Clinical trial results:
A Multi-Center, Investigator-Masked, Randomized, Crossover, Equivalence Study of the Safety and Efficacy of Once Daily Brimonidine Tartrate 0.35% Ophthalmic Suspension Compared with Brimonidine Tartrate 0.1% Ophthalmic Solution (Alphagan® P 0.1%) Dosed Three Times Daily in Subjects with Open Angle Glaucoma, Chronic Angle Closure Glaucoma with Patent Iridotomy/Iridectomy, or Ocular Hypertension

Summary

EudraCT number	2015-005540-34
Trial protocol	BG
Global end of trial date	04 September 2017

Results information

Result version number	v1 (current)
This version publication date	14 February 2019
First version publication date	14 February 2019

Trial information

Trial identification

Sponsor protocol code	CLR_14_12

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Sun Pharma Advanced Research Company Limited
Sponsor organisation address	17/B, Mahal Industrial Estate, Off Mahakali Caves Road, near Paperbox, Andheri (E), Mumbai, India, 400093
Public contact	Hany Michail, Sun Pharma Advanced Research Company Limited, 9987096080 609664-1042, clinical.trials@sparcmail.com
Scientific contact	Hany Michail, Sun Pharma Advanced Research Company Limited, 9987096080 609664-1042, clinical.trials@sparcmail.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	08 June 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 June 2017
Global end of trial reached?	Yes
Global end of trial date	04 September 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Evaluate the safety and diurnal IOP efficacy of once daily (QD) dosing with brimonidine tartrate 0.35% ophthalmic suspension compared with brimonidine tartrate 0.1% dosed 3 times a day (TID) in subjects with chronic open-angle glaucoma, chronic angle closure glaucoma with patent iridotomy/iridectomy, pseudoexfoliation, pigment dispersion, or ocular hypertension.

Protection of trial subjects:

In order to minimize potential risk to patients due to IOP elevations during the washout period, investigator could choose to substitute a parasympathomimetic or carbonic anhydrase inhibitor in place of a sympathomimetic, alpha-agonist, beta-adrenergic agent, or prostaglandin.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 July 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	Bulgaria: 137
Worldwide total number of subjects	137
EEA total number of subjects	137

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)	136
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Of the enrolled 137 subjects, 135 subjects completed period 1 and 134 subjects completed period 2.

Pre-assignment

Screening details:

Three subjects were screen failures.
Two subjects did not meet selection criteria and one subject did not attend the randomization visit for rescreening.

Period 1

Period 1 title	Period 1
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind[1]
Roles blinded	Investigator, Data analyst[2]

Blinding implementation details:

This was an Investigator masked study.
Randomized subjects received the study treatments from an unmasked dosing technician.
Adequate measures were taken to ensure that the statistician performing the final analysis remained masked.

Arms

Are arms mutually exclusive?	Yes
Arm title	Brimonidine 0.35%

Arm description:

Brimonidine tartrate 0.35% ophthalmic suspension (brimonidine suspension (brimonidine 0.35%), QD

Arm type	Experimental
Investigational medicinal product name	brimonidine 0.35%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ophthalmic use

Dosage and administration details:

Brimonidine tartrate 0.35% ophthalmic suspension (brimonidine 0.35%), QD

Arm title	Alphagan

Arm description:

alphagan 0.1%

Arm type	Active comparator
Investigational medicinal product name	brimonidine 0.35%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ophthalmic use

Dosage and administration details:

Brimonidine tartrate 0.35% ophthalmic suspension (brimonidine 0.35%), QD

Notes:

[1] - The number of roles blinded appears inconsistent with a single blinded trial. It is expected that there will be one role blinded in a single blind trial.
Justification: The investigator personally did not retrieve or review the study medication diary. Statistician performing final analysis was masked.

An unmasked dosing technician instilled the in-office physician dispensing doses in a room separate from evaluating investigator in order to maintain investigator-masking.

Subjects in brimonidine 0.35% group were taken into the dosing room at different time points, however, received study medication at the 8.00 AM time point only.

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

Justification: This was an investigator masked study. Subjects received treatment on visits from an unmasked dosing technician.
The investigator personally did not review diary.
designated study personnel collected and reviewed the diary at each visit to ensure treatment compliance.
Statistician performing the final analysis remained masked.
The randomization code for all subjects was unmasked only after all subjects completed the study and all data was recorded in the database and locked.

Number of subjects in period 1	Brimonidine 0.35%	Alphagan
Started	70	67
Completed	69	66
Not completed	1	1
Consent withdrawn by subject	-	1
Adverse event, non-fatal	1	-

Period 2	
Period 2 title	Period 2
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind[3]
Roles blinded	Data analyst, Investigator

Arms	
Are arms mutually exclusive?	Yes
Arm title	Period 2 - Brimonidine 0.35%

Arm description:

Brimonidine tartrate 0.35% ophthalmic suspension (brimonidine suspension (brimonidine 0.35%), QD

Arm type	Experimental
Investigational medicinal product name	brimonidine 0.35%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ophthalmic use

Dosage and administration details:

Brimonidine tartrate 0.35% ophthalmic suspension (brimonidine 0.35%), QD

Arm title	Period 2 - Alphagan

Arm description:

alphagan 0.1%

Arm type	Active comparator

Investigational medicinal product name	Alphagan P® 0.1%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ophthalmic use

Dosage and administration details:

Brimonidine tartrate 0.1% ophthalmic solution (Alphagan P® 0.1%), TID.

Notes:

[3] - The roles blinded appear to be inconsistent with a double blind trial.

Justification: The investigator personally did not retrieve or review the study medication diary. Statistician performing final analysis was masked.

An unmasked dosing technician instilled the in-office physician dispensing doses in a room separate from evaluating investigator in order to maintain investigator-masking.

Subjects in brimonidine 0.35% group were taken into the dosing room at different time points, however, received study medication at the 8.00 AM time point only.

Number of subjects in period 2	Period 2 - Brimonidine 0.35%	Period 2 - Alphagan
Started	69	66
Completed	68	66
Not completed	1	0
Adverse event, serious fatal	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Brimonidine 0.35%
Reporting group description:	
Brimonidine tartrate 0.35% ophthalmic suspension (brimonidine suspension (brimonidine 0.35%), QD	
Reporting group title	Alphagan
Reporting group description:	
alphagan 0.1%	

Reporting group values	Brimonidine 0.35%	Alphagan	Total
Number of subjects	70	67	137
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)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	63.7	65.3	
standard deviation	± 10.85	± 10.17	-
Gender categorical Units: Subjects			
Female	42	47	89
Male	28	20	48

End points

End points reporting groups

Reporting group title	Brimonidine 0.35%
Reporting group description: Brimonidine tartrate 0.35% ophthalmic suspension (brimonidine suspension (brimonidine 0.35%), QD	
Reporting group title	Alphagan
Reporting group description: alphagan 0.1%	
Reporting group title	Period 2 - Brimonidine 0.35%
Reporting group description: Brimonidine tartrate 0.35% ophthalmic suspension (brimonidine suspension (brimonidine 0.35%), QD	
Reporting group title	Period 2 - Alphagan
Reporting group description: alphagan 0.1%	
Subject analysis set title	Intent to treat population
Subject analysis set type	Intention-to-treat
Subject analysis set description: all subjects who were randomized into the study	

Primary: Intraocular pressure

End point title	Intraocular pressure
End point description:	
End point type	Primary
End point timeframe: Baseline to 84 days	

End point values	Brimonidine 0.35%	Alphagan	Period 2 - Brimonidine 0.35%	Period 2 - Alphagan
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	70	63	68	66
Units: mean				
arithmetic mean (standard deviation)	15.64 (± 2.861)	15.73 (± 2.669)	15.47 (± 2.692)	15.85 (± 2.936)

Statistical analyses

Statistical analysis title	Summary statistics
Statistical analysis description: Intraocular pressure measurements were summarized using continuous summary statistics by visit and time point for each eye	
Comparison groups	Brimonidine 0.35% v Alphagan

Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9567
Method	t-test, 1-sided
Parameter estimate	t-test
Dispersion value	0.9567

Secondary: Mean intraocular pressure at Day 14

End point title	Mean intraocular pressure at Day 14
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to Day 14	

End point values	Brimonidine 0.35%	Alphagan	Period 2 - Brimonidine 0.35%	Period 2 - Alphagan
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	70	67	68	66
Units: mean				
arithmetic mean (standard deviation)	15.97 (± 2.939)	16.49 (± 2.962)	15.57 (± 3.046)	15.80 (± 2.833)

Statistical analyses

No statistical analyses for this end point

Secondary: Mean intraocular pressure at Day 28

End point title	Mean intraocular pressure at Day 28
End point description:	
End point type	Secondary
End point timeframe:	
Baseline to day 28	

End point values	Brimonidine 0.35%	Alphagan	Period 2 - Brimonidine 0.35%	Period 2 - Alphagan
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	70	67	68	66
Units: mean				
arithmetic mean (standard deviation)	15.70 (± 2.855)	15.91 (± 2.523)	15.17 (± 3.030)	15.54 (± 3.029)

Statistical analyses

No statistical analyses for this end point

Secondary: Mean intraocular pressure at Day 42

End point title	Mean intraocular pressure at Day 42

End point description:

End point type	Secondary

End point timeframe:

Baseline to Day 42

End point values	Brimonidine 0.35%	Alphagan	Period 2 - Brimonidine 0.35%	Period 2 - Alphagan
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	70	67	68	66
Units: mean				
arithmetic mean (standard deviation)	15.25 (± 2.818)	15.86 (± 2.522)	15.55 (± 3.195)	16.00 (± 3.064)

Statistical analyses

No statistical analyses for this end point

Secondary: Mean intraocular pressure at Day 56

End point title	Mean intraocular pressure at Day 56

End point description:

End point type	Secondary

End point timeframe:

Baseline to day 56

End point values	Brimonidine 0.35%	Alphagan	Period 2 - Brimonidine 0.35%	Period 2 - Alphagan
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	70	67	68	66
Units: mean				
arithmetic mean (standard deviation)	15.21 (± 2.467)	15.60 (± 2.272)	15.38 (± 3.128)	15.76 (± 3.092)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 84 days	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0
Reporting groups	
Reporting group title	Brimonidine 0.35%
Reporting group description: -	
Reporting group title	Alphagan P
Reporting group description: -	
Reporting group title	Period 2 - Brimonidine 0.35%
Reporting group description: -	
Reporting group title	Period 2 - Alphagan P
Reporting group description: -	

Serious adverse events	Brimonidine 0.35%	Alphagan P	Period 2 - Brimonidine 0.35%
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 70 (1.43%)	0 / 67 (0.00%)	0 / 66 (0.00%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	1	0	0
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	1 / 70 (1.43%)	0 / 67 (0.00%)	0 / 66 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0

Serious adverse events	Period 2 - Alphagan P		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 68 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	0 / 68 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Brimonidine 0.35%	Alphagan P	Period 2 - Brimonidine 0.35%
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 70 (51.43%)	41 / 67 (61.19%)	22 / 66 (33.33%)
Nervous system disorders			
Somnolence			
subjects affected / exposed	13 / 70 (18.57%)	5 / 67 (7.46%)	5 / 66 (7.58%)
occurrences (all)	15	5	5
Eye disorders			
ocular hyperaemia			
subjects affected / exposed	23 / 70 (32.86%)	26 / 67 (38.81%)	12 / 66 (18.18%)
occurrences (all)	26	25	13
Gastrointestinal disorders			
Dry mouth			
subjects affected / exposed	16 / 70 (22.86%)	17 / 67 (25.37%)	9 / 66 (13.64%)
occurrences (all)	20	20	10

Non-serious adverse events	Period 2 - Alphagan P		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 68 (23.53%)		
Nervous system disorders			
Somnolence			
subjects affected / exposed	3 / 68 (4.41%)		
occurrences (all)	3		
Eye disorders			
ocular hyperaemia			
subjects affected / exposed	10 / 68 (14.71%)		
occurrences (all)	10		
Gastrointestinal disorders			
Dry mouth			
subjects affected / exposed	9 / 68 (13.24%)		
occurrences (all)	11		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 July 2016	All subjects in the study were enrolled as per the Amendment 1 of the protocol dated 16 Jul 2016.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported