



Clinical trial results:

A Prospective Randomized Placebo Controlled Study to Evaluate the Effect of Celecoxib on the Efficacy and Safety of Amlodipine in Subjects with Hypertension Requiring Antihypertensive Therapy

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2013-005381-19 |
| Trial protocol | GB |
| Global end of trial date | 19 November 2015 |

Results information

| | |
|--------------------------------|-------------------|
| Result version number | v1 (current) |
| This version publication date | 13 September 2018 |
| First version publication date | 13 September 2018 |

Trial information

Trial identification

| | |
|-----------------------|---------------|
| Sponsor protocol code | KIT-302-03-01 |
|-----------------------|---------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02172040 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Kitov Pharma Ltd |
| Sponsor organisation address | One Azriele Center, Round Tower, Floor 23, Derech Menachem Begin 132, Tel Aviv, Israel, 6701101 |
| Public contact | Chief Medical Officer/US Agent, Kitov Pharma Ltd, +1 202-965-2215, paul@kitovpharma.com |
| Scientific contact | Chief Medical Officer/US Agent, Kitov Pharma Ltd, +1 202-965-2215, paul@kitovpharma.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 | 19 November 2015 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 19 November 2015 |
| Global end of trial reached? | Yes |
| Global end of trial date | 19 November 2015 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary efficacy objective of this study was to demonstrate that the mean reduction in average daytime (9:00 to 21:00) ambulatory systolic blood pressure (SBPday) after oral administration of amlodipine tablets (10 mg) and celecoxib capsules (200 mg) given together once a day (qd) for 14 days in adult subjects with newly diagnosed hypertension was no less than half the mean reduction in SBPday after oral administration of amlodipine tablets (10 mg) given alone (i.e., with matched celecoxib placebo) qd for 14 days in the same population.

The primary safety objective of this study was to evaluate the safety of amlodipine tablets and celecoxib capsules given together qd for 14 days.

Protection of trial subjects:

This study was in compliance with the ethical principles derived from the principles of Good Clinical Practice (GCP) [current International Conference of Harmonization (ICH) guidelines], and the Declaration of Helsinki (1964) including all amendments up to and including the October 2013 revision.

All local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

The safety assessments included clinical laboratory tests (hematology, serum chemistry and urinalysis), Electrocardiogram, Physical examination findings, Orthostatic Hypotension measurements and Vital signs. Adverse events were monitored throughout the study.

Background therapy:

None

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 18 June 2014 |
| 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 | United Kingdom: 152 |
| Worldwide total number of subjects | 152 |
| EEA total number of subjects | 152 |

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) | 124 |
| From 65 to 84 years | 28 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

This study was conducted across 11 sites in the United Kingdom. The first patient first visit was on the 18th June 2014. The last patient last visit was on the 19th November 2015.

Pre-assignment

Screening details:

Subjects underwent assessments to determine eligibility at the Initial Screening Visit (Day -7 to -2; 458 subjects), Final Screening Visit (Day -1; 228 subjects), and the morning prior to randomization (Study Day 0; 227 subjects). A total of 306 subjects were screen failures and the remaining 152 were randomized.

Period 1

| | |
|------------------------------|--|
| Period 1 title | Period 1 (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Assessor |

Blinding implementation details:

Blinding of the subject and Investigational staff to treatment was achieved by using over-encapsulated (OE) formulations and matched placebo capsules. The appearance of the OE amlodipine tablets and matched placebo capsules were identical. Similarly, the appearance of the OE celecoxib capsules and matched placebo capsules were identical. Each patient kit, and the 2 bottles of study drug within the kit, were labeled in a manner to maintain blinding of the subject and Investigational staff.

Arms

| | |
|------------------------------|----------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Amlodipine+Celecoxib |

Arm description:

Over-encapsulated 10 mg amlodipine besylate tablet + over-encapsulated 200 mg celecoxib capsule once a day for two weeks

Over-encapsulated 10 mg amlodipine besylate tablet: Over-encapsulated 10 mg amlodipine besylate tablet once a day for two weeks

Over-encapsulated 200 mg celecoxib capsule: Over-encapsulated 200 mg celecoxib capsule once a day for two weeks

| | |
|--|------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | OE 10mg amlodipine besylate tablet |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

Over-encapsulated 10 mg amlodipine besylate tablet once a day for two weeks

| | |
|--|----------------------------|
| Investigational medicinal product name | OE 200mg celecoxib capsule |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

Over-encapsulated 200 mg celecoxib capsule once a day for two weeks

| | |
|------------------|--------------------|
| Arm title | Amlodipine+Placebo |
|------------------|--------------------|

Arm description:

Over-encapsulated 10 mg amlodipine besylate tablet + matched placebo capsule for over-encapsulated celecoxib capsule once a day for two weeks

Over-encapsulated 10 mg amlodipine besylate tablet: Over-encapsulated 10 mg amlodipine besylate tablet once a day for two weeks

Matched placebo capsule for over-encapsulated celecoxib capsule: Matched placebo capsule for over-encapsulated celecoxib capsule once a day for two weeks

| | |
|--|------------------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | OE 10mg amlodipine besylate tablet |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

Over-encapsulated 10 mg amlodipine besylate tablet once a day for two weeks

| | |
|--|--|
| Investigational medicinal product name | Matched placebo capsule for OE celecoxib capsule |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

Matched placebo capsule for over-encapsulated celecoxib capsule once a day for two weeks

| | |
|------------------|-------------------|
| Arm title | Placebo+Celecoxib |
|------------------|-------------------|

Arm description:

Matched placebo capsule for over-encapsulated amlodipine besylate tablet + over-encapsulated 200 mg celecoxib capsule once a day for two weeks

Over-encapsulated 200 mg celecoxib capsule: Over-encapsulated 200 mg celecoxib capsule once a day for two weeks

Matched placebo capsule for over-encapsulated amlodipine besylate tablet: Matched placebo capsule for over-encapsulated amlodipine besylate tablet once a day for two weeks

| | |
|--|--|
| Arm type | Placebo comparator |
| Investigational medicinal product name | Matched placebo capsule for OE amlodipine tablet |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

Matched placebo capsule for over-encapsulated amlodipine besylate tablet once a day for two weeks.

| | |
|--|----------------------------|
| Investigational medicinal product name | OE 200mg celecoxib capsule |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

Over-encapsulated 200 mg celecoxib capsule once a day for two weeks.

| | |
|------------------|-----------------|
| Arm title | Placebo+Placebo |
|------------------|-----------------|

