14 September 2023
EMA/CHMP/448508/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Catiolanze

International non-proprietary name: latanoprost

Procedure No. EMEA/H/C/005933/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

API	Active Pharmaceutical Ingredient
AS	active substance
ASMF	Active Substance Master File = Drug Master File
BAK	Benzalkonium Chloride
CEP	Certificate of Suitability of the EP
CKC	Cetalkonium chloride
CRS	Chemical Reference Substance
EDQM	European Directorate for the Quality of Medicines
FP	finished product
GMP	Good Manufacturing Practice
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IPC	In Process Control
IUPAC	International Union of Pure and Applied Chemistry
LDPE	Low Density Polyethylene
LOQ	Limit of Quantitation / List of Questions
MAH	Marketing Authorisation Holder
MCT	Medium Chain Triglycerides
MIA	Manufacturing / Importation Authorisation
MO	Major Objection
Ph. Eur.	European Pharmacopoeia
RH	Relative Humidity
SD	Single Dose

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Santen Oy submitted on 8 September 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for Catiolanze, through the centralised procedure under Article 3 (2)(b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 24 June 2021. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of significant technical innovation.

The applicant initially applied for the following indication:

"*Reduction of elevated intraocular pressure (IOP) in patients with open angle glaucoma or ocular hypertension in adults (including the elderly), especially in patients having, or who are at risk of developing, concomitant ocular surface disease (OSD).*

Reduction of elevated IOP in paediatric patients with elevated IOP and paediatric glaucoma."

Subsequently, the applicant amended the indication applied for to:

"*Catiolanze is indicated for the reduction of elevated intraocular pressure (IOP) in adult patients with open angle glaucoma or ocular hypertension.*

Catiolanze is indicated for the reduction of elevated IOP in children from 4 years of age and adolescents with elevated IOP and paediatric glaucoma."

1.2. Legal basis, dossier content

The legal basis for this application refers to: Article 10(3) of Directive 2001/83/EC.

The application submitted is composed of administrative information, complete quality data and non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 10 years in the EEA:

- Product name, strength, pharmaceutical form: Xalatan, 50 µg/ml, eye drops, solution
- Marketing authorisation holder: Viatris Pharma GmbH
- Date of authorisation: 01-07-1997
- Marketing authorisation granted by:
  - Member State (EEA) Germany
  - MRP/DCP number DE/H/6157/001
- Marketing authorisation number: 40466.00.00

Medicinal product authorised in the Union/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Xalatan, 50 µg/ml, eye drops, solution
- Marketing authorisation holder: Viatris Pharma GmbH
- Date of authorisation: 01-07-1997
- Marketing authorisation granted by:
  - Member State (EEA) Germany
  - MRP/DCP number DE/H/6157/001
- Marketing authorisation number: 40466.00.00

Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

Not applicable.

1.3. Information on Paediatric requirements

Not applicable.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Scientific advice

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

Date	**Reference**	**SAWP co-ordinators**
22 October 2009	EMEA/CHMP/SAWP/629141/2009	Dr Kristina Dunder and Dr Armin Koch
14 December 2017	EMA/CHMP/SAWP/797001/2017	Prof Andrea Laslop and Dr Sheila Killalea

EMEA/CHMP/SAWP/629141/2009; On 22 October 2009, the Company Novagali Pharma S.A received scientific advice for their product Latanoprost. The Scientific advice pertained to the following quality, non-clinical, and clinical aspects:

- Quality: proposed acceptance criteria
- Non-clinical: proposed non-clinical data package,
- Clinical aspects: proposed non-inferiority clinical study design, including primary endpoint, noninferiority margin, the proposed safety data package

EMA/CHMP/SAWP/797001/2017; On 14 December 2017, the applicant Santen OY received follow-up scientific advice on their product. The Scientific advice pertained to the following clinical aspects:

- Clinical: proposed clinical study of non-inferiority design and analysis, the proposed safety database.

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jayne Crowe Co-Rapporteur: Tomas Radimersky

The application was received by the EMA on	8 September 2022
The procedure started on	29 September 2022

The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	19 December 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	3 January 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	26 January 2023
The applicant submitted the responses to the CHMP consolidated List of Questions on	19 April 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	30 May 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	8 June 2023
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	22 June 2023
The applicant submitted the responses to the CHMP List of Outstanding Issues on	9 August 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	30 August 2023
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Catiolanze on	14 September 2023

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Ocular hypertension is defined as consistently elevated IOP above an upper normal value of 21 mmHg by Goldmann applanation tonometry on two or more occasions, in one or both eyes and in the absence of optic nerve damage, visual field defects, or other pathology.

Glaucoma refers to a group of conditions characterised by cupping (excavation) of the optic disc and damage to the optic nerve leading to gradual visual loss. Patients with glaucoma develop progressive thinning of the neuro-retinal rim of the optic nerve, thereby enlarging the optic-nerve cup. Disease progression rates are variable depending on the type of glaucoma and on patient characteristics. In one report, the cumulative rate of blindness from glaucoma after 22 years was 19% (Kwon et al., 2001).

2.1.2. Epidemiology

There are various types of glaucoma which are classified according to the appearance of the iridocorneal angle (anterior-segment variations) that can lead to elevated IOP (Kwon et al., 2009). The various types of glaucoma are classified according to the appearance of the iridocorneal angle (anterior segment variations) that can lead to elevated IOP (Kwon et al., 2009). These are OAG, angle closure glaucoma, and developmental categories which are further divided into primary and secondary types. The most common form of glaucoma in Western countries is primary open angle glaucoma (POAG), a chronic condition which is due to increased resistance in the drainage of aqueous humour through the trabecular meshwork. IOP increases gradually, and the condition is usually asymptomatic until well advanced and visual field loss has occurred. Both eyes are usually affected (European Glaucoma Society, 2021).

The estimated prevalence of OHT ranges from 4.5% to 9.4% in adults aged >40 years and increases with age. Longitudinal studies show that 10% of persons with OHT will develop OAG within five years if left untreated (Burr et al., 2012).

2.1.3. Aetiology and pathogenesis

Glaucoma is a progressive optic neuropathy that causes characteristic loss of visual fields and can eventually lead to blindness due to progressive degeneration of retinal ganglion cells and resulting changes in the head of the optic nerve. The pathophysiology of open angle glaucoma is not fully understood. Elevated intraocular pressure is a major risk factor for glaucomatous visual field loss though ocular hypertension is not a feature in all cases of glaucoma. The intraocular pressure is influenced by the balance between the aqueous humour secreted by the ciliary body and drainage through two independent pathways, the trabecular meshwork and the uvoscleral outflow pathway. Patients with raised intraocular pressure and open angle glaucoma have increased resistance to aqueous outflow through the trabecular meshwork.

2.1.4. Clinical presentation, diagnosis

Glaucoma is a leading cause of irreversible blindness globally. The early stages of the condition are asymptomatic and patients may not present until they have significant visual field loss. The condition is often detected during routine eye examinations on the basis of raised intraocular pressure or fundal changes. Visual acuity is unaffected, as long as central vision is preserved. Glaucoma is diagnosed in patients with characteristic nerve damage on fundus examination and visual field testing, usually in the presence of elevated intraocular pressure (IOP).

The only effective treatment is to reduce intra-ocular pressure (IOP) by medical or surgical means. Prostaglandin analogues are well established IOP-lowering drugs and are frequently recommended as the first choice of therapy on the basis of their high efficacy, single daily dosing regimen and established safety profile (European Glaucoma Society, 2021).

Ocular hypertension is defined as consistently elevated IOP above an upper normal value of 21 mmHg by Goldmann applanation tonometry on two or more occasions, in one or both eyes and in the absence of optic nerve damage, visual field defects, or other pathology.

2.1.5. Management

The clinical guidelines for the management of glaucoma published by the European Glaucoma Society (EGS) in 2020 state that there is substantial evidence that treatment of raised IOP reduces the risk of

conversion to glaucoma and disease progression. Glaucoma therapy aims to lower IOP to slow the rate of visual field deterioration sufficiently to maintain quality of life. For patients with advanced visual field loss at presentation, surgery may be considered (European Glaucoma Society, 2021; Lichter et al., 2001). Clinical trials have demonstrated that long-term IOP-lowering therapy in patients with OHT reduces the relative risk of glaucoma by 50% (Kass et al., 2002). In patients with glaucoma, a 25% reduction in IOP reduced the relative progression risk by 50% after six years (Leske, 2007).

Current therapy for glaucoma is therefore directed at lowering IOP to prevent further damage to the optic nerve and is highly individual. For patients with early-stage glaucoma, an IOP of 18 to 20 mmHg with a reduction of at least 20% may be adequate. For patients with moderately severe glaucoma, an IOP of 15 to 17 mmHg and at least a 30% reduction may be appropriate. For patients with advanced glaucoma, a lower IOP of 10 to 12 mmHg may be required (European Glaucoma Society, 2021). Regular monitoring of IOP is required to assess progression and guide choice of the target IOP and treatment intensity. Treatment is life-long and monotherapy is recommended when possible to minimise the occurrence of side effects (European Glaucoma Society, 2021).

Available IOP-lowering treatments are prostaglandin analogues, non-selective beta blockers, Rho kinase inhibitors, alpha adrenergic agonists, selective beta blockers and topical carbonic anhydrase inhibitors. If initial therapy is ineffective or not tolerated by the patient, switching to another monotherapy or laser trabeculoplasty is considered. If monotherapy does not lower the IOP to the target pressure but it is well tolerated and effective, addition of a second class of drug is considered. However, multiple topical treatments can reduce compliance and increase exposure to preservatives (European Glaucoma Society, 2021). Prostaglandin analogues such as latanoprost are frequently used as first-line therapy on the basis of their high efficacy, single daily dosing regimen, and established safety profile (European Glaucoma Society, 2021).

Treatment of early onset glaucoma in children is frequently surgical, but medical treatment has a role and follows the same principles as treatment of glaucoma in adults. However, medical treatment options are more limited. Brimonidine crosses the blood–brain barrier and is absolutely contraindicated in infants and young children due to central nervous system toxicity. It should also be used with caution in older children and has been shown to not have a significant effect on IOP reduction. Beta blockers are often used but may not be suitable for all children, e.g., those with asthma or other respiratory conditions. Prostaglandin analogues, considered first-line treatment in adults, are also well tolerated in children. They may be most effective in older children with juvenile open-angle glaucoma as monotherapy.

2.2. About the product

Latanoprost is a prostaglandin 2α analogue that acts as a selective prostanoid FP receptor agonist that reduces IOP by increasing uveo-scleral outflow. Latanoprost, marketed as Xalatan®, has been approved for the treatment of open angle glaucoma (OAG) and ocular hypertension (OHT) for more than two decades and in over 130 countries. Xalatan® was approved for the treatment of paediatric glaucoma in 2010.

This Marketing Authorisation Application (MAA) concerns a new formulation of latanoprost for ocular administration; Catiolanze 50 µg/mL eye drops, emulsion single dose (SD), using the marketed product Xalatan® (50 µg/mL eye drops, solution) as the reference medicinal product (RefMP) to support the indication for reduction in IOP.

In addition to reducing IOP, Catiolanze 50 µg/mL eye drops, emulsion SD was designed to offer clinical benefit over the RefMP. Xalatan® contains the preservative benzalkonium chloride (BAK) that is known to cause ocular surface inflammation and damage in a high proportion of patients. The applicant

outlines that the new formulation of Catiolanze 50 µg/mL eye drops, emulsion SD is preservative-free. Catiolanze 50 µg/mL eye drops, emulsion SD is formulated with Novasorb® technology-based cationic oil-in-water emulsion eye drops. This same emulsion technology is currently licensed for use as Cationorm® for the management of moderate signs and symptoms of dry eye disease, Cationorm® PRO/Plus for ocular allergy, Ikervis® for severe keratitis in dry eye disease, and Verkazia® for vernal keratoconjunctivitis.

Ocular surface disease (OSD) is associated both with the use of preservative-containing topical eye treatments and also (independently of the use of such treatments) with glaucoma per se. The applicant initially claimed that their product was aimed not only at removing the preservative, considered a potential aggravating factor of OSD, but also to make use of the established Novasorb® technology with a claimed benefit in the management of ocular signs and symptoms associated with OSD.

The applicant stated that the objectives of the development programme for Catiolanze 50 µg/mL eye drops, emulsion SD were therefore to demonstrate therapeutic equivalence to the RefMP through non-clinical pharmacodynamic (PD) and pharmacokinetic (PK) studies, and pivotally non-inferiority in terms of IOP-lowering effect in clinical trials. Additionally, the clinical trials were designed to evaluate if there is a benefit over the RefMP in terms of reducing the signs and symptoms associated with OSD.

Catiolanze was thus initially proposed for topical use for the reduction of IOP in patients with OAG or OHT, with the additional benefit of reducing the risk of developing or exacerbating OSD. Accordingly, the applicant's initially intended therapeutic indication was:

"Reduction of elevated intraocular pressure (IOP) in patients with open angle glaucoma or ocular hypertension in adults (including the elderly), especially in patients having, or who are at risk of developing, concomitant ocular surface disease (OSD).

Reduction of elevated IOP in paediatric patients with elevated IOP and paediatric glaucoma."

During the procedure, the applicant changed the indication requested as follows:

"*Catiolanze is indicated for the reduction of elevated intraocular pressure (IOP) in adult patients with open angle glaucoma or ocular hypertension.*

Catiolanze is indicated for the reduction of elevated IOP in children from 4 years of age and adolescents with elevated IOP and paediatric glaucoma."

2.3. Quality aspects

2.3.1. Introduction

The finished product is presented as eye drops, emulsion containing 50 micrograms/ml of latanoprost as active substance.

Other ingredients are: medium chain triglycerides, cetalkonium chloride, polysorbate 80, glycerol and water for injections.

The product is available in LDPE single dose containers in a sealed aluminium-polyethylene foil pouch.

2.3.2. Active substance

2.3.2.1. General information

The chemical name (IUPAC) of latanoprost (INN) is propan-2-yl (5*Z*)-7-[(1*R*,2*R*,3*R*,5*S*)-3,5-dihydroxy-2-[(3*R*)-3-hydroxy-5-phenylpentyl]cyclopentyl]hept-5-enoate corresponding to the molecular formula $C_{26}H_{40}O_5$. It has a relative molecular mass of 432.58 and the following structure (Figure 1):

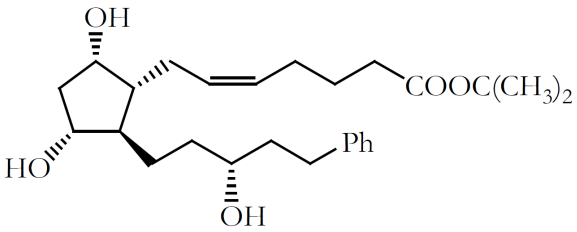


Figure 1. Active substance structure

The active substance (AS) according to Ph. Eur. appears as clear, colourless or yellow, viscous, oily liquid. It is practically insoluble in water, very soluble in acetonitrile, freely soluble in anhydrous ethanol.

As there is a monograph of latanoprost in the European Pharmacopoeia, the manufacturer of the active substance (AS) has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for latanoprost which has been provided within the current Marketing Authorisation Application.

2.3.2.1. Manufacture, characterisation and process controls

The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.

The AS manufacturer is stated in the CEP. The AS is packaging is described in the CEP.

Initially a second AS manufacturer had been also proposed. However, the applicant removed the second manufacturer from their application. This is acceptable considering there is an alternative source of AS supported by a CEP as mentioned above.

2.3.2.2. Specification

Latanoprost is tested by the finished product manufacturer according to the current Ph. Eur. monograph for latanoprost with the additional tests described in the CEP.

The specification of the AS is considered justified as it is line with the Ph. Eur. monograph and the requirements of the CEP. The microbiological specifications are justified by industrial practice applied when determining the limits for the ingredients of aseptic preparations.

Analytical methods are as per the Ph. Eur. monograph. The additional test methods are described in the CEP thus no validation studies have been provided; this is acceptable. Ph. Eur. reference standards are used in the testing of the AS.

Batch analysis data and the respective certificates of analysis were provided for three AS batches support the quality of the AS.

2.3.2.3. Stability

Stability data from three commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 36 months under long term conditions (5°C) and for up to 6 months under accelerated conditions (25°C, 60 % RH) according to the ICH guidelines were provided.The parameters tested are the same as for release except for water determined by volumetric determination per Ph. Eur. 2.5.12. Results showed no degradation and no change in assay under both storage conditions. Furthermore, the appearance of the AS did not show any change in comparison with freshly manufactured batches. All tested parameters remained within the specification.

Photostability testing following the ICH guideline Q1B was performed on three pilot batches as part of the stress testing studies. Results did not degrade to any significant extent on exposure to light.

Stress testing studies were performed on three pilot batches under thermal, humidity photolytic, acidic, basic, and oxidative conditions.

The results of the stress testing studies showed that the AS did not significantly degrade under high temperature, or under oxidative condition. It did not degrade either under high humidity but the water content moderately increased. The AS degraded when exposed to acidic or alkaline conditions (main degradation product was impurity H). Based on the stress testing study, one degradation impurity was identified, impurity H. However, impurity H did not increase under accelerated or long-term conditions.

Based on the overall stability test results, a 36 months' retest period when stored in a refrigerator (2°C to 8°C) in a well-closed, light-resistant container, is acceptable.

2.3.3. Finished Medicinal Product

2.3.3.1. Description of the product and pharmaceutical development

Catiolanze 50 microgram/ml eye drops is a sterile, preservative free, oil-in-water emulsion filled into single-dose containers. The emulsion is a white liquid.

The finished product (FP) is packaged in LDPE single dose containers manufactured by a blow-fill-seal machine. The single dose containers are secondary packaged into a laminate pouch to protect from light and to prevent moisture loss.

Latanoprost solution eye drops are marketed in Europe under the brand name Xalatan and there are also several generic products currently available. Catiolanze 50 microgram/ml eye drops emulsion has been developed as a hybrid to Xalatan. The FP is an oil-in-water emulsion, in which the oil droplets containing latanoprost are dispersed in the aqueous phase and are stabilised by a barrier of surfactants at the oil/water interface. The functions of the excipients in the emulsion are defined, and the quantities justified. The excipients selected are known and well-established for use in eye preparations.

The medicinal product is indicated for paediatric use and reference is made to the centrally authorised product Verkazia, eye drops, emulsion (which also contains the excipient CKC) and the reference product Xalatan eye drops, solution to justify its suitability for use within this population cohort. The formulation used in the Phase III pivotal clinical studies is the same as the proposed commercial formulation.

The manufacturing process selected consists of high shear mixing and high-pressure homogenisation steps which ensure both droplet size uniformity and reproducibility. As the FP is not sensitive to heat,

heat sterilisation of the final bulk emulsion followed by aseptic filling using blow-fill-seal technology was selected for the manufacturing process. The low-density polyethylene (LDPE) containers cannot be terminally sterilised.

The container closure system is a conventional single-dose eye drop container made of LDPE which ensures a good microbial, chemical and physical stability of the product. The containers are created from polyethylene granules which are controlled as per Ph. Eur. 3.1.4 and additional controls over bioburden content.

Each strip of five single dose containers is over-wrapped in an aluminium pouch to protect from light and moisture loss. The immediate packaging material complies with Ph. Eur. requirements and stability and leachable studies performed by the applicant confirm its compatibility with the drug product. Dose delivery performance studies have also been performed and the average drop size was calculated as 33 µl.

Sterility of the FP is controlled by the manufacturing process during which all strips are leak tested to ensure the integrity of the container. The integrity of the container was also evaluated using a static immersion test.

2.3.3.2. Manufacture of the product and process controls

The manufacturing process consists of the preparation of both the aqueous phase and oily phase solutions and combining them through homogenisation to prepare a concentrated emulsion which is further diluted. The bulk solution is heat sterilised followed by aseptic filling into the single dose containers using blow-fill-seal technology.

Critical steps were defined and acceptable in process controls (IPCs) have been defined. A maximum aseptic process time has been defined as supported by media fills.

The manufacturing process comprising aseptic filling, is considered, as such, as non-standard as per the relevant guideline. The CHMP raised a MO about the lack of a full process validation report. However, in their response the applicant has justified that the process is standard for the proposed manufacturer / site in line with the EMA guidance on Process Validation and full process validation will be performed prior to commercial release. This is acceptable and the MO is resolved. The sterilisation cycle for the bulk emulsion has been validated.

2.3.3.3. Product specification

The finished product release and shelf-life specification includes appropriate tests and limits for this kind of dosage form: appearance (visual), identification (HPLC normal and reverse phase), pH (Ph. Eur.), osmolality (Ph. Eur.), zeta potential (electrophoretic mobility measurement), mean droplet size (dynamic light scattering), latanoprost assay (HPLC), related substances (HPLC) and sterility (Ph. Eur.).

The specification limits are based on relevant guidelines and also on batch analysis and stability data. Limits proposed for specified and unspecified impurities are in line with ICH Q3B and the shelf-life limit for latanoprost free acid is toxicologically justified on the basis that it is the active form of latanoprost.

The specification is considered acceptable for the dosage form.

A risk assessment was performed in line with ICH Q3D. All Class 1, class 2A and intentionally added class 2B and 3 were considered. Results from the risk assessment and analysis of finished product

confirmed that elemental impurities were under relevant thresholds and no further testing or specification for elemental impurities was required.

The CHMP raised a MO concerning the missing risk assessment of the potential presence of nitrosamine impurities in the finished product. The risk assessment has been performed and provided as requested, considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

The analytical methods used are either compendial or in house test methods developed by the applicant. In-house methods were appropriately described, and satisfactory validation data has been presented to demonstrate that the methods are suitable for their intended use. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data was presented for three commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.3.3.4. Stability of the product

Stability data from three pilot scale and three production scale batches of finished product stored for up to 36 months under long term (25 ± 2°C / 40% ± 5% RH) and intermediate conditions (30 ± 2°C / 65% ± 5% RH) and for up to six months under accelerated conditions (40 ± 2°C / ⩽ 25% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, identification, pH, osmolality, zeta potential, mean droplet size, related substances, assay and sterility (at release and annually).

All the stability results met the stability specifications under long term, intermediate and accelerated conditions. Minor trends in pH (decrease), osmolality (increase), mean droplet size (increase), and related substances (increase) were observed. More significant changes in assay are observed for some of the batches stored at 30 ± 2°C /65% ± 5% RH and 40 ± 2°C /≤25% RH. Increased impurities levels were observed but remain within specifications limits. The product was sterile up to the studied 36 month time point.

A photostability study as per ICH Q1B was performed on two batches of Latanoprost 50 microgram/ml eye drops emulsion packed without the laminate pouch. Samples were evaluated for appearance, pH, osmolality, mean droplet size, zeta potential, latanoprost and related substances assays and water loss. All results were within the shelf-life specifications. However, a decrease of pH, latanoprost assay and an increase in related substances was observed when the product was exposed to light. The product in the LDPE bottles is therefore susceptible to photodegradation but it has been shown that the laminate pouch provides adequate light protection.

A freeze-thaw cycling study was performed to determine the effects of freezing and thawing on the stability of the FP. Samples were evaluated for appearance, pH, osmolality, mean droplet size, zeta potential, latanoprost and related substances assays and water loss. All results were within the shelf-life specifications and there were no significant changes compared to the control samples. Based on

these results, the single dose containers should be kept in the aluminium pouch, in order to avoid evaporation and to protect the product from light.

In-use stability studies were conducted under conditions intended to simulate the use of the medicinal product at the beginning of the shelf life, at the 24 month timepoint and at the end of shelf-life. The study was conducted to evaluate the effects on the finished product over the 28 day period of patient use. All results were within the product shelf-life specifications and there was no significant difference between the test and control samples.

The Product Information includes instruction to 'Discard any opened individual single dose container immediately after use'. The product information does not specify an in-use storage period of up to 28 days. However, considering the posology, which is one drop in the affected eye(s) daily, the 28 day period is well in excess of the expected storage duration of the opened pouch and therefore specifying a maximum 28 day storage period on the product information is not considered necessary.

Based on available stability data, the proposed shelf-life of 3 years below 30°C and storage precautions as stated in the SmPC (sections 6.3 and 6.4) are acceptable.

2.3.3.5. Adventitious agents

No excipients derived from animal or human origin are used.

2.3.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. During the procedure, two MOs were raised concerning the finished product manufacturing process validation and the risk assessment on potential presence of nitrosamine impurities. These were resolved by provision of additional data and justifications. Also, the withdrawal of a second active substance supplier proposed initially was accepted since an alternative supplier supported by an Ph. Eur. CEP ensures an acceptable source of active substance. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.3.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.3.6. Recommendations for future quality development

Not applicable.

2.4. Non-clinical aspects

2.4.1. Introduction

The applicant has not conducted a full programme of non-clinical studies on Catiolanze because Xalatan® is used as a reference product in this application and an abridged preclinical development program evaluating the pharmacodynamics, ocular drug absorption and safety of the cationic oil-in-water emulsion of latanoprost has been provided. The pharmacology and toxicology profile of the drug substance latanoprost is already well characterised in both animal models and man, including following ocular administration. Thus, the non-clinical assessment has focused on the novel features of the drug product, i.e., the cationic oil-in-water emulsion vehicle, and how the latter may impact the known safety profile (ocular tolerance) of latanoprost. To support the development and registration of the new emulsion formulation of latanoprost 50 µg/mL eye drops, emulsion SD, the applicant has conducted six nonclinical studies including two pharmacology studies (a primary PD study and a secondary PD study), a PK study and three toxicology studies (a repeat dose toxicity study [local tolerance] and two mechanistic studies).

2.4.2. Pharmacology

Latanoprost acts on prostaglandin FP receptors as a selective agonist and is an ester pro-drug of PGF2α. Prostaglandin receptors are located on trabecular meshwork, ciliary muscle and sclera. Latanoprost acts to decrease intraocular pressure (IOP) by increasing the uveoscleral outflow.

As the primary pharmacology of the drug substance latanoprost is well characterised, the applicant performed a single non-GLP compliant comparative study to demonstrate the efficacy of the Catiolanze formulation in an NHP model of glaucoma. Glaucoma was induced by laser photocoagulation of the trabecular meshwork. The efficacy of the latanoprost cationic emulsion for reducing elevated IOP was confirmed and the IOP reduction was considered equivalent to that of the reference product Xalatan.

No information has been provided on the secondary pharmacodynamics of the active substance, latanoprost (i.e. pharmacological effects other than the primary therapeutic activity).

Xalatan solution contains the preservative benzalkonium chloride (BAK, 0.02%), which has been shown to negatively affect the ocular surface and thus there is a scientific justification for the development of a preservative-free latanoprost emulsion formulation. In the secondary pharmacology section, the applicant has presented a series of studies comparing latanoprost emulsion and BAK-containing Xalatan in in vitro and in vivo models of corneal wound healing, though these could more appropriately be considered supportive primary pharmacodynamic experiments. The results of these non-GLP studies are supportive of the scientific rationale for use of the Catiolanze formulation rather than Xalatan in situations where there is damage to the ocular surface. However, the data requirements to support clinical efficacy in the proposed OSD indication were not addressed by these data, and the applicant decided, upon request, to amend the indication to remove the mention of OSD.

No safety pharmacology studies have been performed with Catiolanze.

2.4.3. Pharmacokinetics

Bibliographic PK data for the active substance latanoprost are lacking but the pharmacokinetic profiles of Catiolanze and Xalatan were compared in a GLP-compliant PK study in New Zealand White rabbits. Following ocular instillation of both latanoprost formulations, the prodrug latanoprost was rapidly hydrolysed into latanoprost free acid and was not detectable in any of the evaluated ocular tissues.

Ocular tissue latanoprost free acid levels demonstrated that the prodrug latanoprost is better absorbed at early time points after the instillation of Xalatan when compared with Catiolanze, but no difference was evident between the formulations at later post-instillation time points in the cornea and ciliary body. These differences in PK profiles did not affect the efficacy in the primary pharmacodynamic study in monkeys, as IOP reductions were similar between the formulations. For both Catiolanze and Xalatan, latanoprost free acid was barely detectable 24 h post instillation in any of the evaluated ocular tissues, though a cumulative effect of daily dosing on IOP was noted in the PD study in monkeys.

The validation study (Study 480114) for the rabbit plasma latanoprost/latanoprost free acid LC-MS/MS assay does not meet the set acceptance criteria, which raises uncertainty regarding the accuracy of any measurements reported using this method. In addition, the plasma assay sample run (Study 480137) in the pharmacokinetic study (Study TP021) is invalid, although the representative chromatograms show that there were no peaks of latanoprost/free acid that could be distinguished from baseline and the calibration standards were valid, suggesting that all but one plasma sample were below the LLOQ. Although it has not been clearly demonstrated by these data, on the basis of this supportive information and the known PK of Latanoprost in Xalatan, it is considered plausible that minimal systemic exposure to latanoprost/ free acid occurred following ocular instillation of Catiolanze in rabbits.

2.4.4. Toxicology

The applicant has presented the results of a single, GLP-compliant repeat dose toxicity/local tolerance study comparing Catiolanze and the reference product Xalatan, which is acceptable for an application under article 10(3) of Directive 2001/83/EC.

In the repeat dose study in rabbits, following twice a day instillation over 28 days, minor transient conjunctival irritation (redness/ hyperaemia on palpebral and bulbar conjunctiva) was observed in all groups, though the incidence was lower in the Catiolanze group than in the Xalatan group. On gross necropsy, small holes were observed on the surface of the kidney and spleen in one Catiolanze-treated male rabbit and uterine congestion was observed in one Catiolanze-treated female. Changes in the epithelium (flattening) of the nasal fossae occurred with a greater frequency in Catiolanze-treated animals than in Xalatan-treated animals, although these findings occurred on both the treated and untreated side and no other irritation difference between Catiolanze and Xalatan was observed. Toxicokinetic analysis of plasma samples taken 15 min after the last instillation of Catiolanze or Xalatan on day 28 indicate that systemic exposure to latanoprost and latanoprost free acid were negligible.

The results of non-GLP exploratory toxicity studies appear to show reduced ocular toxicity (damage to the corneal epithelium, inflammatory infiltration, and apoptosis) with cationic emulsions containing CKC with or without latanoprost compared to other ocular preparations, in particular BAK-containing solutions. However, due to a number of caveats such as the lack of GLP compliance, these data are considered supportive only.

2.4.5. Ecotoxicity/environmental risk assessment

The applicant has provided a justification for not submitting ERA studies on the basis that latanoprost is already used in existing marketed products and no significant increase in environmental exposure is anticipated.

Therefore, Catiolanze is not expected to pose a risk to the environment.

2.4.6. Discussion on non-clinical aspects

An abridged non-clinical development programme has been performed in support of this hybrid MAA under Article 10(3) of Directive 2001/83/EC. The package consists of a primary pharmacodynamic (non-GLP) study, an ocular pharmacokinetics (GLP) study and 28-day (GLP) ocular toxicity study. In addition, the applicant has provided a number of exploratory (non-GLP) studies investigating ocular toxicity and the secondary effects of the cationic emulsion formulation in models of corneal damage.

Pharmacology

Latanoprost acts on prostaglandin FP receptors as a selective agonist and is an ester pro-drug of PGF2α. Prostaglandin receptors are located on trabecular meshwork, ciliary muscle and sclera. Latanoprost acts to decrease intraocular pressure (IOP) by increasing the uveoscleral outflow. The applicant performed a single non-GLP comparative pharmacodynamic study on the effect of Catiolanze and the reference product Xalatan in a monkey glaucoma model. The efficacy of the Catiolanze emulsion formulation in reducing elevated IOP was confirmed and there was no significant difference in the IOP reduction between either latanoprost formulation. The applicant also presented a series of studies comparing latanoprost emulsion and BAK-containing Xalatan in in vitro and in vivo models of corneal wound healing. The results of these non-GLP studies could be considered supportive of the scientific rationale for use of the Catiolanze formulation where there is damage to the ocular surface. However, the data requirements to support clinical efficacy in the proposed OSD indication were not addressed by these data (see Clinical section). No secondary pharmacology or safety pharmacology studies have been performed with Catiolanze. However, considering the difference in comparison to the originator is minimal with respect to the mechanism of action, no further data secondary pharmacology data were requested. In addition, wording regarding respiratory findings related to bronchoconstriction in monkeys reported in section 5.3 of the SmPC is consistent with the SmPC wording for the reference product Xalatan and is therefore acceptable for this hybrid application.

Pharmacokinetics

The pharmacokinetic profiles of Catiolanze and Xalatan were compared in a GLP-compliant PK study in New Zealand White rabbits (Tp021). Following ocular instillation of both latanoprost formulations, the prodrug latanoprost was rapidly hydrolysed into latanoprost free acid and was not detectable in any of the evaluated ocular tissues. Ocular tissue latanoprost free acid levels demonstrated that the prodrug latanoprost is better absorbed at early time points after the instillation of Xalatan when compared with Catiolanze, but no difference was evident between the formulations at later post-instillation time points in the cornea and ciliary body. These differences in PK profiles did not affect the efficacy in the primary pharmacodynamic study in monkeys, as IOP reductions were similar between the formulations.

Toxicology

A bibliographic overview on the toxicity of the active substance latanoprost has not been provided. However, wording in section 5.3 of the SmPC is consistent with the SmPC wording for the reference product Xalatan and is therefore acceptable for this hybrid application. The applicant has presented the results of a single, GLP-compliant repeat dose toxicity/ local tolerance study comparing Catiolanze and the reference product Xalatan, which is acceptable for an application under article 10(3) of Directive 2001/83/EC. Minor, transient conjunctival irritation (redness/hyperaemia on palpebral and bulbar conjunctiva) was observed in all groups following twice a day instillation over 28 days, though the incidence was lower in the Catiolanze group than in the Xalatan group. On gross necropsy, small holes on the surface of the kidney and spleen were observed in one Catiolanze-treated male rabbit and uterine congestion was observed in one Catiolanze-treated female, these findings were considered incidental. In addition, changes in the epithelium (flattening) of the nasal fossae occurred with a greater frequency in Catiolanze-treated animals than in Xalatan-treated animals but these findings

occurred on both the treated and untreated side and no other irritation difference between Catiolanze and Xalatan was observed. Toxicokinetic analysis of plasma samples taken 15 min after the last instillation of Catiolanze or Xalatan on day 28 indicate that systemic exposure to latanoprost and latanoprost free acid were negligible. The results of non-GLP exploratory toxicity studies appear to show reduced ocular toxicity (damage to the corneal epithelium, inflammatory infiltration, and apoptosis) with cationic emulsions containing CKC with or without latanoprost compared to other ocular preparations, in particular BAK-containing solutions. However, due to a number of caveats such as the lack of GLP compliance, these data are considered supportive only.

Environmental Risk Assessment

The applicant has provided a justification for not submitting ERA studies on the basis that latanoprost is already used in existing marketed products and no significant increase in environmental exposure is anticipated. Therefore, Catiolanze is not expected to pose a risk to the environment.

2.4.7. Conclusion on the non-clinical aspects

The abridged non-clinical package submitted in support of this hybrid application is considered acceptable. From a non-clinical perspective, the application is approvable.

2.5. Clinical aspects

2.5.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

2.5.2. Clinical pharmacology

2.5.2.1. Pharmacokinetics

No clinical pharmacokinetic studies were conducted with latanoprost 50 µg/mL eye drops, emulsion SD (single dose). The applicant refers to the clinical pharmacokinetic findings for the RefMP (Xalatan SmPC, 2022, the Xalatan Prescribing Information, 2020, and the Assessment Report for Xalatan and Associated names, CHMP, 2010) and two papers from published literature to support the clinical pharmacological profile of Latanoprost 50 µg/mL eye drops, emulsion SD. The applicant completed a non-clinical PK study in New Zealand White (NZW) rabbits (Study Tp021) to provide a scientific justification to the findings of efficacy for the RefMP to support the efficacy of Latanoprost 50 µg/mL eye drops, emulsion SD.

Absorption

Latanoprost (mw 432.58) is an isopropyl ester prodrug which per se is inactive but after hydrolysis to the acid of latanoprost becomes biologically active. The prodrug is well absorbed through the cornea and all drug that enters the aqueous humour is hydrolysed during the passage through the cornea.

Distribution

The distribution volume in humans is 0.16 ± 0.02 L/kg. The latanoprost acid can be measured in the aqueous humour 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 humour is reached about two hours after topical administration. After topical application in monkeys, latanoprost is distributed primarily in the anterior segment, the conjunctivae, and the eyelids. Only minute quantities of the drug reach the posterior segment.

From published literature by Ichhpujani et al., 31 patients undergoing enucleation for an intraocular tumour, the ocular distribution of 0.03% bimatoprost, 0.005% latanoprost and their acid hydrolysis products in aqueous humour, cornea, sclera, iris, and ciliary body at 1, 3, 6 and 12 h prior to surgery were investigated to understand concentration activity relationships. Latanoprost behaved as a prodrug entering the eyes via the corneal route. Levels of latanoprost acid were distributed as cornea>>aqueous humour>iris>sclera>ciliary body.

