

**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 (\pm 2.855) | 15.91 (\pm 2.523) | 15.17 (\pm 3.030) | 15.54 (\pm 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 (\pm 2.818) | 15.86 (\pm 2.522) | 15.55 (\pm 3.195) | 16.00 (\pm 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