Clinical trial results:
Fixed-Dose Combination of Perindopril/Amlodipine (Amlessa®) and Fixed-Dose Combination of Perindopril/Indapamide /Amlodipine (Co-Amlessa®) - Contribution to Management in newly diagnosed and uncontrolled hypertensive patients (PRECIOUS study)

Summary

EudraCT number	2017-001596-23
Trial protocol	PL SI HR
Global end of trial date	27 September 2019

Results information

Result version number	v1
This version publication date	01 November 2020
First version publication date	01 November 2020
Summary attachment (see zip file)	PRECIOUS_SUMMARY (PRECIOUS_CSR_SYNOPSIS_ENG_clean.pdf)

Trial information

Trial identification

Sponsor protocol code	KCT06/2017-PRECIOUS

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03738761
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Krka, d.d., Novo mesto
Sponsor organisation address	Dunajska cesta 65, Ljubljana, Slovenia, 1000
Public contact	Tanja Kohek, Krka, d.d., Novo mesto Dunajska cesta 65 1000 Ljubljana, +386 14751236, tanja.kohek@krka.biz
Scientific contact	Tanja Kohek, Krka, d.d., Novo mesto Dunajska cesta 65 1000 Ljubljana, +386 14751236, tanja.kohek@krka.biz

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	03 September 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 September 2019
Global end of trial reached?	Yes
Global end of trial date	27 September 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of the study is to establish the efficacy and safety of fixed-dose combination (FDC) of perindopril/amlodipine (Amlessa®) and fixed-dose combination of perindopril/indapamide/amlodipine (Co-Amlessa®) in wide populations of uncontrolled patients with arterial hypertension (AH) with special focus on effective continuous 24-hour blood pressure (BP) control. The purpose is also to establish the correlation between 24-hour central and peripheral BP.

Protection of trial subjects:

Patients had 3 main follow-up visits (visit 2, visit 3 and visit 4) and final visit (visit 5) at the end of the study. At each of the three follow-up visits, patient`s office blood pressure (BP) was measured. If normal office blood pressure (NBP - defined as SBP < 140 mmHg and DBP < 90 (85 for patients with type 2 diabetes mellitus) mmHg) was achieved, the patient continued treatment with the study medication prescribed. If NBP was not achieved, study medication dose was increased in order to achieve NBP and to protect the patient.
At visit 1 and visit 5, complete laboratory analysis (blood counts, clinical chemistry, liver enzymes, lipid measurements) was performed. To further protect the patients, on visits 2, 3 and 4 safety assessing laboratory analysis was performed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 February 2018
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	Armenia: 112
Country: Number of subjects enrolled	Serbia: 84
Country: Number of subjects enrolled	Russian Federation: 50
Country: Number of subjects enrolled	Poland: 103
Country: Number of subjects enrolled	Slovenia: 33
Country: Number of subjects enrolled	Croatia: 39
Country: Number of subjects enrolled	Hungary: 50
Worldwide total number of subjects	471
EEA total number of subjects	225

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)	365
From 65 to 84 years	105
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

572 patients were screened from Croatia, Hungary, Poland, Slovenia, Armenia, Serbia and Russia. 471 patients were enrolled in the study and also included in SAS (Safety Analysis Set) populationk, for which safety analyses were performed. 450 patients were included in FAS (Full Analysis Set) population, for which efficacy analyses were performed.

Pre-assignment

Screening details:

In general, eligible patients for the screening procedure were adult patients aged 18 years and above, of both genders, with arterial hypertension (naïve or on previous antihypertensive treatment), who currently do not participate in another clinical trial and who signed Informed Consent Form (ICF).

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Amlessa Arm

Arm description:

In Amlessa arm were allocated antihypertensive medication naïve patients, patients on previous antihypertensive monotherapy and patients on previous dual antihypertensive therapy (based on the decision of the Investigator).
Patients were instructed to take one unit of assigned study medication once daily, at about the same time each day (± 3 hours), preferably in the morning and before a meal. Patients were required to take a dose of the medication on the day of the dispensing visit, but not to take the study medication in the morning of any visit following the initial visit.

