Clinical trial results:
Open, Observer-blind, two Parallel Group, Randomized, Multicentric Clinical Phase III Trial on the Comparison of Efficacy and Tolerability of a New Preservative-free Formulation of Brimonidine 2 mg/ml Eye Drops vs. Alphagan™ Eye Drops in Patients with Open Angle Glaucoma or Ocular Hypertension

Summary

EudraCT number	2013-003083-31
Trial protocol	GR
Global end of trial date	12 December 2014

Results information

Result version number	v1 (current)
This version publication date	29 December 2021
First version publication date	29 December 2021

Trial information

Trial identification

Sponsor protocol code	Becro/OV/Brimo

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	OmniVision
Sponsor organisation address	Lindberghstraße 9, Puchheim, Germany, 82178
Public contact	CLINICAL TRIAL INFORMATION, BECRO, +30 2106729037, trials@becro.gr
Scientific contact	CLINICAL TRIAL INFORMATION, BECRO, +30 2106729037, trials@becro.gr

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	11 December 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 December 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of the clinical trial to confirm the clinical non-inferiority of the preservative-free Brimonidine containing eye drops compared with the marketed preservative-containing Alphagan™ eye drops by the average decrease of diurnal IOP measured between the first and last visit.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 September 2013
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	Greece: 170
Worldwide total number of subjects	170
EEA total number of subjects	170

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)	64
From 65 to 84 years	103
85 years and over	3

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 170 patients who met the inclusion and exclusion criteria signed the ICF and were selected for participation. All patients switched to monotherapy with Alphagan for four weeks (screening period with induction therapy) if not already on treatment with Alphagan (no screening period required).

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Assessor[1]

Blinding implementation details:

The clinical trial was performed as observer-blind because of the differences in the packaging of both drugs. The investigational medicinal product has a special container closure system. The clinical trial site has to have blind and not-blind clinical trial personnel. Blind personnel make all contacts with patients and perform all clinical trial-related examinations, whereas not-blind personnel are responsible for clinical trial medication distribution and collection.

Arms

Are arms mutually exclusive?	Yes
Arm title	Brimonidine

Arm description:

Preservative-free Brimonidine (2mg/ml) eye drops should be administered topically in the eye. The administration of the eye drops must be done as indicated: One drop in each eye twice daily, in the morning and evening approximately 12 hours apart.

Arm type	Experimental
Investigational medicinal product name	Preservative-free Brimonidine (2 mg/ml) eye drops
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops
Routes of administration	Topical use

Dosage and administration details:

Treatment will be eye drops, which should be administered topically in the eye. The administration of the eye drops must be done as indicated: One drop in each eye twice daily, in the morning and evening approximately 12 hours apart,

Arm title	Alphagan

Arm description:

Alphagan eye drops should be administered topically in the eye. The administration of the eye drops must be done as indicated: One drop in each eye twice daily, in the morning and evening approximately 12 hours apart.

Arm type	Active comparator
Investigational medicinal product name	Alphagan eye drops
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops
Routes of administration	Topical use

Dosage and administration details:

Treatment will be eye drops, which should be administered topically in the eye. The administration of the eye drops must be done as indicated: One drop in each eye twice daily, in the morning and evening

approximately 12 hours apart.

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: The clinical trial was performed as observer-blind because of the differences in the packaging of both drugs. The investigational medicinal product has a special container closure system. The clinical trial site has to have blind and not-blind clinical trial personnel. Blind personnel make all contacts with patients and perform all clinical trial-related examinations, whereas not-blind personnel are responsible for clinical trial medication distribution and collection.

Number of subjects in period 1	Brimonidine	Alphagan
Started	86	84
Completed	73	76
Not completed	13	8
Consent withdrawn by subject	6	2
High IOP	-	2
Adverse event, non-fatal	4	2
Lost to follow-up	1	2
Prohibited concomitant treatment	1	-
Protocol deviation	1	-

Baseline characteristics

Reporting groups

Reporting group title	Brimonidine

Reporting group description:

Preservative-free Brimonidine (2mg/ml) eye drops should be administered topically in the eye. The administration of the eye drops must be done as indicated: One drop in each eye twice daily, in the morning and evening approximately 12 hours apart.

Reporting group title	Alphagan

Reporting group description:

Alphagan eye drops should be administered topically in the eye. The administration of the eye drops must be done as indicated: One drop in each eye twice daily, in the morning and evening approximately 12 hours apart.

Reporting group values	Brimonidine	Alphagan	Total
Number of subjects	86	84	170
Age categorical Units: Subjects			
Adults (18-64 years)	32	32	64
From 65-84 years	52	51	103
85 years and over	2	1	3
Gender categorical Units: Subjects			
Female	51	48	99
Male	35	36	71

Subject analysis sets

Subject analysis set title	Per Protocol Population
Subject analysis set type	Per protocol

Subject analysis set description:

The per protocol (PP) population includes all those of the ITT population who had no major protocol violations, who completed IOP measurements within the allowed time frames, who completed at least 4 weeks of treatment with the last dose administered before the 4 week visit, and who did not take prohibited concurrent medication. The primary analysis is based on the PP population.

Subject analysis set title	Intent-to-treat (ITT) Population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The intent-to-treat (ITT) population includes all randomized patients who had at least one post baseline diurnal IOP-measurement.

Reporting group values	Per Protocol Population	Intent-to-treat (ITT) Population	
Number of subjects	149	170	
Age categorical Units: Subjects			
Adults (18-64 years)	56	64	
From 65-84 years	92	103	
85 years and over	1	3	

Gender categorical Units: Subjects			
Female	88	99	
Male	61	71	

End points

End points reporting groups

Reporting group title	Brimonidine

Reporting group description:

Preservative-free Brimonidine (2mg/ml) eye drops should be administered topically in the eye. The administration of the eye drops must be done as indicated: One drop in each eye twice daily, in the morning and evening approximately 12 hours apart.

Reporting group title	Alphagan

Reporting group description:

Alphagan eye drops should be administered topically in the eye. The administration of the eye drops must be done as indicated: One drop in each eye twice daily, in the morning and evening approximately 12 hours apart.

Subject analysis set title	Per Protocol Population
Subject analysis set type	Per protocol

Subject analysis set description:

The per protocol (PP) population includes all those of the ITT population who had no major protocol violations, who completed IOP measurements within the allowed time frames, who completed at least 4 weeks of treatment with the last dose administered before the 4 week visit, and who did not take prohibited concurrent medication. The primary analysis is based on the PP population.

Subject analysis set title	Intent-to-treat (ITT) Population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The intent-to-treat (ITT) population includes all randomized patients who had at least one post baseline diurnal IOP-measurement.

Primary: Mean diurnal IOP change from baseline to last visit

End point title	Mean diurnal IOP change from baseline to last visit

End point description:

The primary endpoint was the mean diurnal IOP change from baseline to last visit and the primary efficacy analysis was planned and carried out as a test of noninferiority.
Then, the analysis of covariance (ANCOVA) model was used to analyse the mean change in diurnal IOP with baseline IOP as the covariate, and treatment as factor. The treatment difference and a two-sided 95% confidence interval (CI) for the difference are calculated. The preservative-free Brimonidine eye drops (Test) is considered to be non-inferior to the marketed Alphagan™ including preservative (Reference), if the upper limit of the 95% CI of the difference is < ΔNI, where ΔNI=1.5 mmHg is the non-inferiority criterion. The ΔNI is non-inferiority margin and the value ΔNI=1.5 mmHg is the commonly used tolerance criterion in non-inferiority glaucoma studies.

End point type	Primary

End point timeframe:

from baseline to week 4

End point values	Brimonidine	Alphagan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	76		
Units: mmHg				
arithmetic mean (standard deviation)				
mean IOP at baseline	16.034 (± 2.140)	15.254 (± 2.605)		
mean IOP at week 1	15.575 (± 2.472)	15.450 (± 2.320)		
mean IOP at week 2	15.493 (± 2.301)	15.412 (± 2.221)		

mean IOP at week 4	15.370 (± 2.294)	15.489 (± 2.362)		

Statistical analyses

Statistical analysis title	Mean change in diurnal IOP

Statistical analysis description:

The main efficacy parameter, diurnal IOP, was evaluated at enrolment, baseline visit, each visit (weeks 1 and 2), and at the end of the treatment period (week 4). At baseline visit and during the following visits (weeks 1, 2 and 4) the IOP was measured at 8am, 12am and 16pm.
Then, the mean diurnal IOP was calculated using the measurements in both eyes. If only one eye fulfilled the criteria the mean was calculated using the measurements in the respective eye.

Comparison groups	Brimonidine v Alphagan
Number of subjects included in analysis	149
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	< 0.05
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.603
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.217
upper limit	0.012
Variability estimate	Standard deviation

Notes:

[1] - The preservative-free Brimonidine 0.2%w/v eye drops (Test, T) is considered to be non-inferior to the marketed Alphagan™ 0.2%w/v eye drops containing preservative (Reference, R), if the upper limit of the 95% CI of the difference (T-R) is < ΔNI, where ΔNI =1.5 mmHg is the non-inferiority criterion as defined in the study protocol.

Secondary: mean change in IOP between baseline and week 1

End point title	mean change in IOP between baseline and week 1

End point description:

A secondary efficacy end point was the mean change in IOP between baseline and week 1.

End point type	Secondary

End point timeframe:

From baseline to week 1

End point values	Brimonidine	Alphagan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	76		
Units: mmHg				
arithmetic mean (standard deviation)				
mean IOP at baseline	16.034 (± 2.140)	15.254 (± 2.605)		

mean IOP at week 1	15.575 (± 2.472)	15.450 (± 2.320)		

Statistical analyses

Statistical analysis title	Analysis of secondary end point, baseline to wk 1
Comparison groups	Brimonidine v Alphagan
Number of subjects included in analysis	149
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.05
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.424
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.985
upper limit	0.137
Variability estimate	Standard deviation

Secondary: mean change in IOP between baseline and week 2

End point title	mean change in IOP between baseline and week 2
End point description:	
End point type	Secondary
End point timeframe:	
From baseline to week 2	

End point values	Brimonidine	Alphagan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	76		
Units: mmHg				
arithmetic mean (standard deviation)				
mean IOP at baseline	16.034 (± 2.140)	15.254 (± 2.605)		
mean IOP at week 1	15.575 (± 2.472)	15.450 (± 2.320)		
mean IOP at week 2	15.493 (± 2.301)	15.412 (± 2.221)		

Statistical analyses

Statistical analysis title	Analysis of secondary end point, baseline to wk 2
Statistical analysis description:	
A secondary efficacy end point was the mean change in IOP between baseline and week 2.	
Comparison groups	Brimonidine v Alphagan
Number of subjects included in analysis	149
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.05
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.403
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.965
upper limit	0.159
Variability estimate	Standard deviation

Secondary: IOP at the end of the clinical trial

End point title	IOP at the end of the clinical trial
End point description:	
Proportion of patients with measured IOP <21 mmHg at the end of the clinical trial,	
End point type	Secondary
End point timeframe:	
End of trial	

End point values	Brimonidine	Alphagan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	76		
Units: percent				
number (not applicable)	100	98.7		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: All adverse events (AEs) that occurred during the study were documented.	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	12.1
Reporting groups	
Reporting group title	Preservative-free Brimonidine 0.2%
Reporting group description: Preservative-free Brimonidine 0.2% w/v eye drops solution	
Reporting group title	Alphagan™ 0.2%
Reporting group description: Alphagan™ 0.2% w/v eye drops solution	

Serious adverse events	Preservative-free Brimonidine 0.2%	Alphagan™ 0.2%	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 86 (0.00%)	0 / 84 (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: 0 %

Non-serious adverse events	Preservative-free Brimonidine 0.2%	Alphagan™ 0.2%	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 86 (23.26%)	16 / 84 (19.05%)	
Nervous system disorders			
Sleep disorder			
subjects affected / exposed	3 / 86 (3.49%)	5 / 84 (5.95%)	
occurrences (all)	3	5	
Eye disorders			
Conjunctival hyperaemia			
subjects affected / exposed	3 / 86 (3.49%)	3 / 84 (3.57%)	
occurrences (all)	3	3	
Burning			

subjects affected / exposed	4 / 86 (4.65%)	2 / 84 (2.38%)	
occurrences (all)	4	2	
Stinging			
subjects affected / exposed	0 / 86 (0.00%)	3 / 84 (3.57%)	
occurrences (all)	0	3	
Itching			
subjects affected / exposed	1 / 86 (1.16%)	1 / 84 (1.19%)	
occurrences (all)	1	1	
Lacrimation			
subjects affected / exposed	1 / 86 (1.16%)	0 / 84 (0.00%)	
occurrences (all)	1	0	
Eye irritation			
subjects affected / exposed	1 / 86 (1.16%)	2 / 84 (2.38%)	
occurrences (all)	1	2	
Eye dryness			
subjects affected / exposed	2 / 86 (2.33%)	2 / 84 (2.38%)	
occurrences (all)	2	2	
Lower eyelid edema			
subjects affected / exposed	1 / 86 (1.16%)	0 / 84 (0.00%)	
occurrences (all)	1	0	
Conjunctivitis			
subjects affected / exposed	2 / 86 (2.33%)	0 / 84 (0.00%)	
occurrences (all)	2	0	
Follicular conjunctivitis			
subjects affected / exposed	0 / 86 (0.00%)	1 / 84 (1.19%)	
occurrences (all)	0	1	
Periorbital redness			
subjects affected / exposed	1 / 86 (1.16%)	0 / 84 (0.00%)	
occurrences (all)	1	0	
Chemosis			
subjects affected / exposed	1 / 86 (1.16%)	1 / 84 (1.19%)	
occurrences (all)	1	1	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 86 (1.16%)	0 / 84 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported