GERMANY
ALBOMED

WHITE PAPER
VISCOELASTICS – Pe-Ha-Luron® F

CLINICAL OBSERVATION ON SAFETY AND PERFORMANCE OF THE VISCOELASTIC DEVICE PE-HA-LURON® F APPLIED DURING OPHTHALMIC SURGERIES

FINAL REPORT
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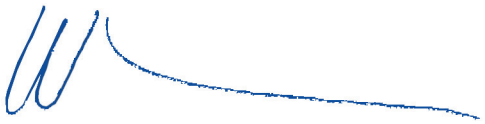
Investigator: Dr. Ch. Winkler von Mohrenfels



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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 OVDs are injectable transparent gels, sterile and isotonic, based on sodium hyaluronate as the main component.
- In this observational study, the safety and efficacy of Pe-Ha-Luron® F OVDs used in five different concentrations (1.0%, 1.4%, 1.6%, 1.8%, and 3.0%) were assessed. Pe-Ha-Luron® F was applied during routine cataract surgery in 270 eyes, and the follow-up was 1-day after surgery.
- Pe-Ha-Luron® F was found to be safe, with no adverse effects reported in any of the 270 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.

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] This is because traces of OVD left in the eye 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 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 and higher viscosity cohesive. 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 spaces during ocular surgeries and are easier to remove. However, they offer a lower corneal protection.

White Paper | VISCOELASTICS – Pe-Ha-Luron® F

This report provides clinical data on the safety and performance of the OVD Pe-Ha-Luron® F from ALBOMED (ALBOMED GmbH, Schwarzenbruck, Germany). 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 increase of intraocular pressure post-operatively; 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 serves as a volume substitute and as adjuvant for the following operations:

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

Description

The range of Pe-Ha-Luron® F intraocular gel products from ALBOMED comprises 5 devices, each with the following properties:

- Injectable transparent gel
- Based on hyaluronic acid (HA) obtained by bacterial biofermentation (i.e. not animal origin)
  HA concentration of 1.0%, 1.4%, 1.6%, 1.8%, 2.2%*, and 3.0%
- Packaged in 2.25 ml borosilicate glass syringes in a volume ranging from 0.8 ml to 2.0 ml
- Used in ophthalmologic applications as adjuvant for anterior chamber surgery
- Equipped with a suitable backstop and plunger rod in the syringe
- Supplied with a sterile single use cannula
- Provided in secondary packaging in a blister that protects the integrity of each syringe
- Can be stored between 2° C and 25° C for 42 months

* The 2.2% concentration is new to the portfolio. This product was not available at the time of the study and is therefore evaluated separately.

Composition

The main component of all Pe-Ha-Luron® F intraocular gel products is sodium hyaluronat abbreviated SH; the sodium salt of hyaluronic acid). The sodium hyaluronate is obtained by bacterial biofermentation 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

Component	Unit formula for 1 ml
Sodium hyaluronate	10.00 mg (Pe-Ha-Luron® F 1.0%)
	14.00 mg (Pe-Ha-Luron® F 1.4%)
	16.00 mg (Pe-Ha-Luron® F 1.6%)
	18.00 mg (Pe-Ha-Luron® F 1.8%)
	30.00 mg (Pe-Ha-Luron® F 3.0%)
Sodium Chloride (NaCl)	8.50 mg
	6.50 mg only for the product variant 3.0%
NaH_2PO_4, $2H_2O$	0.045 mg
Na_2HPO_4, $2H_2O$	0.563 mg
WFI Water For Injection	q.s. 1 ml

Specifications

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

Table 2: Specifications of Pe-Ha-Luron® F intraocular gel products

Specification	Pe-Ha-Luron® F 1.0%	Pe-Ha-Luron® F 1.4%	Pe-Ha-Luron® F 1.6%	Pe-Ha-Luron® F 1.8%	Pe-Ha-Luron® F 2.2%	Pe-Ha-Luron® F 3.0%
Sodium hyaluronate	1.0%	1.4%	1.6%	1.8%	2.2%	3.0%
Molecular weight [mio Daltons]	1.2 – 2.0	1.2 – 2.0	1.2 – 2.2	1.2 – 2.2	1.2 – 2.2	1.0 – 1.8
Viscosity* [mPas]	approx. 20 000	approx. 30 000	approx. 60 000	approx. 100 000	approx. 150 000	approx. 300 000
Osmolality [mOsm/kg]	270 – 400	270 – 400	270 – 400	270 – 400	270 – 400	270 – 400
Storage	2° – 25°C	2° – 25°C	2° – 25°C	2° – 25°C	2° – 25°C	2° – 25°C
pH	6.8 – 7.4	6.8 – 7.4	6.8 – 7.4	6.8 – 7.4	6.8 – 7.4	6.8 – 7.4
Volume [ml]	1.0	1.0	1.0	1.0	1.0	1.0
Shelf life [month]	42	42	42	42	42	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 OVDs from ALBOMED. Lead investigator was MD Ch. Winkler von Mohrenfels and the study was performed at his private clinic (Neutraubling, Germany).

Purpose

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

Study endpoints

The performance of Pe-Ha-Luron® F 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
- Absence of OVD in the anterior chamber: no OVD molecules should remain in the anterior chamber after aspiration
- 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.

Patients and Methods

Study population

The study population included male and female 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
- Pseudoexfoliation syndrome
- Previous corneal surgery (LASIK, PRK, LASEK)
- 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, 270 eyes were included in the study and received Pe-Ha-Luron® F. The number of eyes receiving each concentration is shown in Table 3.

Higher concentrations of Pe-Ha-Luron® F were not used as frequently for 2 main reasons: the surgeon had a personal preference for OVDs with lower viscosity and therefore lower injections forces, and public health insurance does not reimburse the 1.8% and 3.0% hyaluronate concentrations.

Mixed concentrations were used in 3 eyes of 3 patients; in these eyes, the surgeon used both 1.4% and 1.8% concentration during surgery to achieve maximum endothelium protection and maintenance of the anterior chamber pressure.

Table 3: Distribution of devices used

Product	Number of eyes (n)	Percentage of eyes (%)
Pe-Ha-Luron® F 1.0%	60	22.2
Pe-Ha-Luron® F 1.4%	98	36.3
Pe-Ha-Luron® F 1.6%	77	28.5
Pe-Ha-Luron® F 1.8%	32	11.8
Pe-Ha-Luron® F 3.0%	0	0.0
Pe-Ha-Luron® F mixed concentratrions	3	1.1
Total	**270**	**100.0**

Efficacy: Duration of treatment (in minutes)

On average, treatment time was 11.97 minutes, ranging from 6 to 25 minutes for all eyes together. As shown on Table 4, there were some small differences in duration between all groups. There was a trend for the duration of treatment to be lower for Pe-Ha-Luron® F 1.0%, and to be higher for Pe-Ha-Luron® F 1.8%. However, as total treatment time includes both insertion and removal time of the OVD as well as phacoemulsification time, it is difficult to conclude. The surgeon might have adjusted his choice of OVD according to the type of cataract, or according to the density of the cataract - mature cataracts needing longer phacoemulsification time. Overall, mean treatment duration was longest in the mixed concentration group, which can be explained by the use of two different OVDs.

Table 4: Treatment duration (in minutes)

		Treatment duration (minutes)	
Product	**N**	**Mean ± SD**	**Range**
All eyes	270	11.97 ± 3.42	6 - 25
Pe-Ha-Luron® F 1.0%	60	10.42 ± 2.63	6 - 18
Pe-Ha-Luron® F 1.4%	98	12.22 ± 3.35	6 - 22
Pe-Ha-Luron® F 1.6%	77	12.03 ± 3.40	8 - 25
Pe-Ha-Luron® F 1.8%	32	13.97 ± 3.66	8 - 22
Pe-Ha-Luron® F 3.0%	0	NA	NA
Pe-Ha-Luron® F mixed concentrations	3	16.33 ± 4.50	11 - 22

Safety: IOP (in mmHg)

On average, the IOP measured at the 1-day postoperative visit was 15.4 mmHg, ranging from 5 to 24 mmHg for all eyes together. As shown on Table 5, the mean postoperative IOP was almost the same for all groups.

Table 5: IOP values at the 1-day postoperative visit (in mmHg)

		IOP (mmHg)	
Product	**N**	**Mean ± SD**	**Range**
All eyes	270	15.4 ± 4.2	5 – 24
Pe-Ha-Luron® F 1.0%	60	15.7 ± 3.8	8 – 22
Pe-Ha-Luron® F 1.4%	98	15.2 ± 4.1	7 – 23
Pe-Ha-Luron® F 1.6%	77	15.3 ± 4.2	5 - 24
Pe-Ha-Luron® F 1.8%	32	15.6 ± 4.6	6 - 22
Pe-Ha-Luron® F 3.0%	0	NA	NA
Pe-Ha-Luron® F mixed concentrations	3	15.3 ± 5.7	8 - 22

The distribution of IOP values at day-1 is shown in Tables 6 and 7 and Figure 1. Assuming that the normal distribution of IOP ranges from 10 mmHg to 21 mmHg, 8.2% of all eyes treated with Pe-Ha-Luron® F had an IOP above 21 mmHg at the 1-day follow-up visit, with a maximum of 24 mmHg. There were 6.7% of eyes with an IOP above 21 mmHg in eyes treated with Pe-Ha-Luron® F 1.0%, 7.1% in eyes treated with Pe-Ha-Luron® F 1.4%, 7.8% in eyes treated with Pe-Ha-Luron® F 1.6%, and 12.5% in eyes treated with Pe-Ha-Luron® F 1.8%. However, in the 1.8% group, a maximum IOP of 22 mmHg was observed, which is just above the normal value. In the group of mixed concentrations (3 eyes), IOP values were 8 mmHg, 16 mmHg and 22 mmHg.

Table 6: Frequency of IOP values per concentration

	Eyes treated with Pe-Ha-Luron® F (NaHA)						
IOP	**All eyes**	**NaHA 1.0%**	**NaHA 1.4%**	**NaHA 1.6%**	**NaHA 1.8%**	**NaHA 3.0%**	**Mixed concentrations**
	Frequency (in number of eyes)						
5	1	0	0	1	0	0	0
6	2	0	0	1	1	0	0
7	2	0	2	0	0	0	0
8	4	1	2	0	0	0	1
9	8	0	5	3	0	0	0
10	24	7	5	7	5	0	0
11	10	1	5	3	1	0	0
12	22	5	10	5	2	0	0
13	28	4	11	8	5	0	0
14	25	9	6	8	2	0	0
15	16	4	10	2	0	0	0
16	16	1	3	10	1	0	1
17	20	6	6	7	1	0	0
18	21	7	9	3	2	0	0
19	16	3	5	4	4	0	0
20	7	2	3	1	1	0	0
21	26	6	9	8	3	0	0
22	18	4	6	3	4	0	1
23	3	0	1	2	0	0	0
24	1	0	0	1	0	0	0
Total (∑)	270	60	98	77	32	0	3

Table 7: Frequency of IOP values per concentration (shown in percentage)

IOP	Eyes treated with Pe-Ha-Luron® F (NaHA)						
	All eyes	NaHA 1.0%	NaHA 1.4%	NaHA 1.6%	NaHA 1.8%	NaHA 3.0%	Mixed concentrations
	Frequency (in percentage)						
5	0.37%	0.00%	0.00%	1.30%	0.00%	0.00%	0.00%
6	0.74%	0.00%	0.00%	1.30%	3.13%	0.00%	0.00%
7	0.74%	0.00%	2.04%	0.00%	0.00%	0.00%	0.00%
8	1.48%	1.67%	2.04%	0.00%	0.00%	0.00%	33.33%
9	2.96%	0.00%	5.10%	3.90%	0.00%	0.00%	0.00%
10	8.89%	11.67%	5.10%	9.09%	15.63%	0.00%	0.00%
11	3.70%	1.67%	5.10%	3.90%	3.13%	0.00%	0.00%
12	8.15%	8.33%	10.20%	6.49%	6.25%	0.00%	0.00%
13	10.37%	6.67%	11.22%	10.39%	15.63%	0.00%	0.00%
14	9.26%	15.00%	6.12%	10.39%	6.25%	0.00%	0.00%
15	5.93%	6.67%	10.20%	2.60%	0.00%	0.00%	0.00%
16	5.93%	1.67%	3.06%	12.99%	3.13%	0.00%	33.33%
17	7.41%	10.00%	6.12%	9.09%	3.13%	0.00%	0.00%
18	7.78%	11.67%	9.18%	3.90%	6.25%	0.00%	0.00%
19	5.93%	5.00%	5.10%	5.19%	12.50%	0.00%	0.00%
20	2.59%	3.33%	3.06%	1.30%	3.13%	0.00%	0.00%
21	9.63%	10.00%	9.18%	10.39%	9.38%	0.00%	0.00%
22	6.67%	6.67%	6.12%	3.90%	12.50%	0.00%	33.33%
23	1.11%	0.00%	1.02%	2.60%	0.00%	0.00%	0.00%
24	0.37%	0.00%	0.00%	1.30%	0.00%	0.00%	0.00%
Total (∑)	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%	100.00%

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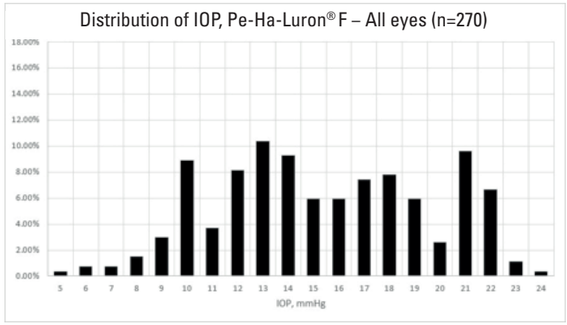
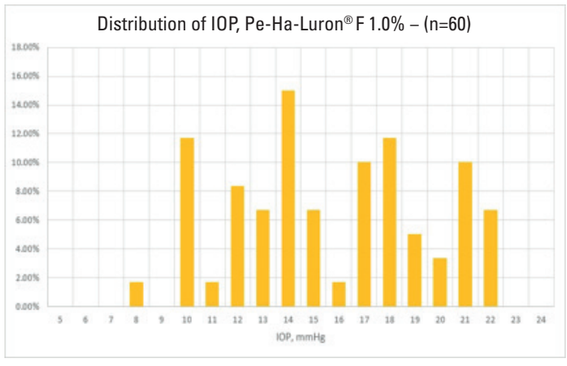
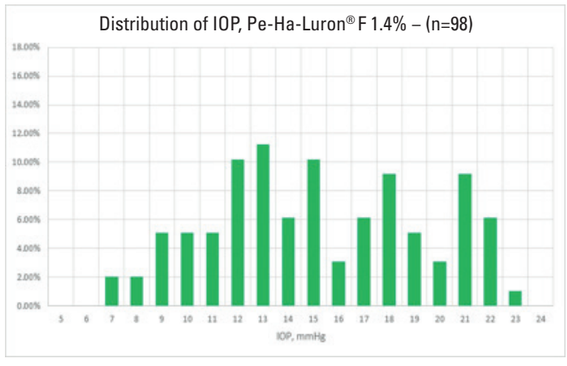
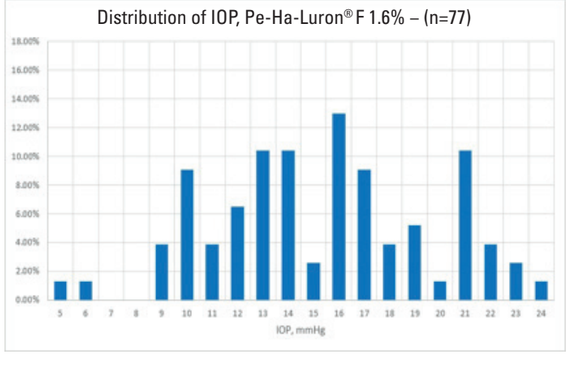
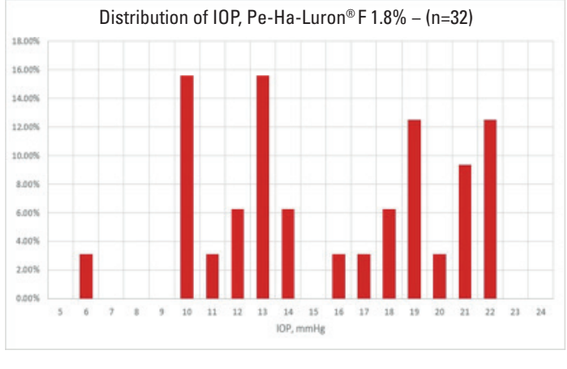
Figure 1: Distribution of IOP values 1-day postoperatively for all eyes (black bars), for eyes treated with the 1.0% concentration (orange bars), for eyes treated with the 1.4% concentration (green bars), for eyes treated with the 1.6% concentration (blue bars), and for eyes treated with the 1.8% concentration (red bars). Eyes treated with mixed concentrations are not represented in an individual bar chart as there were only 3 eyes; IOP values were 8 mmHg, 16 mmHg and 22 mmHg.











Safety

Traces of OVD:

In all 270 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 270 eyes, corneal edema was reported in 1 eye (0.37%) treated with the Pe-Ha-Luron® F 1.8%. In this case, the edema was caused by a very long phacoemulsification time during surgery (cat. Matura).

Additional follow-up visits

Because of corneal edema, 1 patient required an additional follow-up examination 7 days after surgery, respectively. At the follow-up visit, an improvement was noted with minimum residual corneal edema left.

Summary and Conclusion

The present study was able to confirm the efficacy and safety of the Pe-Ha-Luron® F product line in the field.

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[6,7] (15.4 ± 4.2 mmHg, ranging from 5 to 24 mmHg).

Some studies have shown that within a family of molecularly similar OVDs, lower viscosity OVDs appeared to cause slightly lower mean elevations in IOP in normal patients at 24 hours.[8] However, other studies have reported no difference at 24 hours.[9] This appeared to be the case in this study, where the mean IOP at 1-day ranged between 15.2 ± 4.1 mmHg for eyes treated with Pe-Ha-Luron® F 1.4%, and 15.7 ± 3.8 mmHg for eyes treated with Pe-Ha-Luron® F 1.0%. A similar proportion of eyes in each group had an IOP above 21 mmHg, with no eyes exceeding an IOP of 24 mmHg. This is within normal for ophthalmologic surgeries. Published scientific literature reported that a 1-day postoperative IOP of 30 mmHg or higher occurs under normal conditions in about 2% of treatments.[10, 11] 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 OVD products.

Safety was 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.[12]

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