Arm type	Active comparator
Investigational medicinal product name	Amlessa 4 mg/5 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Each tablet of Amlessa 4 mg/5 mg contains 4 mg perindopril tert-butylamine and 5 mg amlodipine (as amlodipine besilate).

Investigational medicinal product name	Amlessa 8 mg/5 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Each tablet of Amlessa 8 mg/5 mg contains 8 mg perindopril tert-butylamine and 5 mg amlodipine (as amlodipine besilate).

Investigational medicinal product name	Amlessa 8 mg/10 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Each tablet of Amlessa 8 mg/10 mg contains 8 mg perindopril tert-butylamine and 10 mg amlodipine

(as amlodipine besilate).

Arm title	Co-Amlessa Arm

Arm description:

In Co-Amlessa arm were allocated patients on previous dual antihypertensive therapy (based on the decision of the Investigator) and patients on previous triple antihypertensive therapy.
Patients were instructed to take one unit of assigned study medication once daily, at about the same time each day (± 3 hours), preferably in the morning and before a meal. Patients were required to take a dose of the medication on the day of the dispensing visit, but not to take the study medication in the morning of any visit following the initial visit.

Arm type	Active comparator
Investigational medicinal product name	Co-Amlessa 4 mg/5 mg/1.25 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Each tablet of Co-Amlessa 4 mg/5 mg/1.25 mg contains 4 mg perindopril tert-butylamine, 5 mg amlodipine (as amlodipine besylate) and 1.25 mg indapamide.

Investigational medicinal product name	Co-Amlessa 8 mg/5 mg/2.5 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Each tablet of Co-Amlessa 8 mg/5 mg/2.5 mg contains 8 mg perindopril tert-butylamine, 5 mg amlodipine (as amlodipine besylate) and 2.5 mg indapamide.

Investigational medicinal product name	Co-Amlessa 8 mg/10 mg/2.5 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Each tablet of Co-Amlessa 8 mg/10 mg/2.5 mg contains 8 mg perindopril tert-butylamine, 10 mg amlodipine (as amlodipine besylate) and 2.5 mg indapamide.

Number of subjects in period 1	Amlessa Arm	Co-Amlessa Arm
Started	270	201
Completed	234	187
Not completed	36	14
Consent withdrawn by subject	8	-
Adverse event, non-fatal	11	4
Other	4	-
Incorrectly allocated to treatment	9	5
Lost to follow-up	2	-

Noncompliance	1	-
Lack of efficacy	1	5

Baseline characteristics

Reporting groups	
Reporting group title	Amlessa Arm

Reporting group description:

In Amlessa arm were allocated antihypertensive medication naïve patients, patients on previous antihypertensive monotherapy and patients on previous dual antihypertensive therapy (based on the decision of the Investigator).
Patients were instructed to take one unit of assigned study medication once daily, at about the same time each day (± 3 hours), preferably in the morning and before a meal. Patients were required to take a dose of the medication on the day of the dispensing visit, but not to take the study medication in the morning of any visit following the initial visit.

Reporting group title	Co-Amlessa Arm

Reporting group description:

In Co-Amlessa arm were allocated patients on previous dual antihypertensive therapy (based on the decision of the Investigator) and patients on previous triple antihypertensive therapy.
Patients were instructed to take one unit of assigned study medication once daily, at about the same time each day (± 3 hours), preferably in the morning and before a meal. Patients were required to take a dose of the medication on the day of the dispensing visit, but not to take the study medication in the morning of any visit following the initial visit.

Reporting group values	Amlessa Arm	Co-Amlessa Arm	Total
Number of subjects	270	201	471
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	51.8	56.7	
standard deviation	± 12.2	± 12.4	-
Gender categorical Units: Subjects			
Female	102	75	177
Male	168	126	294

End points

End points reporting groups

Reporting group title	Amlessa Arm

Reporting group description:

In Amlessa arm were allocated antihypertensive medication naïve patients, patients on previous antihypertensive monotherapy and patients on previous dual antihypertensive therapy (based on the decision of the Investigator).
Patients were instructed to take one unit of assigned study medication once daily, at about the same time each day (± 3 hours), preferably in the morning and before a meal. Patients were required to take a dose of the medication on the day of the dispensing visit, but not to take the study medication in the morning of any visit following the initial visit.