Arm description:

Matched placebo capsule for over-encapsulated amlodipine besylate tablet + matched placebo capsule for over-encapsulated celecoxib capsule once a day for two weeks

Matched placebo capsule for over-encapsulated celecoxib capsule: Matched placebo capsule for over-encapsulated celecoxib capsule once a day for two weeks

Matched placebo capsule for over-encapsulated amlodipine besylate tablet: Matched placebo capsule for over-encapsulated amlodipine besylate tablet once a day for two weeks

| | |
|--|--|
| Arm type | Sham comparator |
| Investigational medicinal product name | Matched placebo capsule for OE celecoxib capsule |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

Matched placebo capsule for over-encapsulated celecoxib capsule once a day for two weeks

| | |
|--|--|
| Investigational medicinal product name | Matched placebo capsule for OE amlodipine tablet |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

Matched placebo capsule for over-encapsulated amlodipine besylate tablet once a day for two weeks

| Number of subjects in period 1 | Amlodipine+Celecoxib | Amlodipine+Placebo | Placebo+Celecoxib |
|---------------------------------------|----------------------|--------------------|-------------------|
| Started | 49 | 45 | 31 |
| Completed | 49 | 42 | 29 |
| Not completed | 0 | 3 | 2 |
| Consent withdrawn by subject | - | - | 1 |
| Adverse event, non-fatal | - | 2 | - |
| Family emergency abroad | - | - | - |
| Not available for Day 13 & 14 visits | - | - | 1 |
| Protocol deviation | - | 1 | - |

| Number of subjects in period 1 | Placebo+Placebo |
|---------------------------------------|-----------------|
| Started | 27 |
| Completed | 26 |
| Not completed | 1 |
| Consent withdrawn by subject | - |
| Adverse event, non-fatal | - |
| Family emergency abroad | 1 |
| Not available for Day 13 & 14 visits | - |
| Protocol deviation | - |

Baseline characteristics

Reporting groups

| | |
|-----------------------|----------------------|
| Reporting group title | Amlodipine+Celecoxib |
|-----------------------|----------------------|

Reporting group description:

Over-encapsulated 10 mg amlodipine besylate tablet + over-encapsulated 200 mg celecoxib capsule once a day for two weeks

Over-encapsulated 10 mg amlodipine besylate tablet: Over-encapsulated 10 mg amlodipine besylate tablet once a day for two weeks

Over-encapsulated 200 mg celecoxib capsule: Over-encapsulated 200 mg celecoxib capsule once a day for two weeks

| | |
|-----------------------|--------------------|
| Reporting group title | Amlodipine+Placebo |
|-----------------------|--------------------|

Reporting group description:

Over-encapsulated 10 mg amlodipine besylate tablet + matched placebo capsule for over-encapsulated celecoxib capsule once a day for two weeks

Over-encapsulated 10 mg amlodipine besylate tablet: Over-encapsulated 10 mg amlodipine besylate tablet once a day for two weeks

Matched placebo capsule for over-encapsulated celecoxib capsule: Matched placebo capsule for over-encapsulated celecoxib capsule once a day for two weeks

| | |
|-----------------------|-------------------|
| Reporting group title | Placebo+Celecoxib |
|-----------------------|-------------------|

Reporting group description:

Matched placebo capsule for over-encapsulated amlodipine besylate tablet + over-encapsulated 200 mg celecoxib capsule once a day for two weeks

Over-encapsulated 200 mg celecoxib capsule: Over-encapsulated 200 mg celecoxib capsule once a day for two weeks

Matched placebo capsule for over-encapsulated amlodipine besylate tablet: Matched placebo capsule for over-encapsulated amlodipine besylate tablet once a day for two weeks

| | |
|-----------------------|-----------------|
| Reporting group title | Placebo+Placebo |
|-----------------------|-----------------|

Reporting group description:

Matched placebo capsule for over-encapsulated amlodipine besylate tablet + matched placebo capsule for over-encapsulated celecoxib capsule once a day for two weeks

Matched placebo capsule for over-encapsulated celecoxib capsule: Matched placebo capsule for over-encapsulated celecoxib capsule once a day for two weeks

Matched placebo capsule for over-encapsulated amlodipine besylate tablet: Matched placebo capsule for over-encapsulated amlodipine besylate tablet once a day for two weeks

| Reporting group values | Amlodipine+Celecoxib | Amlodipine+Placebo | Placebo+Celecoxib |
|--|----------------------|--------------------|-------------------|
| Number of subjects | 49 | 45 | 31 |
| 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) | 37 | 35 | 28 |

| | | | |
|---|-------|-------|-------|
| From 65-84 years | 12 | 10 | 3 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous Units: years | | | |
| arithmetic mean | 57.7 | 57.3 | 54.9 |
| standard deviation | ± 8.0 | ± 9.4 | ± 8.2 |
| Gender categorical Units: Subjects | | | |
| Female | 17 | 19 | 10 |
| Male | 32 | 26 | 21 |
| Race Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 3 | 0 | 1 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 0 | 2 | 1 |
| White | 46 | 43 | 29 |
| More than one race | 0 | 0 | 0 |
| Unknown or not reported | 0 | 0 | 0 |
| Region of Enrollment Units: Subjects | | | |
| United Kingdom | 49 | 45 | 31 |
| Average Daytime (9:00 to 21:00) Ambulatory Systolic Blood Pressure (SBPday) Units: mmHg | | | |
| arithmetic mean | 148.7 | 147.6 | 150.8 |
| standard deviation | ± 7.4 | ± 8.7 | ± 8.9 |

| Reporting group values | Placebo+Placebo | Total | |
|--|-----------------|-------|--|
| Number of subjects | 27 | 152 | |
| Age categorical Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 24 | 124 | |
| From 65-84 years | 3 | 28 | |
| 85 years and over | 0 | 0 | |
| Age continuous Units: years | | | |
| arithmetic mean | 52.5 | - | |
| standard deviation | ± 9.1 | | |
| Gender categorical Units: Subjects | | | |
| Female | 10 | 56 | |

| | | | |
|------|----|----|--|
| Male | 17 | 96 | |
|------|----|----|--|

| | | | |
|---|-------|-----|--|
| Race | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | |
| Asian | 1 | 5 | |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | |
| Black or African American | 0 | 3 | |
| White | 26 | 144 | |
| More than one race | 0 | 0 | |
| Unknown or not reported | 0 | 0 | |
| Region of Enrollment | | | |
| Units: Subjects | | | |
| United Kingdom | 27 | 152 | |
| Average Daytime (9:00 to 21:00) Ambulatory Systolic Blood Pressure (SBPday) | | | |
| Units: mmHg | | | |
| arithmetic mean | 147.3 | | |
| standard deviation | ± 8.4 | - | |

