Clinical trial results:
Additive Effect of Twice Daily Brinzolamide 1% /Brimonidine 0.2% Fixed Dose Combination as an Adjunctive Therapy to a Prostaglandin Analogue

Summary

EudraCT number	2015-000736-15
Trial protocol	DE ES GB FR GR
Global end of trial date	27 February 2018

Results information

Result version number	v1 (current)
This version publication date	01 December 2018
First version publication date	01 December 2018

Trial information

Trial identification

Sponsor protocol code	GLH694-P001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02419508
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Alcon Research Ltd
Sponsor organisation address	6201 S. Freeway, Fort Worth, TX, United States, 76134
Public contact	EMEA Regulatory Affairs, Alcon Eye Care (UK) Ltd, eurmea.ra@alcon.com
Scientific contact	EMEA Regulatory Affairs, Alcon Eye Care (UK) Ltd, eurmea.ra@alcon.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 February 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 February 2018
Global end of trial reached?	Yes
Global end of trial date	27 February 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to evaluate the additive intraocular pressure (IOP) lowering effect of brinzolamide 1%/brimonidine 0.2% (dosed twice per day (BID)) when added to a prostaglandin analogue (PGA) in subjects with open-angle glaucoma or ocular hypertension.

Protection of trial subjects:

Prior to the start of the study, the study protocol, the informed consent and assent documents, patient instruction sheets, the Investigator's Brochure, as well as any advertising materials used to recruit patients were submitted to institutional review boards (IRBs) and independent ethics committees (IECs). The IRB/IECs reviewed all documents and approved required documents; copies of the approval letters were provided to Alcon. Consistent with both the IRB/IEC's requirements and all applicable regulations, the Investigators periodically provided study updates to the IRB/IEC. A patient or parent/legal guardian (if necessary, a legally authorized representative) provided informed consent, and children signed an approved assent form when appropriate. This study was conducted in accordance with Good Clinical Practices (GCP) and the ethical principles that have their origins in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 August 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 28
Country: Number of subjects enrolled	United Kingdom: 18
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Germany: 14
Country: Number of subjects enrolled	Greece: 14
Country: Number of subjects enrolled	Australia: 6
Country: Number of subjects enrolled	Israel: 8
Country: Number of subjects enrolled	Argentina: 49
Country: Number of subjects enrolled	Canada: 47
Country: Number of subjects enrolled	Chile: 2
Worldwide total number of subjects	188
EEA total number of subjects	76

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 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	67
From 65 to 84 years	115
85 years and over	6

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 37 sites located in Argentina (3), Australia (4), Canada (12), Chile (3), France (1), Germany (3), Greece (2), Israel (3), Spain (3), and United Kingdom (3).

Pre-assignment

Screening details:

Of the 290 subjects enrolled in the study, 102 were exited during the Screening/Eligibility period. This reporting group includes all randomized subjects. One randomized subject did not receive investigational product and is excluded from the Full Analysis Set and the Safety Analysis Set.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	SIMBRINZA + PGA

Arm description:

Brinzolamide 1%/brimonidine 0.2% tartrate ophthalmic suspension, 1 drop instilled 2 times per day in affected eye(s) (09:00 and 21:00) plus designated prostaglandin analogue, 1 drop instilled in each eye once per day in the evening for 42 days

Arm type	Experimental
Investigational medicinal product name	Brinzolamide 1%/brimonidine 0.2% tartrate ophthalmic suspension
Investigational medicinal product code	
Other name	SIMBRINZA® suspension
Pharmaceutical forms	Eye drops, suspension
Routes of administration	Ophthalmic use

Dosage and administration details:

One drop instilled 2 times per day in affected eye(s) (09:00 and 21:00) for 42 days

Investigational medicinal product name	Prostaglandin analogue
Investigational medicinal product code	
Other name	TRAVATAN® PQ, LUMIGAN®, XALATAN®
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ophthalmic use

Dosage and administration details:

One drop of designated prostaglandin analogue instilled in each eye once per day in the evening for 42 days

Arm title	Vehicle + PGA

Arm description:

Brinz/brim vehicle, 1 drop instilled 2 times per day in affected eye(s) (09:00 and 21:00) plus designated prostaglandin analogue, 1 drop instilled in each eye once per day in the evening for 42 days

Arm type	Active comparator
Investigational medicinal product name	Brinz/brim vehicle
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops
Routes of administration	Ophthalmic use

Dosage and administration details: One drop instilled 2 times per day in affected eye(s) (09:00 and 21:00) for 42 days	
Investigational medicinal product name	Prostaglandin analogue
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ophthalmic use

Dosage and administration details:

One drop of designated prostaglandin analogue instilled in each eye once per day in the evening for 42 days

Number of subjects in period 1	SIMBRINZA + PGA	Vehicle + PGA
Started	96	92
Completed	86	88
Not completed	10	4
Consent withdrawn by subject	1	-
Adverse event, non-fatal	9	3
Other - Reason not specified	-	1

Baseline characteristics

Reporting groups	
Reporting group title	SIMBRINZA + PGA
Reporting group description:	
Brinzolamide 1%/brimonidine 0.2% tartrate ophthalmic suspension, 1 drop instilled 2 times per day in affected eye(s) (09:00 and 21:00) plus designated prostaglandin analogue, 1 drop instilled in each eye once per day in the evening for 42 days	
Reporting group title	Vehicle + PGA
Reporting group description:	
Brinz/brim vehicle, 1 drop instilled 2 times per day in affected eye(s) (09:00 and 21:00) plus designated prostaglandin analogue, 1 drop instilled in each eye once per day in the evening for 42 days	

Reporting group values	SIMBRINZA + PGA	Vehicle + PGA	Total
Number of subjects	96	92	188
Age categorical			
Units: Subjects			

Age continuous			
This analysis population includes all randomized subjects.			
Units: years			
arithmetic mean	66.5	67.9	
standard deviation	± 10.65	± 11.65	-
Gender categorical			
This analysis population includes all randomized subjects.			
Units: Subjects			
Female	56	43	99
Male	40	49	89

End points

End points reporting groups

Reporting group title	SIMBRINZA + PGA
Reporting group description:	
Brinzolamide 1%/brimonidine 0.2% tartrate ophthalmic suspension, 1 drop instilled 2 times per day in affected eye(s) (09:00 and 21:00) plus designated prostaglandin analogue, 1 drop instilled in each eye once per day in the evening for 42 days	
Reporting group title	Vehicle + PGA
Reporting group description:	
Brinz/brim vehicle, 1 drop instilled 2 times per day in affected eye(s) (09:00 and 21:00) plus designated prostaglandin analogue, 1 drop instilled in each eye once per day in the evening for 42 days	
Subject analysis set title	SIMBRINZA + PGA
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects in FAS with values at both baseline and time point	
Subject analysis set title	Vehicle + PGA
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects in FAS with values at both baseline and time point	

Primary: Mean Change From Baseline (on PGA) in Diurnal IOP (Mean of 09:00 and 11:00 Time Points) at Week 6

End point title	Mean Change From Baseline (on PGA) in Diurnal IOP (Mean of 09:00 and 11:00 Time Points) at Week 6
End point description:	
IOP (fluid pressure inside the eye) was measured using Goldmann applanation tonometry and averaged over the 09:00 AM and 11:00 AM time points. A more negative change from baseline indicates a greater improvement, i.e., a reduction of IOP. One eye (study eye) contributed to the analysis. This analysis population includes all randomized subjects who received a dose of study medication and had at least 1 of the 2 scheduled on-treatment visits [Full Analysis Set (FAS)]. Only subjects with a value at both baseline and time point are included in the calculation of change. Here, "N" is the number of subjects at baseline for each arm group, respectively.	
End point type	Primary
End point timeframe:	
Baseline (BL), Week 6	

End point values	SIMBRINZA + PGA	Vehicle + PGA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	86	88		
Units: millimeters mercury (mmHg)				
arithmetic mean (standard deviation)				
Baseline, N=95, 92	22.8 (± 2.39)	22.9 (± 2.32)		
Mean change from baseline	-5.6 (± 2.72)	-2.1 (± 2.61)		

Statistical analyses

Statistical analysis title	Mean Change From Baseline (on PGA) in Diurnal IOP
Statistical analysis description: Mean of 09:00 and 11:00 Time Points at Week 6	
Comparison groups	SIMBRINZA + PGA v Vehicle + PGA
Number of subjects included in analysis	174
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis

Secondary: Mean Diurnal IOP at Week 6

End point title	Mean Diurnal IOP at Week 6
End point description: IOP (fluid pressure inside the eye) was measured using Goldmann applanation tonometry and averaged over the 09:00 AM and 11:00 AM time points. A higher IOP can be a greater risk factor for developing glaucoma or glaucoma progression (leading to optic nerve damage). One eye (study eye) contributed to the analysis. FAS with data available.	
End point type	Secondary
End point timeframe: Week 6	

End point values	SIMBRINZA + PGA	Vehicle + PGA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	86	88		
Units: mmHg				
arithmetic mean (standard deviation)	17.2 (± 3.49)	20.9 (± 3.59)		

Statistical analyses

Statistical analysis title	Mean Diurnal IOP at Week 6
Comparison groups	Vehicle + PGA v SIMBRINZA + PGA
Number of subjects included in analysis	174
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis

Secondary: Mean Percentage Change From Baseline in Diurnal IOP at Week 6

End point title	Mean Percentage Change From Baseline in Diurnal IOP at Week 6

End point description:

IOP (fluid pressure inside the eye) was measured using Goldmann applanation tonometry and averaged over the 09:00 AM and 11:00 AM time points. A more negative percent change from baseline indicates a greater improvement, i.e., a reduction of IOP. One eye (study eye) contributed to the analysis. FAS. Only subjects with a value at both baseline and time point are included in the calculation of change. Here, "N" is the number of subjects at baseline for each arm group, respectively.

End point type	Secondary

End point timeframe:

Baseline, Week 6

End point values	SIMBRINZA + PGA	Vehicle + PGA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	86	88		
Units: percent change				
arithmetic mean (standard deviation)	-24.7 (± 12.17)	-9.5 (± 10.92)		

Statistical analyses

Statistical analysis title	Mean Percent Change From Baseline in Diurnal IOP
Comparison groups	SIMBRINZA + PGA v Vehicle + PGA
Number of subjects included in analysis	174
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis

Secondary: Mean Change From Baseline in IOP at 11:00 at Week 6

End point title	Mean Change From Baseline in IOP at 11:00 at Week 6

End point description:

IOP (fluid pressure inside the eye) was measured using Goldmann applanation tonometry at 11:00 AM. A more negative change from baseline indicates a greater improvement, i.e., a reduction of IOP. One eye (study eye) contributed to the analysis. FAS. Only subjects with a value at both baseline and time point are included in the calculation of change. Here, "N" is the number of subjects at baseline for each arm group, respectively.

End point type	Secondary

End point timeframe:

Baseline, Week 6

End point values	SIMBRINZA + PGA	Vehicle + PGA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	86	88		
Units: mmHg				
arithmetic mean (standard deviation)				
Baseline, N=95, 92	22.4 (± 2.70)	22.6 (± 2.69)		
Change from Baseline	-7.0 (± 3.19)	-2.4 (± 2.78)		

Statistical analyses

Statistical analysis title	Mean Change From BL in IOP at 11:00 at Week 6
Comparison groups	SIMBRINZA + PGA v Vehicle + PGA
Number of subjects included in analysis	174
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis

Secondary: Mean Percentage Change From Baseline in IOP at 11:00 at Week 6

End point title	Mean Percentage Change From Baseline in IOP at 11:00 at Week 6

End point description:

IOP (fluid pressure inside the eye) was measured using Goldmann applanation tonometry at 11:00 AM. A more negative percent change from baseline indicates a greater improvement, i.e., a reduction of IOP. One eye (study eye) contributed to the analysis. FAS. Only subjects with a value at both baseline and time point are included in the calculation of change. Here, "N" is the number of subjects at baseline for each arm group, respectively.

End point type	Secondary

End point timeframe:

Baseline, Week 6

End point values	SIMBRINZA + PGA	Vehicle + PGA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	86	88		
Units: Percent change				
arithmetic mean (standard deviation)	-31.3 (± 14.81)	-10.8 (± 11.86)		

Statistical analyses

Statistical analysis title	Mean Percent Change From BL in IOP at 11:00
Comparison groups	SIMBRINZA + PGA v Vehicle + PGA

Number of subjects included in analysis	174
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis

Secondary: Mean Change From Baseline in IOP at 09:00 at Week 6

End point title	Mean Change From Baseline in IOP at 09:00 at Week 6

End point description:

IOP (fluid pressure inside the eye) was measured using Goldmann applanation tonometry at 09:00 AM. Baseline is defined as the average of the 9:00 hour values at both Eligibility visits. A more negative change from baseline indicates a greater improvement, i.e., a reduction of IOP. One eye (study eye) contributed to the analysis. FAS. Only subjects with a value at both baseline and time point are included in the calculation of change. Here, "N" is the number of subjects at baseline for each arm group, respectively.

End point type	Secondary

End point timeframe:

Baseline, Week 6

End point values	SIMBRINZA + PGA	Vehicle + PGA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	86	88		
Units: Percent change				
arithmetic mean (standard deviation)				
Baseline, N=95, 92	23.4 (± 2.40)	23.4 (± 2.22)		
Change from baseline	-4.9 (± 3.06)	-2.5 (± 2.87)		

Statistical analyses

Statistical analysis title	Mean Change From BL in IOP at 09:00 at Week 6
Comparison groups	SIMBRINZA + PGA v Vehicle + PGA
Number of subjects included in analysis	174
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis

Secondary: Mean Percentage Change From Baseline at 09:00 at Week 6

End point title	Mean Percentage Change From Baseline at 09:00 at Week 6

End point description:

IOP (fluid pressure inside the eye) was measured using Goldmann applanation tonometry at 9:00 AM. Baseline is defined as the average of the 9:00 hour values at both Eligibility visits.A more negative

percent change from baseline indicates a greater improvement, i.e., a reduction of IOP. One eye (study eye) contributed to the analysis. FAS. Only subjects with a value at both baseline and time point are included in the calculation of change. Here, "N" is the number of subjects at baseline for each arm group, respectively.

End point type	Secondary
End point timeframe:	
Baseline, Week 6	

End point values	SIMBRINZA + PGA	Vehicle + PGA		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	86	88		
Units: percent change				
arithmetic mean (standard deviation)	-21.0 (± 13.36)	-10.9 (± 11.83)		

Statistical analyses

Statistical analysis title	Mean Percent Change From BL 09:00 at Week 6
Comparison groups	SIMBRINZA + PGA v Vehicle + PGA
Number of subjects included in analysis	174
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline through study completion, an average of 6 weeks.	
Adverse event reporting additional description:	
Adverse Events (AEs) were obtained through solicited and spontaneous comments from subjects and through observations by the Investigator as outlined in the study protocol.This analysis population includes all subjects who received a dose of study medication (Safety Analysis Set).	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups	
Reporting group title	SIMBRINZA + PGA
Reporting group description:	
Subjects exposed to Brinz/brim + PGA	
Reporting group title	Vehicle + PGA
Reporting group description:	
Subjects exposed to brinz/brim vehicle + PGA	

Serious adverse events	SIMBRINZA + PGA	Vehicle + PGA	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 95 (1.05%)	0 / 92 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	1 / 95 (1.05%)	0 / 92 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	SIMBRINZA + PGA	Vehicle + PGA	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 95 (10.53%)	1 / 92 (1.09%)	
Eye disorders			
Ocular hyperaemia			

subjects affected / exposed occurrences (all)	5 / 95 (5.26%) 9	1 / 92 (1.09%) 1	
Gastrointestinal disorders Dry mouth subjects affected / exposed occurrences (all)	 5 / 95 (5.26%) 5	 0 / 92 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 March 2017	Removed an IOP collection time point at all visits to reduce subject commitment and aid in recruitment. Reduced the entry IOP, allowing more subjects to be eligible while maintaining an IOP baseline that was reasonable to observe the efficacy.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported