Clinical trial results:
A PHASE III, MULTICENTRE, RANDOMISED, INVESTIGATOR-MASKED, CROSS- OVER, COMPARATIVE CLINICAL TRIAL EVALUATING THE EFFICACY AND SAFETY OF THE GENERIC BRINZOLAMIDE 10 MG/ML + TIMOLOL 5 MG/ML EYE DROPS SUSPENSION (AZAD PHARMA AG) WITH BRINZOLAMIDE 10 MG/ML + TIMOLOL 5 MG/ML EYE DROPS SUSPENSION AZARGA® (ALCON LTD) IN OPEN- ANGLE GLAUCOMA AND OCULAR HYPERTENSION PATIENTS

Summary

EudraCT number	2016-000946-69
Trial protocol	HU AT PL
Global end of trial date	22 August 2017

Results information

Result version number	v1 (current)
This version publication date	03 June 2022
First version publication date	03 June 2022
Summary attachment (see zip file)	2016-000946-69_summary of results (2016-000946-69_summary of results.pdf)

Trial information

Trial identification

Sponsor protocol code	AZ07

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	AZAD Pharma AG
Sponsor organisation address	Durachweg 15 , Schaffhausen , Switzerland, CH-8200
Public contact	Van Van Khov, AZAD Pharma AG, +41 52 632, contact@azad.ch
Scientific contact	Van Van Khov, AZAD Pharma AG, +41 52 632, contact@azad.ch

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	17 July 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 August 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to show non-inferiority of the test product AZAD (BT) versus the reference product Azarga in accordance with the "Guideline on the Choice of the Noninferiority Margin", section 3.2. "Two arm trials: test and reference" EMEA/CPMP/EWP/2158/99.

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. Exclusion criteria based on the experience of the approved, well known reference drug prevent harm to test subjects, which are not suited for the treatment. The test product is a generic version to the reference product.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 August 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: 31
Country: Number of subjects enrolled	Hungary: 22
Country: Number of subjects enrolled	Austria: 13
Worldwide total number of subjects	66
EEA total number of subjects	66

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)	42
From 65 to 84 years	24
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 79 patients were screened, thirteen (13) of them were screening failures. Sixty-six (N=66) patients were randomised and received at least one dose of the test or reference product, therefore 66 patients are defined as safety population (SAF).

Pre-assignment

Screening details:

The most common reason for screening failure was that one or more eligibility criteria were not met (N=8). Four (4) patients withdrew informed consent prior to starting treatment.

Pre-assignment period milestones

Number of subjects started	66
Number of subjects completed	64

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Physician decision: 2

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	Investigator[1]

Blinding implementation details:

The study is investigator-masked, since the commercially available Azarga® was used. Azarga® was relabelled according to GMP annex 13. The bottles were different. The investigators who were assigned to evaluate the efficacy and safety outcomes were masked (blinded), i.e. they did not know the identity of the product given to the patient, in order to avoid bias.

Arms

Are arms mutually exclusive?	Yes
Arm title	Period I, AZAD (BT) then AZARGA

Arm description:

AZAD (BT) then AZARGA

Arm type	crossover
Investigational medicinal product name	AZAD (BT) then AZARGA
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, suspension
Routes of administration	Ophthalmic use

Dosage and administration details:

1 drop per eye

Arm title	Period I, AZARGA then AZAD (BT)

Arm description:

AZARGA then AZAD (BT)

Arm type	crossover

No investigational medicinal product assigned in this arm

Notes:

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

Justification: The study is investigator-masked.

Number of subjects in period 1[2]	Period I, AZAD (BT) then AZARGA	Period I, AZARGA then AZAD (BT)
Started	35	29
Completed	30	25
Not completed	5	4
Protocol deviation	5	4

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: From the Safety Analysis Set 2 patients were withdrawn to the ITT set due to deviations from the ITT definitions.

Baseline characteristics

Reporting groups	
Reporting group title	Period I, AZAD (BT) then AZARGA
Reporting group description: AZAD (BT) then AZARGA	
Reporting group title	Period I, AZARGA then AZAD (BT)
Reporting group description: AZARGA then AZAD (BT)	

Reporting group values	Period I, AZAD (BT) then AZARGA	Period I, AZARGA then AZAD (BT)	Total
Number of subjects	35	29	64
Age categorical Units: Subjects			
18-75	35	29	64
Age continuous Units: years			
arithmetic mean	60.0	61.8	
standard deviation	± 11.18	± 11.76	-
Gender categorical Units: Subjects			
Female	22	16	38
Male	13	13	26

End points

End points reporting groups	
Reporting group title	Period I, AZAD (BT) then AZARGA
Reporting group description: AZAD (BT) then AZARGA	
Reporting group title	Period I, AZARGA then AZAD (BT)
Reporting group description: AZARGA then AZAD (BT)	

Primary: Primary Endpoint	
End point title	Primary Endpoint
End point description:	
End point type	Primary
End point timeframe: 42 days	

End point values	Period I, AZAD (BT) then AZARGA	Period I, AZARGA then AZAD (BT)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35	29		
Units: Non Inferior				
Non Inferior	35	29		

Statistical analyses

Statistical analysis title	Non-inferiority Margin mean IOP
Comparison groups	Period I, AZARGA then AZAD (BT) v Period I, AZAD (BT) then AZARGA
Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.167 [1]
Method	ANCOVA
Parameter estimate	Mean difference (final values)

Notes:

[1] - The difference in IOP lowering effect between the two treatments was not significant (p-value 0.167 > 0.05) and the lower limit of the confidence interval was within the non-inferiority margin (-0.162 > -1.5 mm Hg).

Adverse events

Adverse events information	
Timeframe for reporting adverse events: whole study timeframe	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.0
Reporting groups	
Reporting group title	AZAD Test product
Reporting group description: -	
Reporting group title	AZARGA Reference
Reporting group description: -	

Serious adverse events	AZAD Test product	AZARGA Reference	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 65 (0.00%)	0 / 64 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

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

Non-serious adverse events	AZAD Test product	AZARGA Reference	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 65 (60.00%)	36 / 64 (56.25%)	
Nervous system disorders			
Headache			
subjects affected / exposed	10 / 65 (15.38%)	7 / 64 (10.94%)	
occurrences (all)	10	7	
Eye disorders			
blurred vision			
subjects affected / exposed	39 / 65 (60.00%)	36 / 64 (56.25%)	
occurrences (all)	39	36	
Dysgeusia			
subjects affected / exposed	19 / 65 (29.23%)	14 / 64 (21.88%)	
occurrences (all)	19	14	
eye itching			

subjects affected / exposed	6 / 65 (9.23%)	7 / 64 (10.94%)	
occurrences (all)	6	7	
eyes stingeling			
subjects affected / exposed	7 / 65 (10.77%)	6 / 64 (9.38%)	
occurrences (all)	7	6	
Eye pain			
subjects affected / exposed	4 / 65 (6.15%)	0 / 64 (0.00%)	
occurrences (all)	4	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