Metabolism and Elimination

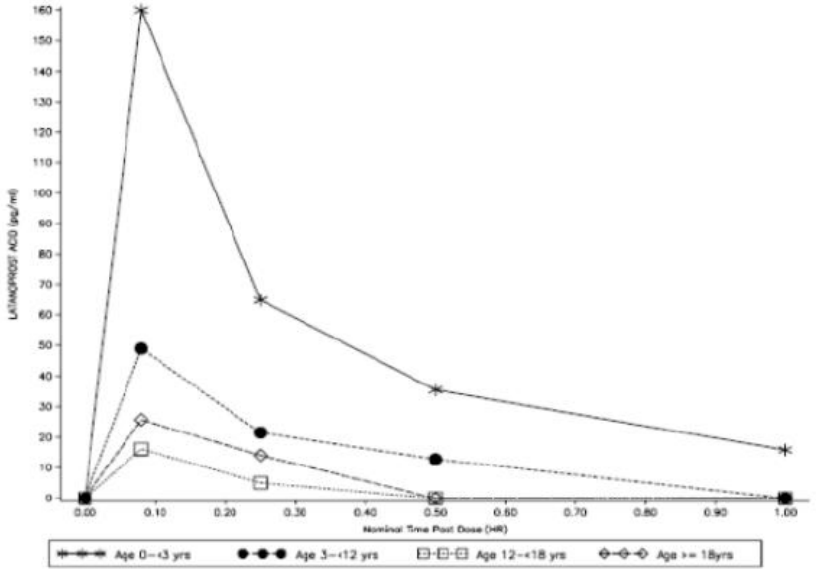
Latanoprost is an isopropyl ester prodrug which is hydrolysed in the cornea by esterases to become the biologically active acid. There is almost no metabolism of the acid of latanoprost in the eye. Metabolism occurs in the liver by fatty acid beta-oxidation. The main metabolites, the 1,2-dinor and 1,2,3,4-tetranor metabolites, exert no or only weak biological activity in animal studies and are excreted primarily in the urine via the kidneys. The elimination of the acid of latanoprost from human is rapid (half-life = 17 minutes). Systemic clearance is approx. 7 mL/min/kg. Approximately 88% of the administered dose is recovered in the urine after topical dosing.

Special populations

Children

A single open-label study of the systemic PK of latanoprost acid (Xalatan®) was undertaken in 47 male or female subjects (22 adults and 25 paediatric patients (from birth to < 18 years of age) with glaucoma or OHT for two weeks. The aim of the study was to evaluate the systemic exposure of latanoprost acid in paediatric patients administered with the adult dose of latanoprost 1.5µg/eye topically (1 drop of 0.005%). The paediatric subjects were subdivided by age range - 0 to <3yrs (n = 8), 3 to <12yrs (n = 10) and 12 to <18yrs – (n = 7). Subjects received latanoprost 50 µg/mL, one drop daily in each eye for a minimum of 2 weeks. None of the pre-dose samples contained detectable levels of latanoprost. The peak concentration following latanoprost (Cmax) was observed 5 minutes post dose across all age groups (Figure 2, Table 4). However, exposure was higher for 0 to <3 years age group. The slope of terminal elimination was similar across age groups.

Figure 2 **Latanoprost Acid Concentration-Time Plot (Median Values) Evaluable Pharmacokinetic Analysis Set**



Summary calculations have been calculated by setting concentration values below the lower limit of quantification to zero.

Table 4 **Summary of PK Parameters**

	Age group			
	0 - <3 years	3 to <12 years	12 to <18 years	≤18 years
N[a]	8	10	7	22
C_{max} (pg/mL)				
N[b]	7	9	6	17
Mean	140.4	67.5	24.3	29.2
CV%	46	81	65	43
Median	166	49	16.2	25.8
Range	32.6 – 214	14.7 – 167	11.0 – 49.7	10.8 – 53.3
Geometric mean (95% CI)	121 (81.1 – 181)	49.1 (34.5 – 6)9.9	20.8 (13.5 – 32.0)	26.7 (20.7 – 34.5)
T_{max} (min)				
N[b]	7	9	6	17
Median	5	5	5	5
Range	5 – 15	5 – 5	5-5	4-18
T_{last} (min)				
N[b]	7	9	6	17
Median	60	30	10	20
Range	5 – 60	5 – 30	5 – 15	5 – 30
AUC_{last} (pg/min/mL)				
N_b	7	9	6	17
Mean	3016	865	173	448
CV%	71	92	99	76
Median	2716	588	106	380
Range	81.5 – 6550	36.8 – 2220	27.5 – 420.0	27 – 1140
Geometric mean (95% CI)	1830 (799 – 4195)	439 (211 – 911)	99.7 (40.7 – 244)	296 (174 – 504)
$T_{1/2}$ (min)				
N[b]	5	5	0	4
Mean	20.1	12	-	20.5
CV%	24	29	-	35
Median	19.0	11.3	-	18.4
Range	14.9 – 28	9 – 17.3	-	14.3 – 30.8

CV% = Coefficient of variation, CI = confidence interval, min = minimum, CSR = Clinical Study Report
[a]Total number of subjects in the treatment group; [b]Number of subjects contributing to the mean; [c]None of the subjects had sufficient data to characterise the terminal elimination phase.
Summary calculations have been calculated by setting concentration values below the lower limit of quantification to zero.

No accumulation is expected to occur in paediatric patients since all subjects received latanoprost for at least four days prior to PK investigation and none of the pre-dose samples contained measurable plasma levels of latanoprost.

The median plasma elimination half-life of latanoprost acid was short (< 20 minutes), similar for paediatric and adult patients, and resulted in no accumulation of latanoprost acid in the systemic circulation under steady-state conditions.

Latanoprost acid systemic exposure was approximately 2-fold higher in younger children (3 to < 12-year-olds) and approximately 5 - 7-fold higher in the 0 to < 3 years old compared to adults. Although these substantial differences were transient and probably explained by the lower body weight and volume of distribution, an estimation of the safety margin was performed for this group of patients. The maximum tolerated dose for the ocular route was estimated to be 11 µg/kg, approximately 275-fold higher than the approved ophthalmic dose. Consequently, the safety margin in adult patients is approximately 275 as well. Taking into account the higher systemic exposure (5 to 7-fold higher) evidenced in children of less than 3 years old, the safety margin in this younger subgroup of patients was estimated to be 40 to 55-fold higher, approximately. Therefore, the observed higher exposure to latanoprost in the youngest age group is unlikely to have negative consequences on systemic tolerability to the treatment with latanoprost.

The duration of systemic exposure assessed by the time to last measurable concentration (tmax) was brief following a once-daily dose administration regimen. Plasma latanoprost acid concentrations were below the lower limit of quantitation (LLOQ) of the assay by 60 minutes post-dose in all group ages except the 0 to 3yrs group.

The relationship between Cmax values and body weight as well as the inter subject variability seemed to indicate that exposure to latanoprost acid trended with body weight. As body weight decreased plasma latanoprost acid concentrations tended to increase.

Pharmacokinetic interaction studies

In vitro studies show that precipitation occurs when latanoprost (Xalatan®) is mixed with thiomersal). Therefore, if such drugs are used there should be an interval of at least 5 minutes between applications. The Summary of Product Characteristics (SmPC) of the RefMP Xalatan® includes the following statements:

Section 4.5 Interaction with other medicinal products and other forms of interaction

Definitive drug interaction data are not available. There have been reports of paradoxical elevations in IOP following the concomitant ophthalmic administration of two prostaglandin analogues. Therefore, the use of two or more prostaglandins, prostaglandin analogues or prostaglandin derivatives is not recommended.

2.5.2.2. Pharmacodynamics

No clinical pharmacokinetic studies were conducted with latanoprost 50 µg/mL eye drops, emulsion SD (single dose). The applicant refers to the clinical pharmacokinetic findings for the RefMP (Xalatan SmPC, 2022, and the Xalatan Prescribing Information, 2020) to support the clinical pharmacological profile of Latanoprost 50 µg/mL eye drops, emulsion SD. The applicant completed a non-clinical PD study in glaucomatous monkeys (Study PCS09B001) to provide a scientific justification to refer to the findings of efficacy for the RefMP to support the efficacy of latanoprost 50 µg/mL eye drops, emulsion SD. In addition, a clinical Phase III study (Study 0130A01SA) has been conducted to show that latanoprost 50 µg/mL eye drops, emulsion SD is therapeutically non-inferior to the RefMP (Xalatan®)

in terms of the reduction in IOP for peak and trough at Week 12. However, the provided non-clinical pharmacokinetic data does not account for the observed differences in efficacy (i.e higher efficacy seen in the Catiolanze group at Week 12) and the fact that these differences are observed at Week 12 and not at Week 4.

Mechanism of action

Latanoprost, a prostaglandin F2α analogue, is a selective prostanoid FP receptor agonist which reduces the IOP by increasing the outflow of aqueous humour. Studies in animals and man indicate that the main mechanism of action is increased uveoscleral outflow, although some increase in outflow facility (decrease in outflow resistance) has been reported in man.

Primary and Secondary pharmacology

Reduction of the IOP in man starts about three to four hours after administration and maximum effect is reached after eight to twelve hours. Pressure reduction is maintained for at least 24 hours (Xalatan SmPC, 2022).

Pivotal studies have demonstrated that latanoprost is effective as monotherapy. A summary of 16 meta-analyses of clinical trials that included latanoprost monotherapy for the treatment of OAG or OHT. Meta-analyses showed consistent trends. Treatment with latanoprost monotherapy induced inductions in IOP of between 3.6-9.28 mmHg at 1 month and of 4.72-11 at 3 months. The observed percentage reduction in IOP ranged from 14.90-38.9%. 24.49-33.46% reduction in IOP was sustained through 16 months of treatment. A meta-regression analysis using data from 73 studies (11,519 patients) over 18 months of treatment found that after 3 months of treatment with latanoprost monotherapy, 71% of patients achieved a $\geqslant$20% reduction in IOP and 84% had a an absolute IOP of <20 mmHg (Orme et al. 2010).

Table 1: Summary of meta-analyses reporting change in IOP after treatment with latanoprost

Author	Years studied	Number of articles included	Age	Total number of patients	Treatment period	Mean reduction or % IOP lowering effect
(Lee *et al.* 2022)	Until April 2021	4	≥18 years	635 (latanoprost)	Week 2	-5.62 to -7.29 mmHg
					Week 4-6	-5.88 to -7.55 mmHg
(Clement Freiberg *et al.* 2022)	Until 11 Dec 2020	17	≥18 years	4953	<6 months	-6.62 mmHg (95% CI -5.67 to -7.57)
(Harasymowycz *et al.* 2022)	2014-2020	106	NR	18,523	3 months	-4.72 mmHg (-5.39 to -4.04)
(Steensberg *et al.* 2020)	1995-2019	6	NR	598	3-16 weeks	-5.4 to -8.0 mmHg
(Tang *et al.* 2019)	2000-2018	17	Range of means 52-68	2433	1 month	-3.6 to -9.28 mmHg
					3 months	-4.8 to -11 mmHg
					6 months	-5.4 to -10.6 mmHg
(Li *et al.* 2016)	2009-2014	114	NR	20,275	3 months	-4.85 mmHg
(Lin *et al.* 2014)	1965-2013	32	Range of means 47-75	4834	1 month	-7.8 mmHg
(Cheng *et al.* 2009)	Until April 2008	14	NR	2149	1 month	29.59%
					2 months	28.38%
					3 months	24.83%
					6 months	30.62%
(Cheng *et al.* 2008)	Until Feb 2008	13	Range of means 52-71	1302	1 month	27.59 to 38.90%
					3 months	26.11 to 33.46%
					6 months	22.39 to 31.44%
(Aptel *et al.* 2008)	Until July 2006	8	≥18 years	1610	16 months	24.49% to 33.46%
(Hodge *et al.* 2008)	Until 2006	9	NR	1131	3 months	-5.80 to -8.90 mmHg
(Stewart *et al.* 2008)	Until 2007	11	NR	386	24 hours	24%
(Fung *et al.* 2007)	1966-2006	15	Adults	1784	<6 months	-3.00 to -6.70 mmHg
(Li *et al.* 2006)	Until Aug 2005	12	Range of means 51.9–67.7	3048	2 weeks to 12 months	14.90% to 18.30%
					>8 months	-5.70 to -9.50 mmHg
(Zhang *et al.* 2001)	1966-2000	11	Range of means 46-67	1256	1 month	28.7% (SE 2.3)
					2 months	27.3% (SE 4.0)
					3 months	31.2% (SE 2.3)
					6 months	29.9% (SE 2.6)
					12 months	24.1 (SE 4.6)
(Einarson *et al.* 2000)	1992-1999	8		23152	3 months	-8.4 mmHg (33%)
					6 months	-8.0 mmHg (NR)

IOP, intra-ocular pressure; NR, not reported; SE, standard error

In addition, clinical trials investigating combination use have been performed. These include studies that show that latanoprost is effective in combination with beta-adrenergic antagonists (timolol). Short-term (one or two weeks) studies suggest that the effect of latanoprost is additive in combination with adrenergic agonists (dipivalyl epinephrine), oral carbonic anhydrase inhibitors (acetazolamide) and at least partly additive with cholinergic agonists [pilocarpine].

Clinical trials have shown that latanoprost has no significant effect on the production of aqueous humour. Latanoprost has not been found to have any effect on the blood-aqueous barrier. Latanoprost has no or negligible effects on the intraocular blood circulation when used at the clinical dose and studied in monkeys. However, mild to moderate conjunctival or episcleral hyperaemia may occur during topical treatment. Chronic treatment with latanoprost in monkey eyes, which had undergone

extracapsular lens extraction, did not affect the retinal blood vessels as determined by fluorescein angiography.

Latanoprost has not induced fluorescein leakage in the posterior segment of pseudophakic human eyes during short-term treatment. Latanoprost in clinical doses has not been found to have any significant pharmacological effects on the cardiovascular or respiratory system.

2.5.3. Discussion on clinical pharmacology

No clinical pharmacology studies were conducted with latanoprost 50 µg/mL eye drops, emulsion SDCatiolanze (single dose). The justification for the lack of clinical pharmacodynamic studies with Catiolanze is considered acceptable for the RefMP indications, in accordance with a Note for guidance on the clinical requirements for locally acting products containing known active constituents (CPMP/EWP/239/95 final), which indicates that animal models may be used to demonstrate therapeutic equivalence provided that the studies are adequately validated and the relevance of the model is justified. The applicant also received Scientific Advice from the CHMP in August 2009, where the CHMP indicated that the proposed non-clinical package and a single clinical non-inferiority study would be sufficient to support an identical indication to the RefMP. The acceptability of non-clinical data in lieu of clinical pharmacology data for an identical RefMP indication is acceptable.

The applicant refers to the clinical pharmacology findings for the RefMP to support the clinical pharmacological profile of Catiolanze. To provide a justification for the reliance on the available data for the RefMP, non-clinical studies were conducted to support establishing therapeutic equivalence of Catiolanze with the RefMP. The applicant refers to the clinical pharmacology findings for the RefMP and eight papers from the published literature to support the clinical pharmacology profile of Catiolanze.

The applicant completed a non-clinical PK study in New Zealand White (NZW) rabbits (Study Tp021) to provide a scientific justification to the findings of efficacy for the RefMP to support the efficacy of Catiolanze. Study Tp021 conducted in NZW rabbits shows at early timepoints, Catiolanze results in lower local tissue concentrations compared to Xalatan®. However, for timepoints beyond one hour post instillation, the concentrations were similar for both formulations. Thus, except for early timepoints, the local target tissue concentrations for Catiolanze and Xalatan® are comparable. Exposure in target tissues is slightly lower than after Xalatan® administration. Systemic exposure is minimal for both formulations.

The applicant completed a non-clinical PD study in glaucomatous monkeys (Study PCS09B001), and a clinical Phase III study (Study 0130A01SA) to provide a scientific justification for the findings of efficacy for the RefMP to support the efficacy of Catiolanze. Study PCS09B001 conducted in the monkey glaucomatous eye model showed that the PD profile of Catiolanze is similar to Xalatan. Study 0130A01SA conducted in patients with Open-Angle Glaucoma or Ocular Hypertension showed that the primary efficacy endpoint of non-inferiority was achieved, however the provided non-clinical pharmacokinetic data does not account for the observed differences in efficacy (i.e higher efficacy seen in the Catiolanze group at Week 12) and the fact that these differences are observed at Week 12 and not at Week 4.

2.5.4. Conclusions on clinical pharmacology

The dossier is approvable from a clinical pharmacology perspective.

2.5.5. Clinical efficacy

Latanoprost is a prostaglandin 2α analogue that acts as a selective prostanoid FP receptor agonist that reduces IOP by increasing uveo-scleral outflow. Latanoprost, marketed as Xalatan®, has been approved in for the treatment of open angle glaucoma (OAG) and ocular hypertension (OHT) for more than two decades and in over 130 countries. Xalatan was approved for the treatment of paediatric glaucoma in 2010.

Santen Oy (the applicant) is submitting an article 10(3) Marketing Authorisation Application (MAA) for a new formulation of latanoprost; Catiolanze, using the marketed product Xalatan® (50 µg/mL eye drops, solution) as the reference medicinal product (RefMP) to support the indication for reduction in IOP.

In addition (**as it is claimed by the applicant)** to reducing IOP, latanoprost 50 µg/mL eye drops, emulsion SD was designed to offer significant clinical benefit over the RefMP:

1) Xalatan® contains the preservative benzalkonium chloride (BAK) that is known to cause ocular surface inflammation and damage (Baudouin et al., 2021) in a high proportion of patients. The new formulation of Latanoprost 50 µg/mL eye drops, emulsion SD is preservative-free;

2) Catiolanze is formulated with Novasorb® technology-based cationic oil-in-water emulsion eye drops. This same emulsion technology is currently licensed for use as Cationorm® for the management of moderate signs and symptoms of dry eye disease, Cationorm® PRO/Plus for ocular allergy, Ikervis® for severe keratitis in dry eye disease, and Verkazia® for vernal keratoconjunctivitis.

Latanoprost 50 µg/mL eye drops, emulsion SD is thus intended for topical use for the reduction of IOP in patients with OAG or OHT, with the additional benefit of reducing the risk of developing or exacerbating OSD.

To support the development of Catiolanze, the applicant has conducted three clinical studies: two Phase II clinical trials in patients with OAG or OHT and OSD; and one pivotal Phase III, randomised, active-controlled, non-inferiority study, which compared Catiolanze with the RefMP Xalatan® in patients with OAG or OHT with or without OSD for three months, followed by a 12-month open label safety extension. All three studies evaluated the efficacy and safety of Catiolanze in terms of reducing both IOP and the signs and symptoms of OSD.

A summary of the clinical trials conducted with of Catiolanze is provided in table below.

Table 2: Summary of clinical studies performed with Latanoprost 50 µg/ml eye drops, emulsion SD

Study Number (country)	Study Design	Control	Objective	Duration	Population	Study groups	Regimen and dose
Phase II studies							
NVG09E115 (France)	Single arm open label, multicentre	None	Efficacy and safety of Latanoprost 50 µg/mL eye drops, emulsion *SD* after switching from Xalatan®	3 months	Patients with OAG or OHT and with mild-moderate OSD	Latanoprost 50 µg/mL eye drops, emulsion *SD*: 22	50 µg/mL, 1 drop in the evening, daily
NVG10E118 (United States)	Two arm, randomised (1:1), multicentre, investigator masked, active control	sofZia®-preserved Travatan Z®	Efficacy and safety of Latanoprost 50 µg/mL eye drops, emulsion *SD* compared to Travatan Z®	3 months	Patients with OAG or OHT and OSD	Latanoprost 50 µg/mL eye drops, emulsion *SD*: 51 Control: 54	50 µg/mL, 1 drop in the evening, daily
Phase III study							
0130A01SA (Austria, Belgium, Estonia, Finland, France, Germany, Italy, Latvia, Poland, Spain, United Kingdom, Russia, South Korea)	Two arm, multicentre, investigator masked, randomised (1:1), active controlled study with open label extension	BAK-preserved Xalatan®	Non-inferiority of Latanoprost 50 µg/mL eye drops, emulsion *SD* to Xalatan®	3 months with 12 months safety extension	Patients with OAG or OHT with or without OSD	Period 1 Latanoprost 50 µg/mL eye drops, emulsion *SD*: 193 Control:193 Period 2 Latanoprost 50 µg/mL eye drops, emulsion *SD*: 137	50 µg/mL, 1 drop in the evening, daily investigator masked (Period 1) and 12 months open label (Period 2)

BAK, benzalkonium chloride; OAG, open angle glaucoma; OHT, ocular hypertension; OSD, Ocular surface disease

In relation to the clinical development program the following was noted:

- A comparative PK study between Catiolanze and the RefMP was not considered necessary (or ethical) due to the low systemic absorption of this locally applied product. Low systemic absorption was confirmed in a non-clinical PK study (study Tp021), where latanoprost and latanoprost free acid plasma concentrations were below the lower limit of quantitation (30 pg/mL) in all animals and at all time-points.
- Efficacy and safety in the paediatric population was not specifically assessed. However, the RefMP is approved for use in the paediatric population and the CKC-containing cationic emulsion has been approved for use in children as Verkazia. Extrapolation of efficacy and safety data to the new product Catiolanze can be justified based on demonstration of non-inferiority to Xalatan and on substantial clinical experience with the Novasorb emulsion, which does not contain a pharmacologically active moiety.

2.5.5.1. Dose response study(ies)

No formal dose finding study was performed. The applicant indicated that the selection of dose was based primarily on the prescribing information for latanoprost ophthalmic solution 0.005% (Xalatan), in addition to supporting data from preclinical studies of Catiolanze that support its pharmacokinetic and pharmacodynamic equivalence to Xalatan. Effectiveness of a single daily dose of Catiolanze in reducing IOP was also investigated in Phase II studies (NVG10E118 and NVG09E115).

2.5.5.2. Main study(ies)

Study 0130A01SA

A Phase III, Multinational, Multicentre, Investigator-Masked, Randomised, Active- Controlled Trial, comparing the efficacy and safety of Catiolanze with Xalatan® in Patients with Open-Angle Glaucoma

or Ocular Hypertension over a 3-Month period, followed by a 12-Month Follow-Up with Open-Label Catiolanze Treatment.

Methods

This Phase III study was a prospective, interventional, multinational, multi-centre investigator-masked, randomised, active-controlled trial to demonstrate the non-inferior IOP-reducing effect of Catiolanze (latanoprost 50 µg/ml preservative-free eye drops emulsion) compared to Xalatan (latanoprost 50 µg/ml BAK-preserved eye drops emulsion) over a 12-week treatment period (Period 1) in patients with OHT or OAG.

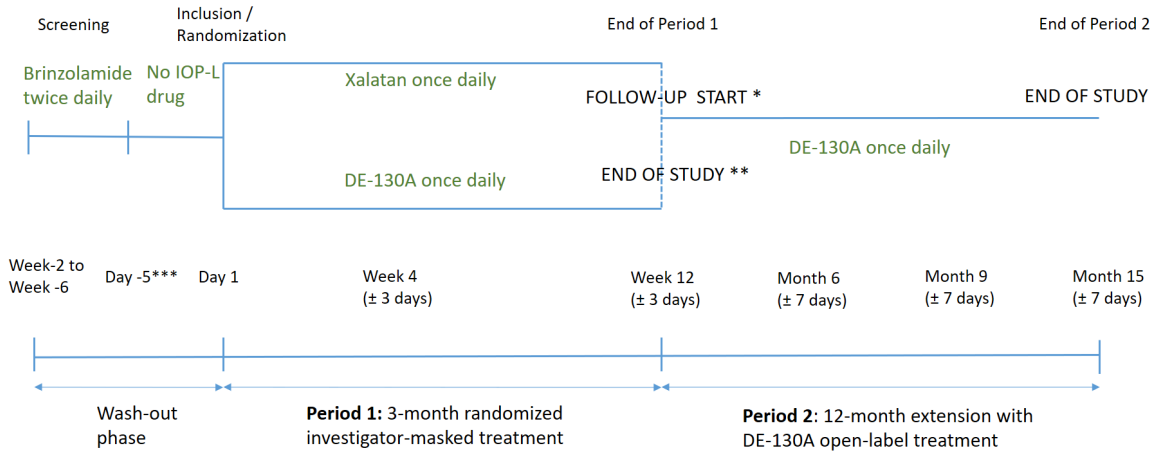
At the end of the investigator-masked period 1, a subgroup of patients who completed the Week 12 visit and agreed to participate in the safety follow-up entered the open-label period and received Catiolanze once daily for an additional 12 months (Period 2).

After a washout phase (5 days to 6 weeks) depending on previous IOP lowering medication used, patients were randomised in a 1:1 ratio to receive either:

- **Test regimen** - Catiolanze (latanoprost 50 µg/ml preservative-free eye drops emulsion) once daily at 9 PM for 12-week duration of the investigator-masked treatment period.
- **Control regimen -** Xalatan® group (latanoprost 50 µg/ml BAK-preserved eye drops solution once daily at 9 PM for 12-week duration of the investigator-masked treatment period.

The study duration (including the washout period) was up to 16 months, and patients attended up to 6scheduled visits after the Screening visit.

Figure 2: Study Design and Schedule of Assessments



IOP-L drug: intraocular pressure-lowering drug

** Start of the open-label Catiolanze 12-month safety follow-up for the first 130 patients who completed their Week 12 visit and*

some patients enrolled in Belgium, and who agreed to participate in the open-label period of the study.

*** End of study for patients who do not participate in the open-label period of the study.*

**** Brinzolamide will be stopped 5 days before randomisation (6 to 7 days if over the weekend). At Day 1, if IOP is <22 mmHg, the wash-out period can be extended and the IOP should be re-assessed two to three days after the first measurement.*

If the IOP is still < 22 mmHg at the second measurement, a third assessment should be performed two to three days after the

second measurement. If the IOP is still < 22 mmHg at the third measurement, the patient cannot be randomized in the study.

Washout Phase

After the signing of the informed consent and upon completion of the screening visit, all eligible study participants underwent a washout period.

Prior therapies for OAG or IOP were to be discontinued during a washout phase of at least 5 days and up to 6 weeks. The duration of the washout phase was assigned based on the IOP lowering medications used at the screening visit as follows:

1. Prostaglandin analogues = 4 weeks
2. Topical beta blockers ≥ 3 weeks and ≤ 4 weeks
3. Topical carbonic anhydrase inhibitors ≥ 5 days and ≤ 4 weeks
4. All other IOP lowering medication ≥ 2 weeks and ≤ 4 weeks

During the washout phase, topical IOP-lowering medication were replaced by brinzolamide* (Azopt®) one drop twice daily. Azopt was provided by the Sponsor. Brinzolamide was stopped 5 days (6 to 7 days if over the weekend) before randomisation at the baseline visit.

Patients already receiving brinzolamide prior to the screening visit stopped their treatment for a 5-day washout phase before randomisation.

The purpose of the washout phase was to select patients for study inclusion with a post-washout peak IOP ≥ 22 mmHg and ≤ 32 mmHg (defined as the baseline visit [Day 1] mean IOP at 9:00 am [±1 hour], in at least one eye.

The baseline visit (Day 1) was conducted at the end of the washout phase. Patients who met the inclusion criteria for IOP ≥ 22 mmHg and ≤ 32 mmHg [defined by a mean IOP at 9:00 am (±1 hour)], in at least one eye, were randomised in 1:1 ratio to receive either Catiolanze or Xalatan® (one drop once daily in the evening) for Period 1 of the study.

BASELINE VISIT

The baseline visit (Day 1) was when the patient was randomised. If an endpoint was not measured at the Day 1 baseline visit, the nearest data prior to the first dosing day was defined as the baseline. Patients who meet the inclusion criteria for IOP ≥ 22 mmHg and ≤ 32 mmHg [defined by a mean IOP at 9:00 am (±1 hour)] in at least one eye, were randomised in 1:1 ratio to receive either Catiolanze or Xalatan (one drop once daily in the evening) for Period 1 of the study.

Period 1: study treatment period

At the baseline visit (Day 1), patients were instructed to instil one drop of the investigator-masked study treatment once daily in the affected eye(s) (unilateral or bilateral OHT/OAG), and they were scheduled for two additional study visits [Week 4 (± 3 days), Week 12 (± 3 days)] to assess peak and trough IOPsat 9:00 am (±1 hour) and 4:00 pm (±1 hour), respectively.

Period 2: follow-up period with open-label treatment with Catiolanze

At Week 12 visit, patients entering Period 2 started 12-months of open-label Catiolanze treatment to assess the safety and tolerability of Catiolanze:

During Period 2, three additional study visits [Month 6 (± 7days), Month 9 (± 7 days), and Month 15 (± 7 days)] were scheduled to measure morning IOP at 9:00 am (± 1 hour)].

Study Participants

Main inclusion criteria:

- Male or female, 18 years of age or older
- Diagnosis of OAG (primary open angle glaucoma, pseudo exfoliative glaucoma, or pigmentary glaucoma), or OHT in eligible eye(s) currently on monotherapy. Unilateral OAG, or OHT was permissible as long as the physician did not anticipate significant IOP changes to the fellow eye that would require treatment during the duration of the study
- Current treatment with monotherapy for OAG or OHT with a controlled IOP ≤ 18 mmHg in each eye (pre-washout)
- Stable visual field (based on at least two visual fields available within the last 18 months prior to screening, including one in the last 6 months; a visual field test was performed at screening if not already performed within the last 6 months prior to screening) in each eye. If historical visual fields were not available within the last 18 months prior to screening, but at least two optical coherence tomography (OCT) scans were available, including one in the last 6 months and are stable, the patient could be enrolled in the study if a visual field test was also performed at screening and showed no defect or only an early visual field loss in either eye (mean deviation lesser than -6 dB)
- Post-washout IOP ≥ 22 mmHg in at least one eye (defined at baseline visit [Day 1] by IOP measurement at both 9:00 am ± 1 hour and 4:00 pm ± 1 hour)
- If IOP was <22 mmHg, the washout phase could be extended and the IOP had to be re-assessed two to three days after the first measurement
- If the IOP was still < 22 mmHg at the second measurement, a third assessment had to be performed two to three days after the second measurement
- If the IOP was still < 22 mmHg at the third measurement, the patient could not be randomised in the study
- Post-washout IOP ≤ 32 mmHg (defined at baseline visit [Day 1] by IOP measurement at both 9:00 am ± 1 hour and 4:00 pm ± 1 hour) in both eyes
- Ability to discontinue their current topical IOP-lowering medication for the required washout period. Washout periods were as follows;
    - Prostaglandin analogues = 4 weeks
    - Topical beta blockers ≥ 3 weeks and ≤ 4 weeks
    - Topical carbonic anhydrase inhibitors ≥ 5 days and ≤ 4 weeks
    - All other IOP lowering medication ≥ 2 weeks and ≤ 4 weeks
- BCDVA Snellen score of 20/100 or better in each eye

Main exclusion criteria

- Any form of glaucoma other than primary open angle glaucoma, pseudo exfoliative glaucoma, and pigmentary glaucoma in either eye
- IOP at any time point during the Screening or Baseline visits (Visits 1 or 2) of > 32 mmHg in either eye
- Current treatment for glaucoma with a fixed-combination therapy or more than one drug in either eye or with an oral drug within 6 months prior to screening
- Corneal abnormalities that would interfere with accurate IOP readings with an applanation tonometer in either eye
- Central corneal thickness ≤ 480 µm or ≥ 600 µm in either eye (historical data or at the screening visit)
- Significant visual field loss (absolute defect in the 10° central point or mean deviation worse than -12 dB) or progressive field loss during the year before screening in either
- Significant optic nerve abnormality, other than glaucomatous abnormalities in the opinion of the investigator as determined by ophthalmoscopy in either eye
- Significant changes of the optic neuropathy (e.g., increase cupping since the last examination, optic nerve haemorrhage) in either eye
- Inability to visualise the patient's optic nerve in either eye
- Gonioscopy consistent with potential angle closure glaucoma in either eye
- Patients with severe blepharitis and/or Meibomian Gland Disease (MGD). Patients enrolled with mild to moderate blepharitis and/or MGD were treated as appropriate during the study in either eye
- Use of oral or topical ophthalmic steroid within the past 14 days from screening date, or anticipated need for ocular steroid treatment during the study in either eye
- Use of intravitreal or peribulbar injection of depot steroid or placement of an intravitreal steroid implant within the past 3 months from screening date in either eye.
- Known hypersensitivity to sulfonamides, severe renal impairment or hyperchloraemic acidosis.
- Active or expected ocular allergy during period 1
- Any active ocular disease (e.g. uveitis, ocular infection, severe dry eye with CFS grade 4 or more on the modified Oxford scale) in either eye. Patients might have mild cataracts, age-related maculopathy or background diabetic retinopathy if, in the opinion of the Investigator, it would not interfere with the conduct of the study
- Intraocular surgery within 6 months prior to screening in either eye
- Past history of any filtering surgery for glaucoma in either eye
- Refractive surgery of any type within 1 year prior to screening in either eye
- Uncontrolled systemic disease of any type
- Anticipated alteration in chronic therapy with or introduction of agents known to have a substantial effect on IOP (e.g., α-adrenergic agonists, β-adrenergic antagonists, calcium channel blockers, ACE inhibitors and/or angiotensin II receptor blockers), unless the patient

and the medication dosage had been stable for three months prior to the screening visit and the dosage was not expected to change during the study

- Anticipated change in dosage of or introduction of new medications for chronic cardiac, pulmonary or hypertensive conditions

Treatments

Investigational medicinal product

Catiolanze (Santen OY) (latanoprost ophthalmic emulsion 0.005%) was supplied in a single-dose sterile container. Each single-dose container is filled with 0.3 mL of the eye drop emulsion, containing 0.015mg latanoprost. Each drop of Catiolanze contains 1.5 µg of latanoprost, each single dose container is sufficient for both eyes. The excipients include medium chain triglycerides, cetalkonium chloride, polysorbate 80, glycerol and water for injection. Catiolanze must be stored below 30°C and must not be frozen.

Comparator

Xalatan® (Pfizer) (latanoprost ophthalmic solution 0.005%) was supplied as a clear, isotonic, buffered, preserved colourless solution as a 2.5 mL solution in a 5-mL dropper container. Each drop of Xalatan contains 1.5 µg of latanoprost.

The excipients include sodium chloride, BAK 0.02%, sodium dihydrogen phosphate monohydrate, anhydrous disodium phosphate, water for injections. Xalatan® must not be stored above 25°C and after opening of container, used within four weeks.

Other treatment provided during the study: Azopt (Novartis) was provided to patients for the wash out phase prior to the baseline visit (Day 1). The active substance of Azopt® is brinzolamide (10 mg/ml).

Patients already receiving brinzolamide prior to screening visit will have to stop their treatment for a 5-day washout.

Dose selection

The selection of dose was based primarily on the prescribing information for latanoprost ophthalmic solution 0.005% (Xalatan), in addition to supporting data from preclinical studies of Catiolanze that support its pharmacokinetic and pharmacodynamic equivalence to Xalatan® as described in Module IV.

Effectiveness of a single daily dose of Catiolanze in reducing IOP was also demonstrated in Phase II studies (NVG10E118 and NVG09E115).

Timing of the dose

The selection of the timing of the dose was based primarily on the prescribing information for latanoprost ophthalmic solution 0.005% (Xalatan®), which is dosed 1 drop in the affected eye(s) once daily in the evening, in addition to supporting data from preclinical studies of Catiolanze that support its pharmacokinetic and pharmacodynamic equivalence to Xalatan® as described in Module IV.

Subjects were instructed not to use artificial tears for 30 minutes prior to or after dosing. Timing of dosing in relation to meals was not specified.

Prior and concomitant therapy

This study included patients who had received prior medications including prostaglandin analogues, topical β-blockers, topical carbonic anhydrase inhibitor, and all other IOP lowering medication.

Appropriate washout period of up to 6 weeks were assigned before the study.

Prohibited concomitant therapy

Concomitant therapies included any treatment or medication given concurrently with the study medication. The following concomitant medication(s)/treatment(s) were prohibited during study participation:

- Use of any artificial tears containing preservative
- Use of preservative free artificial tears outside the SmPC recommended regimen
- Use of Cationorm®
- Use of any topical ocular treatments other than the study medication except preservative free artificial tears used according to the SmPC recommended regimen (but artificial tears usage should remain stable during the course of the study)
- Any refractive surgery (LASIK, LASEK, PRK, etc.) during the course of the study.

Allowed concomitant therapy

In addition to the study medication, patients were allowed to use unpreserved artificial tears to improve their dry eye symptoms, if needed. Preservative free artificial tears were to be used according to the Summary of Product Characteristics (SmPC) recommended regimen. Patients were instructed not to use artificial tears within 30 minutes before or after use of the study medication and within two hours before a scheduled study visit.

Objectives

Outcomes/endpoints

Primary objectives

The primary objective of the study was to demonstrate that the IOP reducing effect of Catiolanze (latanoprost 50 µg/ml preservative-free eye drops emulsion) **was non-inferior to that of Xalatan**® (latanoprost 50 µg/ml BAK-preserved eye drops solution), in patients with OAG or OHT at Week 12 without using any rescue medication(s).

Secondary objectives

The secondary objectives were as follows:

- To compare the effect on improving OSD signs and symptoms between treatment groups over 3 months (Period 1)
- To estimate the effect of Catiolanze on OSD signs and symptoms up to 15 months (Periods 1 & 2)
- To compare the efficacy on IOP reduction between treatment groups over 3 months (Period 1)
- To estimate the effect of Catiolanze on IOP up to 15 months (Periods 1 & 2)
- To estimate the local ocular tolerance and systemic safety of the two treatments over 3 months (Period 1)
- To estimate the local ocular tolerance and systemic safety of Catiolanze up to 15 months (Periods 1 & 2)

Primary Endpoint

The primary efficacy endpoint was the **change from baseline** in peak (9:00 am ± 1 hour) and trough (4:00 pm ± 1 hour) IOPs, respectively, at Week 12 between the two treatment groups in the study eye.

Secondary Endpoints

The key secondary endpoints were:

- Change from baseline in CFS score in the study eye at Week 12 in patients with baseline CFS ≥ 1.
- Change from baseline in OSD symptom score (average of 3 symptoms: dry eye sensation, blurred/poor vision, and burning/stinging/itching) in the study eye at Week 12 in patients with baseline symptom average score >0.

Other secondary efficacy endpoints were:

OSD related endpoints:

- CFS in the study eye at Week 4 in patients with baseline CFS ≥ 1
- TFBUT in the study eye at Week 4 and Week 12 in patients with baseline TFBUT ≤ 10.
- Conjunctival hyperaemia (measured by slit lamp scored using the photographic scale derived from McMonnies scale [1 to 6]) in the study eye at Week 4, Week 12.
- CFS in the study eye at Week 4 and Week 12 in patients with baseline CFS ≥ 1.
- Dry eye sensation symptom in the study eye at Week 4 and Week 12
- Blurred/poor vision symptom in the study eye at Week 4 and Week 12
- Burning/stinging/itching symptom in the study eye at Week 4 and Week 12
- Slit lamp examination (Meibomian gland dysfunction, conjunctival chemosis, lids and tear film debris) in the study eye at Week 4 and Week 12
- CFS in the study eye at Month 6, Month 9 and Month 15/early termination in patients with

baseline CFS ≥ 1

- TFBUT in the study eye at Month 6, Month 9 and Month 15/early termination in patients with baseline TFBUT ≤ 10
- Conjunctival hyperaemia (measured by slit lamp scored using the photographic scale derived from McMonnies scale [1 to 6]) in the study eye at Month 6, Month 9 and Month 15/early termination
- CFS in the study eye at Month 6, Month 9 and Month 15/early termination in patients with baseline CFS ≥ 1
- Dry eye sensation symptom in the study eye at Month 6, Month 9 and Month 15/early Termination
- Blurred/poor vision symptom in the study eye at Month 6, Month 9 and Month 15/earl termination
- Burning/stinging/itching symptom in the study eye at Month 6, Month 9 and Month 15/early termination
- Slit lamp examination (Meibomian gland dysfunction, conjunctival chemosis, lids and tear fil debris) in the study eye at Month 6, Month 9 and Month 15/early termination

IOP related endpoints:

- Change from baseline in mean diurnal IOP in the study eye at Week 12
- Change from baseline in peak, trough, and mean diurnal IOPs in the study eye at Week 4
- Peak, trough and mean diurnal IOP response in the study eye at Week 4 and Week 12:
- IOP 20% response (reduction in mean IOP of ≥ 20% from Baseline at the specified follow-up visit)
- IOP 25% response (reduction in mean IOP of ≥ 25% from Baseline at the specified follow-up visit)
- IOP 30% response (reduction in mean IOP of ≥ 30% from Baseline at the specified follow-up visit)
- IOP < 18 mmHg response (mean IOP < 18 mmHg at the specified follow-up visit)
- Morning (9:00 am ± 1 hour) IOP in the study eye of patients treated with Catiolanze at Month 6, Month 9, Month 15/early termination (Period 2) and change from baseline at each Period 2 visit.

Other endpoints:

- Patient global rating of treatment at Month 15/early termination and Week 12.
- Glaucoma Quality of Life-15 scores at baseline visit, Week 12, and Month 15/early termination visits.

Safety and Tolerability Endpoints

In the Safety population, at all visits and for each treatment (Period 1) and for the Open-Label population for Catiolanze at all visits (Period 2 and Periods 1 & 2 combined), safety and tolerability endpoints were:

- The incidence and severity of ocular and systemic adverse events

- Best-corrected distance visual acuity (BCDVA)
- Slit lamp examination (lashes, anterior chamber and lens)
- Dilated and undilated (cup-to-disc ratio) fundoscopy

Sample size

For the primary efficacy endpoint of change from baseline in peak IOP and trough IOP, separately, at Week 12 visit, the sample size calculation was based on data obtained from the phase II study (NVG10E118). The sample size was thus calculated assuming a mean difference in IOP change from baseline of 0 mmHg and a common standard deviation of 4.26 mmHg in the peak or trough IOPs, respectively, for the comparison between the Catiolanze and the control (Xalatan®) groups. A total sample size of approximately 380 subjects (190 per treatment arm) anticipated 90% power to demonstrate the non-inferiority of the Catiolanze group to the control group (one-sided $\alpha = 0.025$) for non-inferiority margin of 1.5 mmHg, assuming 10% dropout rate.

The sample size calculation is appropriate. However, the statistical justification of the NI margin has not been provided in the protocol or SAP. In line with the CHMP GUIDELINE ON THE CHOICE OF THE NON-INFERIORITY MARGIN, "The selection of the non-inferiority margin is based upon a combination of statistical reasoning and clinical judgement."

Randomisation and blinding (masking)

At the baseline visit (Day 1), eligible patients were randomly assigned by the Interactive Web Response Systems in a 1:1 ratio to receive either Catiolanze or Xalatan® for 12 weeks. Randomisation was stratified according to the CFS score of the study eye at baseline visit (CFS $\leqslant$ 1 vs. CFS $\geqslant$ 2, modified Oxford scale).

A computer algorithm for random number generation was used to generate the treatment assignments. Each patient who qualified for entry was to be assigned a patient number according to the randomisation code. The patient number was to be recorded. Precautions were taken to ensure that the Investigator remained masked.

Treatment assignments was masked to Investigators. The investigator was not to be present in the room during dispensing or/and dosing. The randomisation code was to be broken only in the event of a medical emergency or when knowing the treatment assignment was absolutely necessary for the medical management of the study patient. The investigator was to inform the Sponsor immediately after unmasking. Patients unmasked for the management of a SAE were discontinued from the study. Treatment masking to the patients was not feasible due to the difference in the appearance of the Catiolanze and Xalatan eye drops. However, patients were not told the name of the study drug by the drug dispensing staff and every effort was made to keep all study team members involved in the study masked during Period 1.

Statistical methods

Several analyses populations were defined, with the primary being the FAS. The primary outcome of the change from baseline in peak (9:00 am ± 1 hour) and trough 4:00 pm ± 1 hour) IOPs, respectively, at Week 12 between the Catiolanze and Xalatan® groups in the study eye were analysed using MMRM methods. The primary estimand as written in the SAP dated 11/03/2022 specifies the estimand for the primary endpoint as:

"The difference between the mean change from baseline IOP (peak and trough) after Week 12 in subjects with OAG or OHT treated with Catiolanze versus Xalatan. For subjects who had received IOP rescue medication before Week 12 or who discontinued due to any reason during double masked period, the data of IOP will be censored (treated as missing value), then primary model will be applied".

Two per protocol populations were defined, but the major protocol deviations were not stated *a priori* in the SAP, in detail. These appear to have been determined during a blinded data review. For the two key secondary outcomes, testing using a hierarchical approach for superiority using an MMRM approach was adopted.

The use of the FAS as the primary population in a non-inferiority trial is not supported. The applicant has also defined a per protocol (PP) population which should be considered the primary analysis. It is noted that the applicant has not formally defined an estimand consistent with the ICH E9 (R1) framework, despite the SAP having been finalised in March 2022. Furthermore, the primary analysis of MMRM is not supported as the justification for the mechanism of missingness was not provided. However, given consistency of results across analyses, and the very low proportion of missingness, the impact of these shortcomings cannot be such to change the main efficacy conclusions.

The approach of the hierarchical multiple testing approach for controlling type I error for the key secondary endpoints is acceptable.

Results

Participant flow

Out of 488 patients screened, 386 were randomised at Visit 2, n=193 to the Catiolanze group and n=193 to the control (Xalatan) group.

Of 386 treated patients, 384 had at least one IOP measurement in both peak and trough times during Period 1 and contributed to the FAS.

There were 380 patients who completed Period 1. Six patients discontinued the study prematurely during Period 1. Three patients discontinued due to an AE; two discontinuations were for ocular AEs (one each in the Catiolanze and control groups) and one patient in the Catiolanze group died due to acute heart failure that was considered by the investigator to be unrelated to the study drug. Additionally, there were two withdrawals by the subject and one withdrawal for 'other' reasons (the sponsor temporarily discontinued the study).

Table 3: Disposition of Patients Enrolled into Period 1

	DE-130A (N=193)	Control (Xalatan®) (N=193)	Overall (N=386)
	n (%)	n (%)	n (%)
Number screened	-	-	488
Number randomised	193 (100%)	193 (100%)	386 (100%)
Safety Population	193 (100%)	193 (100%)	386 (100%)
Full Analysis Set	192 (99.5%)	192 (99.5%)	384 (99.5%)
Glaucoma Per-Protocol Set	188 (97.4%)	189 (97.9%)	377 (97.7%)
Ocular Surface Per-Protocol Set	184 (95.3%)	187 (96.9%)	371 (96.1%)
Study completion	190 (98.4%)	190 (98.4%)	380 (98.4%)
Premature Discontinuation	3 (1.6%)	3 (1.6%)	6 (1.6%)
Adverse Event	2 (1.0%)	1 (0.5%)	3 (0.8%)
Non-compliance with Study Drug	0 (0.0%)	0 (0.0%)	0 (0.0%)
Protocol Deviation	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lack of Efficacy	0 (0.0%)	0 (0.0%)	0 (0.0%)
Withdrawal by Subject	1 (0.5%)	1 (0.5%)	2 (0.5%)
Lost to Follow-up	0 (0.0%)	0 (0.0%)	0 (0.0%)
Study Termination	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	0 (0.0%)	1 (0.5%)	1 (0.3%)

Source: Table 14.1.1.1
Number of patients of each group (N of the header) is based on the randomised group.

Number of patients of each group (N of the header) is based on the randomised group.

There were 137 patients who participated in Period 2. Of these, 71 had previously received treatment with Catiolanze and 66 had received Xalatan® during Period 1 (group Catiolanze/Catiolanze and group Xalatan®/Catiolanze, respectively). All 137 patients were administered at least one dose of Catiolanze during Period 2, however one patient was excluded due to no morning IOP therefore 136 patients were included in the Open-Label-Population. Among 137 treated patients, 125 patients completed Period 2, 8 patients discontinued prematurely, and treatment is ongoing in 4 patients. Two patients discontinued due to an AE: one patient had abnormal sensation in eye and macular fibrosis, and the other patient reported eye pain.

Table 4: Disposition of Patients Enrolled into Period 2

	DE-130A /DE-130A (N=71)	Xalatan /DE-130A (N=66)	Overall DE-130A (N=137)
Enrolled Population	71 (100.0%)	66 (100.0%)	137 (100.0%)
Open-Label Population	70 (98.6%)	66 (100.0%)	136* (99.3%)
Open-Label Safety Population	71 (100.0%)	66 (100.0%)	137 (100.0%)
Study completion	65 (91.5%)	60 (90.9%)	125 (91.2%)
Ongoing	2 (2.8%)	2 (3.0%)	4 (2.9%)
Prematurely Discontinued	4 (5.6%)	4 (6.1%)	8 (5.8%)
Adverse Event	0 (0.0%)	2 (3.0%)	2 (1.5%)
Non-compliance with Study Drug	0 (0.0%)	0 (0.0%)	0 (0.0%)
Protocol Deviation	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lack of Efficacy	0 (0.0%)	0 (0.0%)	0 (0.0%)
Withdrawal by Subject	2 (2.8%)	2 (3.0%)	4 (2.9%)
Lost to Follow-up	0 (0.0%)	0 (0.0%)	0 (0.0%)
Study Termination	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	2 (2.8%)	0 (0.0%)	2 (1.5%)
Source: Table 14.1.1.2			

Recruitment

This was a multi-centre study involving 59 sites. Fifty-two (52) of the sites screened at least one patient and 47 sites successfully randomized at least one patient. The study was conducted in the following

countries: Austria, Belgium, Estonia, Finland, France, Germany, Italy, Latvia, Poland, Spain, United

Kingdom, Russia and South Korea.

The data lock point for Period 2 was 15 March 2022.

The database lock for Period 2 was 11 April 2022.

Conduct of the study

The protocol was amended once (Amendment 01) on 26 February 2021. The main objectives of the amendment were to clarify the secondary endpoints and the statistical analysis approach.

Major revisions included:

- Clarification of secondary objectives.
- Optimisation of the statistical analysis of the primary and key secondary endpoints with the addition of the MMRM and of a superiority endpoint at week 12. Incorporation of a hierarchical testing approach to control the overall Type I error.
- Modification of the statistical methods for the primary endpoint to allow adjustment for baseline variables to improve the precision of estimates on treatment effect; and to use a newer approach to handle missing data.

- Clarification of the duration of the washout period and incorporation of extending the washout period if the IOP remained < 22 mmHg.
- Addition of an inclusion criterion allowing optical coherence tomography for disease monitoring prior to enrolment.
- Update of the exclusion criteria to include known hypersensitivity to sulfonamides, severe renal impairment or hyperchloraemic acidosis.
- Deletion of the use of artificial tears as secondary endpoint since, per protocol, their use should remain stable over the study per protocol.
- Updating the safety vigilance reporting details.
- Update of countries participating in the study.

Clarifications to the protocol (v5.0, dated 26 February 2021) were made in the final SAP (v1.0, 11 March 2022;). Key changes in the final analysis conducted are as follows:

- Patients with only peak IOP measured (no trough IOP measured) during the double masked period were entered into the Open-Label Period. The original definition of Open-Label Population and Open-Label Safety population was that these were subsets of the FAS. The Open-Label efficacy endpoint was the change from baseline in mean morning (9:00 am ± 1 hour) IOP at Week 4, Week 12, Month 6, Month 9 and Month 15. Because a lacking IOP trough measurement would have no impact on efficacy in the Open-Label Period evaluation, "a subset of FAS patients" was removed from these definitions.
- OSD symptoms were evaluated in all patients and was not restricted to patients with OSD symptoms at baseline, as specified in the protocol.

Estimands:

Primary estimands of the primary objective is:

The difference between the mean change from baseline IOP (peak and trough) after Week 12 in subjects with OAG or OHT treated with Catiolanze versus Xalatan. For subjects who had received IOP rescue medication before Week 12 or who discontinued due to any reason during double masked period, the data of IOP will be censored (treated as missing value), then primary model will be applied.

Supplementally, estimand for key-secondary endpoint are also described. This will be used when statistical testing strategy (step down approach) is applied.

Changes following study unmasking and post-hoc analyses

The following endpoint was not included in the protocol and the analysis was conducted after unmasking:

- The OSD symptom score (average of 3 symptoms: dry eye sensation, blurred/poor vision and burning/stinging/itching) at Month 6, Month 9 and Month 15/early termination.
- The following post hoc analyses were performed after unmasking: Cochran Mantel Haenszel test was additionally conducted to generate p-value for the subject global rating of treatment at Week 12.
- Statistical methodology was updated from Chi-squared test (or Fisher's exact test) defined in protocol to Cochran Mantel Haenszel test (stratified by baseline CFS score) to generate p-value for the McMonnies scale (1 to 6) of conjunctival hyperaemia at Week 4 and Week 12 due to multiple zero cells.
- Descriptive statistics of two devices of visual field (Octopus and other) was removed due to small number of subjects although original analysis was planned to summarize by each device (Humphrey, Octopus and other).

Baseline data

In Period 1, The mean age (SD) of all patients was 63.1 years (11.16) and 51.0 % (n=196) were < 65 years of age. Majority of patients (96.4%, n=370) were White, and 61.5% (n=236) were female. Demographic characteristics were similar in the treatment and control groups.

Table 5: Demographic Characteristics of Treated Patients (FAS, Period 1)

	DE-130A (N=192)	Control Xalatan® (N=192)	Overall (N=384)
Age (year)			
N	192	192	384
Mean (SD)	62.3 (12.07)	63.9 (10.14)	63.1 (11.16)
Median	64.0	65.0	64.0
Min, Max	18, 88	18, 83	18, 88
Age (Category)			
N	192	192	384
< 65 years, n (%)	102 (53.1%)	94 (49.0%)	196 (51.0%)
≥ 65 years, n (%)	90 (46.9%)	98 (51.0%)	188 (49.0%)
Sex			
N	192	192	384
Male, n (%)	72 (37.5%)	76 (39.6%)	148 (38.5%)
Female, n (%)	120 (62.5%)	116 (60.4%)	236 (61.5%)
Race			
N	192	192	384
American Indian or Alaska Native, n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Asian, n (%)	4 (2.1%)	4 (2.1%)	8 (2.1%)
Black or African American, n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Native Hawaiian or Other Pacific Islander, n (%)	2 (1.0%)	2 (1.0%)	4 (1.0%)
White, n (%)	184 (95.8%)	186 (96.9%)	370 (96.4%)
Other, n (%)	1 (0.5%)	0 (0.0%)	1 (0.3%)
Unknown, n (%)	1 (0.5%)	0 (0.0%)	1 (0.3%)

Source: Table 14.1.4.1.1

SD, standard deviation; Min, Max, minimum and maximum values; n, number of patients

Baseline characteristics of treated patients: Period 1

The primary diagnosis was OAG, with Primary Open-angle Glaucoma affecting 75.8% (n=291) of patients, Pseudo Exfoliative Glaucoma or Pigmentary Glaucoma were present in 3.1% (n=12) patients and OHT affecting 21.1% (n=81) of patients. The mean (SD) time since diagnosis was 6.0 years (5.27), with a median of 4.5 years.

The most frequently used IOP-lowering drugs prior to study entry were prostaglandin analogues (72.8%, n=279), followed by carbonic anhydrase inhibitors (13.6%, n=52), and beta-blocking agents (9.4%, n=36). All other drugs were used by six patients or fewer.

Table 6: Baseline Characteristics of Treated Patients (Study Eye, FAS, Period 1)

Baseline Characteristics	DE-130A (N=192)	Control Xalatan® (N=192)	Overall (N=384)
Primary Diagnosis n (%)			
N	192	192	384
Primary OAG	141 (73.4%)	150 (78.1%)	291 (75.8%)
Pseudo Exfoliative Glaucoma	4 (2.1%)	4 (2.1%)	8 (2.1%)
Pigmentary Glaucoma	2 (1.0%)	2 (1.0%)	4 (1.0%)
OHT	45 (23.4%)	36 (18.8%)	81 (21.1%)
Time Since Diagnosis (Year)			
N	192	192	384
Mean (SD)	5.9 (5.29)	6.1 (5.26)	6.0 (5.27)
Median	4.0	4.5	4.0
Min, Max	0, 31	0, 29	0, 31
Baseline IOP-Lowering Medication(s) n (%)			
N	192	191	383
Beta Blocking Agents	15 (7.8%)	21 (11.0%)	36 (9.4%)
Prostaglandin Analogues	142 (74.0%)	137 (71.7%)	279 (72.8%)
Carbonic Anhydrase Inhibitors	25 (13.0%)	27 (14.1%)	52 (13.6%)
Other*	3 (1.6%)	1 (0.5%)	4 (1.0%)
Beta Blocking Agents and Carbonic Anhydrase Inhibitors	2 (1.0%)	1 (0.5%)	3 (0.8%)
Beta Blocking Agents and Prostaglandin Analogues	1 (0.5%)	0 (0.0%)	1 (0.3%)
Prostaglandin Analogues and Carbonic Anhydrase Inhibitors	3 (1.6%)	3 (1.6%)	6 (1.6%)
Prostaglandin Analogues and Other*	0 (0.0%)	1 (0.5%)	1 (0.3%)
Beta Blocking Agents and Prostaglandin Analogues and Carbonic Anhydrase Inhibitors	1 (0.5%)	0 (0.0%)	1 (0.3%)

Source: Table 14.1.5.1.1
IOP, intraocular pressure; OAG, open angle glaucoma; OHT, ocular hypertension; n, number of patients; SD, standard deviation
**: Other: Sympathomimetic*

Baseline characteristics of the study eye: period 1

At baseline, the mean (SD) peak IOP was 24.52 (2.185) mm Hg, the mean trough IOP was 23.74 (1.785) mm Hg and the mean diurnal IOP was 24.131 (1.8127) mmHg.

At baseline, the mean overall CFS score was 0.73 (SD 0.694). There were 30.7% (n=118) of patients with a CFS grade of 0 at baseline, 24.0% (n=92) with a grade of 0.5, and 30.7% (n=118) with a grade of 1.

Table 7: Baseline IOP and CFS Scores (Study Eye, FAS, Period 1)

Baseline Characteristics	DE-130A (N=192)	Control Xalatan® (N=192)	Overall (N=384)
Peak IOP at 9 am (mmHg)			
N	192	192	384
Mean (SD)	24.55 (2.029)	24.49 (2.335)	24.52 (2.185)
Median	24.00	24.00	24.00
Min, Max	22.0, 31.0	22.0, 32.0	22.0, 32.0
Trough IOP at 4 pm (mmHg)			
N	192	192	384
Mean (SD)	23.67 (1.618)	23.81 (1.940)	23.74 (1.785)
Median	23.00	23.25	23.00
Min, Max	22.0, 29.0	22.0, 32.0	22.0, 32.0
Mean Diurnal IOP (mmHg)			
N	192	192	384
Mean (SD)	24.110 (1.6315)	24.151 (1.9815)	24.131 (1.8127)
Median	23.750	23.625	23.750
Min, Max	22.00, 30.00	22.00, 32.00	22.00, 32.00

Baseline Characteristics	DE-130A (N=192)	Control Xalatan® (N=192)	Overall (N=384)
CFS Score			
N	192	192	384
Mean (SD)	0.73 (0.692)	0.73 (0.698)	0.73 (0.694)
Median	0.50	0.50	0.50
Min, Max	0.0, 3.0	0.0, 3.0	0.0, 3.0
CFS Grade			
N	192	192	384
0	58 (30.2%)	60 (31.3%)	118 (30.7%)
0.5	49 (25.5%)	43 (22.4%)	92 (24.0%)
1	56 (29.2%)	62 (32.3%)	118 (30.7%)
2	27 (14.1%)	24 (12.5%)	51 (13.3%)
3	2 (1.0%)	3 (1.6%)	5 (1.3%)
4	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: Table 14.1.5.1.1
CFS = Corneal fluorescein staining; FAS = full analysis set; IOP = intraocular pressure; Min, Max = minimum and maximum values; n = number of patients; SD = standard deviation

Medical and surgical history – Period 1

The most common ocular medical history was cataract (33.1%), dry eye (17.4%) and myopia (8.6%).

Prior and concomitant medications – Period 1

The most commonly used concomitant medications were lipid modifying agents, plain (15.9%), beta blocking agents (15.6%), and other ophthalmologicals (14.6%).

Patient demography: Period 2

The demographic characteristics of the 136 patients of the Open Label Population were similar to those observed for the overall population Period 1.

In Period 2, the mean age (SD) of all patients was 63.6 years (10.50), 50.0% (n=68) were aged < 65 years, and 61.8% (n=84) were female. Demographic characteristics were similar in the Catiolanze/ Catiolanze and Xalatan®/Catiolanze groups.

Baseline characteristics of treated patients: Period 2

The baseline (Day 1) characteristics of patients who participated in Period 2 were similar to those observed in Period 1, indicating that the patients enrolled in period 2 were an acceptable representation of the entire study population.

In Period 2, the primary diagnosis was OAG, with Primary Open-angle Glaucoma affecting 74.3% (n=101) of patients, Pseudo Exfoliative Glaucoma or Pigmentary Glaucoma affecting 2.2% (n=3) of patients, and OHT affecting 23.5% (n=32). The mean (SD) time since diagnosis was 5.9 years (5.28), with a median of 4.0 years.

The most frequently used IOP-lowering drugs prior to study entry were prostaglandin analogues (71.9%, n=97), followed by carbonic anhydrase inhibitors (13.3%, n=18), and beta-blocking agents (9.6%, n=13).

Baseline characteristics of the study eye: period 2

The baseline (Day 1) characteristics of the study eyes of patients participating in Period 2 were similar to those observed in Period 1.

At baseline (Day 1), the mean (SD) peak IOP was 24.30 (2.107) mmHg in the Catiolanze/Catiolanze group and 23.93 (1.729) in the Xalatan®/Catiolanze group. The mean trough IOP was 23.58 (1.880) mmHg in the Catiolanze/Catiolanze group and 23.43 (1.292) in the Xalatan/Catiolanze group. The mean diurnal IOP was 23.938 (1.7650) mmHg in the Catiolanze/Catiolanze group and 23.679 (1.3283) in the Xalatan/Catiolanze group.

The mean overall CFS score at baseline was 0.79 (SD 0.740) in the Catiolanze/Catiolanze group and 0.80 (0.794) in the Xalatan®/Catiolanze group. Approximately 30% of patients in each group had a CFS grade of 0 at baseline.

Outcomes and estimation

Primary efficacy endpoint – period 1

The primary efficacy endpoint was change from baseline in peak and trough IOP at Week 12 in the study eye. Non-inferiority was established if the upper limit of the one-sided 97.5% CI is ≤ 1.5 mmHg at both the peak and trough timepoints.

Pre-specified non-inferiority criteria were achieved for both peak and trough measurements; the upper limit of the one-sided 97.5% CI was ≤ 1.5 mmHg at both timepoints. The LS mean treatment

difference (two-sided 95% CI) between the Catiolanze and control groups was -0.6 (95% CI -1.2, -0.1) at the peak timepoint, and -0.5 (95% CI -1.0, 0.1) at the trough timepoint at Week 12.

The upper limit of the two-sided 95% CI was ≤ 0 mmHg at the peak (9am) measurement at Week 12 (-0.1), indicating a statistically significant difference of Catiolanze versus control at this timepoint (nominal p=0.0226). In addition, Catiolanze was numerically better than control for the trough IOP (nominal p value=0.0803).

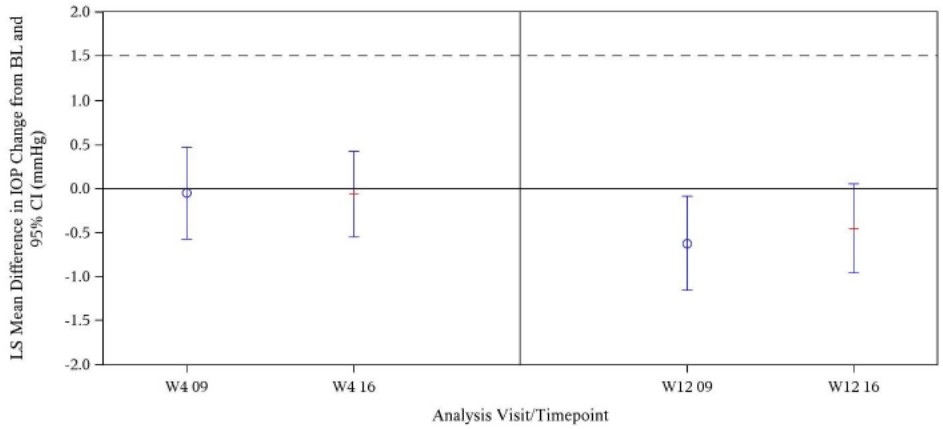
The primary endpoint is supported by the observation that IOP in the Catiolanze group decreased by Week 4 and continued to slightly decrease until Week 12, whereas no additional decrease between Week 4 and Week 12 was observed for the control group 12. Furthermore, the upper limit of the two-sided 95% CI was also < 1.5 mmHg at Week 4 at the peak and trough timepoints.

Table 8: Primary Efficacy Endpoint Results: MMRM on Observed Cases Period 1 (Study Eye, FAS)

Endpoint	Analysis Visit (Timepoint)		DE-130A (N=192)	Control Xalatan® (N=192)
IOP Change from baseline (Peak)	Week 4 (9:00) **Secondary endpoint**	N	189	189
		LS Mean (SE)	-8.4 (0.25)	-8.4 (0.26)
		Difference (SE), DE-130A *minus* Xalatan®	-0.0 (0.27)	
		95% CI of Difference	-0.6, 0.5	
		Nominal P-Value	0.8536	
	Week 12 (9:00) **Primary endpoint**	N	188	189
		LS Mean (SE)	-8.8 (0.25)	-8.2 (0.26)
		Difference (SE), DE-130A *minus* Xalatan®	-0.6 (0.27)	
		95% CI of Difference	-1.2, -0.1	
		Nominal P-Value	0.0226	
IOP Change from Baseline (Trough)	Week 4 (16:00) **Secondary endpoint**	n	188	188
		LS Mean (SE)	-8.3 (0.23)	-8.2 (0.24)
		Difference (SE), DE-130A *minus* Xalatan®	-0.1 (0.25)	
		95% CI of Difference	-0.5, 0.4	
		Nominal P-Value	0.8093	
	Week 12 (16:00) **Primary endpoint**	N	186	188
		LS Mean (SE)	-8.6 (0.24)	-8.1 (0.25)
		Difference (SE), DE-130A *minus* Xalatan®	-0.5 (0.26)	
		95% CI of Difference	-1.0, 0.1	
		Nominal P-Value	0.0803	

Source: Table 14.2.1.1.1
CI, confidence interval; FAS, full analysis set; IOP, intra-ocular pressure; MMRM, mixed-effects model for repeated measures; SE, standard error
The 95% CI of the treatment difference is two-sided (the limit of each side is 2.5%). When the upper limit is only considered (ignored lower limit of CI) as one-sided confidence interval, it is equivalent to 97.5% of one-sided CI.

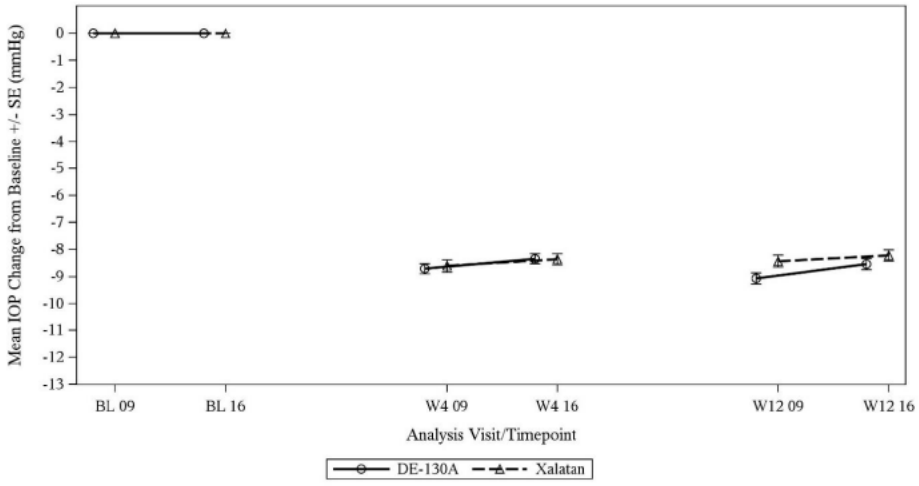
Figure 3: IOP LS Mean Treatment Difference of Catiolanze vs Xalatan® (control) with 95% CI (FAS)



Source Figure 14.2.1.4.1

BL, baseline visit; CI, confidence intervals; FAS, full analysis set; IOP, intraocular pressure; LS mean, Least square mean

Figure 4: IOP Raw Mean Change from Baseline with SE by Analysis Visit (FAS)



Source: Figure 14.2.1.2.1

FAS, full analysis set; IOP, intraocular pressure; SE, standard error

Sensitivity analyses of the primary endpoint

The results of the sensitivity analysis conducted on the PP population were consistent with the main analysis. The non-inferiority criterion was achieved for both peak and trough measurements; the upper limit of the one-sided 97.5% CI was ≤ 1.5 mmHg at both timepoints at Week 12. The LS mean treatment difference (two-sided 95% CI) between the Catiolanze group and the control group was -0.6 (95% CI -1.1, -0.0) at the peak timepoint, and -0.4 (95% CI -0.9, 0.1) at the trough timepoint at Week 12.

Table 9: IOP Analysis of change from baseline using MMRM on observed cases (study eye) – PP population – Investigator masked (Period 1)

Analysis visit	Timepoint	Unit	DE-130A N = 188	Xalatan N = 189
Week 12	9am	N	186	188
		LS mean (SE)	-8.8 (0.25)	-8.2 (0.27)
		Difference (SE), DE-130A – Xalatan	-0.6 (2.7)	
		95% CI of difference	-1.1, -0.0	
		P value	0.0374	
	4pm	N	186	188
		LS Mean (SE)	-8.5 (0.24)	-8.1 (0.25)
		Difference (SE), DE-130A – Xalatan	-0.4 (0.26)	
		95% CI of difference	-0.9, 0.1	
		P value	0.1230	

Source: Study 0130A10SA CSR Table 14.2.1.1.2. CI = confidence interval; IOP = intraocular pressure; LS = least squares; MMRM = mixed-effects model for repeated measures; SE = standard error. LS means and p-values were obtained by fitting a MMRM model to the IOP change from baseline of each visit at each timepoint (09:00, 16:00) respectively. Each model included treatment, visit, and treatment-by-visit interaction as fixed effects, and baseline IOP at the respective timepoint and country as covariates. Within-subject errors were modelled using an unstructured covariance matrix.

Similarly, the results of primary analysis repeated with multiple imputation using pattern mixture model were consistent with the main analysis. The non-inferiority criterion was achieved for both peak and trough measurements; the upper limit of the one-sided 97.5% CI was ≤ 1.5 mmHg at both timepoints at Week 12. The LS mean treatment difference (two-sided 95% CI) between the Catiolanze and control groups was -0.6 (95% CI -1.5, 0.3) at the peak timepoint, and -0.4 (95% CI -1.3, 0.4) at the trough timepoint at Week 12.

Table 10: IOP Analysis of change from baseline using MMRM using Multiple Imputation with Pattern Mixture Model (study eye) – FAS population – Investigator masked (Period 1)

Analysis visit	Timepoint	Unit	DE-130A N = 192	Xalatan N = 192
Week 12	9am	N	192	192
		LS mean (SE)	-8.4 (0.38)	-7.8 (0.39)
		Difference (SE), DE-130A – Xalatan	-0.6 (0.45)	
		95% CI of difference	-1.5, 0.3	
		P value	0.1981	
	4pm	N	192	192
		LS Mean (SE)	-8.2 (0.36)	-7.8 (0.38)
		Difference (SE), DE-130A – Xalatan	-0.4 (0.43)	
		95% CI of difference	-1.3, 0.4	
		P value	0.3304	

Key secondary efficacy endpoints – period 1

The primary efficacy endpoints of non-inferiority and superiority were achieved, and the pre-specified testing hierarchy step-down procedure proceeded to the key secondary endpoints.

First key secondary endpoint: CFS change from baseline

In total 170 patients presented with a CSF score ≥1 at baseline and were included in this analysis. Catiolanze demonstrated superiority in terms of improvement in CFS score versus the control (Xalatan®) at Week 12 (p value =0.0006).

These results are supported by the observation that the change from baseline in CFS score was also numerically higher in the Catiolanze group than the control group at Week 4, although statistical significance was not reached (nominal p=0.646).

Second key secondary endpoint: OSD change from baseline

In total 208 patients presented with an OSD score >0 at baseline and were included in this analysis.

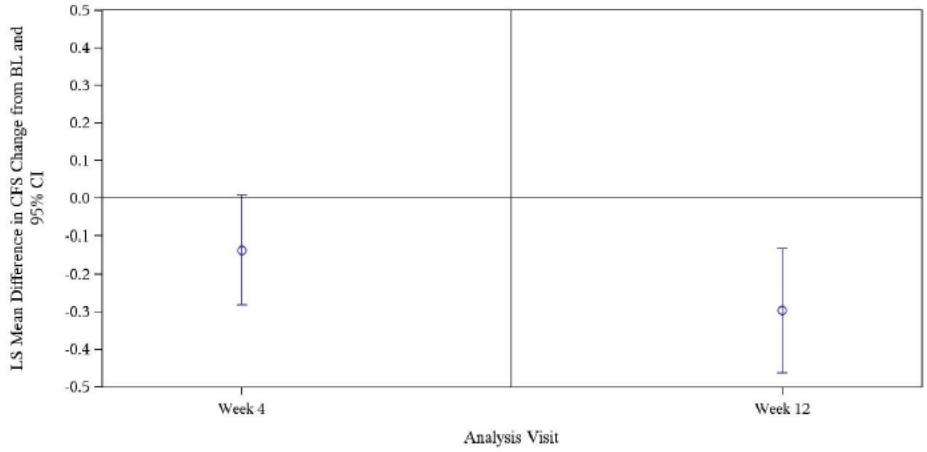
At Week 12, the average OSD score was numerically higher in the Catiolanze group than in the control group, but the difference between treatment groups was not statistically significant (p value =0.0900). The change in OSD score was statistically significantly higher in the Catiolanze group than the control group at Week 4 (nominal p value = 0.0188).

Table 11: Key Secondary Efficacy Endpoint Results: MMRM on Observed Cases (Study Eye) - FAS (with CFS baseline >=1 and baseline OSD score >0) – Investigator masked - Period 1

Endpoint	Analysis Visit		DE-130A (N=85)	Control Xalatan® (N=89)
CFS change from baseline in patients with baseline CFS score ≥ 1	Week 4	N	83	87
		LS Mean (SE)	-0.58 (0.061)	-0.44 (0.071)
		Difference (SE), DE-130A *minus* Xalatan®	-0.14 (0.073)	
		95% CI of Difference	-0.28, 0.01	
		Nominal P-Value	0.0646	
	Week 12	N	80	86
		LS Mean (SE)	-0.71 (0.069)	-0.41 (0.077)
		Difference (SE), DE-130A *minus* Xalatan®	-0.30 (0.084)	
		95% CI of Difference	-0.46, -0.13	
		P-Value	0.0006	
OSD change from baseline in patients with baseline OSD score >0	Week 4	n	103	105
		LS Mean (SE)	-0.21 (0.059)	-0.08 (0.061)
		Difference (SE), DE-130A *minus* Xalatan®	-0.14 (0.057)	
		95% CI of Difference	-0.25, -0.02	
		Nominal P-Value	0.0188	
	Week 12	N	99	104
		LS Mean (SE)	-0.26 (0.058)	-0.17 (0.060)
		Difference (SE), DE-130A *minus* Xalatan®	-0.09 (0.055)	
		95% CI of Difference	-0.20, 0.01	
		P-Value	0.0900	

Source: Table 14.2.2.1.1, and Table 14.2.3.1.1.
CFS, Corneal fluorescein staining; CI, confidence interval; FAS, full analysis set; n, number of patients; LS mean, Least square mean; MMRN, mixed-effects model for repeated measures; OSD, ocular surface disease; SE, standard error
The analysis is applied to all patients in the FAS with baseline CFS score ≥ 1 for CFS and to all patients with baseline average score >0 for OSD.
**: Original scale of each symptom was integer (0-4). Because the key secondary endpoint of OSD was an average of 3 symptoms, the decimal of each patient was 1 (+1 decimal) as per the SAP. This analysis was therefore conducted after adding an additional decimal point (e.g., 2 decimals of the LS-Mean).*

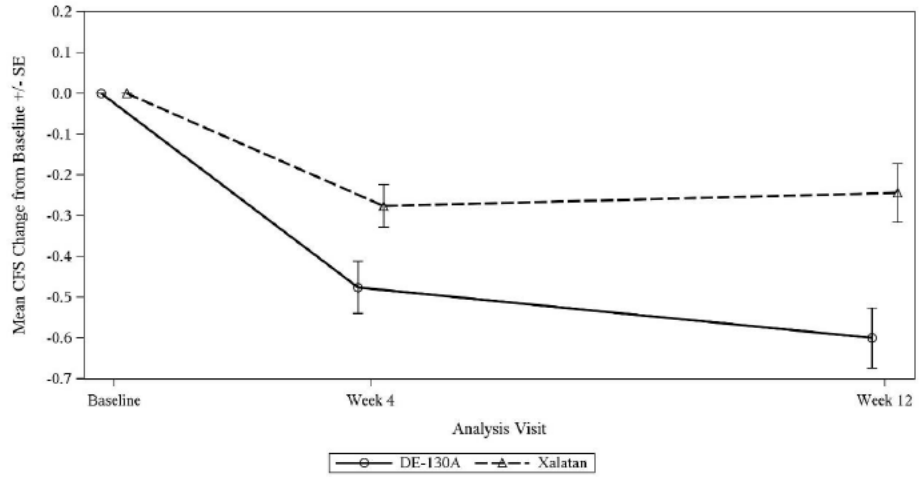
Figure 5: CFS LS Mean Treatment Difference of Catiolanze vs Xalatan® with 95% CI in Patients with Baseline CFS score ≥ 1 (FAS)



Source: Figure 14.2.2.4.1

CFS, Corneal fluorescein staining; CI, confidence interval; FAS, full analysis set

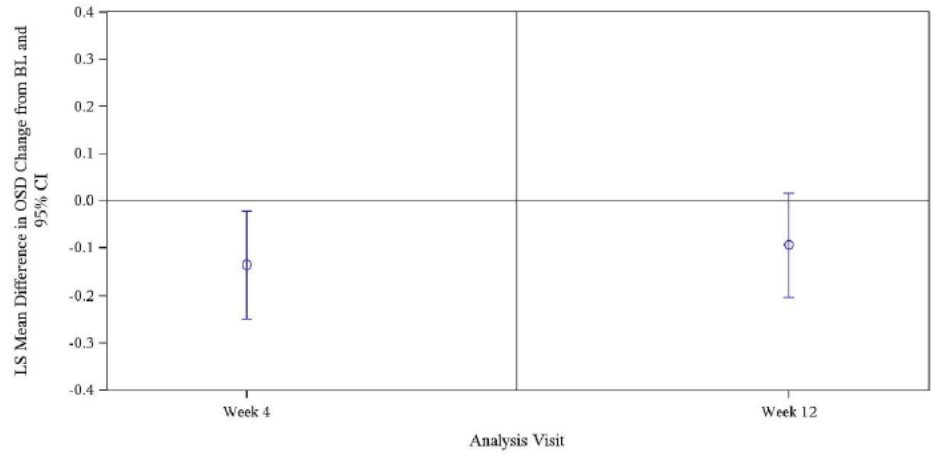
Figure 6: CFS Raw Mean Change from Baseline with SE by Analysis Visit in Patients with Baseline CFS score ≥ 1 (FAS)



Source: Figure 14.2.2.2.1

CFS, Corneal fluorescein staining; FAS, full analysis set; SE, standard error

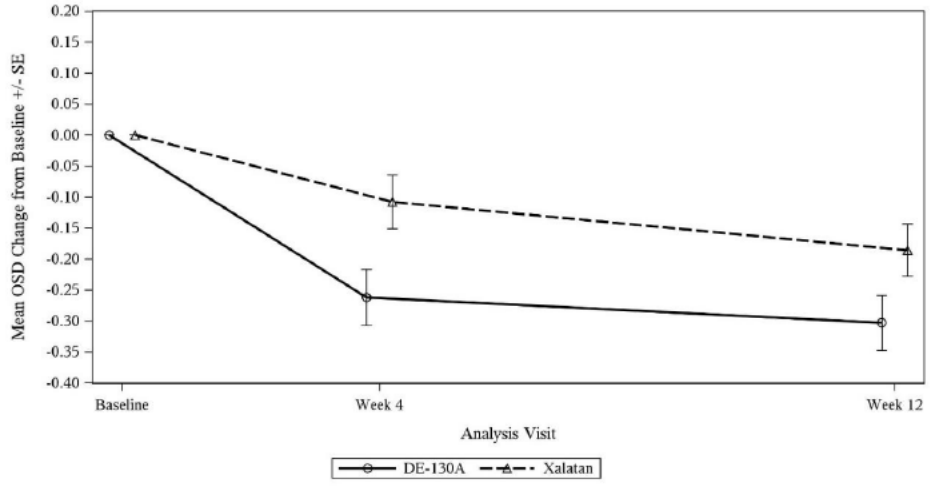
Figure 7: OSD Average Symptom Score: LS Mean Treatment Difference of Catiolanze vs Xalatan® with 95% CI in Patients with Baseline OSD score ≥ 0 (FAS)



Source: Figure 14.2.3.4.1

CI, confidence interval; FAS, full analysis set; LS mean, least square mean; OSD, ocular surface disease

Figure 8: OSD Average Symptom Score: Raw Mean Change from Baseline with SE by Analysis Visit in Patients with Baseline OSD score ≥ 0 (FAS)



Source: Figure 14.2.3.2.1

FAS, full analysis set; OSD, ocular surface disease; SE, standard error

Sensitivity analyses of the secondary endpoints

The results of the sensitivity analysis conducted on the PP population were consistent with the main analysis of the Key Secondary endpoints. Catiolanze demonstrated a statistically significantly greater improvement in CFS score versus the control (Xalatan®) at Week 12 (p=0.0006). The average OSD score was numerically higher in the Catiolanze group than in the control group as Week 12, but the difference between treatment groups was not statistically significant (p=0.0753).

Table 12: Corneal Fluorescein staining (CFS): Analysis of change from baseline using MMRM on observed cases (with CFS baseline ≥1) (study eye) – PP population (with CFS baseline ≥1)

Analysis visit	Unit	DE-130A N = 80	Xalatan N = 86
Week 12	N	79	86
	LS Mean (SE)	-0.69 (0.071)	-3.9 (0.079)
	Difference (SE), DE-130A – Xalatan	-0.29 (0.084)	
	95% CI of difference	-4.6, 0.13	
	P value	0.006	

Source: Study 0130A10SA CSR Table 14.2.2.1.2. Staining using fluorescein is graded using the modified Oxford scale (7-point ordinal scale, score 0, 0.5, and 1 to 5 per area for cornea and conjunctiva separately. The score 0 corresponds to no staining dots and the score 0.5 corresponds to one staining dot per area). CI = confidence interval; LS = least squares; MMRM = mixed-effects model for repeated measures; SE = standard error. LS means and p-values were obtained by fitting a MMRM model to the CFS change from baseline at each visit. Each model included treatment, visit, and treatment-by-visit interaction as fixed effects, and baseline CFS and country as covariates. Within-subject errors were modelled using an unstructured covariance matrix.

Table 13: OSD average symptoms score: Analysis of change from baseline using MMRM on observe cases (with baseline score >0) (study eye) – PP population (with baseline score >0)

Analysis visit	Unit	DE-130A N = 98	Xalatan N = 104
Week 12	N	97	104
	LS Mean (SE)	-0.25 (0.059)	-0.15 (0.060)
	Difference (SE), DE-130A – Xalatan	-0.10 (0.056)	
	95% CI of difference	-0.21, 0.01	
	P value	0.0753	

Source: Study 0130A10SA CSR Table 14.2.3.1.2. OSD = ocular surface disease, CI = confidence interval; LS = least squares; MMRM = mixed-effects model for repeated measures; SE = standard error. Ocular symptoms were graded on a 5 point scale 0 = absent, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe. LS means and p-values were obtained by fitting a MMRM model to the OSD average change from baseline at each visit. Each model included treatment, visit, and treatment-by-visit interaction as fixed effects, and baseline value and country as covariates. Within-subject errors were modelled using an unstructured covariance matrix.

Similarly, the results of primary analysis repeated with multiple imputation using pattern mixture model were consistent with the main analysis of the Key Secondary endpoints. Catiolanze demonstrated a statistically significantly greater improvement in CFS score versus the control (Xalatan®) at Week 12

(p=0.0103). The average OSD score was numerically higher in the Catiolanze group than in the control group as Week 12, but the difference between treatment groups was not statistically significant (p=0.2038).

Table 14: Corneal Fluorescein staining (CFS): Analysis of change from baseline using Multiple Imputation with Pattern Mixture Model (with CFS baseline ≥1) (study eye) – FAS population

Analysis visit	Unit	DE-130A N = 192	Xalatan N = 192
Week 12	N	85	89
	LS Mean (SE)	-0.57 (0.081)	-0.31 (0.090)
	Difference (SE), DE-130A – Xalatan	-0.26 (0.101)	
	95% CI of difference	-0.46, -0.06	
	P value	0.0103	

Source: Study 0130A10SA CSR Table 14.2.2.1.4. Staining using fluorescein is graded using the modified Oxford scale (7-point ordinal scale, score 0, 0.5, and 1 to 5 per area for cornea and conjunctiva separately. The score 0 corresponds to no staining dots and the score 0.5 corresponds to one staining dot per area). CI = confidence interval; LS = least squares; MMRM = mixed-effects model for repeated measures; SE = standard error. LS means and p-values were obtained by combining MMRM outputs of each umputed dataset. A MMRM was fitted to the CFS change from baseline at each visit. Each model included treatment, visit, and treatment-by-visit interaction as fixed effects, and baseline CFS and country as covariates. Within-subject errors were modelled using an unstructured covariance matrix. Pattern mixture model was applied with two different multiple imputation (MI) approach depending on the reasons, (1) discontinuing for lack of efficacy, AE, rescue medication (censoring after taking) or (2) other reasons. The missing data are filled in and 50 complete datasets are created for this approach.

Table 15: OSD average symptoms score: Analysis of change from baseline using MMRM using Multiple imputation with Pattern Mixture Model (with baseline score >0) (study eye) – FAS population – Investigator masked (Period 1)

Analysis visit	Unit	DE-130A N = 192	Xalatan N = 192
Week 12	N	105	108
	LS Mean (SE)	-0.19 (0.068)	-0.11 (0.070)
	Difference (SE), DE-130A – Xalatan	-0.08 (0.067)	
	95% CI of difference	-0.22, 0.05	
	P value	0.2038	

Source: Study 0130A10SA CSR Table 14.2.3.1.4. OSD = ocular surface disease, CI = confidence interval; LS = least squares; MMRM = mixed-effects model for repeated measures; SE = standard error. Ocular symptoms were graded on a 5 point scale 0 = absent, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe. LS means and p-values were obtained by combining MMRM outputs of each imputed dataset, A MMRM was fitted to the OSD average change from baseline at each visit. Each model included treatment, visit, and treatment-by-visit interaction as fixed effects, and baseline value and country as covariates. Within-subject errors were modelled using an unstructured covariance. Pattern mixture model was applied with two different multiple imputation (MI) approach depending on the reasons, (1) discontinuing for lack of efficacy, AE, rescue medication (censoring after taking) or (2) other reasons. The missing data are filled in and 50 complete datasets are created for this approach.

Other secondary efficacy endpoints:

At Week 4, Catiolanze was numerically better than Xalatan® for the CFS score and was statistically significantly better versus Xalatan® for the OSD symptom average score (nominal p value = 0.0188).

Mean TFBUT scores were numerically higher in the control group than the Catiolanze group at all study timepoints. At Week 12 the mean (SD) TFBUT scores were 6.67 (3.141) in the Catiolanze group and 7.03 (3.586) in the control group.

The mean conjunctival hyperaemia scores were numerically lower in the Catiolanze group than the control group at all study timepoints. At Week 12 the mean (SD) conjunctival hyperaemia score was 1.34 (0.546) in the Catiolanze group and 1.42 (0.658) in the control group.

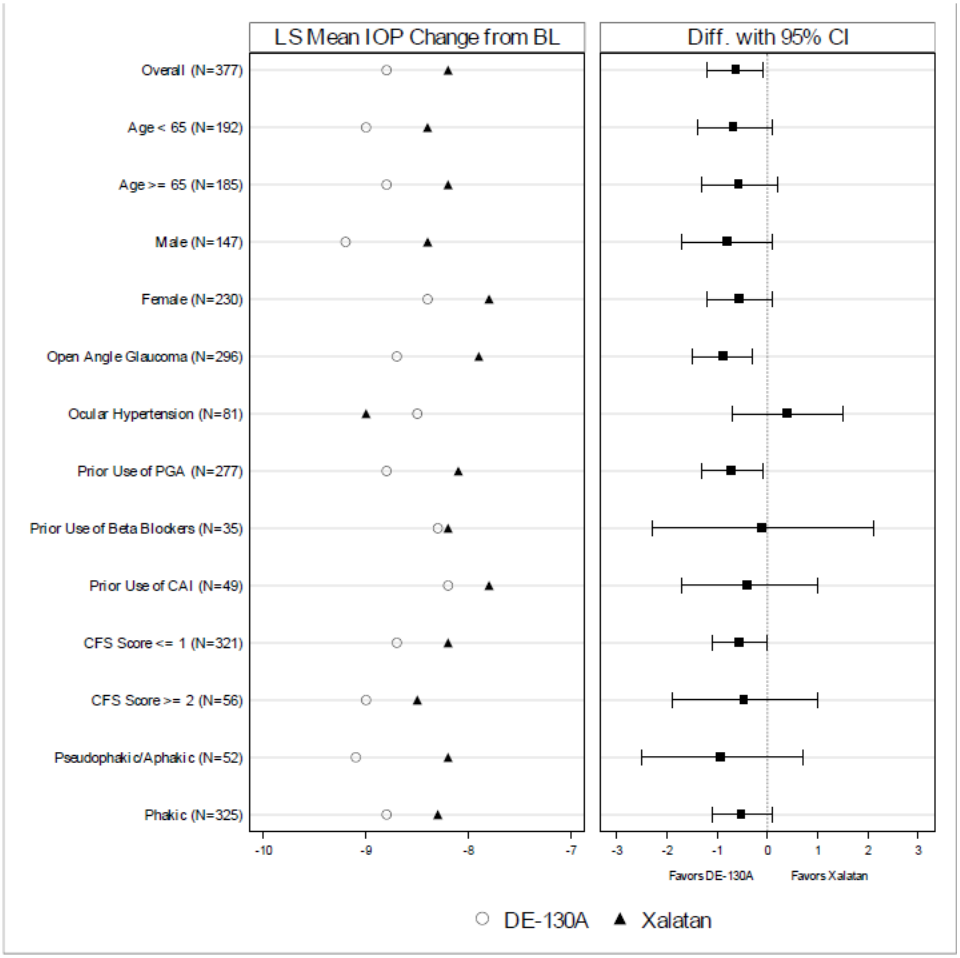
The mean (SD) change from baseline to Week 12 for dry eye sensation was -0.1 (0.55) in the Catiolanze group and -0.1 (0.63) in the control group. The mean (SD) change from baseline to Week 12 for blurred/poor vision was -0.1 (0.55) and -0.1 (0.42), respectively. The mean (SD) change from baseline to Week 12 for burning/stinging/itching was -0.2 (0.57) and 0.0 (0.72), respectively.

At the end of Period 1, 98.4% (n=188) of patients who provided a Global Rating Treatment Summary in the Catiolanze group and 90.5% (n=172) in the control group reported that the treatment was 'satisfactory' or 'very satisfactory'. In addition, 52.4% (n=100) of patients in the Catiolanze group versus 36.3% (n=69) in the control group reported that the treatment was 'very satisfactory'

Subgroup analyses

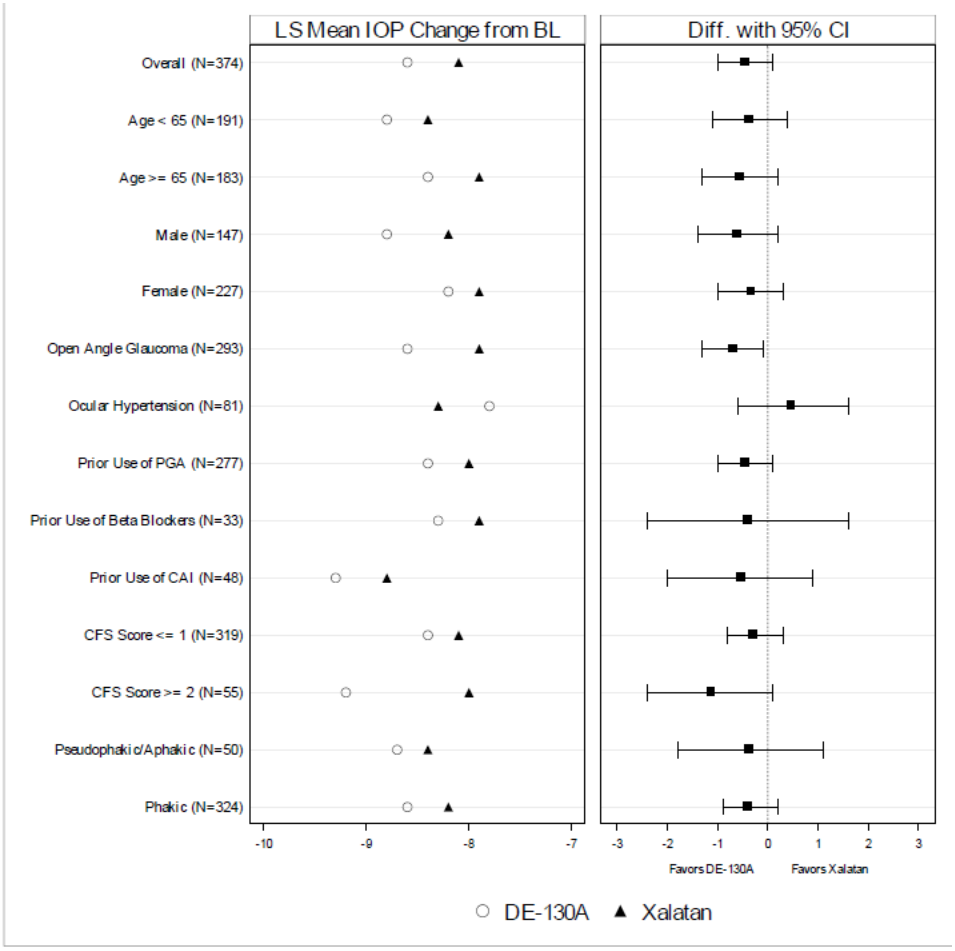
There was a consistent trend in most subgroups, as point estimates for the Catiolanze group were numerically better than the control group for both peak and trough IOPs, with the exception of the subgroup of patients with OHT in whom the point estimate for IOP was numerically higher in the control group at both timepoints.

Figure 9: Forest Plot: Change from Baseline in Peak (9AM) IOP at Week 12 (FAS)



CAI, carbonic anhydrase inhibitors; CFS, Corneal fluorescein staining; CI, confidence interval; Diff., difference; FAS, full analysis set; IOP, intraocular pressure; PGA, Prostaglandin analogues

Figure 10: Forest Plot: Change from Baseline in Trough (4PM) IOP at Week 12 (FAS)



CAI, carbonic anhydrase inhibitors; CFS, Corneal fluorescein staining; CI, confidence interval; Diff., difference; FAS, full analysis set; IOP, intraocular pressure; PGA, Prostaglandin analogues

2.5.5.3. Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 16: Summary of efficacy for trial 0130A01SA

Title: A Phase III, Multinational, Multicenter, Investigator-Masked, Randomised, Active-Controlled Trial, comparing the efficacy and safety of Catiolanze with Xalatan® in Patients with Open-Angle Glaucoma or Ocular Hypertension over a 3-Month period, followed by a 12-Month Follow-Up with Open-Label Catiolanze Treatment.			
Study identifier	Trial 0130A01SA EudraCT number: 2017-004262-95		
Design	Parallel, multicenter, randomized, single masked study		
	Duration of main phase: Duration of Run-in phase:	3 months 5 days to 6 weeks (depending on previous anti glaucoma medication)	
Hypothesis	Non-inferiority for primary endpoint with 1.5 mmHg of margins, and Superiority for two key secondary endpoints with 0.05 (two-sided) of type I error		
Treatments groups	Latanoprost 50 µg/mL eye drops, emulsion SD, single masked	Latanoprost 50 µg/mL eye drops, emulsion SD, Catiolanze, 3 months, N=192	
	Xalatan®, single masked	Xalatan®, 3 months, N=192	
	Latanoprost 50 µg/mL eye drops, emulsion SD, open label	Latanoprost 50 µg/mL eye drops, emulsion SD, Catiolanze, 12 months, N=136	
Endpoints and definitions	Primary endpoint	PE	The primary efficacy endpoint is the change from baseline in peak (9:00 am ± 1 hour) and trough (4:00 pm ± 1 hour) IOPs, respectively, at Week 12 between the two treatment groups in the study eye.
	Key secondary endpoint	<label>	Change from baseline in CFS score in the study eye at Week 12 in patients with baseline CFS ≥ 1.
	Key secondary endpoint	<label>	Change from baseline in OSD symptom score (average of 3 symptoms: dry eye sensation, blurred/poor vision and burning/stinging/itching) in the study eye at Week 12 in patients with baseline symptom average score>0.

Database lock	15 March 2022 (Period 1) 11 April 2022 (Period 2)		
Results and Analysis			
Analysis description	**Primary Analysis (Primary Endpoint)**		
Analysis population and visit/time point description	Analysis population for primary analysis was defined as Full Analysis Set (All randomised subjects who received at least one dose of study medication and provided at least one post-baseline IOP measurement at peak and trough timepoints, separately.)		
Point estimate of the primary statistical analysis model and the estimate variability	Treatment group	Catiolanze	Xalatan®
	Number of subjects (FAS)	192	192
	IOP change from baseline in peak (9AM) IOP at Week 12	-8.8	-8.2
	Standard Error	0.25	0.26
	IOP change from baseline in trough (4PM) IOP at Week 12	-8.6	-8.1
	Standard Error	0.24	0.25
Effect estimate per comparison	Primary endpoint: IOP change from baseline in peak (9AM) IOP	Comparison groups: Catiolanze - Xalatan	
		Treatment Difference of LS-Means: -0.6	
		Standard Error: 0.27 95% Confidence Interval (two-sided): (-1.2, -0.1)	
		P-value (Superiority from MMRM): 0.0226	
	Primary endpoint: IOP change from baseline in trough (4PM) IOP	Comparison groups: Catiolanze – Xalatan	
		Treatment Difference of LS-Means: -0.5	
		Standard Error: 0.26 95% Confidence Interval (two-sided): (-1.0, 0.1)	
		P-value (Superiority from MMRM): 0.0803	

Notes	LS means and p-values were obtained by fitting a MMRM model to the IOP change from baseline of each visit at each timepoint (09:00, 16:00) respectively. Each model included treatment, visit, and treatment-by-visit interaction as fixed effects, and baseline IOP at the respective timepoint and country as covariates. Hierarchical testing strategy was employed to maintain overall type I error for both primary and two key-secondary endpoints.
Analysis description	As sensitivity analysis, same MMRM model with different analysis set (per protocol) and MMRM after applying multiple imputation approach (of pattern mixture model) with FAS were conducted.

Analysis description	**Primary Analysis (First key secondary Endpoint)**		
Analysis population and visit/time point description	Analysis population for key secondary endpoint was defined as Full Analysis Set that is same as primary endpoint.		
Point estimate of the primary statistical analysis model and the estimate variability	Treatment group	Catiolanze	Xalatan®
	Number of subjects (FAS patients with baseline CFS ≥ 1)	85	89
	Change from baseline in CFS score at Week 12 in patients with baseline CFS ≥ 1. (LS-Mean)	-0.71	-0.41
	Standard Error	0.069	0.077
Effect estimate per comparison	First key secondary endpoint: Change from baseline in CFS score at Week 12 in patients with baseline CFS ≥ 1	Comparison groups: Catiolanze - Xalatan	
		Treatment Difference of LS-Means: -0.30	
		Standard Error: 0.084 95% Confidence Interval (two-sided): (-0.46, -0.13)	
		P-value (Superiority from MMRM): 0.0006	
Notes	LS means and p-values were obtained by fitting a MMRM model to the CFS change from baseline at each visit. Each model included treatment, visit, and treatment-by-visit interaction as fixed effects, and baseline CFS and country as		
Analysis description	As sensitivity analysis, same MMRM model with different analysis set (per protocol) and MMRM after applying multiple imputation approach (of pattern mixture model) with FAS were conducted.		

Analysis description	**Primary Analysis (Second key secondary Endpoint)**		
Analysis population and visit/time point description	Analysis population for key secondary endpoint was defined as Full Analysis Set that is same as primary endpoint.		
Point estimate of the primary statistical analysis model and the estimate variability	Treatment group	Catiolanze	Xalatan®
	Number of subjects (FAS patients with baseline symptom average score>0)	105	108
	Change from baseline in OSD symptom score (average of 3 symptoms) at Week 12 in patients with baseline symptom average score>0.	-0.26	-0.17
	Standard Error	0.058	0.060
Effect estimate per comparison	Second key secondary endpoint: Change from baseline in OSD symptom score (average of 3 symptoms) at Week 12 in patients with baseline symptom average score>0.	Comparison groups: Catiolanze - Xalatan	
		Treatment Difference of LS-Means: -0.09	
		Standard Error: 0.055 95% Confidence Interval (two-sided): (-0.20, 0.01)	
		P-value (Superiority from MMRM): 0.0900	
Notes	LS means and p-values were obtained by fitting a MMRM model to the OSD average change from baseline at each visit. Each model included treatment, visit, and treatment-by-visit interaction as fixed effects, and baseline value and country as covariates.		
Analysis description	As sensitivity analysis, same MMRM model with different analysis set (per protocol) and MMRM after applying multiple imputation approach (of pattern mixture model) with FAS were conducted.		

Reasons for drop-outs At Month 3		Catiolanze	Xalatan®
	Premature Discontinuation	3 (1.6%)	3 (1.6%)
	Adverse Event	2 (1.0%)	1 (0.5%)
	Non-compliance with Study Drug	0 (0.0%)	0 (0.0%)
	Protocol Deviation	0 (0.0%)	0 (0.0%)
	Lack of Efficacy	0 (0.0%)	0 (0.0%)
	Withdrawal by Subject	1 (0.5%)	1 (0.5%)
	Lost to Follow-up	0 (0.0%)	0 (0.0%)
	Study Termination	0 (0.0%)	0 (0.0%)
	Other	0 (0.0%)	1 (0.5%)
Reasons for drop-outs At Month 15		Catiolanze/Catiolanze	Xalatan®/Catiolanze
	Prematurely Discontinued	4 (5.6%)	4 (6.1%)
	Adverse Event	0 (0.0%)	2 (3.0%)
	Non-compliance with Study Drug	0 (0.0%)	0 (0.0%)
	Protocol Deviation	0 (0.0%)	0 (0.0%)
	Lack of Efficacy	0 (0.0%)	0 (0.0%)
	Withdrawal by Subject	2 (2.8%)	2 (3.0%)
	Lost to Follow-up	0 (0.0%)	0 (0.0%)
	Study Termination	0 (0.0%)	0 (0.0%)

2.5.5.4. Clinical studies in special populations

2.5.5.5. Not applicable Supportive study(ies)

Study NVG09E115

Study NVG09E115 was a prospective, single arm, open-label, multicentre, Phase II pilot study that assessed the safety and efficacy of Latanoprost 50 µg/mL eye drops, emulsion *SD* (one drop in the evening for three months) in **22 patients with OHT or OAG, with mild to moderate OSD.** All patients had been initially treated with BAK-preserved latanoprost. The objectives of this first-in-human study were to describe the efficacy of Latanoprost 50 µg/mL eye drops, emulsion SD in reducing IOP and to explore its impact on the signs and symptoms of OSD.

Study population

Adult subjects presenting with uni- or bilateral controlled OHT or OAG (primary OAG, pseudo exfoliative glaucoma and pigmentary glaucoma), with IOP ≤ 22mmHg at baseline and treated with BAK-preserved latanoprost either in monotherapy or in non-fixed combination with BAK-free anti-hypertensive treatment(s) for at least one month were enrolled.

Subjects had at least 1-month documented history of mild to moderate OSD on OHT or OAG affected eye(s), and at least two symptoms of OSD with score ≥ 1 (4-point grading scale) and fulfilled the two following objective parameters in the affected eye to be included in the study: mean TFBUT ≥ 5 seconds and ≤ 10 seconds and corneal fluorescein staining (CFS) with a score of 1, 2 or 3 (Oxford scale). OSD treatment had to be unchanged for at least one month prior to study entry.

Efficacy assessment

The efficacy was assessed at Day 28 and Day 84.

As this was a pilot study, no formal statistical calculation of the sample-size as well as no formal statistical significance testing were performed.

Results

Mean IOP improved over the study period, with a mean change from baseline of -0.6 mmHg at Day 28 and -0.8 mmHg at Day 84. Regarding changes by shift classes IOP decreased in 60% of the subjects (n=12) at Day 84; among them 40% (n=8) had a decrease of 2 mmHg or more. 10% (n=2) had no change on IOP, and 30% (n=6) of subjects had increased IOP over 1 mmHg.

For three of these last subjects, IOP increased by 2 mmHg or more with values remaining within the normal range.

Considering the subjects with OSD signs at baseline, very light (grade 1) or absence of corneal fluorescein staining was observed in 90% of the subjects at Day 84, with an improvement from baseline for 70% of the subjects on the Oxford scale. Similar results were observed with temporal and nasal bulbar fluorescein staining, and with the sum of corneal and conjunctival fluorescein staining.

At Day 84, the proportion of subjects without eye dryness increased from 40% at baseline to 80% and without burning/stinging from 40% to 75%. Improvements of lesser extent were observed in itching from 40% at baseline to 65% at Day 84, foreign body sensation from 55% to 80%, blurred vision from 55% to 75%, and tearing from 70% to 90%. Half of the subjects were symptom-free after three months of treatment for burning/stinging and photophobia (from 40% at baseline to 55% at Day 84, and from 35% to 50%, respectively). All improvements already started at Day 28. No change from baseline was reported for pain at Day 84 (however 80% of subjects had no pain at baseline). No sticky feeling was reported at baseline and no worsening was experienced.

Mean TFBUT improved considerably over the study period, with a mean change from baseline at Day 84 of 1.9 sec, improvement started as early as Day 28 (mean change: 0.5 sec).

At Day 84, three subjects over 20 (15%) reached a normal TFBUT. In most of the subjects, more than one-month study treatment was necessary to observe a clear improvement of TFBUT.

At Day 84 the proportion of subjects with normal Meibomian gland and without lid and lid margin erythema did not change from baseline (55% and 50% respectively). A slight change was observed for subjects without blepharitis (from 55% to 65%). while a clear improvement between baseline and Day 84 was observed for subjects without conjunctival erythema/hyperaemia (from 45% to 70%), tear film debris (from 75% to 100%), and lid and lid margin swelling (from 65% to 85%), All improvements started as early as Day 28.

No anterior chamber inflammation was reported at baseline and no worsening was experienced.

Baseline values for exploratory analyses (confocal microscopy, tear osmolarity, HLA-DR estimates) were normal and did not show any significant change at Day 84. The median HLADR level of expression at baseline was 16 676 AUF and remained at a normal value after treatment with Latanoprost 50 µg/ml eye drops, emulsion SD (value of 35 396 AUF).

Study NVG10E118

Study NVG10E118 was a multi-centre, Phase II, randomised, investigator-masked, active control study that evaluated the safety and efficacy of Latanoprost 50 µg/mL eye drops, emulsion *SD* compared to TravatanZ (40µg/mL eye drops, solution) in **105 subjects with OAG or OHT and OSD**. The study objectives were to compare Latanoprost 50 µg/mL eye drops, emulsion *SD* and TravatanZ® with respect to their IOP-lowering effects and effects on the signs and symptoms of OSD.

Study population

Adult subjects within a documented diagnosis of OHT, OAG (with or without pseudoexfoliation or pigment dispersion component) or chronic angle closure glaucoma with a patent iridotomy requiring treatment with an OHT therapy in the study eye, a best corrected visual acuity of 1.0 log MAR or better in both eyes as measured using an early treatment of diabetic retinopathy study (ETDRS) chart, a baseline hour 0 IOP ≥ 22 mmHg, an ocular discomfort score ≥ 2 on the ocular symptomology scale (0 – 5 symptom scale) at Visit 1 and 2, a CFS score (modified oxford scale) ≥ 1 at Visit 1, and a TFBUT ≤ 10 seconds at Visit 1 and 2 were enrolled.

Objectives

The objectives of the study were:

- to compare the IOP-lowering effect (measured at 8am, 10am and 4 pm) and safety of Latanoprost 50 µg/ml eye drops, emulsion *SD* and Travatan Z® in subjects with OAG or OHT and OSD The objective/hypothesis of the study (regarding IOP) was to show that the effects of Latanoprost 50 µg/ml eye drops, emulsion *SD* and Travatan Z® were similar.

-to compare the effect of Latanoprost 50 µg/ml eye drops, emulsion SD to the active control Travatan Z on the signs and symptoms of OSD in subjects with OAG or OHT and OSD

Efficacy measurements

IOP after one month and three months of treatment

At each visit (once at Visit 1 and 3 times per day [diurnal: 8 AM, 10 AM, and 4 PM] at Visits 2, 3, and 4), IOP was measured (in mmHg) using Goldmann applanation tonometry in both eyes. Ocular surface disease (OSD) after one month and three months of treatment

The goal of the study with respect to OSD endpoints was to show a positive effect of Latanoprost 50 µg/ml eyedrops, emulsion *SD* on the ocular surface in subjects with signs and symptoms of OSD, whereas it was expected that subjects treated with Travatan Z® would be unchanged.

CFS - At each study visit, CFS was measured using the Ora scale in the inferior, superior, central, temporal, and nasal regions (the corneal sum was also calculated as the sum of the inferior, superior, and central regions), as well as the modified Oxford scale.

Global symptoms - ocular discomfort, burning, dryness, grittiness, and stinging were measured at each study visit using the Ora Ocular Symptomology 0-5 Symptom Query Scale. TFBUT -At each study visit, TFBUT was measured in each eye. Bulbar conjunctival hyperaemia - At each study visit, bulbar conjunctival hyperaemia was assessed by the investigator using the slit-lamp and graded using the McMonnie's scale (1-6 points).

Other efficacy measures

Blepharitis assessment - At each study visit, a blepharitis assessment was conducted to evaluate the meibomian glands (0-3 scale), the lid and lid margin (Ora Lid Margin Redness 0-3 scale), and swelling of the lid and lid margin (0-4 scale)

Ora QoL questionnaire – At each study visit, subjects were asked to rate to what extent their ability to perform the activities of reading and watching movies/TV is impacted by their dry eye (both eyes) using a scale of 0 (no interference) to 4 (severe interference).

OSD symptom diary -Subjects were asked to rate their symptoms of ocular discomfort, burning, dryness, grittiness, and stinging on a visual/numerical analogue severity scale of 0 (least severe) to 5 (most severe) in the OSD symptom diary for each morning, afternoon, and evening during the treatment period (Visits 2-3 and 3-4). An average score of the morning, afternoon, and evening values was also calculated from these data.

AT usage (diary) - Subjects were provided diaries in which to record AT usage each day during

the washout period (Visits 1-2) and during the treatment period (Visits 2-3 and 3-4). Subject global rating of treatment - At Visit 4, the subjects rated the overall effect of the study medication in the study eye. The global rating used the following descriptors as a rating scale: very satisfactory, satisfactory, not very satisfactory and unsatisfactory.

Results

Mean IOP was numerically lower in the Latanoprost 50 µg/ml eye drops, emulsion *SD* group than in the Travatan Z group at each of the post-treatment time points at Visits 3 and 4 except for the 4 PM time point at Visit 3. While a threshold for clinically meaningful difference between the treatment groups was not pre-specified, the 95% CI of the difference between the groups either included 0 or was completely negative at each time point, which suggests at least the non-inferiority of Latanoprost 50 µg/ml eye drops, emulsion *SD* versus Travatan Z in lowering IOP in this population. Thus, it was confirmed that the IOP-lowering effect of Latanoprost 50 µg/ml eye drops, emulsion *SD* was comparable to that of Travatan Z.

For CFS, a statistically significant treatment effect in favour of Latanoprost 50 µg/ml eye drops, emulsion was seen using the Ora scale in the corneal sum score (Visit 4, FAS and PP) and in the superior region (Visit 4, FAS), temporal region (Visit 4, FAS and PP), and inferior region (Visit 4, PP) and also using the modified Oxford scale (Visit 4, PP). A statistically significant treatment effect in favour of Latanoprost 50 µg/ml eye drops, emulsion *SD* was also seen for the OSD symptom of burning (Visit 3, PP).

Though the changes were not tested statistically, there was a greater decrease in AT usage in the Latanoprost 50 µg/ml eye drops, emulsion *SD* group compared with the Travatan Z group.

There were modest, non-statistically significant decreases in blepharitis and QoL scores in both groups. Additionally, though the differences between groups were not statistically significant, the majority of subjects rated the respective treatment as satisfactory, or very satisfactory.

2.5.6. Discussion on clinical efficacy

Latanoprost is a prostaglandin 2α analogue that acts as a selective prostanoid FP receptor agonist that reduces IOP by increasing uveo-scleral outflow. Latanoprost, marketed as Xalatan, has been approved for the treatment of open angle glaucoma (OAG) and ocular hypertension (OHT). Xalatan was approved for the treatment of paediatric glaucoma in 2010.

Santen OY (the applicant), submitted an Article 10(3) Marketing Authorisation Application for a new formulation of latanoprost; Latanoprost 50 µg/mL eye drops, emulsion single dose (Catiolanze), using the marketed product Xalatan (50 µg/mL eye drops, solution) as the reference medicinal product (RefMP) to support the indication for reduction in IOP.

At the last round of assessment, the proposed indication is:

Catiolanze is indicated for the reduction of elevated intraocular pressure (IOP) in adult patients with open angle glaucoma or ocular hypertension.

Catiolanze is indicated for the reduction of elevated IOP in children from 4 years of age and adolescents with elevated IOP and paediatric glaucoma.

This indication differs from the indication of the reference product as the minimal age of children to be treated is specified, which is considered acceptable as the safety data on the use of this formulation are available for children older than 4 (see safety sections)

Design and conduct of clinical studies

The main study supporting this application is a Phase III, prospective, investigator-masked, randomised, active-controlled trial performed to investigate the IOP-reducing effect of Catiolanze compared to Xalatan in patients with Open-Angle Glaucoma (OAG) or Ocular Hypertension (OHT).

The study consisted of a 12-week treatment period (Period 1) which was followed by 12-month extension period. After a washout phase (5 days to 6 weeks) during the treatment period patients were randomised in a 1:1 ratio to receive either Catiolanze once daily or Xalatan once daily. In both groups the treatment was given to patients at 9 pm. At Week 12 all patients entering Period 2 started 12-months of open-label Catiolanze treatment to assess the safety and tolerability of Catiolanze.

The main purpose of this pivotal study was to compare the IOP-reducing effects of Catiolanze versus Xalatan. The main features of the study (i.e. 3-month duration of the treatment period, primary endpoint at 12-week, comparator and non-inferiority design) were discussed and agreed during the EMA scientific advices procedure.

Of note, studies with non-inferiority design have been accepted in previous procedures investigating essential similarity of preservative-free eye-drop formulations, in comparison with preserved or unpreserved innovator products.

This study was also aiming to investigate the effect of the Catiolanze on ocular surface disease with the objective of providing justification for the originally proposed indication wording.

Study population

The inclusion criteria and selected trial population are relevant for the assessment of the IOP reducing effect of Catiolanze in comparison to Xalatan. The study enrolled patients with the diagnosis of OAG (primary open angle glaucoma, pseudo exfoliative glaucoma, or pigmentary glaucoma), or OHT in eligible eye(s) currently on monotherapy. At enrolment all patients had post-washout IOP $\geqslant$ 22 mmHg and IOP $\leqslant$ 32 mmHg. The study population did not reflect a full range of target population, as patients

with IOP> 32 mmHg were not included. Further, only adults were included in this study (see the discussion below).

The Phase III study inclusion criteria did not require participants to have signs or symptoms of OSD at enrolment. Some patients who had CFS score ⩾1 and those with an OSD symptom score >0 were considered as having evidence of ocular surface disease i.e. the applicant indicated that the OSD population is defined as patients with a baseline CFS score of ⩾1 and/or patients with symptom score >0.

The relevance of the selected population for the review of the effect on ocular surface disease was questioned as it was considered that the provided publications and discussion insufficiently substantiate the claim that the OSD population could be defined as patients with a baseline CFS score of ⩾1 and/or patients with symptom score >0. Although as highlighted by Jung et al. 2022 some patients could have a sign of OSD without symptoms and vice versa, however specificity and sensitivity of a single test (CFS score ⩾1 or OSD symptom score >0) especially for diagnosis of mild disease is likely to be very low.

Of note, in the study performed by the applicant most patients had mild disease. Further, the applicant has not provided any publication which describes specificity and sensitivity of OSD symptom score (version used by the applicant) for diagnosis of ocular surface disease (or more specifically dry eye disease), especially when used on its own.

Comparator

Xalatan (Pfizer) (latanoprost ophthalmic solution 0.005%) was selected as an active comparator in this study. Xalatan is an acceptable comparator when used for comparison of the IOP-reducing effects between these two latanoprost formulations. The applicant confirmed that the reference product (Xalatan (Pfizer) (latanoprost ophthalmic solution 0.005%)) used in clinical and pre-clinical studies was sourced from the EU.

In the use of unpreserved artificial tears were allowed in the study to improve dry eye symptoms however, the number of patients taking these medications was small (<5% in either group) and therefore it can be agreed that artificial tears taken by these patients were unlikely to affect the study results.

The primary efficacy endpoint in the study was the change from baseline in peak (9:00 am ± 1 hour) and trough (4:00 pm ± 1 hour) IOPs, respectively, at Week 12 between the two treatment groups in the study eye. The primary endpoint is acceptable. The peak and trough IOPs were also measured at one earlier time-point i.e. at week 4. During the SA the applicant was recommended to measure the peak and trough IOP at week 2, 6 and 12 however, based on the clarification provided by the applicant the approach taken by the applicant can be accepted.

As described in the statistical plan for the primary endpoint, non-inferiority is established if the upper limit of the one-sided 97.5% CI is ⩽ 1.5 mmHg at both the peak and trough timepoints. As discussed in the SA the chosen non-inferiority margin of 1.5 could be accepted.

In the study there were two key secondary endpoints which were under multiplicity adjustments. These two key secondary endpoints were testing for superiority.

These endpoints were: change from baseline in corneal fluorescein staining (CFS) score in the study eye at Week 12 in patients with baseline CFS ⩾ 1 and change from baseline in ocular surface disease (OSD) symptom scores (average of 3 symptoms: dry eye sensation, blurred/poor vision, and burning/stinging/itching) in the study eye at Week 12 in patients with baseline symptom average score

>0.

Uncertainties regarding the use of key secondary endpoints for the assessment of ocular surface disease were highlighted to the applicant. Although, it can be agreed that endpoints investigating changes from baseline in CFS and also endpoints investigating symptoms are valid and important for the assessment of diseases associated with damage to the surface layers of the eye under the umbrella term "ocular surface disease" however there are uncertainties in relation the OSD symptom score used specifically in this study. In other applications referenced by the applicant, a different outcome measure was used to investigate symptoms i.e OSDI and no references were provided supporting the use of the OSD symptom score.

There were several additional secondary endpoints which investigated CFS, TFBUT and symptoms (such dry eye sensation symptom, blurred/poor vision symptom, burning/stinging/itching symptom) at different timepoints (Week 4, Week 12, Month 6, Month 9 and Month 15). Slit lamp examination was also performed. As all these endpoints were outside of multiplicity adjustments, therefore they are considered as supplementary only.

Efficacy data and additional analyses

386 patients were randomised into two treatment groups: the Catiolanze group (193 patients) and Xalatan group (193 patients). Of 386 treated patients, 384 had at least one IOP measurement in both peak and trough times during Period 1 and contributed to the FAS. Most patients completed Period 1 of the study (i.e 380 patients) however, only 137 patients participated in Period 2. Among these patients 71 had previously received treatment with Catiolanze and 66 had received Xalatan during Period 1 (group Catiolanze/Catiolanze and group Xalatan/ Catiolanze, respectively).

Among 137 treated patients, 125 patients completed Period 2.v

The mean age (SD) of all patients was 63.1 years and 63.6 years for period 1 and 2 respectively. The majority of patients were white (>96%) in both treatment periods and female.

The primary diagnosis was OAG, with Primary Open-angle Glaucoma affecting 75.8% (n=291) of patients, Pseudo Exfoliative Glaucoma or Pigmentary Glaucoma were present in 3.1% (n=12) patients and OHT affecting 21.1% (n=81) of patients. In line with the inclusion criteria all patients received IOP-lowering medications prior to enrolment and prostaglandin analogues were most frequently used (72.8%). Only patients who met the inclusion criteria for IOP $\geqslant$ 22 mmHg and $\leqslant$ 32 mmHg were enrolled. Mean IOP at enrolment was 24.5 mmHg.

At baseline CFS and OSD symptom scores were assessed

Only 30.7% (118) of patients had CFS with a grade of 1 whereas 54% (208) of patients presented with an OSD score >0 which means that they reported any of the following symptom: dry eye sensation, blurred/poor vision, and burning/stinging/itching. These patients were included in the kay secondary endpoints assessment.

In general, the demographic characteristics as well as other baseline parameters such as primary diagnosis, time since diagnosis, type of used IOP-lowering drugs, values of IOPs, CFS score and grade, were balanced between treatment arms.

In relation to 136 patients enrolled to period 2, the applicant presented their baseline characteristics as per Day 1 of the study (i.e prior to period 1). These characteristics were similar to those observed for the overall population.

The applicant was requested to present the list of medications taken during the study (including the use of artificial tears other ophthalmological drugs, other anti-infectives, anti-inflammatory, antiallergic medications) which could affect the CFS score and OSD symptom score results. This information was

provided but this issue was not pursued further as the applicant modified the indication so that the treatment of OSD is not part of this application.

Primary endpoint

The primary efficacy endpoint in the pivotal study (0130A01SA) was change from baseline in peak and trough IOP at Week 12 in the study eye. Based on the results reported for this endpoint, it can be agreed that non-inferiority in IOP lowering effect of Catiolanze was shown as compared to the reference product as the upper limit of the one-sided 97.5% CI was $\leqslant$ 1.5 mmHg at both the peak and trough timepoints.

For change from baseline to Week 12 in peak IOP, 95% CI is (-1.2 mmHg, -0.1 mmHg) for FAS, (-1.1 mmHg, -0.0 mmHg) for PPS and (-1.5 mmHg, 0.3 mmHg) for FAS using multiple imputation (MI) with pattern mixture model (PMM). For change from baseline to Week 12 in trough IOP, 95% CI is (-1.0 mmHg, 0.1 mmHg) for FAS, (-0.9 mmHg, 0.1 mmHg) for PPS and (-1.3 mmHg, 0.4 mmHg) for FAS using MI with PMM.

A trend towards a higher decrease in IOP in patients treated with Catiolanze as compared to Xalatan was noted. At week 12, change from baseline in IOP was higher in patients receiving Catiolanze as compared to Xalatan especially at the peak timepoint. The LS mean treatment difference (two-sided 95% CI) between the Catiolanze and control groups was -0.6 (95% CI -1.2, -0.1) at the peak timepoint, and -0.5 (95% CI -1.0, 0.1) at the trough timepoint at Week 12. These differences could be considered as borderline clinically significant only. The results of the sensitivity analyses including the analysis performed on the PP population were consistent with the main analysis i.e. non-inferiority criterion was fulfilled.

The results depending on the baseline IOP values were also evaluated. Of note, most of enrolled patients had baseline IOP within 22-28 mm Hg, whereas the available data for patients with baseline IOP $\geqslant$ 28 mmHg were limited. At baseline, 12 patients in the Latanoprost 50 µg/mL eye drops, emulsion SD group and 17 patients in the Xalatan group had baseline IOP >28 mmHg at 9 am and 3 patients and 8 patients respectively, had baseline IOP >28 mmHg at 4 pm. Nevertheless, the presented analyses do not indicate significant differences in efficacy depending on the baseline IOP values.

Secondary endpoints investigating changes in IOP- period 1

The results of secondary endpoints investigating changes in IOP at week 12 were in line with the primary endpoint results showing a slightly higher decrease in IOP in the Catiolanze group as compared to the Xalatan group. At week 12 at 9 am there was more patients with 30% decrease in mean IOP from baseline in the Catiolanze treatment arm (74.5%) as compared to the Xalatan arm (64.0%), CI 95% CI 1.2-19.7. In addition, the percentage of patients with IOP reduced to 18 mmHg or lower was also higher at week 12 in the Catiolanze group.

Key secondary endpoints

In relation to change from baseline in corneal fluorescein staining (CFS) score in the study eye at Week 12 in patients with baseline CFS $\geqslant$ 1, statistically significant differences were reported. The LS mean treatment difference between the Catiolanze and Xalatan groups was -0.30 (95% CI -0.46, -0.13, p= 0.0006. The results of this key secondary endpoint are described in section 5.1 of the SmPC.

On the other hand, no statistically significant differences were reported for the second key secondary endpoint i.e the change from baseline in ocular surface disease (OSD) symptom scores in the study eye at Week 12 in patients with baseline symptom average score >0.

Other secondary endpoints – period 1

At week 12 the mean TFBUT scores were numerically higher in the control group than in the Catiolanze group however, this result was confounded by the fact that at baseline there was imbalance between groups. There was also only a minimal change from baseline in relation to the mean conjunctival hyperaemia scores and again there was imbalance in baseline for this endpoint. Of note these endpoints was not adjusted for multiplicity.

Efficacy results – period 2

The efficacy was also assessed during the open label phase of this study. For the entire study period, the mean (SD) change from baseline (Day 1) in the peak IOP (9am) for the overall Catiolanze group was -8.60 (2.790) mmHg at Month 6, -8.59 (2.743) mmHg at Month 9, and - 8.13 (2.626) mmHg at Month 15. These efficacy results were similar to those reported at week 12 indicating that the lowering effect of Catiolanze was maintained.

For CFS score as well as OSD score there were only minimal changes in period 2 of the study.

The mean change in CFS from baseline over the entire study period for the overall Catiolanze group was -0.68 at Month 6, -0.66 at Month 9, and -0.78 at Month 15. The mean change in OSD from baseline for the entire study period in the overall Catiolanze group was -0.32 at Month 6, -0.33 at Month 9, and -0.44 at Month 15.

Phase II studies

To support the development of Latanoprost 50 µg/mL eye drops, emulsion SD, the applicant has conducted two Phase II clinical trials in patients with OAG or OHT and OSD. However, the results of these studies cannot be considered as confirmatory due methodological limitations, i.e. Study NVG09E115 lacks formal statistical testing, calculation of sample size, comparator, blinding and Study NVG10E118 doesn’t have formal endpoints and no multiplicity adjustments were made due to exploratory purposes of the study. Therefore, the results from these studies cannot firmly confirm effect of Latanoprost 50 µg/mL eye drops.

Conclusion

In conclusion, it can be agreed that intraocular pressure lowering effects of Catiolanze is not inferior as compared to Xalatan.

Use in paediatric patients

Additional studies in paediatric patients were not performed. It is noted that the reference product is approved for use in the paediatric population and the CKC-containing cationic emulsion has been approved for use in children.

Based on similarities between PK and efficacy profiles of latanoprost in adults and children as highlighted in the Xalatan SmPC and lack of biologically plausible expectation that the response to

treatment with Xalatan compared to Latanoprost 50 µg/mL eye drops, emulsion SD would be different in adults and children extrapolation of the study results to children aged 4 and above were considered acceptable. The use in children under age 4 was not considered as sufficiently justified due to the lack of safety data supporting the use of this new formulation in this age group (please see the safety section for further discussion on this issue).

2.5.7. Conclusions on the clinical efficacy

The efficacy has been satisfactorily demonstrated.

2.5.8. Clinical safety

2.5.8.1. Patient exposure

Three clinical studies were conducted to assess the safety of Latanoprost 50 µg/mL eye drops, emulsion, SD: two phase II studies (Study NVG09E115 and Study NVG10E118) and one Phase III study (Study 0130A01SA) in patients with open angle glaucoma OAG or ocular hypertension OHT with or without ocular surface disease OSD.

- Pivotal Study: 0130A01SA (P3 Investigator-Masked Period 1)
- Supportive Studies: NVG10E118 (P2 US), NVG09E115 (P2 France), and 0130A01SA (P3 Open Label Period 2)

Table 17: Summary of completed clinical studies performed with Latanoprost 50 µg/ml eye drops, emulsion SD

Study Number (country) Phase	Study Design	Control	Objective	Duration	Population	Study groups	Regimen and dose
NVG09E115 (France) Phase II	Single arm open label	None	Efficacy and safety of DE-130A after switching from Xalatan®	3 months	Patients with OAG or OHT and with mild-moderate OSD	DE-130A: 22	50 µg/mL, 1 drop daily for 3 months
NVG10E118 (United States) Phase II	Two arm, randomised (1:1), investigator masked, active control	sofZia®-preserved Travatan Z®	Efficacy and safety of DE-130A compared to Travatan Z®	3 months	Patients with OAG or OHT and OSD	DE-130A: 51 Control: 54	DE-130A = 50 µg/mL, Travatan® = 40 µg/mL 1 drop daily for 3 months
0130A01SA (Austria, Belgium, Estonia, Finland, France, Germany, Italy, Latvia, Poland, Spain, United Kingdom, Russia, South Korea) Phase III	Multicentre, investigator masked, randomised, active controlled study with open label extension	BAK-preserved Xalatan®	Non inferiority of DE-130A to Xalatan®	3 months with 12 months safety extension	Patients with OAG or OHT with or without OSD	Period 1 DE-130A: 193 Control:193 Period 2 DE-130A: 137 *	50 µg/mL, 1 drop daily for 3 months investigator masked (Period 1) and 12 months open label (Period 2)

**137 patients were enrolled into Period 2 of Study 1030A10SA. However, one patient withdrew during clinical hold and therefore only 136 were included in the analyses population. BAK = benzalkonium chloride; OAG = open angle glaucoma; OHT = ocular hypertension; OSD = ocular surface disease*

The three clinical studies of the new latanoprost formulation were presented separately and pooling of the safety data has also been conducted in line with the recommendations for an integrated presentation and analysis of safety data from all clinical trials and is accepted.

Overall extent of exposure

Exposure to Study Medication, Safety Population (Global Safety Data Cohort)

The pooled analysis of safety includes a total of 330 patients with OAG or OHT who received at least one dose of latanoprost 50 µg/ml eye drops, emulsion *SD*, including 137 patients who received latanoprost 50 µg/mL eye drops, emulsion *SD* during the 12-month extension phase of study 0130A01SA. Patients treated with latanoprost 50 µg/mL eye drops, emulsion *SD* included 58.4% with primary OAG, 9.4% with OAG, 26.4% with OHT, 3.3% with glaucoma, 1.5% with pseudo-exfoliative glaucoma, and 0.9% with pigmentary glaucoma. 63.66% of patients were female, and the mean age was 63.5 years (standard deviation 11.27 years).

The mean treatment exposure was 211.9 days in the latanoprost 50 µg/mL eye drops, emulsion *SD* group, which was substantially longer than the Xalatan® group (83.6 days) and the TravatanZ® group (80.4 days). This difference is likely to have impacted AE reporting rates, with higher rates expected when the drug exposure period is longer. 53.9% (n=178) of patients were exposed to Latanoprost 50 µg/mL eye drops, emulsion *SD* for 61 – 90 days and 38.2% (n=126) were exposed for more than 331 days (up to 481 days).

Table 18

Duration of Exposure to Treatment (days)	DE-130A (N=330)	Xalatan (N=193)	Travatan (N=54)
n	330	193	54
Mean (SD)	211.9 (159.77)	83.6 (7.82)	80.4 (15.13)
Median	86.0	84.0	84.0
Min, Max	23, 462	10, 98	9, 91
< 31 days	1 (0.3%)	2 (1.0%)	2 (3.7%)
31 - 60 days	2 (0.6%)	0 (0.0%)	2 (3.7%)
61 - 90 days	178 (53.9%)	186 (96.4%)	49 (90.7%)
91 - 150 days	15 (4.5%)	5 (2.6%)	1 (1.9%)
151 - 240 days	5 (1.5%)	0 (0.0%)	0 (0.0%)
241 - 330 days	3 (0.9%)	0 (0.0%)	0 (0.0%)
331 - 420 days	62 (18.8%)	0 (0.0%)	0 (0.0%)
421 - 481 days	64 (19.4%)	0 (0.0%)	0 (0.0%)
> 481 days	0 (0.0%)	0 (0.0%)	0 (0.0%)

Studies included: NVG09E115, NVG10E118, 0130A01SA (Investigator-Masked Period and Open Label Period)
Abbreviations: SD = standard deviation
All subjects who received at least one dose of the medication are included in each group. If a subject was treated in Xalatan during investigator-masked period and DE-130A during open label period in 0130A01SA, the subject was included in both groups for exposure duration to each medication.
For ongoing subjects, last non-missing visit data is used to calculate the exposure

Table 19

Duration of exposure to treatment (days)	DE-130A[a] (N=122)	Xalatan®[b] (N=127)	DE-130A /DE-130A (N=71)	Xalatan® /DE-130A (N=66)	Overall DE-130A[c] (N=259)
N	122	127	71	66	259
Mean (SD)	83.5 (7.79)	83.0 (9.39)	434.5 (55.27)	431.5 (66.55)	268.4 (180.40)
Median	84.0	84.0	450.0	450.0	273.0
Min, Max	23, 102	10, 98	180, 462	176, 492	23, 492
< 31 days	1 (0.8%)	2 (1.6%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
31 - 60 days	1 (0.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)
61 - 90 days	116 (95.1%)	122 (96.1%)	0 (0.0%)	0 (0.0%)	116 (44.8%)
91 - 150 days	4 (3.3%)	3 (2.4%)	0 (0.0%)	0 (0.0%)	4 (1.5%)
151 - 240 days	0 (0.0%)	0 (0.0%)	2 (2.8%)	3 (4.5%)	5 (1.9%)
241 - 330 days	0 (0.0%)	0 (0.0%)	3 (4.2%)	3 (4.5%)	6 (2.3%)
331 - 420 days	0 (0.0%)	0 (0.0%)	2 (2.8%)	0 (0.0%)	2 (0.8%)
421 - 481 days	0 (0.0%)	0 (0.0%)	64 (90.1%)	59 (89.4%)	123 (47.5%)
> 481 days	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.5%)	1 (0.4%)
Source: Study 0130A12SA CSR.					

Extent of exposure (reference product/active substance latanoprost)

The reference product Xalatan® has been on the market for more than two decades since its approval in 1996.

In the studies conducted for the RefMP, more than 460 patients were exposed to latanoprost for

up to six months. There is also extensive post-marketing exposure available for the active substance latanoprost.

Paediatric Data

There is no paediatric clinical data available for the proposed new formulation Latanoprost 50 µg/mL eye drops, emulsion SD group since there was no paediatric exposure during the clinical trials, which were conducted in adults only.

The applicant is seeking an adult and paediatric indication in line with the reference product, Xalatan, which is approved for use in both populations. Supportive data for the safety of the cationic emulsion vehicle in children is provided by a randomised trial of Verkazia (EU licensed product containing the Novasorb® technology vehicle but with a different active substance, ciclosporin) in which 169 children aged 4-17 years with severe vernal kerato-conjunctivitis were randomised 1:1:1 to receive Verkazia (2 or 4 times per day; qid or bd groups) or vehicle. Additional justification to support paediatric use was provided during the procedure and the proposed paediatric age range was limited to use in children from the age of 4 years onwards to reflect the currently available data.

2.5.8.2. Adverse event

The applicant performed two different analyses of safety data. The primary data consists of the pivotal study's outcome (IM cohort) and the pooled Global Safety Data (GSD) Cohort included all safety data from the pivotal and supportive studies (with the addition of safety data from the open label extension of phase III and both phase II studies).

Phase III Study Catiolanze10SA Pivotal study

Period 1 (12 weeks)

Adverse Events data are displayed as follows:

- Ocular Adverse Events by System Organ Class and Preferred Term (Safety Population)
- Non-Ocular Adverse Events by System Organ Class and Preferred Term (Any Preferred Term > 1%) (Safety Population)
- Suspected Adverse Reactions by System Organ Class and Preferred Term (Related to Study Drug) (Safety Population)

All AEs reported in the following text were treatment emergent unless specified otherwise.

The analysis of safety was conducted on the Safety Population (n= 386) that included all patients randomised in the study who received at least one dose of the study medication (193 in Catiolanze group and 193 in Xalatan® group).

In total, **18.1%** (n=35) of patients in the Catiolanze group and **21.8%** (n=42) in the control (Xalatan®) group reported **any AE.**

There were **three discontinuations** due to AEs, two in the Catiolanze group and one in the control group. Two discontinuations from Catiolanze group were relapse of burning mouth syndrome (coded as not resolved) and fatal acute heart failure and eye irritation with ocular hyperaemia in the control group. Both AEs from Catiolanze group are stated as not related.

Three SAEs were reported during Period 1. One in the Catiolanze group (acute heart failure) and two in the control group (bilateral pulmonary thrombosis, bladder cancer). All were non-ocular and considered by the investigator to be unrelated to study drugs. There were no CSI or sight-threatening AEs reported during Period 1.

Any **ocular AE** was reported for **10.4%** (n=20) of patients in the Catiolanze group and **13.5%** (n=26) in the control group.

Any **ocular SAR** was reported for **5.2%** (n=10) of patients in the Catiolanze group and for **10.9%** (n=21) in the control group.

Table 20

Table 14.3.1.1.1
Adverse Events: Overall Summary
Safety Population
Investigator Masked (Period 1)

Subjects with Any	DE-130A (N=193)	Xalatan (N=193)
AE(s)	35 (18.1%)	42 (21.8%)
SAE(s)	1 (0.5%)	2 (1.0%)
SAR(s) Related to Study Drug	11 (5.7%)	21 (10.9%)
SAR(s) Related to Study Procedure	0 (0.0%)	0 (0.0%)
SAR(s) Related to Artificial Tears	0 (0.0%)	0 (0.0%)
Serious SAR(s) Related to Study Drug	0 (0.0%)	0 (0.0%)
Serious SAR(s) Related to Study Procedure	0 (0.0%)	0 (0.0%)
Serious SAR(s) Related to Artificial Tears	0 (0.0%)	0 (0.0%)
AE(s) Leading to Discontinuation from Study	2 (1.0%)	1 (0.5%)
Death	1 (0.5%)	0 (0.0%)
Ocular AE(s)	20 (10.4%)	26 (13.5%)
SAE(s)	0 (0.0%)	0 (0.0%)
SAR(s) Related to Study Drug	10 (5.2%)	21 (10.9%)
SAR(s) Related to Study Procedure	0 (0.0%)	0 (0.0%)
SAR(s) Related to Artificial Tears	0 (0.0%)	0 (0.0%)
Serious SAR(s) Related to Study Drug	0 (0.0%)	0 (0.0%)
Serious SAR(s) Related to Study Procedure	0 (0.0%)	0 (0.0%)
Serious SAR(s) Related to Artificial Tears	0 (0.0%)	0 (0.0%)
AE(s) Leading to Discontinuation from Study	0 (0.0%)	1 (0.5%)
Death	0 (0.0%)	0 (0.0%)

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event; SAR = suspected adverse reaction. Subjects were classified by actual treatment received.
AEs were coded using MedDRA Version 23.1.

Ocular AEs

Phase III Study Catiolanze10SA Period 1

The most frequently reported **ocular AE** was **ocular hyperaemia,** reported for **1.6%** (n=3) patients in the Latanoprost 50 µg/ml eye drops, emulsion *SD* group, and **2.6%** (n=5) in the Xalatan® group.

Other ocular AEs occurring in 1% or more patients in any treatment group were:

- conjunctival hyperaemia (1.0% of patients in the Latanoprost 50 µg/ml eye drops, emulsion *SD* group and 1.6% in the Xalatan® group),
- dry eye (1.0% vs 0.5%, respectively),
- erythema of eyelid (1.0% in each group),
- keratitis (1.0% in the Latanoprost 50 µg/ml eye drops, emulsion *SD* group vs 0 cases in the Xalatan® group),
- vision blurred (1.0% vs 0, respectively), eye pruritus (0.5% vs 1.6%, respectively), swelling of eyelid (0.5% vs 1.0%, respectively), abnormal sensation in eye (0 vs 2.1%, respectively), eye irritation (0 vs 1.0%, respectively), foreign body sensation in eyes (0 vs 1.6%, respectively), seasonal allergy (1.0% vs 0, respectively), and instillation site pain (0 vs 1.6% respectively).

Ocular Adverse Events by System Organ Class and Preferred Term (Safety Population, Period 1)

Table 21

System organ class Preferred term	DE-130A (N=193)	Control Xalatan® (N=193)
Subjects with any ocular adverse events	20 (10.4%)	26 (13.5%)
Eye disorders	19 (9.8%)	23 (11.9%)
Ocular hyperaemia	3 (1.6%)	5 (2.6%)
Conjunctival hyperaemia	2 (1.0%)	3 (1.6%)
Dry eye	2 (1.0%)	1 (0.5%)
Erythema of eyelid	2 (1.0%)	2 (1.0%)
Keratitis	2 (1.0%)	0 (0.0%)
Vision blurred	2 (1.0%)	0 (0.0%)
Blepharitis	1 (0.5%)	0 (0.0%)
Chalazion	1 (0.5%)	0 (0.0%)
Conjunctival haemorrhage	1 (0.5%)	1 (0.5%)
Conjunctival oedema	1 (0.5%)	0 (0.0%)
Eye pain	1 (0.5%)	1 (0.5%)
Eye pruritus	1 (0.5%)	3 (1.6%)
Eyelid oedema	1 (0.5%)	0 (0.0%)
Growth of eyelashes	1 (0.5%)	0 (0.0%)
Ocular discomfort	1 (0.5%)	0 (0.0%)
Swelling of eyelid	1 (0.5%)	2 (1.0%)
Abnormal sensation in eye	0 (0.0%)	4 (2.1%)
Eye irritation	0 (0.0%)	2 (1.0%)
Foreign body sensation in eyes	0 (0.0%)	3 (1.6%)
Lacrimal disorder	0 (0.0%)	1 (0.5%)
Vitreous detachment	0 (0.0%)	1 (0.5%)
Immune system disorders	2 (1.0%)	0 (0.0%)
Seasonal allergy	2 (1.0%)	0 (0.0%)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	1 (0.5%)	0 (0.0%)
Blepharal papilloma	1 (0.5%)	0 (0.0%)
General disorders and administration site conditions	0 (0.0%)	3 (1.6%)
Instillation site pain	0 (0.0%)	3 (1.6%)
Source: Table 14.3.1.3.1		

Non-ocular AEs

Any **non-ocular AE** was reported for **10.4%** (n=20) of patients in the Latanoprost 50 µg/ml eye drops, emulsion *SD* group and **10.9%** (n=21) in the control group.

Any **non-ocular SAR** was reported for **1.0%** (n=2) of patients in the Latanoprost 50 µg/ml eye drops, emulsion *SD* group, and for **0.0%** (n=0) in the control group.

The most frequently reported **non-ocular AEs** by SOC in both groups were Infectious and Infestations, reported for 3.1% (n=6) patients in the Latanoprost 50 µg/ml eye drops, emulsion *SD* group,

and 4.1% (n=8) in the control group, and Musculoskeletal and connective tissue disorders (2.1%, n=4 in both groups).

The only PTs reported by more than 1.0% of patients were Arthralgia (1.6%, n=3 in the Latanoprost 50 µg/ml eye drops, emulsion *SD* group, all stated as not related) and Back pain (1.6%, n=3 in the control group).

Non-Ocular Adverse Events by System Organ Class and Preferred Term (Any Preferred Term > 1%) (Safety Population, Period 1)

Table 22

System organ class Preferred term	DE-130A (N=193)	Control Xalatan® (N=193)
Subjects with any non-ocular adverse events	20 (10.4%)	21 (10.9%)
Infections and infestations	6 (3.1%)	8 (4.1%)
COVID-19	1 (0.5%)	2 (1.0%)
Nasopharyngitis	1 (0.5%)	2 (1.0%)
Musculoskeletal and connective tissue disorders	4 (2.1%)	4 (2.1%)
Arthralgia	3 (1.6%)	1 (0.5%)
Back pain	0 (0.0%)	3 (1.6%)
Nervous system disorders	3 (1.6%)	1 (0.5%)
Dizziness	2 (1.0%)	1 (0.5%)
Investigations	1 (0.5%)	2 (1.0%)
Body temperature increased	0 (0.0%)	2 (1.0%)
Source: Table 14.3.1.4.1		

Suspected adverse reactions (SARs)

(Note: In the Phase II studies AEs related to the drug were identified as treatment related AEs. In the Phase III study, AEs related to the drug were identified as SARs.)

Period 1

Any SAR was reported for **5.7%** (n = 11) of patients in the latanoprost 50 µg/ml eye drops,

emulsion *SD* group and **10.9%** (n = 21) for the control group.

Any ocular SAR was reported for 5.2% (n = 10) and 10.9% (n = 21), respectively and any non-ocular SAR was reported for 1.0% (n = 2) and 0.0% (n = 0), respectively

SARs occurring in more than 1% of patients in either treatment group were ocular hyperaemia (1.6% of patients in the latanoprost 50 µg/ml eye drops, emulsion *SD* group and 2.6% in the Xalatan® group), conjunctival hyperaemia (1.0% vs 1.6%, respectively), abnormal sensation in eye (0 vs 1.6%, respectively), and instillation site pain (0 vs 1.6%, respectively).

The non-ocular SARs were dizziness and dysgeusia.

Suspected Adverse Reactions by System Organ Class and Preferred Term (Related to Study Drug) (Safety Population, Period 1)

Table 23

Table 14.3.1.9.1
Adverse Events: Summary of Suspected Adverse Reactions by System Organ Class and Preferred Term (Related to Study Drug)
Safety Population
Investigator Masked (Period 1)

System organ class Preferred term	DE-130A (N=193)	Xalatan (N=193)
Subjects with any SAR(s)	11 (5.7%)	21 (10.9%)
Eye disorders	10 (5.2%)	18 (9.3%)
Ocular hyperaemia	3 (1.6%)	5 (2.6%)
Conjunctival hyperaemia	2 (1.0%)	3 (1.6%)
Blepharitis	1 (0.5%)	0 (0.0%)
Conjunctival oedema	1 (0.5%)	0 (0.0%)
Erythema of eyelid	1 (0.5%)	2 (1.0%)
Eye pruritus	1 (0.5%)	2 (1.0%)
Eyelid oedema	1 (0.5%)	0 (0.0%)
Ocular discomfort	1 (0.5%)	0 (0.0%)
Swelling of eyelid	1 (0.5%)	2 (1.0%)
Vision blurred	1 (0.5%)	0 (0.0%)
Abnormal sensation in eye	0 (0.0%)	3 (1.6%)
Dry eye	0 (0.0%)	1 (0.5%)
Eye irritation	0 (0.0%)	2 (1.0%)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; SAR = suspected adverse drug reactions.
Any subject who experienced multiple events within a system organ class or preferred term was counted only once for that system organ class or preferred term.
Subjects were classified by actual treatment received.
AEs were coded using MedDRA Version 23.1.

Table 24

Table 14.3.1.9.1
Adverse Events: Summary of Suspected Adverse Reactions by System Organ Class and Preferred Term (Related to Study Drug)
Safety Population
Investigator Masked (Period 1)

System organ class Preferred term	DE-130A (N=193)	Xalatan (N=193)
Eye disorders (cont'd)		
Eye pain	0 (0.0%)	1 (0.5%)
Foreign body sensation in eyes	0 (0.0%)	2 (1.0%)
Lacrimal disorder	0 (0.0%)	1 (0.5%)
Nervous system disorders	2 (1.0%)	0 (0.0%)
Dizziness	1 (0.5%)	0 (0.0%)
Dysgeusia	1 (0.5%)	0 (0.0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.5%)	0 (0.0%)
Blepharal papilloma	1 (0.5%)	0 (0.0%)
General disorders and administration site conditions	0 (0.0%)	3 (1.6%)
Instillation site pain	0 (0.0%)	3 (1.6%)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; SAR = suspected adverse drug reactions.
Any subject who experienced multiple events within a system organ class or preferred term was counted only once for that system organ class or preferred term.
Subjects were classified by actual treatment received.
AEs were coded using MedDRA Version 23.1.

Suspected adverse reactions by System Organ Class and Preferred Term -

Safety population, Period 1, study Catiolanze10SA

Table 25

System organ class Preferred term	Latanoprost 50 µg/ml eye drops, emulsion *SD* (N = N = 193)	Xalatan® (N = 193)
Subjects with any SAR(s) n (%)	11 (5.7%)	21 (10.9%)
Eye disorders n (%)	10 (5.2%)	21 (10.9%)
Ocular hyperaemia	3 (1.6%)	5 (2.6%)
Conjunctival hyperaemia	2 (1.0%)	3 (1.6%)
Blepharitis	1 (0.5%)	0 (0.0%)
Conjunctival oedema	1 (0.5%)	0 (0.0%)
Erythema of eyelid	1 (0.5%)	2 (1.0%)
Eye pruritus	1 (0.5%)	2 (1.0%)
Eyelid oedema	1 (0.5%)	0 (0.0%)
Ocular discomfort	1 (0.5%)	0 (0.0%)
Swelling of eyelid	1 (0.5%)	2 (1.0%)
Vision blurred	1 (0.5%)	0 (0.0%)
Abnormal sensation in eye	0 (0.0%)	3 (1.6%)
Dry eye	0 (0.0%)	1 (0.5%)
Eye irritation	0 (0.0%)	2 (1.0%)
Eye pain	0 (0.0%)	1 (0.5%)
Foreign body sensation in eyes	0 (0.0%)	2 (1.0%)
Lacrimal disorder	0 (0.0%)	1 (0.5%)
Nervous system disorders n (%)	2 (1.0%)	0 (0.0%)
Dizziness	1 (0.5%)	0 (0.0%)
Dysgeusia	1 (0.5%)	0 (0.0%)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps) n (%)	1 (0.5%)	0 (0.0%)
Blepharal papilloma	1 (0.5%)	0 (0.0%)
General disorders and administration site conditions n (%)	0 (0.0%)	3 (1.6%)
Instillation site pain	0 (0.0%)	3 (1.6%)
Source: Table 14.3.1.9.1 *SAR, suspected adverse drug reaction*		

Adverse events by organ system

Period 1

The table below shows AEs by SOC. **Eye disorders** were the most common **(9.8%)** followed by Infections and infestations (3.1%) and Musculoskeletal and connective tissue disorders (2.1%).

Table 26: Adverse events reported by >1% of subjects by System Organ Class – Safety population, Period 1

SOC	Latanoprost 50 µg/ml eye drops, emulsion *SD* N = 193	Xalatan® N = 193
Eye disorders	19 (9.8%)	23 (11.9%)
Immune system disorders	2 (1.0%)	0 (0.0%)
Infections and infestations	6 (3.1%)	8 (4.1%)
Investigations	1 (0.5%)	2 (1.0%)
Musculoskeletal and connective tissue disorders	4 (2.1%)	4 (2.1%)
Nervous system disorders	3 (1.6%)	1 (0.5%)
Neoplasm, benign, malignant and unspecified (incl cysts and polyps)	1 (0.5%)	0 (0.0%)
General disorders and administration site conditions	0 (0.0%)	3 (1.6%)
Source: Table 30 and 31 of Study 130A10SA CSR		

Global Safety Data (GSD) Cohort:

The second analyses of safety data performed is the Global Safety Data (GSD) Cohort**:** All safety data of pivotal and supportive studies: [NVG10E118 (P2 US), NVG09E115 (P2 France), and 0130A01SA (P3 Open Label Period)] are included in this pooled dataset. This is **supportive information** of IM cohort to evaluate broader population including supportive studies.

Supportive studies:

Study 0130A01SA (Phase 3 Open Label Period)

Period 2 (12-month follow-up from Week 12, open-label Latanoprost 50µg/ml eye drops, emulsion SD treatment for the first 130 patients who complete their Week 12 visit and agree to participate in the open-label period of the study): Month 6 (± 7days), Month 9 (± 7 days) and Month 15 (± 1 week) visits.

During this safety follow-up, only the peak IOP was measured to minimise the patient burden. Prior to the IOP measurement, the following assessments were performed: OSD signs, quality-of-life questionnaire, evaluation of ocular tolerance. At 15 month visit, the assessment of the Patient Global Rating of Treatment was carried out. At month 15 and at any early termination visit, a urine pregnancy test was performed on all females of childbearing potential.

Period 2 was open in these countries: Belgium, Estonia, France, Germany, Italy, Poland, Spain,

UK, South Korea and Russia. Patients from Belgium were allowed to enter Period 2 even after the first 130 patients had been recruited to Period 2 as required by Belgian health authorities (total number of patients in Period 2 was 137).

Safety objectives (secondary)

To estimate the local ocular tolerance and systemic safety of Catiolanze up to 15 months (Periods 1 & 2, Open-Label population).

In the Safety population, at all visits and for each treatment (Period 1) and for the Open-Label population for Catiolanze at all visits (Period 2 and Periods 1 & 2 combined), safety and tolerability endpoints are:

• The incidence and severity of ocular and systemic adverse events

• Best-corrected distance visual acuity (BCDVA)

• Slit lamp examination (lashes, anterior chamber and lens).

• Dilated and undilated (for cup-to-disc ratio) fundoscopy

The **Full analysis set (FAS)** consisted of 384 subjects. 137 patients were enrolled into the open label Period 2 of Study 1030A10SA and all 137 were included in the safety analysis.

One hundred and thirty-seven (137) patients continued into Period 2. Of these 137, 71 had received Latanoprost 50 µg/mL eye drops, emulsion *SD* in Period 1 and continued treatment in Period 2 *(*Latanoprost 50 µg/mL eye drops, emulsion *SD/*Latanoprost 50 µg/mL eye drops, emulsion *SD* group) while 66 had received Xalatan® in Period 1 and switched to Latanoprost 50 µg/mL eye drops, emulsion *SD* in Period 2 (Xalatan/ Latanoprost 50 µg/mL eye drops, emulsion *SD* group*)*. One hundred and twenty-five (125) completed Period 2 and eight patients discontinued (two due to an ocular AE), while four patients were ongoing.

Statistical methods

The safety population consisted of all randomised patients who received at least one dose of the study medication. The safety population was the analysis population for all safety analyses in period 1 and used treatment as actually received.

The open label safety population included subjects who are the first 130 subjects and some subjects who completed their Week 12 Visit and agreed to participate in the open-label period of the study and received at least one dose of the study medication during the open-label period. The Open-Label Safety population is the analysis population for all safety analyses in Period 2 and for Periods 1 & 2 combined data and used treatment as actually received.

Period 2

29.6% (n=21) of patients in the Catiolanze / Latanoprost

50µg/ml eye drops, emulsion *SD* group and **30.3%** (n=20) in the Xalatan®/ Latanoprost

50µg/ml eye drops, emulsion *SD* group reported **any AE**.

Any SAR was reported for **8.5%** (n=6) of patients in the Catiolanze / Catiolanze group and for **10.6%** (n=7) in the Xalatan®/ Catiolanze group, all were **ocular events.**

There were **two discontinuations** due to AEs: one patient had abnormal sensation in eye and macular fibrosis, and one reported relapse of eye pain. All AEs were classified with moderate intensity and only abnormal sensation in eye (initially reported as dry eye sensation) was stated as related.

There were **no SAEs** or **deaths** reported during Period 2.

Table 27: Summary of adverse events - Open Label Safety population, study Catiolanze10SA

	Latanoprost 50 µg/ml eye drops, emulsion *SD* / Latanoprost 50 µg/ml eye drops, emulsion *SD* (N = 71)	Xalatan®/ Latanoprost 50 µg/ml eye drops, emulsion *SD* (N = 66)
Subjects with AE(s)	**n (%)**	**n (%)**
Any AE(s)	21 (29.6%)	20 (30.3%)
SAE(s)	0 (0.0%)	0 (0.0%)
SAR(s) Related to Study Drug	6 (8.5%)	7 (10.6%)
SAR(s) Related to Study Procedure	0 (0.0%)	0 (0.0%)
SAR(s) Related to Artificial Tears	0 (0.0%)	0 (0.0%)
Serious SAR(s) Related to Study Drug	0 (0.0%)	0 (0.0%)
Serious SAR(s) Related to Study Procedure	0 (0.0%)	0 (0.0%)
Serious SAR(s) Related to Artificial Tears	0 (0.0%)	0 (0.0%)
AE(s) Leading to Discontinuation from Study	0 (0.0%)	2 (3.0%)
Death	0 (0.0%)	0 (0.0%)
Ocular AE(s)	16 (22.5%)	12 (18.2%)
SAE(s)	0 (0.0%)	0 (0.0%)
SAR(s) Related to Study Drug	6 (8.5%)	7 (10.6%)
SAR(s) Related to Study Procedure	0 (0.0%)	0 (0.0%)
SAR(s) Related to Artificial Tears	0 (0.0%)	0 (0.0%)
Serious SAR(s) Related to Study Drug	0 (0.0%)	0 (0.0%)
Serious SAR(s) Related to Study Procedure	0 (0.0%)	0 (0.0%)
Serious SAR(s) Related to Artificial Tears	0 (0.0%)	0 (0.0%)
AE(s) Leading to Discontinuation from Study	0 (0.0%)	2 (3.0%)
Death	0 (0.0%)	0 (0.0%)
Non-Ocular AE(s)	10 (14.1%)	8 (12.1%)
SAE(s)	0 (0.0%)	0 (0.0%)
SAR(s) Related to Study Drug	0 (0.0%)	0 (0.0%)
SAR(s) Related to Study Procedure	0 (0.0%)	0 (0.0%)
SAR(s) Related to Artificial Tears	0 (0.0%)	0 (0.0%)
Serious SAR(s) Related to Study Drug	0 (0.0%)	0 (0.0%)
Serious SAR(s) Related to Study Procedure	0 (0.0%)	0 (0.0%)
Serious SAR(s) Related to Artificial Tears	0 (0.0%)	0 (0.0%)
AE(s) Leading to Discontinuation from Study	0 (0.0%)	0 (0.0%)
Death	0 (0.0%)	0 (0.0%)
N = number of patients, AE = adverse event, SAR = suspected adverse reactions		

Ocular AEs – Period 2

Any **ocular AE** was reported for **22.5%** (n=16) of patients in the Latanoprost 50µg/ml eye drops, emulsion *SD* / Catiolanze group and for **18.2%** (n=12) in the Xalatan®/ Catiolanze group.

The most frequently reported ocular AE during Period 2 was **abnormal sensation in eye** which was reported for 3.6% of patients in the Overall Latanoprost 50 µg/ml eye drops, emulsion *SD* group. Other ocular AEs occurring in ≥ 1% of patients in the overall Latanoprost 50 µg/ml eye drops,

emulsion, *SD* group were growth of eyelashes (2.9%), ocular hyperaemia (2.9%), swelling of eyelid (2.2%), blepharitis (1.5%), conjunctival hyperaemia (1.5%), and eye pain (1.5) All ocular AEs were mild or moderate in severity, except for eye pruritus (table below).

Table 28: Ocular adverse events by Preferred Term - Open Label Safety population, study Catiolanze10SA

System organ class Preferred term	Latanoprost 50 µg/ml eye drops, emulsion *SD* / Latanoprost 50 µg/ml eye drops, emulsion *SD* (N = 71)	Xalatan®/ Latanoprost 50 µg/ml eye drops, emulsion *SD* (N = 66)	Overall Latanoprost 50 µg/ml eye drops, emulsion *SD* (N=137)
Subjects with any Ocular AE(s), n (%)	16 (22.5%)	12 (18.2%)	28 (20.4%)
Eye disorders, n (%)	13 (18.3%)	12 (18.2%)	25 (18.2%)
Growth of eyelashes	2 (2.8%)	2 (3.0%)	4 (2.9%)
Ocular hyperaemia	2 (2.8%)	2 (3.0%)	4 (2.9%)
Abnormal sensation in eye	1 (1.4%)	4 (6.1%)	5 (3.6%)
Blepharitis	1 (1.4%)	1 (1.5%)	2 (1.5%)
Cataract	1 (1.4%)	0 (0.0%)	1 (0.7%)
Chalazion	1 (1.4%)	0 (0.0%)	1 (0.7%)
Conjunctival hyperaemia	1 (1.4%)	1 (1.5%)	2 (1.5%)
Dry eye	1 (1.4%)	0 (0.0%)	1 (0.7%)
Eye pain	1 (1.4%)	1 (1.5%)	2 (1.5%)
Eye paraesthesia	1 (1.4%)	0 (0.0%)	1 (0.7%)
Retinal haemorrhage	1 (1.4%)	0 (0.0%)	1 (0.7%)
Swelling of eyelid	1 (1.4%)	2 (3.0%)	3 (2.2%)
Vision blurred	0 (0.0%)	0 (0.0%)	0 (0.0%)
Visual impairment	1 (1.4%)	0 (0.0%)	1 (0.7%)
Vitreous detachment	1 (1.4%)	0 (0.0%)	1 (0.7%)
Vitreous floaters	1 (1.4%)	0 (0.0%)	1 (0.7%)
Conjunctival haemorrhage	0 (0.0%)	0 (0.0%)	0 (0.0%)
Erythema of eyelid	0 (0.0%)	1 (1.5%)	1 (0.7%)

System organ class Preferred term	Latanoprost 50 µg/ml eye drops, emulsion *SD* / Latanoprost 50 µg/ml eye drops, emulsion *SD* (N = 71)	Xalatan®/ Latanoprost 50 µg/ml eye drops, emulsion *SD* (N = 66)	Overall Latanoprost 50 µg/ml eye drops, emulsion *SD* (N=137)
Eye pruritus	0 (0.0%)	1 (1.5%)	1 (0.7%)
Foreign body sensation in eyes	0 (0.0%)	1 (1.5%)	1 (0.7%)
Macular fibrosis	0 (0.0%)	1 (1.5%)	1 (0.7%)
Photopsia	0 (0.0%)	1 (1.5%)	1 (0.7%)
Infections and infestations, n (%)	3 (4.2%)	0 (0.0%)	3 (2.2%)
Conjunctivitis	1 (1.4%)	0 (0.0%)	1 (0.7%)
Conjunctivitis viral	1 (1.4%)	0 (0.0%)	1 (0.7%)
Hordeolum	1 (1.4%)	0 (0.0%)	1 (0.7%)
Immune system disorders, n (%)	1 (1.4%)	0 (0.0%)	1 (0.7%)
Seasonal allergy	1 (1.4%)	0 (0.0%)	1 (0.7%)
General disorders and administration site conditions, n (%)	0 (0.0%)	2 (3.0%)	2 (1.5%)
Instillation site pain	0 (0.0%)	1 (1.5%)	1 (0.7%)
Pain	0 (0.0%)	1 (1.5%)	1 (0.7%)

Source: Table 41, study 130A10SA CSR. AE = adverse event.

Non-ocular AE

Any **non-ocular AE** was reported for **14.1%** (n = 10) of patients in the latanoprost 50 µg/ml eye drops, emulsion *SD*/latanoprost 50 µg/ml eye drops, emulsion *SD* group and for **12.1%** (n = 8) in the Xalatan®/latanoprost 50 µg/ml eye drops, emulsion *SD* group.

Non-ocular AEs were reported for **13.11%** (n = 18) patients in the overall latanoprost 50 µg/ml eye drops, emulsion *SD* group during Period 2. The only PT reported by more than one patient was Covid-19 infection (two patients in the Xalatan®/latanoprost 50 µg/ml eye drops, emulsion *SD* group).

Table 29

Table 14.3.1.7.2
Adverse Events: Summary of Non-Ocular Adverse Events by System Organ Class and Preferred Term and Maximum Severity
Open Label Safety Population
Open Label (Period 2)

System Organ Class Preferred Term Maximum Severity	DE-130A /DE-130A (N=71)	Xalatan /DE-130A (N=66)	Overall DE-130A (N=137)
Subjects with any Non-Ocular AE(s)	10 (14.1%)	8 (12.1%)	18 (13.1%)
Infections and infestations	4 (5.6%)	4 (6.1%)	8 (5.8%)
Ear infection	1 (1.4%)	0 (0.0%)	1 (0.7%)
Mild	1 (1.4%)	0 (0.0%)	1 (0.7%)
Herpes simplex	1 (1.4%)	0 (0.0%)	1 (0.7%)
Mild	1 (1.4%)	0 (0.0%)	1 (0.7%)
Influenza	1 (1.4%)	0 (0.0%)	1 (0.7%)
Mild	1 (1.4%)	0 (0.0%)	1 (0.7%)
Rhinitis	1 (1.4%)	1 (1.5%)	2 (1.5%)
Mild	1 (1.4%)	1 (1.5%)	2 (1.5%)
Upper respiratory tract infection	1 (1.4%)	0 (0.0%)	1 (0.7%)
Mild	1 (1.4%)	0 (0.0%)	1 (0.7%)

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities.
Any subject who experienced multiple events within a system organ class or preferred term was counted only once for that system organ class or preferred term, at the maximum severity.
Subjects were classified by actual treatment received.
AEs were coded using MedDRA Version 23.1.

Table 30

Table 14.3.1.7.2
Adverse Events: Summary of Non-Ocular Adverse Events by System Organ Class and Preferred Term and Maximum Severity
Open Label Safety Population
Open Label (Period 2)

System Organ Class Preferred Term Maximum Severity	DE-130A /DE-130A (N=71)	Xalatan /DE-130A (N=66)	Overall DE-130A (N=137)
Infections and infestations (cont'd)			
COVID-19	0 (0.0%)	2 (3.0%)	2 (1.5%)
Mild	0 (0.0%)	1 (1.5%)	1 (0.7%)
Moderate	0 (0.0%)	1 (1.5%)	1 (0.7%)
Coronavirus infection	0 (0.0%)	1 (1.5%)	1 (0.7%)
Moderate	0 (0.0%)	1 (1.5%)	1 (0.7%)
Cardiac disorders	2 (2.8%)	0 (0.0%)	2 (1.5%)
Atrial fibrillation	1 (1.4%)	0 (0.0%)	1 (0.7%)
Mild	1 (1.4%)	0 (0.0%)	1 (0.7%)
Palpitations	1 (1.4%)	0 (0.0%)	1 (0.7%)
Mild	1 (1.4%)	0 (0.0%)	1 (0.7%)
Musculoskeletal and connective tissue disorders	2 (2.8%)	3 (4.5%)	5 (3.6%)

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities.
Any subject who experienced multiple events within a system organ class or preferred term was counted only once for that system organ class or preferred term, at the maximum severity.
Subjects were classified by actual treatment received.
AEs were coded using MedDRA Version 23.1.

Table 31

Table 14.3.1.7.2
Adverse Events: Summary of Non-Ocular Adverse Events by System Organ Class and Preferred Term and Maximum Severity
Open Label Safety Population
Open Label (Period 2)

System Organ Class Preferred Term Maximum Severity	DE-130A /DE-130A (N=71)	Xalatan /DE-130A (N=66)	Overall DE-130A (N=137)
Musculoskeletal and connective tissue disorders (cont'd)			
Musculoskeletal chest pain	1 (1.4%)	0 (0.0%)	1 (0.7%)
Mild	1 (1.4%)	0 (0.0%)	1 (0.7%)
Plantar fasciitis	1 (1.4%)	0 (0.0%)	1 (0.7%)
Mild	1 (1.4%)	0 (0.0%)	1 (0.7%)
Arthralgia	0 (0.0%)	1 (1.5%)	1 (0.7%)
Moderate	0 (0.0%)	1 (1.5%)	1 (0.7%)
Back pain	0 (0.0%)	1 (1.5%)	1 (0.7%)
Mild	0 (0.0%)	1 (1.5%)	1 (0.7%)
Mobility decreased	0 (0.0%)	1 (1.5%)	1 (0.7%)
Moderate	0 (0.0%)	1 (1.5%)	1 (0.7%)
Osteoarthritis	0 (0.0%)	1 (1.5%)	1 (0.7%)
Moderate	0 (0.0%)	1 (1.5%)	1 (0.7%)

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities.
Any subject who experienced multiple events within a system organ class or preferred term was counted only once for that system organ class or preferred term, at the maximum severity.
Subjects were classified by actual treatment received.
AEs were coded using MedDRA Version 23.1.

Table 32

Table 14.3.1.7.2
Adverse Events: Summary of Non-Ocular Adverse Events by System Organ Class and Preferred Term and Maximum Severity
Open Label Safety Population
Open Label (Period 2)

System Organ Class Preferred Term Maximum Severity	DE-130A /DE-130A (N=71)	Xalatan /DE-130A (N=66)	Overall DE-130A (N=137)
Musculoskeletal and connective tissue disorders (cont'd)			
Spinal pain	0 (0.0%)	1 (1.5%)	1 (0.7%)
Mild	0 (0.0%)	1 (1.5%)	1 (0.7%)
Injury, poisoning and procedural complications	1 (1.4%)	0 (0.0%)	1 (0.7%)
Skin laceration	1 (1.4%)	0 (0.0%)	1 (0.7%)
Mild	1 (1.4%)	0 (0.0%)	1 (0.7%)
Metabolism and nutrition disorders	1 (1.4%)	0 (0.0%)	1 (0.7%)
Gout	1 (1.4%)	0 (0.0%)	1 (0.7%)
Mild	1 (1.4%)	0 (0.0%)	1 (0.7%)
Skin and subcutaneous tissue disorders	1 (1.4%)	0 (0.0%)	1 (0.7%)
Hyperkeratosis	1 (1.4%)	0 (0.0%)	1 (0.7%)
Mild	1 (1.4%)	0 (0.0%)	1 (0.7%)
Vascular disorders	1 (1.4%)	0 (0.0%)	1 (0.7%)

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities.
Any subject who experienced multiple events within a system organ class or preferred term was counted only once for that system organ class or preferred term, at the maximum severity.
Subjects were classified by actual treatment received.
AEs were coded using MedDRA Version 23.1.

Table 33

Table 14.3.1.7.2
Adverse Events: Summary of Non-Ocular Adverse Events by System Organ Class and Preferred Term and Maximum Severity
Open Label Safety Population
Open Label (Period 2)

System Organ Class Preferred Term Maximum Severity	DE-130A /DE-130A (N=71)	Xalatan /DE-130A (N=66)	Overall DE-130A (N=137)
Vascular disorders (cont'd)			
Hypertension	1 (1.4%)	0 (0.0%)	1 (0.7%)
Mild	1 (1.4%)	0 (0.0%)	1 (0.7%)
Surgical and medical procedures	0 (0.0%)	1 (1.5%)	1 (0.7%)
Dental implantation	0 (0.0%)	1 (1.5%)	1 (0.7%)
Mild	0 (0.0%)	1 (1.5%)	1 (0.7%)

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities.
Any subject who experienced multiple events within a system organ class or preferred term was counted only once for that system organ class or preferred term, at the maximum severity.
Subjects were classified by actual treatment received.
AEs were coded using MedDRA Version 23.1.

Suspected Adverse Reactions (SARs) Period 2

Any SAR was reported for 8.5% (n = 6) of patients in the Latanoprost 50 µg/ml eye drops, emulsion *SD* group/ Latanoprost 50 µg/ml eye drops, emulsion *SD* group and for 10.6% (n = 7) in the Xalatan/ Latanoprost 50 µg/ml eye drops, emulsion *SD* group, all were ocular AEs.

SARs were reported for 13 patients (9.5%) in the overall Latanoprost 50 µg/ml eye drops, emulsion *SD* group. SARs occurring in more than 1% of patients in the overall Latanoprost 50 µg/ml eye drops, emulsion *SD* group during Period 2 were ocular hyperaemia (2.9%), abnormal sensation in eye (2.2%), growth of eyelashes (2.2%), conjunctival hyperaemia (1.5%), and swelling of eyelid (1.5%) (table below).

Table 34: Suspected adverse reactions by System Organ Class and Preferred Term - Open Label Safety population, study Catiolanze10SA

System organ class	Latanoprost 50 µg/ml eye drops, emulsion *SD*/ Latanoprost 50 µg/ml eye drops, emulsion SD N = 71	Xalatan®/ Latanoprost 50 µg/ml eye drops, emulsion *SD* N = 66	Overall Latanoprost 50 µg/ml eye drops, emulsion *SD* N = 137
Subjects with any Suspected AR	6 (8.5%)	7 (10.6%)	13 (9.5%)
Eye disorders	6 (8.5%)	6 (9.1%)	12 (8.8%)
Ocular hyperaemia	2 (2.8%)	2 (3.0%)	4 (2.9%)
Abnormal sensation in eye	1 (1.4%)	2 (3.0%)	3 (2.2%)
Blepharitis	1 (1.4%)	0 (0.0%)	1 (0.7%)
Conjunctival hyperaemia	1 (1.4%)	1 (1.5%)	2 (1.5%)
Eye paraesthesia	1 (1.4%)	0 (0.0%)	1 (0.7%)
Growth of eyelashes	1 (1.4%)	2 (3.0%)	3 (2.2%)
Vision blurred	0 (0.0%)	0 (0.0%)	0 (0.0%)
Erythema of eyelid	0 (0.0%)	1 (1.5%)	1 (0.7%)
Eye pain	0 (0.0%)	0 (0.0%)	0 (0.0%)
Eye pruritus	0 (0.0%)	1 (1.5%)	1 (0.7%)
Swelling of eyelid	0 (0.0%)	2 (3.0%)	2 (1.5%)
Nervous system disorders, n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Dizziness	0 (0.0%)	0 (0.0%)	0 (0.0%)
General disorders and administration site conditions, n (%)	0 (0.0%)	1 (1.5%)	1 (0.7%)
Instillation site pain	0 (0.0%)	1 (1.5%)	1 (0.7%)
SAR = Suspected adverse reaction			

Period 2

The table below shows AEs by SOC. Eye disorders were the most common (18.2%) followed by infections and infestations (12.4%) and musculoskeletal and connective tissue disorders (5.8%).

Table 35: Adverse events reported by >1% of subjects by System Organ Class – Safety population, Period 2, study Catiolanze10SA

SOC	Latanoprost 50 µg/ml eye drops, emulsion *SD*/ Latanoprost 50 µg/ml eye drops, emulsion *SD* N = 71	Xalatan®/ Latanoprost 50 µg/ml eye drops, emulsion *SD* N = 193	Overall Latanoprost 50 µg/ml eye drops, emulsion *SD* N = 137
Eye disorders	13 (18.3%)	12 (18.2%)	25 (18.2%)
Immune system disorders	1 (1.4%)	0 (0.0%)	1 (0.7%)
Infections and infestations			
Ocular	3 (4.2%)	0 (0.0%)	3 (2.2%)
Non ocular	6 (3.1%)	8 (4.1%)	14 (10.2%)
Investigations	1 (0.5%)	2 (1.0%)	3 (2.2%)
Musculoskeletal and connective tissue disorders	4 (2.1%)	4 (2.1%)	8 (5.8%)
Nervous system disorders	3 (1.6%)	1 (0.5%)	4 (2.9%)
Cardiac disorders	2 (1.0%)	0 (0.0%)	2 (1.5%)
Gastrointestinal disorders	2 (1.0%)	0 (0.0%)	2 (1.5%)
Respiratory, thoracic and mediastinal disorders	2 (1.0%)	2 (1.0%)	4 (2.9%)
General disorders and administration site conditions			
Ocular	0 (0.0%)	2 (3.0%)	2 (1.5%)
Non ocular	1 (0.5%)	2 (1.0%)	3 (2.1%)

Pooled safety data from Global Safety Data (GSD) Cohort:

The GSD Cohort (pooled dataset) includes all safety data of pivotal Study 0130A01SA Period 1 and supportive studies: [NVG10E118 (Phase 2), NVG09E115 (Phase 2), and 0130A01SA (Phase 3 Open Label Period)]. This is supportive information of IM cohort to evaluate broader population including supportive studies.

Table 36: Subject Disposition, Safety Population (Global Safety Data Cohort)

	DE-130A (N=330)	Xalatan (N=193)	Travatan (N=54)
Safety Population	330	193	54
Completers	315 (95.5%)	190 (98.4%)	51 (94.4%)
Ongoing	4 (1.2%)	0 (0.0%)	0 (0.0%)
Prematurely Discontinued	11 (3.3%)	3 (1.6%)	3 (5.6%)
Adverse Event	4 (1.2%)	1 (0.5%)	3 (5.6%)
Withdrawal by Subject	5 (1.5%)	1 (0.5%)	0 (0.0%)
Other	2 (0.6%)	1 (0.5%)	0 (0.0%)

Studies included: NVG09E115, NVG10E118, 0130A01SA (Investigator-Masked Period and Open Label Period)
If a subject had Xalatan/DE-130A treatment in 0130A01SA, the subject was counted twice in both DE-130A and Xalatan treatment groups.
Other: Pregnancy (subject 6160008-1049), early termination (subject 6430011-1265) and sponsor temporarily discontinued study (subject 2460001-1001)

Global Safety Data cohort – Pooled AE data from all studies

Table 37: Adverse Events: Overall Summary, Safety Population (Global Safety Data Cohort)

Subjects with Any	DE-130A (N=330)	Xalatan (N=193)	Travatan (N=54)
AE(s)	74 (22.4%)	42 (21.8%)	8 (14.8%)
SAE(s)	1 (0.3%)	2 (1.0%)	1 (1.9%)
SAR(s) Related to Study Drug	19 (5.8%)	21 (10.9%)	3 (5.6%)
Serious SAR(s) Related to Study Drug	0 (0.0%)	0 (0.0%)	0 (0.0%)
AE(s) Leading to Discontinuation from Study	4 (1.2%)	1 (0.5%)	3 (5.6%)
Death	1 (0.3%)	0 (0.0%)	0 (0.0%)
Ocular AE(s)	42 (12.7%)	26 (13.5%)	3 (5.6%)
SAE(s)	0 (0.0%)	0 (0.0%)	0 (0.0%)
SAR(s) Related to Study Drug	18 (5.5%)	21 (10.9%)	3 (5.6%)
Serious SAR(s) Related to Study Drug	0 (0.0%)	0 (0.0%)	0 (0.0%)
AE(s) Leading to Discontinuation from Study	2 (0.6%)	1 (0.5%)	2 (3.7%)
Death	0 (0.0%)	0 (0.0%)	0 (0.0%)
Non-Ocular AE(s)	41 (12.4%)	21 (10.9%)	5 (9.3%)
SAE(s)	1 (0.3%)	2 (1.0%)	1 (1.9%)
SAR(s) Related to Study Drug	2 (0.6%)	0 (0.0%)	0 (0.0%)
Serious SAR(s) Related to Study Drug	0 (0.0%)	0 (0.0%)	0 (0.0%)
AE(s) Leading to Discontinuation from Study	2 (0.6%)	0 (0.0%)	1 (1.9%)
Death	1 (0.3%)	0 (0.0%)	0 (0.0%)

Studies included: NVG09E115, NVG10E118, 0130A01SA (Investigator-Masked Period and Open Label Period)
Abbreviations: AE = adverse event; SAE = serious adverse event; SAR = suspected adverse reaction; MedDRA = Medical Dictionary for Regulatory Activities
Subjects were classified by actual treatment received

An overall summary of all AEs for all three studies conducted for Catiolanze is shown in the table above. The proportion of subjects with any AE was similar between

the Catiolanze and RefMP group (22.4% vs 21.8%) despite the longer mean exposure to Catiolanze. Four subjects reported SAEs across all three studies and only one of these occurred when receiving the Catiolanze.

There were 43 subjects with SARs, none were serious, and the proportion was smaller in subjects taking Catiolanze than for RefMP (5.8% vs 10.9%) despite the shorter mean exposure in the RefMP group.

Eight subjects reported AEs leading to discontinuation, 4 of these were in the Catiolanze group.

There was one death in all three studies in the Catiolanze group which was considered unrelated to study drug. There were slightly more ocular AEs in the RefMP group than for Catiolanze (13.5% vs 12.7%) and slightly more non ocular AEs with Catiolanze than the RefMP (12.4% vs 10.9), only one was serious and was considered not related to study drug.

Ocular AEs

The table below shows the **ocular AEs** by system organ class (SOC) and preferred term (PT).

The majority were mild in intensity. Of the eye disorders reported, ocular hyperaemia was most common across all treatment groups (1.5% vs 2.6% vs 1.9% in the Catiolanze, Xalatan and Travatan Z groups respectively).

Table 38: Summary of ocular adverse events by System Organ Class and Preferred Term – Global Safety Data cohort

SOC Preferred term	Latanoprost 50 µg/ml eye drops, emulsion *SD* N = 330	Xalatan® N = 193	Travatan Z® N = 54
Subjects with any ocular AE	42 (12.7%)	26 (13.5%)	3 (5.6%)
Eye disorders	37 (11.2%)	23 (11.9%)	2 (3.7%)
Ocular hyperaemia	5 (1.5%)	5 (2.6%)	1 (1.9%)
Growth of eyelashes	4 (1.2%)	0 (0.0%)	0 (0.0%)
Swelling of eyelid	4 (1.2%)	0 (00.0%)	0 (0.0%)
Abnormal sensation in eye	3 (0.9%)	4 (2.1%)	0
Conjunctival hyperaemia	3 (0.9%)	3 (1.6%)	0
Dry eye	3 (0.9%)	1 (0.5%)	0 (0.0%)
Erythema of eyelid	3 (0.9%)	2 (1.0%)	0 (0.0%)
Blepharitis	2 (0.6%)	0	0
Eye pain	2 ((0.6%)	1 (0.5%)	0 (0.0%)
Keratitis	2 (0.6%)	0	0
Vision blurred	2 (0.6%)	0	0
Cataract	1 (0.3%)	0	0
Chalazion	1(0.3%)	0	0
Conjunctival haemorrhage	1 (0.3%)	1(0.5%)	0
Conjunctival oedema	1 (0.3%)	0	0
Eye paraesthesia	1 (0.3%)	0	0
Eye pruritis	1 (0.3%)	3 (1.6%)	0
Eyelid oedema	1 (0.3%)	0	0
Foreign body sensation in eyes	1 (0.3%)	3 (1.6%)	0
Macular fibrosis	1 (0.3%)	0	0
Meibomianitis	1 (0.3%)	0	0
Ocular discomfort	1 (0.3%)	0	0
Photopsia	1 (0.3%)	0	0
Punctuate keratitis	1 (0.3%)	0	0
Retinal haemorrhage	1 (0.3%)	0	0
Visual impairment	1(0.3%)	0	0
Vitreous detachment	1 (0.3%)	1 (0.5%)	0
Vitreous floaters	1 (0.3)	0	0
Conjunctivitis allergic	0	0	1 (1.9%)
Eye irritation	0	2(1.0%)	0
Lacrimal disorder	0	1(0.5%)	0
Infections and infestations	3 (0.9%)	0	0
Conjunctivitis	1 (0.3%)	0	0
Conjunctivitis viral	1 (0.3%)	0	0
Hordeolum	1 (0.3%)	0	0
General disorders and administration site conditions	2 (0.6%)	3 (1.6%)	1 (1.9%)
Instillation site pain	1 (0.3%)	3 (1.6%)	1 (1.9%)
Pain	1 (0.3%)	0	0
Immune system disorders	2 (0.6%)	0	0
Seasonal allergy	2 (0.6%)	0	0
Investigations	1 (0.3%)	0	0
Intraocular pressure increased	1 (0.3%)	0	0

Neoplasms, benign, malignant and unspecified (incl cyst and polyps)	1 (0.3%)	0	0
Blepheral papilloma	1 (0.3%)	0	0

Source ISS Table 14.3.2.3. Studies included: NVG09E115, NVG10E118, 0130A01SA (Investigator-Masked Period and Open Label Period). AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities.

Any subject who experienced multiple events within a system organ class or preferred term was counted only once for that system organ class or preferred term. Subjects were classified by actual treatment received.

Ocular SARs

The proportion of subjects reporting **ocular SARs** by SOC and PT which were considered related to study drug is outlined in the table below.

Any ocular SARs were reported in 5.2% (n = 17) of patients receiving Catiolanze, 9.33% (n = 18) of patients receiving Xalatan® and 3.7% (n =2) of patients receiving Travatan Z®. The ocular SAR occurring in more than 1% of patients was ocular hyperaemia (1.2%) for those patients receiving Catiolanze.

Table 39: Summary of ocular suspected adverse reactions by Preferred Term – Global Safety Data cohort

SOC PT	Latanoprost 50 µg/ml eye drops, emulsion *SD* N = 330	Xalatan® N = 193	Travatan Z® N = 54
Eye disorders n (%)	17 (5.2%)	18(9.33%)	2 (3.7%)
Ocular hyperaemia	4 (1.2%)	5 (2.6%)	1 (1.9%)
Conjunctival hyperaemia	3 (0.9%)	3 (1.6%)	0 (0.0%)
Growth of eyelashes	3 (0.9%)	0 (0.0%)	0 (0.0%)
Swelling of eyelid	3 (0.9%)	2 (1.0%)	0 (0.0%)
Abnormal sensation in eye	2(0.6%)	3 (1.6%)	0 (0.0%)
Erythema of eyelid	2 (0.6%)	2 (1.0%)	0 (0.0%)
Blepharitis	1 (0.3%)	0 (0.0%)	0 (0.0%)
Conjunctival oedema	1 (0.3%)	0 (0.0%)	0 (0.0%)
Eye paraesthesia	1 (0.3%)	0 (0.0%)	0 (0.0%)
Eye pruritus	1 (0.3%)	2 (1.0%)	0 (0.0%)
Eyelid oedema	1 (0.3%)	0 (0.0%)	0 (0.0%)
Ocular discomfort	1 (0.3%)	0 (0.0%)	0 (0.0%)
Vision blurred	1 (0.3%)	0 (0.0%)	0 (0.0%)
Conjunctivitis allergic	0 (0.0%)	0 (0.0%)	1 (1.9%)
Dry eye	0 (0.0%)	1 (0.5%)	0 (0.0%)
Eye irritation	0	2 (1.0%)	0 (0.0%)
Eye pain	0 (0.0%)	1 (0.5%)	0 (0.0%)
Foreign body sensation in eyes	0 (0.0%)	2 (1.0%)	0 (0.0%)
Lacrimal disorder	0 (0.0%)	1 (0.5%)	0 (0.0%)
General disorders and administration site conditions n (%)	1 (0.3%)	3 (1.6%)	1 (1.9%)
Instillation site pain	1 (0.3%)	3 (1.6%)	1 (1.9%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) n (%)	1 (0.3%)	0 (0.0%)	0 (0.0%)
Blepharal papilloma	1 (0.3%)	0 (0.0%)	0 (0.0%)

Source: ISS Table 14.3.5.1. Studies included: NVG09E115, NVG10E118, 0130A01SA (Investigator-Masked Period and Open Label Period). MedDRA = Medical Dictionary for Regulatory Activities; SAR = suspected adverse drug reactions. Any subject who experienced multiple events within a system organ class or preferred term was counted only once for that system organ class or preferred term, at the maximum severity. Subjects were classified by actual treatment received.

Non-ocular AEs
The majority of non-ocular AEs were mild infections and infestations and were not considered related to study drugs.

Non-ocular SARs were reported in less than 1% (0.3% each) of patients: dizziness and dysguesia.

AEs by SOC.

The table below shows a summary of AEs by SOC.
Eye disorders were the most represented SOC, as expected with an eye drop emulsion product. The proportion of subjects reporting eye disorders was similar between the Latanoprost 50 µg/ml eye drops, emulsion *SD* and RefMP groups (11.2% vs 11.9%). This was followed by infections and infestations (6.1%) and then musculoskeletal and connective tissue disorders (2.7%) for those patients treated with Latanoprost 50 µg/ml eye drops, emulsion *SD*.

The proportion of subjects reporting administration site disorders under the SOC General disorders and administration site conditions was higher in the RefMP group than for Catiolanze (0.2% vs 2.6%).

Table 40: Summary of adverse events by System Organ Class – Global Safety Data cohort

SOC	Latanoprost 50 µg/ml eye drops, emulsion *SD* N = 330	Xalatan® N = 193	Travatan Z® N = 54
Subjects with any AE	74 (22.4%)	42 (21.8%)	8 (14.8%)
Eye disorders	37 (11.2%)	23 (11.9%)	2 (3.7%)
Infections and infestations	20 (6.1%)	8 (4.1%)	1 (1.9%)
Musculoskeletal and connective tissue disorders	9 (2.7%)	4 (2.1%)	0
Cardiac disorders	4 (1.2%)	0	0
Injury, poisoning and procedural complications	4 (1.2%)	1 (0.5%)	0
Nervous system disorders	4 (1.2%)	1 (0.5%)	0
Gastrointestinal disorders	3 (0.9%)	0	1 (1.9%)
General disorders and administration site conditions	3 (0.9%)	5 (2.6%)	1 (1.9%)
Immune system disorders	2 (0.6%)	0	0
Investigations	2 (0.6%)	2 (1.0%)	0
Respiratory, thoracic and mediastinal disorders	2 (0.6%)	2 91.0%)	1 (1.9%)
Vascular disorders	1 (0.3%)	0	1(1.9%)
Endocrine disorders	0	0	1 (1.9%)
Hepatobiliary disorders	0	1 (0.5%)	0
Renal and urinary disorders	0	0	1 (1.9%)

Additional Safety Parameters:

Visual acuity

In all three studies there were no clinically significant changes in visual acuity as measured by BCDVA between baseline and Day 84.

Slit lamp biomicroscopy

In Study NVG10E118 and Study 0130A01SA, there were no clinically significant findings during slit lamp examination in terms of lens examination, proportion of abnormal lashes, optic nerve findings, retina, macula, choroid, and vitreous.

Dilated fundoscopy and cup to disc ratio

In Study NVG10E118, there were no clinically significant findings at Visit 4, except for one patient in the Catiolanze group for whom the cup to disc ratio of 9 was considered abnormal in the optic nerve region OD/in the worse eye (the ratio of 8 at baseline had been normal).

In Study 0130A01SA , there was no worsening of findings from baseline to Week 4, Week 12 or Month 15 in any of the treatment groups.

Visual fields

In Study 0130A01SA , small improvements in the Visual Field Index were observed in the Catiolanze/ Catiolanze group at Month 9 compared to baseline. The mean (SD) change was 0.9 (2.84) in the Catiolanze/Catiolanze group and 0.1 (2.26) in the Xalatan®/ Catiolanze group.

Hyperaemia

The proportion of subjects reporting ocular hyperaemia was lower in the latanoprost 50µg/ml eye drops, emulsion *SD* group (1.5%) than for Xalatan® (2.6%) and similar to Travatan Z (1.9%).

2.5.8.3. Serious adverse event/deaths/other significant events

Serious Adverse Events (SAEs)

Four subjects reported serious adverse events (SAEs) across the three studies. None were

considered by the investigator as related to the study drugs or procedures:

- Acute cardiac failure in a patient receiving Latanoprost 50 µg/mL eye drops, emulsion *SD* with onset on Day 87.
- Bladder cancer in a patient receiving Xalatan® with onset on Day 62.
- Pulmonary thrombosis in a patient receiving Xalatan® with onset on Day 69.
- Colonic abscess in a patient receiving Travatan Z®.

Study NVG09E115 – Phase II

There were no SAEs were reported during this study.

Study NVG10E118 – Phase II

Two serious non-ocular TEAEs (severe intestinal abscess and moderate abscess drainage) were reported in one subject in the Travatan Z® group which resolved.

Additionally, one serious pre-treatment non-ocular SAE (severe pneumonia) occurred which was considered life threatening and led to hospitalisation. All three events were considered unrelated to study drug.

Phase III

Period 1

Three SAEs were reported during the study. All occurred during Period 1, all were non-ocular and considered by the investigator to be unrelated to study drugs.

1. One patient (ID=6430007-1158) in the Catiolanze group had acute cardiac failure and died

2. One patient in the control group (ID=4280008-1369) had bilateral pulmonary thrombosis with onset on Day 69. The event resolved and treatment with Xalatan® continued uninterrupted.

3. One patient in the control group (ID=7240004-1463) had bladder cancer with onset on

Day 62. The outcome was recovering/resolving and treatment with Xalatan® continued uninterrupted.

During the washout period (no study drug administered) there was an SAE (foot fracture which recovered with sequelae).

Global Safety Data cohort – Pooled data from all studies

The table below shows the proportion of subjects reporting SAE across all three clinical studies. There were no serious ocular AEs reported.

There was only one SAE reported with Catiolanze: acute cardiac failure which resulted in death but was considered not related to the study drug.

Table 41: Summary of serious adverse events – Global Safety Data cohort

SOC PT	Latanoprost 50 µg/ml eye drops, emulsion *SD* N = 330	Xalatan® N = 193	Travatan Z® N = 54
Subjects with any AEs	1 (0.3%)	2 (1.0%)	1 (1.9%)
Cardiac disorders	1 (0.3%)	0	0
Cardiac failure acute	1 (0.3%)	0	0
Infections and infestations	0	0	1 (1.9%)
Colonic abscess	0	0	1 (1.9%)
Neoplasm, benign, malignant and unspecified (incl cysts and polyps)	0	1 (0.5%)	0
Bladder cancer	0	1 (0.5%)	0
Respiratory thoracic and mediastinal disorders	0	1 (0.5%)	0
Pulmonary thrombosis	0	1 (0.5%)	0

Deaths

- There was one death in all three studies. A 74-year-old male treated with Catiolanze group died due to acute cardiac failure considered unrelated to study drug or procedures by the investigator. The onset of the event was Day 87.

2.5.8.4. Laboratory findings

According to the study reports, laboratory findings/measurements were not performed. Physical examination parameters (such as visual acuity or dilated fundoscopy) were measured and outlined as additional safety parameters in other parts of the assessment reports. In relation to the reported events assigned under the MedDRA SOC Investigations, no significant safety findings can be gained.

2.5.8.5. Safety in special populations

Elderly population

The table below shows the breakdown of subjects reporting AEs across different elderly age groups <65, 65 – 74 and >75 years in the Phase III Study Catiolanze10SA only. This shows similar or less AEs across all age groups for Catiolanze compared to RefMP (15.5% vs 21.1% for the <65 group, 20% vs 19.7% for the 65 – 74 group, and 24% vs 29.6% for the >75 group). The reporting of AEs was slightly lower in the <65 group (15.5%) compared to the 65 – 74 group (20%) and the >75 group (24.0%) for patients treated by Catiolanze. Due to differences in comparator drugs between the three conducted studies, comparisons between age groups in the GDS cohort was not considered relevant. Thus, the AE summary by age group for the global safety data cohort is not provided.

Table 42: Summary of adverse events by age subgroup – Safety population, Period 1, study Catiolanze10SA

	Age < 65		Age 65 - 74		Age ≥ 75	
Subjects, n (%), with any	**Latanoprost 50 µg/ml eye drops, emulsion *SD* N = 103**	**Xalatan® n = 95**	**Latanoprost 50 µg/ml eye drops, emulsion *SD* N = 65**	**Xalatan® N = 71**	**Latanoprost 50 µg/ml eye drops, emulsion *SD* N = 25**	**Xalatan® N = 27**
All AEs n (%)	16 (15%)	20 (21.1%)	13 (20%)	14 (19.7%)	6 (24.0%)	8 (29.6%)
SAEs	0 (0.0%)	0 (0.0%)	1 (1.5%)	2 (2.8%)	0 (0.0%)	0 (0.0%)
SARs related to study drug	6 (5.8%)	11 (11.6%)	4 (6.2%)	5 (7%)	1 (4%)	5 (18.5%)
AEs leading to discontinuation study	1 (1.0%)	1 (1.1%)	1 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Death	0 (0.0%)	0 (0.0%)	1 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ocular AEs n (%)	9 (8.7%)	14 (14.7%)	7 (10.8%)	7 (9.9%)	4 (16.0%)	5 (18.5%)
SAEs	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
SARs related to study drug	5 (4.9%)	11 (11.6%)	4 (6.2%)	5 (7.0%)	1 (4.0%)	5 (18.5%)
Serious SARs related to study drug	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
AEs leading to discontinuation from study drug	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Non ocular AEs n (%)	9 (8.7%)	8 (8.4%)	7 (10.8%)	9 (12.7%)	4 (16.0%)	4 (14.8%)
SAEs	0 (0.0%)	0 (0.0%)	1 (1.5%)	2 (2.8%)	0 (0.0%)	0 (0.0%)
SARs related to study drug	11 (1.0%)	0 (0.0%)	1 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Serious SARs	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
AEs leading to discontinuation from study drug	1 (1.0 %)	0 (0.0%)	1 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 43: Adverse Events: Overall Summary (by Age Subgroup) Safety Population

	Age < 65		Age 65-74		Age >=75	
Subjects with Any	DE-130A (N=103)	Xalatan (N=95)	DE-130A (N=65)	Xalatan (N=71)	DE-130A (N=25)	Xalatan (N=27)
AE(s)	16 (15.5%)	20 (21.1%)	13 (20.0%)	14 (19.7%)	6 (24.0%)	8 (29.6%)
SAE(s)	0 (0.0%)	0 (0.0%)	1 (1.5%)	2 (2.8%)	0 (0.0%)	0 (0.0%)
SAR(s) Related to Study Drug	6 (5.8%)	11 (11.6%)	4 (6.2%)	5 (7.0%)	1 (4.0%)	5 (18.5%)
Serious SAR(s) Related to Study Drug	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
AE(s) Leading to Discontinuation from Study	1 (1.0%)	1 (1.1%)	1 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Death	0 (0.0%)	0 (0.0%)	1 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ocular AE(s)	9 (8.7%)	14 (14.7%)	7 (10.8%)	7 (9.9%)	4 (16.0%)	5 (18.5%)
SAE(s)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
SAR(s) Related to Study Drug	5 (4.9%)	11 (11.6%)	4 (6.2%)	5 (7.0%)	1 (4.0%)	5 (18.5%)
Serious SAR(s) Related to Study Drug	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
AE(s) Leading to Discontinuation from Study	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Non-Ocular AE(s)	9 (8.7%)	8 (8.4%)	7 (10.8%)	9 (12.7%)	4 (16.0%)	4 (14.8%)
SAE(s)	0 (0.0%)	0 (0.0%)	1 (1.5%)	2 (2.8%)	0 (0.0%)	0 (0.0%)
SAR(s) Related to Study Drug	1 (1.0%)	0 (0.0%)	1 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Serious SAR(s) Related to Study Drug	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
AE(s) Leading to Discontinuation from Study	1 (1.0%)	0 (0.0%)	1 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Death	0 (0.0%)	0 (0.0%)	1 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Studies included:0130A01SA (Investigator-Masked Period)
Abbreviations: AE = adverse event; SAE = serious adverse event; SAR = suspected adverse reaction; MedDRA = Medical Dictionary for Regulatory Activities
Subjects were classified by actual treatment received
AEs were coded using MedDRA Version 23.1
Max age of each group was 88 years old for DE-130A and 83 years old for Xalatan. Due to limited age older than 85 years old (no subject in Xalatan), the oldest age range is defined as >= 75 years old.

Death	0 (0.0%)	0 (0.0%)	1 (1.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source – Table 14.3.1.2 in Module 5.3.5.3. Studies included 0130A01SA (Investigator masked) AE = adverse event; SAE = serious adverse event; SAR = suspected adverse reaction. Subjects were classified by actual treatment received. Max age of each group was 88 years old for DE-130A and 83 years old for Xalatan®. Due to limited age older than 85 years old (no subject in Xalatan), the oldest age range is defined as >= 75 years old.

Paediatric population

A paediatric indication is proposed for Catiolanze, in line with the reference product; however, this is a new topical latanoprost formulation for ocular use which has not been studied in the paediatric population. The applicant proposes to include data from the reference product paediatric studies.

The applicant outlined that the availability of Catiolanze for children could be justified based on extrapolation of the mode of action of the active substance, demonstration of efficacy and safety of latanoprost in children, safety of the cationic emulsion extrapolated from Verkazia® and Cationorm® which is based on the same emulsion and clinical trial safety data in which children from four years of age received vehicle alone.

Catiolanze was not specifically evaluated in children during the clinical development of the emulsion formulation for this MAA under the legal basis of Article 10(3), (hybrid application). Nevertheless, the applicant considered that an indication for the use of Catiolanze in children is justified based on non-inferiority to the RefMP which is approved for use in children, and the currently available clinical experience with Verkazia® which contains the Novasorb® cationic emulsion and is approved for the treatment of severe vernal keratoconjunctivitis from the age of four years and adolescents, albeit in a different indication.

In the context of totality of the currently available data for the active substance and the new formulation, an indication in paediatric patients from the age of 4 years onwards was proposed during the procedure

Supportive data for the safety of the cationic emulsion vehicle is provided by reference to a randomised trial of Verkazia® in which 169 children aged 4-17 years with severe vernal kerato-

conjunctivitis were randomised 1:1:1 to receive Verkazia® (2 or 4 times per day; qid or bd groups) or vehicle (Leonardi et al., 2019). Treatment-related AEs were reported for 15.5% of children who received vehicle alone, versus 19.3% and 9.3% in the Verkazia® qid and bd groups, respectively. None were serious. In the vehicle group, the most common treatment-related AEs were reported by two subjects (3.4%) each; instillation site pain, instillation site pruritus, and instillation site erythema. There were no related SAEs during the study. BCDVA improved over the 4-month treatment period in all treatment groups and IOP remained stable.

Younus et al studied latanoprost in a 3-year prospective cohort study in 14 countries including 175 paediatric patients with glaucoma or OHT to receive either latanoprost or non- prostaglandin treatment. There was no statistically significant difference between the groups in terms of change in BCVA from baseline, corneal thickness, or ocular hyperpigmentation.

Latanoprost had an acceptable safety profile with no evidence of inducing clinically meaningful changes in ocular development or ocular hyperpigmentation (Younus et al., 2018).

Other safety parameters did not raise any concerns (Leonardi et al., 2019). The safety profile remained unchanged over an 8-month extended follow-up period (Bremond-Gignac et al., 2020).

Table 44: Any and treatment-related treatment-emergent adverse events in children who received vehicle in study NVG09B113 (Leonardi et al., 2019)

SOC PT	Vehicle (N=58) Any TEAE	 Related TEAE
Any	**23 (39.7%)**	**9 (15.5%)**
EYE DISORDERS	10 (17.2%)	4 (6.9%)
Ulcerative keratitis	3 (5.2%)	0
Corneal leukoma	1 (1.7%)	1 (1.7%)
Eye irritation	1 (1.7%)	0
Ocular hyperaemia	1 (1.7%)	0
Cataract subcapsular	1 (1.7%)	1 (1.7%)
Conjunctivitis	1 (1.7%)	0
Corneal deposits	1 (1.7%)	0
Eyelid oedema	1 (1.7%)	1 (1.7%)
Visual acuity reduced	1 (1.7%)	1 (1.7%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	5 (8.6%)	3 (5.2%)
Instillation site pain	2 (3.4%)	2 (3.4%)
Instillation site pruritus	2 (3.4%)	2 (3.4%)
Instillation site erythema	2 (3.4%)	2 (3.4%)
Pyrexia	2 (3.4%)	0
Application site discharge	1 (1.7%)	1 (1.7%)
INFECTIONS AND INFESTATIONS	3 (5.2%)	0
Nasopharyngitis	1 (1.7%)	0
Hordeolum	1 (1.7%)	0
Bronchiolitis	1 (1.7%)	0
Rhinitis	1 (1.7%)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	4 (6.9%)	1 (1.7%)
Oropharyngeal pain	1 (1.7%)	0
Asthma	1 (1.7%)	0

SOC PT	Vehicle (N=58) Any TEAE	 Related TEAE
Sneezing	1 (1.7%)	0
Throat tightness	1 (1.7%)	1 (1.7%)
NERVOUS SYSTEM DISORDERS	1 (1.7%)	0
Headache	1 (1.7%)	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	3 (5.2%)	1 (1.7%)
Dermatitis allergic	1 (1.7%)	0
Rash	1 (1.7%)	1 (1.7%)
Urticaria	1 (1.7%)	0
GASTROINTESTINAL DISORDERS	2 (3.4%)	0
Aphthous stomatitis	1 (1.7%)	0
Vomiting	1 (1.7%)	0
Nausea	1 (1.7%)	0
INVESTIGATIONS	2 (3.4%)	1 (1.7%)
Aspartate aminotransferase increased	1 (1.7%)	0
Blood creatine phosphokinase increased	1 (1.7%)	0
Blood lactate dehydrogenase increased	1 (1.7%)	0
Intraocular pressure increased	1 (1.7%)	1 (1.7%)
Protein total increased	1 (1.7%)	0
EAR AND LABYRINTH DISORDERS	1 (1.7%)	0
Ear pain	1 (1.7%)	0

Source: CSR NVG09B113 22 August 2016. Table 12.3 and 12.4
TEAE, treatment-emergent adverse event

2.5.8.6. Discontinuation due to adverse events

Significant adverse events/ adverse events leading to discontinuation

Study NVG09E115 – Phase II

There were no significant AEs in this study and no subjects discontinued.

Study NVG10E118 – Phase II

Three subjects in the Travatan Z® group were withdrawn from the study due to TEAEs (table below).

Table 45: Subjects withdrawn from the study – Safety population, study NVG10E118

SOC PT	Latanoprost 50 µg/ml eye drops, emulsion *SD* N = 51		Travatan Z® N = 54		All subjects N = 105	
	n (%)	N events	n (%)	N events	n (%)	N events
Total no of TEAEs leading to discontinuation	0 (0.0%)	0	3 (5.6%)	3	3 (2.9%)	3
Eye disorders	0 (0.0%)	0	2 (3.7%)	2	2 (1.9%)	2
Conjunctivitis allergic	0 (0.0%)	0	1 (1.9%)	1	1 (1.0%)	1
Ocular hyperaemia	0 (0.0%)	0	1 (1.9%)	1	1 (1.0%)	1
Infections and infestations	0 (0.0%)	0	1 (1.9%)	1	1 (1.0%)	1
Abscess intestinal	0 (0.0%)	0	1 (1.9%)[3]	1	1 (1.0%)[3]	1

Source: Table 22 Study NVG10E188 CSR. Subjects experiencing more than 1 TEAE within a given MedDRA SOC or PT are counted once within that MedDRA SOC or PT.
MedDRA = Medical Dictionary for Regulatory Activities, PT = preferred term, SOC = system organ class, TEAE = treatment-emergent adverse event.

Study Catiolanze10SA – Phase III

Period 1

There were no sight threatening AEs or CSIs reported during Period 1. Three patients

discontinued due to an AE. Two discontinuations were for eye related AEs; eye pain, eye

pruritus, and relapse of burning mouth syndrome in the Catiolanze group (patient number 4100002-1097), and eye irritation and ocular hyperaemia in the control group (patient number 2330002-1025). All events resolved after discontinuation, except for burning mouth syndrome.

One patient in the Catiolanze/latanoprost 50 µg/ml eye drops, emulsion SD group (patient number 6430007-1158) died due to acute heart failure that was considered by the investigator to be unrelated to the study drug.

Period 2

Two patients discontinued due to an AE during Period 2. Both were ocular AEs in the Xalatan®/Latanoprost 50 µg/ml eye drops, emulsion SD group. One patient had abnormal sensation in eye and macular fibrosis, and the other patient had eye pain. All AEs were moderate in severity. Abnormal sensation in eye was considered as treatment related. Macular fibrosis and eye pain were considered by the investigator as not treatment related.

In the Period 2 of the phase III study, the event of macular fibrosis was assessed as not related by investigator. This ocular event occurred in a subject no. 2330004-1103 from the Xalatan/Catiolanze arm. Based on the Listing 16.2.7.1.1.2, the event "worsening of epiretinal membrane" was reported. A clinical background is therefore quite unclear. A discrepancy in a terminology between the clinical study report and its appendix, and the applicant's data summarisation (Summary of Clinical Safety) distorts the meaning of such event. Therefore, general concerns on the applied AE terminology and its presentation within the dossier exist. The applicant is requested to provide a detailed case narrative to this event, together with appropriate discussion on its impact on the product's safety.

There were no sight threatening AEs or CSIs reported during **Period 2**.

Global Safety Data cohort – Pooled data from all studies

The table below shows premature study discontinuations across the pooled safety population. No patients withdrew from study NCG09E115 and no patients in Study NVG10E118 discontinued whilst receiving Catiolanze.

In study 0Catiolanze10SA, four patients receiving Catiolanze withdrew from the study due to an AE. Only one was considered related to study drug, this was moderate abnormal sensation in the eye and resolved.

Table 46: Patients who prematurely discontinued from the emulsion formulation clinical studies – Global Safety Data cohort

Study Treatment group	Subject number	Reason for discontinuation	Adverse event	Severity	Relationship to study drug	Outcome
NVG10E118						
Travatan Z®	N11805017- 227	Ocular AE	Conjunctivitis allergic	Mild	Related	Resolved (treatment unmasked)
Travatan Z®	N11807015- 235	Ocular AE	Ocular hyperaemia	Moderate	Probably related	Resolved
Travatan Z®	N11807029- 142	Non-ocular SAE	Abscess intestinal	Severe	Not related	Resolved
0130A01SA						
DE-130A	4100002-1097	Ocular AE	Burning mouth syndrome	Mild	Not Related	Not recovered/ Not resolved
DE-130A	6430007-1158	Non-ocular SAE	Death due to heart failure	Severe	Not related	Fatal
Xalatan®	2330002-1025	Ocular AE	Eye irritation	Severe	Related	Recovered/Resolved
			Ocular hyperaemia	Severe	Related	Recovered/Resolved
Xalatan®/DE-130A	2330004-1103	Ocular AE	Abnormal sensation in eye	Moderate	Related	Recovered/Resolved
			Macular fibrosis	Moderate	Not related	Not recovered/ Not resolved
Xalatan®/DE-130A	4100001-1114	Ocular AE	Eye pain	Moderate	Not related	Not recovered/ Not resolved

Source: *Study* NVG10E118 CSR Appendix 16.2.1 and 16.2.7.1, *Study* 0130A01SA CSR Listing 16.2.7.7.1 and 16.2.7.7.2
AE, adverse event; SAE, serious adverse event

2.5.8.7. Post marketing experience

Catiolanze has not been approved in any country and no post-marketing data are available. However, such data are available for the reference product containing latanoprost as the active substance and for other approved products containing the same cationic emulsion (Novasorb® technology) as Latanoprost 50 µg/ml eye drops, emulsion SD (Cationorm®, Cationorm® Plus/PRO, Verkazia® and Ikervis®).

Latanoprost has been on the market for more than two decades since the first regulatory approval of Xalatan® in the US and the UK in 1996. The UK acted as the reference member state for the mutual recognition procedure (UK/H/0179/001) in the European Union in 1997.

This was followed by a paediatric indication (EMEA/H/A-29 PAE/1270) in 2010. Latanoprost has since been approved in over 130 countries and is currently marketed in over 120 countries.

The safety profile of latanoprost for ocular administration in patients with glaucoma and ocular hypertension has been well characterised.

Cationorm® uses the same cationic vehicle as Latanoprost 50 µg/ml eye drops, emulsion SD. Cationorm® was first approved in 2006 for the treatment of dry eye with no age restrictions.

Cationorm® Plus/PRO follows the same Novasorb® technology characterised by a slight increase in the concentration of CKC. It has been on the market since 2019 for treatment of dry eye symptoms (no age restrictions) and signs and symptoms of ocular allergy (in patients >4 years of age). The most recent Periodic Safety Update Report (PSUR) covering the year 2020 confirmed the safety and efficacy of Cationorm® and Cationorm® Plus/PRO and did not change the positive benefit/risk assessment of the products. Most AEs were reported under the System Organ Class 'Eye disorders' in relation with the pathology of dry eye symptoms. No specific safety concerns were identified in the paediatric population.

Verkazia® is a 1 mg/mL eye drops, cationic emulsion containing cyclosporin for the treatment of severe vernal keratoconjunctivitis in children from 4 years of age and adolescents. It has been marketed since approval by the EMA in 2018. Of note, safety in paediatric patients is not listed as a safety concern for Verkazia® in the approved European Union Risk Management Plan.

Ikervis® is a 1 mg/mL eye drops, emulsion containing cyclosporin for the treatment of severe keratitis in adult patient with dry eye disease which has not improved despite treatment with tear substitute. It has been marketed since approval by the EMA in 2015.

A three-year post-approval efficacy study is ongoing to assess Ikervis® in 350 adults with dry eye disease (NVG14L127). An analysis after one year of treatment (CSR report date 26 January 2022) found that individual symptoms of dry eye disease improved by Ikervis® treatment.

Novasorb technology safety discussion

Catiolanze is a novel latanoprost-containing treatment for glaucoma and OHT that according to the applicant is preservative-free and contains a cationic emulsion (Novasorb® technology that has been approved as a treatment for dry eye and ocular allergy (Cationorm®) and is included in treatments for severe keratitis in dry eye disease (Ikervis®) and for vernal keratoconjunctivitis (Verkazia®).

Catiolanze is a new formulation of latanoprost in a cationic emulsion based on Novasorb® technology (Lallemand et al., 2012). Novasorb® is a patented eye drop formulation platform developed to optimise the interaction of the eye drop - the cationic nano-emulsion - with the different layers of the tear film and the ocular surface and take advantage of the negatively charged mucin layer the use of cationic nano-emulsions in topical ophthalmic treatments is well established.

Four approved ophthalmological medical devices Cationorm® and Cationorm® PRO as well as medicinal products Ikervis® and Verkazia®, use the cationic nanoemulsion vehicle (Table 3).Cationorm®/Cationorm® PRO, are topical ophthalmic medical devices that have been marketed since April 2008 and 2019 respectively. Ikervis® is a 1 mg/mL eye drops emulsion containing cyclosporin A which was approved in March 2015. Verkazia® is a 1mg/mL eye drops emulsion containing cyclosporin A which was approved in 2018.

Table 47: Other products using Novasorb® technology

Product	Active ingredient	Targeted/ approved indication	Market /Authorisation status
Cationorm®	Medical device	Dry eye	Marketed in many European and Asian countries
Cationorm® PRO	Medical device	Dry eye	Marketed in Italy
Ikervis®	0.1% cyclosporine A	Severe keratitis in dry eye disease	Centralised procedure MAA 8(3) in EU, many Asian countries and Australia
Verkazia®	0.1% cyclosporine A	Vernal keratoconjunctivitis	MAA in EU, many Asian countries, US and Canada
Latanoprost 50 µg/mL eye drops, emulsion *SD*	0.005% latanoprost	Open angle glaucoma and ocular hypertension	Phase III completed (this application)

EU, European Union; MAA, marketing authorisation application; OSD, ocular surface disease; US, United States (modified from (Lallemand et al., 2012).

Discussion on safety of excipients:

Catiolanze contains the following excipients: MCTs, CKC, polysorbate 80, glycerol, water for injections. Most of the excipients used in Catiolanze are commonly found in eye preparations and are listed in the Ph Eur.

Catiolanze does not contain the BAK preservative (an established eye irritant). It contains small quantities of cetalkonium chloride (CKC) as a cationic agent (Novasorb® technology). CKC is a quaternary ammonium compound and is described in the European Pharmacopeia (Ph Eur) as a component of BAK. However, CKC in the cationic nanoemulsion exhibits neither detergent nor preservative role. Consequently, CKC cationic o/w nanoemulsion does not exhibit any of the observed ocular side effects related to BAK (Daull et al., 2014). It is the most lipophilic homologue of BAK and its solubility in oil is increased, which allows the development of an emulsion. CKC is used as a cationic surfactant to provide the oil droplets with positive charges, i.e., quaternary amine groups. The positive charge plays a role in the stability of the product. It was determined that was the amount of CKC needed to confer a positive zeta potential and achieve a narrow monomodal droplets distribution within the emulsion. A lower concentration of CKC resulted in less stable emulsions.

For further discussion on quality aspects relating to CKC, please also refer to the **Quality section.**

The use of CKC at similar quantities in already approved ophthalmic products is referred to by the applicant as follows: Supportive safety data from other licensed products containing the Novasorb® technology vehicle is referred to. The safety of the cationic emulsion technology is supported by four products currently on the market that contain the same cationic emulsion vehicle as Catiolanze . These are Cationorm® (on the market since 2008), Cationorm Pro/Plus® (on the market since 2019), Ikervis® (on the market since 2015) and Verkazia® (on the market since 2018, paediatric indication from aged 4 years onwards).

Cationorm® and Cationorm® Plus/PRO

Cationorm® uses the same cationic vehicle as Latanoprost 50 µg/ml eye drops emulsion *SD*, it was first approved in 2006 for the treatment of dry eye with no age restrictions.

Cationorm® Plus/PRO follows the same Novasorb® technology characterised by a slight increase in the concentration of CKC. It has been on the market since 2019 for treatment of dry eye symptoms (no age restrictions) and signs and symptoms of ocular allergy (in patients >4 years of age). No safety concerns related to CKC have been detected in patients using Cationorm® or Cationorm Pro/Plus®. The latest PSUR covering interval January 2020 to December 2020 showed that no significant safety incidents have been reported during this period confirming the positive risk-benefit profile. Most AEs were reported under the System Organ Class 'Eye disorders' in relation with the pathology of dry eye symptoms.

Verkazia®/ Ikervis®

Ikervis® is a 1mg/mL eye drops, emulsion containing cyclosporin for the treatment of severe keratitis in adult patient with dry eye disease which has not improved despite treatment with tear substitute. Verkazia® is a 1 mg/mL eye drops, cationic emulsion containing cyclosporin (CsA) for the treatment of severe vernal keratoconjunctivitis in children from 4 years of age and adolescents. The latest PSUR and PSUSA assessment (process number EMEA/H/C/PSUSA/00010362/202103) for cyclosporin (i.e., Ikervis® and Verkazia®) confirmed positive risk-benefit profile. The most commonly reported adverse drug reactions were non-serious local ocular reactions. No new safety concerns related to CKC were observed in adults and children.

A three-year post-approval efficacy study is ongoing to assess Ikervis® in 350 adults with dry eye disease (NVG14L127). An analysis after one year of treatment (CSR report date 26 January 2022) found that individual symptoms of dry eye disease improved by Ikervis® treatment.

Ikervis® demonstrated an acceptable safety profile with no signal in clinical findings.

Medium-Chain Triglycerides (MCTs) as oily agent

As a solvent for latanoprost, MCTs constitute the main droplet core component and represent the emulsions oily agent. MCTs are currently in use in several parenteral products (up to 20% concentration) and topical ophthalmic products (up to 1%) in Europe.

MCT is described in the Ph Eur. MCTs are generally regarded as essentially non-toxic and non-irritating and are known to be non-irritating to eyes. The content of MCT within Catiolanze was chosen to ensure complete solubilisation of latanoprost and to obtain a physically stable emulsion.

Polysorbate 80 as Surfactant

Catiolanze contains polysorbate 80 to ensure the physical stability of the dispersed oil phase within the water phase. Polysorbate 80 is a non-ionic surfactant commonly used in topical ophthalmic solutions. Polysorbate 80 is described in the Ph Eur. The concentration of polysorbate 80 in Catiolanze was selected to obtain a physically stable emulsion.

2.5.9. Discussion on clinical safety

As this application is submitted under Article 10 (3), hybrid application, the applicant refers to the established safety profile for the reference product Xalatan, which is approved in the EU for the treatment of glaucoma and OHT in adults and paediatric patients.

In addition, further safety data specific to the proposed new latanoprost formulation is provided from one pivotal phase III clinical study and supporting data from two phase II clinical studies.

The safety profile of the active substance latanoprost is well-characterised and the overall safety data provided with this application is generally considered to be in accordance known class effects. In this context, general safety information is reflected in the SmPC, which is in line with the established safety profile of the active substance latanoprost and that of the reference product, Xalatan.

However, from a product-specific point of view, a number of limitations of the safety database were identified during the assessment of clinical safety of the proposed new latanoprost formulation, Catiolanze.

In relation to patient exposure, the applicant provided safety data from three clinical studies of the new latanoprost formulation (two phase II and one phase III studies) which were conducted in the adult population only.

Overall, there were no unexpected AEs reported during the clinical studies.

The applicant clarified the approach taken in relation to the evaluation of AEs and AE reporting across the clinical studies, particularly the pivotal phase III trial. The applicant provided the rationale for the use of the term SAR in the SmPC and in the reporting of safety data from the pivotal phase III clinical study. It has been clarified why certain AEs were reported as AEs rather than SARs or ADR. The applicant has outlined that to ensure consistency, the term SAR has been amended to treatment-related AE throughout the clinical modules 2.7.4 and 2.5 and provided updated clinical modules to reflect this clarification.

The applicant was also requested to submit with the Day 120 response a document outlining the revisions, together with their assessments of impact on the safety evaluation.

In the provided study listings vs. analyses performed by the applicant, some discrepancies in used terminology for the documented adverse events (AEs) were observed. E.g., reported AEs describing relapses or worsening are coded as PTs without this specification and therefore it can lead to a shift in meaning of the observed risks (e.g., patient number 4100002-1097, subject ID-4100001-1114, 2330004-1098 and others). Therefore, the applicant was requested to go through the whole submitted clinical safety dossier and provide the relevant justifications for such discrepancy and submit a document outlining the revisions, together with their assessments of impact on the safety evaluation and the proposed product information. This was subsequently provided by the applicant with further responses.

In the pivotal evaluation of safety from period 1 of the phase III clinical trial (to completion of 12 weeks study visit), the overall proportion of AEs (any AE, ocular AE, and non- ocular AE) were 18.1%, 10.4% and 10.4 % for Catiolanze group and 21.8%, 13.5% and 10.9% for Xalatan® group.

The proportion of subjects with any AE was slightly less in the Catiolanze group at 18.1% (n=35) of patients versus 21.8% (n=42) in the and Xalatan® group.

Ocular AEs overall were numerically lower for the Catiolanze group at 10.4% (n=20) versus 13.5% (n=26) in the control group. All ocular AEs reported in patients in the Catiolanze group were of mild or moderate intensity. Severe AEs were only reported for patients receiving Xalatan® including one case of ocular hyperaemia. Any Ocular AE was reported for 10.4% (n=20) of patients in the Catiolanze group and 13.5% (n=26) in the control group.

Based on a review of specific Ocular AEs, there was a slightly lower incidence of the following AEs reported in the Catiolanze group, relative to the Xalatan® group: Ocular hyperaemia, was the most frequently reported ocular AE, reported for 1.6% (n=3) patients in the Catiolanze group, and 2.6%

(n=5) in the Xalatan® group, conjunctival hyperaemia (1.0% vs 1.6% respectively), eye pruritus (0.5% vs 1.6%, respectively), swelling of eyelid (0.5% vs 1.0%), eye irritation (0% vs 1%) foreign body sensation in eyes (0% vs 1.6%) instillation site pain (0% vs 1.6%). abnormal sensation in eye (0 vs 2.1%) respectively.

However, for the following ocular AEs the trend was reversed and there was a slightly lower incidence reported in the Xalatan® group relative to the Catiolanze group: dry eye 1% vs 0.5%, keratitis 1% vs 0% (2 cases) blurred vision 1% vs 0%seasonal eye allergy 1% vs 0%, Blepharitis 0.5%vs 0%, Chalazion 0.5% vs 0, Conjunctival oedema 0.5% vs 0,Eyelid oedema 0.5% vs 0 Growth of eyelashes 0.5% vs 0%, Ocular discomfort 0.5% vs 0 and erythema of eyelid 1.0% in each group, conjunctival haemorrhage 0.5 v 0.5%.

Ocular and non-ocular AEs have been presented as exposure-adjusted data also to account for differences in exposure across treatment arms. Both ocular and non-ocular AEs were broadly comparable between both treatment groups.

As previously outlined, the applicant used the term Suspected adverse reactions (SARs) defined as any AEs that are deemed related to study drug, or study procedure, or artificial tears by the Investigators. The applicant subsequently clarified their approach which was used in the Phase III study. The applicant confirmed that SARs were considered equal to Treatment-related AEs. Therefore, in the responses the applicant clarified that there was no need for them to provide a re representation of the available safety data.

In relation to reporting of ocular SARs, these were listed as 5.7% for the Catiolanze group vs 10.9% for the Xalatan group. Eye disorders were also listed as 5.2 % vs 9.3% respectively in a further table, therefore clarification was requested on these slight differences. The applicant confirmed that this was an error.

There is a decrease in frequency when comparing Ocular AEs to Ocular SARs, a drop from 10.4 % to 5.2% is noted in the Catiolanze group, and a lesser decrease in the control group (13.5% to 10.9%). In this context, the applicant was requested to provide the narratives of all Ocular AEs and outline the rationale for categorisation of the Ocular AEs to Ocular SARs in both the Catiolanze group, and the control group.

The applicant has satisfactorily clarified how it was deemed that the following AEs were not SARs, two cases of Keratitis, one case of chalazion, two cases of conjunctival haemorrhage, one case of growth of eyelashes especially considering that these are known Adverse reactions of Latanoprost and are listed in the product information of the RefMP.

The proportion of non -ocular AEs was similar in both Catiolanze group and Xalatan® group (10.4% vs 10.9% respectively).

The most frequently reported non-ocular AEs by SOC in both groups were Infections and infestations, reported for 3.1% (n = 6) patients in the Catiolanze group, and 4.1% (n = 8) in the Xalatan® group, and Musculoskeletal and connective tissue disorders (2.1%, n = 4 in both groups).The only PTs reported by more than 1.0% of patients were Arthralgia (1.6%, n = 3 in the Catiolanze group, and back pain (1.6%, n = 3 in the control group).

Full details on the 6 cases of infections and infestations, reported for the patients in the Latanoprost 50 µg/ml eye drops, emulsion SD group, have now been provided. The applicant has confirmed there were no ocular infections and infestations in Period 1.

Any non-ocular SAR was reported for 1.0% (n = 2) of patients in the Catiolanze group, and for 0.0% (n = 0) in the control group.

Three subjects had non ocular SAEs, none of which were considered related to study drug. The other two subjects treated with Xalatan® had one SAE each: bilateral pulmonary thrombosis which has resolved and bladder cancer which is recovering. Treatment was uninterrupted in both cases.

In relation to the analysis of serious adverse events (SAEs), the observed SAEs are considered isolated cases only. Thus, no pattern can be identified on the basis of the data provided. In the Catiolanze arm, only 1 subject had any AEs, a fatal event of acute cardiac failure which was assessed as unrelated to the study drug, which is accepted. It occurred in a 74-year-old male (no. 6430007-1158) diagnosed with POAG during the Period 1 of the phase III study. A detailed case narrative was provided.

The applicant has discussed the rationale for the chosen CSIs in this clinical development program (corneal ulceration, decrease in visual acuity of 3-6 lines, medication error, overdose, abuse, misuse and sight threatening AEs). There were no CSI or sight-threatening AEs reported during Period 1.

In period 2 of the pivotal phase III clinical trial**,** the number of patients reporting any AE was similar between both treatment groups: 29.6% (n=21) of patients in the Catiolanze / Catiolanze group and 30.3% (n=20) in the Xalatan®/ Catiolanze group reported any AE.

The frequency of any ocular AE was higher in the Catiolanze / Catiolanze group reported for 22.5% (n=16) of patients and for 18.2% (n=12) in the Xalatan®/ Catiolanze group.

The most frequently reported ocular AE during Period 2 was abnormal sensation in eye which was reported for 3.6% of patients in the Overall Latanoprost 50 µg/ml eye drops, emulsion *SD* group. Other ocular AEs occurring in ≥ 1% of patients in the overall Latanoprost 50 µg/ml eye drops, emulsion, *SD* group were growth of eyelashes (2.9%), ocular hyperaemia (2.9%), swelling of eyelid (2.2%), blepharitis (1.5%), conjunctival hyperaemia (1.5%), and eye pain (1.5) All ocular AEs were mild or moderate in severity, except for eye pruritus.

Ocular Infections and infestations were 4.2% in Catiolanze / Catiolanze group vs 0 % Xalatan®/ Catiolanze group. One case each of conjunctivitis, conjunctivitis viral and hordeolum in the Catiolanze / Catiolanze group. The applicant has provided further information on these cases and has discussed why they were not deemed to be SARs. No safety concerns were identified from the data presented and the response is acceptable. In general, this topic should continue to be routinely monitored.

In period II of the pivotal study, any SAR was reported for 8.5% (n=6) of patients in the Catiolanze / Catiolanze group and for 10.6% (n=7) Xalatan®/ Catiolanze group. All reports were ocular SARs. SARs occurring in more than 1% of patients in the overall Catiolanze / Catiolanze group during Period 2 were ocular hyperaemia (2.9%), abnormal sensation in eye (2.2%), growth of eyelashes (2.2%), conjunctival hyperaemia (1.5%) and swelling of eyelid (1.5%).

In terms of non-ocular AEs, any non-ocular AE was reported for 14.1% (n = 10) of patients in the Latanoprost 50 µg/ml eye drops, emulsion *SD* / Latanoprost 50 µg/ml eye drops, emulsion *SD* group and for 12.1% (n = 8) in the Xalatan®/ Latanoprost 50 µg/ml eye drops, emulsion *SD* group.

There were no SAEs or deaths reported during Period 2.

Although the applicant is seeking an indication in adult and paediatric patients, no paediatric clinical safety data for the proposed new formulation had been provided in the submission. Nonclinical data provided within the submission are considered to be broadly supportive but cannot be considered conclusive for establishing safety.

For the proposed paediatric indication in children aged from 4 years onwards, the applicant has used a bridging approach by referring to the currently available safety data for the ocular administration of the active substance latanoprost, and in addition, by referring to the EU approved ocular products Verkazia and Ikervis which contain the same Novasorb emulsion as the proposed Catiolanze formulation, albeit

with different active substance. Clinical trial data for the Novasorb emulsion was provided in paediatric patients from the age of 4 years onwards as part of the approval of Verkazia in the EU. The applicant also referred to bibliographic discussion and bridged to EU approved range of ocular products Cationorm/Cationorm Pro which are approved for paediatric use in Europe in all ages. These products are approved as medical devices for the treatment of dry eye and allergy and contain only the Novasorb emulsion component. The totality of data is considered to be supportive of the bridging approach taken by the applicant to justify the use of Catiolanze in children from the age of 4 years onwards and is considered acceptable in the context of this hybrid application.

In terms of bridging to safety data and exposure to the new formulation of Catiolanze in children from 4 years and under, the applicant broadly referred to the approved product Cationorm (CKC formulation). The applicant stated that Cationorm is approved for all ages for dry eye indications and indicates that post-marketing do not raise any safety concern, however specific justification to confirm adequate exposure and safety profile in paediatric patients aged 4 years and under was not explicitly discussed, therefore during the evaluation of this application, the applicant amended the proposed indication to reflect that the product should be indicated in children from 4 years onwards.

During the procedure, the applicant has provided a more extensive discussion on potential safety issues related to the new formulation of latanoprost using the Novasorb technology in the paediatric population. However, robust supporting data/justification to support the use of the Novasorb emulsion in children under 4 years is lacking, including long term data. Therefore, the applicant's proposal to include an indication in paediatric patients from the age of 4 years onwards is considered acceptable. In line with the update to the paediatric indication, the applicant was also requested to update section 4.2 of the SmPC to provide specific recommendations in relation to paediatric use, ie. to reflect that this product is intended for use in children from 4 years of age upwards and in adolescents. The applicant updated the PI accordingly.

It is agreed that no changes to the RMP with regards to risk management or risk minimisation activities are considered necessary now that the indication in patients aged <4 years is withdrawn. However, it is recommended that long term safety in the intended paediatric population should be followed by routine pharmacovigilance measures and further focused updates on paediatric safety data in general should be provided by the applicant post-approval in the form of focused reviews of paediatric safety which will submitted through regular product specific PSURs for Catiolanze.

In general, whilst it is acknowledged that the safety of topically applied latanoprost as an active substance is considered to be well characterised, a key part of the safety evaluation of the new latanoprost formulation needs to centre on other aspects of the formulation such as excipients.

It is highlighted from the EMA SA in 2017 (EMEA/CHMP/SAWP/797001/2017) that:

In relation to other approved eye drop products sharing the cationic emulsion technology (Cationorm, Ikervis), there are also significant differences with regards to the composition (active compound and excipients) of these and Catiolanze Catiolanze which confound the extrapolation of longer- term safety data.

In relation to other approved eye drop products sharing the cationic emulsion technology (Cationorm, Ikervis), there are also significant differences with regards to the composition (active compound and excipients) of these and Catiolanze Catiolanze which confound the extrapolation of longer- term safety data.

Furthermore, these data reflect a different patient population/disease context, which also limits the weight of these data to support longer term Catiolanze Catiolanze treatment in patients with open angle glaucoma.

In this context, in relation to the general safety of Novasorb emulsion component of the proposed formulation, it is noted that Cationorm Plus, Verkazia and Ikervis contain the same concentration of CKC as Catiolanze . It was highlighted to the applicant that the CKC component of the proposed product has, in theory, the potential to act as a possible source of eye irritation in both adults and children, particularly over long-term use. This is clearly highlighted in the EU approved SmPCs for Ikervis and Verkazia, in which the following warnings are included in section 4.4 specifically in relation to CKC, which is present in the same concentration as the proposed product:

Cetalkonium chloride content

IKERVIS contains cetalkonium chloride. Contact lenses should be removed prior to application and may be reinserted at wake-up time. Cetalkonium chloride may cause eye irritation. Patients should be monitored in case of prolonged use.

Verkazia: section 4.4: contains CKC which can cause eye irritation.

In this context, it was considered important to reflect the above warnings in the PI, in line with other approved ocular products for topical use with the same concentration of CKC, to which the applicant refers. This is of relevance to the paediatric population as well as adults, particularly in the context of long-term exposure.

In response to this concern, the applicant has provided a justification to support their conclusion that a warning that CKC may cause eye irritation is not warranted in the PI at this time. However, the applicant's conclusion that no warning is currently required in the PI is not fully endorsed.

Although it is acknowledged that the role of CKC in ocular irritation is reduced when compared to BAK, as a precautionary approach and to ensure harmonisation, the applicant is requested to follow the precedent of the EU approved ocular products Ikervis and Verkazia with the inclusion of a general warning in section 4.4 to inform that the product can cause eye irritation.

Furthermore, cases specifically reporting 'eye irritation' have been reported in the post-marketing safety database for the ocular lubricant product Cationorm (which contains the same Novasorb technology but no active latanoprost component. The Cationorm range of products are approved in the EU as a medical device for the treatment of dry eye (all ages) and allergy (from 4 years onwards).

In the context of their response to this question, the applicant provided a PSUR which covers the Cationorm range of products. It includes the following products: Cationorm single-dose (SD) / Retaine MGD, Cationorm PFMD (Preservative Free Multi-Dose) and Cationorm Plus single dose. Cationorm Plus single-dose was launched in October 2019 in only one country (Italy) and the Post Market Surveillance data are limited. Cationorm Plus follows the same Novasorb technology present in Cationorm, characterised by a slight increase in the concentration of cetalkonium chloride (CKC), a cationic surfactant, compared to Cationorm.

Within the most recent PSUR, it is highlighted that cases of non-serious eye irritation continue to be reported for Cationorm products.

Although reported in small numbers and generally non-serious in nature, it is noted that in terms of cumulative safety data received and based on the company causality assessment, a total of n=52 cases of 'eye irritation' were reported from 2018-2021 for Cationorm MD product.

In addition, a total of n=41 cases of 'eye irritation' were reported from 2018-2021 for Cationorm SD product.

Notwithstanding the limitations of the post-marketing safety data provided and considering the precedent for inclusion of relevant warnings in other ocular medicinal products containing CKC which are currently approved in Europe, the CHMP recommended that section 4.4 of the proposed SmPC (and

PL) should contain a warning to state that the product 'contains CKC which can cause eye irritation. Patients should be monitored in case of prolonged use'. This recommendation was implemented.

It is also recommended that this issue should continue to be specifically monitored through routine pharmacovigilance measures going forward, particularly over the longer term.

In relation to the **RMP**, the applicant provided further discussion in relation to the product-specific concerns regarding which were raised during the assessment, as follows:
i) limited product-specific data on long-term safety of Latanoprost 50 µg/mL eye drops, emulsion SD and ii) the absence of product-specific paediatric safety, of Latanoprost 50 µg/ml eye drops, emulsion SD.

The applicant clarified that adequate long-term exposure in the adult population is available. Although this is still considered somewhat limited for the new formulation and therefore follow up should be provided in the PSURs in relation to this issue.

In relation to paediatric use, satisfactory exposure (Including long term exposure) of the proposed product was not completely justified by the applicant, particularly for the subgroup of patients under 4 years. Therefore, the applicant proposed that the indication for use be restricted to children from 4 years of age, noted above. In the context of the applicant's proposal for an updated indication, it is agreed that no additional changes to the RMP with regards to risk management or risk minimisation activities are considered necessary at this time, now that the indication in patients aged <4 years is withdrawn. However, it is recommended that long term safety in the intended paediatric population should be specifically followed by routine pharmacovigilance measures and further focused updates on paediatric safety data in general should be provided in the PSURs by the applicant post-approval.

2.5.10. Conclusions on the clinical safety

The safety of Catiolanze in the intended population is satisfactorily demonstrated. Residual uncertainties are adequately managed and will be addressed post-approval.

2.6. Risk Management Plan

The applicant had initially submitted a Risk Management plan as part of this application as RMP **version 0.1**, DLP: 11 April 2022.

The RMP is submitted within a hybrid marketing authorisation application (Article 10(3) of Directive 2001/83/EC) with the marketed product Xalatan as the Reference medicinal product (RefMP). Therefore, the applicant relies on the RefMP in respect of the epidemiology of open angle glaucoma and ocular hypertension in adults and with elevated IOP and paediatric glaucoma in children.

With respect to the RMP safety specification, the applicant applied the approach to follow the criteria given in the GVP Module V, Rev. which is considered fully acceptable. In the Part II, Module SVII of the submitted RMP, the justification of the differences from the reference product's RMP is provided. It is considered sufficient.

The applicant's overall presentation of the RMP was generally acceptable. Upon updates of the dossier in response to questions, the applicant submitted subsequent versions including the final version 0.3.

2.6.1. Safety concerns

None.

2.6.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.6.3. Risk minimisation measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

2.6.4. Conclusion

The CHMP considers that the risk management plan version 0.3 is acceptable.

2.7. Pharmacovigilance

2.7.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.7.2. Periodic Safety Update Reports submission requirements

Though it is acknowledged that the safety of topically applied latanoprost as an active substance is characterised in children (Xalatan), no product-specific data pertaining to use in children was provided. The applicant mainly justifies use in children by extrapolating data from other products sharing the cationic emulsion technology (Verkazia and Cationorm). However, safety data of the sister product Verkazia (ciclosporin) are limited to children aged 4 years and above, and clinical safety data (VEKTIS study) from the emulsion are only available in a small group (±50) of patients for only 4 months. Moreover, there was no data pertaining to post-marketing exposure in children in the last PSUR (Jan-Dec 2021) for Cationorm (emulsion only). Lastly, as expressed by the SAWP, there are safety concerns in relation to the extrapolation of data from other ocular products using the same cationic emulsion technology (i.e. many safety aspects concerning eye drop formulations derive from the complex interaction of the totality of excipients together with the active compound).

Considering all the above and the fact that Catiolanze will be indicated for use in patients from 4 years onwards, it is recommended to closely monitor 'Use in paediatric patients' in the post-marketing setting. Therefore, 'Use in paediatric patients' should be listed and discussed as missing information in the PSUR. The already existing entries for latanoprost have a PSUR cycle of 5 years, a frequency considered inappropriate for close monitoring. Hence, the PRAC Rapporteur is of the opinion that, at present, a separate entry in the EURD list for Catiolanze is needed.

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did not request the alignment of the new PSUR cycle with the international birth date (IBD). The new EURD list entry will therefore use the EBD to determine the forthcoming Data Lock Points.

2.8. Product information

2.8.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

3.1. Therapeutic context

3.1.1. Disease or condition

OHT is defined as consistently elevated IOP above an upper normal value of 21 mmHg by Goldmann applanation tonometry on two or more occasions, in one or both eyes and in the absence of optic nerve damage, visual field defects, or other pathology. The estimated prevalence of OHT ranges from 4.5% to 9.4% in adults aged >40 years and increases with age. Longitudinal studies show that 10% of persons with OHT will develop OAG within five years if left untreated (Burr et al., 2012).

Glaucoma refers to a group of conditions characterised by cupping (excavation) of the optic disc and damage to the optic nerve leading to gradual visual loss. Patients with glaucoma develop progressive thinning of the neuro-retinal rim of the optic nerve, thereby enlarging the optic-nerve cup. Disease progression rates are variable depending on the type of glaucoma and on patient characteristics. In one report, the cumulative rate of blindness from glaucoma after 22 years was 19% (Kwon et al., 2001).

The various types of glaucoma are classified according to the appearance of the iridocorneal angle (anterior segment variations) that can lead to elevated IOP (Kwon et al., 2009). These are OAG, angle closure glaucoma, and developmental categories which are further divided into primary and secondary types. The most common form of glaucoma in Western countries is primary open angle glaucoma (POAG), a chronic condition which is due to increased resistance in the drainage of aqueous humour through the trabecular meshwork. IOP increases gradually, and the condition is usually asymptomatic until well advanced and visual field loss has occurred. Both eyes are usually affected (European Glaucoma Society, 2021).

3.1.2. Available therapies and unmet medical need

The clinical guidelines for the management of glaucoma published by the European Glaucoma Society (EGS) in 2020 state that there is substantial evidence that treatment of raised IOP reduces the risk of conversion to glaucoma and disease progression. Glaucoma therapy aims to lower IOP to slow the rate of visual field deterioration sufficiently to maintain quality of life. For patients with advanced visual field loss at presentation, surgery may be considered (European Glaucoma Society, 2021; Lichter et al., 2001). Clinical trials have demonstrated that long-term IOP-lowering therapy in patients with OHT reduces the relative risk of glaucoma by 50% (Kass et al., 2002). In patients with glaucoma, a 25% reduction in IOP reduced the relative progression risk by 50% after six years (Leske, 2007).

Current therapy for glaucoma is therefore directed at lowering IOP to prevent further damage to the optic nerve and is highly individual. For patients with early-stage glaucoma, an IOP of 18 to 20 mmHg with a reduction of at least 20% may be adequate. For patients with moderately severe glaucoma, an IOP of 15 to 17 mmHg and at least a 30% reduction may be appropriate. For patients with advanced glaucoma, a lower IOP of 10 to 12 mmHg may be required (European Glaucoma Society, 2021). Regular monitoring of IOP is required to assess progression and guide choice of the target IOP and treatment intensity. Treatment is life-long, and monotherapy is recommended, when possible, to minimise the occurrence of side effects (European Glaucoma Society, 2021).

Available IOP-lowering treatments are prostaglandin analogues, non-selective beta blockers, Rho kinase inhibitors, alpha adrenergic agonists, selective beta blockers and topical carbonic anhydrase inhibitors. If initial therapy is ineffective or not tolerated by the patient, switching to another monotherapy or laser trabeculoplasty is considered. If monotherapy does not lower the IOP to the target pressure but it is well tolerated and effective, addition of a second class of drug is considered. However, multiple topical treatments can reduce compliance and increase exposure to preservatives (European Glaucoma Society, 2021). Prostaglandin analogues such as latanoprost are frequently used as first-line therapy on the basis of their high efficacy, single daily dosing regimen, and established safety profile (European Glaucoma Society, 2021).

Treatment of early onset glaucoma in children is frequently surgical, but medical treatment has a role and follows the same principles as treatment of glaucoma in adults. However, medical treatment options are more limited. Brimonidine crosses the blood–brain barrier and is absolutely contraindicated in infants and young children due to central nervous system toxicity. It should also be used with caution in older children and has been shown to not have a significant effect on IOP reduction. Beta blockers are often used but may not be suitable for all children, e.g., those with asthma or other respiratory conditions. Prostaglandin analogues, considered first-line treatment in adults, are also well tolerated in children. They may be most effective in older children with juvenile open-angle glaucoma as monotherapy.

3.1.3. Available therapies and unmet medical need

3.1.4. Main clinical studies

To support the development of Catiolanze, the applicant has conducted three clinical studies: two Phase II clinical trials in patients with OAG or OHT and OSD; and one pivotal Phase III, randomised, active-controlled, non-inferiority study, which compared Catiolanze with the RefMP Xalatan in patients with OAG or OHT, with or without OSD for three months, followed by a 12-month open label safety extension. All three studies evaluated the efficacy and safety of Catiolanze in terms of reducing both IOP and the signs and symptoms of OSD.

3.2. Favourable effects

Key favourable effects

The primary efficacy endpoint in the pivotal study (0130A01SA) provided in support of this application was change from baseline in peak and trough IOP at Week 12 in the study eye. Based on the results reported for this endpoint, it can be agreed that non-inferiority in IOP lowering effect of Catiolanze as compared to the reference product was shown, as the upper limit of the one-sided 97.5% CI was $\leq$ 1.5 mmHg at both the peak and trough timepoints.

A trend towards a higher decrease in IOP in patients treated with Catiolanze as compared to Xalatan was noted. At week 12, change from baseline in IOP was higher in patients receiving Catiolanze as compared to Xalatan especially at the peak timepoint. The LS mean treatment difference (two-sided 95% CI) between the Catiolanze and control groups was -0.6 (95% CI -1.2, -0.1) at the peak timepoint, and -0.5 (95% CI -1.0, 0.1) at the trough timepoint at Week 12. These differences could be considered as borderline clinically significant as at the peak timepoint the lower limit of 95% CI was - 1.2.

Supporting outcomes

Statistically significant differences were reported only for the first key secondary endpoint i.e. change from baseline in corneal fluorescein staining (CFS) score in the study eye at Week 12 in patients with baseline CFS $\geq$ 1. The LS mean treatment difference between the Catiolanze and control groups was - 0.30 (95% CI -0.46, -0.13, p= 0.0006).

3.3. Uncertainties and limitations about favourable effects

The results of the sensitivity analyses were consistent with the main analysis. There are no additional remaining uncertainties and limitations in relation to efficacy that have an impact on the benefit-risk balance.

3.4. Unfavourable effects

In **period 1** of the pivotal study, the proportion of subjects with any AE was 18.1% (n=35) in the Catiolanze and 21.8% (n=42) in the Xalatan comparator group. The proportion of AEs (any AE, ocular AE, and non- ocular AE) were 18.1%, 10.4% and 10.4 % for Catiolanze group and 21.8%, 13.5% and 10.9% for Xalatan® group. **Ocular AEs** were reported for 10.4% (n=20) and 13.5% (n=26), respectively. The most frequently reported **ocular AE** was **ocular hyperaemia,** reported for **1.6%** (n=3) patients in the Latanoprost 50 µg/ml eye drops, emulsion *SD* group, and **2.6%** (n=5) in the Xalatan® group. **Other ocular AEs** with ≥ 1% occurrence in the Catiolanze group versus Xalatan treatment group were conjunctival hyperaemia (1% vs 1.6%), dry eye (1% vs 0.5%, erythema of eyelid (1% vs 1%), keratitis (1% vs 0%), blurred vision (1% vs 0%), eye irritation (0% vs 1%), foreign body sensation in eyes (0% vs 1.6%, seasonal eye allergy (1% vs 0%) and instillation site pain (0% vs 1.6%).

The safety profile of Catiolanze in the **12-month Open Label Phase** was similar to that observed during Period 1 of the Phase III clinical study. **29.6%** (n=21) of patients in the Catiolanze / Catiolanze group and **30.3%** (n=20) in the Xalatan®/ Catiolanze group reported **any AE**. The frequency of any **ocular AE** was higher in the Catiolanze / Catiolanze group reported for **22.5%** (n=16) of patients and for **18.2%** (n=12) in the Xalatan®/ Catiolanze group. The most frequently reported ocular AE during Period 2 was **abnormal sensation in eye** which was reported for 3.6% of patients in the Overall Catiolanze group.

3.5. Uncertainties and limitations about unfavourable effects

In relation to AEs reported during the clinical studies, it is noted that the lack of patient masking to treatment allocation in the pivotal study means that symptoms rated by patients may have been susceptible to bias. If patients on Catiolanze expected to experience fewer ocular symptoms, the

potential benefits observed may have been overestimated but this approach has been used in other similar ocular products and could be accepted in that context. If any, the bias is expected to be small.

There was some uncertainty as to the case selection for consideration as CSIs (cases of special interest) which has now been adequately clarified. The potential for eye irritation related to CKC is of interest. The applicant did not consider other AEs as Cases of Special Interest (CSI) such as AEs focusing on ocular tolerability such as conjunctival hyperaemia, ocular hyperaemia, photophobia, eye irritation, punctate keratitis (mostly without symptoms), corneal opacity.

In this application, the applicant has sought both adult and paediatric indications for this new formulation of latanoprost. It was highlighted that there is no product-specific clinical safety data relating to the use of Catiolanze in the paediatric population had been provided within this application. The applicant provided a more robust product specific justification and overview of paediatric information from the reference product and has referred to other topically administered ocular products with the Novasorb emulsion which are approved for paediatric use within the EU, including Verkazia, Ikervis, Cationorm and Cationorm Pro. In addition, a more detailed discussion of all the available bibliographic and safety data relevant to paediatric use has been submitted. A number of points for clarification were raised in the non-clinical section in relation to possible exposure differences in PK and toxicology data and the relevance of these findings should be considered as part of the response-see also non-clinical section. It is highlighted that nonclinical data provided within the submission are considered supportive only and cannot be considered conclusive for establishing safety. The applicant provided a satisfactory justification to support the safety of Catiolanze in children from 4 years of age and adolescents. It is recommended that this aspect is closely monitored and that focused reviews of paediatric safety specific to the Catiolanze product are provided through the PSURs, post approval. In this context, 'Use in paediatric patients' will be listed and discussed as missing information in the PSUR and focused safety updates should be provided. A separate entry in the EURD list for Catiolanze is therefore needed in order to facilitate focused monitoring of the paediatric population in the PSURs.

There was some uncertainty in relation to the clinical safety aspects of CKC, which is a component of Catiolanze, particularly over long-term use in adults and paediatric patients, a warning in the product information was requested in line with the product information for Ikervis and Verkazia. In response, the applicant provided a justification on why a warning that CKC may cause eye irritation is not warranted at this time. However, the applicant's conclusion that no warning is required in the PI was not endorsed. Although it is acknowledged that the role of CKC in ocular irritation is reduced when compared to BAK, the inclusion of a general warning in section 4.4, to inform that the product can cause eye irritation is warranted. It is also recommended that this issue should continue to be specifically monitored through routine pharmacovigilance measures going forward, particularly over the longer term.

3.6. Effects Table

Table 48: Effects Table for Catiolanze indicated for reduction of elevated intraocular pressure (IOP) in patients with open angle glaucoma or ocular hypertension in adults (including the elderly) Reduction of elevated IOP in paediatric patients with elevated IOP and paediatric glaucoma

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
IOP Change from baseline at Week 12	The primary efficacy endpoint was change from baseline in peak and trough IOP at Week 12 in the study eye.	Unit	**9 am** LS Mean (SE): -8.8 (0.25) **4 pm** LS Mean (SE): -8.6 (0.24)	**9 am** LS Mean (SE): -8.2 (0.26) **4pm** LS Mean (SE): -8.6 (0.24)	Pre-specified non-inferiority criteria were achieved for both peak and trough measurements; the upper limit of the one-sided 97.5% CI was ≤ 1.5 mmHg at both timepoints	Pivotal study
CFS change from baseline in patients with baseline CFS score ≥ 1 at week 12	Key Secondary Efficacy Endpoint	Unit	LS Mean (SE): -0.71 (0.069)	LS Mean (SE): -0.41 (0.077)	Difference (SE), Catiolanze minus Xalatan: -0.30 (0.084) 95% CI of Difference -0.46, -0.13 P-Value 0.0006	Pivotal study
OSD change from baseline in patients with baseline OSD score >0 at week 12	Key Secondary Efficacy Endpoint	Unit	LS Mean (SE): -0.26 (0.058)	LS Mean (SE): -0.17 (0.060)	Difference (SE), Catiolanze minus Xalatan -0.09 (0.055) 95% CI of Difference -0.20, 0.01 P-Value 0.0900	Pivotal study
Unfavourable Effects						
Ocular hyperaemia	Most frequently reported ocular AEs	% (n)	1.6% n=3	2.6% n=5 (Xalatan)	Uncertainty re AE categorisation -To be clarified with Applicant	Pivotal study (period 1)
Dry eye **Keratitis**	Most frequently reported ocular AEs	% (n)	1.0% 1.0%	0.5% 0.0%		Pivotal study (period 1)
Abnormal sensation in eye	SARs occurring in more than 1% of patients in the **overall** Latanoprost 50 µg/ml eye drops Versus total Xalatan/latanoprost group	% (n)	2.2% (n=3)	3.0% (n=2)		Pivotal study (period 2)

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Based on the results the pivotal study provided in support of this application, it can be agreed that non-inferiority in IOP lowering effect of Catiolanze as compared to the reference product was shown as the upper limit of the one-sided 97.5% CI was ≤ 1.5 mmHg at both the peak and trough timepoints. The positive consequences of lowering IOP on longer term clinically meaningful outcomes are well established.

The safety profile of the active substance latanoprost is considered to be well-characterised and the overall safety data provided with this application is generally considered to be in accordance known class effects. In this context, general safety information for latanoprost is reflected in the SmPC which is in line with the established safety profile of the active substance latanoprost and that of the reference product, Xalatan.

Overall, there were no unexpected AEs reported during the clinical studies and the clarifications raised during the assessment in relation to the evaluation of AEs and AE reporting have been provided by the applicant.

3.7.2. Balance of benefits and risks

Overall, the efficacy of Catiolanze 50 µg/ml eye drops, emulsion SD has been shown. It can be agreed that intraocular pressure lowering effects of Catiolanze is not inferior as compared to Xalatan. When weighted against the safety profile that is generally considered to be consistent with that which is already known for other topical ocular prostaglandin analogues, this leads to a positive balance between benefits and risks.

3.8. Conclusions

This application concerns a hybrid version of latanoprost, eye drops solution. The reference product Xalatan is indicated for the reduction of IOP. Nonclinical studies have been provided for this application and considered sufficient. From a clinical perspective, this application contains new data on efficacy and safety, which was considered sufficient to confirm the bridge to the reference product and to demonstrate efficacy and safety of Catiolanze.

The overall benefit/risk balance of Catiolanze is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Catiolanze is favourable in the following indication(s):

Catiolanze is indicated for the reduction of elevated intraocular pressure (IOP) in adult patients with open angle glaucoma or ocular hypertension.

Catiolanze is indicated for the reduction of elevated IOP in children from 4 years of age and adolescents with elevated IOP and paediatric glaucoma.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.