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 (± 4161.929)	23453 (± 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 (± 86.504)	138.667 (± 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) Upper respiratory tract infection subjects affected / exposed occurrences (all)	 5 / 49 (10.20%) 5 0 / 49 (0.00%) 0	 0 / 45 (0.00%) 0 2 / 45 (4.44%) 3	 2 / 31 (6.45%) 2 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) Upper respiratory tract infection subjects affected / exposed occurrences (all)	 0 / 27 (0.00%) 0 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	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. 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.
09 September 2014	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. 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: Inclusion Criteria 2. Newly diagnosed hypertension that requires chronic pharmacological therapy. Specifically, the subject must meet both of the following criteria: a. Resting systolic BP ≥ 140 mmHg and ≤179 mmHg (where resting is defined as supine for at least 10 minutes with minimal interaction) at Initial Screening Visit; b. SBPday > 135 mmHg at Baseline Visit (Day 0); 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.

25 March 2015	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. This change was not anticipated to impact the trial outcomes.
02 September 2015	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." 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. This change was not anticipated to impact the trial outcomes. 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: • 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). 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).

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: