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ALBOMED

WHITE PAPER

VISCOELASTICS – Pe-Ha-Luron® F 2.2%

EVALUATION OF SAFETY AND EFFICACY OF THE VISCOELASTIC DEVICE Pe-Ha-Luron® F 2.2% APPLIED DURING CATARACT SURGERY

FINAL REPORT

June 08, 2021

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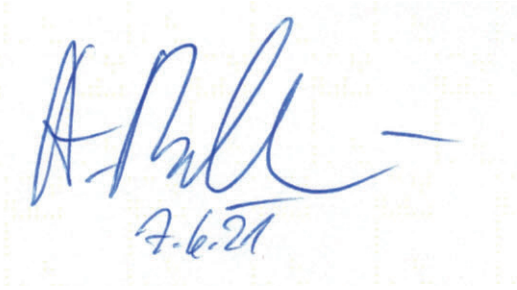


Key Highlights

- Ophthalmic viscoelastic devices (OVDs) are commonly used during cataract surgery to maintain the pressure in the anterior chamber and to protect the corneal endothelium from being damaged.
- Pe-Ha-Luron® F 2.2% OVD is an injectable transparent gel, sterile and isotonic, based on sodium hyaluronate obtained from bacterial fermentation as the main component.
- In this observational study, the safety and efficacy of Pe-Ha-Luron® F in a concentration of 2.2% was assessed. Pe-Ha-Luron® F 2.2% was applied during routine cataract surgery in 54 eyes, the follow-up was 1-day after surgery.
- Pe-Ha-Luron® F 2.2% was found to be safe, with no adverse effects reported in any of the 54 eyes. IOP measured at 1-day after surgery was within the normal range. Slitlamp observations revealed that no residues of OVD were present in the anterior chamber or between the IOL and the capsular bag.
- Pe-Ha-Luron® F 2.2% was successfully used in performing the "visco-polishing technique" in 10 eyes for the removal of capsular fibrosis and cortical residues.

Background & Aim

Ophthalmic viscoelastic devices (OVDs) are used during cataract surgery as they offer numerous advantages. OVDs aim to maintain the pressure in the anterior chamber during surgery in order to keep the intervention safe; they also protect the corneal endothelium and facilitate the surgical procedure. However, OVDs have longer retention time in the eye after surgery which is known to cause a significant increase in postoperative intraocular pressure (IOP) – this occurs irrespective of the OVD type used.[1,2,3,4,5] The reason are traces of OVD left in the eye which can obstruct the trabecular meshwork, affecting the aqueous outflow and resulting in IOP spikes within 24 hours after surgery. This is of particular concern for patients with glaucoma. Therefore, removal of OVD is essential to avoid IOP spikes.

Early research work already demonstrated the advantages of protecting the corneal endothelium and improving control of the anterior chamber during surgery. Today, there is a wide choice of OVDs available on the market with different chemical and physical properties, and research and clinical applications continue to expand our understanding of how OVDs work and how they can be utilized to improve surgical outcomes.

OVDs are commonly classified in 2 main categories depending on their rheologic properties: lower viscosity dispersive OVDs and higher viscosity cohesive OVDs. Dispersive OVDs are low viscosity materials with good adhesion properties to intraocular structures and instruments. They provide

excellent protection for the corneal endothelium during surgery, however, due to their short molecular chains they are fragile and therefore more difficult to remove at the end of surgery. Cohesive OVDs are highly viscous materials with intramolecular adhesion and entanglement. They are ideal for creating and maintaining space during ocular surgeries and are easier to remove. However, they offer a lower corneal protection.

We previously reported on the performance of Pe-Ha-Luron® F from ALBOMED® (ALBOMED GmbH, Schwarzenbruck, Germany) at different concentrations: 1.0%, 1.4%, 1.6%, 1.8%, and 3.0% and demonstrated that the range of products was safe and efficient.[6] The aim of this report is to provide clinical data on the safety and performance of the OVD Pe-Ha-Luron® F in a 2.2% concentration, which was not available for the previous clinical evaluation. Pe-Ha-Luron® F is based on sodium hyaluronate obtained from bacterial fermentation (i.e. not of animal origin) and due to its physical properties, it is classified as a cohesive viscoelastic.

In order to assess the safety of OVD use, it is important to evaluate the occurrence of side effects and in particular the change of IOP postoperatively; the efficacy of the OVD is assessed by investigating the time it takes for the surgeon to perform the procedure.

Specifications of Pe-Ha-Luron® F

Intended purpose

The viscoelastic properties of Pe-Ha-Luron® F hyaluronate intraocular gels allow lubrication, support, and protection of ocular tissues during ophthalmic surgery. Pe-Ha-Luron® F forms a thin protective layer on the ocular cells and tissues and facilitates the insertion of the intraocular lens.
The intended purpose of Pe-Ha-Luron® F is to maintain the depth of the anterior chamber, as well as protect ocular tissues.

Indications

Pe-Ha-Luron® F is used as an adjuvant for the following surgical procedures:

- Cataract surgery with or without intraocular lens implantation
- Glaucoma surgery

Description

Pe-Ha-Luron® F is a clear, sterile, isotonic, and viscoelastic preparation of highly purified sodium hyaluronate for intraocular use, dissolved in a buffered physiological solution (pH 6.8 – 7.4). The hydrogel contains 1.0%, 1.4%, 1.6%, 1.8%, 2.2% or 3.0% sodium hyaluronate and is filled in a ready-to-use glass syringe for single use. The syringe is packaged in a sterile blister pack. The product is free from preservatives. It has been subjected to moist heat sterilization for injectable products and is non-pyrogenic. There are no known inflammatory or immunogenic reactions.

Composition

The main component of all Pe-Ha-Luron® F intraocular gel products is sodium hyaluronate (abbreviated SH; the sodium salt of hyaluronic acid). The sodium hyaluronate is obtained by bacterial fermentation and is not of animal origin.

The following Table 1 summarizes the composition of Pe-Ha-Luron® F OVDs.

Table 1: Composition of Pe-Ha-Luron® F 2.2%

Component	Unit formula for 1 ml
Sodium hyaluronate	22.00 mg (Pe-Ha-Luron© F 2.2%)
Sodium Chloride (NaCl)	8.50 mg
NaH_2PO_4, $2H_2O$	0.045 mg
Na_2HPO_4, $2H_2O$	0.563 mg
WFI Water For Injection	q.s.

Specifications

Table 2 below gives an overview of the specifications of the Pe-Ha Luron® F hyaluronate intraocular gel in the concentration 2.2% from ALBOMED®.

Table 2: Specifications of Pe-Ha Luron® F 2.2% intraocular gel product

Specification	Pe-Ha-Luron® F 2.2%
Sodium hyaluronate	2.2%
Molecular weight [mio Daltons]	1.2 – 2.2
Viscosity* [mPas]	approx. 150 000
Osmolality [mOsm/kg]	270 – 400
Storage	2° – 25°C
pH	6.8 – 7.4
Volume [ml]	1.0
Shelf life [month]	42

*after steam sterilization

Clinical Data

Study design

An open, non-interventional, monocentric study was performed in order to evaluate safety and efficacy of Pe-Ha-Luron® F 2.2% OVD from ALBOMED®. Lead investigator was Dr. med. Andreas Borkenstein and the study was performed at his private clinic (BORKENSTEIN & BORKENSTEIN, Graz, Austria).

Purpose

The main purpose of this observational study was to assess the safety and efficacy of Pe-Ha-Luron® F 2.2% when applied according to its intended purpose for cataract surgery.

Study endpoints

The performance of Pe-Ha-Luron® F 2.2% was assessed according to the following endpoints:

- **Duration of the treatment** (treatment time).
- **Intraocular pressure** (IOP) in mmHg: this was recorded 1 day after surgery.
- **Absence of OVD between the intraocular lens (IOL) and the posterior capsule:** OVD molecules remaining after aspiration could block the trabecular meshwork and result in an IOP increase as well as decenter the IOL and cause capsular block syndrome.
- **Absence of OVD in the anterior chamber:** no OVD molecules should remain in the anterior chamber after aspiration.
- **Stability of the anterior chamber:** the anterior chamber should remain stable throughout the procedure.
- **Corneal transparency:** corneal transparency should be maintained. An opacification of the cornea can occur after an ocular intervention if the corneal endothelium has been damaged during surgery, or as a result of inflammation or infection.
- **Corneal observations:** any abnormal findings were reported.

In addition, Pe-Ha-Luron® F 2.2% was used for visco-polishing of the capsule in cases where cortical residues were left at the end of the procedure, or for the removal of capsular fibrosis.

Patients and Methods

Study population

The study population included males and females undergoing standard cataract surgery fulfilling the following inclusion and exclusion criteria:

Inclusion criteria:

- Males and females between 40 and 80 years of age
- No changes to the cornea
- Patients suitable for participation in the study according to the judgement of the clinical investigator
- Undergoing standard cataract surgery

Exclusion criteria:

- Infant patient
- Active/recurrent/severe uveitis
- Uncontrolled glaucoma
- Retinal detachment
- Serious intraoperative complications
- Several or combined treatments during surgery

Study visits

There was one follow-up visit 1-day after cataract surgery (as per standard cataract surgery follow-up).

Results

In total, 54 eyes (38 right eyes and 16 left eyes) were included in the study and received Pe-Ha-Luron® F 2.2%. Surgery was performed between October 29, 2020 and December 11, 2020. Incision size was 2.4 mm for all eyes. Outcomes are summarized in Table 3.

Efficacy: Duration of treatment (in minutes)

On average, treatment time was 8.15 ± 2.32 minutes, ranging from 5 to 14 minutes.

Safety: IOP (in mmHg)

Mean IOP measured at the 1-day postoperative visit was 14.61±1.87 mmHg, ranging from 10 to 19 mmHg for all eyes. On average, IOP decreased at day-1 compared to before the surgery; the mean difference was -0.94 ± 1.27 mmHg, ranging from -4 to +2 mmHg.

Table 3: Treatment duration and IOP outcomes

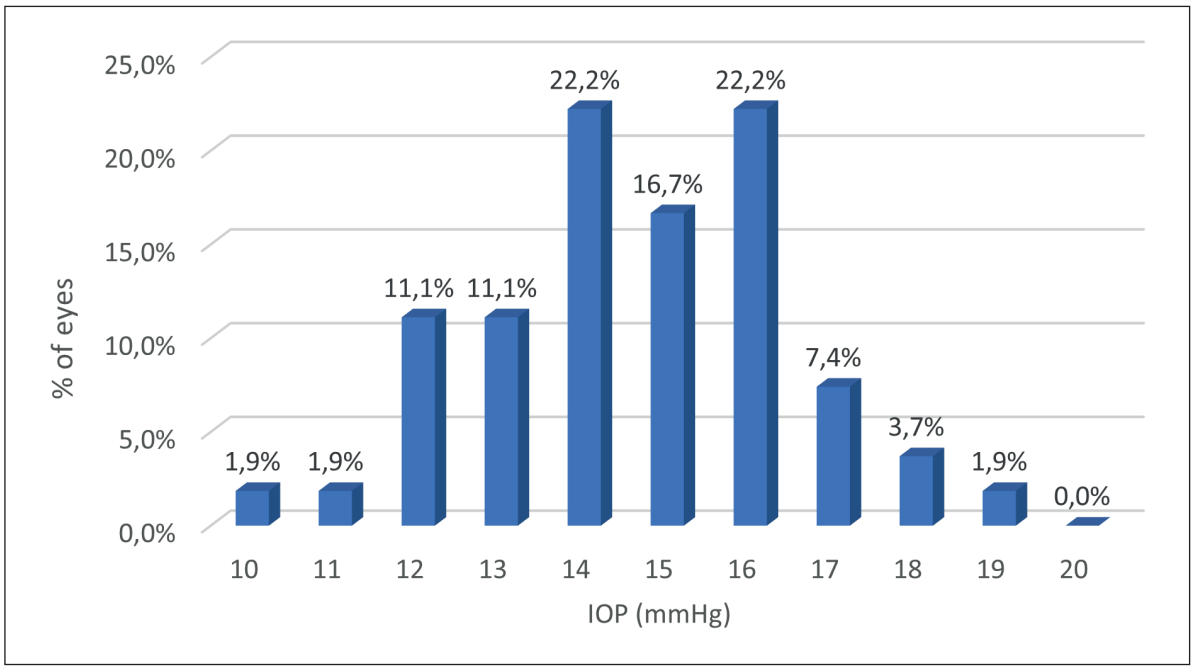
Outcomes	N	Mean ± SD	Range
Treatment duration (min)	54	8.15 ± 2.32	5 – 14
IOP (mmHg) baseline	54	15.56 ± 2.13	10 – 20
IOP (mmHg) day-1	54	14.61±1.87	10 – 19
IOP (mmHg) mean change	54	-0.94 ± 1.27	-4 to +2

The distribution of IOP values at day-1 is shown in Table 4 and Figure 1. Assuming that the normal distribution of IOP ranges from 10 mmHg to 21 mmHg, all eyes treated with Pe-Ha-Luron® F 2.2% had an IOP within the normal range one day after surgery and no eyes had an IOP above 21 mmHg. The maximum IOP was 19 mmHg.

Table 4: Frequency of IOP values shown in number of eyes and percentage

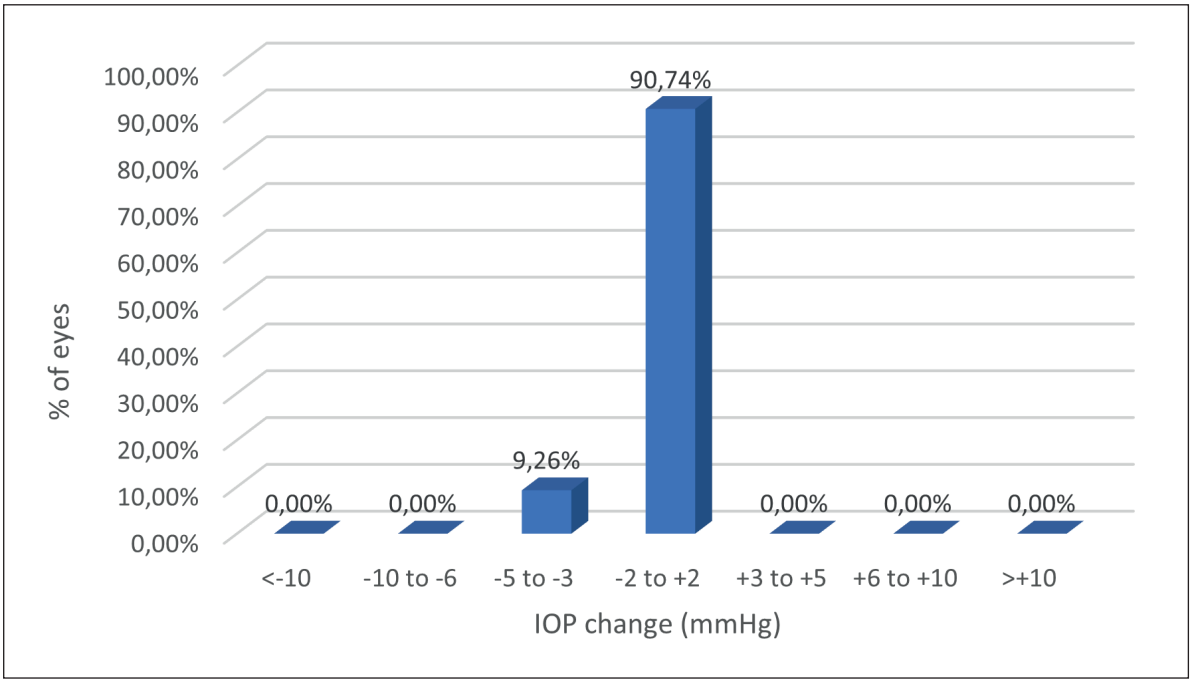
Pe-Ha-Luron® F 2.2%		
IOP	**Frequency (in number of eyes)**	**Frequency (in percentage)**
10	1	1.9%
11	1	1.9%
12	6	11.1%
13	6	11.1%
14	12	22.2%
15	9	16.7%
16	12	22.2%
17	4	7.4%
18	2	3.7%
19	1	1.9%
Total (∑)	54	100%

Figure 1: Distribution of IOP values 1-day postoperatively



The distribution of the IOP change between day-1 and baseline is shown in Figure 2. Negative values indicated a reduction in IOP in 9.3% of eyes (n=5) of between -5 and -3 mmHg. The remaining 90.7% of eyes (n=49) had a small change in IOP between -2 and +2 mmHg.

Figure 2: Distribution of IOP change in mmHg at day-1 compared to baseline



Safety: Slitlamp examination

Traces of OVD

In all 54 eyes, there were no OVD traces visible between the IOL and the posterior capsule. Additionally, no residues of OVD were visible in the anterior chamber.

Corneal transparency

Out of all 54 eyes, corneal transparency was confirmed in 52 eyes (96.3% of eyes). There were 2 eyes in which the cornea was not transparent; however, in both cases the investigator indicated that this was not related to the OVD. In one eye, there were existing scars due to previous keratoconjunctivitis. In the other eye, very mild edema was reported centrally and was caused by a long phacoemulsification during surgery because of a mature cataract. Additionally, no residues of OVD were visible in the anterior chamber.

Additional follow-up visits

It was reported that one eye required an additional follow-up visit; however, this was a planned follow-up visit for a patient diagnosed with primary open-angle glaucoma and attending for examinations every 3-months. There were no follow-up visits required related to the use of the OVD.

Corneal Observations

Corneal observations were noted for 10 eyes as shown in Table 5. In 4 cases, the corneal observations demonstrated a positive outcome despite pre-exisiting conditions: there was 1 case of pseudoexfoliation syndrome (PEX), 1 case of posterior subcapsular wound, 1 case of uveitis, and 1 case of sicca syndrome. In all 4 cases, the cornea was clear on day-1 after surgery despite these pre-existing conditions.

In 4 cases, the observations were related to the surgery: In 2 cases, some slight folds in the Descemet membrane were observed on day-1. In 1 case, slight edema was noticed centrally and associated to the mature cataract and long phacoemulsification. And in 1 case, there was a slight opacity superior to the incision. However, the overall cornea was transparent in all 4 eyes and no follow-up in addition to the standard scheme was required.

In the remaining 2 cases, the corneal observations describe a corneal scar or a corneal opacity that was present before surgery and remained unchanged after surgery.

In the remaining 2 cases, the corneal observations describe a corneal scar or a corneal opacity that was present before surgery and remained unchanged after surgery.

Table 5: List of corneal observations at day-1 after surgery

	Corneal Observations (n=10)	Comment
n=1	Cornea clear despite PEX - everything ok, irritation-free.	Positive outcome
n=1	Cornea clear despite wound at posterior subcapsular cataract	
n=1	Cornea clear despite uveitis. Anterior chamber: cells positive, Tyndall negative (status related to uveitis)	
n=1	Cornea clear despite sicca syndrome, dry eye tear substitute therapy	
n=1	Only slight cloudiness centrally because of a mature cataract and long phacoemulsification	Surgery related observation
n=2	Slight Descemet folds - otherwise clear, anterior chamber clear	
n=1	Slight corneal opacity superior to incision, centrally clear	
n=1	Existing corneal scars due to keratoconjunctivitis epidemica - no association with surgery	Not surgery related
n=1	Pigment dispersion syndrome - central opacity present before and after surgery	

Other Observations and reported advantages of Pe-Ha-Luron® F 2.2%

Table 6 shows a list of other observations noted by the investigator and a description of the advantages of using Pe-Ha-Luron® F 2.2% in specific cases.

The surgeon reported Pe-Ha-Luron® F 2.2% was used in one case of primary open-angle glaucoma, where complete removal of the OVD was performed successfully. In cases of floppy iris and PEX, the OVD helped stabilize the iris shape. The investigator also reported 2 cases of mature cataract where increased energy was required during phacoemulsification, and there was no complication with the use of Pe-Ha-Luron® F 2.2%.

In 2 cases, the investigator noted that a blue colored version of the 2.2% OVD (Pe-Ha-Blue®) would have been advantageous. The remaining 8 observations were not related to the surgery – they described existing ocular conditions.

Table 6: List of general comments at day-1 after surgery

Summary of all comments (n=25)	
n=10	Visco polishing at primary posterior capsular fibrosis and capsule residues or fibrosis residues - works very well
n=1	Primary open-angle glaucoma: complete and safe removal of the OVD is another advantage; IOP lowered
n=1	The OVD maintained the anterior chamber depth very well in this glaucoma case
n=1	Despite floppy iris, good control with „viscous“ OVD which can „tame/control“ the iris, no iris retractors necessary
n=1	Mature cataract - also works well with 2.2 concentration
n=1	Mature cataract- very hard core, a lot of phaco energy required
n=1	Cataract matura/provecta, Vision blue (=trypan blue) and Pe-Ha-Luron® F 2.2 used; note that Pe-Ha-Blue® would have been an advantage here
n=1	Blue coloration of the OVD would have been an advantage. Combination with „Vision blue“ not very good, because too „viscous“, distribution impossible if already in the eye
n=1	Corneal erosion (the patient injured himself with a nail). No association with surgery
n=1	Poor Vision due to corneal dystrophy
n=1	Diabetic Retinopathy - follow-up every 3 months
n=1	Epiretinal macular gliosis. Check every 3 months with OCT
n=1	Secondary Diagnosis: Uveitis (internal control)
n=1	Sicca syndrome - Sjogren‘s signs
n=1	Phaco+ anti-VEGF injection of Eylea - without complications
n=1	Reduced Vision during surgery because of the cornea - Vision Blue (=trypan blue)

Visco-polishing

The visco-polishing technique was used in cases where remaining fibrosis was present in the capsule after routine capsular polishing using the irrigation/aspiration tip during phacoemulsification. The aim was to remove capsular fibrosis and/or capsular or cortical residues.

This technique was performed in 10 cases where the capsule was filled to about 1/3 with Pe-Ha-Luron® F 2.2%. Rinsing was then completed from the anterior chamber with the water jet directly onto the posterior capsule, creating a turbulence similar to a "grindstone effect". This resulted in the thick viscoelastic starting to rotate very quickly in the capsule like a ball, grinding away the turbidity.

Visco-polishing was used successfully in all 10 cases. The surgeon noted that it worked very well, removing capsular fibrosis and/or capsular or cortical residues. In 1 case, it was noted that this saved a lot of time.

It is believed that this technique works well with OVDs that are cohesive with dispersive properties and therefore support visco polishing due to the good coating/lining of the capsular bag and adhesion of the particles to the OVD. Because of this suitable mix of properties, the viscoelastic solution rotates like a bolus in the capsular bag and removes the fibrosis or residues.

In these 10 cases, the mean IOP at day-1 was 14.2 ± 1.40 mmHg (range: 12 to 16 mmHg) and the mean change in IOP from baseline was -1.10 ± 1.29 mmHg, ranging from -4 to +1 mmHg. This was similar to the mean value of all 54 eyes, and there were no cases of elevated IOP.

Summary and Conclusion

The present study was able to confirm the efficacy and safety of Pe-Ha-Luron® F in a concentration of 2.2%.

Several OVDs are available on the market and numerous prospective randomized control trials have been conducted to compare safety, efficacy, and performance of various OVDs used during routine small-incision cataract surgeries and IOL implantation. In our study, mean IOP at 1-day follow-up was within normal limits[7,8] (14.6 ± 1.9 mmHg; range: 10 to 19 mmHg).

Severe elevation of IOP was not reported in any of the 54 eyes. Published scientific literature reported that a 1-day postoperative IOP of 30 mmHg or higher occurs under normal conditions in about 2% of treatments.[9,10] None of the eyes had an IOP of 30 mmHg or above in our sample. This demonstrates the safety of ALBOMED® Pe-Ha-Luron® F 2.2% OVD product.

Safety was further confirmed by the fact that no traces of OVD were visible in any of the study eyes postoperatively, and corneal transparency was maintained in all eyes. In terms of efficacy, treatment duration was found to be within the average reported values in the literature.[11]

A possible advantage of Pe-Ha-Luron® F 2.2% reported in this study is that it could be used safely and efficiently to remove remaining capsular fibrosis after routine capsular polishing. This preliminary finding will need to be confirmed on a larger group of eyes.

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