



## Clinical trial results:

**Therapeutic Equivalence (non-inferiority), Randomized, Observer-blind, two Parallel Group, Clinical Trial for Comparing the Efficacy and Tolerability of a new Generic Formulation of 0.2% Brimonidine/0.5% Timolol fixed-Combination Eye Drops solution free of Preservatives vs. Combigan® Eye Drops solution in Patients with Open- Angle Glaucoma, or Ocular Hypertension, already on Treatment with IOP-lowering Drugs and Low Intraocular Pressure (IOP21 mmHg)**

### Summary

EudraCT number	2015-000160-34
Trial protocol	GR
Global end of trial date	17 June 2016

### 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/BRIMTIM
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#### 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	05 September 2016
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	17 June 2016
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To confirm the clinical non-inferiority of a generic fixed combination of Brimonidine 0.2%/Timolol 0.5% eye drops solution in single dose container which is preservative-free, compared to the marketed preservative-containing Combigan® eye drops solution in patients with open angle glaucoma, or ocular hypertension, already on treatment with IOP-lowering drugs and low intraocular pressure (IOP≤21 mmHg) by examining the average change of diurnal IOP from end of study to baseline.

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	08 June 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	Greece: 180
Worldwide total number of subjects	180
EEA total number of subjects	180

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)	60
From 65 to 84 years	117

85 years and over	3
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## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Patients who required screening period with induction therapy were administered Combigan® once daily for 4 weeks. Patients who were already on treatment with Combigan® required no screening period with induction therapy (enrolment visit coincides with baseline visit).

### 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 <sup>[1]</sup>

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 is a preservative-free preparation, which 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 non-blind personnel are responsible for clinical trial medication distribution.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Brimonidine/Timolol

Arm description:

A new preservative-free formulation of Brimonidine 0.2%/Timolol 0.5% fixed combination eye drops solution in the treatment of open angle glaucoma or intraocular hypertension.

Arm type	Experimental
Investigational medicinal product name	Preservative-free 0.2% Brimonidine/0.5% Timolol fixed-Combination eye drops solution
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, solution in single-dose container
Routes of administration	Topical use

Dosage and administration details:

The drops solution was administered topically in the eye. The administration of the eye drops was done as indicated: One drop in each eye twice daily, once in the morning and once in the evening approximately at 21:00 (about 12 hours apart). In order to ensure that the investigator ophthalmologists remained blinded, they were not allowed to dispense the clinical trial medications to the patients nor to perform the instillations. In each centre, the dispensation and instillation of the clinical trial medications was performed by a designated member of the investigator's staff.

<b>Arm title</b>	Combigan
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Arm description:

The preservative containing marketed medicinal product Combigan® eye drops solution in the treatment of open angle glaucoma or intraocular hypertension

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

Dosage and administration details:

The drops solution was administered topically in the eye. The administration of the eye drops was done

as indicated: One drop in each eye twice daily, once in the morning and once in the evening approximately at 21:00 (about 12 hours apart).

In order to ensure that the investigator ophthalmologists remained blinded, they were not allowed to dispense the clinical trial medications to the patients nor to perform the instillations. In each centre, the dispensation and instillation of the clinical trial medications was performed by a designated member of the investigator's staff.

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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 is a preservative-free preparation, which 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 non-blind personnel are responsible for clinical trial medication distribution.

<b>Number of subjects in period 1</b>	Brimonidine/Timolol	Combigan
Started	91	89
Completed	87	87
Not completed	4	2
Consent withdrawn by subject	3	2
Adverse event, non-fatal	1	-

## Baseline characteristics

### Reporting groups

Reporting group title	Brimonidine/Timolol
Reporting group description: A new preservative-free formulation of Brimonidine 0.2%/Timolol 0.5% fixed combination eye drops solution in the treatment of open angle glaucoma or intraocular hypertension.	
Reporting group title	Combigan
Reporting group description: The preservative containing marketed medicinal product Combigan® eye drops solution in the treatment of open angle glaucoma or intraocular hypertension	

Reporting group values	Brimonidine/Timolol	Combigan	Total
Number of subjects	91	89	180
Age categorical Units: Subjects			
Adults (18-64 years)	33	27	60
From 65-84 years	56	61	117
85 years and over	2	1	3
Gender categorical Units: Subjects			
Female	60	43	103
Male	31	46	77

### Subject analysis sets

Subject analysis set title	Per Protocol Population
Subject analysis set type	Per protocol
Subject analysis set description: 180 patients were randomized to treatment: 90 patients to Reference and 90 to Test. Sixteen (N=16) patients were excluded from the per protocol (PP) data set. Thus, in total 164 patients (Reference, N=82; Test, N=82) resulted in the PP data set.	
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) data set included all the randomized patients.	

Reporting group values	Per Protocol Population	Intent-to-treat (ITT) Population	
Number of subjects	164	180	
Age categorical Units: Subjects			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Gender categorical Units: Subjects			
Female	90	103	
Male	74	77	



## End points

### End points reporting groups

Reporting group title	Brimonidine/Timolol
Reporting group description: A new preservative-free formulation of Brimonidine 0.2%/Timolol 0.5% fixed combination eye drops solution in the treatment of open angle glaucoma or intraocular hypertension.	
Reporting group title	Combigan
Reporting group description: The preservative containing marketed medicinal product Combigan® eye drops solution in the treatment of open angle glaucoma or intraocular hypertension	
Subject analysis set title	Per Protocol Population
Subject analysis set type	Per protocol
Subject analysis set description: 180 patients were randomized to treatment: 90 patients to Reference and 90 to Test. Sixteen (N=16) patients were excluded from the per protocol (PP) data set. Thus, in total 164 patients (Reference, N=82; Test, N=82) resulted in the PP data set.	
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) data set included all the randomized patients.	

### 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 of the clinical trial was the difference between the investigational products with respect to change in mean diurnal IOP in the clinical trial eye(s) between the last visit and baseline.	
End point type	Primary
End point timeframe: between baseline and last visit	

End point values	Brimonidine/Ti molol	Combigan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	82		
Units: mmHg				
arithmetic mean (standard deviation)				
mean IOP at baseline	14.776 (± 2.436)	14.571 (± 2.219)		
mean IOP at week 1	14.199 (± 2.272)	13.949 (± 2.046)		
mean IOP at week 2	13.979 (± 2.175)	14.138 (± 1.926)		
mean IOP at week 4	13.979 (± 2.203)	13.810 (± 2.067)		

### Statistical analyses

<b>Statistical analysis title</b>	Mean change in diurnal IOP
Statistical analysis description:	
According to the clinical trial protocol non-inferiority was tested based on the PP data set. The primary endpoint is the mean diurnal IOP decrease from baseline to last visit. 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 were calculated.	
Comparison groups	Brimonidine/Timolol v Combigan
Number of subjects included in analysis	164
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.05
Method	ANCOVA
Parameter estimate	Median difference (final values)
Point estimate	0.066
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.488
upper limit	0.62
Variability estimate	Standard deviation

### 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:	
End point type	Secondary
End point timeframe:	
average change of diurnal IOP measured between baseline and week 1	

End point values	Brimonidine/Ti molol	Combigan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	82		
Units: mmHg				
arithmetic mean (standard deviation)				
mean IOP at baseline	14.776 (± 2.436)	14.571 (± 2.219)		
mean IOP at week 1	14.199 (± 2.272)	13.949 (± 2.046)		

### Statistical analyses

<b>Statistical analysis title</b>	Analysis of secondary end point, baseline to wk 1
Comparison groups	Brimonidine/Timolol v Combigan

Number of subjects included in analysis	164
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.05
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.121
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.368
upper limit	0.609
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:	
average change of diurnal IOP measured between baseline and week 2	

End point values	Brimonidine/Ti molol	Combigan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	82		
Units: mmHg				
arithmetic mean (standard deviation)				
mean IOP at baseline	14.776 (± 2.436)	14.571 (± 2.219)		
mean IOP at week 1	14.199 (± 2.272)	13.949 (± 2.046)		
mean IOP at week 2	13.979 (± 2.175)	14.138 (± 1.926)		

### Statistical analyses

Statistical analysis title	Analysis of secondary end point, baseline to wk 2
Comparison groups	Brimonidine/Timolol v Combigan

Number of subjects included in analysis	164
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.05
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.269
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.773
upper limit	0.235
Variability estimate	Standard deviation

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### Secondary: proportion of patients with measured IOP <21 mmHg at the end of study (week 4)

End point title	proportion of patients with measured IOP <21 mmHg at the end of study (week 4)
End point description:	proportion of patients with measured IOP <21 mmHg at the end of study (week 4)
End point type	Secondary
End point timeframe:	end of study (week 4)

End point values	Brimonidine/Ti molol	Combigan		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	82		
Units: percent				
number (not applicable)				
proportion of patients	100	100		

### 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
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	12.1
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### Reporting groups

Reporting group title	Brimonidine 0.2%/Timolol 0.5% (Test)
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Reporting group description:

In this clinical trial, 180 patients were randomized to treatment: 90 patients to Combigan® (Reference) and 90 to preservative-free fixed combination Brimonidine 0.2%/Timolol 0.5% (Test). However, one patient was randomized to Reference but this patient received the Test product; thus, N=91 patients received the Test and N=89 patients received the Reference.

Reporting group title	Combigan®
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Reporting group description:

In this clinical trial, 180 patients were randomized to treatment: 90 patients to Combigan® (Reference) and 90 to preservative-free fixed combination Brimonidine 0.2%/Timolol 0.5% (Test). However, one patient was randomized to Reference but this patient received the Test product; thus, N=91 patients received the Test and N=89 patients received the Reference.

Serious adverse events	Brimonidine 0.2%/Timolol 0.5%	Combigan®	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 91 (0.00%)	0 / 89 (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	Brimonidine 0.2%/Timolol 0.5%	Combigan®	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 91 (8.79%)	5 / 89 (5.62%)	
Eye disorders			
Irritation/Burning/Stinging sensation of the eye			
subjects affected / exposed	6 / 91 (6.59%)	4 / 89 (4.49%)	
occurrences (all)	6	4	
Foreign body sensation			

subjects affected / exposed	2 / 91 (2.20%)	0 / 89 (0.00%)	
occurrences (all)	2	0	
Dry eye			
subjects affected / exposed	0 / 91 (0.00%)	2 / 89 (2.25%)	
occurrences (all)	0	2	
Ocular hyperaemia			
subjects affected / exposed	1 / 91 (1.10%)	0 / 89 (0.00%)	
occurrences (all)	1	0	
Ocular lacrimation increased			
subjects affected / exposed	1 / 91 (1.10%)	0 / 89 (0.00%)	
occurrences (all)	1	0	
Eye pruritus			
subjects affected / exposed	1 / 91 (1.10%)	0 / 89 (0.00%)	
occurrences (all)	1	0	
Blurry vision			
subjects affected / exposed	1 / 91 (1.10%)	1 / 89 (1.12%)	
occurrences (all)	1	1	
Eye irritation			
subjects affected / exposed	1 / 91 (1.10%)	0 / 89 (0.00%)	
occurrences (all)	1	0	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported