Clinical trial results:
Non-inferiority, Randomized, Observer-blind, two Parallel Group, Clinical Trial for Comparing the Efficacy and Tolerability of a new Generic BAC-free Formulation of Latanoprost 0.05 mg/mL eye drops, solution in single-dose container vs Xalatan® eye drops in Patients with Open Angle Glaucoma or Ocular Hypertension

Summary

EudraCT number	2020-004307-14
Trial protocol	GR
Global end of trial date	30 December 2021

Results information

Result version number	v1 (current)
This version publication date	24 August 2023
First version publication date	24 August 2023

Trial information

Trial identification

Sponsor protocol code	BECRO/ACT/LATANOS

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	actrevo GmbH
Sponsor organisation address	Großer Burstah 25, Hamburg, Germany, 20457
Public contact	actrevo GmbH, actrevo GmbH, +49 4022864810, info@actrevo.com
Scientific contact	actrevo GmbH, actrevo GmbH, +49 4022864810, info@actrevo.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	25 February 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 December 2021
Global end of trial reached?	Yes
Global end of trial date	30 December 2021
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 BAC-free formulation of Latanoprost 0.05 mg/mL eye drops, solution in single-dose container with the marketed preservative-containing Xalatan® eye drops in patients with open angle glaucoma or ocular hypertension (IOP ≥22 mmHg) by examining the change of IOP at 08:00 am 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, the International Conference on Harmonisation (ICH) and the further guidelines in place on Good Clinical Practice (GCP). All the local regulatory requirements pertinent to the safety of trial subjects were followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 June 2021
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)	60
From 65 to 84 years	103

85 years and over	7

Subject disposition

Recruitment

Recruitment details:

This was an observer-blind, two parallel group, randomized, multi-centre clinical phase III trial planned to enrol 170 patients. Patients diagnosed with open-angle glaucoma or ocular hypertension and IOP ≥22 mmHg were selected to participate in the study.

Pre-assignment

Screening details:

A total of 170 patients who met the inclusion and exclusion criteria signed the ICF and were initially selected to participate in the study. No screening period with induction therapy was foreseen.

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 study was performed as observer-blind because of the differences in the packaging of IMPs. The test product was a preservative-free preparation in single-dose container whereas the reference product was supplied as multi-dose bottle. In the clinical trial site, there were "blind" and "non-blind" clinical trial staff. The "blind" staff contacted the patients and perform all trial-related examinations while the "non-blind" staff was responsible for distributing the drugs (IMPs).

Arms

Are arms mutually exclusive?	Yes
Arm title	Latanoprost

Arm description:

A new preservative-free formulation of Latanoprost 0.05 mg/mL eye drops, solution in single-dose container in the treatment of open-angle glaucoma or ocular hypertension.

Arm type	Experimental
Investigational medicinal product name	Preservative-free Latanoprost 0.05 mg/mL eye drops, solution
Investigational medicinal product code	
Other name	BAC-free Latanoprost 0.05 mg/mL eye drops, solution
Pharmaceutical forms	Eye drops, solution in single-dose container
Routes of administration	Ophthalmic use

Dosage and administration details:

Product was self-administered by the patient as indicated: One drop in the affected eye(s) once daily in the evening.

Arm title	Xalatan®

Arm description:

The preserved medicinal product Xalatan® in the treatment of open-angle glaucoma or ocular hypertension. The reference product is marketed in a multi-dose bottle.

Arm type	Active comparator
Investigational medicinal product name	Xalatan® eye drops, solution
Investigational medicinal product code	
Other name	BAC-preserved Latanoprost 0.05 mg/mL eye drops, solution
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ophthalmic use

Dosage and administration details:

Product was self-administered by the patient as indicated: One drop in the affected eye(s) once daily in the evening.

Notes:
[1] - The roles blinded appear inconsistent with a simple blinded trial.
Justification: The study design was "observer-blind".

Number of subjects in period 1	Latanoprost	Xalatan®
Started	86	84
Completed	84	82
Not completed	2	2
Physician decision	1	-
ICF withdrawal	1	-
Lost to follow-up	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Latanoprost
Reporting group description:	
A new preservative-free formulation of Latanoprost 0.05 mg/mL eye drops, solution in single-dose container in the treatment of open-angle glaucoma or ocular hypertension.	
Reporting group title	Xalatan®
Reporting group description:	
The preserved medicinal product Xalatan® in the treatment of open-angle glaucoma or ocular hypertension. The reference product is marketed in a multi-dose bottle.	

Reporting group values	Latanoprost	Xalatan®	Total
Number of subjects	86	84	170
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)	29	31	60
From 65-84 years	53	50	103
85 years and over	4	3	7
Age continuous Units: years			
arithmetic mean	68.02	67.17	
standard deviation	± 10.70	± 11.67	-
Gender categorical Units: Subjects			
Female	44	36	80
Male	42	48	90

Subject analysis sets	
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) analysis includes all randomized patients who had at least one post-baseline IOP measurement.	
Subject analysis set title	Per protocol (PP) population
Subject analysis set type	Per protocol
Subject analysis set description:	
The per protocol (PP) analysis includes all those of the ITT population who had no major protocol violations, who completed IOP measurements, who completed at least 12 weeks of treatment with the last dose administered before the 12-week visit, and who did not take prohibited concurrent medication.	
Subject analysis set title	Safety population (SP)
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population (SP) comprises all patients who have received at least 1 eye drop of the test or the reference medication.

Reporting group values	Intent-to-treat (ITT) population	Per protocol (PP) population	Safety population (SP)
Number of subjects	169	151	170
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)	60	54	60
From 65-84 years	102	90	103
85 years and over	7	7	7
Age continuous Units: years			
arithmetic mean	67.52	67.68	67.60
standard deviation	± 11.15	± 11.04	± 11.16
Gender categorical Units: Subjects			
Female	79	69	80
Male	90	82	90

End points

End points reporting groups

Reporting group title	Latanoprost
Reporting group description:	
A new preservative-free formulation of Latanoprost 0.05 mg/mL eye drops, solution in single-dose container in the treatment of open-angle glaucoma or ocular hypertension.	
Reporting group title	Xalatan®
Reporting group description:	
The preserved medicinal product Xalatan® in the treatment of open-angle glaucoma or ocular hypertension. The reference product is marketed in a multi-dose bottle.	
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) analysis includes all randomized patients who had at least one post-baseline IOP measurement.	
Subject analysis set title	Per protocol (PP) population
Subject analysis set type	Per protocol
Subject analysis set description:	
The per protocol (PP) analysis includes all those of the ITT population who had no major protocol violations, who completed IOP measurements, who completed at least 12 weeks of treatment with the last dose administered before the 12-week visit, and who did not take prohibited concurrent medication.	
Subject analysis set title	Safety population (SP)
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety population (SP) comprises all patients who have received at least 1 eye drop of the test or the reference medication.	

Primary: Change in IOP in study eye from baseline to last visit

End point title	Change in IOP in study eye from baseline to last visit
End point description:	
The primary endpoint for evaluating the efficacy was the change in IOP at 08:00 am in study eye from end of treatment (week 12) to baseline (week 0) in subjects treated with the test product as compared to subjects treated with the reference product. According to the clinical protocol, the non-inferiority of the test product was evaluated based on the intent-to-treat (ITT) population.	
End point type	Primary
End point timeframe:	
Between baseline (week 0) to last visit (week 12)	

End point values	Latanoprost	Xalatan®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86	83		
Units: mmHg				
arithmetic mean (standard deviation)				
IOP 08:00 am (baseline)	24.94 (± 1.80)	24.63 (± 2.15)		
IOP 08:00 am (week 2)	18.12 (± 2.77)	17.83 (± 3.39)		
IOP 08:00 am (week 6)	17.65 (± 2.77)	17.22 (± 3.17)		
IOP 08:00 am (last visit)	16.57 (± 2.91)	16.70 (± 3.25)		

Statistical analyses

Statistical analysis title	Change in IOP in study eye

Statistical analysis description:

The primary endpoint is the change in IOP at 08:00 am in study eye from end of treatment (week 12) to baseline (week 0) in subjects treated with the test product as compared to subjects treated with the reference product. The analysis of covariance (ANCOVA) model was used to analyse the change in IOP with baseline IOP as the covariate, and treatment as a factor. The treatment difference and a two-sided 95 % confidence interval (CI) for the difference have been calculated.

Comparison groups	Latanoprost v Xalatan®
Number of subjects included in analysis	169
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	< 0.05 [2]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.547
upper limit	0.994
Variability estimate	Standard deviation

Notes:

[1] - The generic preservative-free test product Latanoprost 0.05 mg/mL eye drops, solution in single-dose container is considered to be non-inferior to the marketed reference Xalatan® (preserved with BAC) if the upper limit of the 95 % CI of the difference is <1.5 mmHg. The primary analysis is based on the ITT analysis; the per protocol (PP) analysis is used to validate the results of the ITT analysis.

[2] - A statistical result is considered significant at P <0.05.

Adverse events

Adverse events information	
Timeframe for reporting adverse events: All adverse events occurring during the clinical study were documented.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups	
Reporting group title	Latanoprost
Reporting group description: Test product	
Reporting group title	Xalatan®
Reporting group description: Reference product	

Serious adverse events	Latanoprost	Xalatan®	
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	Latanoprost	Xalatan®	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	40 / 86 (46.51%)	50 / 84 (59.52%)	
Investigations			
Intraocular pressure increased			
subjects affected / exposed	1 / 86 (1.16%)	1 / 84 (1.19%)	
occurrences (all)	1	1	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 86 (1.16%)	0 / 84 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			

Instillation site foreign body sensation			
subjects affected / exposed	0 / 86 (0.00%)	1 / 84 (1.19%)	
occurrences (all)	0	1	
Instillation site pain			
subjects affected / exposed	6 / 86 (6.98%)	7 / 84 (8.33%)	
occurrences (all)	6	7	
Eye disorders			
Abnormal sensation in eye			
subjects affected / exposed	5 / 86 (5.81%)	1 / 84 (1.19%)	
occurrences (all)	5	1	
Blepharitis			
subjects affected / exposed	2 / 86 (2.33%)	1 / 84 (1.19%)	
occurrences (all)	2	1	
Conjunctival hyperaemia			
subjects affected / exposed	1 / 86 (1.16%)	0 / 84 (0.00%)	
occurrences (all)	1	0	
Conjunctival haemorrhage			
subjects affected / exposed	1 / 86 (1.16%)	0 / 84 (0.00%)	
occurrences (all)	1	0	
Dry eye			
subjects affected / exposed	5 / 86 (5.81%)	6 / 84 (7.14%)	
occurrences (all)	5	6	
Erythema of eyelid			
subjects affected / exposed	2 / 86 (2.33%)	2 / 84 (2.38%)	
occurrences (all)	2	2	
Eye irritation			
subjects affected / exposed	4 / 86 (4.65%)	5 / 84 (5.95%)	
occurrences (all)	4	5	
Eye pain			
subjects affected / exposed	1 / 86 (1.16%)	13 / 84 (15.48%)	
occurrences (all)	1	13	
Eye pruritus			
subjects affected / exposed	4 / 86 (4.65%)	4 / 84 (4.76%)	
occurrences (all)	4	4	
Foreign body sensation in eyes			

subjects affected / exposed	4 / 86 (4.65%)	17 / 84 (20.24%)	
occurrences (all)	4	17	
Lacrimation increased			
subjects affected / exposed	1 / 86 (1.16%)	0 / 84 (0.00%)	
occurrences (all)	1	0	
Ocular hyperaemia			
subjects affected / exposed	9 / 86 (10.47%)	6 / 84 (7.14%)	
occurrences (all)	9	6	
Vision blurred			
subjects affected / exposed	5 / 86 (5.81%)	1 / 84 (1.19%)	
occurrences (all)	5	1	
Visual impairment			
subjects affected / exposed	2 / 86 (2.33%)	3 / 84 (3.57%)	
occurrences (all)	2	3	
Respiratory, thoracic and mediastinal disorders			
Sinusitis			
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