Efficacy and Tolerability of a New Thermostable Formulation of Latanoprost in Nanoparticles

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BACKGROUND

• Glaucoma is the second most frequent cause of blindness, with more than 60 million people affected worldwide. It is characterized by progressive optic neuropathy in association with distinctive changes in the optic nerve head and visual field deficits. Control of elevated intraocular pressure (IOP) remains the principal goal in the treatment of glaucoma and ocular hypertension.The PGF2α (Prostaglandin F2α) analogs are the most effective drugs for reducing IOP.

• Most PGF2α analog products contain benzalkonium chloride (BAK) due to its solubilizing properties and its antimicrobial action. However, its toxic and inflammatory effects on the ocular surface in long-term use are well-known. BAK disrupts the lipid layer and damages ocular tissue by inducing apoptosis and increasing the concentrations of inflammatory markers. BAK may solubilize the thin lipid layer thereby permitting free evaporation of water and hence drying. It may also encourage dissolution of the conjunctival mucin layer adsorbed on the surface of the corneal epithelium. BAK alters tear film quality and leads to ocular surface diseases.

• A new latanoprost 0.005% BAK-free ophthalmic nanoemulsion (LNe) was developed to improve patient comfort and tolerability. It is preserved with potassium sorbate. Furthermore, it is stable for 24 months at 30°C, which allows it to be stored at room temperature.

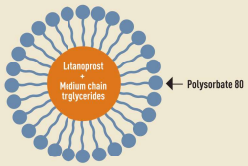


Fig.1: First, latanoprost is dissolved in medium chain triglycerides, forming the oil phase of the emulsion. Then, polysorbate 80 is added to emulsify the oil phase, organizing it into micelles.

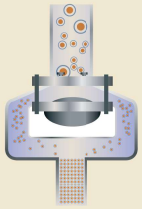
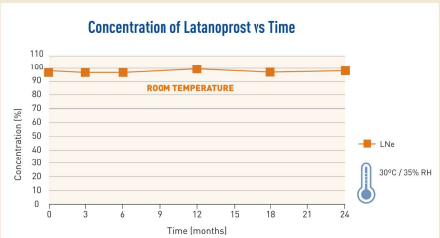


Fig.2: Finally, a High Technology Microfluidizer reduces the size of the micelles to nanometers (100 - 200 nm), obtaining a homogeneous nanoemulsion.



PURPOSE

We hypothesize that this innovative formulation has the same IOP-lowering efficacy and is better tolerated than the BAK-containing latanoprost solution (LSc).

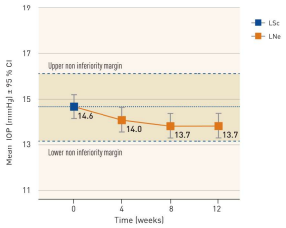
METHODS

A prospective, open-label, single-arm, 12-week study was carried on. Patients over 18 years of age with primary open-angle glaucoma (POAG) under treatment with LSc for ≥ 6 month (baseline) switched to LNe once daily. As primary outcome, IOP-lowering efficacy was evaluated after 4, 8 and 12 weeks of treatment with LNe. Non inferiority was defined as a mean difference (95% CI) from baseline of < 1.5 mm Hg at each timepoint after switching. As secondary outcome, ocular surface damage was determined using Ocular Surface Disease Index (OSDI®) score, Schirmer I Test, Break-up time (BUT), conjunctival hyperemia and corneal staining at baseline and after 4, 8 and 12 weeks of treatment with LNe. Adverse events were reported. Two-tailed repeated measures ANOVA with Bonferroni correction was used, and significance was set at $p < 0.05$.

RESULTS

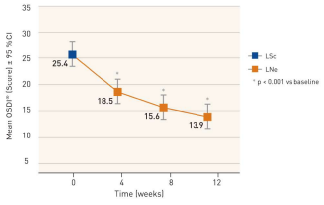
INTRAOCULAR PRESSURE

A total of 103 patients (198 eyes) concluded the study. No patient had IOP > 20 mm Hg. LNe was non inferior in lowering IOP than LSc, as 95% CI of mean IOP at each timepoint after switch to LNe were within the 1.5 mm Hg non inferiority margin from baseline IOP (13.13 - 16.13 mm Hg).



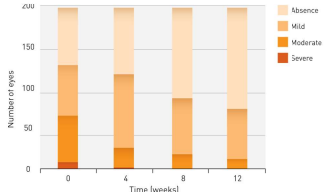
OSDI®

Mean OSDI® score decreased by 11.5 points (7.5 - 15.6, 95% CI) after 12 weeks of treatment with LNe.



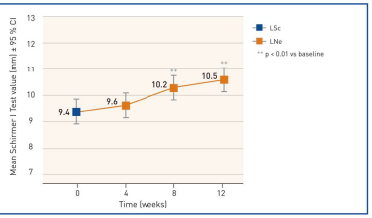
CONJUNCTIVAL HYPEREMIA

After 12 weeks of treatment with LNe the number of eyes with conjunctival hyperemia decreased by 21.7% (21.7 - 33.7, 95% CI).



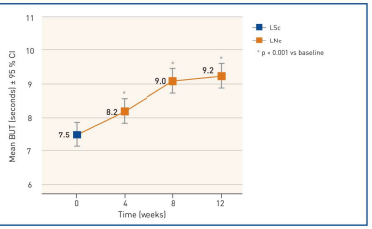
SCHIRMER I

Mean Schirmer I test value increased by 1.2 mm (0.4 - 1.9, 95% CI) after 12 weeks of treatment with LNe.



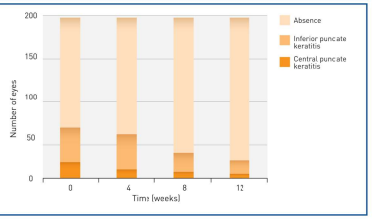
BUT

Mean BUT increased by 1.7 seconds (1.2 - 2.3, 95% CI) after 12 weeks of treatment with LNe.



CORNEAL STAINING

After 12 weeks of treatment with LNe the number of eyes with corneal staining decreased by 19.2% (14.2 - 24.2, 95% CI).



SAFETY

Six patients discontinued the treatment with LNe because of ocular itching, increased tearing, blurred vision, strange body sensation, dry eye or allergic eye reactions. No serious treatment-related adverse effects were reported.

CONCLUSIONS

• The new formulation of latanoprost in nanoemulsion showed **the same IOP-lowering efficacy** as the conventional formulation with **better tolerability** and significant improvements in ocular surface parameters.

• It also has the benefit of not requiring cold chain storage, which may further improve patients' quality of daily life and treatment adherence.

• In summary, the new latanoprost 0.005% BAK-free ophthalmic nanoemulsion offers advantages in comparison with other BAK-preserved latanoprost, promoting **better treatment compliance** in patients with POAG.

Aknowledgment

Brown Arnold J, Cataldi F, Catallini G, Chiari N, Dalmagro J, González G, Lischinsky I, Logioco C, Moussali MA, Nahum P, Ribola L, Sivori D.

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