18 May 2017
EMA/CHMP/490886/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Invented name: Izba

International non-proprietary name: travoprost

Procedure No. EMEA/H/C/002738/II/0005

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

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

Table of contents

List of abbreviations

ADR	Adverse drug reaction
AE	Adverse event
AEMPS	Agencia Española de Medicamentos y Productos Sanitarios
AGIS	Advanced Glaucoma Intervention Study
AL-5848	Travoprost free acid
AL-6221	Travoprost
AM	In the morning (Ante Meridiem)
BAK	Benzalkonium chloride
CAI	Carbonic anhydrase inhibitor
CI	Confidence interval
EU	European Union
F	Female
FP	F-prostanoid Receptor
ICH	International Conference of Harmonization
IOP	Intraocular pressure
ITT	Intent to treat
LOCF	Last observation carried forward
M	Male
mg	Milligram
mL	Millilitre
µg	Microgram
mmHg	Millimetres of mercury
Max	Maximum
Min	Minimum
OAG	Open-angle glaucoma
OHT	Ocular hypertension
OSD	Ocular Surface Disease
PGA	Prostaglandin analogue
PGF2α	Prostaglandin F2α Receptor
PK	Pharmacokinetics
PM	In the evening (Post Meridiem)
PP	Polypropylene
PP	Per protocol
PQ	POLYQUAD Polyquaternium-1
QD	Once a day
SE	Standard error
SmPC	Summary of Product Characteristics
SofZia	An ionic buffer containing borate, sorbitol, propylene glycol, and zinc
sPP	Natural syndiotactic polypropylene
USA	United States of America

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 31 August 2016 an application for a variation.

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, II, IIIA and IIIB

Extension of Indication to include treatment of paediatric patients aged 2 months to < 18 years with ocular hypertension or paediatric glaucoma in order to decrease of elevated intraocular pressure. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package leaflet has been updated accordingly. In addition, the marketing authorisation holder took the opportunity to introduce minor corrections in the SmPC and to update the list of local representatives in the PL. The RMP has updated to version 9.0

Furthermore, the PI is brought in line with the latest QRD template version 10.0.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0194/2016 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0194/2016 was completed.

Scientific advice

The MAH received Scientific Advice from the CHMP on 28 January 2016 (EMEA/H/SA/1643/2/2015/PED/II). The Scientific Advice pertained to clinical aspects in relation to paediatric development of the dossier.

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
Submission date	31 August 2016
Start of procedure:	17 September 2016
CHMP Rapporteur Assessment Report	27 October 2016
CHMP Co-Rapporteur Assessment Report	11 November 2016
PRAC Rapporteur Assessment Report	18 November 2016

Timetable	Actual dates
PRAC members comments	23 November 2016
Updated PRAC Rapporteur Assessment Report	29 November 2016
PRAC Outcome	1 December 2017
CHMP members comments	N/A
Updated CHMP Rapporteur(s) (Joint) Assessment Report	N/A
Request for supplementary information and extension of timetable adopted by the CHMP on:	15 December 2016
MAH's responses submitted to the CHMP on:	19 January 2017
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	27 February 2017
CHMP Members comments	13 March 2017
Rapporteur's updated assessment report on the MAH's responses circulated on	17 March 2017
2nd Request for supplementary information and extension of timetable adopted by the CHMP on:	23 March 2017
MAH's responses to the 2nd RSI submitted to the CHMP on:	18 April 2017
Rapporteur's preliminary assessment report on the MAH's responses to the 2nd RSI circulated on:	25 April 2017
CHMP Members comments	8 May 2017
Rapporteur's updated assessment report on the MAH's responses to the 2nd RSI circulated on:	12 May 2017
CHMP opinion:	18 May 2017

2. Scientific discussion

2.1. Introduction

Paediatric glaucoma is a complex disease characterized by elevated intraocular pressure (IOP), optic disc cupping and progressive visual field loss. Early detection is critical, for treatment before corneal damage, optic nerve damage, and amblyopia occur can lead to significantly improved visual outcomes.

Primary congenital glaucoma, the most common primary childhood glaucoma, is believed to be caused by dysplasia of the anterior chamber angle, and it is generally bilateral. Secondary glaucoma is defined as glaucoma associated with other ocular or systemic disorders and is common in children. Frequent causes of secondary glaucoma in children include trauma, lens-related disorders, phakomatoses, uveitis, anterior segment dysgenesis syndromes, and aniridia. [1]

[1] Fung DS et al. Clinical Ophthalmology 2013:7 1739–1746

Although surgery is the definitive treatment of choice, topical medications are usually also needed as temporary treatment before surgery or as adjunctive postoperative therapy. Beta blockers, carbonic anhydrase inhibitors and prostaglandins have all been used in the treatment of pediatric glaucomas[2].

Travoprost is the isopropyl ester prodrug of a FP prostaglandin receptor agonist. It belongs to the pharmacological class of PGF2α agonists. Prostaglandin analogues have been shown to lower intraocular pressure by increasing the outflow of aqueous humour via trabecular meshwork and uveoscleral pathways.

The first travoprost-containing product to be developed was Travoprost 40 µg/mL eye drops, solution preserved with benzalkonium chloride (BAK). This product, marketed as Travatan, received EU marketing authorization in November 2001 (EU/1/01/199/001-002). Travoprost 0.004% Solution preserved with POLYQUAD (PQ) is the currently available formulation and was approved by the European Medicines Agency (EMA) in November 2010.

Another formulation, Travoprost 0.004% 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. Both formulations confer a potential benefit relative to the original Travoprost 0.004% BAK formulation by providing an alternative to BAK, a preservative associated with conjunctival inflammation, tear film disruption, and symptoms of ocular surface health disease following chronic exposure.

The MAH completed 2 clinical studies as agreed in the Paediatric Investigation Plan (EMEA-001271-PIP01-12- M01). These studies were the basis for the approval of Travoprost 0.004% PQ for the paediatric indication (variation EMEA/H/C/000390/II/046, Commission Decision 19 December 2014).

Izba (Travoprost 0.003% solution) received EU marketing authorization in February 2014 (EMEA/H/C/002738/0000). With the exception of the active drug concentration, the formulation of Travoprost 0.003% solution is identical to the formulation of Travoprost 0.004% PQ. It is indicated for the decrease of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

During the procedure to extend the indication of Travatan to paediatric population the CHMP recommended the MAH to consider submitting a paediatric indication for the lower strength. Dose-response studies conducted during the early development of Travatan revealed that doses equal or higher than 0.002% reached significant (and quantitatively similar) IOP reductions (C-96-52 and C-97-02). 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. In addition, CHMP recommended that the MAH requests Scientific Advice in order to confirm what data would be appropriate to support this extension. The proposed modelling and simulation approach to support the paediatric indication of Travoprost 0.003% was discussed with EMA in January 2016 (EMEA/H/SA/1643/2/2015/PED/II).

This type 2 variation application was seeking an extension of the current indication of Izba to patients from 2 months to <18 years of age at the same posology as in adults.

There were no specific clinical studies conducted in support of the paediatric indication for Travoprost 0.003%. The clinical development plan is based on a modelling and simulation approach.

References to clinical trials submitted at the time of the Travatan MAA or the extension of paediatric indication and those submitted in Izba MAA were also made. Since they have been already evaluated in previous procedures, no further assessment has been made.

[2] Quaranta L et al. Adv Ther (2016) 33:1305–1315

2.2. Non-clinical aspects

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

2.3. Clinical aspects

2.3.1. Introduction

The paediatric indication has recently been approved for Travatan (Travoprost 40 µg/ml). Izba is identical to the current formulation of Travatan with the exception of a 25% reduction in the active substance concentration. The proposed dosage regimen (1 drop once a day in the evening) is also identical.

No new or additional clinical studies have been undertaken to support this application. The Applicant has used a modelling approach and data from four studies to extrapolate the IOP-lowering response for Izba in the paediatric population. It must be noted that there are two formulations of Travatan discussed in these studies: the originally approved formulation included benzalkonium chloride (BAK) as a preservative but it was later reformulated to replace BAK with polyquaternium-1 (PQ).

2.3.2. Clinical pharmacology

The MAH has not conducted any clinical pharmacology studies with Travoprost 0.003% Solution. Instead, reference was made to the rabbit ocular tissue distribution and plasma data that showed both Cmax and AUC_{0-6h} levels were very similar following topical ocular doses of Travoprost 0.004% BAK, and with Travoprost 0.004% PQ that is formulated in the same vehicle as Travoprost 0.003% Solution. Therefore, it is reasonable to expect that ocular and systemic exposure levels would be approximately dose proportionally less with Travoprost 0.003% Solution compared to Travoprost 0.004% BAK and Travoprost 0.004% PQ. Clinical pharmacokinetic studies assessed in previous applications have clearly demonstrated very low systemic plasma levels following topical administration of Travoprost 0.004% BAK with concentrations in most samples from 5 multiple-dose studies being below a sensitive assay's quantitation limit of 10 pg/mL.

2.3.3. Discussion on clinical pharmacology

Non-clinical study P-11-510 supports similar bioavailability of Izba and Travatan[3]. It is not expected that changes in the preservative and the dose would affect differently the bioavailability of travoprost in children versus adults, leading to insufficient/unsafety ocular exposures.

The systemic pharmacokinetics of travoprost free acid following topical ocular administration of Travoprost 40 mcg/mL have been characterized in multiple studies in various adult populations. In addition, a paediatric pharmacokinetic study (Study C-12-009) was conducted as part of the Paediatric Investigation Plan for Travatan. This study was aimed to evaluate the steady-state systemic exposure of travoprost 0.004% in paediatric subjects from 2 month to < 18 years of age with glaucoma or ocular hypertension. Patients were administered the usual adult dose of travoprost. No clear relationship between plasma concentrations and age or body surface area (BSA) was apparent. Generally, the systemic exposure to AL-5848 acid metabolite was low. In most patients plasma levels were undetectable. Concentrations measured were similar to those reported for adults. Younger patients, especially those under 3 years were exposed to higher concentrations of product. The safety profile was consistent with that already known for adults and no further safety concerns have been raised.

Systemic levels of exposure after administering Travoprost 0.003% are expected to be lower than Travoprost 0.004% so no safety concerns arise at this moment. Nevertheless, known factors affecting the bioavailability of the pharmacologically active substance in the site of action (e.g. esterases, protein binding, eye structures) could result in a different clinical response.

Travoprost (40 µg/ml) and latanoprost (50 µg/ml), dosed as in adults, are currently approved for the paediatric population. Age-related reduction in tear volume and ratio of surface area to internal volume can lead to ocular topically applied medications becoming concentrated in younger patients[4]. A new alternative containing a lower strength is welcome.

2.3.4. Conclusions on clinical pharmacology

No studies were conducted to evaluate the pharmacokinetics/pharmacodynamics of Izba in paediatric population. From the available data, it seems that concentrations would be similar to those reported for adults but with some differences in the younger patients, especially those under 3 years that were seen to

[3] EPAR Izba Eye Drops, Solution (EMEA/H/C/002738/0000)
[4] Batchelor HK, Marriott JF. Br J Clin Pharmacol 2015; 79(3):405-418

be exposed to higher concentrations of product. Systemic levels of exposure after administering Travoprost 0.003% are expected to be lower than Travoprost 0.004% so no safety concerns arise at this moment.

2.3.5. Clinical efficacy

Introduction

There were no specific clinical studies conducted in support of the paediatric indication for Travoprost 0.003%.

At the time of designing the Travoprost 0.004% PQ paediatric PK study (C-12-009) and the Phase III efficacy study (C-12-008), the lower dose Izba product was not yet authorised in the EU. The EU application for the Izba product proceeded in parallel with the Travoprost 0.004% PQ paediatric clinical studies and therefore the lower dose product was not included.

Modelling and Simulation Analysis

This Modelling and Simulation Report quantifies the expected morning percent change from baseline IOP response in paediatric patients at the 30 µg/mL travoprost dose, based on the adult patient dose response data and 40 µg/mL travoprost paediatric patient data.

- **Clinical Data Summary**

IOP lowering was assessed in three adult clinical studies (C-97-02, C-00-20, and C-11-034) and one paediatric study (C-12-008). In children, travoprost 40 µg/mL was administered at 9 PM and the IOP response was measured at 9 AM. In adults, travoprost (concentration range from 1 µg/mL to 60 µg/mL) was administered at 8 PM and the percent change from baseline IOP response was measured at 5 time points, including at 8 AM and 10 AM. Except C-00-20, all adult studies had 8 AM as the earliest time-point; in C-00-20 the earliest measured IOP time-point was 10 AM. The eye with the highest average IOP at baseline (i.e. the worst eye) at the 8 AM, and 10 AM time-points was used in this dose response analysis. The adult 8 AM and 10 AM time-points were used since they provided the greatest breadth of doses to include in the dose-response model, while still allowing an approximation of the morning IOP response measured in the paediatric population.

Table 1.- Studies included in travoprost dose-response characterization and paediatric comparison

Study No./ Location	Study Objective	Study Design and Type of Control	Patient Population/IOP Criteria	Duration of Treatment	IOP Assessment Time Points	Treatment Groups; Dosage Regimen; Total Number of Patients Randomised by Treatment Group	IOP Percent Change from Baseline at the Last Visit Across all Time Points [a]
							Day 28
C-97-02 US	To evaluate IOP-lowering efficacy and safety of four travoprost concentrations compared to vehicle in patients with OAG or OHT	Randomised, Triple-masked, Parallel group, Vehicle controlled	Adult patients with OAG or OHT IOP at 8 AM ≥ 24 and ≥ 21 at the 10 AM, 4 PM and 8 PM time-points at both eligibility visits. The patients must also have a mean IOP of ≤ 36 in both eyes at all time points	28 days	8 AM, 10 AM, 12 PM, 4 PM and 8 PM	travoprost 10 µg/mL BAK-preserved; 8 PM QD; n=47 travoprost 20 µg/mL BAK-preserved; 8 PM QD; n=44 travoprost 40 µg/mL BAK-preserved; 8 PM QD; n=48 travoprost 60 µg/mL BAK-preserved; 8 PM QD; n=43 Vehicle; 8PM QD; n=45	-20.5 to -23.9 -24.3 to -29.7 -27.7 to -31.3 -26.0 to -31.0 -6.5 to -9.9

Study No./ Location	Study Objective	Study Design and Type of Control	Patient Population/IOP Criteria	Duration of Treatment	IOP Assessment Time Points	Treatment Groups; Dosage Regimen; Total Number of Patients Randomised by Treatment Group	IOP Percent Change from Baseline at the Last Visit Across all Time Points [a]
							Day 14 [d]
C-00-20 Japan	To evaluate IOP-lowering efficacy, safety and dose response of three concentrations of travoprost ophthalmic solution in patients with OAG or OHT	Randomized, Double-masked, Parallel group, Vehicle controlled	Adult patients with OAG or OHT IOP at baseline exam (10 AM, 12 AM, 4 PM) between 21 and 36 mmHg in at least one eye and not more than 36 mmHg in both eyes	14 days	10 AM, 12 PM and 4 PM	travoprost 1 µg/mL BAK-preserved; 8 PM QD; n=21 travoprost 15 µg/mL BAK-preserved; 8 PM QD; n=22 travoprost 40 µg/mL BAK-preserved; 8 PM QD; n=21 Vehicle; 8 PM QD; n=22	-12.8 to -15.0 -25.1 to -28.8 -27.9 to -29.4 -9.1 to -10.5

Study No./ Location	Study Objective	Study Design and Type of Control	Patient Population/IOP Criteria	Duration of Treatment	IOP Assessment Time Points	Treatment Groups; Dosage Regimen; Total Number of Patients Randomised by Treatment Group	IOP Percent Change from Baseline at the Last Visit Across all Time Points [a]
							Month 3 (ITT)
C-11-034 US, Sweden, Germany, Austria, Spain and Finland	To evaluate IOP-lowering efficacy and safety of travoprost 30 µg/mL PQ-preserved in patents with OAG/OHT	Randomised, Double-masked, Parallel group	Adult patients with OAG or OHT IOP at 8 AM ≥ 24 and ≥ 21 at the 10 AM and 4 PM time-points at both eligibility visits. The patients must also have a mean IOP of ≤ 36 in both eyes at all time points	3 months	8 AM, 10 AM and 4 PM	travoprost 40 µg/mL BAK-preserved; 8 PM QD; n=422 travoprost 30 µg/mL PQ-preserved; 8 PM QD; n=442	-29.4 to -31.0 -28.5 to -30.7

Study No./ Location	Study Objective	Study Design and Type of Control	Patient Population/IOP Criteria	Duration of Treatment	IOP Assessment Time Points	Treatment Groups; Dosage Regimen; Total Number of Patients Randomised by Treatment Group	IOP Percent Change from Baseline at the Last Visit Across all Time Points [a]
							Month 3[c]
C-12-008 US, Germany, Singapore, UK, Taiwan, Philippines, Spain, Saudi Arabia, Columbia, France, Portugal, Belgium, Poland, Romania, Puerto Rico and Mexico	To evaluate IOP-lowering efficacy of travoprost 40 µg/mL in paediatric patients with glaucoma or ocular hypertension	Randomised, Double-masked, Parallel group, Active control	Paediatric patients with glaucoma or ocular hypertension	3 months	9 AM	Travoprost 40 µg/mL PQ-preserved; 9 PM QD; n=77 Timolol 5 mg/mL or Timolol 2.5 mg/mL (patients < 3 yrs); BID 9 AM and 9 PM; n=75	-27.6 -24.9

- **Materials / Methods**
  - **Model generation and selection**

In order to quantify morning (8-10 AM) percent change from baseline IOP dose response for travoprost (1 µg/mL to 60 µg/mL) in adult patients (Objective 1), the IOP dose response for travoprost in adult glaucoma patients was modelled using six different models. Model selection was than based on Akaike information criterion (AIC). The first model built was based on the Sigmoid Emax Hill expression:

$$\frac{IOP_t - IOP_{t,\text{baseline}}}{IOP_{t,\textbf{baseline}}} = E_0 + \frac{(E_{max} - E_0)\text{Dose}^{\gamma}}{\text{Dose}^{\gamma} + ED_{50}^{\gamma}} + \varepsilon \qquad \textbf{(Equation .5-1)}$$

Where,

t = Time-point of IOP-lowering, either 8 am or 10 am

IOP_t = Intraocular Pressure at time-point t.

$IOP_{t,\text{baseline}}$ = Baseline Intraocular Pressure at time-point t.

E_0 = Percent change from baseline IOP lowering of vehicle

E_{max} = Maximum percent change from baseline IOP lowering of travoprost

Dose = Dose of travoprost in µg/mL

ED_{50} = Effective dose to achieve half the maximum travoprost percent change from baseline IOP

γ = Hill factor which indicates the steepness of dose response

ε = Difference from observation and predicted, assumed to be normally distributed with mean and variance s^2

Both the time of day (8 am and 10 am) and the age of the subject would affect the baseline intraocular pressure. For this reason, the travoprost/vehicle induced IOP percent change from baseline was used as the response variable, instead of either absolute IOP response or IOP change from baseline in mmHg. This allowed pooling of data from the 8 AM and 10 AM time-points and the comparison between paediatric and adult populations.

Another family of sigmoid dose-response characterizations are the logit models:

$$\frac{IOP_t - IOP_{t,\text{baseline}}}{IOP_{t,\textbf{baseline}}} = E_0 + \frac{E_{max} - E_0}{1 + \exp\left(\frac{ED_{50} - \text{Dose}}{\delta}\right)} + \varepsilon \qquad \textbf{(Equation 6-2)}$$

The meaning of the parameter are the same as in the Hill/Emax model, with the exception of the δ parameter. For the first logit model, the δ =1. For the second logit model, δ is estimated and determines the shape of the sigmoid, much like the Hill γ parameter.

The last family of sigmoid dose-response characterization are the exponential family models:

$$\frac{IOP_t - IOP_{t,\text{baseline}}}{IOP_{t,\textbf{baseline}}} = E_0 + (E_{max} - E_0) \times \left(1 - \exp\left(-\left[\frac{\text{Dose}}{ED_{63}}\right]^{d}\right)\right)^{H} + \varepsilon \qquad \textbf{(Equation 6-3)}$$

The parameters also have the same meanings as above, with the following additional parameters:

ED63 = Effective dose to achieve half the maximum travoprost percent change from baseline IOP;
d = Douglas Shape Parameter;
H = Hodgkin shape parameter;
For the exponential model, d = 1 and H = 1. For the Douglas model, H = 1 and d is estimated. For the Hodgkin model, H is estimated, and d = 1.

- **Model Qualification for Use in Paediatric Population**

In order to verify if the morning (9 AM) percent change from baseline IOP for 40 µg/mL travoprost in paediatric patients is comparable to the day-time (8 AM and 10 AM) percent change from baseline IOP lowering in adult patients for 40 µg/mL travoprost (Objective 2), the boxplot of individual, repeated measures of the 9 AM paediatric IOP response with 40 µg/mL will be overlaid on the dose response model built on adult IOP data.

- **Model-based simulation**

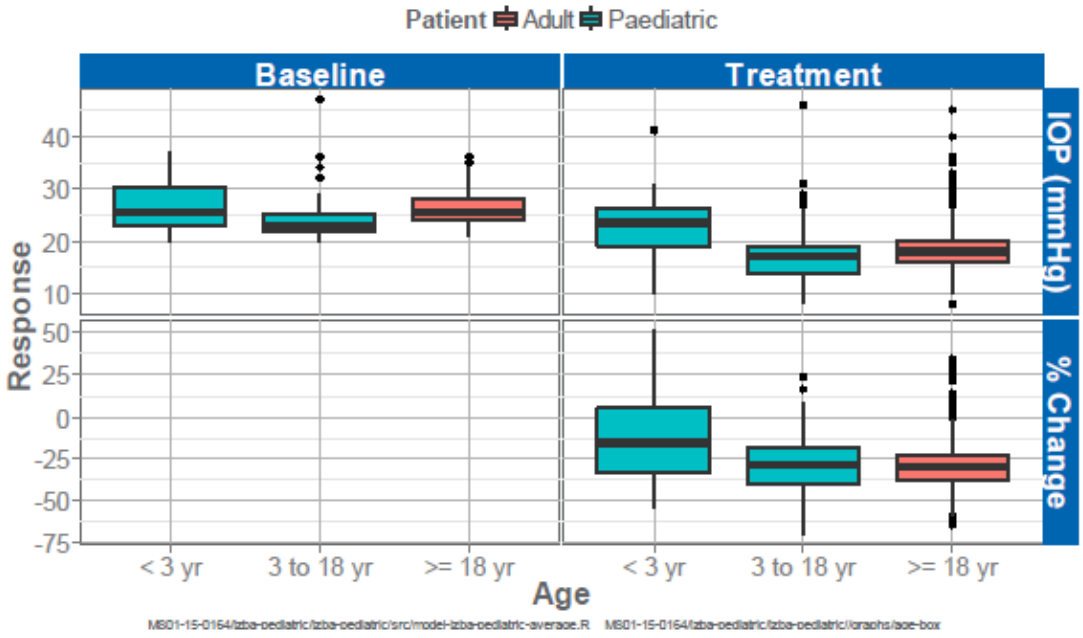
In order to extrapolate the day-time (9 AM) IOP lowering for 30µg/mL travoprost in paediatric patients (Objective 3), and if adult and children have similar percent change-from-baseline for 40 µg/mL, the adult dose-response model will extrapolate the expected percent change-from-baseline in paediatric 30 µg/mL.

- **Results**

Model Data: In the Travatan dose-response studies, travoprost concentrations ranging from 0.0001% to 0.006% were included. The percent change-from-baseline was used to evaluate the travoprost/vehicle induced IOP response. Since both the time-of-day and the age of the subject will affect the baseline IOP, the percent change-from-baseline was used as the appropriate metric to evaluate the dose response.

- Both IOP (mmHg), and IOP change from baseline (%) are comparable between adults and paediatric patients > 3 yrs age. While both are similar in responses, the IOP change from baseline corrects the slight differences in IOP baseline and IOP responses between the paediatric populations.

Figure 6–3 **Adult and Pediatric Baseline and IOP responses measured in mmHg and % change from baseline**



Model Development: The Sigmoid Emax model was the best fit (as measured by Akaike information criterion, AIC) to the dose response.

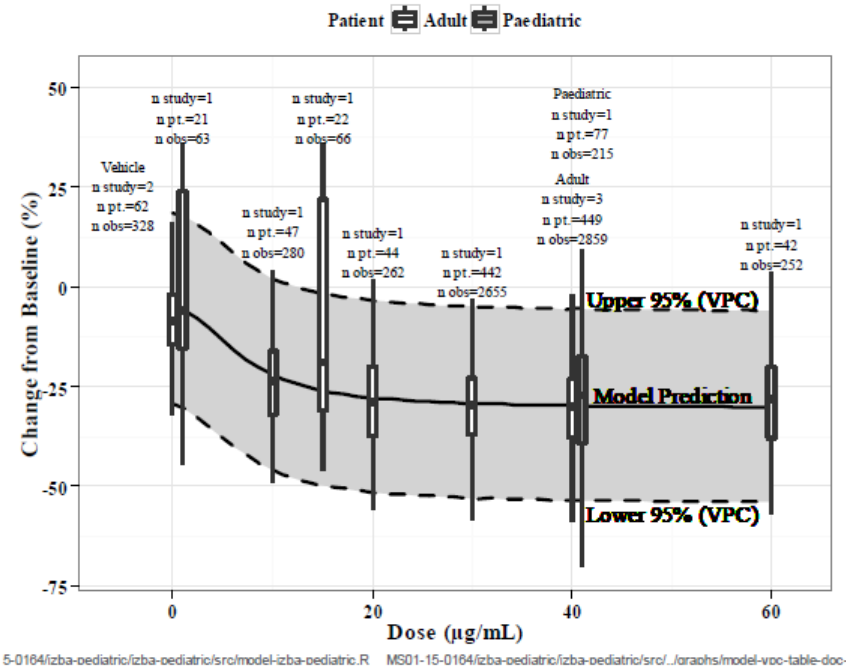
The following conclusions can be drawn:

- The Hill model provides the best fit to the data (smallest AIC).
- All models predict that drug response will plateau at or above a dose of 20 µg/mL.
- Regardless of model structure, a dose of 30 µg/mL is in the satruable región of the dose-response and will give the same response as a dose of 40 µg/mL.

The dose-response model for travoprost QD administered in the evening in adult patients suggests that the maximum efficacy of travoprost may be achieved for concentrations between 20µg/mL to 40µg/mL. Hence, we expect the percent change-from-baseline IOP lowering for 30 µg/mL travoprost to be comparable to the 40 µg/mL travoprost dose. The figure below also summarises the model parameters and their residual standard error.

A visual predictive check (VPC) of the model shows that it provides a good fit to the IOP dose response data in adults, and adequately captures the variability of the data.

Figure 6–1 Travoprost Dose (µg/mL) versus Change From Baseline (%) overlaid with Hill model prediction and 95% Visual Predictive Check interval with table of Hill model estimates and standard errors and estimates of 40 µg/mL (TRAVATAN) and 30 µg/mL (IZBA) IOP lowering.



	Estimate	Std. Error
E_0 (%)	-5.49	0.629
E_{max} (%)	-30.4	0.613
ED_{50} (µg/mL)	7.25	0.709
γ	2.1	0.508
σ (%)	12.2	NA
40 µg/mL (%)	-29.7	NA
30 µg/mL (%)	-29.2	NA

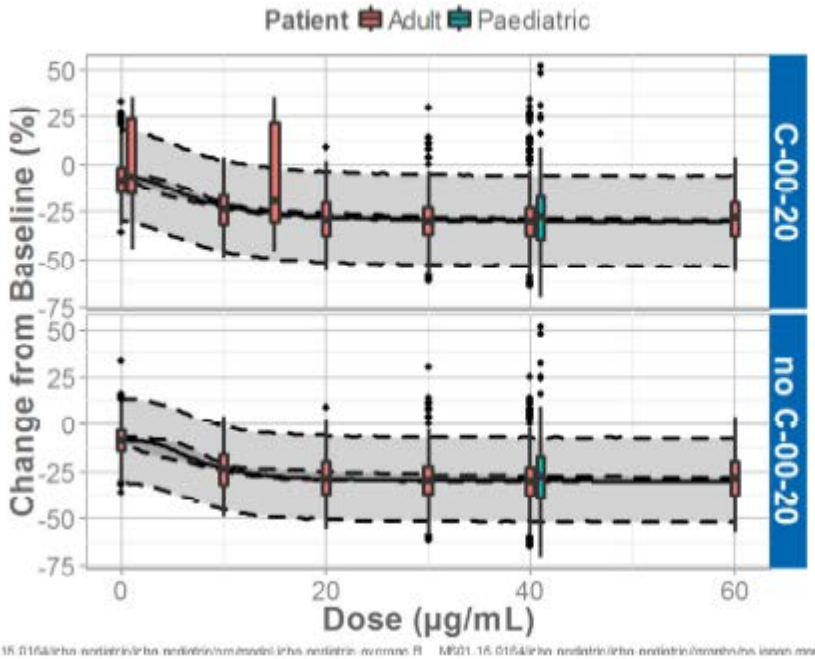
$$\frac{IOP - IOP_{baseline}}{IOP_{baseline}} = E_0 + \frac{(E_{max} - E_0) \cdot Dose^{\gamma}}{Dose^{\gamma} + ED_{50}^{\gamma}}$$

5-0164/izba-pediatric/izba-pediatric/src/model-izba-pediatric.R MS01-15-0164/izba-pediatric/izba-pediatric/src/../graphs/model-vpc-table-doc-no-out-n

n. study = number of studies; n. pt. = number of patients; n. obs = number of observations. Outlier display is suppressed to emphasize central tendencies and show sample sizes

The dose response characterization both including and excluding the Japanese population have equivalent parameter values for the hill equation. Not only are the parameters equivalent, the inclusion/exclusion of the Japanese population did not affect the plateau that starting at > 20 µg/mL dose.

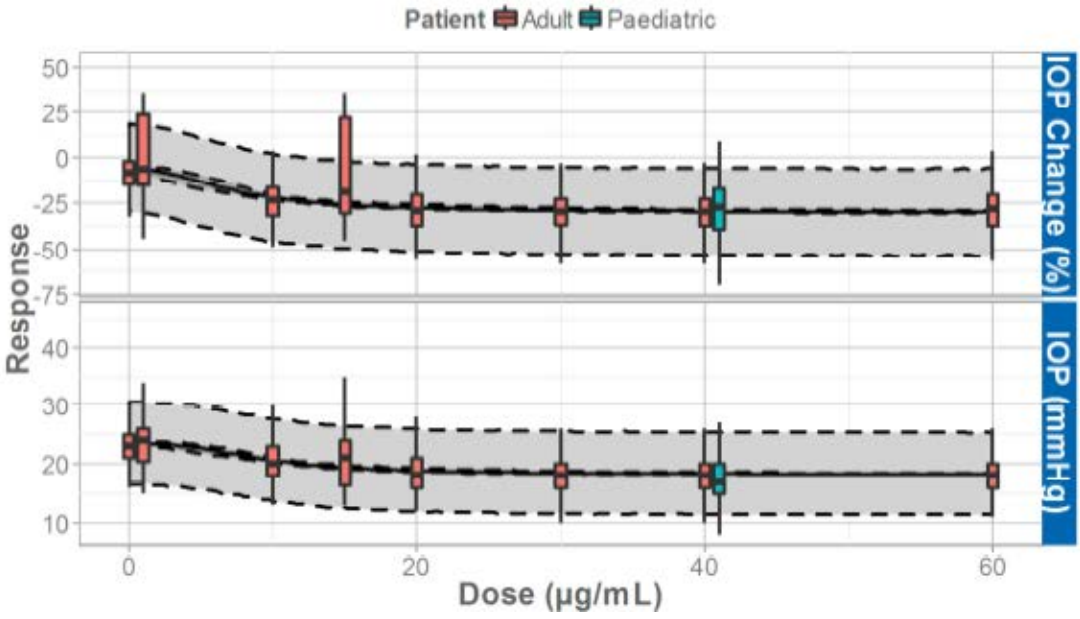
Figure 6–5 **Dose Response Including and Excluding the Japanese Dose Response Study (C-00-20)**



	C-00-20	no C-00-20
E_0	-5.49	-8.55
E_{max}	-30.4	-30
ED_{50}	7.25	7.46
γ	2.1	2.91
α	12.2	11.2
TRAVATAN	-29.7	-29.9
IZBA	-29.2	-29.7

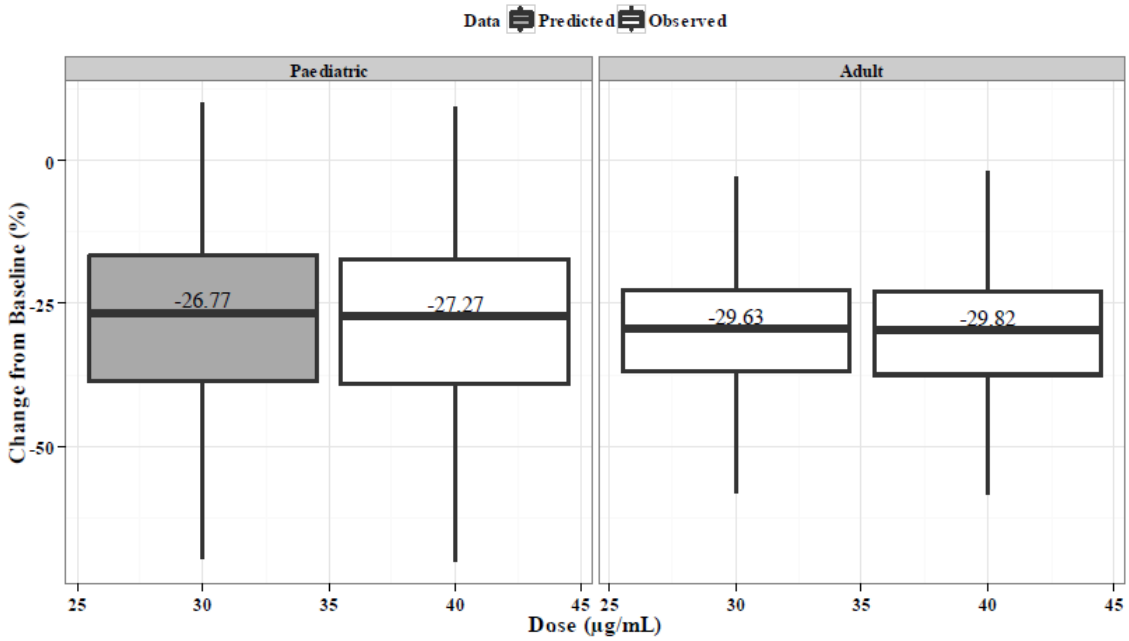
Model Qualification: The shape of the dose response was qualified for its use in paediatric population by modelling observed IOP in addition to IOP change from baseline. In either approach the maximum efficacy is achieved at travoprost concentration ranges from 20 µg/mL to 40 µg/mL (0.002% to 0.004%).

Figure 6–4 **IOP change (%) and IOP (mmHg) for Adults Compared to Peadiatrics**



Extrapolation: The model only predicts a 0.5% difference between 30 µg/mL (IZBA; -26.77% IOP change from baseline) and 40 µg/mL (TRAVATAN; -27.27% IOP change from baseline), which is much smaller than the observed model residual standard error of 12.2% (6761 degrees of freedom).

Figure 6–2 Travoprost % change from baseline IOP for Observed Paediatric 40 µg/mL dose (TRAVATAN) and Predicted Paediatric 30 µg/mL dose (IZBA) compared to Observed Adult 30 µg/mL and 40 µg/mL

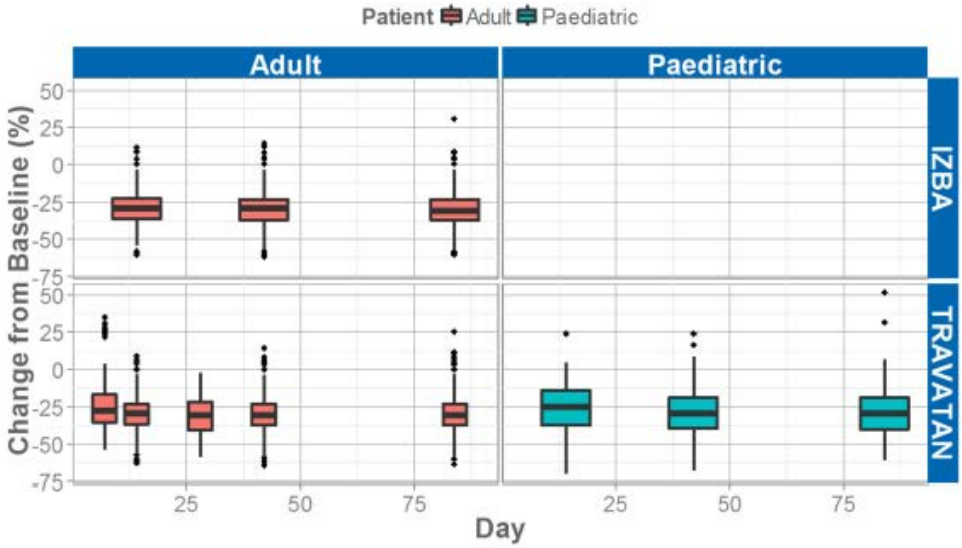


MS01-15-0164/izba-oediatric/izba-oediatric/src/model-izba-oediatric.R MS01-15-0164/izba-oediatric/izba-oediatric/src/../graphs/model-ored-izba-oed

The median values are annotated on the plot. Outliers display is suppressed to show the overall distribution of the change from baseline.

Appropriateness of the Assumption of Steady-State Efficacy: To justify the fact that no time aspect was included in the model (taking into account that the treatment effect was assessed following different length of treatment, from 14 days to 3 months), available clinical data were analysed to confirm that IOP response with Travatan and Izba reaches steady state in 2 weeks' time post initial dose.

Figure 6–8 **The Adult, and Peadiatric IOP change from baseline versus day for IZBA and TRAVATAN**



Comparability between Adult and Paediatric populations

The IOP dose-response model shows that the percent change-from baseline starts to plateau at concentration of 0.002% and that the IOP lowering for travoprost 0.003% is comparable to travoprost 0.004% dose. This was demonstrated in the clinical Study C-11-034 in adult glaucoma subjects, where Izba was equivalent to Travatan BAK-preserved for IOP-lowering efficacy.

In the Model and Simulation analysis it was assumed that the observed IOP percent change-from-baseline in the paediatric subjects is comparable to the response in the adult population for travoprost 40 µg/mL dose. This assumption was used to project IOP lowering effect of Izba in children. To further validate this assumption two aspects were reviewed: (1) physiological evidence of similar concentrations in adults and paediatrics and (2) a comparison between adult and paediatric IOP-lowering responses in the literature.

1. The ocular concentrations of travoprost free acid should be similar between adult and paediatric patients from 3 - 18 yrs for the same dose. Supporting evidence include:
    a. Ocular volume is similar between adults and paediatrics from 3-18 yr. This is a conservative assumption. If the dose-response holds, adjusting the IOP-lowering effect for paediatrics should slightly increase the projected effect.
    b. Esterases, which convert travoprost to the active free acid, are found in ocular tissues. Esterases are fully developed in hepatic tissues by age 3 . Consequently, the conversion rate of travoprost to its active travoprost free acid should be similar between adults and paediatrics (3-18 yrs).
    c. Hence, similar ocular exposure between adults and paediatrics > 3 yrs old is anticipated.
    d. There is limited literature observational evidence on ocular volume and no available literature information about ocular esterase activities in infants (< 3 years old).
    e. There is no evidence in the available literature to support different binding of travoprost free

acid to FP2α receptor in children and adults; therefore ED50 should be similar between adult vs paediatric populations.

f. The IOP-lowering for PGAs is primarily due to a reduction of uveoscleral outflow, and the total effect is likely based on uveoscleral outflow capacity. There is no evidence in the available literature to support differences in uveoscleral outflow between children and adults. Hence the magnitude of effect (Emax) should be similar between adults and paediatric patients. Alcon study C-12-008 data showed observed percent change from baseline in IOP is comparable between adults and children for travoprost 0.004%.

Table 2.5.4-9 Projected IOP lowering based on age of child

Age Range (yr)	Fraction of Adult Dose required for equivalent efficacy[a]	Effective IZBA Dose (µg/mL)[b]	Projected IOP Change (%)[c]
0 – 0.5	0.50	60.0	18.3
0.5 – 1	0.49	61.2	18.3
1 – 2	0.49	61.2	18.3
2 – 3	0.66	45.5	18.4
3 – 4	0.88	34.1	18.4
4 – 5	0.89	33.7	18.4
5 – 6	0.90	33.3	18.4
6 – 7	0.91	33.0	18.5
7 – 8	0.93	32.3	18.5
8 – 9	0.94	31.9	18.5
9 – 10	0.95	31.2	18.5
10 – 11	0.96	30.9	18.5
12 – 13	0.99	30.3	18.5
13 – 14	0.99	30.3	18.5
≥ 14	1.00	30.0	18.5

a – Dose adjustment for equivalent efficacy taken from Patton 1976
b – Effective dose of IZBA, calculated as 30 µg/mL / fraction of adult dose required for equivalent efficacy
c – Projected efficacy calculated based on the model described **Error! Reference source not found.**2.5.4-2 using the effective IZBA dose for the age-group.

2. A review of available literature was carried out for glaucoma drugs to compare data on adult and paediatric subjects. This was done by using the OVID database with the keywords “Pediatric” and “Glaucoma” in the Medline database on May 10, 2016. The search returned 414 articles. These articles were further manually subset to paediatric trials where an ophthalmic drug was administered in the absence of any surgical interventions. The paediatric responses were then compared do adult responses.

Table 2.5.4-10 Adult vs Paediatric IOP-lowering for Glaucoma Drugs

Drug	Class	Reference	Population	Effect
Brinzolamide 1.0% BID	CAI inhibitor	Whitson 2008	0 to 6 yr	5.0 mmHg reduction at 6 weeks Baseline: 24.8 mmHg Extrapolated % change: 20%
Brinzaolamide 1.0% BID	CAI Inhibitor	March 2000	Adult	2.7 to 3.9 mmHg reduction Baseline: 25.1 mmHg Extrapolated % change: 10.8-15.5%
Brinzolamide 1.0% TID	CAI Inhibitor	March 2000	Adult	2.8 to 3.8 mmHg Baseline: 26.1 mmHg Extrapolated % change: 11.2-15.1%
Latanoprost	Prostaglandin	Maeda-Chubachi 2013	0 to <3 yr	22% change from baseline at Week 12
Latanoprost	Prostaglandin	Maeda-Chubachi 2013	3 to <12 yr	24% change from baseline at Week 12
Latanoprost	Prostaglandin	Maeda-Chubachi 2013	12 to 18 yr	30% change from baseline at Week 12
Latanoprost	Prostaglandin	Maeda-Chubachi 2011	0 to 18 yr	7.2 mmHg reduction at Week 12
Latanoprost	Prostaglandin	Urban 2004	12 to 18 yr	36.5% reduction. Treatment duration unspecified
Latanoprost	Prostaglandin	Enyedi 2002	9 to 19 yr	32.5% reduction
Latanoprost	Prostaglandin	Enyedi 1999	0 to 14 yr	Responders: 34% Overall: 0.9%
Latanoprost	Prostaglandin	Watson 1996	Adult	33.7% reduction at 6 months
Travoprost	Prostaglandin	Yanovitch 2009	1 to 13 yr	Baseline: 26.3 mmHg 5.3 mmHg reduction at 1 month 4.2 mmHg reduction at 6 months 5.5 mmHg reduction at 1 year 6.3 mmHg reduction at 1.5 years Extrapolated % Change: 20.2% change at 1 month 16.0% change at 6 months 20.9% change at 1 year 24.0% change at 1.5 year
Betaxolol	β-blocker	Plager 2009	0 to 6 yr	2.3 mmHg reduction at Week 12 Baseline 24.6 mmHg Extrapolated % change: 9.3%
Betaxolol	β-blocker	Buckley 1990	Adult	13-30%
Levobetaxolol	β-blocker	Whitson 2008	0 to 6 yr	1.8 mmHg reduction at week 6 Baseline: 24.5 mmHg Extrapolated % change: 7.3%
Levobetaxolol	β-blocker	Quaranta 2007	Adult	25.9%

Drug	Class	Reference	Population	Effect
Timolol	β-blocker	Maeda-Chubachi 2011	0 to 18 yr	5.7 mmHg reduction at Week 12 Baseline: 27.7 mmHg Extrapolated % change: 20.6%
Timolol	β-blocker	Zimmerman 1983	1 month to 4 yr	30.7% reduction
Timolol	β-blocker	McMahon 1981	Non-infantile glaucoma	30% reduction after 1 month 12% reduction after 3 months
Timolol	β-blocker	McMahon 1981	Infantile glaucoma	24% reduction after 1 month 22% reduction after 3 months
Timolol	β-blocker	Zimmerman 1977	Adult	38-43% reduction
Timolol 0.25% Gel Forming Soultion	β-blocker	Plager 2009	0 to 6 yr	2.9 mmHg reduction at Week 12 Baseline: 23.2 mmHg Extrapolated % change: 12.5%
Timolol 0.5% Gel Forming Soultion	β-blocker	Plager 2009	0 to 6 yr	3.7 mmHg reduction at Week 12 Baseline: 24.4 mmHg Extrapolated % change: 15.2%

Note: The results of travoprost 0.004% PQ paediatric studies are not yet published and are not listed in the table. This study was included in the model analysis.

2.3.6. Discussion on clinical efficacy

No new efficacy and safety data have been submitted in this application. Data from Travoprost adult dose response studies (C-97-02 and C-00-20), the pivotal study for Travoprost 0.003% Solution (C-11-034) and the phase 3 clinical trial completed with Travoprost 0.004% in paediatric patients (C-12-009), were used to project the IOP lowering by Travoprost 0.003% Solution in paediatric patients with glaucoma or ocular hypertension.

The model was developed using data from adults. As stated by the MAH, these adult studies were selected because they were sufficient to characterise the travoprost dose response relationship from 1µg/mL to 60 µg/mL. Other studies including 15 µg/mL and/or 40µg/mL doses were not used in the model as these doses were already well represented in the model. Other adult dose-response study with different posology (e.g.morning dosing) were not considered. This approach appears, in principle, appropriate.

During the CHMP Scientific Advice procedure, the MAH was requested to show evidence for the appropriateness of using the change from baseline instead of IOP raw data. This efficacy endpoint could result in biased parameters as the error in the baseline observations will be carried on to all subsequent observations. The performance of this method would be better the smaller the residual error of the baseline observations. Furthermore, if the baseline depends on, for example age, by expressing the variable as percent of change there is a risk of masking a relationship between age and the efficacy of the drug. However, the model was built on data from adults where a relationship between age and response may not be expected. The MAH has presented a comparison of models using data with or without expressing the variable as change from baseline and no differences appear to be present.

The inclusion of Japanese population was object of discussion as this population seems to have a much higher inter-individual variability than other populations. The MAH presented an additional analysis showing that the inclusion/exclusion of data from Japanese people produces similar parameter values for the model and the plateau of the effect starts at the same point (i.e., 20 µg/mL).

With respect to the fact that no time aspect was included in the model (taking into account that the treatment effect was assessed following different length of treatment, from 14 days to 3 months) the MAH has proven that the steady-state in the response is achieved at day 14 both in adults treated with Travatran and Izba, and in paediatric population treated with Travatan.

The model that best described the dose-response relationship was a sigmoidal Emax model. A comparison of the selected model (Hill equation) versus other six different models has proven that the chosen model was the best one at statistical level, and no worse than the other models when graphical tools were used. All tested models predict a plateau of the effect at doses higher or equal to 20 µg/mL.

The model predicted the observed data from adults adequately, and predicted an effect for children with the marketed tavoprost (0.004%) of -27.27% IOP change from baseline (which is similar to the observed data in the only study performed in children) and -26.77% IOP change from baseline with travoprost 0.003%. Both IOP (in terms of absolute values) and IOP change from baseline are comparable between adults and paediatric patients > 3 years of age. This is not the case for the paediatric patients ≤ 3 years of age.

Physiological evidence of similar ocular concentrations of travoprost free acid (active substance disposable in the site of action) in adult and paediatric population for the same dose seems to be clear in patients aged 3-18 years. According to literature ocular volume is similar between adults and paediatric population from 3-18 years, and that esterases are fully developed in hepatic tissues by age 3. Similarly, a comparable response in terms of IOP change from baseline between adults and paediatric patients has been reported for travoprost 0.004%. However, less predictable response was observed in paediatric patients < 3 years of age. This was also reported for latanoprost 0.005% in which the variability in IOP response to treatment was greatest among the youngest patients (< 3 years), even though comparable mean IOP reductions were observed across the 3 age groups.

In summary, the assumption that there are no differences both in physiological and pathogenic characteristics of children and adults, and in the IOP response to IOP lowering agents cannot be accepted in the youngest group of age (< 3 years) without further reassurance from clinical data. The indication in paediatric population was consequently restricted to patients 3-18 years old.

2.3.7. Conclusions on the clinical efficacy

The CHMP agreed that the modelling approach allows to confirm efficacy of Izba in children aged 3-18 years old.

2.4. Clinical safety

Introduction

No new clinical studies have been undertaken to support this variation.

Comparison of safety data from patients dosed with Izba and Travatan BAK

The MAH has evaluated safety data from patients enrolled in clinical trial C-11-034, which was used to

support the initial MAA for Izba. Safety parameters assessed during the clinical trial included adverse events (AEs), visual acuity, ocular signs (eyelids/conjunctiva, cornea, iris/anterior chamber, aqueous cells and flare, and lens), ocular hyperemia, pachymetry, visual fields, and dilated fundus parameters (vitreous, optic nerve, retina/macula/choroid, and cup/disc ratio).

The majority of AEs reported for either treatment group during clinical trial C-11-034 were local ocular effects with a known causal association with the use of travoprost and topical ocular PGAs in general. As expected, lower exposure to travoprost resulted in a slightly lower incidence of adverse drug reactions (ADRs) reported in patients dosing with Izba versus Travatan BAK. The most common ADR reported in the study was hyperemia of the eye (ADRs for ocular and conjunctival combined). A numerically lower incidence of hyperemia of the eye was reported in the Izba group (ocular 6.1% and conjunctival 5.7%) relative to the Travatan BAK group (ocular 7.6% and conjunctival 6.9%). The severity of hyperemia was similar between the 2 treatment groups, as approximately 90% of the reports in each group were assessed as mild. Based on a review of AEs associated with ocular intolerance to study medication (defined as the MedDRA preferred terms of conjunctival hyperemia, eye irritation, eye pain, eye pruritus, eyelids pruritus, foreign body sensation in eyes and ocular hyperemia), no difference between the treatment groups was observed.

Comparison of safety data from patients dosed with Izba and historical safety data for Travatan BAK, sofZia and PQ

In addition, a comparison of safety data between IZBA and historical safety data from confirmatory clinical trials involved in the development of Travatan BAK, Travatan sofZia, and Travatan PQ was performed. Safety parameters evaluated in the comparison included adverse events and ocular hyperemia. Overall, the types of ADRs reported with the use of IZBA were consistent with ADRs reported in the development of Travatan preserved with BAK, sofZia, or PQ (C-97-71, C-97-72, and C-97-79 each utilizing the BAK formulation; C-04-17 the sofZia formulation; and C-08-40 the PQ formulation). No ADR was reported at an incidence that would indicate an unanticipated safety issue for the use of IZBA.

In conclusion, consistent with the safety profile of Travatan BAK, adverse events associated with the use of Izba are predominantly local ocular side effects associated with hyperemia of the eye and comfort related side-effects. A decrease of the active ingredient in Travatan (preserved with BAK, sofZia, or PQ) by 25% (from 40 µg/mL to 30 µg/mL) provides a formulation of travoprost to help mitigate some of these local ocular side-effects.

Post marketing experience

Since the introduction of travoprost to the marketplace, as with topical ocular PGAs in general, no significant safety concerns have been identified in any subgroup of patients (with regards to age, gender, race, iris colour) that would negatively impact the overall favourable safety profile of this class of medication.

2.4.1. Discussion on clinical safety

Clinical safety of Travoprost 0.003% was assessed during the Izba initial marketing authorization procedure (EMEA/H/C/002738/0000). Travoprost 0.003% safety profile appeared to be more favourable than that of Travoprost 0.004% BAK formulation. Most AEs reported for Izba were local ocular effects and they were

generally consistent with the known safety profile related to the use of travoprost. A lower incidence of the most common adverse events (eye hyperaemia and AEs classified as ocular intolerance of travoprost) was reported with the low concentration of travoprost with respect to Travatan.[3]

The clinical safety of Travoprost 0.004% in the paediatric population has been assessed in the procedure for the extension of indication for Travatan (EMEA/H/C/000390/II/0046). The most common adverse drug reactions were eye disorders (ocular hyperemia - 16.9% and growth of eyelashes – 6.5%). 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 was higher in children as compared to adults and this is reflected in the SmPC.[5]

The MAH claims that the safety profile of Travoprost 0.003% is expected to be similar to the approved Travoprost 0.004% PQ in the paediatric population have been acknowledged.

2.4.2. Conclusions on clinical safety

Adverse events associated with the use of Izba appear consistent with the known safety profile of Travatan. In principle, the potential for local ocular adverse effects may be reduced as the Izba formulation provides lower drug exposure.

Overall based on the clinical safety data presented, the safety profile of Izba in children is considered acceptable. Long-term safety data in children is not available and these should continue to be addressed in the post-marketing stage.

2.4.3. PSUR cycle

The PSUR cycle remains unchanged.

The annex II related to the PSUR, refers to the EURD list which remains unchanged.

2.5. Risk management plan

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

The PRAC considered that the RMP version 9.0 is acceptable. The PRAC endorsed PRAC Rapporteur updated assessment report dated 25 November 2016 is attached.

The CHMP endorsed the PRAC advice and approved the RMP version 9.0 with the following content:

Safety concerns

Table 1. Summary of the safety concerns

Important identified risks	• Macular oedema • Hyperpigmentation • Hypertrichoses • Iris and uveal inflammations • Cardiac and vascular disorders • Respiratory disorders • Hypersensitivity reactions

Important potential risks	• Melanoma • Corneal damage due to use of preserved eye drops • Use during pregnancy and lactation
Missing information	• Long term safety in the paediatric population • Potential interactions

Pharmacovigilance plan

N/A

Risk minimisation measures

Table 2. Summary table of the risk minimisation measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Important identified risks		
Macular oedema	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		

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Long term safety in the paediatric population	Appropriate identification in the medicinal product labelling	Not applicable.
Potential interactions	Appropriate identification in the medicinal product labelling	Not applicable.

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

2.6. 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.

Changes were also made to the PI to bring it in line with the current QRD template which were reviewed and accepted by the CHMP.

In addition, the list of local representatives in the PL has been revised to amend contact details for the representative of Spain.

2.6.1. User consultation

The CHMP considered that the submitted type II variation to include a paediatric indication 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

Benefits

Beneficial effects

Data from Travoprost adult studies were used to project the IOP lowering by Travoprost 0.003% solution in paediatric patients with glaucoma or ocular hypertension. It was considered that the response in the paediatric population and in the adult patients were comparable. This assumption was based on two facts: a) the physiological evidence of similar concentrations in adults and paediatrics and b) a comparable IOP lowering response between adult and children according to the literature reports.

The model predicted the observed data from adults adequately, and predicted an effect for children with the marketed travoprost (0.004%) of -27.27% IOP change from baseline (which is similar to the observed data in the only study performed in children) and -26.77% IOP change from baseline with travoprost 0.003%.

Uncertainty in the knowledge about the beneficial effects

The clinical development plan for the extension of this indication is based on a modelling and simulation approach. The selection of paediatric dose is one of the modelling and simulation objectives. The biological plausibility of the assumptions made is of major relevance. These assumptions are not applicable to the paediatric patients ≤ 3 years of age in whom less predictable response was observed. This variability may result from several factors. Among them the status of the cornea, the presence or absence of surgery, the consistency of the IOP measurement technique, or the use of different sedation/ anesthesia may have a role. Also, this group includes a large proportion of Primary Congenital Glaucoma patients, in which lower responder rate to treatment has been reported with respect to non-PCG patients[5].

Pharmacokinetic and clinical data for similar products also reinforce this conclusion. Systemic exposure was higher in younger patients (< 3 years) when pharmacokinetics of travoprost was characterised in paediatric patients with glaucoma or ocular hypertension after being treated with the usual adult dose of travoprost (0.004%) for 7 days[4]. Similar findings were observed when systemic pharmacokinetics (PK) of latanoprost was evaluated in paediatric subjects with glaucoma or ocular hypertension who received the adult latanoprost dose[6]. The availability of a lower dose appears to address this issue. However, this reduced dose should also be sufficient to achieve an adequate response. This uncertainty would require further reassurance from clinical data in this population (≤ 3 years).

Risks

Unfavourable effects

Travoprost 0.003% safety profile appeared to be more favourable than that of Travoprost 0.004% BAK formulation. Most AEs reported for Izba were local ocular effects and they were generally consistent with the known safety profile related to the use of travoprost. A lower incidence of the most common adverse events (eye hyperaemia and AEs classified as ocular intolerance of travoprost) was reported with the low concentration of travoprost with respect to Travatan. [3]

The clinical safety of Travoprost 0.004% in the paediatric population has been assessed in the procedure for the extension of indication for Travatan (EMEA/H/C/000390/II/0046). The most common adverse drug reactions were eye disorders (ocular hyperemia - 16.9% and growth of eyelashes – 6.5%). 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.

Travatan PQ (Travoprost 0.004%) is authorized for the decrease of elevated intraocular pressure in patients from 2 months to <18 years of age with ocular hypertension or paediatric glaucoma. Izba (Travoprost 0.003% Solution) formulation is identical to the Travoprost 0.004% but represents 25% reduction in the active drug concentration. In principle, this would reduce the drug exposure in patients while maintaining the efficacy and improving the safety profile.

[5] Maeda-Chubachi T. J Glaucoma 2013;22:614–619
[6] Raber S et al. Ophthalmology 2011; 118: 2022–2027

Uncertainty in the knowledge about the unfavourable effects

The clinical development of Travatan in the paediatric population meant a limited exposure (both in number of patients and duration of treatment) to travoprost in this population. Some adverse events already known for topical PGAs generally occur after several months to years of dosing (e.g.: periocular skin hyperpigmentation or discolouration, iris hyperpigmentation, and changes in eyelash characteristics). It is unknown the true incidence of these adverse events in children. As these events are considered identified risks in the RMP further information is to be provided also for paediatric population.

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.

Data from different doses of travoprost in adults were modelled in order to predict the clinical effects expected in the paediatric population, assuming that the IOP dose response curve to travoprost is comparable between adult and paediatric patients. The predicted -26.77% IOP change from baseline is similar to change observed previously for Travatan and is considered to be clinically relevant.

The MAH claims that the safety profile of Travoprost 0.003% is expected to be similar to the approved Travoprost 0.004% PQ in the paediatric population. This has been acknowledged. Nonetheless, post marketing experience available for Travatan used in the paediatric population would be supportive for this application.

Benefit-risk balance

Benefit-risk balance of Izba in paediatric population aged 3 to 18 years is considered to be positive.

Discussion on the Benefit-Risk Balance

The CHMP noted that insufficient justification has been provided that there are no important differences in physiological and pathogenic characteristics in paediatric patients aged less than 3 years of age compared to adults, and hence that the modelling and simulation approach can be accepted as the basis for the Izba indication in this age group. Consequently, the MAH agreed to accept restriction of the indication to 3 to 18 years of age.

4. Recommendations

Outcome

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

Variation accepted		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, II, IIIA and IIIB

Extension of Indication to include treatment of paediatric patients aged 3 years to < 18 years with ocular hypertension or paediatric glaucoma in order to decrease of elevated intraocular pressure. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package leaflet has been updated accordingly. In addition, the marketing authorisation holder took the opportunity to introduce minor corrections in the SmPC and to update the list of local representatives in the PL. The RMP has updated to version 9.0

Furthermore, the PI is brought in line with the latest QRD template version 10.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

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

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

When the submission of a PSUR and the update of a RMP coincide, they should be submitted at the same time.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

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