Reporting group title	Co-Amlessa Arm

Reporting group description:

In Co-Amlessa arm were allocated patients on previous dual antihypertensive therapy (based on the decision of the Investigator) and patients on previous triple antihypertensive therapy.
Patients were instructed to take one unit of assigned study medication once daily, at about the same time each day (± 3 hours), preferably in the morning and before a meal. Patients were required to take a dose of the medication on the day of the dispensing visit, but not to take the study medication in the morning of any visit following the initial visit.

Primary: Proportion of patients reaching NBP after 16 weeks of treatment

End point title	Proportion of patients reaching NBP after 16 weeks of treatment[1]

End point description:

Based on the blood pressure measured on visit 5, for each patient was determined if he reached NBP after 16 weeks of treatment with Amlessa or Co-Amlessa. NBP was defined as SBP < 140 mmHg and DBP < 90 mmHg (SBP < 140 mmHg and DBP < 85 mmHg for patients with type 2 diabetes mellitus). This end point display the proportion of all 450 patients in FAS population that has reached NBP after 16 weeks of treatment.

End point type	Primary

End point timeframe:

Each patient was monitored for 16 weeks. Timeframe was the same throughout the whole trial.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The inferential part of statistical analysis was based on two-sided confidence intervals. Two-sided "equal-tails" Clopper-Pearson exact 95%-confidence intervals were calculated to estimate the population proportion of patients meeting a target office NBP achievement endpoint. There was no comparison between groups for primary endpoint evaluation. Each treatment arm was evaluated for primary endpoint separately and whole FAS was evaluated for primary efficacy endpoint.

End point values	Amlessa Arm	Co-Amlessa Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	256	194		
Units: Proportion of patients				
number (confidence interval 95%)				
Proportion of patients with NBP after 16 weeks	77.7 (72.1 to 82.7)	83.0 (76.9 to 88.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of patients reaching NBP after 4, 8 and 12 weeks of treatment

End point title	Proportion of patients reaching NBP after 4, 8 and 12 weeks of treatment

End point description:

Based on the blood pressure measured on visit 2, visit 3 and visit 4, for each patient was determined if he reached NBP after 4, 8 and 12 weeks of treatment with Amlessa or Co-Amlessa. NBP was defined as SBP < 140 mmHg and DBP < 90 mmHg (SBP < 140 mmHg and DBP < 85 mmHg for patients with type 2 diabetes mellitus). This end point displays the proportion of all 450 patients in FAS population that has reached NBP after 4, 8 and 12 weeks of treatment.

End point type	Secondary

End point timeframe:

For secondary endpoint each patient was monitored for 4, 8 and 12 weeks.

End point values	Amlessa Arm	Co-Amlessa Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	256	194		
Units: Proportion of patients				
number (confidence interval 95%)				
Proportion of patients with NBP after 4 weeks	48.8 (42.6 to 55.1)	35.6 (28.8 to 42.7)		
Proportion of patients with NBP after 8 weeks	64.1 (57.9 to 69.9)	62.4 (55.1 to 69.2)		
Proportion of patients with NBP after 12 weeks	74.6 (68.8 to 79.8)	80.9 (74.7 to 86.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean absolute and relative change from baseline in office SBP and DBP after 4, 8, 12 and 16 weeks of treatment

End point title	Mean absolute and relative change from baseline in office SBP and DBP after 4, 8, 12 and 16 weeks of treatment

End point description:

Based on the blood pressure measured on visits 1-5, for each patient was calculated absolute and relative change from baseline in office SBP and DBP after 4, 8, 12 and 16 weeks of treatment with Amlessa or Co-Amlessa. This endpoint summarizes mean absolute and relative changes from baseline in office SBP and DBP after 4, 8, 12 and 16 weeks of treatment for all 450 patients in FAS population.

End point type	Secondary

End point timeframe:

Each patient was monitored for 16 weeks. Timeframe was the same throughout the whole trial.

End point values	Amlessa Arm	Co-Amlessa Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	256	194		
Units: mmHg or %				
arithmetic mean (confidence interval 95%)				
Mean absolute change in SBP after 4 weeks (mmHg)	-17.1 (-18.8 to -15.3)	-14.4 (-16.5 to -12.2)		
Mean absolute change in SBP after 8 weeks (mmHg)	-21.1 (-22.8 to -19.4)	-20.9 (-23.2 to -18.7)		
Mean absolute change in SBP after 12 weeks (mmHg)	-23.6 (-25.2 to -22.0)	-25.5 (-27.6 to -23.5)		
Mean absolute change in SBP after 16 weeks (mmHg)	-26.8 (-28.4 to -25.2)	-28.8 (-31.0 to -26.5)		
Mean relative change in SBP after 4 weeks (%)	-10.6 (-11.7 to -9.6)	-8.7 (-10.0 to -7.5)		
Mean relative change in SBP after 8 weeks (%)	-13.3 (-14.3 to -12.2)	-12.9 (-14.3 to -11.6)		
Mean relative change in SBP after 12 weeks (%)	-14.8 (-15.8 to -13.9)	-15.8 (-17.0 to -14.6)		
Mean relative change in SBP after 16 weeks (%)	-16.9 (-17.8 to -16.0)	-17.9 (-19.2 to -16.6)		
Mean absolute change in DBP after 4 weeks (mmHg)	-10.9 (-12.1 to -9.7)	-9.0 (-10.5 to -7.5)		
Mean absolute change in DBP after 8 weeks (mmHg)	-13.3 (-14.4 to -12.2)	-13.2 (-14.7 to -11.7)		
Mean absolute change in DBP after 12 weeks (mmHg)	-15.1 (-16.2 to -13.9)	-15.0 (-16.4 to -13.6)		
Mean absolute change in DBP after 16 weeks (mmHg)	-16.6 (-17.6 to -15.5)	-16.7 (-18.2 to -15.2)		
Mean relative change in DBP after 4 weeks (%)	-10.7 (-11.9 to -9.6)	-8.7 (-10.2 to -7.2)		
Mean relative change in DBP after 8 weeks (%)	-13.1 (-14.2 to -12.1)	-13.0 (-14.5 to -11.6)		
Mean relative change in DBP after 12 weeks (%)	-15.0 (-16.0 to -13.9)	-14.8 (-16.1 to -13.6)		
Mean relative change in DBP after 16 weeks (%)	-16.5 (-17.5 to -15.6)	-16.6 (-18.0 to -15.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean absolute and relative changes from baseline to 16 weeks in average 24h SBP and DBP, average awake time SBP and DBP and average sleep time SBP and DBP

End point title	Mean absolute and relative changes from baseline to 16 weeks in average 24h SBP and DBP, average awake time SBP and DBP and average sleep time SBP and DBP

End point description:

Based on the 24h blood pressure measurement at the baseline and at 16 weeks of treatment with Amlessa and Co-Amlessa, for each patient was calculated absolute and relative change after 16 weeks of treatment in 24h SBP and DBP as well as awake time and sleep time SBP and DBP. This end point summarizes mean absolute and relative change after 16 weeks of treatment for all 450 patients in FAS population.

End point type	Secondary

End point timeframe:

Each patient was monitored for 16 weeks. Timeframe was the same throughout the whole trial.

End point values	Amlessa Arm	Co-Amlessa Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	256	194		
Units: mmHg or %				
arithmetic mean (confidence interval 95%)				
Mean absolute change in 24h SBP after 16w (mmHg)	-16.1 (-17.6 to -14.6)	-21.8 (-23.8 to -19.9)		
Mean relative change in 24h SBP after 16w (%)	-11.1 (-12.0 to -10.1)	-14.5 (-15.7 to -13.3)		
Mean absolute change in 24h DBP after 16w (mmHg)	-10.8 (-11.9 to -9.7)	-13.5 (-14.8 to -12.3)		
Mean relative change in 24h DBP after 16w (%)	-11.3 (-12.4 to -10.2)	-14.2 (-15.5 to -13.0)		
Mean absolute change in awake SBP after 16w (mmHg)	-16.6 (-18.2 to -15.0)	-22.9 (-25.0 to -20.8)		
Mean relative change in awake SBP after 16w (%)	-11.1 (-12.1 to -10.1)	-14.9 (-16.1 to -13.6)		
Mean absolute change in awake DBP after 16w (mmHg)	-10.8 (-12.0 to -9.7)	-14.2 (-15.5 to -12.9)		
Mean relative change in awake DBP after 16w (%)	-10.9 (-12.1 to -9.8)	-14.4 (-15.7 to -13.1)		
Mean absolute change in sleep SBP after 16w (mmHg)	-14.6 (-16.3 to -12.8)	-18.7 (-20.9 to -16.6)		
Mean relative change in sleep SBP after 16w (%)	-10.4 (-11.6 to -9.2)	-13.1 (-14.5 to -11.6)		
Mean absolute change in sleep DBP after 16w (mmHg)	-10.3 (-11.5 to -9.0)	-11.5 (-13.0 to -10.1)		
Mean relative change in sleep DBP after 16w (%)	-11.4 (-12.8 to -10.1)	-12.9 (-14.5 to -11.2)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Each patient was monitored for 16 weeks. Timeframe for AE reporting was the same throughout the whole trial.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Amlessa Arm

Reporting group description:

In Amlessa arm were allocated antihypertensive medication naïve patients, patients on previous antihypertensive monotherapy and patients on previous dual antihypertensive therapy (based on the decision of the Investigator).
Patients were instructed to take one unit of assigned study medication once daily, at about the same time each day (± 3 hours), preferably in the morning and before a meal. Patients were required to take a dose of the medication on the day of the dispensing visit, but not to take the study medication in the morning of any visit following the initial visit.

Reporting group title	Co-Amlessa Arm

Reporting group description:

In Co-Amlessa arm were allocated patients on previous dual antihypertensive therapy (based on the decision of the Investigator) and patients on previous triple antihypertensive therapy.
Patients were instructed to take one unit of assigned study medication once daily, at about the same time each day (± 3 hours), preferably in the morning and before a meal. Patients were required to take a dose of the medication on the day of the dispensing visit, but not to take the study medication in the morning of any visit following the initial visit.

Serious adverse events	Amlessa Arm	Co-Amlessa Arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 270 (0.37%)	1 / 201 (0.50%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 270 (0.00%)	1 / 201 (0.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 270 (0.37%)	0 / 201 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Amlessa Arm	Co-Amlessa Arm	
Total subjects affected by non-serious adverse events subjects affected / exposed	44 / 270 (16.30%)	23 / 201 (11.44%)	
Investigations			
Alanine aminotransferase increased subjects affected / exposed	5 / 270 (1.85%)	5 / 201 (2.49%)	
occurrences (all)	8	6	
Blood potassium increased subjects affected / exposed	5 / 270 (1.85%)	0 / 201 (0.00%)	
occurrences (all)	7	0	
Blood triglycerides increased subjects affected / exposed	5 / 270 (1.85%)	3 / 201 (1.49%)	
occurrences (all)	5	4	
Gamma-glutamyltransferase increased subjects affected / exposed	4 / 270 (1.48%)	5 / 201 (2.49%)	
occurrences (all)	8	10	
Aspartate aminotransferase increased subjects affected / exposed	3 / 270 (1.11%)	4 / 201 (1.99%)	
occurrences (all)	4	5	
Blood potassium decreased subjects affected / exposed	0 / 270 (0.00%)	2 / 201 (1.00%)	
occurrences (all)	0	3	
Blood cholesterol increased subjects affected / exposed	2 / 270 (0.74%)	1 / 201 (0.50%)	
occurrences (all)	2	1	
Vascular disorders			
Oedema peripheral subjects affected / exposed	4 / 270 (1.48%)	0 / 201 (0.00%)	
occurrences (all)	9	0	
Hypotension			

subjects affected / exposed	2 / 270 (0.74%)	3 / 201 (1.49%)	
occurrences (all)	2	3	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 270 (0.74%)	0 / 201 (0.00%)	
occurrences (all)	3	0	
Somnolence			
subjects affected / exposed	1 / 270 (0.37%)	0 / 201 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	9 / 270 (3.33%)	3 / 201 (1.49%)	
occurrences (all)	15	4	
Musculoskeletal and connective tissue disorders			
Joint swelling			
subjects affected / exposed	2 / 270 (0.74%)	0 / 201 (0.00%)	
occurrences (all)	3	0	
Infections and infestations			
Viral infection			
subjects affected / exposed	0 / 270 (0.00%)	2 / 201 (1.00%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported