iyuzeh™

(latanoprost ophthalmic solution) 0.005%

FREQUENTLY ASKED QUESTIONS

INDICATIONS AND USAGE

IYUZEH™ (latanoprost ophthalmic solution) 0.005% is a prostaglandin F2α analogue indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

Known hypersensitivity to latanoprost or any other ingredients in this product.

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FREQUENTLY ASKED QUESTIONS

iyuzeh™
(latanoprost ophthalmic solution) 0.005%

INDICATION

Q. What is the indication for IYUZEH™?

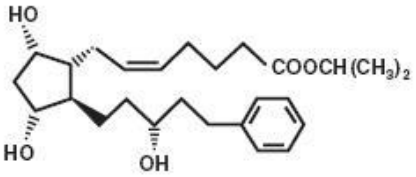
A. IYUZEH (latanoprost ophthalmic solution) 0.005% is a prostaglandin F2α analogue indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

DESCRIPTIONS OF IYUZEH

Q. What is latanoprost?

A. Latanoprost is a prostaglandin F2α analogue. Its chemical name is isopropyl-(Z)-7[(1R,2R,3R,5S)3,5-dihydroxy-2-[(3R)-3-hydroxy-5-phenylpentyl]cyclopentyl]-5-heptenoate. Its molecular formula is $C_{26}H_{40}O_5$ and its chemical structure is:

M.W. 432.58



Q. What is the physical appearance of latanoprost?

A. A colorless to yellow oil.

Q. What is the pH of IYUZEH?

A. Approximately pH 7

Q. What is the osmolarity of IYUZEH?

A. Approximately 280 mOsmol/kg

Q. What is the solubility of latanoprost?

A. It is very soluble in acetonitrile and freely soluble in ethanol, ethyl acetate, and methanol. It is practically insoluble in water and hexanes.

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Q. What is PROTRIAX'In®?

A. A proprietary drug delivery system that helps to provide a consistent product experience by ensuring the drug product maintains excellent stability, even at room temperature.

Q. How much latanoprost is in each drop of IYUZEH™?

A. Approximately 1.5 µg of latanoprost

Q. In terms of formulation, how does the vehicle for IYUZEH differ from that of XALATAN® (latanoprost ophthalmic solution) 0.005%?

A. The vehicle for IYUZEH is composed of Polyoxyl 40 hydrogenated castor oil, sorbitol, carbomer 974P, polyethylene glycol 4000, disodium edetate, sodium hydroxide (for pH adjustment), and water for injection. The vehicle for XALATAN is composed of sodium chloride, sodium dihydrogen phosphate monohydrate, disodium hydrogen phosphate anhydrous, and water (XALATAN Prescribing Information, 2017). XALATAN contains 0.02% of the preservative benzalkonium chloride (BAK). IYUZEH is a topical, preservative-free formulation of latanoprost ophthalmic solution 0.005%. Unlike preserved formulations of latanoprost, IYUZEH does not contain BAK or other known chemical entities as a preservative.

Q. Does IYUZEH contain the same preservative as XELPROS®?

A. No. IYUZEH is a topical, preservative-free formulation of latanoprost ophthalmic solution 0.005%. XELPROS contains potassium sorbate as a preservative.

Q. How does IYUZEH differ from ZIOPTAN®?

A. While both IYUZEH and ZIOPTAN are indicated to lower intraocular pressure (IOP), they differ by the following:

- Active ingredient: IYUZEH is latanoprost whereas tafluprost is the active ingredient of ZIOPTAN. Both have active ingredients that are prostaglandin analogs.
- Chemical structure: The major modification of ZIOPTAN (tafluprost) is the substitution of the C-15 hydroxyl group with two fluorine atoms.
- Vehicle: IYUZEH is composed of Polyoxyl 40 hydrogenated castor oil, sorbitol, carbomer 974P, polyethylene glycol 4000, disodium edetate, sodium hydroxide (for pH adjustment), and water for injection. The vehicle for ZIOPTAN contains glycerol, sodium dihydrogen phosphate dihydrate, disodium edetate, polysorbate 80, hydrochloric acid and/or sodium hydroxide (to adjust pH), and water for injection.
- Storage: Unopened foil pouches of IYUZEH can be stored at room temperature prior to opening; however, ZIOPTAN must be refrigerated prior to opening.

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DOSING INSTRUCTIONS/DRUG INTERACTIONS

iyuzeh™
(latanoprost ophthalmic solution) 0.005%

Q. How is IYUZEH™ administered?

A. The recommended dosage is one drop in the affected eye(s) once daily in the evening. The dosage of IYUZEH should not exceed once daily. It has been shown that administration of these prostaglandin drug products more than once daily may decrease the IOP-lowering effect or cause paradoxical elevations in IOP.

Q. Does IYUZEH need to be shaken prior to usage?

A. No. Because it is a solution, IYUZEH does not need to be shaken prior to use.

Q. What if a patient misses a dose of IYUZEH?

A. If one dose is missed, treatment should continue with the next dose as normal.

Q. If a patient is already on a prostaglandin analogue (PGA), should he or she discontinue its use prior to initiating treatment with IYUZEH?

A. Yes, if a patient is using a PGA, it should be discontinued prior to initiating treatment with IYUZEH, which contains the PGA latanoprost. The combined use of two or more prostaglandin analogs, including latanoprost ophthalmic solution 0.005%, is not recommended. It has been shown that administration of these prostaglandin drug products more than once daily may decrease the IOP-lowering effect or cause paradoxical elevations in IOP. However, patients should not discontinue any medication without consulting with their physician.

Q. Can IYUZEH be used in combination with other topical IOP-lowering drug products? If so, are there any special precautions?

A. Yes. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

Q. Is it possible to get multiple doses of IYUZEH from a single vial?

A. The solution from one individual unit is to be used immediately after opening for administration to one or both eyes. The cap on the single-dose vial cannot be resecured once opened. Remaining contents should be discarded immediately after use.

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Q. Can IYUZEH™ be overdosed?

A. Potentially. Intravenous infusion of up to 3 µg/kg of latanoprost in healthy volunteers produced mean plasma concentrations 200 times higher than during clinical treatment with latanoprost ophthalmic solution and no adverse reactions were observed. However, IV dosages of 5.5 to 10 µg/kg did cause abdominal pain, dizziness, fatigue, hot flushes, nausea, and sweating.

Q. If a patient is not responding to Selective Laser Trabeculoplasty (SLT), can the patient still use IYUZEH?

A. No data are available on the use of IYUZEH in these patients. The US Phase 3 clinical development program excluded patients with ocular surgery or laser treatment of any kind in the study eye within 3 months before baseline.

Q. Can IYUZEH be used in combination with other non-PGA IOP-lowering agents?

A. IYUZEH may be used concomitantly with other topical ophthalmic drug products to lower IOP. If more than one topical ophthalmic drug is being used, the drugs should be administered at least 5 minutes apart.

Q. Has the efficacy of adjunctive use of IYUZEH been studied?

A. Adjunctive use of once-daily IYUZEH has not been formally studied. IYUZEH may be used concomitantly with other topical ophthalmic drug products to lower IOP. If more than one topical ophthalmic drug is being used, the drugs should be administered at least 5 minutes apart.

CONTRAINDICATIONS

Q. Are there any contraindications with IYUZEH?

A. Patients with known hypersensitivities to latanoprost or any other component of this product.

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WARNINGS AND PRECAUTIONS

Q. Does IYUZEH™ cause pigmentation changes on or around the treated eye?

A. Possibly. Topical latanoprost ophthalmic products, including IYUZEH, have been reported to cause changes to pigmented tissues. The most frequently reported changes have been increased pigmentation of the iris, periorbital tissue (eyelid), and eyelashes. Pigmentation is expected to increase while latanoprost is administered. Iris color change may not be noticeable for several months to years. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris, and the entire iris or parts of the iris become more brownish.

Q. Is the mechanism of this pigmentation change due to PGA treatments like IYUZEH known?

A. Yes. The pigmentation change is due to increased melanin content in the melanocytes rather than an increase in the number of melanocytes.

Q. Are these pigmentation changes permanent? Are there long-term effects?

A. After discontinuation of latanoprost, pigmentation of the iris is likely to be permanent, while pigmentation of the periorbital tissue and eyelash changes have been reported to be reversible in some patients. Neither nevi nor freckles of the iris appear to be affected by treatment. The long-term effects of increased pigmentation are unknown.

Q. Should IYUZEH be continued in patients who develop noticeable increased iris pigmentation?

A. It may; however, these patients should be examined regularly.

Q. Does IYUZEH use result in changes to the eyelashes? If so, is this reversible?

A. Possibly. Latanoprost ophthalmic products, including IYUZEH, may gradually change eyelashes and vellus hair in the treated eye; these changes include increased length, thickness, pigmentation, the number of lashes or hairs, and misdirected growth of the eyelashes.

Eyelash changes are usually reversible upon treatment discontinuation.

Q. Can IYUZEH be used for patients with a history of iritis/uveitis (intraocular inflammation)?

A. Generally, no. Treatment with IYUZEH may exacerbate iritis/uveitis.

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Q. Is there a risk of developing macular edema while being treated with IYUZEH™?

A. Yes. Macular edema, including cystoid macular edema (CME), has been reported during treatment with latanoprost ophthalmic products, including IYUZEH.

Q. Are there specific patient populations at greater risk of developing macular edema while on IYUZEH?

A. IYUZEH should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

Q. Can patients with a history of recurrent herpetic keratitis use IYUZEH?

A. IYUZEH should be used with caution in patients with a history of herpetic keratitis as reactivation of herpes simplex has been reported during treatment with latanoprost.

Q. Should patients with active herpes simplex keratitis be treated with IYUZEH?

A. No, as it may result in exacerbated inflammation.

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ADVERSE EVENTS

Q. What are the most frequent ocular adverse events with IYUZEH™?

A. In two clinical trials, the most frequently reported ocular adverse reactions were conjunctival hyperemia and eye irritation. For additional ocular adverse reactions reported by ≥1% of subjects receiving IYUZEH, refer to the below table:

	Adverse Reactions (Incidence [%])[1]	
Symptom/Finding	IYUZEH (n=378)	XALATAN (n=358)
Conjunctival hyperemia	129 (34)	133 (37)
Eye irritation	72 (19)	112 (31)
Eye pruritus	57 (15)	58 (16)
Abnormal sensation in eye	51 (14)	52 (15)
Foreign body sensation in eyes	44 (12)	36 (10)
Vision blurred	28 (7)	30 (8)
Lacrimation increased	19 (5)	14 (4)
Photophobia	13 (3)	17 (5)

Q. Were any systemic adverse events noted with IYUZEH?

A. Systemic adverse events were reported at similar rates in two Phase 3 clinical trials with incidences in both the IYUZEH and XALATAN® groups ranging from between 13% and 17%. However, no systemic adverse events were deemed to be related to IYUZEH treatment.

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CLINICAL PHARMACOLOGY

Q. What is the mechanism of action of IYUZEH™?

A. Latanoprost is a prostaglandin F2α analogue that is believed to reduce the IOP by increasing the outflow of aqueous humor. Studies in animals and patients suggest that activation of a molecular transduction cascade and an increase in the biosynthesis of certain metalloproteinases (MMP 1, 2 & 3) and collagenase 12. This leads to reduction of extracellular matrix components within the ciliary muscle, iris root, and sclera. It is possible that this reduction of extracellular matrix present within portions of the uveoscleral pathway may contribute to the mechanism of increased uveoscleral outflow. Additional mechanisms that may contribute to the PG-mediated increase of uveoscleral outflow include relaxation of the ciliary muscle, cell shape changes, cytoskeletal alteration, or compaction of the extracellular matrix within the tissues of the uveoscleral outflow pathway.

Q. Does IYUZEH have the same IOP-lowering efficacy as preserved latanoprost?

A. IYUZEH demonstrated consistent IOP-lowering effects across multiple clinical and post-marketing trials in the U.S. and Europe. In a randomized, controlled clinical trial, conducted in the US (n=335), of patients with OAG or OHT with mean baseline IOP of 19-24 mmHg, IYUZEH lowered IOP by 3-8 mmHg versus 4-8 mmHg by XALATAN® (latanoprost ophthalmic solution) 0.005%, which is preserved with BAK.

Q. How long does it take for IYUZEH to work (lower IOP)?

A. Reduction of the IOP in patients starts about 3-4 hours after administration and maximum effect is reached after 8-12 hours.

Q. Are there improvements in patients using IYUZEH compared to preserved IOP-lowering medications that are co-morbid with ocular surface disease?

A. Although recently launched in the US, IYUZEH has been available as the same formulation in Europe under the name MONOPROST since 2013. Numerous post-marketing/Phase 4 studies have been conducted over the past decade that have examined ocular surface disease-related symptoms (conjunctival hyperemia, blepharitis, instillation site reactions, and signs such as TBUT) and patient-reported improvements in tolerability compared to their previous preserved medications. Summaries of these key studies:

1. FREE Study: Confirmed the clinical benefits of preservative-free latanoprost over preserved eye drops for 12 months with no significant difference in IOP-lowering efficacy, higher patient satisfaction, and improved local tolerance. (Economou et al, 2018)

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2. PASSY Study: Suggested that preservative-free latanoprost could be a valuable option for patients switching from preserved treatments or as a first choice for newly diagnosed glaucoma patients, potentially leading to improved treatment adherence and reduced need for tear substitutes after 3 months. (Erb et al, 2021)
3. RELIEF Study: Found that Monoprost has similar IOP-lowering effectiveness as BAK-preserved latanoprost over 3 months, with a better tolerability profile that might result in improved treatment control and quality of life for patients. (Misiuk-Hojlo et al, 2019)
4. Real-world study: Found a better subjective and objective ocular tolerance when patients were treated with preservative-free latanoprost than with other preserved prostaglandin analogue monotherapy. Switching to preservative-free latanoprost maintained intraocular pressure at the same level as preserved prostaglandin analogue, but improved ocular surface tolerance. (El Ameen et al, 2018)

Q. How long does a single dose of IYUZEH™ lower IOP in patients?

A. IOP reduction is present for at least 24 hours.

Q. How was IYUZEH evaluated for approval by the US Food and Drug Administration (FDA)?

A. Clinical data from five clinical studies conducted globally were included in the regulatory submission to the US FDA: Phase 2 (30 patients); Europe Phase 3 (404 patients); US Phase 3 (335 patients). A prospective, randomized, multicenter, observer-masked, parallel-group study enrolled 335 patients diagnosed with POAG or OHT in the United States who had adequately controlled intraocular pressure (≤18 mmHg) with latanoprost monotherapy. After a ≥72-hour washout period, patients were randomized to IYUZEH (n=165) or XALATAN® (n=170) groups. Study drugs were dosed once daily from Day 0 to Day 84 in one or both eyes. The study eye was the eye with lower baseline IOP. The primary efficacy measure was the between-group comparison of the mean IOP values in the study eye at each time point at each of the day 15, 42, and 84 visits. Safety measurements included ocular and systemic adverse events (AEs).

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SUPPLY AND STORAGE

Q. How is IYUZEH™ supplied?

A. As a sterile solution in a translucent low-density polyethylene single-dose container packaged in foil pouches (5 single-dose containers per pouch).

Q. Will there be a multidose bottle for IYUZEH?

A. A multidose bottle is currently in development and will be announced by Thea when available to patients in the US.

Q. Are there other preservative-free latanoprost formulations to prescribe if IYUZEH is not available?

A. No.

Q. What is the drop size of IYUZEH?

A. 28.5 µl

Q. How many drops are in each single-dose container filled with IYUZEH?

A. ~5 drops

Q. Can a single-dose container be utilized to treat patients who require IOP lowering in both eyes?

A. Yes. Each container is sufficiently filled to treat both eyes.

Q. How should IYUZEH be stored?

A. Store at room temperature (59°F to 77°F, or 15°C-25°C) and in the original pouch. Patients should be advised to write down the date the foil pouch is opened in the space provided on the pouch.

Q. How long can IYUZEH be stored after opening?

A. After the pouch is opened, the single-dose containers may be stored in the opened foil pouch for up to 30 days at room temperature (59°F to 77°F, or 15°C-25°C). Discard any unused containers 30 days after first opening the pouch.

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Q. What is the temperature range for IYUZEH™ allowed during shipping?

A. Short-term temperature excursions from -4°F to 131°F (-20°C up to 55°C) can be tolerated during transport for maximum of 14 days.

Q. Is IYUZEH light sensitive? Does it need to be protected from light?

A. No.

Q. Where is IYUZEH manufactured?

A. IYUZEH is manufactured by Excelvision in France.

USE IN SPECIFIC POPULATIONS

Q. Is IYUZEH appropriate for pediatric use?

A. The safety and effectiveness of IYUZEH have not been established in pediatric patients.

Q. Is IYUZEH appropriate for geriatric use?

A. No overall differences in safety or effectiveness have been observed between elderly and younger adult patients.

Q. Can IYUZEH be utilized with nursing mothers?

A. It is not known whether this drug or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when IYUZEH is administered to a nursing woman. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for IYUZEH and any potential adverse effects on the breastfed child from IYUZEH.

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Q. Can IYUZEH™ be used during pregnancy?

A. There are no adequate and well-controlled studies of IYUZEH administration in pregnant women to inform drug-associated risks. In animal reproduction studies, intravenous (IV) administration of latanoprost to pregnant rabbits and rats throughout the period of organogenesis produced malformations, embryofetal lethality, and spontaneous abortion at clinically relevant doses (equivalent to 1.3-324 times the maximum recommended human ophthalmic dose [RHOD], on a mg/m^2 basis, assuming 100% absorption).

Embryofetal studies were conducted in pregnant rabbits administered latanoprost daily by IV injection on gestation days 6 through 18, to target the period of organogenesis. A no observed adverse effect level (NOAEL) was not established for rabbit developmental toxicity. Post-implantation loss due to late resorption was shown at doses ≥0.2 µg/kg/day (equivalent to 1.3 times the maximum RHOD, on a mg/m^2 basis, assuming 100% absorption). Spina bifida and abortion occurred at 5 µg/kg/day (equivalent to 32 times the maximum RHOD). Total litter loss due to early resorption was observed at doses ≥50 µg/kg/day (324 times the maximum RHOD). Transient signs of maternal toxicity were observed after IV dosing (increased breathing, muscle tremors, slight motor incoordination) at 300 µg/kg/day (1946 times the maximum RHOD). No maternal toxicity was observed at doses up to 50 µg/kg/day. Embryofetal studies were conducted in pregnant rats administered latanoprost daily by IV injection on gestation days 6 through 15, to target the period of organogenesis. An NOAEL for rat developmental toxicity was not established. Cleft palate was observed at 1 µg/kg (equivalent to 3.2 times the maximum RHOD, on a mg/m^2 basis, assuming 100% absorption). Brain porencephalic cyst(s) were observed ≥50 µg/kg (162 times the maximum RHOD). Skeletal anomalies were observed at 250 µg/kg (811 times the maximum RHOD). No maternal toxicity was detectable at 250 µg/kg/day.

Prenatal and postnatal development was assessed in rats. Pregnant rats were administered latanoprost daily by IV injection from gestation day 15, through delivery, until weaning (lactation day 21). No adverse effects on rat offspring were observed at doses up to 10 µg/kg/day (32 times the maximum RHOD, on a mg/m^2 basis, assuming 100% absorption). At 100 µg/kg/day (324 times the maximum RHOD), maternal deaths and pup mortality occurred.

Q. Can contact lenses be worn while being treated with IYUZEH?

A. Contact lenses should be removed prior to the administration of IYUZEH and may be reinserted 15 minutes after administration.

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Q. Can IYUZEH™ be used in patients with pseudoexfoliative syndrome or glaucoma?

A. No data are available on the use of IYUZEH in these patients because the Phase 3 study excluded patients with a pseudoexfoliation component (secondary glaucoma).

Q. Can IYUZEH be used in patients with narrow or closed angles?

A. No data are available on the use of IYUZEH in these patients because the Phase 3 study excluded patients with secondary glaucoma (narrow or closed angles).

PHARMACOKINETICS

Q. How is IYUZEH absorbed?

A. Latanoprost is absorbed through the cornea where the isopropyl ester prodrug is hydrolyzed to the acid form to become biologically active.

Q. What is the tissue distribution of IYUZEH?

A. The distribution volume in humans is 0.16 ± 0.02 L/kg. The acid of latanoprost can be measured in aqueous humor during the first 4 hours, and in plasma only during the first hour after local administration. Studies in man indicate that the peak concentration in the aqueous humor is reached about two hours after topical administration.

Q. How is IYUZEH metabolized?

A. Latanoprost, an isopropyl ester prodrug, is hydrolyzed by esterases in the cornea to the biologically active acid. The active acid of latanoprost reaching the systemic circulation is primarily metabolized by the liver to the 1,2-dinor and 1,2,3,4-tetranor metabolites via fatty acid β-oxidation.

Q. What is the half-life of IYUZEH? How is it eliminated from systemic circulation?

A. The elimination of the acid of latanoprost from human plasma is rapid ($t_{1/2}$=17 min) after both IV and topical administration. Systemic clearance is approximately 7 mL/min/kg. Following hepatic β-oxidation, the metabolites are mainly eliminated via the kidneys. Approximately 88% and 98% of the administered dose are recovered in the urine after topical and IV dosing, respectively.

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CLINICAL TRIALS

Q. What clinical data is available for IYUZEH™?

A. Patients treated with either IYUZEH or XALATAN® provided clinically meaningful reductions in IOP from baseline to all follow-up visits and time points (n=335). At day 84, the mean ± SD diurnal IOP was 16.3±2.5 mmHg in the IYUZEH group and 15.7±2.6 mmHg in the XALATAN group, representing percentage IOP decreases of 13.8% and 17.7%, respectively.

For the primary efficacy endpoint, the two-sided 95% CI of both IYUZEH and XALATAN were within 1.5 mmHg for all time points (9/9) assessed in the study eye of the Per Protocol population. However, only 1/9 time points (day 84, 4 PM) was within the noninferiority margin of 1.0 mmHg, with 4/9 time points exceeding this non-inferiority margin by 0.07 mmHg or less.

Q. How many clinical trials were conducted for the approval of IYUZEH? Are all the trials conducted in the US?

A. Three trials: A Phase 2 and two Phase 3 trials were performed. The Phase 2 trial was conducted at 3 sites in India. One Phase 3 trial was conducted at 31 sites across the US. The other Phase 3 trial was conducted at 87 sites located throughout Europe.

Q. What was the discontinuation rates of IYUZEH and XALATAN in the US and European clinical trials?

A. Treatment withdrawals occurred for IYUZEH at a rate comparable to the other prostaglandins studied. In both pivotal Phase 3 studies, there were 10 subjects in the IYUZEH groups (2.6%) where treatment was withdrawn, and 7 in the XALATAN group (2.0%).

Q. What was the rate of treatment discontinuation from the US Phase 3 trial?

A. In this clinical trial, 1.8% of patients in both the IYUZEH and the XALATAN groups discontinued treatment, with the most common reasons for early discontinuation from the study being TEAEs and consent withdrawal.

Q. What was the primary efficacy endpoint in the US Phase 3 trial?

A. It was the between-group comparison of the mean change in IOP values from baseline in the study eye at each time point (8 AM, 10 AM, 4 PM; ±30 minutes) at day 15, 42, and 84 visits, as measured by tonometry.

Q. How was non-inferiority determined? Was it achieved in the US Phase 3 trial?

A. Non-inferiority was demonstrated if both of the following conditions were met: (1) the two-sided 95% CI of each between-group comparison was within ±1.5 mmHg; and (2) if the 95% CI was within ±1.0 mmHg for the majority of the measured time points. For the primary efficacy endpoint, the two-sided 95% CI of both IYUZEH and XALATAN were within 1.5 mmHg for all time points (9/9) assessed in the study eye of the per-protocol (PP) population. However, only 1/9 time points (day 84, 4 PM) was within the non-inferiority margin of 1.0 mmHg, with 4/9 time points exceeding this noninferiority margin by 0.07 mmHg or less.

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Q. What were the key inclusion criteria for the US Phase 3 trial?

A. For inclusion into the study, patients were required to fulfill all of the following criteria:

1. Age ≥18 years.

2. POAG or OHT with IOP treated and adequately controlled (IOP ≤18 mmHg) with latanoprost 0.005% ophthalmic solution monotherapy for at least 4 weeks before screening.

3. Each eye being treated with latanoprost 0.005% ophthalmic solution monotherapy was to have had mean IOP ≤ 18 mmHg at screening and mean IOP ≤28 mmHg at baseline; measurements were to be taken at each visit at 8 AM, 10 AM, and 4 PM (each ± 30 minutes) with AM measurements of IOP at least 2 hours apart. If only one eye qualified but both eyes had glaucoma and the contralateral eye required antiglaucoma medications other than latanoprost, the patient did not qualify for the trial.

4. Stable VF, defined as no sign of VF degradation between two consecutive 30-2 or two consecutive 24-2 VF examinations. For patients with no VF defect (e.g., those with OHT), a single normal VF examination performed <6 months before the screening visit was allowed to determine eligibility. For patients who had an abnormal VF examination, the following criteria applied:

5. Two VFs (most recent VF and past VF) examinations performed at least ≥6 months and ≤18 months apart were to be compared;

6. The most recent VF examination should have been performed <6 months before the screening visit;

7. The past VF examination should have been performed ≥6 months and ≤18 months before the most recent VF examination.

8. Stable corrected Snellen visual acuity (VA) of better than 20/200 in the study eye. Patients had to see ≥50% of the letters on a single line to accept that VA line.

9. Central corneal thickness 480 to 620 µm in the study eye

10. Shaffer gonioscopic grade of ≥3 (in at least 3 quadrants) in both eyes.

11. Female patients were required to be 1-year postmenopausal, surgically sterilized, or have a negative urine pregnancy test at screening. Women of childbearing potential were to use an acceptable form of contraception throughout the study. Acceptable methods included the use of at least one of the following: intrauterine (intrauterine device), hormonal (oral, injection, patch, implant, ring), barrier with spermicide (condom, diaphragm), or abstinence.

12. All patients were required to provide signed written consent before participation in any study-related procedures.

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Q. What were the key exclusion criteria for the US Phase 3 trial?

A. Any of the following was regarded as a criterion for exclusion from the study. In the study eye:

1. A mean deviation of <-20 dB on VF examination.

2. A mean IOP >28 mmHg at baseline.

3. Presence of a scotoma within 5° of fixation on VF examination.

4. Aphakia.

5. Use of any antiglaucoma medication in addition to latanoprost 0.005% ophthalmic solution within 2 weeks before screening and any antiglaucoma medication (other than latanoprost) during the study period other than the randomized study medication.

6. Use of any topical ophthalmic steroid within 2 weeks before baseline. A short course of oral steroids was acceptable if the course was completed >2 weeks before screening. Inhaled and intranasal steroids were acceptable.

7. Use of topical nonsteroidal anti-inflammatory drug within 2 weeks before baseline.

8. Use of any ophthalmic medications during the study period (nonpreserved artificial tears were allowed).

9. Ocular surgery or laser treatment of any kind in the study eye within 3 months before baseline.

10. History of ocular allergy/inflammation and/or severe blepharitis and/or uveitis. Seasonal allergic conjunctivitis was acceptable (as long as the patient was not expected to experience seasonal flare-up during the study period). Mild blepharitis/blepharoconjunctivitis, typically associated with prostaglandin usage, on the lid was acceptable.

11. History of ocular trauma or ocular infection within 3 months of screening.

12. History of herpes simplex keratitis

13. Current proliferative diabetic retinopathy or age-related macular degeneration, unless deemed not clinically significant by the investigator.

14. Severe dry eye (e.g., clinically relevant superficial punctate keratitis, epithelial erosions of the cornea, and/or use of dry eye medication [including artificial tears] with a frequency exceeding 8 instillations per day).

15. Contact lens wear during the study period. Contact lens wear in an untreated contralateral eye was allowed.

16. Any secondary glaucoma or OHT (e.g., congenital glaucoma, closed-angle glaucoma, uveitic glaucoma, or pseudoexfoliation syndrome).

17. Any severe glaucoma defined by cupping (cup-to-disc ratio ≥0.8)

Please see continued Important Safety Information on page 20.
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18. Any nonlaser glaucoma surgery.

19. Any abnormality preventing accurate assessment (e.g., resulting in unreliable applanation tonometry or VF examination).

20. Pregnancy or lactation.

21. Uncontrolled asthma (defined as asthma that did not respond to the maximum guideline-directed therapy)

22. Allergy to BAK.

23. History of moderate or severe renal or hepatic impairment.

24. Participation in any study of an investigational product within 30 days before screening or at any time during the study period.

Q. What was the rate of treatment discontinuation from the US Phase 3 trial?

A. In the study, 1.8% of patients in both the IYUZEH™ and the XALATAN® groups discontinued treatment, with the most common reasons for early discontinuation from the study being TEAEs and consent withdrawal.

Q. What were the key differences between the US and the European Phase 3 trials?

A.

Parameter	US Phase 3 (n=335)	European Phase 3 (n=404)
Primary Purpose	Pivotal	Pivotal
Inclusion Diagnoses Permitted	POAG or OHT	POAG or OHT
Entry Status	Stable on latanoprost monotherapy for 4 weeks	Stable on latanoprost monotherapy for 9 months
Washout Period	≥3 days (range: 3-372 days)	5 weeks brinzolamide which was stopped 5 days before inclusion
Duration of treatment	84 days	84 days
Study Eye	Better (lower baseline IOP)	Worse (higher baseline IOP)
Primary Efficacy Analysis	Per-protocol population	Modified ITT population

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IMPORTANT SAFETY INFORMATION *(cont'd)*

iyuzeh™
(latanoprost ophthalmic solution) 0.005%

WARNINGS AND PRECAUTIONS

IYUZEH™ may cause changes to pigmented tissues. Most frequently reported changes are increased pigmentation of the iris, periorbital tissue (eyelid), and eyelashes. Pigmentation is expected to increase as long as IYUZEH is administered. Iris pigmentation is likely to be permanent. Eyelid skin darkening and eyelash changes may be reversible.

IYUZEH may cause gradual change to eyelashes including increased length, thickness, and number of lashes. These changes are usually reversible upon discontinuation of treatment.

IYUZEH should be used with caution in patients with a history of intraocular inflammation (iritis/uveitis) and should generally not be used in patients with active intraocular inflammation.

IYUZEH should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

Reactivation of herpes simplex keratitis has been reported during treatment with latanoprost. IYUZEH should be used with caution in patients with a history of herpetic keratitis.

Contact lenses should be removed prior to the administration of IYUZEH and may be reinserted 15 minutes after administration.

ADVERSE REACTIONS

The most common adverse reactions (5% to 35%) for IYUZEH are: conjunctival hyperemia, eye irritation, eye pruritus, abnormal sensation in eye, foreign body sensation in eyes, vision blurred, and lacrimation increased.

DRUG INTERACTIONS

The combined use of two or more prostaglandins or prostaglandin analogs including IYUZEH is not recommended. It has been shown that administration of these prostaglandin drug products more than once daily may decrease the IOP lowering effect or cause paradoxical elevations in IOP.

Please click here for full Prescribing Information.

References

iyuzeh™
(latanoprost ophthalmic solution) 0.005%

1. Thea data on file. 2022. Monoprost discussion guide. **2.** IYUZEH. US Package insert. Théa Pharma Inc.; 2022. **3.** Rouland JF, Traverso CE, Stalmans I, et al. Efficacy and safety of preservative-free latanoprost eyedrops, compared with BAK-preserved latanoprost in patients with ocular hypertension or glaucoma. *Br J Ophthalmol.* 2013;97(2):196-200. **4.** Xalatan. US Package Insert. Pfizer; 2020. **5.** Aptel F, Choudhry R, Stalmans I. Preservative-free versus preserved latanoprost eye drops in patients with open-angle glaucoma or ocular hypertension. *Curr Med Res Opin.* 2016;32(8):1457-1463. **6.** Bacharach J, Ahmed IIK, Sharpe ED, Korenfeld MS, Zhang S, Baudouin C. Preservative-free versus benzalkonium chloride–preserved latanoprost ophthalmic solution in patients with primary open-angle glaucoma or ocular hypertension: a phase 3 US clinical trial. Paper presented at: ASCRS, ASOA Symposium & Congress; May 5-8, 2023; San Diego, CA. **7.** Thea data on file. 2023. Clinical overview of T2345.

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