



Clinical trial results:

A prospective, phase III, multicenter, randomized, investigator-masked, parallel groups, non-inferiority clinical trial for the comparison of efficacy and safety and of a generic fixed combination of Brinzolamide 10mg/ml / Timolol 5 mg/ml eye drops suspension versus Azarga®/ALCON 10mg/ml – 5mg/ml eye drops suspension in subjects with open angle glaucoma or ocular hypertension.

Summary

EudraCT number	2019-000921-39
Trial protocol	GR CY
Global end of trial date	12 April 2021

Results information

Result version number	v1 (current)
This version publication date	17 June 2022
First version publication date	17 June 2022

Trial information

Trial identification

Sponsor protocol code	PH-BRINLOL-01
-----------------------	---------------

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Pharmathen S.A
Sponsor organisation address	Dervenakion 6 , Pallini, Attica, Greece, 15351
Public contact	Lida Kalantzi, PhD Director of Scientific Affairs Pharmaceutical Research Operations / Finished F, PHARMATHEN SA, 0030 2106604300, lkalantzi@pharmathen.com
Scientific contact	Lida Kalantzi, PhD Director of Scientific Affairs Pharmaceutical Research Operations / Finished F, PHARMATHEN SA, 0030 2106604300, lkalantzi@pharmathen.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	No

1901/2006 apply to this trial?

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	05 July 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 April 2021
Global end of trial reached?	Yes
Global end of trial date	12 April 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to confirm the non-inferiority of the generic fixed combination of Brinzolamide 10mg/ml / Timolol 5mg/ml eye drops suspension (test product of Pharmathen S.A) in lowering the intra-ocular pressure (IOP) when compared to Brinzolamide 10mg/ml / Timolol 5mg/ml eye drops suspension marketed product Azarga® (reference product, ALCON) in subjects with open-angle glaucoma or ocular hypertension, by examining the mean diurnal IOP change from baseline to week 12 visit. The mean diurnal IOP change will be calculated as the average of the 08:00 a.m. and 10:00 a.m. time point measurements.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 August 2019
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	Cyprus: 1
Country: Number of subjects enrolled	Greece: 214
Worldwide total number of subjects	215
EEA total number of subjects	215

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)	63
From 65 to 84 years	146
85 years and over	6

Subject disposition

Recruitment

Recruitment details:

Greece : 13 Sites : Hospitals : G.Gennimatas Hospital, Agios Panteleimon, Papageorgiou, PAGNH Crete, 251 Air Force General Hospital, Evaggelismos, University General Hospital of Ioannina, General Hospital of Lamia, Tzaneio, AHEPA University General Hospital, Konstantopouleio, Hospital of Kerkyra Agia Eirini
Cyprus : 1 site : Pantheo Eye Center

Pre-assignment

Screening details:

Study was conducted in clinical sites in Greece and Cyprus from 22 August 2019 to 12 April 2021

Period 1

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

Blinding implementation details:

This was an investigator-masked study. The investigator (PI) at each site designated an independent site staff member to handle, store, dispense & collect the investigational products (IPs). He/she has been instructed NOT to disclose any details on the identity of the dispensed IP to other study staff including the investigator(s). The same instructions have been given to the patients.

Arms

Are arms mutually exclusive?	Yes
Arm title	Test

Arm description:

Brinzolamide 10mg/ml /Timolol 5mg/ml eye drops, suspension (Pharmathen S.A.)

Arm type	Test
Investigational medicinal product name	Brinzolamide 10mg/ml / Timolol 5 mg/ml eye drops suspension, Pharmathen S.A
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, suspension
Routes of administration	Ocular use

Dosage and administration details:

One drop in the conjunctival sac of the affected eye(s) BID

Arm title	Reference
------------------	-----------

Arm description:

Azarga®, Brinzolamide 10 mg/ml / Timolol 5 mg/ml eye drops suspension (Alcon)

Arm type	Active comparator
Investigational medicinal product name	Azarga®, Brinzolamide 10 mg/ml / Timolol 5 mg/ml eye drops suspension, Alcon
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, suspension
Routes of administration	Ocular use

Dosage and administration details:

One drop in the conjunctival sac of the affected eye(s) BID

Notes:

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

Justification: Due to differences in the packaging of study medication, the investigator measuring IOP was masked to study medication.

Number of subjects in period 1	Test	Reference
Started	107	108
Completed	91	80
Not completed	16	28
Consent withdrawn by subject	1	4
Physician decision	-	1
Adverse event, non-fatal	1	4
Circumstances defined as exclusion criterion	-	1
Lost to follow-up	1	2
Due to COVID-19 pandemic	8	12
Protocol deviation	5	4

Baseline characteristics

Reporting groups

Reporting group title	Test
Reporting group description: Brinzolamide 10mg/ml /Timolol 5mg/ml eye drops, suspension (Pharmathen S.A.)	
Reporting group title	Reference
Reporting group description: Azarga®, Brinzolamide 10 mg/ml / Timolol 5 mg/ml eye drops suspension (Alcon)	

Reporting group values	Test	Reference	Total
Number of subjects	107	108	215
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	35	28	63
From 65-84 years	71	75	146
85 years and over	1	5	6
Age continuous			
Units: years			
arithmetic mean	67.7	70.3	-
standard deviation	± 11.0	± 8.6	-
Gender categorical			
Units: Subjects			
Female	59	48	107
Male	48	60	108

Subject analysis sets

Subject analysis set title	Test_ITT_Population
Subject analysis set type	Intention-to-treat
Subject analysis set description: The Test_ ITT (Intention To Treat) population set is defined as all randomized patients, who have received the test product : Brinzolamide 10mg/ml /Timolol 5mg/ml eye drops, suspension (Pharmathen S.A.) and have at least one pre and post baseline efficacy measurement based on the protocol.	
Subject analysis set title	Reference_ITT Population
Subject analysis set type	Intention-to-treat
Subject analysis set description: The Reference_ ITT (Intention To Treat) population set is defined as all randomized patients, who have received the reference Azarga®, Brinzolamide 10 mg/ml / Timolol 5 mg/ml eye drops suspension (Alcon) and have at least one pre and post baseline efficacy measurement based on the protocol.	
Subject analysis set title	Test_Per_Protocol_Population

Subject analysis set type	Per protocol
---------------------------	--------------

Subject analysis set description:

The Test Per Protocol Population (PP) set consists of all randomized patients who received Brinzolamide 10mg/ml /Timolol 5mg/ml eye drops, suspension (Pharmathen S.A.) and completed all study primary efficacy endpoint assessments, without any major protocol deviation.

Subject analysis set title	Reference_Per_Protocol_Population
----------------------------	-----------------------------------

Subject analysis set type	Per protocol
---------------------------	--------------

Subject analysis set description:

The Reference Per Protocol (PP) Population set consists of all randomized patients who received Azarga®, Brinzolamide 10 mg/ml / Timolol 5 mg/ml eye drops suspension (Alcon) and completed all study primary efficacy endpoint assessments, without any major protocol deviation.

Reporting group values	Test_ITT_Population	Reference_ITT Population	Test_Per_Protocol_Population
Number of subjects	96	84	91
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	32	24	30
From 65-84 years	63	56	60
85 years and over	1	4	1
Age continuous Units: years			
arithmetic mean	79.14	67.31	67.5
standard deviation	± 11.01	± 8.97	± 11.1
Gender categorical Units: Subjects			
Female	52	35	41
Male	44	49	50

Reporting group values	Reference_Per_Protocol_Population		
Number of subjects	80		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	22		
From 65-84 years	54		
85 years and over	4		

Age continuous			
Units: years			
arithmetic mean	70.4		
standard deviation	± 9.0		
Gender categorical			
Units: Subjects			
Female	33		
Male	47		

End points

End points reporting groups

Reporting group title	Test
-----------------------	------

Reporting group description:

Brinzolamide 10mg/ml /Timolol 5mg/ml eye drops, suspension (Pharmathen S.A.)

Reporting group title	Reference
-----------------------	-----------

Reporting group description:

Azarga®, Brinzolamide 10 mg/ml / Timolol 5 mg/ml eye drops suspension (Alcon)

Subject analysis set title	Test_ITT_Population
----------------------------	---------------------

Subject analysis set type	Intention-to-treat
---------------------------	--------------------

Subject analysis set description:

The Test_ ITT (Intention To Treat) population set is defined as all randomized patients, who have received the test product : Brinzolamide 10mg/ml /Timolol 5mg/ml eye drops, suspension (Pharmathen S.A.) and have at least one pre and post baseline efficacy measurement based on the protocol.

Subject analysis set title	Reference_ITT Population
----------------------------	--------------------------

Subject analysis set type	Intention-to-treat
---------------------------	--------------------

Subject analysis set description:

The Reference_ ITT (Intention To Treat) population set is defined as all randomized patients, who have received the reference Azarga®, Brinzolamide 10 mg/ml / Timolol 5 mg/ml eye drops suspension (Alcon) and have at least one pre and post baseline efficacy measurement based on the protocol.

Subject analysis set title	Test_Per_Protocol_Population
----------------------------	------------------------------

Subject analysis set type	Per protocol
---------------------------	--------------

Subject analysis set description:

The Test Per Protocol Population (PP) set consists of all randomized patients who received Brinzolamide 10mg/ml /Timolol 5mg/ml eye drops, suspension (Pharmathen S.A.) and completed all study primary efficacy endpoint assessments, without any major protocol deviation.

Subject analysis set title	Reference_Per_Protocol_Population
----------------------------	-----------------------------------

Subject analysis set type	Per protocol
---------------------------	--------------

Subject analysis set description:

The Reference Per Protocol (PP) Population set consists of all randomized patients who received Azarga®, Brinzolamide 10 mg/ml / Timolol 5 mg/ml eye drops suspension (Alcon) and completed all study primary efficacy endpoint assessments, without any major protocol deviation.

Primary: Change in IOP in study eye from baseline (Week 0) to Week 12 (End of treatment) (Main Analysis)

End point title	Change in IOP in study eye from baseline (Week 0) to Week 12 (End of treatment) (Main Analysis)
-----------------	---

End point description:

The primary efficacy endpoint is the difference between test and reference product of the mean diurnal IOP change from baseline (week 0) to week 12 (End of treatment) visit, in study eye. The mean diurnal IOP change was calculated as the average of the 08:00 a.m. and 10:00 time point measurements at each visit (baseline, week 12).

End point type	Primary
----------------	---------

End point timeframe:

From baseline (Week 0) to week 12 (End of treatment)

End point values	Test_Per_Protocol_Population	Reference_Per_Protocol_Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	91	80		
Units: mmHg				
least squares mean (confidence interval 95%)	8.57 (8.11 to 9.03)	8.41 (7.92 to 8.90)		

Statistical analyses

Statistical analysis title	IOP change from W0 to W12 (Main analysis)
-----------------------------------	---

Statistical analysis description:

The analysis was performed using the average IOP measurements at 8:00am and 10:00am. Generalized Linear ANCOVA Model was employed with IOP reduction from W0 to W12 as dependent variable, treatment as fixed factor and baseline IOP as model covariate. The treatment difference and a two-sided 95% confidence interval (CI) for the difference were calculated. The non-inferiority was declared if the lower limit of the between-group difference in mean change from W0 to W12 in diurnal IOP was $> -1.5\text{mmHg}$

Comparison groups	Test_Per_Protocol_Population v Reference_Per_Protocol_Population
Number of subjects included in analysis	171
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[1]
Parameter estimate	Mean difference (final values)
Point estimate	0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.52
upper limit	0.83

Notes:

[1] - The prespecified noninferiority margin is $\delta = -1.5\text{ mmHg}$ is the commonly used and accepted tolerance criterion in non-inferiority glaucoma studies

Other pre-specified: Change in IOP in study eye from Week 0 (baseline) to Week 12 (End of treatment) (Sensitivity Analysis)

End point title	Change in IOP in study eye from Week 0 (baseline) to Week 12 (End of treatment) (Sensitivity Analysis)
-----------------	--

End point description:

The supportive endpoint is the difference between test and reference product of the mean diurnal IOP change from baseline (week 0) to week 12 (End of treatment) visit, in study eye. The mean diurnal IOP change was calculated as the average of the 08:00 a.m. and 10:00 a.m. and 16:00 time point measurements at each visit (baseline, week 12).

End point type	Other pre-specified
----------------	---------------------

End point timeframe:

Week 0 to Week 12

End point values	Test_ITT_Population	Reference_ITT Population	Test_Per_Protocol_Population	Reference_Per_Protocol_Population
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	96	84	91	80
Units: mmHg				
least squares mean (confidence interval 95%)	8.42 (8.00 to 8.86)	8.33 (7.86 to 8.80)	8.36 (7.90 to 8.81)	8.31 (7.83 to 8.79)

Statistical analyses

Statistical analysis title	IOP change from W0 to W12 (Sensitivity analysis)PP
Statistical analysis description:	
The analysis was performed using the average IOP measurements at 8:00am,10:00am and 16:00. Generalized Linear ANCOVA Model was employed with IOP reduction from W0 to W12 as dependent variable, treatment as fixed factor and baseline IOP as model covariate. The treatment difference and a two-sided 95% confidence interval for the difference were calculated. The non-inferiority was declared if the lower limit of the between-group difference in mean change from W0 to W12 in diurnal IOP is > -1.5mmHg	
Comparison groups	Reference_Per_Protocol_Population v Test_Per_Protocol_Population
Number of subjects included in analysis	171
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Mean difference (final values)
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.61
upper limit	0.71

Statistical analysis title	IOP change from W0to W12 (Sensitivity analysis)ITT
Statistical analysis description:	
The analysis was performed using the average IOP measurements at 8:00am,10:00am and 16:00. Generalized Linear ANCOVA Model was employed with IOP reduction from W0 to W12 as dependent variable, treatment as fixed factor and baseline IOP as model covariate. The treatment difference and a two-sided 95% confidence interval for the difference were calculated. The non-inferiority was declared if the lower limit of the between-group difference in mean change from W0 to W12 in diurnal IOP is > -1.5mmHg	
Comparison groups	Test_ITT_Population v Reference_ITT Population
Number of subjects included in analysis	180
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Mean difference (final values)
Point estimate	0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.54
upper limit	0.72

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Week 0 to week 12

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	24.0
--------------------	------

Reporting groups

Reporting group title	Test
-----------------------	------

Reporting group description: -

Reporting group title	Reference
-----------------------	-----------

Reporting group description: -

Serious adverse events	Test	Reference	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 107 (0.00%)	0 / 108 (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	Test	Reference	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 107 (23.36%)	19 / 108 (17.59%)	
Investigations			
Blood pressure increased			
subjects affected / exposed	0 / 107 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	
Heart rate decreased			
subjects affected / exposed	0 / 107 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	2	
Injury, poisoning and procedural complications			
Muscle strain			
subjects affected / exposed	0 / 107 (0.00%)	1 / 108 (0.93%)	
occurrences (all)	0	1	

Surgical and medical procedures Respiratory therapy subjects affected / exposed occurrences (all)	1 / 107 (0.93%) 1	0 / 108 (0.00%) 0	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	1 / 107 (0.93%) 2	0 / 108 (0.00%) 0	
General disorders and administration site conditions Therapeutic product ineffective subjects affected / exposed occurrences (all)	0 / 107 (0.00%) 0	1 / 108 (0.93%) 2	
Eye disorders Eye irritation subjects affected / exposed occurrences (all)	6 / 107 (5.61%) 8	0 / 108 (0.00%) 0	
Eye pain subjects affected / exposed occurrences (all)	6 / 107 (5.61%) 6	6 / 108 (5.56%) 6	
Foreign body sensation in eyes subjects affected / exposed occurrences (all)	4 / 107 (3.74%) 5	1 / 108 (0.93%) 1	
Vision blurred subjects affected / exposed occurrences (all)	4 / 107 (3.74%) 4	5 / 108 (4.63%) 6	
Chalazion subjects affected / exposed occurrences (all)	1 / 107 (0.93%) 1	0 / 108 (0.00%) 0	
Corneal epithelium defect subjects affected / exposed occurrences (all)	1 / 107 (0.93%) 1	0 / 108 (0.00%) 0	
Eye discharge subjects affected / exposed occurrences (all)	1 / 107 (0.93%) 1	2 / 108 (1.85%) 2	
Eye pruritus			

subjects affected / exposed occurrences (all)	1 / 107 (0.93%) 2	1 / 108 (0.93%) 1	
Lacrimation increased subjects affected / exposed occurrences (all)	1 / 107 (0.93%) 2	1 / 108 (0.93%) 1	
Ocular hyperaemia subjects affected / exposed occurrences (all)	1 / 107 (0.93%) 1	1 / 108 (0.93%) 1	
Photopsia subjects affected / exposed occurrences (all)	1 / 107 (0.93%) 1	0 / 108 (0.00%) 0	
Ocular discomfort subjects affected / exposed occurrences (all)	0 / 107 (0.00%) 0	1 / 108 (0.93%) 1	
Keratopathy subjects affected / exposed occurrences (all)	0 / 107 (0.00%) 0	1 / 108 (0.93%) 1	
Dry eye subjects affected / exposed occurrences (all)	0 / 107 (0.00%) 0	1 / 108 (0.93%) 1	
Dysgeusia subjects affected / exposed occurrences (all)	4 / 107 (3.74%) 5	1 / 108 (0.93%) 1	
Reproductive system and breast disorders Benign prostatic hyperplasia subjects affected / exposed occurrences (all)	0 / 107 (0.00%) 0	1 / 108 (0.93%) 1	
Psychiatric disorders Neurosis subjects affected / exposed occurrences (all)	0 / 107 (0.00%) 0	1 / 108 (0.93%) 1	
Infections and infestations Eyelid infection subjects affected / exposed occurrences (all)	0 / 107 (0.00%) 0	1 / 108 (0.93%) 1	
Herpes simplex			

subjects affected / exposed occurrences (all)	0 / 107 (0.00%) 0	1 / 108 (0.93%) 1	
Hordeolum subjects affected / exposed occurrences (all)	0 / 107 (0.00%) 0	1 / 108 (0.93%) 1	
Viral infection subjects affected / exposed occurrences (all)	0 / 107 (0.00%) 0	1 / 108 (0.93%) 1	
Urinary tract infection subjects affected / exposed occurrences (all)	1 / 107 (0.93%) 1	0 / 108 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 May 2019	Addition of investigational sites : University General Hospital of Ioannina, University Ophthalmology Clinic, Piraeus General Hospital "TZANEIO", Ophthalmology Clinic, University General Hospital of Thessaloniki AHEPA, Ophthalmology Clinic
08 January 2020	Addition of 2 clinical sites : Nea Ionia General Hospital Konstantopouleio - Patision, Ophthalmology Clinic and General Hospital Pammakaristos, Ophthalmology Clinic
25 February 2020	Additional of investigational site : Ophthalmology Clinic, Corfu General Hospital
03 August 2020	The amendment included : 1) Protocol revision , Information Form and Patient Consent Form (Main study) : Greek Version 2.0, dated 26 March 2020, 3) Extension of the duration of the clinical trial . The overall rationale of the amendment of the protocol aims to protect study patients of the study from COVID-19 by reducing risk of potential exposure to COVID-19. Visits that are not essential to the health and/or well-being of the participants have been changed from in-person visits to telephone visits. Duration of in-person visits at sites has been reduced by modifying required assessments. The mean diurnal IOP change will be calculated as the average of the 08:00 a.m. and 10:00 a.m. time point measurements at each visit. 16:00 p.m. time point measurement was removed as at trough (08:00 a.m.) and peak (+2h, 10:00 a.m.), IOP is expected to be at the highest and lowest points respectively, on the diurnal curve for most patients. In-Person Visits at Week2 and Week6 have been changed to telephone visits. Study medication compliance and subjects' well-being will be assessed during these visits. During the interview with the patients, if investigator deems necessary patient to proceed to an in-person visit, an unscheduled visit should be arranged and the appropriate assessments to take place. Secondary evaluation criterion of difference between test and reference of the mean diurnal IOP change from baseline to week 2 and week 6 has been removed. Secondary Efficacy Analysis of IOP timepoints at Week2 and Week6 has been removed. Additionally, pigmentary & pseudo-exfoliating open angle glaucoma were removed from exclusion criteria and added in inclusion criteria.
05 August 2020	Cyprus was added in participating countries

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported