28 January 2016
EMA/CHMP/108077/2016 corr.1[1]
Procedure Management and Committees Support Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Lumigan

bimatoprost

Procedure no: EMEA/H/C/000391/P46/033

Note

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

[1] Editorial amendments

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Table of contents

1. Introduction

On November 4th, 2015, the MAH submitted a completed paediatric study for bimatoprost in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

2. Scientific discussion

2.1. Information on the development program

The intent of this pediatric study was to evaluate the safety and efficacy of bimatoprost preservative-free (PF) ophthalmic solution in the management of glaucoma in pediatric patients in whom surgical intervention was not indicated or anticipated for intraocular pressure (IOP) lowering within 12 weeks after baseline, and who required treatment with a topical IOP-lowering medication. The study was part of a paediatric investigational plan (PIP) as requested by the European Medicines Agency's Paediatric Committee (EMA's PDCO).

Despite recruitment efforts over 2.5 years, only 6 patients were enrolled in this study. This study was terminated early following the European Medicines Agency decision of 30 October 2014 (P/0293/2014) on the acceptance of a modification of an agreed paediatric investigation plan for bimatoprost (Lumigan and associated names) (EMEA-000917-PIP01-10-M04) in accordance with regulation No 1901/2006 of the European Parliament and of the Council.

Due to the small study population, the protocol-specified data analyses were not performed; instead efficacy, safety, and pharmacokinetic (PK) data are presented in by-patient listings and described in this abbreviated CSR based upon these listings.

This prematurely terminated paediatric study of bimatoprost PF versus timolol eye drops provided limited individual efficacy and safety data for 6 enrolled patients with glaucoma. No unexpected or clinically significant safety findings were noted. Limited individual IOP data indicated IOP lowering for paediatric patients aged 12 to 15 years treated with bimatoprost PF consistent with the known profile of the drug in adults. Limited pharmacokinetic data were collected only from 1 patient in this study, and blood concentrations of bimatoprost and bimatoprost acid were detectable approximately 10 minutes post dose in the systemic circulation following once daily topical dosing of bimatoprost PF for 6 weeks.

Therefore no regulatory consequences were identified by the MAH.

2.2. Information on the pharmaceutical formulation used in the study

Test product: Bimatoprost 0.03% preservative-free (PF) ophthalmic solution for topical ocular administration

Reference Therapy: Timolol 0.5% or 0.25% ophthalmic solution for topical ocular administration

Bimatoprost vehicle: Allergan formulation number 10135X

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- *Study to evaluate the safety and intraocular pressure-lowering efficacy of once-daily bimatoprost 0.03% preservative-free ophthalmic solution compared with twice-daily timolol (0.5% or 0.25%, based on age group) ophthalmic solution for 12 weeks in pediatric patients with glaucoma (*study 192024-056)

2.3.2. Clinical study

Description

Methods

Objective

The primary objective of the study was to evaluate the safety and IOP-lowering efficacy of once-daily bimatoprost 0.03% PF ophthalmic solution compared with twice-daily timolol (0.5% or 0.25%, based on age group) ophthalmic solution for 12 weeks in pediatric patients with glaucoma.

Study design

This was a multicenter, double-masked, randomized, parallel-group study. Enrollment was to start with the oldest pediatric patients (aged 12 to <18 years) and progress in a step-wise fashion to permit enrollment of younger patients (5 to < 12 years; 2 months to < 5 years) following safety assessments of the older age group(s). Total study duration was 13 months per patient: 4 weeks of screening/qualification period, 12 weeks of treatment, followed by safety follow-up for 9 months. Patients were stratified by age group: 12 to < 18 years, 5 to < 12 years, and < 5 years. Within each age stratum, patients were further stratified by baseline IOP (≤ 26 mm Hg; > 26 mm Hg).

Patients were randomized to receive either bimatoprost 0.03% PF ophthalmic solution administered once daily or timolol 0.5% (for patients aged 12 to < 18 years) or 0.25% (for patients aged < 12 years) ophthalmic solution administered twice daily, in a 1:1 allocation ratio. Bimatoprost vehicle was used for masking purposes.

Study population /Sample size

At least 80 patients and up to 120 patients were planned to be enrolled. Despite recruitment efforts over 2.5 years, only 6 patients were enrolled in this study (3 patients randomized to each of the 2 treatment groups). In agreement with the European Medicines Agency' s Paediatric Committee (EMA' s PDCO), this study was prematurely terminated.

Treatments

Bimatoprost 0.03% PF ophthalmic solution: Patients received active bimatoprost PF in the evening and bimatoprost vehicle in the morning, up to and including the morning of the week 6 visit; after that visit they received bimatoprost vehicle in the evening and active medication in the morning, up to and including the evening before the week 12 visit. Patients in the bimatoprost group who followed the

original protocol or Amendment 1 administered active medication in the evening (and bimatoprost vehicle in the morning) daily throughout the 12-week treatment period.

The control treatment was timolol 0.25% or 0.5%. For masking purposes of this study, timolol, manufactured by Allergan, was configured into unit dose containers. No other formulation changes to timolol were made.

Timolol 0.5% ophthalmic solution was used as the control treatment in patients aged 12 to < 18 years. Timolol 0.25% ophthalmic solution was to be used as the control treatment in patients < 12 years (note that none of the 6 patients enrolled was administered 0.25%, since none were under 12 years of age). The study treatment bimatoprost 0.03% PF ophthalmic solution was administered once daily, whereas the control treatment timolol 0.5% or 0.25% ophthalmic solution was administered twice daily. Patients in the timolol group received active medication both in the evening and in the morning up until the evening preceding the week 12 visit.

To protect masking, in patients randomized to treatment with bimatoprost, bimatoprost vehicle was instilled once daily in the mornings through the morning of the week 6 visit and in the evenings starting at the week 6 visit. Bimatoprost vehicle (Allergan formulation number 10135X) contains sodium phosphate dibasic heptahydrate, sodium chloride, citric acid monohydrate, hydrochloric acid, sodium hydroxide, and purified water.

Outcomes/endpoints

Efficacy:

The primary efficacy endpoint was IOP, measured in each eye. At the week 2 and 6 visits, IOP measurements were performed at hour 2 (2 hours after the morning dosing time); at the week 8 and 12 visits, IOP measurements were performed at hour 0. This was prior to morning administration of the study medication at week 8 and at the usual time of the morning dose at week 12 (although no medication was administered at week 12); at both visits this was approximately 12 hours after the previous dose of study medication. Up to and including the week 6 visit, hour 2 corresponded to the expected peak IOP-lowering effect of bimatoprost and timolol. Starting the day after the week 6 visit, hour 0 (before study medication administration) corresponded to the expected trough IOP-lowering effect of bimatoprost and timolol.

Drug Concentration:

In patients who were treated with study medication in both eyes and provided additional consent for blood sampling,

Blood concentrations of bimatoprost and its acid metabolite AGN-191522 were determined only for patients who received bimatoprost treatment.

Safety:

Safety measures included adverse events (AEs), visual acuity, biomicroscopy, ophthalmoscopy, physical examination, vital signs, and urine pregnancy tests for females of childbearing potential.

Statistical Methods

Due to early termination of the study and the small patient population (N = 6), efficacy, pharmacokinetic (PK), and safety data were listed by patient rather than analyzed or summarized in

graphic or tabular format; the protocol specified statistical analyses of efficacy, PK, and safety were not performed.

Results

Recruitment / Number analysed

Six patients were enrolled in the study. Three subjects were randomized to each treatment group. Of the 6 patients randomized and treated, 3 patients completed the study. Of the 3 patients not completing the study, 1 patient in the timolol group experienced an AE of moderate elevated IOP considered related to the study drug that resulted in discontinuation from the study. The remaining 2 patients did not complete the study because the study itself was discontinued prior to these patients completing all visits.

Baseline data

Of the 6 patients enrolled, 3 were males and 3 were females, aged 12 to 15 years. Two of the males and 2 of the females were Caucasian, one male was Asian, and 1 female was black. Three of the patients had light iris color (blue, gray, green-brown) and 3 patients had dark iris color (brown). In the timolol group, prestudy corneal pachymetry measurements ranged from 483 to 614 (right eye; OD) and from 481 to 671 (left eye; OS). In the bimatoprost PF group, these measurements ranged from 573 to 621 (OD) and from 542 to 615 (OS).

Efficacy results

Change from baseline (follow-up minus baseline) in the study eye IOP at week 6 (hour 2) was the planned primary efficacy variable. Due to early termination of the study, no statistical analysis was performed and no data summaries were generated.

In the bimatoprost PF-treated patients, decreases from baseline in study eye IOP ranged from -9.0 to -11.5 mm Hg at week 6, hour 2, which corresponds to the anticipated timing of bimatoprost PF peak effect. The IOP decrease from baseline at week 6, hour 12 was -7.5 and 0.5 mm Hg for the 2 patients with data at that timepoint, corresponding to the timing of the anticipated trough effect of bimatoprost PF.

Therefore, the IOP lowering observed in pediatric patients treated with bimatoprost PF was consistent with the known profile of the drug in adults.

For the 2 patients treated with timolol with week 6 IOP data, the range of changes from baseline observed at week 6, hour 2 (-9.5 to -10.0 mm Hg) were consistent with the anticipated timing of timolol peak effect (2 hours post morning dosing). The third patient treated with timolol discontinued treatment early due to an AE of increased IOP.

Pharmacokinetic results

Blood samples were collected from 2 patients: Patient 10003-1004 followed the study schedule under Amendment 1 of the study protocol, and Patient 14902-1007 followed the study schedule under Amendment 2 of the study protocol.

Patient 10003-1004, a 15-year-old black female, was treated in both eyes with bimatoprost PF, and the blood concentrations of bimatoprost and bimatoprost acid for this patient at approximately 10

minutes post dose (actual time of blood collection) at the week 6 visit were 0.028 ng/mL and 0.252 ng/mL, respectively (Report PK14006-BM). Blood concentration of bimatoprost observed from Patient 10003-1004 appeared to be lower than those observed at approximately 10 minutes post dose in adult volunteers from a previous study (0.0822 ng/mL), who were dosed with topical Lumigan 0.03% once daily to both eyes for 2 weeks (Report PK-98-119). However, blood concentration of bimatoprost acid observed from Patient 10003-1004 appeared to be higher than the adults, as blood concentration of bimatoprost acid in adults was below the lower limit of quantitation (0.05 ng/mL) at all timepoints in the previous study (Report PK-98-119). This finding is not considered clinically significant, as no unexpected or clinically significant safety findings were noted in this patient. Moreover, determination of drug concentrations in a single patient must be interpreted with caution due to limited sample size.

Patient 14902-1007 was treated in both eyes with timolol, and the blood concentrations of bimatoprost and bimatoprost acid were not determined for this patient.

Safety results

Two of the patients treated with bimatoprost PF (Patients 10003-1004 and 13402-1001) completed the study; these patients received 77 and 83 days of treatment, respectively. The remaining patient treated with bimatoprost PF (Patient 13404-1008) received 88 days of treatment, but did not complete the study due to premature termination of the study. One patient treated with timolol completed the study (Patient 13402-1002); this patient received 83 days of treatment. The other 2 patients treated with timolol (Patients 10501-1005 and 14902-1007) received 42 and 84 days of treatment, respectively. Patient 10501-1005 discontinued the study due to an adverse event (IOP increased), and Patient 14902-1007 did not complete the study due to premature termination of the study.

A total of 12 treatment-emergent AEs (AEs occurring during the treatment period) were reported for 4 patients during the study (Table 12-1). Most of the AEs were within the SOC of eye disorders. The only AEs reported in more than 1 patient were growth of the eyelashes and conjunctival hyperaemia. Two patients (1 patient treated with bimatoprost PF and 1 patient treated with timolol) experienced mild growth of the eyelashes considered by the investigator to be related to study treatment. Two patients treated with bimatoprost PF experienced moderate conjunctival hyperaemia, also considered by the investigator to be related to study treatment.

Table 12-1 Overview of Adverse Events Occurring During the Treatment Period (All Enrolled Subjects)

Patient/ Treatment	Study Eye	System Organ Class	Adverse Event (Preferred Term) / Affected Eye	Severity	Relationship to Study Treatment[a]
10003-1004/ Bimatoprost PF	OS (both eyes treated)	Eye disorders	Conjunctival hyperaemia / OD	Moderate	Related
			Eyelid oedema / OD	Mild	Unrelated
10501-1005/ Timolol	OS	Eye disorders	Eyelash hyperpigmentation / OS	Mild	Related
			Growth of eyelashes / OS	Mild	Related
		Investigations	Intraocular pressure increased[b] / OS	Moderate	Related
13402-1001/ Bimatoprost PF	OS	Eye disorders	Blepheral pigmentation / OS	Mild	Related
			Growth of eyelashes / OS	Mild	Related
		Gastrointestinal	Diarrhoea	Mild	Not related
		General disorders and administration site conditions	Pyrexia	Moderate	Not related
		Nervous system disorders	Headache	Mild	Not related
		Infections and infestations	Influenza	Mild	Not related
13404-1008/ Bimatoprost PF	OS	Eye disorders	Conjunctival hyperaemia / OS	Moderate	Related

OD = right eye; OS = left eye; PF = preservative free

[a] Treatment-related adverse events include those that, in the investigator's opinion, may have been caused by the study medication with reasonable possibility.

[b] This adverse event led to permanent discontinuation of study drug.

Source: Listing 14.3.1

Based on limited individual safety data (AEs, vital signs, macroscopic evaluation of bulbar hyperaemia, visual acuity assessments, biomicroscopy, and funduscopic examinations), no unexpected or clinically significant safety findings were noted.

2.3.3. Discussion on clinical aspects

The very limited data in patients aged 12-15 years showed an expected lowering of IOP and a safety profile similar to the well-established safety profile in adults. Because of the very limited data, no firm conclusions can be made regarding the efficacy and safety in the paediatric population aged 12-15 years. It is agreed that no update to the product information is warranted based on this study.

CHMP's overall conclusion and recommendation

The very limited data in patients aged 12-15 years showed expected clinical efficacy and safety results. However, due to the very limited data no firm conclusion can be made regarding efficacy and safety in this age group. No changes to the current product information are required.

☒ **Fulfilled:**

No regulatory action required.

☐ **Not fulfilled:**