End points

End points reporting groups

| | |
|---|----------------------|
| Reporting group title | Amlodipine+Celecoxib |
| Reporting group description: | |
| Over-encapsulated 10 mg amlodipine besylate tablet + over-encapsulated 200 mg celecoxib capsule once a day for two weeks | |
| Over-encapsulated 10 mg amlodipine besylate tablet: Over-encapsulated 10 mg amlodipine besylate tablet once a day for two weeks | |
| Over-encapsulated 200 mg celecoxib capsule: Over-encapsulated 200 mg celecoxib capsule once a day for two weeks | |
| Reporting group title | Amlodipine+Placebo |
| Reporting group description: | |
| Over-encapsulated 10 mg amlodipine besylate tablet + matched placebo capsule for over-encapsulated celecoxib capsule once a day for two weeks | |
| Over-encapsulated 10 mg amlodipine besylate tablet: Over-encapsulated 10 mg amlodipine besylate tablet once a day for two weeks | |
| Matched placebo capsule for over-encapsulated celecoxib capsule: Matched placebo capsule for over-encapsulated celecoxib capsule once a day for two weeks | |
| Reporting group title | Placebo+Celecoxib |
| Reporting group description: | |
| Matched placebo capsule for over-encapsulated amlodipine besylate tablet + over-encapsulated 200 mg celecoxib capsule once a day for two weeks | |
| Over-encapsulated 200 mg celecoxib capsule: Over-encapsulated 200 mg celecoxib capsule once a day for two weeks | |
| Matched placebo capsule for over-encapsulated amlodipine besylate tablet: Matched placebo capsule for over-encapsulated amlodipine besylate tablet once a day for two weeks | |
| Reporting group title | Placebo+Placebo |
| Reporting group description: | |
| Matched placebo capsule for over-encapsulated amlodipine besylate tablet + matched placebo capsule for over-encapsulated celecoxib capsule once a day for two weeks | |
| Matched placebo capsule for over-encapsulated celecoxib capsule: Matched placebo capsule for over-encapsulated celecoxib capsule once a day for two weeks | |
| Matched placebo capsule for over-encapsulated amlodipine besylate tablet: Matched placebo capsule for over-encapsulated amlodipine besylate tablet once a day for two weeks | |

Primary: Mean Change in Average Daytime (9:00 to 21:00) Ambulatory Systolic Blood Pressure (SBPday) - Primary Endpoint [Time Frame: Baseline and 2 weeks]

| | |
|---|--|
| End point title | Mean Change in Average Daytime (9:00 to 21:00) Ambulatory Systolic Blood Pressure (SBPday) - Primary Endpoint [Time Frame: Baseline and 2 weeks] |
| End point description: | |
| Intent-to-treat (ITT): All randomized subjects who received at least 1 dose of study drug and had at least a valid baseline ambulatory blood pressure monitor measurement (ABPM) and either: a) a valid Day 13-14 ABPM, where subject completed treatment or b) a valid Day 6-7 or Day 0-1 ABPM, where subject was withdrawn early. | |
| End point type | Primary |
| End point timeframe: | |
| Baseline and 2 weeks | |

| End point values | Amlodipine+Celecoxib | Amlodipine+Placebo | Placebo+Celecoxib | Placebo+Placebo |
|--------------------------------------|----------------------|--------------------|-------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 49 | 45 | 30 | 26 |
| Units: mmHg | | | | |
| arithmetic mean (standard deviation) | | | | |
| Mean Change in Average SBPday | -10.6 (± 9.2) | -8.83 (± 8.13) | -0.5 (± 8.8) | -2.11 (± 8.2) |

Statistical analyses

| Statistical analysis title | StatisticalAnalysis1 Mean Change in Average SBPday |
|----------------------------|--|
|----------------------------|--|

Statistical analysis description:

A serial gatekeeping strategy was used for the primary efficacy endpoint analysis. The primary comparison was a two-sample t-test to test the one-sided hypothesis that treatment with amlodipine + celecoxib was non-inferior to half of the effect achieved with amlodipine.

| | |
|---|---|
| Comparison groups | Amlodipine+Celecoxib v Amlodipine+Placebo |
| Number of subjects included in analysis | 94 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[1] |
| P-value | = 0.001 |
| Method | t-test, 1-sided |

Notes:

[1] - Non-inferiority margin definition: lower limit of the 95% confidence interval (CI) for amlodipine + celecoxib arm did not cross the 50% value for the amlodipine arm.

| Statistical analysis title | StatisticalAnalysis2 Mean Change in Average SBPday |
|----------------------------|--|
|----------------------------|--|

Statistical analysis description:

A serial gatekeeping strategy was used for the primary efficacy endpoint analysis. The secondary comparison was a two-sample t-test to test the one-sided hypothesis that treatment with placebo was superior to treatment with celecoxib. This was only to be performed if statistical significance was achieved for the primary comparison.

| | |
|---|-------------------------------------|
| Comparison groups | Placebo+Celecoxib v Placebo+Placebo |
| Number of subjects included in analysis | 56 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.491 |
| Method | t-test, 1-sided |

Primary: Frequency of Adverse Events (Number of Subjects Affected/Number of Subjects at Risk) [Time Frame: 1 month]

| | |
|-----------------|--|
| End point title | Frequency of Adverse Events (Number of Subjects Affected/Number of Subjects at Risk) [Time Frame: 1 month] |
|-----------------|--|

End point description:

Including any untoward medical occurrence in a subject administered study drug, which do not necessarily have a causal relationship with the study drug [i.e., any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of

the study drug, whether or not related to the study drug].

Safety population: all randomized subjects who received at least one dose of study drug.

| | |
|----------------------|---------|
| End point type | Primary |
| End point timeframe: | |
| 1 month | |

| End point values | Amlodipine+Celecoxib | Amlodipine+Placebo | Placebo+Celecoxib | Placebo+Placebo |
|-----------------------------|----------------------|--------------------|-------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 49 | 45 | 31 | 27 |
| Units: Subjects | | | | |
| number (not applicable) | | | | |
| Frequency of Adverse Events | 27 | 28 | 14 | 10 |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | StatisticalAnalysis1 Frequency of Adverse Events |
| Comparison groups | Amlodipine+Celecoxib v Amlodipine+Placebo v Placebo+Celecoxib v Placebo+Placebo |
| Number of subjects included in analysis | 152 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.166 |
| Method | Chi-squared |

Secondary: Mean Change in Average 24-hour Ambulatory Systolic Blood Pressure (SBP24h) [Time Frame: Baseline and 2 weeks]

| | |
|--|---|
| End point title | Mean Change in Average 24-hour Ambulatory Systolic Blood Pressure (SBP24h) [Time Frame: Baseline and 2 weeks] |
| End point description: | |
| ITT population as described for primary outcome. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline and 2 weeks | |

| End point values | Amlodipine+Celecoxib | Amlodipine+Placebo | Placebo+Celecoxib | Placebo+Placebo |
|--------------------------------------|----------------------|--------------------|-------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 49 | 45 | 30 | 26 |
| Units: mmHg | | | | |
| arithmetic mean (standard deviation) | | | | |
| Mean Change in Average SBP24h | -10.3 (± 8.9) | -8.02 (± 7.6) | -0.5 (± 7.8) | -1.19 (± 5.87) |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | StatisticalAnalysis1 Mean Change in Average SBP24h |
| Comparison groups | Amlodipine+Celecoxib v Amlodipine+Placebo |
| Number of subjects included in analysis | 94 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.177 |
| Method | t-test, 1-sided |

| | |
|---|--|
| Statistical analysis title | StatisticalAnalysis2 Mean Change in Average SBP24h |
| Comparison groups | Amlodipine+Celecoxib v Placebo+Celecoxib |
| Number of subjects included in analysis | 79 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | t-test, 1-sided |

| | |
|---|--|
| Statistical analysis title | StatisticalAnalysis3 Mean Change in Average SBP24h |
| Comparison groups | Amlodipine+Celecoxib v Placebo+Placebo |
| Number of subjects included in analysis | 75 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | t-test, 1-sided |

| | |
|---|--|
| Statistical analysis title | StatisticalAnalysis4 Mean Change in Average SBP24h |
| Comparison groups | Amlodipine+Placebo v Placebo+Celecoxib |
| Number of subjects included in analysis | 75 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | t-test, 1-sided |

| | |
|-----------------------------------|--|
| Statistical analysis title | StatisticalAnalysis5 Mean Change in Average SBP24h |
|-----------------------------------|--|

| | |
|---|--------------------------------------|
| Comparison groups | Amlodipine+Placebo v Placebo+Placebo |
| Number of subjects included in analysis | 71 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | t-test, 1-sided |

| | |
|---|--|
| Statistical analysis title | StatisticalAnalysis6 Mean Change in Average SBP24h |
| Comparison groups | Placebo+Celecoxib v Placebo+Placebo |
| Number of subjects included in analysis | 56 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.719 |
| Method | t-test, 1-sided |

Secondary: Mean Change in Average Night-time (01:00 to 06:00) Ambulatory Systolic Blood Pressure (SBPnight) [Time Frame: Baseline and 2 weeks]

| | |
|---|---|
| End point title | Mean Change in Average Night-time (01:00 to 06:00) Ambulatory Systolic Blood Pressure (SBPnight) [Time Frame: Baseline and 2 weeks] |
| End point description: | |
| ITT Population as described for primary outcome | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline and 2 weeks | |

| End point values | Amlodipine+Celecoxib | Amlodipine+Placebo | Placebo+Celecoxib | Placebo+Placebo |
|--------------------------------------|----------------------|--------------------|-------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 49 | 45 | 30 | 26 |
| Units: mmHg | | | | |
| arithmetic mean (standard deviation) | | | | |
| Mean Change in Average SBPnight | -10.5 (± 10.6) | -6.35 (± 11.35) | -1.7 (± 12.3) | -1.42 (± 9.15) |

Statistical analyses

| | |
|-----------------------------------|---|
| Statistical analysis title | StatisticalAnalysis1 Mean Change Average SBPnight |
| Comparison groups | Amlodipine+Celecoxib v Amlodipine+Placebo |

| | |
|---|-----------------|
| Number of subjects included in analysis | 94 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.069 |
| Method | t-test, 1-sided |

| | |
|---|---|
| Statistical analysis title | StatisticalAnalysis2 Mean Change Average SBPnight |
| Comparison groups | Amlodipine+Celecoxib v Placebo+Celecoxib |
| Number of subjects included in analysis | 79 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.001 |
| Method | t-test, 1-sided |

| | |
|---|---|
| Statistical analysis title | StatisticalAnalysis3 Mean Change Average SBPnight |
| Comparison groups | Amlodipine+Celecoxib v Placebo+Placebo |
| Number of subjects included in analysis | 75 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | t-test, 1-sided |

| | |
|---|---|
| Statistical analysis title | StatisticalAnalysis4 Mean Change Average SBPnight |
| Comparison groups | Amlodipine+Placebo v Placebo+Celecoxib |
| Number of subjects included in analysis | 75 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.097 |
| Method | t-test, 1-sided |

| | |
|---|---|
| Statistical analysis title | StatisticalAnalysis5 Mean Change Average SBPnight |
| Comparison groups | Amlodipine+Placebo v Placebo+Placebo |
| Number of subjects included in analysis | 71 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.064 |
| Method | t-test, 1-sided |

| | |
|---|---|
| Statistical analysis title | StatisticalAnalysis6 Mean Change Average SBPnight |
| Comparison groups | Placebo+Celecoxib v Placebo+Placebo |
| Number of subjects included in analysis | 56 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.924 |
| Method | t-test, 1-sided |

Secondary: Mean Change in Average 24-hour Ambulatory Diastolic Blood Pressure (DBP24h) [Time Frame: Baseline and 2 weeks]

| | |
|---|--|
| End point title | Mean Change in Average 24-hour Ambulatory Diastolic Blood Pressure (DBP24h) [Time Frame: Baseline and 2 weeks] |
| End point description: | |
| ITT Population as described for primary outcome | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline and 2 weeks | |

| End point values | Amlodipine+Celecoxib | Amlodipine+Placebo | Placebo+Celecoxib | Placebo+Placebo |
|--------------------------------------|----------------------|--------------------|-------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 49 | 45 | 30 | 26 |
| Units: mmHg | | | | |
| arithmetic mean (standard deviation) | | | | |
| Mean Change in Average DBP24h | -7.1 (± 5.6) | -4.8 (± 4.83) | -0.5 (± 4.6) | 0.22 (± 4.28) |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | StatisticalAnalysis1 Mean Change in Average DBP24h |
| Comparison groups | Amlodipine+Celecoxib v Amlodipine+Placebo |
| Number of subjects included in analysis | 94 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.038 |
| Method | t-test, 1-sided |

| | |
|-----------------------------------|--|
| Statistical analysis title | StatisticalAnalysis2 Mean Change in Average DBP24h |
| Comparison groups | Amlodipine+Celecoxib v Placebo+Celecoxib |

| | |
|---|-----------------|
| Number of subjects included in analysis | 79 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | t-test, 1-sided |

| | |
|---|--|
| Statistical analysis title | StatisticalAnalysis3 Mean Change in Average DBP24h |
| Comparison groups | Amlodipine+Celecoxib v Placebo+Placebo |
| Number of subjects included in analysis | 75 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | t-test, 1-sided |

| | |
|---|--|
| Statistical analysis title | StatisticalAnalysis4 Mean Change in Average DBP24h |
| Comparison groups | Amlodipine+Placebo v Placebo+Celecoxib |
| Number of subjects included in analysis | 75 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | t-test, 1-sided |

| | |
|---|--|
| Statistical analysis title | StatisticalAnalysis5 Mean Change in Average DBP24h |
| Comparison groups | Amlodipine+Placebo v Placebo+Placebo |
| Number of subjects included in analysis | 71 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | t-test, 1-sided |

| | |
|---|--|
| Statistical analysis title | StatisticalAnalysis6 Mean Change in Average DBP24h |
| Comparison groups | Placebo+Celecoxib v Placebo+Placebo |
| Number of subjects included in analysis | 56 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.562 |
| Method | t-test, 1-sided |

Secondary: Mean Change in Average Daytime (9:00 to 21:00) Ambulatory Diastolic Blood Pressure (DBPday) [Time Frame: Baseline and 2 weeks]

| | |
|---|--|
| End point title | Mean Change in Average Daytime (9:00 to 21:00) Ambulatory Diastolic Blood Pressure (DBPday) [Time Frame: Baseline and 2 weeks] |
| End point description: ITT Population as described for primary outcome | |
| End point type | Secondary |
| End point timeframe: Baseline and 2 weeks | |

| End point values | Amlodipine+Celecoxib | Amlodipine+Placebo | Placebo+Celecoxib | Placebo+Placebo |
|--------------------------------------|----------------------|--------------------|-------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 49 | 45 | 30 | 26 |
| Units: mmHg | | | | |
| arithmetic mean (standard deviation) | | | | |
| Mean Change in Average DBPday | -7.5 (± 6.4) | -5.53 (± 5.06) | -1.5 (± 5.6) | -0.32 (± 5.39) |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | StatisticalAnalysis1 Mean Change in Average DBPday |
| Comparison groups | Amlodipine+Celecoxib v Amlodipine+Placebo |
| Number of subjects included in analysis | 94 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.104 |
| Method | t-test, 1-sided |

| | |
|---|--|
| Statistical analysis title | StatisticalAnalysis2 Mean Change in Average DBPday |
| Comparison groups | Amlodipine+Celecoxib v Placebo+Celecoxib |
| Number of subjects included in analysis | 79 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | t-test, 1-sided |

| | |
|-----------------------------------|--|
| Statistical analysis title | StatisticalAnalysis3 Mean Change in Average DBPday |
| Comparison groups | Amlodipine+Celecoxib v Placebo+Placebo |

| | |
|---|-----------------|
| Number of subjects included in analysis | 75 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | t-test, 1-sided |

| | |
|---|--|
| Statistical analysis title | StatisticalAnalysis4 Mean Change in Average DBPday |
| Comparison groups | Amlodipine+Placebo v Placebo+Celecoxib |
| Number of subjects included in analysis | 75 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.002 |
| Method | t-test, 1-sided |

| | |
|---|--|
| Statistical analysis title | StatisticalAnalysis5 Mean Change in Average DBPday |
| Comparison groups | Amlodipine+Placebo v Placebo+Placebo |
| Number of subjects included in analysis | 71 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | t-test, 1-sided |

| | |
|---|--|
| Statistical analysis title | StatisticalAnalysis6 Mean Change in Average DBPday |
| Comparison groups | Placebo+Celecoxib v Placebo+Placebo |
| Number of subjects included in analysis | 56 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.419 |
| Method | t-test, 1-sided |

Secondary: Mean Change in Average Night-time (01:00 to 06:00) Ambulatory Diastolic Blood Pressure (DBPnight) [Time Frame: Baseline and 2 weeks]

| | |
|-----------------|--|
| End point title | Mean Change in Average Night-time (01:00 to 06:00) Ambulatory Diastolic Blood Pressure (DBPnight) [Time Frame: Baseline and 2 weeks] |
|-----------------|--|

End point description:

ITT Population as defined for primary outcome

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and 2 weeks

| End point values | Amlodipine+Celecoxib | Amlodipine+Placebo | Placebo+Celecoxib | Placebo+Placebo |
|--------------------------------------|----------------------|--------------------|-------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 49 | 45 | 30 | 26 |
| Units: mmHg | | | | |
| arithmetic mean (standard deviation) | | | | |
| Mean Change in Average DBPnight | -7.0 (± 8.6) | -3.23 (± 7.79) | 0.3 (± 7.1) | 0.01 (± 6.23) |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | StatisticalAnalysis1 Mean Change Average DBPnight |
| Comparison groups | Amlodipine+Celecoxib v Amlodipine+Placebo |
| Number of subjects included in analysis | 94 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.028 |
| Method | t-test, 1-sided |

| | |
|---|---|
| Statistical analysis title | StatisticalAnalysis2 Mean Change Average DBPnight |
| Comparison groups | Amlodipine+Celecoxib v Placebo+Celecoxib |
| Number of subjects included in analysis | 79 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | t-test, 1-sided |

| | |
|---|---|
| Statistical analysis title | StatisticalAnalysis3 Mean Change Average DBPnight |
| Comparison groups | Amlodipine+Celecoxib v Placebo+Placebo |
| Number of subjects included in analysis | 75 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | t-test, 1-sided |

| | |
|-----------------------------------|---|
| Statistical analysis title | StatisticalAnalysis4 Mean Change Average DBPnight |
| Comparison groups | Amlodipine+Placebo v Placebo+Celecoxib |

| | |
|---|-----------------|
| Number of subjects included in analysis | 75 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.051 |
| Method | t-test, 1-sided |

| | |
|---|---|
| Statistical analysis title | StatisticalAnalysis5 Mean Change Average DBPnight |
| Comparison groups | Amlodipine+Placebo v Placebo+Placebo |
| Number of subjects included in analysis | 71 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.074 |
| Method | t-test, 1-sided |

| | |
|---|---|
| Statistical analysis title | StatisticalAnalysis6 Mean Change Average DBPnight |
| Comparison groups | Placebo+Celecoxib v Placebo+Placebo |
| Number of subjects included in analysis | 56 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.878 |
| Method | t-test, 1-sided |

Secondary: Mean Non-transformed Amlodipine Plasma Concentration [Time Frame: 24 hours post-dose on Day 14]

| | |
|-----------------|--|
| End point title | Mean Non-transformed Amlodipine Plasma Concentration [Time Frame: 24 hours post-dose on Day 14] ^[2] |
|-----------------|--|

End point description:

Pharmacokinetic (PK) population: subset of overall trial population, consisting of subjects at Investigational sites capable of obtaining PK blood samples in a protected light environment. No amlodipine PK statistical analyses were performed for the PK subjects in the placebo+celecoxib and placebo+placebo arms.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

24 hours post-dose on Day 14

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Per protocol, no "amlodipine" PK statistical analyses were performed for the PK subjects in the placebo + celecoxib and placebo + placebo arms (i.e., the arms that did not receive amlodipine). No subjects in these arms had detectable levels of amlodipine in their plasma, and as such, PK analysis was not possible for these subjects.

| End point values | Amlodipine+Celecoxib | Amlodipine+Placebo | | |
|--|----------------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 24 | 20 | | |
| Units: pg/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Mean Nontransformed Amlodipine PlasmaConcentration | 15800.83 (\pm 4161.929) | 23453 (\pm 5746.337) | | |

Statistical analyses

| Statistical analysis title | MeanNontransformed Amlodipine PlasmaConcentration |
|---|---|
| Comparison groups | Amlodipine+Celecoxib v Amlodipine+Placebo |
| Number of subjects included in analysis | 44 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | t-test, 1-sided |

Secondary: Mean Non-transformed Celecoxib Plasma Concentration [Time Frame: 24 hours post-dose on Day 14]

| | |
|-----------------|---|
| End point title | Mean Non-transformed Celecoxib Plasma Concentration [Time Frame: 24 hours post-dose on Day 14] ^[3] |
|-----------------|---|

End point description:

PK population: subset of overall trial population, consisting of subjects at Investigational sites capable of obtaining PK blood samples in a protected light environment. No celecoxib PK statistical analyses were performed for the PK subjects in the amlodipine+placebo and placebo+placebo arms.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

24 hours post-dose on Day 14

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Per protocol, no "celecoxib" PK statistical analyses were performed for the PK subjects in the amlodipine + placebo and placebo + placebo arms (i.e., the arms that did not receive celecoxib). No subjects in these arms had detectable levels of celecoxib in their plasma, and as such, PK analysis was not possible for these subjects.

| End point values | Amlodipine+Celecoxib | Placebo+Celecoxib | | |
|--|-------------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 24 | 15 | | |
| Units: ng/ml | | | | |
| arithmetic mean (standard deviation) | | | | |
| Mean Non-transformed Celecoxib PlasmaConcentration | 139.708 (\pm 86.504) | 138.667 (\pm 118.811) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Mean Non-transformed Celecoxib PlasmaConcentration |
| Comparison groups | Placebo+Celecoxib v Amlodipine+Celecoxib |
| Number of subjects included in analysis | 39 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.977 |
| Method | t-test, 1-sided |

Secondary: Mean Log-transformed Amlodipine Plasma Concentration [Time Frame: 24 hours post-dose on Day 14]

| | |
|-----------------|--|
| End point title | Mean Log-transformed Amlodipine Plasma Concentration [Time Frame: 24 hours post-dose on Day 14] ^[4] |
|-----------------|--|

End point description:

PK population: subset of overall trial population, consisting of subjects at Investigational sites capable of obtaining PK blood samples in a protected light environment. No amlodipine PK statistical analyses were performed for the PK subjects in the placebo+celecoxib and placebo+placebo arms.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

24 hours post-dose on Day 14

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Per protocol, no "amlodipine" PK statistical analyses were performed for the PK subjects in the placebo + celecoxib and placebo + placebo arms (i.e., the arms that did not receive amlodipine).

No subjects in these arms had detectable levels of amlodipine in their plasma, and as such, PK analysis was not possible for these subjects.

| | | | | |
|--|----------------------|--------------------|--|--|
| End point values | Amlodipine+Celecoxib | Amlodipine+Placebo | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 24 | 20 | | |
| Units: log(pg/mL) | | | | |
| arithmetic mean (standard deviation) | | | | |
| MeanLog-transformed Amlodipine PlasmaConcentration | 9.634 (± 0.268) | 10.025 (± 0.310) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | MeanLog-transformed Amlodipine PlasmaConcentration |
| Comparison groups | Amlodipine+Celecoxib v Amlodipine+Placebo |
| Number of subjects included in analysis | 44 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | < 0.001 |
| Method | t-test, 1-sided |

Secondary: Mean Log-transformed Celecoxib Plasma Concentration [Time Frame: 24 hours post-dose on Day 14]

| | |
|-----------------|---|
| End point title | Mean Log-transformed Celecoxib Plasma Concentration [Time Frame: 24 hours post-dose on Day 14] ^[5] |
|-----------------|---|

End point description:

PK population: subset of overall trial population, consisting of subjects at Investigational sites capable of obtaining PK blood samples in a protected light environment. No celecoxib PK statistical analyses were performed for the PK subjects in the amlodipine+placebo and placebo+placebo arms.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

24 hours post-dose on Day 14

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Per protocol, no "celecoxib" PK statistical analyses were performed for the PK subjects in the amlodipine + placebo and placebo + placebo arms (i.e., the arms that did not receive celecoxib). No subjects in these arms had detectable levels of celecoxib in their plasma, and as such, PK analysis was not possible for these subjects.

| End point values | Amlodipine+Celecoxib | Placebo+Celecoxib | | |
|---|----------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 24 | 15 | | |
| Units: log(ng/mL) | | | | |
| arithmetic mean (standard deviation) | | | | |
| MeanLog-transformed Celecoxib PlasmaConcentration | 4.785 (± 0.564) | 4.636 (± 0.781) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Mean Log-transformed Celecoxib PlasmaConcentration |
| Comparison groups | Amlodipine+Celecoxib v Placebo+Celecoxib |
| Number of subjects included in analysis | 39 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.527 |
| Method | t-test, 1-sided |

Secondary: Mean Change in Average Daytime (9:00 to 21:00) Ambulatory Systolic Blood Pressure (SBPday) - Secondary Endpoint [Time Frame: Baseline and 2 weeks]

| | |
|-----------------|--|
| End point title | Mean Change in Average Daytime (9:00 to 21:00) Ambulatory Systolic Blood Pressure (SBPday) - Secondary Endpoint [Time Frame: Baseline and 2 weeks] |
|-----------------|--|

End point description:

ITT Population as described for primary outcome

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline and 2 weeks

| End point values | Amlodipine+Celecoxib | Amlodipine+Placebo | Placebo+Celecoxib | Placebo+Placebo |
|--------------------------------------|----------------------|--------------------|-------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 49 | 45 | 30 | 26 |
| Units: mmHg | | | | |
| arithmetic mean (standard deviation) | | | | |
| Mean Change in Average SBPday | -10.6 (± 9.2) | -8.83 (± 8.13) | -0.5 (± 8.8) | -2.11 (± 8.2) |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | StatisticalAnalysis1 Mean Change in Average SBPday |
| Comparison groups | Amlodipine+Celecoxib v Placebo+Celecoxib |
| Number of subjects included in analysis | 79 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | t-test, 1-sided |

| | |
|---|--|
| Statistical analysis title | StatisticalAnalysis2 Mean Change in Average SBPday |
| Comparison groups | Amlodipine+Celecoxib v Placebo+Placebo |
| Number of subjects included in analysis | 75 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | t-test, 1-sided |

| | |
|---|--|
| Statistical analysis title | StatisticalAnalysis3 Mean Change in Average SBPday |
| Comparison groups | Amlodipine+Placebo v Placebo+Celecoxib |
| Number of subjects included in analysis | 75 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | t-test, 1-sided |

| | |
|-----------------------------------|--|
| Statistical analysis title | StatisticalAnalysis4 Mean Change in Average SBPday |
| Comparison groups | Amlodipine+Placebo v Placebo+Placebo |

| | |
|---|-----------------|
| Number of subjects included in analysis | 71 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.001 |
| Method | t-test, 1-sided |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

1 month

Adverse event reporting additional description:

Adverse Events (AEs) were monitored continuously during the study starting immediately after the first dose of study drugs was administered. Subjects were instructed to report all AEs experienced during the study, and subjects were assessed for the occurrence of AEs throughout the study.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 17.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|----------------------|
| Reporting group title | Amlodipine+Celecoxib |
|-----------------------|----------------------|

Reporting group description:

Over-encapsulated 10 mg amlodipine besylate tablet + over-encapsulated 200 mg celecoxib capsule once a day for two weeks

Over-encapsulated 10 mg amlodipine besylate tablet: Over-encapsulated 10 mg amlodipine besylate tablet once a day for two weeks

Over-encapsulated 200 mg celecoxib capsule: Over-encapsulated 200 mg celecoxib capsule once a day for two weeks

| | |
|-----------------------|--------------------|
| Reporting group title | Amlodipine+Placebo |
|-----------------------|--------------------|

Reporting group description:

Over-encapsulated 10 mg amlodipine besylate tablet + matched placebo capsule for over-encapsulated celecoxib capsule once a day for two weeks

Over-encapsulated 10 mg amlodipine besylate tablet: Over-encapsulated 10 mg amlodipine besylate tablet once a day for two weeks

Matched placebo capsule for over-encapsulated celecoxib capsule: Matched placebo capsule for over-encapsulated celecoxib capsule once a day for two weeks

| | |
|-----------------------|-------------------|
| Reporting group title | Placebo+Celecoxib |
|-----------------------|-------------------|

Reporting group description:

Matched placebo tablet for over-encapsulated amlodipine besylate tablet + over-encapsulated 200 mg celecoxib capsule once a day for two weeks

Over-encapsulated 200 mg celecoxib capsule: Over-encapsulated 200 mg celecoxib capsule once a day for two weeks

Matched placebo tablet for over-encapsulated amlodipine besylate tablet: Matched placebo tablet for over-encapsulated amlodipine besylate tablet once a day for two weeks

| | |
|-----------------------|-----------------|
| Reporting group title | Placebo+Placebo |
|-----------------------|-----------------|

Reporting group description:

Matched placebo tablet for over-encapsulated amlodipine besylate tablet + matched placebo capsule for over-encapsulated celecoxib capsule once a day for two weeks

Matched placebo capsule for over-encapsulated celecoxib capsule: Matched placebo capsule for over-encapsulated celecoxib capsule once a day for two weeks

Matched placebo tablet for over-encapsulated amlodipine besylate tablet: Matched placebo tablet for over-encapsulated amlodipine besylate tablet once a day for two weeks

| Serious adverse events | Amlodipine+Celecoxib | Amlodipine+Placebo | Placebo+Celecoxib |
|---|----------------------|--------------------|-------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 0 / 45 (0.00%) | 0 / 31 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |

| Serious adverse events | Placebo+Placebo | | |
|---|-----------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 27 (0.00%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |

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

| Non-serious adverse events | Amlodipine+Celecoxib | Amlodipine+Placebo | Placebo+Celecoxib |
|---|----------------------|--------------------|-------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 17 / 49 (34.69%) | 17 / 45 (37.78%) | 5 / 31 (16.13%) |
| Vascular disorders | | | |
| Orthostatic hypotension | | | |
| subjects affected / exposed | 0 / 49 (0.00%) | 2 / 45 (4.44%) | 0 / 31 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 4 / 49 (8.16%) | 6 / 45 (13.33%) | 2 / 31 (6.45%) |
| occurrences (all) | 5 | 10 | 3 |
| General disorders and administration site conditions | | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 4 / 49 (8.16%) | 7 / 45 (15.56%) | 0 / 31 (0.00%) |
| occurrences (all) | 4 | 8 | 0 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 2 / 49 (4.08%) | 4 / 45 (8.89%) | 0 / 31 (0.00%) |
| occurrences (all) | 2 | 4 | 0 |
| Musculoskeletal and connective tissue disorders | | | |

| | | | |
|--|----------------------|---------------------|---------------------|
| Joint swelling subjects affected / exposed occurrences (all) | 5 / 49 (10.20%) 5 | 3 / 45 (6.67%) 4 | 0 / 31 (0.00%) 0 |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) | 5 / 49 (10.20%) 5 | 0 / 45 (0.00%) 0 | 2 / 31 (6.45%) 2 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 0 / 49 (0.00%) 0 | 2 / 45 (4.44%) 3 | 2 / 31 (6.45%) 2 |
| Metabolism and nutrition disorders Gout subjects affected / exposed occurrences (all) | 0 / 49 (0.00%) 0 | 0 / 45 (0.00%) 0 | 0 / 31 (0.00%) 0 |

| | | | |
|---|---------------------|--|--|
| Non-serious adverse events | Placebo+Placebo | | |
| Total subjects affected by non-serious adverse events subjects affected / exposed | 6 / 27 (22.22%) | | |
| Vascular disorders Orthostatic hypotension subjects affected / exposed occurrences (all) | 2 / 27 (7.41%) 2 | | |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 2 / 27 (7.41%) 2 | | |
| General disorders and administration site conditions Oedema peripheral subjects affected / exposed occurrences (all) | 0 / 27 (0.00%) 0 | | |
| Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) | 0 / 27 (0.00%) 0 | | |
| Musculoskeletal and connective tissue disorders Joint swelling | | | |

| | | | |
|--|---------------------|--|--|
| subjects affected / exposed occurrences (all) | 0 / 27 (0.00%) 0 | | |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed occurrences (all) | 0 / 27 (0.00%) 0 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed occurrences (all) | 1 / 27 (3.70%) 1 | | |
| Metabolism and nutrition disorders | | | |
| Gout | | | |
| subjects affected / exposed occurrences (all) | 2 / 27 (7.41%) 2 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---|
| 01 September 2014 | <p>The reason for this substantial amendment was to change the primary efficacy endpoint of this trial from "...the change in 24-hour mean SBP from baseline to day 14..." to "...the change in daytime mean SBP from baseline to day 14...". This was done based on a preliminary review of baseline ABPM recordings (after randomization of four subjects and screening of over three dozen patients), where it became apparent that the differences between the daytime and night-time SBPs were so great that they would compromise the statistical validity of the data if SBP24h was used as the endpoint, as well as a review of the literature.</p> <p>Inclusion criterion 3 was changed to "SBP24h > 135 mmHg at baseline (Day 0)" to "SBPday > 135 mmHg at baseline (Day 0)". Similarly, exclusion criterion 2 was changed from "SBP24h < 135 mmHg at baseline (Day 0)" to "SBPday < 135 mmHg at baseline (Day 0)". This was done for consistency with the above referenced endpoint revisions.</p> |
| 09 September 2014 | <p>1. The reason for this substantial amendment was to revise exclusion criterion number 1 to specify that subjects are excluded from participating in the study if their resting systolic BP at Screening was > 179 mmHg (previously 169 mmHg). The required mean SBP as measured by ABPM during the baseline 24 hours remained < 169 mmHg. This change was made in response to initial recruitment results showing that a relatively large proportion of potential subjects were hypertensive at Screening but were subsequently found to be normotensive by ambulatory BP monitoring at baseline/randomization. No impact on the trial outcomes were anticipated by this change.</p> <p>2. The reason for this modified Substantial Amendment was to address the concerns set out in the MHRA grounds for non-acceptance letter, dated 8th August 2014, for Substantial Amendment 2.0, Version 1.0 dated 7th July 2014. Inclusion criterion number 2 was revised, as requested, to specify that the patients eligible for this study are those that require chronic pharmacological therapy. Inclusion criterion number 3 was deleted, and is instead now part of inclusion criterion number 2. New wording is as follows:</p> <p>Inclusion Criteria</p> <p>2. Newly diagnosed hypertension that requires chronic pharmacological therapy. Specifically, the subject must meet both of the following criteria:</p> <p>a. Resting systolic BP \geq 140 mmHg and \leq 179 mmHg (where resting is defined as supine for at least 10 minutes with minimal interaction) at Initial Screening Visit;</p> <p>b. SBPday > 135 mmHg at Baseline Visit (Day 0);</p> <p>To address the concerns of both the MHRA and the Investigators, the inclusion criterion was clarified as noted above. These changes were simply clarifications, and no impact on the trial outcomes were anticipated by these changes.</p> |

| | |
|-------------------|--|
| 25 March 2015 | <p>The reason for this amendment was to request that the maximum age for enrollment in this trial be increased from 65 to 75 years. This was done for multiple reasons. First, this change was requested by the study investigators to facilitate recruitment into the study. In addition, this age will be more reflective of the age of patients who will eventually receive this medication when and if it is approved for marketing. Having enrolled 56 patients and reviewed the blinded efficacy and safety data, including the ABPM data from these patients, it was clear that there had been no instances of clinically significant hypotension or hypertension among these patients. Thus, the data now justified a conclusion that it was safe to increase the enrollment age. It should further be noted that since patients were monitored while on the study, including have an ABPM for the initial 24 hours following initiation of therapy, if any patient were to develop symptomatic hypotension or hypertension, this should be quickly noted by the investigators.</p> <p>This change was not anticipated to impact the trial outcomes.</p> |
| 02 September 2015 | <p>1.The Study Protocol exclusion criterion number 17 regarding a positive drug screen at Screening was amended. Specifically, the following exception was added: “A positive drug screen for opiates only (with all other drug tests negative) will not be a basis for exclusion if the subject took over-the-counter narcotics as indicated on the product label within 24 hours prior to the drug screen.”</p> <p>This exception was added to take into account that there are several over-the-counter narcotics available in the United Kingdom, and that the protocol does not specifically restrict these medications prior to enrollment. Thus, there was the potential to have to screen fail an otherwise eligible subject for taking a common over-the-counter medication.</p> <p>This change was not anticipated to impact the trial outcomes.</p> <p>2. Appendix F of the Study Protocol was revised to replace the January 2013 product label for commercial amlodipine besylate [Norvasc® (amlodipine besylate) tablets] with the current label approved by FDA on March 23, 2015. The updated label included the following safety-related revisions:</p> <ul style="list-style-type: none"> • Addition of a possible association between extrapyramidal disorder and amlodipine during post-marketing reporting. • Addition of clarithromycin as a strong inhibitor of CYP3A that may increase the plasma concentrations of amlodipine. • Addition of a possible drug interaction between tacrolimus and amlodipine (increase in tacrolimus exposure). <p>None of the above findings were anticipated to pose a significant risk to the subjects in the ongoing trial due to how the study was designed (i.e., restricted eligibility/patient population, intensive safety monitoring, restricted concomitant medications, and relatively short exposure to amlodipine).</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

No limitations

Notes: