Clinical trial results:
A Multicenter, Double-masked, Randomized, Active-controlled, Parallel Study of the Safety and Efficacy of Once-daily Bimatoprost Preservative-free Ophthalmic Solution Compared to Twice-daily Timolol Ophthalmic Solution in Paediatric Patients with Glaucoma

Summary

EudraCT number	2011-003278-10
Trial protocol	FR GB DE
Global end of trial date	30 October 2014

Results information

Result version number	v1 (current)
This version publication date	06 March 2016
First version publication date	06 March 2016

Trial information

Trial identification

Sponsor protocol code	192024-056

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01426113
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Allergan Limited
Sponsor organisation address	Allergan Limited Marlow International The Parkway, Marlow, Buckinghamshire, United Kingdom, SL7 1YL
Public contact	Allergan Limited EU Regulatory Dept, Allergan Limited, 44 1628 494444, ml-eu_reg_affairs@allergan.com
Scientific contact	Allergan Limited EU Regulatory Dept, Allergan Limited, 44 1628 494444, ml-eu_reg_affairs@allergan.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000917-PIP01-10
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 January 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 October 2014
Global end of trial reached?	Yes
Global end of trial date	30 October 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to evaluate the safety and IOP-lowering efficacy of once-daily bimatoprost ophthalmic solution compared with twice-daily timolol ophthalmic solution for 12 weeks in pediatric patients with glaucoma.

Protection of trial subjects:

Parent(s) or legal guardian(s) were required to read and sign an Informed Consent Form. Subjects may have signed an assent, if applicable, prior to any study procedures being performed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 September 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	9 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Taiwan: 1
Country: Number of subjects enrolled	United States: 3
Worldwide total number of subjects	6
EEA total number of subjects	2

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	6
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was discontinued prematurely after enrollment of 6 patients.

Pre-assignment

Screening details:

The Screening period was from Day -28 to Day -2. All randomized patients are noted in the overall study period.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Carer, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	bimatoprost ophthalmic solution formulation A and vehicle

Arm description:

1 drop bimatoprost vehicle in the affected eye(s) in the morning and 1 drop of bimatoprost ophthalmic solution formulation A in the affected eye(s) in the evening for 6 weeks, followed by 1 drop bimatoprost ophthalmic solution formulation A in the affected eye(s) in the morning and 1 drop bimatoprost vehicle in the affected eye(s) in the evening for 6 additional weeks.

Arm type	Experimental
Investigational medicinal product name	bimatoprost
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops
Routes of administration	Ocular use

Dosage and administration details:

1 drop bimatoprost vehicle in the affected eye(s) in the morning and 1 drop of bimatoprost ophthalmic solution formulation A in the affected eye(s) in the evening for 6 weeks, followed by 1 drop bimatoprost ophthalmic solution formulation A in the affected eye(s) in the morning and 1 drop bimatoprost vehicle in the affected eye(s) in the evening for 6 additional weeks.

Arm title	timolol ophthalmic solution

Arm description:

1 drop timolol ophthalmic solution in the affected eye(s) in the morning and evening for 12 weeks.

Arm type	Active comparator
Investigational medicinal product name	timolol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops
Routes of administration	Ocular use

Dosage and administration details:

1 drop timolol ophthalmic solution in the affected eye(s) in the morning and evening for 12 weeks.

Number of subjects in period 1	bimatoprost ophthalmic solution formulation A and vehicle	timolol ophthalmic solution
Started	3	3
Completed	2	1
Not completed	1	2
Study Discontinued	1	1
Adverse event, non-fatal	-	1

Baseline characteristics

Reporting groups	
Reporting group title	bimatoprost ophthalmic solution formulation A and vehicle
Reporting group description:	
1 drop bimatoprost vehicle in the affected eye(s) in the morning and 1 drop of bimatoprost ophthalmic solution formulation A in the affected eye(s) in the evening for 6 weeks, followed by 1 drop bimatoprost ophthalmic solution formulation A in the affected eye(s) in the morning and 1 drop bimatoprost vehicle in the affected eye(s) in the evening for 6 additional weeks.	
Reporting group title	timolol ophthalmic solution
Reporting group description:	
1 drop timolol ophthalmic solution in the affected eye(s) in the morning and evening for 12 weeks.	

Reporting group values	bimatoprost ophthalmic solution formulation A and vehicle	timolol ophthalmic solution	Total
Number of subjects	3	3	6
Age categorical Units: Subjects			
Adolescents (12-15 years)	3	3	6
Age continuous Units: years			
arithmetic mean	14.7	12.7	
standard deviation	± 0.58	± 0.58	-
Gender, Male/Female Units: Participants			
Female	3	0	3
Male	0	3	3

End points

End points reporting groups

Reporting group title	bimatoprost ophthalmic solution formulation A and vehicle

Reporting group description:

1 drop bimatoprost vehicle in the affected eye(s) in the morning and 1 drop of bimatoprost ophthalmic solution formulation A in the affected eye(s) in the evening for 6 weeks, followed by 1 drop bimatoprost ophthalmic solution formulation A in the affected eye(s) in the morning and 1 drop bimatoprost vehicle in the affected eye(s) in the evening for 6 additional weeks.

Reporting group title	timolol ophthalmic solution

Reporting group description:

1 drop timolol ophthalmic solution in the affected eye(s) in the morning and evening for 12 weeks.

Primary: Change from Baseline in Intraocular Pressure (IOP) in the Study Eye

End point title	Change from Baseline in Intraocular Pressure (IOP) in the Study Eye[1]

End point description:

IOP is a measure of the fluid pressure inside the study eye. A negative number change from baseline indicates a reduction in IOP (improvement) and a positive change from baseline indicates an increase in IOP (worsening). Due to lack of enrollment, analysis was not performed for this outcome measure.

End point type	Primary

End point timeframe:

Baseline, Week 6

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This study was discontinued after the enrollment of 6 patients; therefore, statistical analyses were not performed.

End point values	bimatoprost ophthalmic solution formulation A and vehicle	timolol ophthalmic solution		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[2]	0[3]		
Units: Millimeters of Mercury (mmHg)				
number (not applicable)				

Notes:

[2] - Due to lack of enrollment, analysis was not performed for this outcome measure.

[3] - Due to lack of enrollment, analysis was not performed for this outcome measure.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from signing consent through Month 12/Exit.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	bimatoprost ophthalmic solution formulation A and vehicle

Reporting group description:

1 drop bimatoprost vehicle in the affected eye(s) in the morning and 1 drop of bimatoprost ophthalmic solution formulation A in the affected eye(s) in the evening for 6 weeks, followed by 1 drop bimatoprost ophthalmic solution formulation A in the affected eye(s) in the morning and 1 drop bimatoprost vehicle in the affected eye(s) in the evening for 6 additional weeks.

Reporting group title	timolol ophthalmic solution

Reporting group description:

1 drop timolol ophthalmic solution in the affected eye(s) in the morning and evening for 12 weeks.

Serious adverse events	bimatoprost ophthalmic solution formulation A and vehicle	timolol ophthalmic solution	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	bimatoprost ophthalmic solution formulation A and vehicle	timolol ophthalmic solution	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	1 / 3 (33.33%)	
Investigations			
Intraocular Pressure Increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Nervous system disorders			

Headache			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
General disorders and administration site conditions			
Pyrexia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Eyelash Hyperpigmentation			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Growth of Eyelashes			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	
occurrences (all)	1	1	
Eyelid Oedema			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Conjunctival Hyperaemia			
subjects affected / exposed	2 / 3 (66.67%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Blepharal Pigmentation			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Diarrhoea			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			

Influenza subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 3 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 July 2012	1) allow the use of Icare and Perkins tonometers; 2) remove PK sampling at baseline; and 3) change the noninferiority margin for analysis of the primary efficacy variable and update sample size calculations accordingly.
19 April 2013	1) remove evening office visits; 2) change the primary efficacy endpoint to week 6 (hour 2); 3) in the bimatoprost group, change the dosing of bimatoprost to the morning and vehicle to the evening from week 6 to week 12; 4) add a week 8 visit and move pharmacokinetic measurements from week 6 to week 8; 5) change the IOP measurement in weeks 8 and 12 to occur at time 0 (for trough effect); and 6) increase the study sample size to ensure that at least 80 patients were evaluable at weeks 6 and 12 (previous discontinuation rates predicted that approximately 90 patients would be needed to be randomized at baseline, but up to 120 patients could be enrolled if needed).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported