



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 November 2014
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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Invented name: Travatan

International non-proprietary name: travoprost

Procedure No. EMEA/H/C/000390/II/0046

Marketing authorisation holder (MAH): Alcon Laboratories (UK) Ltd

Note

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



Table of contents

1. Background information on the procedure	5
1.1. Type II variation	5
1.2. Steps taken for the assessment of the product	6
2. Scientific discussion	6
2.1. Introduction	6
2.2. Non-clinical aspects	7
2.2.1. Ecotoxicity/environmental risk assessment	7
2.2.2. Discussion on non-clinical aspects	8
2.2.3. Conclusion on the non-clinical aspects	8
2.3. Clinical aspects	8
2.3.1. Introduction.....	8
2.3.2. Pharmacokinetics	9
2.3.3. Pharmacodynamics.....	10
2.3.4. Discussion on clinical pharmacology.....	10
2.3.5. Conclusions on clinical pharmacology.....	11
2.4. Clinical efficacy	11
2.4.1. Main study	11
2.4.2. Discussion on clinical efficacy.....	20
2.4.3. Conclusions on the clinical efficacy	22
2.5. Clinical safety	22
2.5.1. Discussion on clinical safety.....	32
2.5.2. Conclusions on clinical safety	34
2.5.3. PSUR cycle	34
2.6. Risk management plan	34
2.7. Update of the Product information.....	36
2.7.1. User consultation	36
3. Benefit-Risk Balance	36
4. Recommendations.....	39

List of abbreviations

ACG	Angle closure glaucoma
ADR	Adverse drug reaction
AE	Adverse event
AL-5848	Travoprost free acid
AM	In the morning (Ante Meridiem)
BAK	Benzalkonium chloride
BLQ	Below the limit of quantitation
CI	Confidence interval
CSR	Clinical study report
ECG	Electrocardiogram
EDC	Electronic data capture
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FP	F-prostanoid receptor
ICH	International Conference on Harmonisation
IOP	Intraocular pressure
ITT	Intent to treat
IWRS	Interactive Web Response System
JOAG	Juvenile open angle glaucoma
LOCF	Last observation carried forward
MAH	Marketing Authorisation Holder
mL	Millilitre
mmHg	Millimeters of mercury
mg	Milligram
µg	Microgram
NDA	New Drug Application
OHT	Ocular hypertension
PBT	Persistence, bioaccumulation and toxicity
PCG	Primary congenital glaucoma

PDCO	Paediatrics Committee
PEC	Predicted Environmental Concentration
PGA	Prostaglandin analogue
PGF2 α	Prostaglandin F2 α receptor
PIP	Paediatric Investigation Plan
PK	Pharmacokinetics
PM	In the evening (Post Meridiem)
PP	Per protocol
PQ	POLYQUAD Polyquaternium-1
SD	Standard deviation
SE	Standard error
SAE	Serious adverse event
SofZia zinc	An preservative system containing borate, sorbitol, propylene glycol, and zinc

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Alcon Laboratories (UK) Ltd submitted to the European Medicines Agency on 12 June 2014 an application for a variation.

This application concerns the following medicinal product:

Centrally authorised Medicinal product(s):	International non-proprietary name
For presentations: See Annex A	
Travatan	travoprost

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of the therapeutic indication for decrease of elevated intraocular pressure in paediatric patients with ocular hypertension or paediatric glaucoma.

The variation proposed amendments to the Summary of Product Characteristics and Package Leaflet

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0298/2013 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0298/2013 was completed.

The PDCO issued an opinion on compliance for the PIP P/0298/2013.

Information relating to orphan market exclusivity

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.

Scientific advice

The applicant did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Concepcion Prieto Yerro Co-Rapporteur: Greg Markey

Timetable	Actual dates
PRAC Rapporteur Assessment Report	27 October 2014
CXMP Rapporteur Assessment Report	28 October 2014
Rapporteur's preliminary assessment report circulated on:	18 August 2014
CoRapporteur's preliminary assessment report circulated on:	19 August 2014
Joint Rapporteur's updated assessment report circulated on:	23 September 2014
Request for supplementary information and extension of timetable adopted by the CHMP on:	25 September 2014
MAH's responses submitted to the CHMP on:	17 October 2014
PRAC Rapporteur's assessment report on the MAH's responses circulated on:	27 October 2014
Joint Rapporteur's assessment report on the MAH's responses circulated on:	28 October 2014
PRAC RMP advice and assessment overview adopted by PRAC	06 November 2014
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	14 November 2014
CHMP opinion:	20 November 2014

2. Scientific discussion

2.1. Introduction

Travoprost belongs to the pharmacological class of PGF_{2α} (prostaglandin F_{2α} receptor) agonists that includes latanoprost (Xalatan), bimatoprost (Lumigan) and tafluprost (Taflotan). Prostaglandin analogues have been shown to lower intraocular pressure (IOP) by increasing the outflow of aqueous humour via trabecular meshwork and uveoscleral pathways. They are currently the most widely prescribed first-line ocular hypotensive agents in most developed countries because of their IOP-lowering efficacy and established safety.

Travoprost 40 µg/mL eye drops, solution preserved with benzalkonium chloride (BAK) received EU marketing authorisation in November 2001 (EU/1/01/199/001-002). Travoprost 40 µg/mL solution preserved with polyquaternium-1 (PQ) was approved by the European Medicines Agency (EMA) in November 2010 (EMEA/H/C/II/0035G). Another Travoprost 40 µg/mL solution preserved with SofZia (a zinc-based preservative system) was approved in the USA in September 2006 (NDA 21-994), and also is marketed in Canada and Japan. In addition, Alcon recently developed a PQ-preserved formulation that contains

travoprost 30 µg/mL (Travoprost 0.003%, Solution) which was approved in the EU on the 20 Feb 2014 (EMA/H/C/002738/0000).

Travoprost 40 µg/mL solution is indicated for the decrease of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension. The current type II variation application submitted by the MAH (Marketing Authorisation Holder) is to extend the currently authorised indication to include paediatric patients from 2 months to <18 years of age at the same posology as in adults.

Glaucoma in infancy and childhood is a potentially blinding condition characterized by elevated intraocular pressure. Increased IOP leads to optic nerve damage and consequent visual loss. Additional damage to the visual system, including large refractive error, strabismus and amblyopia, may occur. Overall, glaucoma is responsible for 5% of blindness in children worldwide. Early diagnosis and referral are crucial to ensuring optimal visual outcome.

Paediatric glaucoma is classified into primary and secondary types. Primary glaucomas are those with isolated angle malformations. Primary glaucoma may have onset at birth, in the first few years of life, or later in life (congenital, primary infantile, and juvenile glaucoma, respectively).

The goal of infantile glaucoma therapy is preservation of vision rather than control of IOP, although IOP is used to monitor treatment success. Depending on the degree of angle dysgenesis and angle abnormalities in children with primary glaucoma, surgery is the mainstay of treatment, although initial therapy for aphakic glaucoma and JOAG (juvenile open angle glaucoma) is usually pharmacological.

Many children may require pharmacological management either as a long-term treatment or as temporizing measures before and/or after surgical intervention. Medications used in the treatment of glaucoma include beta-blockers, alpha-2-adrenergic agonists, carbonic anhydrase inhibitors, prostaglandin analogues, miotics, and sympathomimetics. The data supporting the use of these medicinal products in paediatric population are scarce.

The clinical development plan of Travoprost 40 µg/mL solution dosed once daily for the indication of decrease of elevated intraocular pressure in paediatric patients with glaucoma or ocular hypertension consists of 2 clinical studies including, 1 safety and pharmacokinetic study (C-12-009) and 1 Phase 3 safety and efficacy study (C-12-008). These studies are used to support this application for the indication of decrease in elevated IOP in paediatric patients with glaucoma or ocular hypertension.

Both studies were agreed with the EMA Paediatric Committee (PDCO) in a formal Paediatric Investigation Plan (EMA-001271-PIP01-12-M01). This variation application has been subject to a PIP compliance verification by the PDCO which agreed that the conducted studies were fully compliant with the agreed PIP.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

To support the addition of paediatric indications for Travoprost, a justification statement concerning Environmental Risk Assessment was provided by the MAH.

The paediatric use follows identical posology, administered via the same route of administration and using the same product concentration as in adults. The MAH stated that the addition of the new paediatric population is not likely to cause a significant increase of the overall Predicted Environmental Concentration (PEC) in the environment.

However, the results of the persistence, bioaccumulation and toxicity (PBT) screening test (LogKow

determined experimentally by slow-stirring method) need to be submitted. Furthermore, if the value obtained for the product would be higher than 4.5, Travoprost should be screened by the Applicant in a step-wise procedure for persistence, bioaccumulation and toxicity. The CHMP recommended that an updated ERA is submitted.

2.2.2. Discussion on non-clinical aspects

No new nonclinical pharmacology, pharmacokinetics and toxicology data have been submitted in this application, which was considered acceptable by the CHMP.

For Environmental Risk Assessment, the MAH has submitted a justification for not performing ERA studies, as it does not expect a significant increase in Predicted Environmental Exposure deriving from this paediatric extension. The justification provided by the MAH is generally agreed upon. However, the CHMP recommended the MAH to conduct PBT screening test (LogKow study) and submit the results and an updated ERA accordingly.

2.2.3. Conclusion on the non-clinical aspects

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of Travoprost. However, the CHMP recommends that an updated ERA with the results of PBT study is submitted.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

- Tabular overview of clinical studies

Table 2.3.1-1 Summary of Completed Studies with Travoprost 0.004% in Paediatric Patients

Study Identifier/ Study Type	Study Design	Study Population	Treatment Groups	Number of Patients ¹	Dosing Regimen	Dosing Duration
Safety/Pharmacokinetic Study						
C-12-009 (TDOC-0017019)	Multicenter, open-label, pharmacokinetic and safety study	Males and females of any race/ethnicity, 2 months to less than 18 years of age, with a diagnosis of glaucoma or ocular hypertension in at least one eye	Travoprost	25	Travoprost one drop, once daily in each eye	7 days

Phase 3 Safety and Efficacy Study						
C-12-008 (TDOC-0017018)	Multicenter, randomized, double-masked, parallel group, active-controlled study	Males and females of any race/ethnicity, 2 months to less than 18 years of age, with a diagnosis of glaucoma or ocular hypertension with an IOP of at least 20 mmHg in at least one eye.	Travoprost Timolol	77 75	Travoprost – one drop in each eye once daily Timolol – one drop in each eye twice daily	3 months

1 Number of patients represents the intent-to-treat (ITT) dataset

2.3.2. Pharmacokinetics

The systemic pharmacokinetics of travoprost free acid (AL-5848) following topical ocular administration of Travoprost 0.004% eye drops, solution has been characterized in multiple studies in adult populations.

In addition, a paediatric pharmacokinetic study (Study C-12-009) was conducted as part of the Paediatric Investigation Plan to compare systemic AL-5848 exposure in paediatric patients to historical data in adults.

• Study C-12-009

This was a Phase 1, multicenter, open-label study. The primary objectives of this study were to assess the safety and evaluate the steady-state plasma concentrations of AL-5848 following once daily administration of Travoprost 0.004% PQ in paediatric patients with glaucoma or ocular hypertension.

Methods

Patients aged 2 months to less than 18 years of age who had a diagnosis of glaucoma or ocular hypertension in at least 1 eye were enrolled. Patients with conditions requiring chronic treatment with glucocorticosteroids resulting in steroid-induced glaucoma and aphakic patients with contact lenses were also eligible for enrolment. A minimum of 3 patients were planned for enrolment in each of the following age subgroups: 2 months to < 3 years, 3 to < 12 years, and 12 to < 18 years.

Patients received Travoprost 0.004% PQ instilled as 1 drop in each eye once daily at 9 AM (\pm 60 minutes) for 7 days. Patients were evaluated for safety at Day 1 and Day 7. In addition, during the Day 7 visit, patients underwent PK plasma sampling within 30 minutes prior to instillation of the final dose of study drug and at various time points (10, 20, 40, and 80 minutes) post-dose.

Criteria for Evaluation were as follows:

- Pharmacokinetic: C_{max}, T_{max}, T_{last}, AUC_{0-last}, AUC_{0-∞}, t_{1/2}
- Safety: Adverse events, vital signs, alertness evaluations, ECG, slit-lamp examination, ocular hyperemia, intraocular pressure, best corrected visual acuity, dilated fundus examination

Descriptive statistics (mean, median, geometric mean, standard deviation, number, minimum, and maximum values) were provided for plasma concentration levels at each sampling time and for all estimated PK parameters. Scatter plots of concentration versus time and peak plasma concentration versus weight were also generated.

Results

Overall, 25 patients were enrolled into and completed the study. A total of 24 of the 25 patients were included in the PK analysis set. The mean age of the patients in the PK analysis set was 9.6 years: 2 months to <3 years (N = 4); 3 to <12 years (N = 9); 12 to <18 years (N = 11). 50% of the patients were male and 50% of the patients were White; a substantial percentage of the patients were Black/African American (45.8%). There were no relevant demographic differences among patients included in both the PK and safety analysis sets.

Pharmacokinetic Results:

A total of 25 patients were dosed. Of the 24 patients included in the PK analysis set, 11 had at least 1 sample with quantifiable AL-5848 concentrations (≥ 0.0100 ng/mL); 5 of these patients had 2 quantifiable samples, and 1 patient had quantifiable drug levels at all 4 post-dose time points. Of the 119 study samples analysed, only 19 (16.4%) had quantifiable drug concentrations.

C_{max} was achieved at 10 minutes post-dose in 8 of the 11 patients with quantifiable data. Two other patients had maximum exposures at 20 minutes, and 1 patient had a maximum exposure at 40 minutes. All Day 7 pre-dose trough samples were BLQ (below the limit of quantitation), indicating no accumulation of AL-5848 in plasma over the course of treatment.

AL-5848 plasma concentrations ranged from BLQ to 0.0545 ng/mL. This range was similar to that found in 4 previous PK studies in various adult populations.

No clear relationship between age or body surface area (BSA) was apparent. While the highest individual AL-5848 concentration in the study (0.0545 ng/mL) was observed in the youngest patient (aged 3 months) with the lowest BSA (0.366 m²), 2 other patients in the less than 3 years age cohort did not show any quantifiable AL-5848 exposure. In addition, the highest AUC_{0-last} value (0.0303 ng*hr/mL) was observed in a 6 year old patient (BSA = 0.837 m²).

Historical data in adults

The exposure data in paediatric patients were compared with historical data in four studies in adult populations including healthy volunteers, renally-impaired subjects, hepatically-impaired subjects and healthy male Japanese volunteers. Of the 107 patients in these 4 adult studies, nearly two-thirds (68 of 107) had no quantifiable AL-5848 plasma concentrations. The mean C_{max} for the 60 adult PK profiles with quantifiable AL-5848 concentrations was 0.0180 ± 0.007 ng/mL and the quantifiable concentrations ranged from 0.0100 to 0.0520 ng/mL.

The range of quantifiable AL-5848 exposure in the 4 adult populations was 10.0 to 52.0 pg/mL, similar to that observed in paediatric patients.

2.3.3. Pharmacodynamics

No additional pharmacodynamic studies in children have been conducted.

2.3.4. Discussion on clinical pharmacology

The pharmacokinetics of travoprost in adults have been characterised and reported previously in the Marketing Authorisation Application for Travatan 40 µg/mL eye drops solution. The MAH has performed one PK study to evaluate the steady-state systemic exposure of travoprost in paediatric patients with glaucoma or ocular hypertension. Patients were administered the usual adult dose of travoprost.

Only paediatric patients were included in the trial so that the comparison with adult parameters is based on historical data. Of note, paediatric patients received travoprost solution preserved with polyquad (Travoprost 0.004% PQ). Travatan formulation was modified in 2010 in order to replace the preservative used benzalkonium chloride (BAK) by polyquaternium-1 (POLYQUAD, PQ). The reference data for adults were obtained with Travoprost 0.004% preserved with BAK. However, as the bioequivalence between Travoprost 0.004% BAK and PQ formulations was already demonstrated, Travoprost 0.004% BAK has been considered to be acceptable as reference.

Whereas the optimal effect is obtained if the product is administered in the evening, the treatment was scheduled to be administered in the morning. It is considered that it was due to feasibility reasons and although it could have some relevance for the IOP lowering effect it has no significant impact on the travoprost pharmacokinetics.

Peak concentrations ranged from 0.0105 to 0.0545 ng/mL, plasma levels being higher in younger patients. Although a potentially relevant systemic exposure in the youngest group of patients cannot be excluded, no signs of accumulation have been seen in any group and in general the measured exposure is similar to that reported for adults. No relevant findings were observed in terms of safety in comparison to adults and between the different groups of paediatric patients. However, the limited number of patients in each group and the wide inter-subject variability do not allow reaching full conclusions.

Since the safety profile is consistent with that already known for adults (no new signals associated with exposure), it is a topically administered medicine and no signs of accumulation were seen, no further concerns have been raised.

2.3.5. Conclusions on clinical pharmacology

The MAH has performed one PK study in paediatric patients with glaucoma or ocular hypertension. Following once daily topical ocular administration for 7 days the systemic exposure to AL-5848 was low. In most of patients plasma levels were undetectable (below 0.0100 ng/mL assay quantifiable concentration). Only a minority of samples analysed (16.4%) showed measurable concentrations.

After analysis of the PK data obtained from the Study C-12-009 and data from adult PK studies, no dose adjustment has been recommended by age for the phase 3 study. This is consistent with the recommendations for other prostaglandin F_{2α} agonist eye drops used in paediatric population.

The pharmacodynamics of Travoprost have been adequately characterised in adults and the pertinent data are appropriately reflected in the currently approved harmonized SmPC for Travoprost. Additional studies in children are not considered necessary.

2.4. Clinical efficacy

One single clinical trial has been submitted to support the efficacy of travoprost in the paediatric population. This study was designed to establish comparability (non inferiority) between Travoprost 0.004% PQ and Timolol in the reduction of IOP in paediatric patients with glaucoma or ocular hypertension.

2.4.1. Main study

Study C-12-008 - A 3 Month, Multicenter, Double-Masked Safety and Efficacy Study of Travoprost Ophthalmic Solution, 0.004% Compared to Timolol (0.5% or 0.25%) in Paediatric Glaucoma Patients.

Methods

This was a multicenter, randomized, double-masked, parallel-group, active-controlled study intended to evaluate the safety and efficacy of Travoprost 0.004% PQ in paediatric patients with glaucoma or ocular hypertension.

The study was designed to demonstrate that the IOP-lowering efficacy of Travoprost 0.004% PolyQuad was noninferior to Timolol 0.5% (0.25% for patients < 3 years of age) in paediatric patients with glaucoma or ocular hypertension. The primary efficacy endpoint was IOP change from baseline at Month 3.

Following the Screening and Eligibility visits, eligible patients were randomized to receive either Travoprost 0.004% PQ once daily in each eye in the evening (with Travoprost Vehicle instilled once daily in the morning to maintain masking) or Timolol twice daily in each eye (once in the morning and once in the evening); the assigned study drugs were instilled as 1 drop in each eye for 3 months. Patients were evaluated for safety and efficacy at Week 2, Week 6, and Month 3.

At the assessment visits, IOP was measured in both eyes at 9 AM (\pm 60 minutes) at all study visits using a calibrated tonometer (Goldmann or Perkins instrument was preferred, although a Tono-Pen® was acceptable) and a combination of a topical anesthetic and a coloring agent. The same 2 individuals (an operator and a reader) measured IOP for a given patient at all study visits and the same method (including the same fluorescein and anesthetic agent) for measuring IOP should have been used for each individual patient at all study visits whenever possible. Two consecutive IOP measurements were taken for each eye at every assessment.

Study participants

The study population included males and females of any race/ethnicity who were 2 months to less than 18 years of age, and who had a diagnosis of paediatric glaucoma or ocular hypertension, including patients with conditions requiring chronic treatment with glucocorticosteroids resulting in steroid-induced glaucoma; aphakic patients who wore contact lenses were also eligible for enrolment. The mean IOP measurement in at least 1 eye must have been greater than or equal to 20 mmHg at the 9 AM (\pm 60 minutes) time point at the Eligibility visit.

Eligible patients must not have had recent histories of chronic, recurrent, or severe inflammatory eye disease, ocular trauma, intraocular surgery, clinically significant or progressive retinal disease, other severe ocular pathologies (eg, dry eye), any abnormality preventing reliable tonometry, or current signs and symptoms that were associated with these or other ocular and non ocular conditions.

Patients were stratified by primary diagnosis (primary congenital glaucoma (PCG), or non-PCG, including secondary glaucomas and juvenile open-angle glaucoma [JOAG]) and baseline IOP in the study eye (< 27, 27–31, and > 31 mmHg).

Treatments

Eligible patients were randomized to receive either Travoprost 0.004% PQ once daily in each eye in the evening (with Travoprost Vehicle instilled once daily in the morning to maintain masking) or Timolol 0.5% twice daily in each eye (0.25% for patients < 3 years of age)

Objectives

The primary objective of this study was to demonstrate that the intraocular pressure (IOP)-lowering efficacy of Travoprost 40 µg/mL, eye drops solution, preserved with POLYQUAD (Travoprost 0.004% PQ) is

noninferior to Timolol 5 mg/mL, eye drops solution (2.5 mg/mL for patients < 3 years of age) (Timolol) in paediatric patients with glaucoma or ocular hypertension.

Outcomes/endpoints

Efficacy:

The primary efficacy endpoint was:

- IOP change from baseline at Month 3

The supportive efficacy endpoints were:

- IOP change from baseline at Week 2 and Week 6
- IOP and IOP percent change from baseline at each visit (Week 2, Week 6, and Month 3)
- Percentage of patients who achieved at least a 15% reduction in IOP at each visit (Week 2, Week 6, and Month 3)
- Percentage of patients who achieved IOP within the normal range

Safety:

- Extent of exposure
- Adverse events (AEs)
- Vital signs (pulse, blood pressure, respiratory rate, and body temperature)
- Alertness evaluations (responsiveness, speech, facial expression, and eyes)
- Best-corrected visual acuity (BCVA)
- Slit-lamp examination of eyelids and conjunctiva, cornea, lens, and iris/anterior chamber, including the presence of aqueous flare and inflammatory cells
- Automated perimetry
- Central corneal thickness
- Corneal diameter
- Ocular hyperemia
- Dilated fundus examinations (vitreous, retina/macula/choroid, optic nerve, and measurements of cup/disc ratio)
- 12-lead electrocardiogram (ECG) parameters

Sample size

With 65 patients per group with a Month 3 endpoint in the ITT analysis, there is approximately 90% power to demonstrate that Travoprost 0.004% PQ is noninferior to Timolol using a noninferiority margin of + 3.0 mmHg, ie, that the upper limit of the 95% 2-sided CI for the difference in IOP change (Travoprost 0.004% PQ group minus Timolol group) is less than the noninferiority margin. Assuming a 10% dropout rate due to the initiation of open-label concomitant therapy or losses to follow-up, the resultant sample size of approximately 58 patients per group would provide approximately 87% power to demonstrate noninferiority.

In addition to the noninferiority margin, the sample size estimate further assumed an SD for IOP change of 7 mmHg, a 5% chance of a Type I error, and that the mean IOP change for the Travoprost 0.004% PQ group would be at least 1 mmHg better than the Timolol group.

Randomisation

Patients who satisfied the eligibility criteria were randomized (1:1), using an interactive web response system (IWRS), to 1 of 2 study treatment groups: Travoprost 0.004% PQ or Timolol. A centralized randomization scheme was implemented, and randomization was at the study level, stratified by primary diagnosis (primary congenital glaucoma [PCG], or non- PCG, including secondary glaucomas, juvenile open-angle glaucoma [JOAG]) and ocular hypertension and baseline IOP in the study eye (< 27, 27–31, and > 31 mmHg).

Masking

The patients (or their parents/legal guardians) were dispensed study medication along with instructions to instill 1 drop of study medication in each eye from the bottle labeled “morning” at 9 AM (\pm 30 minutes) and 1 drop of study medication in each eye from the bottle labeled “evening” at 9 PM (\pm 30 minutes) through the day prior to the Month 3/Exit visit. In order to maintain the masking, patients in the Travoprost 0.004% PQ group instilled Vehicle in the morning and Travoprost 0.004% PQ in the evening each day, while patients in the Timolol group instilled Timolol once in the morning and again in the evening each day; thus, patients in both groups instilled study medication twice daily.

Statistical methods

The efficacy parameters were evaluated using the ITT and PP analysis sets. The ITT analysis set included all patients who received study drug and completed at least 1 scheduled on-therapy visit; the PP analysis set included all patients who received study drug, satisfied prerandomization inclusion/exclusion criteria, and completed at least 1 scheduled on-therapy study visit. Safety was evaluated using the safety analysis set, which included all patients who received study drug.

In order to provide a robust evaluation of the primary efficacy endpoint, the results obtained using both the PP and ITT analysis sets were considered jointly when evaluating whether the study successfully demonstrated non inferiority.

Primary Efficacy Endpoint

Treatment differences in mean IOP change from baseline were examined with a pairwise test at the Month 3 visit. The pairwise test was based on the least squares means derived from an analysis of covariance with treatment and primary diagnosis as factors and baseline IOP as a covariate in the model. The IOP change was calculated as IOP at Month 3 minus IOP at baseline. Thus, within-group efficacy was evidenced by more negative values of IOP change. For the test of noninferiority, a 95% 2-sided confidence interval (CI) was constructed for the difference in the mean change from baseline in IOP between treatment groups at Month 3. The test for demonstrating noninferiority was based on a margin of + 3.0 mmHg. Thus, noninferiority was established if the upper limit of the differences in mean IOP change from baseline between treatment groups (ie, the mean IOP change from baseline in the Travoprost 0.004% PQ group minus the mean IOP change from baseline in the Timolol group) was less than + 3.0 mmHg at the Month 3 visit.

If noninferiority was achieved, then superiority was to be tested at an alpha level of 0.05. Superiority would be concluded if the upper limit of the 2-sided 95% CI for the difference in IOP change (ie, the mean IOP change from baseline in the Travoprost 0.004% PQ group minus the mean IOP change from baseline in the Timolol group) was less than 0 mmHg at the Month 3 visit.

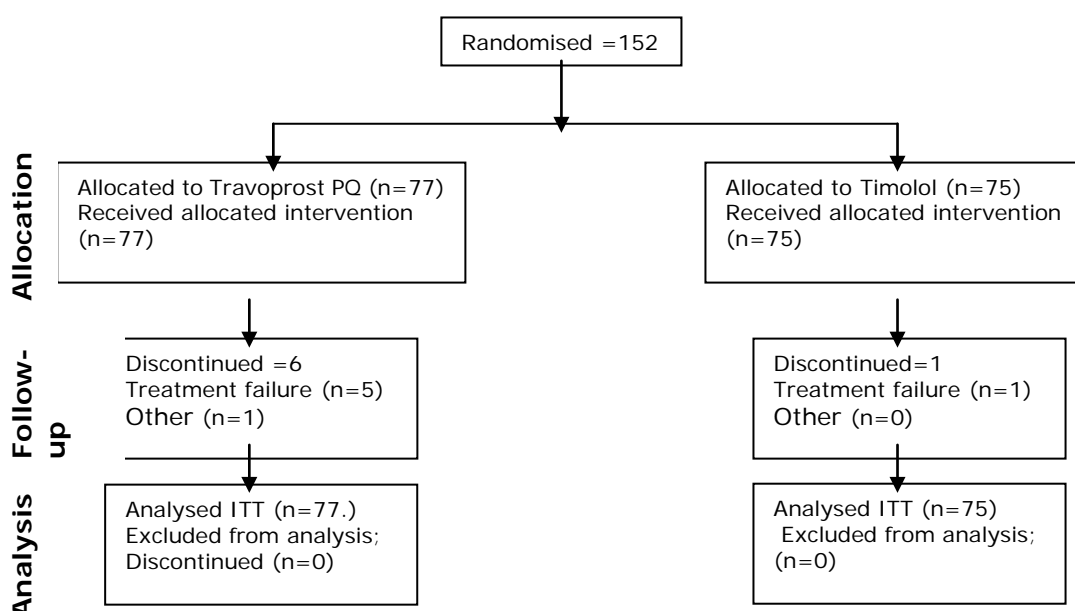
The primary efficacy endpoint was also summarized descriptively according to the primary diagnosis (primary congenital glaucoma, non primary congenital glaucoma, including secondary glaucomas and juvenile open-angle glaucoma).

Supportive Efficacy Endpoints

The assessment of the supportive endpoints was based on descriptive summaries of the specified outcomes. No formal hypothesis tests were conducted.

Results

Participant flow



Recruitment

Patients in this study were enrolled across 38 investigational centres in the United States, Germany, Singapore, United Kingdom, Taiwan, Philippines, Spain, Saudi Arabia, Columbia, France, Portugal, Belgium, Poland, Romania, Puerto Rico, and Mexico.

Study Period: 05 September 2012 to 25 March 2014

Conduct of the study

The study protocol was amended three times. Some of the important changes that were made include:

- The patient population was divided into 2 cohorts defined by age: Cohort 1 included patients 3 to < 18 years of age and Cohort 2 included patients 2 months to < 3 years of age. Enrolment was planned to begin with Cohort 1, while Cohort 2 was opened for enrolment once pharmacokinetic data were available in patients < 3 years of age.
- A minimum IOP entrance criterion of at least 20 mmHg in 1 eye at the Eligibility visit was added

- The statistical analyses were updated to clarify that a test of superiority would be performed on the primary endpoint if noninferiority was first met (based on CPMP/EWP/482/99) and to include a descriptive supportive analysis of the percentage of patients who reached an IOP within a normal range.
- Changes to the efficacy analysis plan for clarification and to address concerns over bias arising from regression to mean among the small number of patients diagnosed with ocular hypertension for whom a sustained increase in IOP could not be documented.

Patient disposition

Overall, 152 patients were randomized to study drug, including 77 patients in the Travoprost 0.004% PQ group and 75 patients in the Timolol group. Across treatment groups, 95.4% of the patients (145 of 152 patients) completed the study. All 152 randomized patients were included in the ITT and safety analysis sets. One patient in the Travoprost 0.004% PQ group was excluded from the PP analysis set due to a violation of the inclusion criteria.

Demographic and baseline characteristics

Within the ITT analysis set, the greatest proportion of patients was 3 to less than 12 years of age (52.0%; overall mean age = 9.6 years), female (52.6%), and White (40.8%). Substantial proportion of patients were also Black or African American (19.7%), Asian (12.5%), or other (26.3%). The patients were generally diagnosed with non-paediatric congenital glaucoma (70.4%). These patients were most commonly classified as having ocular hypertension (17.8%), juvenile open-angle glaucoma (17.1%), or glaucoma following lensectomy for congenital cataracts (11.8%). Overall, most of the randomized patients had a baseline IOP < 27 mmHg (77.0%). There were no clinically meaningful differences between treatment groups in regard to any of the demographic parameters or baseline characteristics.

Efficacy results

For the primary efficacy endpoint using the PP analysis set, the least squares mean (standard error [SE]) reduction in IOP was 6.4 (1.05) mmHg in the Travoprost 0.004% PQ group and 5.8 (0.96) mmHg in the Timolol group (Table 2-1). The least squares mean difference between treatment groups was -0.5 mmHg (95% CI: -2.1, 1.0 mmHg).

Table 2-1:
Comparison of Mean IOP Change from Baseline (mmHg) at Month 3
Trav versus Timolol
(Per Protocol Data)

Visit	Trav		Timolol		Mean Difference ^a	(95% CI)
	N	Mean (SE)	N	Mean (SE)		
Month 3	53	-6.4 (1.05)	60	-5.8 (0.96)	-0.5	(-2.1, 1.0)

Trav = Travoprost 40 µg/mL eye drops solution, preserved with POLYQUAD

Timolol = Timolol 5mg/mL eye drops solution (2.5 mg/mL for patients < 3 yrs)

SE = Standard Error; CI = Confidence Interval; Baseline = Eligibility Visit

^aEstimates based on least squares means derived from a statistical model that accounts for correlated IOP measurements within patient where actual primary diagnosis and actual baseline IOP stratum are in the model.

The results obtained using the ITT analysis set were consistent with those obtained using the PP analysis set. Specifically, the mean (SE) reduction in IOP was 5.4 (0.98) mmHg in the Travoprost 0.004% PQ group and 5.3 (0.93) mmHg in the Timolol group (Table 2-2). The least squares mean difference between treatment groups was -0.1 mmHg (95% CI: -1.5, 1.4 mmHg).

Table 2-2:
Comparison of Mean IOP Change from Baseline (mmHg) at Month 3
Trav versus Timolol
(Intent-to-Treat Data)

Visit	Trav		Timolol		Mean Difference^a (95% CI)	
	N	Mean (SE)	N	Mean (SE)		
Month 3	71	-5.4 (0.98)	74	-5.3 (0.93)	-0.1	(-1.5, 1.4)

Trav = Travoprost 40 µg/mL eye drops solution, preserved with POLYQUAD

Timolol = Timolol 5mg/mL eye drops solution (2.5 mg/mL for patients < 3 yrs)

SE = Standard Error; CI = Confidence Interval; Baseline = Eligibility Visit

^aEstimates based on least squares means derived from a statistical model that accounts for correlated IOP measurements within patient where actual primary diagnosis and actual baseline IOP stratum are in the model.

In this study, the prespecified non inferiority margin was 3.0 mmHg. Thus, the study met its objective and demonstrated that Travoprost 0.004% PQ is non inferior to Timolol. The results did not support a conclusion of superiority as the upper limit of the 95% CIs did not lie entirely below 0.

Sensitivity analyses were planned using the PP and ITT analysis sets for mean IOP change from baseline to Month 3 to evaluate the potential for bias resulting from the inclusion of patients with ocular hypertension. The results obtained in Sensitivity Analysis 1 were nearly identical to the results obtained using the full PP and ITT analysis sets, indicating that the study results were not biased by the inclusion of patients who did not have a confirmed history of sustained IOP elevation. The results obtained in Sensitivity Analysis 2 were similar to the results obtained using the full PP and ITT analysis sets, indicating that the study results were not biased by the inclusion of patients with ocular hypertension.

The supportive efficacy endpoints were consistent with the primary efficacy conclusion of non inferiority. The mean IOP measurements were similar in the Travoprost 0.004% PQ and Timolol groups at each study visit at Week 2, Week 6 and Month 3. The percentage of patients who achieved at least a 15% reduction in IOP was similar in the Travoprost 0.004% PQ (83.1%) and Timolol groups (74.3%). Finally, the percentage of patients who achieved an IOP measurement within the normal range was somewhat greater at all study visits in the Travoprost 0.004% PQ group (71.8%) than in the Timolol group (66.2%).

The youngest cohort in the study (2 months to < 3 years of age) included 16 patients. 10 patients were randomized to the Travoprost arm and 6 received timolol. The IOP measurements of all the patients in this group at the study visits are provided below in Table 4-1.

Table 4-1
Individual Efficacy Response Data for IOP for Patients <3 Years Old
(Intent-to-Treat Data)

Treatment	Inv.	Pat.	Age	Age Unit	Worse Eye ^a	Diagnosis ^b	Baseline IOP Stratum ^a	Baseline	Week 2	Week 6	Month 3		
Timolol	6051	1594	9	Months	OD	IOP	Non-PCG	< 27 mmHg	25	*	14	20	24
	6283	1020	2	Years	OD	IOP	PCG	> 31 mmHg	34		22	18	17
	6286	1596	2	Months	OD	IOP	Non-PCG	< 27 mmHg	22	*	---	9	13
	6652	1457	20	Months	OS	IOP	PCG	27 - 31 mmHg	29		18	20	18
	6711	1106	13	Months	OD	IOP	PCG	< 27 mmHg	23		21	20	20
Trav	6812	1272	2	Years	OS	IOP	PCG	< 27 mmHg	22	*	22	15	19
	2909	1657	2	Years	OS	IOP	Non-PCG	> 31 mmHg	34		23	16	27
	3639	1005	2	Years	OS	IOP	PCG	< 27 mmHg	24	*	---	---	15
		1458	15	Months	OD	IOP	PCG	27 - 31 mmHg	29	*	---	---	31
	6282	1773	14	Months	OS	IOP	PCG	27 - 31 mmHg	27	*	---	---	26
	6283	1270	6	Months	OD	IOP	PCG	< 27 mmHg	20	*	---	---	10
	6286	1128	4	Months	OD	IOP	Non-PCG	27 - 31 mmHg	27	*	---	23	41
		1595	2	Years	OS	IOP	Non-PCG	< 27 mmHg	22	*	---	---	29
	6652	1271	20	Months	OS	IOP	PCG	< 27 mmHg	23		24	25	23
	6666	1778	3	Months	OD	IOP	Non-PCG	< 27 mmHg	24		20	11	---
6746	1723	23	Months	OS	IOP	Non-PCG	> 31 mmHg	37	*	---	---	25	

Trav = Travoprost 40 µg/mL eye drops solution, preserved with POLYQUAD

Timolol = Timolol 5mg/mL eye drops solution (2.5 mg/mL for patients < 3 yrs)

Inv. = Investigator Number; Pat. = Patient Number

^aWorse eye and Actual Baseline IOP Stratum are constructed from data entered into EDC by the site.

^bActual Baseline Diagnosis is constructed from data entered into EDC by the site.

*Collected under anesthesia

Summary of main study

The following table summarise the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment.

Table 2.4.1-1. Summary of efficacy for trial C-12-008

Title: A 3 Month, Multicenter, Double-Masked Safety and Efficacy Study of Travoprost Ophthalmic Solution, 0.004% Compared to Timolol (0.5% or 0.25%) in Paediatric Glaucoma Patients		
Study identifier	C-12-008	
Design	This was a 3-month, multicenter, randomized, double-masked, parallel-group, active-controlled safety and efficacy study in pediatric patients with glaucoma.	
	Duration of main phase:	3 months
	Duration of Run-in phase:	not applicable
	Duration of Extension phase:	not applicable
Hypothesis	Non-inferiority of Travoprost as compared to Timolol	
Treatments groups	Travoprost 0.004% one drop in each eye, once daily in the evening	Treatment duration = 3 months, n (randomized) = 77
	Timolol 0.5%/0.25% one drop in each eye, twice daily (morning and evening)	Treatment duration = 3 months n (randomized) = 75
Endpoints and definitions	Primary endpoint	IOP change from baseline at month 3

	Secondary endpoints	<p>IOP change from baseline at week 2 and week 6</p> <p>IOP and IOP percent change from baseline at each visit (Week 2, Week 6, and Month 3)</p> <p>Percentage of patients who achieved at least a 15% reduction in IOP at each visit</p> <p>Percentage of patients who achieved IOP within the normal range</p>
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Results and Analysis

Analysis description	Primary Analysis		
Analysis population and time point description	Per protocol (PP) and Intent to treat (ITT): Mean change in IOP from baseline at month 3		
Descriptive statistics and estimate variability (PP population)	Treatment group	Travoprost 0.004%	Timolol
	Month 3 Number of subject (n) Mean change in IOP (SE)	53 -6.4 (1.05)	60 -5.8 (0.96)
Effect estimate per comparison	Primary endpoint	Travoprost 0.004% (n=53) vs Timolol (n=60)	
	Mean difference between treatments at month 3 (95% C.I)	-0.5 (-2.1, 1.0)	
Descriptive statistics and estimate variability (ITT population)	Treatment group	Travoprost 0.004%	Timolol
	Month 3 Number of subject (n) Mean change in IOP (SE)	71 -5.4 (0.98)	74 -5.3 (0.93)
Effect estimate per comparison	Primary endpoint	Travoprost 0.004% (n=71) vs Timolol (n=74)	
	Mean difference between treatments at month 3 (95% C.I)	-0.1 (-1.5, 1.4)	

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The overall design of the clinical study (including the selection criteria of the patients, the duration of the study, the choice of endpoints) have been discussed with the PDCO and are in agreement with other clinical trials in this field.

Patients 2 months to < 18 years of age with glaucoma or ocular hypertension were included.

A randomized, double-masked, parallel-group, active-controlled study is an acceptable study design. The absence of placebo arm can be justified as it would be considered unacceptable to include a placebo arm in paediatric patients when suitable treatment options are available. Moreover from published literature the IOP-lowering efficacy of timolol is established and hence a comparative study of Travoprost and timolol is acceptable.

The MAH has chosen to demonstrate adequate efficacy and safety of children as compared to timolol, when the results from this study is taken in to consideration along with the efficacy and safety data of travoprost in adults. The sample size was estimated based on a non-inferiority margin of 3 mm Hg and the assumption that the mean IOP change for travoprost group will be at least 1 mm Hg better than timolol group, which is in line with the published literature.

The dose for this Phase 3 study (ie, Travoprost 0.004% PQ, 1 drop once daily) was that currently recommended in the product information. No specific dose-response studies were conducted in the paediatric population. The dose choice is supported on the results of the pK study (C-12-009) where no dose adjustment by age was judged necessary. This is in line with other PGF2 α analogues dosage.

A lower dose of Travoprost has been recently approved by the EMA. Izba eye drops (containing Travoprost 0.003% eye drops solution) showed certain advantages on safety without having impact on the IOP lowering effect in comparison to Travatan 0.004%. In principle, it would be expected that Travoprost 0.003% solution may also work in paediatric population. The CHMP recommends the MAH to consider submitting a line extension of the Travatan marketing authorisation to include a lower strength formulation for a paediatric indication. In addition, CHMP recommends that the MAH requests Scientific Advice in order to confirm what data would be appropriate to support this extension.

The shorter wash-out of previous IOP-lowering medication has been allowed to minimize the risk of treatment withdrawn in children and is therefore accepted. The use of two different doses of timolol can affect the interpretation of results, but the rationale to minimize risk of timolol in the younger children is understood and accepted.

The main analysis of efficacy was based on the reduction of IOP levels after 3 months of treatment. The study also investigated the effect of Travoprost at different time points (at Week 2 and 6) and the control of IOP in terms of responder rates. IOP was measured in both eyes at every visit at 9 AM (\pm 60 min), approximately 12 hours after the study drug administration. The measurement of diurnal IOP variations (intended to detect the peak and trough effect of the medicinal product) would have been of interest. The difficulties of IOP measurement in children are acknowledged. As the morning IOP level represents the highest point during the day the proposed time point can be considered an acceptable measurement.

This 3-month study addresses the question of the short-term efficacy of the product. In principle there are no reasons to believe that efficacy data beyond 3 months would differ from that measured within this period.

For the comparison between travoprost and timolol a non-inferiority margin of + 3.0 mmHg has been used. This margin seems wide but it has been considered to be acceptable in this case. It has been also accepted in the past for other compounds (e.g Study A6111137, where Latanoprost 0.005% BAK and Timolol 0.5%

were compared; Maeda-Chubachi et al, 2011). Both the ITT and PP analysis sets were used to evaluate the primary efficacy endpoint. Although the Per Protocol (PP) set is the preferred population for a non-inferiority analysis, both analyses are expected to lead to similar conclusions. The lack of disparities between ITT and PP analyses would also provide robustness to the results.

It is noted that the study did not use any formal methods to evaluate compliance of patients in using study medications. However, the study had other measures like informal enquiries by the study personnel who were trained to discuss the dosing regimen at each study visit and also ensure that the patients had been dosing the medications appropriately. In the light of reasonable compliance reported in paediatric glaucoma, the above measures are considered acceptable.

6 out of 10 patients in the youngest age group (2 months to 3 years) showed a positive response to treatment with Travoprost and 3 out of 10 patients showed a negative response. While 2 out of the 3 non-responders had Non-PCG, the numbers available are too small to draw any robust inferences. Based on the limited data available, it can be accepted that a relevant treatment effect of Travoprost is seen in some patients in this age group and the difference in the mean change in IOP between two treatments is affected significantly by one patient who had a large negative treatment response of +14 mmHg change in IOP from baseline. Therefore, an indication in age group 2 to < 3 years is accepted, especially as the limited data in this age group is appropriately highlighted to the prescriber in the Product Information.

Efficacy data and additional analyses

All 152 randomized patients were included in the ITT and safety analysis sets (77 patients in Travoprost 0.004% PQ group and 75 patients in Timolol group). A total of 151 patients were included in the PP analysis set.

Most of the recruited subjects (70.4%) had non congenital glaucoma. Ocular hypertension was present in 17.8% of study patients. The mean baseline IOP measurements were similar across study drug groups regardless of whether the patients were diagnosed with PCG or non-PCG (25.1 and 24.2 mmHg, respectively). About two thirds had a baseline IOP < 27 mmHg (77.0%). Most of the randomized patients were 3 to less than 12 years of age (52.0%) and there were more females (52.6%) than males. No patients with corticosteroid-induced ocular hypertension and glaucoma were specifically recruited. The MAH has provided the response data to travoprost (and timolol) from patients on stable corticosteroid treatment during the study. Although the limited number of patients precludes achieving comprehensive conclusions, no different response to travoprost is observed in this subgroup.

The majority of patients (62%) had been on anti-glaucoma treatment at recruitment: prostaglandin analogue, α_2 adrenergic agonist, carbonic anhydrase inhibitor or β adrenergic agonist.

A total of 38 out of 151 evaluable patients for PP analysis (30.3% of patients on Travatan 0.004% PQ and 20% of patients on Timolol) were not finally analysed. The most frequent reason for exclusion was the visit outside the study window without significant imbalance between both groups.

According PP and ITT analysis sets results it was demonstrated that Travatan 0.004% was non inferior to Timolol. The upper confidence limits of the differences in the mean IOP change from baseline between study drug groups (Travatan and Timolol groups) was well less than 3.0 mmHg margin.

The mean IOP reduction achieved after three month treatment was similar for both compounds (PP data Travatan -6.4 mmHg, Timolol -5.8 mmHg). The results from ITT analysis were also consistent. The reduction in IOP from baseline is a clinically relevant reduction in both treatment groups. As it was pre-specified, superiority of Travoprost to Timolol was evaluated. It was not achieved in either the PP or ITT analysis sets.

The IOP lowering effect of Travatan does not appear to be significantly different when patients with or without ocular hypertension were taken into account. The results of the primary analysis were obtained

based on the ANCOVA model that was pre-specified in the protocol. The pre-specified ANCOVA model included baseline IOP, treatment and diagnosis.

The use of LOCF in the handling of missing data was justified as being appropriately conservative in this setting. In addition, the MAH provided sensitivity analysis where all missing IOP changes from baseline were imputed with the worst on-therapy IOP change experienced during the study. The results of the sensitivity analysis were consistent with the results of the LOCF imputation.

In general, the effect evidenced in the primary endpoint was also translated into the main secondary endpoints. No relevant differences were observed between Travoprost and Timolol. The IOP lowering effect was apparent from the first two weeks under both treatments. After three months the IOP level achieved was 17.9 mmHg and 18.0 mmHg, respectively. Patients treated with Travatan experienced a 27.6% reduction of the baseline IOP and the reduction for Timolol group was 24.9%.

The relevance of the IOP reduction has been evaluated as responder rates. Overall, 83% of patients on travoprost and 74.3% of patients on timolol attained a 15% reduction in IOP. Similarly, 71.8% of patients treated with travoprost and 66.2% of patients treated with timolol achieved a normal IOP, according to the pre-established age normal range.

In general, exploratory comparison between travoprost and timolol showed numerical differences in favour of travoprost.

The number of patients who were withdrawn due to treatment failure was higher in travoprost (n=6) as compared to timolol (n=1). Sensitivity analyses conducted by the MAH in order to address the impact of this difference did not show potential bias.

Subgroup analyses were conducted by age category (2 months to < 3 years, 3 to < 12 years, and 12 to < 18 years), sex, ethnicity, race, iris colour, baseline IOP stratum (< 27 mmHg, 27–31 mmHg, and > 31 mmHg), and diagnosis primary congenital glaucoma (PCG or non-PCG). No substantial differences between Travoprost and Timolol in IOP lowering effect were observed by different subgroups. Of note, the youngest group of patients (from 2 months to < 3 years) responded better to Timolol than to Travoprost. This may be due to small numbers and the high variability of this subgroup. Additionally, the lack of differences between treatments in other related subgroups such as the primary congenital glaucoma patients prevent from drawing sound conclusions in this regard. Appropriate clarification and additional warning statements regarding the limited efficacy data in the youngest age group are included in the Product Information.

The applicant provided additional analyses which include an estimated treatment effect with centre as fixed effect in the model. This analysis is supportive of travoprost in both the ITT and PP sets.

2.4.3. Conclusions on the clinical efficacy

Based on the results from study C-12-008, Travatan 0.004% eye drops solution has shown non-inferiority to Timolol 0.5% in the IOP lowering effect produced in paediatric patients aged 2 months to < 18 years of age, with glaucoma or ocular hypertension.

2.5. Clinical safety

2.5.1 Introduction

The clinical development of Travoprost 0.004% PQ in patients < 18 years of age with glaucoma or ocular hypertension consisted of one pharmacokinetic (PK) clinical trial (C-12-009) of 7 days duration and one

phase 3 safety and efficacy clinical trial (C-12-008) of 3 month duration. An evaluation of safety was conducted on all patients who were enrolled into these two clinical trials and received study drug.

Four travoprost formulations have been approved in adult patients: Travoprost 0.004% BAK, PQ and SofZia and Travoprost 0.003% PQ. Therefore, clinical data and the postmarketing experience with the already approved travoprost formulations in adult patients are of relevance and supportive.

In addition, safety data regarding the off-label use of travoprost in paediatric patient from two literature articles (Helmanova, 2007 and Yanovitch, 2009) and from the MAH's safety database have been provided. This information is considered supportive to characterize the long-term safety profile of Travoprost 0.004% PQ in paediatric patients.

On the whole, the MAH's approach established for the safety analysis is considered acceptable.

Indirect comparison between Travoprost 0.004% PQ (C-12-008) and historical data of Travoprost 0.004% PQ has been provided in order to obtain an estimated conclusion regarding the overall safety profile of Travoprost 0.004% in paediatric patients in comparison to adult patients.

Safety parameters have been measured during studies C-12-008 and C-12-009 and included the following:

- Adverse events
- Vitals signs (pulse, blood pressure, respiration rate and body temperature)
- Patient alertness
- Visual acuity
- Slit-lamp examination (eyelids/conjunctiva, cornea, lens, and iris/anterior including aqueous flare and inflammatory cells)
- Visual fields
- Central corneal thickness
- Ocular hyperemia
- Corneal diameter
- Fundus parameters (vitreous, retina, macula, choroid, optic nerve, and cup/disc ratio)
- 12-lead ECG
- Intraocular pressure (PK study only)

In both clinical trials adverse events were collected by:

- Solicited comments from study patients and/or the patient's parents (or legal guardian)
- Observations by the study investigator

Patient exposure

102 paediatric patients were exposed to one drop administration of Travoprost 0.004% PQ once daily during the clinical development (77 patients exposed to Travoprost 0.004% PQ in study C-12-008 and 25 patients exposed to Travoprost 0.004% PQ in study C-12-009). The sample size of the safety population is considered limited for the overall safety analysis and firm conclusions with regards to some adverse events could be difficult to draw. As previously stated, safety data collected from historical confirmatory clinical trials in adults are considered supportive.

	Patients enrolled	Patients exposed to Travoprost 0.004% PQ	Patients with long term* safety data
Active –controlled study (C-12-008)	152	77	None
Pharmacokinetic study (C-12-009)	25	25	None

* 6 months and 12 months continuous exposure data, or intermittent exposure.

The cumulative adult patient exposure since the first launch of Travoprost 0.004% (preserved with BAK, PQ or SofZia) is estimated to be approximately 16,189,436 patient-years (calculated based on worldwide sales).

Regarding the duration of exposure, the majority of patients were exposed during approximately 3 months (61% patients exposed higher than 87 days and 33.8% patients exposed between 46-48 days). The mean duration of exposure to travoprost 0.004% PQ is 84 days.

Table 2.7.4.1–3 Duration of Exposure to Study Drug – C-12-008 (Safety Population)

	Trav (N = 77)		Timolol (N = 75 ^a)	
	n	(%)	n	(%)
1-15 Days	0	(0.0)	0	(0.0)
16-45 Days	4	(5.2)	1	(1.3)
46-87 Days	26	(33.8)	16	(21.3)
>87 Days	47	(61.0)	58	(77.3)

Trav = Travoprost 40 µg/mL eye drops solution, preserved with POLYQUAD

Timolol = Timolol 5mg/mL eye drops solution (2.5 mg/mL for patients < 3 yrs)

^aPatient 6711.1513 received Timolol 0.25% for 4 days before switching to Tim 0.5% for the remainder of the study.

Some adverse events already known for topical PGAs generally occur after several months to years of dosing (eg. periocular skin hyperpigmentation or discolouration, iris hyperpigmentation, changes in eyelash characteristics and stimulation of melanogenesis). Indeed, five cases with growth of eyelashes were reported during C-12-008. Given that the potential incidence of these AEs with the prolonged use of travoprost cannot be ruled out, they are already included in the RMP and should be closely monitored in the PSURs. The absence of long-term clinical data is a limitation. However, long-term data from the off-label use of travoprost 0.004% PQ in paediatric patients were provided: two studies published of 18 and 28 month duration (*Yanovitch, 2009 and Helmanova, 2007, respectively*) and a safety database collected by Alcon since Travatan was approved in 2001 for adult patients (see Figure 1). This information reveals that the type of the adverse events reported were similar to adults. Eyelash thickening and elongation, ocular hyperaemia, ocular irritation, conjunctival redness and skin pigmentation were the most common adverse events. No new risks, no systemic adverse events and no increase in the incidence of the already known adverse events were observed with long-term exposure to travoprost 0.004% PQ.

Figure 1

Adverse Events with Off-Label use in Paediatric Patients

System Organ Classification Preferred Term	Counts of Preferred Term
Eye disorders	13
Blepharal pigmentation	2
Dark circles under eyes	1
Eye irritation	1
Eye pruritus	1
Ocular hyperaemia	8
Gastrointestinal disorders	1
Nausea	1
General disorders and administration site conditions	102
Drug ineffective	3
No adverse event	97
Pyrexia	2
Infections and infestations	1
Conjunctivitis	1
Injury, poisoning and procedural complications	5
Accidental exposure to product	1
Accidental exposure to product by child	1
Medication error	3
Investigations	2
Intraocular pressure fluctuation	1
Intraocular pressure increased	1
Nervous system disorders	4
Ataxia	1
Headache	2
Syncope	1
Respiratory, thoracic and mediastinal disorders	1
Dyspnoea	1
Skin and subcutaneous tissue disorders	5
Skin discolouration	5
Social circumstances	1
Childhood	1
Vascular disorders	2
Hypertension	1
Pallor	1
Grand Total	137

The demographic characteristics of patients include three groups of age (from 2 months to less than 18 years) with approximately 50% of patients between 3 and 12 years and mean age of 9.6 years. Around 70% of patients were diagnosed with non-primary congenital glaucoma (Non-PCG). A high variety of races was included. In general, the studied population is considered representative of the population that is expected to receive Travoprost 0.004% PQ.

Adverse events

The majority of treatment-emergent AEs reported for either treatment group during the main study were local ocular effects with a known causal association with the use of topical ocular eye drops and the use of prostaglandin analogue (PGAs) or beta-blocker. For instance, eye disorders such as ocular hyperaemia, conjunctival hyperaemia, growth of eyelashes, eye pruritus were more commonly reported in the Travatan group in comparison to the timolol group.

No systemic adverse drug reaction (ADR) or serious ADR was reported with the use of Travoprost 0.004% PQ. Regarding results from C-12-009 PK study, lower systemic exposure is expected when travoprost is topically administered. Therefore, no systemic adverse events are anticipated. In addition, the occurrence of adverse events is unlikely regarding the limited number of patients exposed to travoprost and the short duration of the studies.

The most common adverse drug reactions were eye disorders. Ocular hyperemia was the most common ADR (16.9%) reported with the use of Travoprost 0.004% PQ and is a very common local side effect that has been reported in adult patients (\geq 18 years of age) with the use of Travoprost and other topical ocular prostaglandin analogues (PGAs) (eg. latanoprost, bimatoprost). Other ocular ADRs reported with the use of Travoprost 0.004% PQ were for local ocular effects associated with the use of a topical ocular medication (eg. ocular discomfort, photophobia, tearing, dry eye, corneal surface irritation) and occurred as single events within a study treatment or with a known causal association with the use of a topical ocular PGA (ie. growth of eyelashes).

In C-12-008 study when both treatment groups are compared, a higher incidence of adverse drug reactions in travoprost group (26%) versus timolol group (12%) is observed. From a qualitative point of view, different ADRs are reported due to the different mechanism of action of the active substances.

When both populations exposed to travoprost (paediatric versus adult patients) are compared, from a qualitative point of view the overall safety profile in paediatric patients might be similar to the one observed in adult patients as the formulation is the same as the one approved for adults (travoprost 0.004% PQ). However, from a quantitative point of view, the most common adverse drug event observed with travoprost (i.e ocular hyperemia) has been reported with a higher incidence in paediatric population (16.9%) compared to adults (11.4%). However, given that this adverse event is not considered serious and disappears when the treatment is discontinued, this increase in ocular hyperemia in paediatric patients is not considered particularly worrisome.

Study C-12-008

Table 2-3 summarizes treatment-emergent AEs through Month 3 of the study.

Table 2-3:
Summary of Treatment-Emergent Adverse Events

Adverse Event Category	TRAV		Timolol	
	N=77		N = 75	
	N	%	N	%
Deaths	0	0.0	0	0.0
Patients experiencing nonfatal SAE	0	0.0	2	2.7
Not related to treatment	0	0.0	2	2.7
Patients discontinued due to an AE	0	0.0	0	0.0
Patients with at least 1 treatment-emergent AE (related and not related combined)	40	51.9	28	37.3
Treatment-emergent AEs \geq 5%				
Ocular hyperaemia	15	19.5	3	4.0
Conjunctival hyperaemia	4	5.2	1	1.3
Growth of eyelashes	5	6.5	0	0.0
Headache	5	6.5	2	2.7
Patients with at least 1 treatment-emergent AE related to treatment (adverse drug reaction; ADR)	20	26.0	9	12.0
All ADRs				
Ocular hyperaemia	13	16.9	1	1.3
Conjunctival hyperaemia	0	0.0	1	1.3
Growth of eyelashes	5	6.5	0	0.0
Eye pruritus	1	1.3	1	1.3
Dry eye	0	0.0	1	1.3
Eye pain	1	1.3	0	0.0

Table 2-3:
Summary of Treatment-Emergent Adverse Events

Adverse Event Category	TRAV		Timolol	
	N=77		N = 75	
	N	%	N	%
Deaths	0	0.0	0	0.0
Patients experiencing nonfatal SAE	0	0.0	2	2.7
Not related to treatment	0	0.0	2	2.7
Patients discontinued due to an AE	0	0.0	0	0.0
Patients with at least 1 treatment-emergent AE (related and not related combined)	40	51.9	28	37.3
Treatment-emergent AEs $\geq 5\%$				
Ocular hyperaemia	15	19.5	3	4.0
Conjunctival hyperaemia	4	5.2	1	1.3
Growth of eyelashes	5	6.5	0	0.0
Headache	5	6.5	2	2.7
Patients with at least 1 treatment-emergent AE related to treatment (adverse drug reaction; ADR)	20	26.0	9	12.0
All ADRs				
Ocular hyperaemia	13	16.9	1	1.3
Conjunctival hyperaemia	0	0.0	1	1.3
Growth of eyelashes	5	6.5	0	0.0
Eye pruritus	1	1.3	1	1.3
Dry eye	0	0.0	1	1.3
Eye pain	1	1.3	0	0.0
Lacrimation increased	1	1.3	0	0.0
Photophobia	1	1.3	1	1.3
Erythema of eyelid	1	1.3	0	0.0
Eye irritation	0	0.0	1	1.3
Foreign body sensation	0	0.0	1	1.3
Keratitis	1	1.3	0	0.0
Ocular discomfort	0	0.0	1	1.3
Dizziness	0	0.0	1	1.3
Visual field defect	0	0.0	1	1.3

Overall, based on a review of ADRs, no new AEs different from the already known safety profile for travoprost 0.004% were reported in paediatric population. Moreover, no increased risk for the use of Travoprost 0.004% PQ was identified for paediatric patients including patients below the age of 2 years. The types and characteristics of the ADRs reported with the use of Travoprost 0.004% PQ in the paediatric population were consistent with ADRs reported in previous clinical trial experience with Travoprost 0.004% (preserved with BAK, sofZia, or PQ) involving adult patients.

Study C-12-009

Table below summarizes treatment-emergent AEs reported in the study. All AEs reported during the study were reported as single events. No patient experienced more than 1 AE (ie, MedDRA Preferred Term) during the study.

**Table 2-1:
Summary of Treatment-Emergent Adverse Events**

Adverse Event Category	TRAV 0.004% PQ N = 25	
	N	%
Deaths	0	0.0
Patients experiencing nonfatal SAE		
Not related to treatment	1	4.0
Patients discontinued due to an AE	0	0.0
Patients with at least 1 treatment-emergent AE (related and not related combined)	5	20.0
All treatment-emergent AEs		
Ocular hyperaemia	1	4.0
Eye pain	1	4.0
Eye pruritus	1	4.0
Conjunctival haemorrhage	1	4.0
Ear pain	1	4.0
Trabeculectomy*	1	4.0
Patients with at least 1 treatment-emergent AE related to treatment (adverse drug reaction; ADR)	3	12.0
All ADRs		
Ocular hyperaemia	1	4.0
Eye pain	1	4.0
Eye pruritus	1	4.0

*Scheduled overnight hospitalization for trabeculectomy surgery

Adverse drug reactions (ie, treatment related AEs) (ADRs) reported in the study included single events for ocular hyperemia, eye pruritus, and eye pain. No patient experienced an ADR associated with an untoward change in their systemic health. Patients under the age of 3 years did not experience an ADR.

Serious adverse event/deaths/other significant events

No deaths nor serious adverse drug reactions or discontinuations of the study participation were reported during both clinical studies. Only one paediatric patient underwent a trabeculectomy surgery in the travoprost group. However, this serious adverse event was not considered related to the study drug what is reassuring.

Table 2.5.5–2 Listing of Nonfatal Serious Adverse Event – C-12-008 and C-12-009

Protocol	Inv	Sub	Treatment	Age/Sex	Coded Adverse Event	C/A	D/C
C-12-008	6652	1457	Timolol 0.25%	20 Mo/M	Pneumonia	NR	No
C-12-008	6652	1774	Timolol 0.5%	9Y/M	Keratitis bacterial*	NR	No
					Viral infection	NR	No
C-12-009	2023	1501	TRAV 0.004% PQ	3 month/M	Trabeculectomy	NR	No

Inv = Investigator number Sub = Subject number F= Female M = Male C/A = causality

NR = Not Related Tx = Treatment D/C = Patient discontinued from the clinical trial due to the nonfatal SAE

*Described as a central microbial keratitis

Data in table are a subset of [Table 2.7.4.7-20](#) and [Table 2.7.4.7-21](#)

Laboratory findings

No clinical laboratory evaluations were performed in the paediatric clinical development of Travoprost 0.004% PQ.

In general, a review of changes from baseline in safety assessments (ie. vital signs (pulse, blood pressure, respiration rate, and body temperature), 12-lead ECG, patient alertness, visual acuity, slit-lamp exam (ocular signs), ocular hyperemia, intraocular pressure (C-12-009 only), corneal diameter, central corneal thickness, dilated fundus exam, and visual fields) did not reveal an increased safety concern for the use of Travoprost 0.004% PQ in paediatric patients relative to adult patients. With respect to 12-lead electrocardiogram, given that low exposure to systemic travoprost is expected, changes in 12-lead ECG are unlikely. Literature regarding the off-label use of Travoprost 0.004% in paediatric patients and studies performed with other topical PGAs show reassuring data in relation to systemic adverse events. Overall, data submitted do not seem to have a relevant impact on the cardiovascular system. However, no firm conclusions can be drawn due to the low number of patients included in the studies and the short duration of exposure to travoprost.

As previously mentioned, the most common ocular sign change from baseline reported in travoprost group was ocular hyperemia. The higher incidence of ocular hyperemia in travoprost group (16.9%) in comparison to timolol group (1.3%) is not unpredicted due to the already known safety profile for the prostaglandin analogues.

Table 2.7.4.4–28 Frequency of Patients by Hyperemia Score Category By Visit According to Maximum Change from Baseline at Each Visit (Safety Population) – C-12-008

Visit	Hyperemia Change	Trav n (%)	Timolol n (%)
Week 2	Total	77	74
	0 ^a	61 (79.2)	68 (91.9)
	0.5 Increase	6 (7.8)	4 (5.4)
	1 Increase	6 (7.8)	2 (2.7)
	1.5 Increase	3 (3.9)	0 (0.0)
	2 Increase	1 (1.3)	0 (0.0)
	2.5 Increase	0 (0.0)	0 (0.0)
	3 Increase	0 (0.0)	0 (0.0)
Week 6	Total	76	74
	0 ^a	57 (75.0)	70 (94.6)
	0.5 Increase	12 (15.8)	2 (2.7)
	1 Increase	7 (9.2)	2 (2.7)
	1.5 Increase	0 (0.0)	0 (0.0)
	2 Increase	0 (0.0)	0 (0.0)
	2.5 Increase	0 (0.0)	0 (0.0)
	3 Increase	0 (0.0)	0 (0.0)
Month 3	Total	71	74
	0 ^a	56 (78.9)	70 (94.6)
	0.5 Increase	8 (11.3)	2 (2.7)
	1 Increase	5 (7.0)	2 (2.7)
	1.5 Increase	1 (1.4)	0 (0.0)
	2 Increase	1 (1.4)	0 (0.0)
	2.5 Increase	0 (0.0)	0 (0.0)
	3 Increase	0 (0.0)	0 (0.0)

Trav = Travoprost 40 µg/mL eye drops solution, preserved with POLYQUAD

Timolol = Timolol 5mg/mL eye drops solution (2.5 mg/mL for patients < 3 yrs)

Baseline = Eligibility Visit

^aZero represents either no change from baseline at any visit or a decrease in hyperemia score from baseline at the visit.

Maximum change in hyperemia score is defined as the maximum increase from baseline to any visit for either study eye compared to the same eye at baseline.

Optic nerve changes from baseline were reported in both treatment groups. However, the incidence of this adverse event was higher in travoprost group (8.6%) in comparison to timolol group (2.8%). This difference between treatment groups has been further clarified by the MAH. According to the justification and data provided, changes in optic nerve and the increase in the cup/disc ratio value could indicate a progression of glaucoma rather than an adverse event linked to the exposure to Travatan.

Table 2.7.4.4–32 Frequency of Patients with Any Fundus Parameter Change from Baseline to Exit Visit (Safety Population) – C-12-008

Fundus	Trav			Timolol		
	N	n	(%)	N	n	(%)
Vitreous	70	0	(0.0)	72	0	(0.0)
Retina/Macula/Choroid	70	0	(0.0)	71	0	(0.0)
Optic Nerve	70	6	(8.6)	71	2	(2.8)

Trav = Travoprost 40 µg/mL eye drops solution, preserved with POLYQUAD

Timolol = Timolol 5mg/mL eye drops solution (2.5 mg/mL for patients < 3 yrs)

Baseline = Eligibility (if non-missing) otherwise Screening Visit

Change in fundus parameter is defined as one or more unit increase from baseline to exit visit in either study eye compared to the same eye at baseline.

Safety in special populations

Regarding the incidence of adverse events by age group, in the travoprost group it was similar for children (2 to 11 years) and adolescents (12 to 17 years). Infants and toddlers (28 days to 23 months) were the

population with lower incidence of ADRs. However, no firm conclusions can be drawn due to the low number of patients included in the studies and the short duration of exposure to travoprost.

**Table 2.7.4.7-5 Overall Frequency and Incidence of Adverse Events by Age
– C-12-008**

Coded Adverse Event	Trav (N=77)											
	0 to 11 Months (N=3)			12 to 23 Months (N=4)			2 to 11 Years (N=43)			12 to 17 Years (N=27)		
	R	NR	Total	R	NR	Total	R	NR	Total	R	NR	Total
Cardiac disorders												
Palpitations										1	3.7	1 3.7
Supraventricular extrasystoles										1	3.7	1 3.7
Ear and labyrinth disorders												
Auricular swelling							1	2.3	1 2.3			
Ear pain												
Eye disorders												
Ocular hyperaemia				1	25.0	1 25.0	7	16.3	2 4.7	8	18.6	6 22.2
Conjunctival hyperaemia								3	7.0	3 7.0	1	3.7
Growth of eyelashes							2	4.7	2 4.7	3	11.1	3 11.1
Eye pruritus								2	4.7	2 4.7	1	3.7
Dry eye								1	2.3	1 2.3		
Conjunctivitis												
Eye pain							1	2.3	1 2.3			
Lacrimation increased		1	33.3	1	33.3		1	2.3	1 2.3			
Photophobia							1	2.3	1 2.3			
Blepharitis								1	2.3	1 2.3		
Dark circles under eyes								1	2.3	1 2.3		

Safety related to drug-drug interactions and other interactions

No drug interactions were reported in clinical trials C-12-008 and C-12-009. Drug-drug interactions with other concomitantly administered drugs are not likely given that plasma levels following topical ocular administration of Travoprost 0.004% are very low.

Discontinuation due to adverse events

No patient in clinical trial C-12-008 or C-12-009 discontinued study participation due to an AE.

Post marketing experience

Travoprost is currently not marketed for use in patients younger than 18 years of age. However, Travoprost 0.004% preserved with BAK, SofZia and POLYQUAD have been marketed in adult patients since 2001, 2006 and 2010, respectively, and Travoprost 0.003% preserved with POLYQUAD was approved for marketing in the adult population by the EMA in February 2014 and has since been launched in the EU. The latest Periodic Safety Update Report (PSUR) for Travoprost (40 and 30 µg/mL) summarizing the safety data received from world-wide sources by the MAH's Medical Safety Department covering the time period from 01 March 2013 to 28 February 2014 was submitted. This PSUR did not indicate new or changing safety signals associated with the use of Travoprost (40 or 30 µg/mL) and their benefit/risk assessments remained favourable (and unchanged), for the indication of lowering IOP in patients with open-angle glaucoma or ocular hypertension.

2.5.1. Discussion on clinical safety

This extension of indication to include paediatric patients is supported by two clinical studies: C-12-008 (a 3-month phase 3 safety and efficacy study) and C-12-009 (7-day pharmacokinetic study). Clinical data and the post-marketing experience available with the already approved travoprost formulations in adult patients are of relevance and supportive for this application.

The studied population is considered representative of the population that is expected to receive Travoprost 0.004% PQ.

On the whole, the MAH's approach established for the safety analysis is considered acceptable. Travoprost has been authorised in adults for a number of years and its safety profile in adults has been well characterised in clinical studies and post-marketing monitoring in adults. An indirect comparison between Travoprost 0.004% PQ (C-12-008) and historical data of Travoprost 0.004% PQ has been provided by the MAH. The most common adverse reactions reported in adults were ocular hyperaemia and iris hyperpigmentation occurring in approximately 20% and 6% respectively. The other common adverse reactions reported in adults include eye pain, ocular discomfort, dry eye, eye pruritus and eye irritation. The adverse event profile in children appears to be broadly similar to that in adults.

The current clinical development program in children has evaluated the short-term exposure of travoprost for up to 12 weeks in 102 children (77 patients exposed to Travoprost 0.004% PQ in study C-12-008 and 25 patients exposed to Travoprost 0.004% PQ in study C-12-009). The sample size of the safety population is considered limited for the overall safety analysis. Regarding the duration of exposure, the majority of patients were exposed during approximately 3 months (mean duration of exposure is 84 days). Given the possibility of new risks and the potential occurrence of some events with the prolonged use of travoprost (i.e. periocular skin hyperpigmentation or discolouration, iris hyperpigmentation, changes in eyelash characteristics and stimulation of melanogenesis), the lack of long-term safety data is considered a limitation of this application. However, supportive data coming from two published studies of 18 and 28 month duration and a safety database prepared by the MAH concerning the off-label use of Travoprost 0.004% PQ in the paediatric population were provided. This information reveals that the type of the adverse events reported were similar to adults. Eyelash thickening and elongation, ocular hyperaemia, ocular irritation, conjunctival redness and skin pigmentation were the most common adverse events. No new risks, no systemic adverse events and no increase in the incidence of the already known adverse events were observed with long-term exposure to travoprost 0.004% PQ.

In study C-12-008, the treatment emergent adverse events with an incidence of 5% or more included ocular hyperaemia (19.5%), conjunctival hyperaemia (5.2%), growth of eyelashes (6.5%) and headache (6.5%). Ocular hyperaemia events related to the treatment with travoprost have been reported with a higher incidence in paediatric population (16.9%) compared to adults (11.4%). Given that this adverse event is not considered serious and disappears when the treatment is discontinued, this increase in ocular hyperemia in paediatric patients is not considered particularly worrisome.

The CHMP noted that study C-11-034 submitted in support of Marketing Authorisation Application for Izba (travoprost 0,003%) which compared Izba versus Travatan (Travoprost 0.004% PQ) in adults revealed that lower exposure to travoprost caused less incidence of hyperemia of the eye (ocular hyperemia with travoprost 0.003% PQ: 6.1% versus 11.4% with travoprost 0.004% PQ) without having a relevant impact on the IOP lowering effect. Therefore, the CHMP recommends that the MAH considers submitting a line extension of the Travatan marketing authorisation to include this lower concentration formulation in a paediatric indication. In addition, CHMP recommends that the MAH requests Scientific Advice in order to confirm what data would be appropriate to support this extension.

There have been no significant new safety concerns identified with this exposure in children. Nevertheless it is noted that the adverse events of headache and growth of eyelashes were reported at higher frequency (>5%) in children while the SmPC reports these reactions as uncommon in adults. All the events of growth of eyelashes were considered related and is therefore an adverse reaction occurring with high incidence in children which needs to be included in the SmPC. The events of headache all appear to be considered not-related as a review of the event characteristics (eg, severity, outcome, causality, and effect on study participation) of the headaches revealed that they were similar between the Travoprost 0.004% PQ and Timolol groups.

In general, it is reassuring that there were no serious adverse reactions or significant changes in the ocular assessments. Optic nerve changes from baseline were reported in both treatment groups. However, the incidence of this adverse event was higher in travoprost group (8.6%) in comparison to timolol group (2.8%). This difference between treatment groups has been further clarified by the MAH. According to the justification and data provided, changes in optic nerve and the increase in the cup/disc ratio value could indicate a progression of glaucoma rather than an adverse event linked to the exposure to Travatan. It is also reassuring that an analysis of safety events based on pre-specified paediatric age-groups did not show any meaningful differences in the types and characteristics of adverse events between the different age groups. However, no firm conclusions can be drawn due to the low number of patients included in the studies and the short duration of exposure to travoprost.

2.5.2. Conclusions on clinical safety

This extension of indication to include paediatric patients is supported by two clinical studies: C-12-008 (a 3-month phase 3 safety and efficacy study) and C-12-009 (7-day pharmacokinetic study). Safety data coming from clinical trials and post marketing experience available with the already approved travoprost formulations in adult patients are considered of relevance and supportive for this application.

As expected, the most common adverse drug reactions were eye disorders (ocular hyperemia - 16.9% and growth of eyelashes – 6.5%) with higher incidence of adverse events in travoprost group compared to timolol group was observed. Overall, the safety profile in paediatric population is consistent with the safety profile for adult population and with the one already known for other topical ocular prostaglandin analogues (i.e. latanoprost, bimatoprost). The incidence of growth of eye-lashes is higher in children as compared to adults and this is reflected in the SmPC.

Generally, short-term data submitted are reassuring. However, the absence of long-term data is considered a weakness of the dossier. To address this issue, the MAH has provided available literature and a safety database produced by Alcon related to the off-label use of travoprost in paediatric population. Given that no concern has been raised from this data, the submission of annual PSURs is considered sufficient to control long-term safety profile.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 8 is acceptable. In addition, minor revisions were recommended to be taken into account with the next RMP update. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The CHMP endorsed the Risk Management Plan version 8 with the following content:

Safety concerns

Important identified risks	<ul style="list-style-type: none">• Macular oedema• Hyperpigmentation• Hypertrichoses• Iris and uveal inflammations• Cardiac and vascular disorders• Respiratory disorders• Hypersensitivity reactions•
Important potential risks	<ul style="list-style-type: none">• Melanoma• Corneal damage due to use of preserved eye drops• Use during pregnancy and lactation
Missing information	<ul style="list-style-type: none">• Long term safety in the paediatric population• Potential interactions

Pharmacovigilance plan

Routine pharmacovigilance activities are considered to be sufficient for safety monitoring of identified and potential risks. To date, the reporting of adverse events from both clinical studies and spontaneous post marketing events has not indicated the need for any alteration in the known risk or intended population to treat.

There are no studies as additional pharmacovigilance activities at this time point.

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
Macular edema	Appropriate identification in the medicinal product labelling.	Not applicable.
Hyperpigmentation	Appropriate identification in the medicinal product labelling.	Not applicable.
Hypertrichoses	Appropriate identification in the medicinal product labelling.	Not applicable.
Iris and uveal inflammations	Appropriate identification in the medicinal product labelling.	Not applicable.
Cardiac and vascular disorders	Appropriate identification in the medicinal product labelling.	Not applicable.
Respiratory disorders	Appropriate identification in the medicinal product labelling.	Not applicable.
Hypersensitivity reactions	Appropriate identification in the medicinal product labelling.	Not applicable.
Important potential risks		
Melanoma	Appropriate identification in the medicinal product labelling.	Not applicable.
Corneal damage due to use of preserved eye drops	Appropriate identification in the medicinal product labelling.	Not applicable.
Use during pregnancy and lactation	Appropriate identification in the medicinal product labelling.	Not applicable.
Missing information		
Long term safety in the paediatric population	Appropriate identification in the medicinal product labelling.	Not applicable.
Potential interactions	Appropriate identification in the	Not applicable.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	medicinal product labelling.	

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

The CHMP considered that the submitted type II variation to include a paediatric indication for Travatan 0.004% does not represent a significant change to the Package Leaflet (PL) and therefore the user consultation with target patient groups on the PL is not required.

3. Benefit-Risk Balance

Travatan 0.004% eye drops Solution (containing Travoprost, a prostaglandin analogue) is indicated for the decrease of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension. The MAH is seeking an extension of the indication to paediatric patients 2 months to < 18 years of age with ocular hypertension or glaucoma.

Benefits

Beneficial effects

One phase 3 clinical trial supported the proposed extension of the indication. The study was aimed to demonstrate that Travoprost 0.004% PQ was comparable (non inferior) to Timolol 0.5% in the reduction of IOP in paediatric patients with glaucoma or ocular hypertension.

Travoprost has been authorised since 2001 for reducing IOP and has a well-established safety and efficacy profile in adults. The options for children with raised IOP are comparatively limited and the development of travoprost for use in children will offer an additional treatment option which is reasonably supported by prospective clinical data.

The treatment with Travoprost showed to have a similar IOP lowering efficacy to that achieved by Timolol. After three month treatment the mean IOP was reduced by 6.4 mmHg (Timolol lowering effect was 5.8 mmHg). The upper confidence limits of the differences in the mean IOP change from baseline between study drug groups (Travatan and Timolol groups) were well within the 3.0 mmHg margin. Results were consistent for PP and ITT analyses. The IOP lowering effect of Travatan does not appear to be significantly different when patients with or without ocular hypertension were taken into account.

The IOP-lowering effect was observed from Week 2 of treatment to the end of the study (Month 3).

Patients treated with Travatan experienced a 27.6% reduction of the baseline IOP and the reduction for Timolol group was 24.9%. The IOP levels achieved in Travatan and Timolol groups were 17.9 mmHg and 18.0 mmHg, respectively. When the relevance of the IOP reduction was evaluated as responder rates, 83% of patients on travoprost and 74.3% of patients on timolol attained a 15% reduction in IOP. Similarly, 71.8% of patients treated with travoprost and 66.2% of patients treated with timolol achieved a normal IOP, according to the pre-established age normal range.

In general, exploratory comparison between travoprost and timolol showed numerical differences in favour of travoprost. No substantial differences between Travoprost and Timolol were observed when the effect was

analysed by age, sex, ethnicity, race, iris colour, baseline IOP stratum and diagnosis primary congenital glaucoma (PCG or non-PCG).

Uncertainty in the knowledge about the beneficial effects

Only short-term data of the use of Travoprost in paediatric glaucoma and ocular hypertension have been evaluated. Although paediatric glaucoma is a primarily surgical condition some patients may require chronic pharmacological treatment. In principle there is no reason to believe that efficacy data beyond 3 months would differ from that measured during this period.

No specific dose-response studies were conducted in the paediatric population. The dose selected for this Phase 3 study was based on the results from Study C-12-009 where no dose adjustment by age was judged necessary so that in the Phase 3 study paediatric patients received the dose recommended for adults.

In the efficacy study a total of 38 out of 151 evaluable patients for PP analysis (30.3% of patients on Travatan 0.004% PQ and 20% of patients on Timolol) were not finally analysed. The most frequent reason for exclusion was the visit outside the study window without significant imbalance between both groups. Sensitivity analyses conducted by the MAH in order to address the impact of this difference did not show in principle potential bias.

The IOP diurnal curve in children treated with Travoprost is unknown. IOP was measured in both eyes at 9 AM (\pm 60 min), approximately 12 hours after the study drug administration. The difficulties of measurement and interpretation of IOP in children are acknowledged. As the morning IOP level represents the highest point during the day the assessment of the Travoprost IOP lowering effect is acceptable.

Children aged 2 months to less than 3 years showed higher plasma levels and lesser response to Travoprost than the older group (from 3 to 18 years). The mean change in IOP caused by Travoprost (-1.8 mm Hg) was lower than the lowering of IOP caused by timolol (-7.3) after 3 months treatment, and this is reflected in the SPC. Nevertheless, 60% of patients in this age group who received Travoprost, showed IOP reduction.

It is acknowledged that the number of patients in both the treatment groups from this age range was small (9 patients in the Travoprost group and 6 patients in the timolol group) and therefore these results may not be inferential. In addition, given the mechanism of action of each compound (beta-blockers act by reducing the rate of aqueous production and prostaglandin analogues reduce IOP by increasing uveoscleral outflow) and that congenital glaucoma may be associated to developmental anomalies in the trabecular meshwork area the existence of true differences cannot be totally discarded. The limitations of data collected in this age group have been highlighted to the prescribers in the Product Information.

Infants younger than 2 month were excluded from the study. A waiver was granted to this group of patients on the grounds that the specific medicinal product does not represent a significant therapeutic benefit as clinical studies are not feasible. There are no data to support the use in this population.

Risks

Unfavourable effects

Safety data from the two clinical studies submitted by the MAH (a 7-day pharmacokinetic study - C-12-009 and a 3-month phase 3 safety and efficacy study - C-12-008) reveal that the most common adverse drug reactions observed with Travoprost 0.004% PQ in the paediatric population are ocular hyperemia (16.9%) and growth of eyelashes (6.5%). These events were associated with the use of travoprost. In addition, eye pruritus, photophobia, erythema of eyelid and keratitis were reported with an incidence of 1.3% in the travoprost group. These AEs are compatible with the already known safety profile of Travoprost 0.004% in adults and with the known effects derived from the use of topical ocular PGAs. Although iris hyperpigmentation, which is a frequently reported adverse event in adults, has not been reported in children

in study C-12-008, this is possibly due to the short treatment duration in this study and it is anticipated that this event may also occur in children.

In general, the overall incidence of adverse drug reactions in travoprost group was higher than in timolol group (26% and 12%, respectively). Ocular hyperemia was the most common ADR and was reported with a higher incidence in paediatric population (16.9%) compared to adults (11.4%). Given that this adverse event is not considered serious and is reversible, this increase in ocular hyperemia in paediatric patients is not considered particularly worrisome. However, it is noted that the adverse events of headache and growth of eyelashes were reported at higher frequency (>5%) in children while the currently approved SmPC reports these reactions as uncommon in adults. A review of the headache characteristics confirmed that none of the reported headaches were related to treatment. The relatively larger incidence of 'growth of eyelashes' in children as compared to adults may not lead to a clinically significant adverse effect like keratitis, but nevertheless the increase in incidence has been included in the SmPC.

Uncertainty in the knowledge about the unfavourable effects

Considering the safety data provided in this application, the main uncertainty refers to the lack of long-term safety data in the paediatric population. Some adverse events already known for topical PGAs (i.e. periocular skin hyperpigmentation or discolouration, iris hyperpigmentation, changes in eyelash characteristics and stimulation of melanogenesis) and the potential occurrence of new risks can appear over time. Therefore, the short duration of exposure is considered a limitation of this application. To address the absence of long-term data the MAH has provided available literature and a safety database produced by the MAH related to the off-label use of travoprost in paediatric population. Given that no concern has been raised from this data, the submission of annual PSURs is considered sufficient to carefully monitor long-term safety profile.

Based on data provided regarding optic nerve changes from baseline, the higher incidence reported in travoprost group compared to timolol group (8.6% vs 2.8%) could indicate a progression of glaucoma rather than an adverse event linked to the exposure to Travatan.

Benefit-risk balance

Importance of favourable and unfavourable effects

Travoprost provides a useful, proven and well-tolerated alternative treatment option to treat children with raised IOP. The efficacy of travoprost in children has been shown to be comparable to timolol. The established safety profile of travoprost in adults has less of the systemic side effects as compared to timolol. The low systemic exposure ascertained in the paediatric PK study (study C-12-009) provides reassurance that the systemic safety of travoprost in children may be similar to that of adults. The safety data from study C-12-008, where children were treated for up to 12 weeks, did not raise any new safety concerns.

However, a higher frequency of 'growth of eyelashes' in children compared to adults has been specified in the product information.

Furthermore, the overall safety data in children is limited and there is no long-term safety data in children. The submission of annual PSURs is considered sufficient to carefully monitor long-term safety profile in paediatric patients.

Discussion on the benefit-risk balance

Travoprost has a well-established efficacy and safety profile in adults. Available data in children has shown that travoprost has comparable efficacy to timolol in lowering IOP in children aged 2 months to 18 years. However a sub-group analysis based on age showed that in children aged 2 months to less than 3 years, the effects of travoprost on lowering IOP was lower than timolol. This information has been included in the SmPC.

With respect to the safety profile of Travoprost 0.004% PQ in the paediatric population, adverse events

reported during study C-12-008 seem compatible with the already known safety profile of Travoprost 0.004% in adults and with the effects already known with the use of topical ocular PGAs. No new safety concern of significance was reported. The PK evaluations in children showed that systemic exposures were generally lower than currently measurable levels, therefore it is not possible to conclude that the systemic exposure in children is comparable to that in adults and this has been appropriately communicated in the SmPC.

Moreover, long-term safety data in the paediatric population will be monitored through routine pharmacovigilance as part of the annual PSURs.

4. Recommendations

Final Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation(s) to the terms of the Marketing Authorisation, concerning the following change(s):

Variation(s) accepted		Type
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II

Extension of the therapeutic indication for the decrease of elevated intraocular pressure in paediatric patients aged 2 months to < 18 years with ocular hypertension or paediatric glaucoma. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC and the package leaflet are updated.

The requested variation proposed amendments to the SmPC and Package Leaflet.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0298/2013 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.