Clinical trial results:
Safety and Efficacy with Twice Daily Brinzolamide 1% / Brimonidine 0.2% (SIMBRINZA®) as an Adjunctive Therapy to Travoprost 0.004% / Timolol 0.5% (DUOTRAV®)

Summary

EudraCT number	2016-000176-20
Trial protocol	ES BE GB DE GR FR NL
Global end of trial date	13 July 2018

Results information

Result version number	v1 (current)
This version publication date	09 May 2019
First version publication date	09 May 2019

Trial information

Trial identification

Sponsor protocol code	GLJ576-P001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02730871
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Alcon Research
Sponsor organisation address	6201 S. Freeway, Fort Worth, TX, United States, 76134
Public contact	EMEA Regulatory Affairs, Alcon Eye Care UK Ltd, emea.ra@alcon.com
Scientific contact	EMEA Regulatory Affairs, Alcon Eye Care UK Ltd, emea.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	13 July 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 July 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to evaluate the additive intraocular pressure (IOP) lowering effect of Brinzolamide 1%/Brimonidine 0.2% (SIMBRINZA®) dosed twice daily (BID) when added to Travoprost 0.004%/Timolol 0.5% (DUOTRAV®) 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. 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	24 June 2016
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	Poland: 11
Country: Number of subjects enrolled	Spain: 20
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	Greece: 4
Country: Number of subjects enrolled	Argentina: 33
Country: Number of subjects enrolled	Australia: 2
Country: Number of subjects enrolled	Chile: 1
Country: Number of subjects enrolled	Colombia: 12
Country: Number of subjects enrolled	Malaysia: 6
Country: Number of subjects enrolled	Taiwan: 6
Country: Number of subjects enrolled	Italy: 23
Worldwide total number of subjects	134
EEA total number of subjects	74

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)	50
From 65 to 84 years	79
85 years and over	5

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited from sites located in Argentina, Australia, Belgium, Chile, Columbia, Germany, Greece, Italy, Malaysia, Poland, Spain, Taiwan, and the United Kingdom.

Pre-assignment

Screening details:

Of the 173 enrolled, 39 subjects were exited as screen failures prior to randomization. This reporting group includes all randomized and treated subjects (134).

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 + Duotrav

Arm description:

Brinzolamide 1%/brimonidine tartrate 0.2% ophthalmic suspension, 1 drop instilled 2 times per day in affected eye(s) (09:00 and 21:00 hrs) plus travoprost 0.004%/timolol 0.5% solution, 1 drop instilled in the affected eye(s) daily in the morning (at 9:00) or in the evening (at 21:00) for 42 days (Treatment Phase)

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

Dosage and administration details:

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

Investigational medicinal product name	Travoprost 0.004%/timolol 0.5% solution
Investigational medicinal product code	
Other name	DUOTRAV®
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ocular use

Dosage and administration details:

One drop instilled in the affected eye(s) daily in the morning (at 9:00) or in the evening (at 21:00) for 42 days (Treatment Phase)

Arm title	Vehicle + Duotrav

Arm description:

Brinzolamide/brimonidine vehicle, 1 drop instilled 2 times per day in affected eye(s) (09:00 and 21:00 hrs) plus travoprost 0.004%/timolol 0.5% solution, 1 drop instilled in the affected eye(s) daily in the morning (at 9:00) or in the evening (at 21:00) for 42 days (Treatment Phase)

Arm type	Placebo

Investigational medicinal product name	Brinzolamide/brimonidine vehicle
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, suspension
Routes of administration	Ocular use

Dosage and administration details:

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

Investigational medicinal product name	Travoprost 0.004%/timolol 0.5% solution
Investigational medicinal product code	
Other name	DUOTRAV®
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ocular use

Dosage and administration details:

One drop instilled in the affected eye(s) daily in the morning (at 9:00) or in the evening (at 21:00) for 42 days (Treatment Phase)

Number of subjects in period 1	Simbrinza + Duotrav	Vehicle + Duotrav
Started	67	67
Completed	61	67
Not completed	6	0
Adverse event, non-fatal	6	-

Baseline characteristics

Reporting groups	
Reporting group title	Simbrinza + Duotrav
Reporting group description:	
Brinzolamide 1%/brimonidine tartrate 0.2% ophthalmic suspension, 1 drop instilled 2 times per day in affected eye(s) (09:00 and 21:00 hrs) plus travoprost 0.004%/timolol 0.5% solution, 1 drop instilled in the affected eye(s) daily in the morning (at 9:00) or in the evening (at 21:00) for 42 days (Treatment Phase)	
Reporting group title	Vehicle + Duotrav
Reporting group description:	
Brinzolamide/brimonidine vehicle, 1 drop instilled 2 times per day in affected eye(s) (09:00 and 21:00 hrs) plus travoprost 0.004%/timolol 0.5% solution, 1 drop instilled in the affected eye(s) daily in the morning (at 9:00) or in the evening (at 21:00) for 42 days (Treatment Phase)	

Reporting group values	Simbrinza + Duotrav	Vehicle + Duotrav	Total
Number of subjects	67	67	134
Age categorical Units: Subjects			
Age continuous			
This analysis population includes all randomized subjects with a baseline assessment who completed at least 1 scheduled on-therapy visit (Full Analysis Set).			
Units: years			
arithmetic mean	65.7	65.7	
standard deviation	± 13.47	± 11.77	-
Gender categorical Units: Subjects			
Female	32	41	73
Male	35	26	61
Intraocular Pressure (IOP)			
IOP (fluid pressure inside the eye) was assessed using Goldmann applanation tonometry and reported in millimeters mercury (mmHg).			
Units: mmHg			
arithmetic mean	21.6	21.8	
standard deviation	± 1.78	± 1.90	-
IOP at 9:00 Hr			
IOP (fluid pressure inside the eye) was assessed at 09:00 using Goldmann applanation tonometry and reported in millimeters mercury (mmHg).			
Units: mmHg			
arithmetic mean	22.2	22.5	
standard deviation	± 1.84	± 1.80	-
IOP at 11:00 Hr			
IOP (fluid pressure inside the eye) was assessed at 11:00 using Goldmann applanation tonometry and reported in millimeters mercury (mmHg).			
Units: mmHg			
arithmetic mean	21.4	21.4	
standard deviation	± 1.93	± 2.26	-

End points

End points reporting groups

Reporting group title	Simbrinza + Duotrav
Reporting group description:	
Brinzolamide 1%/brimonidine tartrate 0.2% ophthalmic suspension, 1 drop instilled 2 times per day in affected eye(s) (09:00 and 21:00 hrs) plus travoprost 0.004%/timolol 0.5% solution, 1 drop instilled in the affected eye(s) daily in the morning (at 9:00) or in the evening (at 21:00) for 42 days (Treatment Phase)	
Reporting group title	Vehicle + Duotrav
Reporting group description:	
Brinzolamide/brimonidine vehicle, 1 drop instilled 2 times per day in affected eye(s) (09:00 and 21:00 hrs) plus travoprost 0.004%/timolol 0.5% solution, 1 drop instilled in the affected eye(s) daily in the morning (at 9:00) or in the evening (at 21:00) for 42 days (Treatment Phase)	

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

End point title	Mean Change From Baseline in Diurnal Intraocular Pressure (IOP) (Mean of Changes at 09:00 and 11:00 Time Points) at Week 6
End point description:	
IOP (fluid pressure inside the eye) was assessed using Goldmann applanation tonometry. Diurnal IOP change was defined as the average of the two changes from baseline (timepoints 9 AM, 11 AM). A more negative change from baseline indicates a greater improvement, i.e., a reduction of IOP. Only one eye (study eye) was used for the analyses. Full Analysis Set. At each time point, only subjects with a value at both baseline and that time point are included in the calculation of change.	
End point type	Primary
End point timeframe:	
Baseline, Week 6	

End point values	Simbrinza + Duotrav	Vehicle + Duotrav		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	67		
Units: mmHg				
arithmetic mean (standard deviation)	-4.5 (± 2.69)	-2.4 (± 3.01)		

Statistical analyses

Statistical analysis title	Mean Change From Baseline in Diurnal IOP
Comparison groups	Simbrinza + Duotrav v Vehicle + Duotrav

Number of subjects included in analysis	128
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.8
upper limit	-1.5
Variability estimate	Standard error of the mean
Dispersion value	0.342

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 assessed using Goldmann applanation tonometry. Diurnal IOP was defined as the average of the two time points measured (9 AM, 11 AM). A higher IOP can be a greater risk factor for developing glaucoma or glaucoma progression (leading to optic nerve damage). Only one eye (study eye) was used for the analyses. Full Analysis Set with non-missing values.

End point type	Secondary

End point timeframe:

Week 6

End point values	Simbrinza + Duotrav	Vehicle + Duotrav		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	67		
Units: mmHg				
arithmetic mean (standard deviation)	17.1 (± 2.96)	19.4 (± 3.45)		

Statistical analyses

Statistical analysis title	Mean Diurnal IOP at Week 6
Comparison groups	Simbrinza + Duotrav v Vehicle + Duotrav
Number of subjects included in analysis	128
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.15

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.8
upper limit	-1.5
Variability estimate	Standard error of the mean
Dispersion value	0.342

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

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

End point description:

IOP (fluid pressure inside the eye) was assessed using Goldmann applanation tonometry. Diurnal IOP percentage change was defined as the average of the two changes from baseline (timepoints 9 AM, 11 AM). A more negative percentage change from baseline indicates a greater improvement, i.e., a reduction of IOP. Only one eye (study eye) was used for the analyses. Full Analysis Set. At each time point, only subjects with a value at both baseline and that time point are included in the calculation of change.

End point type	Secondary

End point timeframe:

Baseline, Week 6

End point values	Simbrinza + Duotrav	Vehicle + Duotrav		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	67		
Units: percentage change				
arithmetic mean (standard deviation)	-20.7 (± 12.00)	-11.1 (± 13.86)		

Statistical analyses

Statistical analysis title	Mean Percentage Change From BL in Diurnal IOP

Statistical analysis description:

At Week 6

Comparison groups	Simbrinza + Duotrav v Vehicle + Duotrav
Number of subjects included in analysis	128
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-9.98

Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.1
upper limit	-6.9
Variability estimate	Standard error of the mean
Dispersion value	1.572

Secondary: Mean Change From Baseline in IOP (09:00, 11:00) at Week 6

End point title	Mean Change From Baseline in IOP (09:00, 11:00) at Week 6

End point description:

IOP (fluid pressure inside the eye) was assessed using Goldmann applanation tonometry. A more negative change from baseline indicates a greater improvement, i.e., a reduction of IOP. Only one eye (study eye) was used for the analyses. Full Analysis Set. At each time point, only subjects with a value at both baseline and that time point are included in the calculation of change.

End point type	Secondary

End point timeframe:

Baseline, Week 6

End point values	Simbrinza + Duotrav	Vehicle + Duotrav		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	67		
Units: mmHg				
arithmetic mean (standard deviation)				
Change from Baseline 9:00 Hr	-4.4 (± 3.07)	-3.2 (± 3.40)		
Change from Baseline 11:00 Hr	-5.4 (± 2.84)	-2.5 (± 2.98)		

Statistical analyses

Statistical analysis title	Change From Baseline in IOP at 09:00

Statistical analysis description:

At Week 6

Comparison groups	Simbrinza + Duotrav v Vehicle + Duotrav
Number of subjects included in analysis	128
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.022
Method	Repeated measures model
Parameter estimate	Mean difference (final values)
Point estimate	-1.33

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.5
upper limit	-0.2
Variability estimate	Standard error of the mean
Dispersion value	0.576

Statistical analysis title	Change From Baseline in IOP at 11:00
Statistical analysis description:	
At Week 6	
Comparison groups	Simbrinza + Duotrav v Vehicle + Duotrav
Number of subjects included in analysis	128
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Repeated measures model
Parameter estimate	Mean difference (final values)
Point estimate	-2.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.9
upper limit	-1.9
Variability estimate	Standard error of the mean
Dispersion value	0.506

Secondary: Mean Percentage Change From Baseline in IOP (09:00, 11:00) at Week 6

End point title	Mean Percentage Change From Baseline in IOP (09:00, 11:00) at Week 6
End point description:	
IOP (fluid pressure inside the eye) was assessed using Goldmann applanation tonometry. A more negative percentage change from baseline indicates a greater improvement, i.e., a reduction of IOP. Only one eye (study eye) was used for the analyses. Full Analysis Set. At each time point, only subjects with a value at both Baseline and that time point are included in the calculation of change.	
End point type	Secondary
End point timeframe:	
Baseline, Week 6	

End point values	Simbrinza + Duotrav	Vehicle + Duotrav		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61	67		
Units: percentage change				
arithmetic mean (standard deviation)				
Percent change at 9:00 Hr	-20.2 (± 13.56)	-14.1 (± 15.10)		
Percent change at 11:00 Hr	-25.0 (± 12.73)	-11.7 (± 13.63)		

Statistical analyses

Statistical analysis title	Percentage Change From Baseline in IOP at 09:00
Statistical analysis description: At Week 6	
Comparison groups	Simbrinza + Duotrav v Vehicle + Duotrav
Number of subjects included in analysis	128
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.018
Method	Repeated measures model
Parameter estimate	Mean difference (final values)
Point estimate	-6.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.2
upper limit	-1.1
Variability estimate	Standard error of the mean
Dispersion value	2.567

Statistical analysis title	Percentage Change from Baseline in IOP at 11:00
Comparison groups	Simbrinza + Duotrav v Vehicle + Duotrav
Number of subjects included in analysis	128
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Repeated measures model
Parameter estimate	Mean difference (final values)
Point estimate	-13.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.8
upper limit	-8.6
Variability estimate	Standard error of the mean
Dispersion value	2.34

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Baseline through study completion, an average of 42 days

Adverse event reporting additional description:

Adverse Events (AE) were obtained through solicited and spontaneous comments from subjects and through observations by the Investigator as outlined in the study protocol. Includes all subjects who received a dose of masked investigational product (Safety Analysis Set).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Simbrinza + Duotrav

Reporting group description:

Brinzolamide 1%/brimonidine tartrate 0.2% ophthalmic suspension, 1 drop instilled 2 times per day in affected eye(s) (09:00 and 21:00 hrs) plus travoprost 0.004%/timolol 0.5% solution, 1 drop instilled in the affected eye(s) daily in the morning (at 9:00) or in the evening (at 21:00) for 42 days (Treatment Phase)

Reporting group title	Vehicle + Duotrav

Reporting group description:

Brinzolamide/brimonidine vehicle, 1 drop instilled 2 times per day in affected eye(s) (09:00 and 21:00 hrs) plus travoprost 0.004%/timolol 0.5% solution, 1 drop instilled in the affected eye(s) daily in the morning (at 9:00) or in the evening (at 21:00) for 42 days (Treatment Phase)

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: No non-serious adverse events occurred greater than the 5% threshold.

Serious adverse events	Simbrinza + Duotrav	Vehicle + Duotrav	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 67 (0.00%)	1 / 67 (1.49%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 67 (0.00%)	1 / 67 (1.49%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Simbrinza + Duotrav	Vehicle + Duotrav	
Total subjects affected by non-serious adverse events subjects affected / exposed	0 / 67 (0.00%)	0 / 67 (0.00%)	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 April 2017	In order to facilitate subject recruitment, the amendment lowered the qualifying IOP criteria at both the Eligibility 1 and Eligibility 2 visits, removed the late day (15:00) IOP measurement time point reducing subject commitment, and allowed subjects currently on treatment with DUOTRAV for at least 28 days prior to screening in the morning or evening to be eligible for the study. To minimize unnecessary patient enrollment in the trial, an interim analysis was added at 50% completion to test for statistical differences between treatments. If it was achieved, the study enrollment would have been stopped and subjects in the study completed their visits.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported