/Preop ECC)
[d] 95% CI: -0.52, 2.74

**How supplied**

The Healon GV® PRO OVD is a sterile, non-pyrogenic, viscoelastic preparation supplied in disposable glass syringes, delivering 0.85 mL sodium hyaluronate (18 mg/mL) dissolved in physiological sodium chloride phosphate buffer (pH 6.8 – 7.6). Each mL of Healon GV® PRO OVD contains 18 mg of sodium hyaluronate.

The Healon GV® PRO OVD syringes are terminally sterilized and aseptically packaged.

A sterile, single-use 27G cannula is enclosed in the 0.85mL blister.

**Preparation and storage**

Refrigerated Healon GV® PRO OVD should be held at room temperature for approximately 30 minutes before use. Protect from freezing and exposure to light.

For intraocular use.

Store between 2 to 8°C (36 to 46°F).

**Definition of symbols**

| | |
|---|---|
| | Caution, see instructions for use |
| | See instructions for use |
| | Do not reuse |
| | Protect from light |
| | Do not use if the packaging has been opened or damaged |
| | Protect from freezing |
| 2°C (36°F) 8°C (46°F) | Temperature limitation |
| STERILE | Sterilized using steam (solution) |
| STERILE R | Sterilized using irradiation (cannula) |
| STERILE A | Sterilized using aseptic processing techniques (blister packaging) |
| | Manufacturer |
| LOT | Batch code |
| | Use by (YYYY-MM-DD: year-month-day) |
| REF | Catalogue number |

**References**


1. Balazs, E.A.: Ultrapure hyaluronic acid and the use thereof. U.S. patent 4,141,973 (1979)
2. Fry L.L. & Yee R.W. (1993): Healon GV in extracapsular cataract extraction with intraocular lens implantation. Cataract Refract. Surg. 19:409-412.
3. Gaskel A. & Haining W. (1991): A double blind randomized multicentre clinical trial of "Healon GV," compared with "Healon" in ECCE with IOL implantation. Eur J. Implant Ref. Surg. 3:241.
4. Pape, L.G. & Balazs, E.A.: The use of sodium hyaluronate (Healon®) in human anterior segment surgery. Ophthalmol 87 (1980) p 699-705


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Revision date: 11/2020



52-0501-00

# Healon GV® PRO

Sodium Hyaluronate

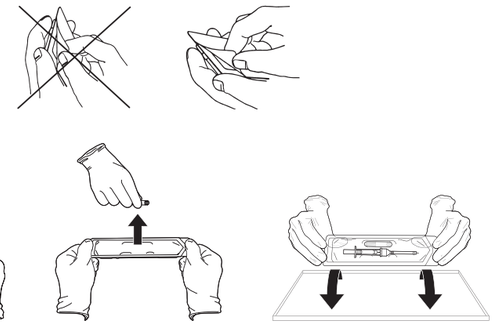
**NOT MADE WITH NATURAL RUBBER LATEX**

## Instructions

**Sterile opening technique**

Tear off the paper covering.

Remove syringe and place on sterile field.

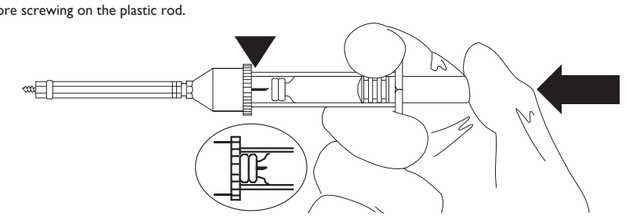


**Assembly**

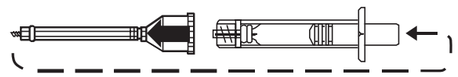
Press the vial completely into the holder so that the needle perforates the membrane.

**Important**

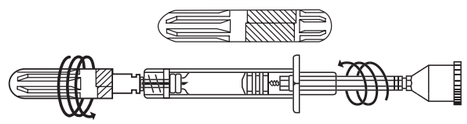
Perforate the membrane before screwing on the plastic rod.



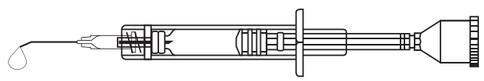
Remove the plastic rod.



Screw the plastic rod into the plunger.
Connect the cannula.



Check for proper function.



**Store at 2 to 8°C (36 to 46°F).** **For single use only.**

Johnson & Johnson VISION

# Healon GV® PRO

℞ only

**NOT MADE WITH NATURAL RUBBER LATEX**

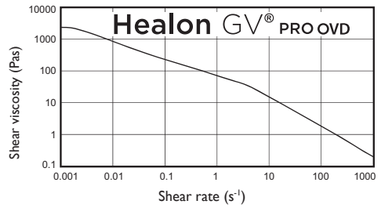
Sodium Hyaluronate

## Product information

**Description**
The Healon GV® PRO Ophthalmic Viscosurgical Device (OVD) is a sterile, non-pyrogenic, transparent viscoelastic preparation of a highly purified, noninflammatory, high molecular weight (average = 3.2 million daltons) fraction of sodium hyaluronate from fermented bacteria. The Healon GV® PRO OVD contains 18 mg/mL of sodium hyaluronate, dissolved in a physiological sodium chloride phosphate buffer (pH 6.8-7.6). This polymer consists of repeating disaccharide units of N-acetylglucosamine and sodium glucuronate linked by glycosidic bonds.

Sodium hyaluronate is a physiological substance that is widely distributed in the extracellular matrix of connective tissues in both animals and man. For example, it is present in the vitreous and aqueous humor of the eye, the synovial fluid, the skin, and the umbilical cord. Sodium hyaluronates derived from various human or animal tissues do not differ chemically.

The viscosity of the Healon GV® PRO OVD at rest is about 2000 Pas, 2 million times higher than that of aqueous humor. At high shear rates, such as during injection, the viscosity of the Healon GV® PRO OVD decreases dramatically due to shear thinning, facilitating injection through a 27G cannula. The graph below represents the flow curve (shear viscosity versus shear rate).




**Indications**
The Healon GV® PRO OVD is intended for use in anterior segment ophthalmic surgical procedures of the human eye. The Healon GV® PRO OVD is designed to create and maintain a deep anterior chamber which facilitates manipulation inside the eye with reduced trauma to the corneal endothelium and other ocular tissues. The Healon GV® PRO OVD can also be used to efficiently separate and control ocular tissues. The Healon GV® PRO OVD is not designed to have any pharmacological effect.

**Contraindications**
There are no known contraindications to the use of the Healon GV® PRO OVD when used as recommended.

**Warnings**
Healon GV® PRO OVD is difficult to remove from the eye. It is a high viscosity cohesive OVD that displays dispersive behavior during removal. This behavior during removal is different compared to the similarly named Healon GV® OVD. Adequate removal of Healon GV® PRO OVD may require the specific surgical removal techniques described below. Users should weigh the potential benefit/risk ratio of using this device based on their own personal skill and comfort level with the recommended surgical removal techniques.

**Precautions**
As with any high viscosity OVD, retained Healon GV® PRO OVD in the eye could lead to increase in IOP if left in the eye.

As a result of non-clinical and clinical experience, during removal, Healon GV® PRO OVD performs similarly to Healon5® and Healon5® PRO OVDs, two high-viscosity OVDs that are more difficult to remove from the eye compared to typical cohesive OVDs. Two surgical removal techniques were previously studied with the original Healon5® OVD and were shown to be effective at removing Healon5® OVD from the eye; The Behind the Lens or the Two-Compartment Technique (TCT) was superior to the Rock'n Roll technique with regards to IOP elevation in a clinical study. Since Healon GV® PRO OVD performs similarly to Healon5® OVD during OVD removal, the following two surgical techniques are recommended to remove Healon GV® PRO OVD from the eye. The safety and effectiveness of other removal techniques have not been demonstrated in a clinical study.

The following removal technique (Behind the Lens or TCT) is one option to ensure efficient removal of the Healon GV® PRO OVD.

Use a standard I/A tip, 0.3 mm, with effectual flow of 20-25 ml/min and vacuum of 250-300 mmHg with a potential maximum setting at 500 mmHg. When using a machine with a peristaltic pump, use the upper limits of the suggested settings. When using a Venturi pump use the lower limits of the suggested settings. Bottle height should be 60-70 cm above eye level.

1. Start the removal directly after the IOL implantation, while the anterior chamber is still filled with the Healon GV® PRO OVD and before the IOL has been centered. Go behind the IOL optic without engaging the flow of the I/A tip (port up) and then start flow. Remove the Healon GV® PRO OVD from the capsular bag first and ensure that the lens has adequately centered. During removal of the Healon GV® PRO OVD from the capsular bag, the continuous flow of irrigation fluid keeps the bag inflated and reduces the risk of aspirating the capsular bag. While maintaining continuous flow remove the tip from behind the optic and place it on top of the optic.
2. Continue the removal by circling the I/A tip at the iris plane, or on the optic surface, then make an additional sweep in the anterior chamber paying particular attention to the angles.

Healon GV® PRO OVD may be removed by creating maximum turbulence to make the Healon GV® PRO OVD fracture into large pieces. This can be accomplished by using the Rock'n Roll technique (described below) with standard I/A tip, 0.3 mm, with high settings, flow rates should be 25-30 ml/min and vacuum 350-500 mmHg, depending on the type of pump. If a peristaltic pump is used, the vacuum should be set towards the higher limit. If a Venturi pump is used, the vacuum should be set towards the lower limit. Bottle height should be 60-70 cm above eye level. For phacoemulsification machines that use linear foot pedal control, the suggested settings can only be achieved if the surgeon operates the phacoemulsification machine with fully depressed foot pedal. Settings will vary according to user preference for different types of programmable foot pedals.

1. Start by circling the hand piece in the anterior segment at iris plane.
2. Gently rest the I/A piece on the anterior surface of the optic. Press on the IOL optic on one side and rotate the I/A hand piece directing the flow into the bag. Direct the hand piece port towards the equator of the capsular bag and stay in this position for a few seconds and then repeat on the other side of the IOL optic until the Healon GV® PRO OVD is completely removed. Finally, sweep the anterior chamber including the angles and repeat step 2 if necessary.

Note: The above phacoemulsification machine settings were used in a Healon5® clinical study. Individual phacoemulsification system parameters vary. Although phacoemulsification machine settings may need to be altered due to differences in phacoemulsification machine technology, only the machine settings that are described above were shown to be effective at removing Healon5® OVD in a clinical study. The safety and effectiveness of other phacoemulsification machine settings have not been demonstrated in a clinical study.

A transient myopic shift may also occur if the Healon GV® PRO OVD is not completely removed from the capsular bag behind the intraocular lens.

Postoperative intraocular pressure (IOP) may be increased if the Healon GV® PRO OVD is left in the eye. Special care should be taken to ensure complete removal of the Healon GV® PRO OVD from the entire eye including behind the lens and the chamber angles. Continued irrigation/aspiration after displacement of the initial bolus of viscoelastic from the eye should facilitate removal of viscoelastic if remaining in the anterior segment; additional surgical maneuvers are likely needed to remove OVD that is trapped behind the lens. Due to the greater viscosity of the Healon GV® PRO OVD, increase in postoperative IOP may be higher than that caused by leaving the same amount of other sodium hyaluronate viscoelastic products with lower zero shear viscosity in the anterior chamber. Since rises in postoperative intraocular pressure, including cases of significant elevation and rare incidents of complications (including ischemic optic neuropathy, retinal vascular occlusion, corneal edema, increased light sensitivity/photophobia, swelling of capsular bag, unexpected post-operative refraction, pain, nausea, poster-operative iris constriction and loss of vision in glaucoma patients), have been reported, the following precautions are strongly recommended:

Postoperative IOP may be elevated as a result of pre-existing glaucoma, other causes of compromised outflow, higher preoperative intraocular pressure and complications in surgical procedures (e.g. enzymatic zonulysis, absence of an iridectomy, trauma to filtration structures, and by blood and lenticular remnants in the anterior chamber) may also lead to increased intraocular pressure. Since the exact role of these factors is difficult to predict in any individual case, the following precautions are recommended: do not overfill the eye chambers with the Healon GV® PRO OVD, completely remove the Healon GV® PRO OVD by irrigation and/or aspiration at the close of the surgery and carefully monitor intraocular pressure, especially during the immediate postoperative period. Treat with appropriate intraocular pressure lowering therapy, if required. Prophylactic pressure lowering treatment should always be considered.

Since clinical data with use of Healon GV® PRO OVD in glaucoma patients are limited, it is strongly recommended that extra care be taken to remove OVD from the eye (see above) and prophylactic pressure-lowering treatment should always be considered for these patients.

The potential for early and short-term post-operative IOP spikes exists with cohesive OVDs, that require time and care to remove from the eye. Therefore, it is recommended that Healon GV® PRO OVD be removed from the eye completely by irrigating and aspirating with sterile irrigation solution to reduce the risk of early postoperative IOP spikes.

Overfilling the anterior segment of the eye with the Healon GV® PRO OVD may cause increased intraocular pressure, glaucoma, or other ocular damage.

Using higher molecular weight, high concentration viscoelastics, such as Healon GV® PRO OVD, may impede aspiration and/or potentially lead to blockage of aspiration flow through phaco tubing, especially when reuse of aspiration tubing, use of multiple vials of viscoelastics and/or lens fragments are combined.

Before initiating phacoemulsification, use irrigation/aspiration to create a fluid filled space above the lens. This reduces the risk of initial visco-occlusion of the phaco tip or the irrigation line which could cause phaco tip heating.

Because of reports of an occasional release of minute rubber particles, presumably formed when the diaphragm is punctured, the physician should be aware of this potential problem. Express a small amount of the Healon GV® PRO OVD from the syringe prior to use and carefully examine the remainder and as it is injected and during use to avoid injecting minute rubber particles which may be released when the syringe diaphragm is punctured.

Sodium hyaluronate solution, like Healon GV® PRO OVD may appear cloudy or form precipitates when it is injected. The clinical significance of these reports, if any, is not known since the majority received to date does not indicate any harmful effects on ocular tissues. The physician should be aware of this phenomenon and, should it be observed, remove the cloudy or precipitated material by irrigation and/or aspiration. Based on *in vitro* laboratory studies, this phenomenon may be related to interactions with concomitantly used ophthalmic medications or detergents which remain in reused cannulas. *In vitro* studies have also shown incompatibility, resulting in opalescence, between sodium hyaluronate and solutions containing cationic components, e.g., detergents, quaternary ammonium compounds and benzalkonium chloride.

Care should be taken to avoid trapping air bubbles behind the Healon GV® PRO OVD.

Use only if solution is clear.

The Healon GV® PRO OVD is a highly purified fraction extracted from fermented bacteria which may contain minute amounts of protein.

Use only the cannula provided in the package. Reprocessed cannulas should not be used.

Product and cannula are for single use only. Re-use may cause eye inflammation.

Do not resterilize.

Do not use if the blister pack has been damaged.

**Adverse events**
Increased intraocular pressure has been reported after use of the Healon GV® PRO OVD:

- Increased intraocular pressure is likely to occur if the Healon GV® PRO OVD is not removed as completely as possible. Clinical judgement concerning the use of this product should be considered in cases where thorough removal may not be possible. The Precautions noted above should be taken to manage any increased postoperative intraocular pressure and to reduce the likelihood of occurrence of related postoperative complications such as optic neuropathy, pupillary atonia and dilation, and iris atrophy.

Rarely, postoperative inflammatory reactions (iritis, hypopyon, endophthalmitis) following the use of sodium hyaluronate, as well as incidents of corneal edema and corneal decompensation, have been reported. Their relationship to sodium hyaluronate has not been established.

**Applications**
Cataract surgery - IOL implantation
A sufficient amount of the Healon GV® PRO OVD is slowly, and carefully introduced (using a cannula or needle) into the anterior chamber.

Injection of the Healon GV® PRO OVD can be performed either before or after delivery of the lens. Injection prior to lens delivery will, however, have the additional advantage of protecting the corneal endothelium from possible damage arising from the removal of the cataractous lens[4]. The Healon GV® PRO OVD may also be used to coat surgical instruments and the IOL prior to insertion.

Additional Healon GV® PRO OVD can be injected during surgery to replace any Healon GV® PRO OVD lost during surgical manipulation (see Precautions section).

**Clinical Trial Of the Fermented Healon5® OVD (2016-2017)**
A clinical trial was conducted in the United States in 2016-2017 that was designed to evaluate safety and effectiveness of the fermented Healon5® OVD compared to the animal-derived Healon5® OVD control. This study was a prospective, multicenter, paired-eye, randomized, masked, 3 month clinical investigation with the fermented Healon5® OVD used in one eye and the animal-derived Healon5® OVD used in the fellow eye as the control. A total of 226 subjects were randomized with 213 subjects treated in either one or both eyes across 8 sites in the US. A total of 211 eyes received the fermented Healon5® OVD (fermented group) and 210 eyes received animal-derived Healon5® OVD (control group). Of the treated subjects, 208 were bilaterally treated with the fermented OVD in one eye and the control OVD in the fellow eye, and five subjects were unilaterally treated.

The results of the study demonstrated non-inferiority of the fermented Healon5® OVD compared to the animal-derived Healon5® OVD as all study endpoints were achieved and results were comparable between OVD groups.

*Intraocular Pressure*
The primary safety endpoint of the cumulative rate of intraocular pressure (IOP) spikes ≥30 mmHg was achieved in both the Intent-to-Treat (ITT) and Safety population analyses. For the difference between OVD groups in the cumulative rate of IOP spikes ≥30 mmHg, the lower 95% CIs were within the non-inferiority margin of -10%, meeting the criteria for success and demonstrating the cumulative rate of IOP spikes ≥30 mmHg in the fermented group was statistically non-inferior to the cumulative spike rate in the control group as shown in **Table 1**. The mean difference in IOP spike rates between OVD groups was 2.21% with a lower 95% CI of 5.73% in the ITT population and 1.9% with a lower 95% CI of -5.46 in the safety population.

**Table 1: Difference in Cumulative Rates of IOP Spikes ≥30 mmHg**

| Population | % Difference between Fermented and Control | Lower 95% Confidence Limit | Upper 95% Confidence Limit |
|---|---|---|---|
| ITT: All Randomized Subjects | -2.2% | -5.73% | 1.31% |
| Safety: All Paired-Eye Subjects | -1.9% | -5.46% | 1.61% |

**Table 2** presents IOP spike rates over time for the safety population of all paired-eye subjects. All IOP spikes in both the fermented and control OVD groups occurred within 1 day postoperative, with the majority occurring at the 6-hour postoperative time point. There were no IOP spikes in either OVD group at 1 week postoperative or later. The rates of IOP spikes ≥30 mmHg over time in the fermented group were non-inferior to that in the control group at both 6 hours (-3.4% difference; lower 95% CI -6.48%) and 1 day (0.5% difference; lower 95% CI -2.36%) in the safety population.

**Table 2: IOP Spikes Over Time (Safety Population- All Paired-Eye Subjects, N=208)**

| OVD Group | IOP | 6 Hours N=208 | | 1 Day N=208 | | 1 Week N=208 | | 1 Month N=208 | | 3 Months N=208 | | Cumulative N=208 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | n | % | n | % | n | % | n | % | n | % | n | % |
| Fermented | IOP < 30 | 192 | 92.3 | 204 | 98.1 | 208 | 100 | 208 | 100 | 208 | 100 | 191 | 91.8 |
| | IOP >= 30 | 16 | 7.7 | 4 | 1.9 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 17 | 8.2 |
| Control | IOP < 30 | 199 | 95.7 | 203 | 97.6 | 208 | 100 | 208 | 100 | 208 | 100 | 195 | 93.8 |
| | OP >= 30 | 9 | 4.3 | 5 | 2.4 | 0 | 0.0 | 0 | 0.0 | 0 | 0.0 | 13 | 6.3 |

There were no significant differences between groups in the mean change in IOP from baseline at any postoperative time point based on evaluation of the 95% CIs of the difference in mean change in IOP (**Table 3**).

**Table 3: Mean IOP and Change in IOP from Baseline (mmHg) (Safety Population- All Paired-Eye Subjects, N=208)**

| | | Preop | | 6 Hours | | 1 Day | | 1 Week | | 1 Month | | 3 Months | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | OVD | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| IOP | Fermented | 15.3 | 2.3 | 21.1 | 6.7 | 19.2 | 7.1 | 16.0 | 2.9 | 14.7 | 2.4 | 13.9 | 2.3 |
| (mmHg) | Control | 15.2 | 2.5 | 20.4 | 5.9 | 18.8 | 5.2 | 16.1 | 3.0 | 14.6 | 2.6 | 13.9 | 2.4 |
| | Difference | -0.1 | 1.2 | -0.7 | 6.0 | -0.4 | 8.5 | 0.1 | 3.4 | -0.0 | 1.5 | -0.0 | 1.3 |
| IOP | Fermented | - | - | 5.8 | 6.9 | 3.9 | 7.0 | 0.7 | 3.3 | -0.6 | 2.8 | -1.4 | 2.6 |
| Difference | Control | - | - | 5.2 | 5.9 | 3.6 | 4.9 | 0.9 | 3.5 | -0.6 | 2.8 | -1.3 | 2.8 |
| (postop-preop) | Difference | - | - | -0.6 | 6.2 | -0.3 | 8.5 | 0.2 | 3.5 | 0.0 | 1.9 | 0.0 | 1.6 |

*Adverse Events and Complications*
There were no differences between groups for the secondary safety endpoint of serious and/or device-related adverse events (**Table 4**). Twenty-one (21) eyes in both OVD groups experienced ocular serious adverse events during the study, none of which were unanticipated. Of the 42 total events reported, 34 were determined to be device-related. Of these, 31 were IOP spikes ≥30 mmHg (18 in the fermented group and 13 in the control group) and 3 were IOP spikes of <30 mmHg (all in the control group) requiring treatment. One IOP spike ≥30 mmHg occurred in a non-paired eye subject in the fermented group; therefore, there was a total of 18 IOP spikes in the fermented group overall vs. 17 spikes in paired-eye subjects in the fermented group. Of the three cases with IOP spikes <30 mmHg (all in the control group), it was determined that treatment was in the best interest of the subjects.

**Table 4: Ocular Serious Adverse Events and Secondary Surgical Interventions (Safety Population of All Treated Eyes)**

| | Fermented Group N=211 | | Control Group N=210 | |
|---|---|---|---|---|
| **Serious Adverse Events** | **n** | **%** | **n** | **%** |
| Conjunctival Laceration | 0 | 0.0 | 1 | 0.5 |
| Cystoid macular edema | 0 | 0.0 | 1 | 0.5 |
| Elevated IOP/IOP spike (30 mmHg or greater)[a] | 18 | 8.5 | 13 | 6.2 |
| IOP spike <30 mmHg, requiring treatment[a] | 0 | 0.0 | 3 | 1.4 |
| Keratitis secondary to Sjogrens | 1 | 0.5 | 0 | 0.0 |
| Mild TASS | 1 | 0.5 | 1 | 0.5 |
| Proliferative Diabetic Retinopathy | 1 | 0.5 | 0 | 0.0 |
| Wound leak | 0 | 0.0 | 1 | 0.5 |
| Mild inflammation secondary to gout | 0 | 0.0 | 1 | 0.5 |
| **Total Eyes with SAEs** | **21** | **10.0** | **21** | **10.0** |
| [a] Determined to be device-related | | | | |
| | | | | |
| **Secondary Surgical Interventions (SSI)** | | | | |
| AC Tap (one or more) | 7 | 3.3 | 3 | 1.4 |
| Cauterization of conjunctival laceration | 0 | 0.0 | 1[b] | 0.5 |
| Retinal Laser Treatment (pan-retinal photocoagulation) | 1 | 0.5 | 0 | 0.0 |
| Suture | 0 | 0.0 | 1 | 0.5 |
| Suture placed in conjunctival laceration | 0 | 0.0 | 1[b] | 0.5 |
| **Total Eyes with SSIs** | **8** | **3.8** | **5** | **2.4** |
| [b] Same eye (two SSIs) | | | | |

Complication and adverse event rates compared favorably to the ISO SPE rates for cataract surgery, with the exception of secondary surgical procedures (**Table 5**). The rates of secondary surgical interventions (SSIs) for both the fermented and control groups (3.8% and 2.4%, respectively) were above the ISO SPE rate (0.8%) and consisted of anterior chamber taps performed to treat elevated IOP in the early postoperative period (6 hours and 1 day postoperative). This is likely due to the withholding of IOP-reducing medications (per the study protocol) that are usually standard of care at the time of cataract surgery. The non-device-related SSIs consisted of pan-retinal photocoagulation for the treatment of diabetic retinopathy (fermented group) and cauterization/suture of a conjunctival laceration and a suture placement at the 1-day postoperative visit due to a wound leak (control group). There were no persistent medical complications or adverse events of corneal edema, cystoid macular edema, iritis, or persistent elevated IOP requiring treatment at the final 3-month visit as defined by ISO 11979-9.

**Table 5: 3-Month Cumulative Medical Complications/Adverse Events vs ISO 11979-9 SPE[a] Rates (Safety Population of all Treated Eyes)**

| | | Fermented N=211 | | Control N=210 | |
|---|---|---|---|---|---|
| **Cumulative Medical Complications/Adverse Events** | **ISO SPE Rate** | **n** | **%** | **n** | **%** |
| Cystoid macular edema | 3.0 | 0 | 0.0 | 1 | 0.5 |
| Hypopyon | 0.3 | 0 | 0.0 | 0 | 0.0 |
| Endophthalmitis | 0.1 | 0 | 0.0 | 0 | 0.0 |
| Lens dislocation | 0.1 | 0 | 0.0 | 0 | 0.0 |
| Pupillary block | 0.1 | 0 | 0.0 | 0 | 0.0 |
| Retinal detachment | 0.3 | 0 | 0.0 | 0 | 0.0 |
| Eyes with secondary surgical intervention | 0.8 | 8 | 3.8 | 5 | 2.4 |
| - Device related | | 7[b] | 3.3 | 3[b] | 1.4 |
| - Not device related | | 1 | 0.5 | 2 | 1.0 |

[a] Per ISO 11979-7: 2006/Amd. 1:2012 (E) Ophthalmic Implants – Intraocular Lenses (Part 7): The SPE rate is the safety and performance endpoint.
[b] AC taps to treat elevated IOP; likely a result of withholding the use of routine IOP-reducing medications per protocol.

There were no statistically significant differences between OVD groups for the occurrence of surgical complications or additional surgical procedures. Surgical complications were rare with only two complications (0.9%, 2/211) occurring in the fermented group and five (2.4%, 5/210) in the control group. None of the surgical complications were related to OVD use.

*Inflammation*
The distributions of the grades of inflammation for epithelial edema, stromal edema, cells, flare, anterior synechiae, posterior synechiae, and fibrin presence were similar over time between OVD groups. The cumulative rates of inflammation are presented in **Table 6**. The most frequently reported types of inflammation were cells and flare. Over time, the frequency of inflammation declined in both OVD groups with the greatest frequency of inflammation occurring at early postoperative periods (6 hours and 1 day).

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