Clinical trial results:
A 26-WEEK INTERNATIONAL, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, ACTIVE-CONTROLLED, PARALLEL GROUP, PHASE 3B TRIAL WITH A BLINDED 26-WEEK LONG-TERM EXTENSION PERIOD TO EVALUATE THE EFFICACY AND SAFETY OF SAXAGLIPTIN CO-ADMINISTERED WITH DAPAGLIFLOZIN IN COMBINATION WITH METFORMIN COMPARED TO SITAGLIPTIN IN COMBINATION WITH METFORMIN IN ADULT PATIENTS WITH TYPE 2 DIABETES WHO HAVE INADEQUATE GLYCEMIC CONTROL ON METFORMIN THERAPY ALONE

Summary

EudraCT number	2014-001102-17
Trial protocol	HU PL
Global end of trial date	26 October 2016

Results information

Result version number	v1 (current)
This version publication date	23 November 2017
First version publication date	23 November 2017

Trial information

Trial identification

Sponsor protocol code	CV181-363

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	Pepparedsleden 1, Mölndal, Sweden, 431 53
Public contact	Eva Johnsson, AstraZeneca, +46 (0) 31 7762484, eva.johnsson@astrazeneca.com
Scientific contact	Eva Johnsson, AstraZeneca, +46 (0) 31 7762484, eva.johnsson@astrazeneca.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	31 July 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 October 2016
Global end of trial reached?	Yes
Global end of trial date	26 October 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the mean change from baseline in glycated hemoglobin (HbA1c) achieved with saxagliptin in co-administration with dapagliflozin added to current background therapy with metformin compared to sitagliptin
added to current background therapy with metformin at week 26.

Protection of trial subjects:

The laws and regulatory requirements of all countries that had sites participating in this study were adhered to. This study was conducted in accordance with Good Clinical Practice, as defined by the International Council for Harmonisation and in accordance with the ethical principles underlying European Union (EU) Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. The rights, safety, and well-being of the study subjects were the most important consideration and prevailed over the interests of science and society.

Background therapy:

Subjects received metformin (≥ 1,500 mg/day) in accordance with the product label for their respective countries. Dose adjustment of metformin was not allowed. Metformin background therapy was not provided by the Sponsor.

Evidence for comparator: -

Actual start date of recruitment	22 December 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 States: 227
Country: Number of subjects enrolled	Romania: 41
Country: Number of subjects enrolled	Hungary: 25
Country: Number of subjects enrolled	Mexico: 88
Country: Number of subjects enrolled	Poland: 36
Country: Number of subjects enrolled	South Africa: 44
Worldwide total number of subjects	461
EEA total number of subjects	102

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)	381
From 65 to 84 years	80
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

461 Patients were Randomized and treated, during the 26-week, Double-blind Treatment Period. 411 patients completed.
402 Patients were Randomized and treated, during the 52-week, Double-blind Treatment Period. 378 patients completed.?

Period 1

Period 1 title	26 week (short term)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	SAXA + DAPA + MET

Arm description:

Saxagliptin 5-mg tablet+Dapagliflozin 10-mg tablet+Placebo capsules matching the sitagliptin 100-mg capsules+Metformin background therapy

Arm type	Experimental
Investigational medicinal product name	saxagliptin and dapagliflozin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

5mg saxagliptin and 10 mg dapagliflozin

Arm title	SITA + MET

Arm description:

Placebo tablet matching the saxagliptin 5-mg tablet +Placebo tablet matching the dapagliflozin 10-mg table+Sitagliptin 100-mg capsules +Metformin background therapy

Arm type	Active comparator
Investigational medicinal product name	sitagliptin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

100 mg

Number of subjects in period 1	SAXA + DAPA + MET	SITA + MET
Started	232	229
Completed	213	198
Not completed	19	31
Adverse event, non-fatal	1	9
Withrawal of the consent by the subject	7	10
other	1	1
Lost to follow-up	3	1
Subject no longer meets study criteria	5	8
Discontinuation by the subject	2	2

Period 2

Period 2 title	52 week (long term)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	SAXA + DAPA + MET

Arm description:

Saxagliptin 5-mg tablet+Dapagliflozin 10-mg tablet+Placebo capsules matching the sitagliptin 100-mg capsules+Metformin background therapy

Arm type	Experimental
Investigational medicinal product name	saxagliptin and dapgliflozin tablets
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

5 mg saxagliptin and 10 mg dapagliflozin

Arm title	SITA + MET

Arm description:

Placebo tablet matching the saxagliptin 5-mg tablet +Placebo tablet matching the dapagliflozin 10-mg table+Sitagliptin 100-mg capsules +Metformin background therapy

Arm type	Active comparator
Investigational medicinal product name	sitagliptin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

100 mg

Number of subjects in period 2[1]	SAXA + DAPA + MET	SITA + MET
Started	209	193
Completed	198	180
Not completed	11	13
Non-Compliance	2	3
Adverse event, non-fatal	3	1
Withrawal of the consent by the subject	4	6
Lost to follow-up	2	2
Subject no longer meets study criteria	-	1

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Subjects discontinued the study prematurely

Subject analysis set description:

Saxagliptin 5-mg tablet +Dapagliflozin 10-mg tablet+Placebo capsules matching the sitagliptin 100-mg capsules+Metformin background therapy

Subject analysis set title	SITA+MET
Subject analysis set type	Full analysis

Subject analysis set description:

Placebo tablet matching the saxagliptin 5-mg tablet+Placebo tablet matching the dapagliflozin 10-mg tablet+Sitagliptin 100-mg capsules+Metformin background therapy

Reporting group values	SAXA+DAPA+MET	SITA+MET	
Number of subjects	232	229	
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)	197	184	
From 65-84 years	35	45	
85 years and over	0	0	
Gender Categorical Units: Subjects			
Female	132	119	
Male	100	110	
Geographic Region Units: Subjects			

The America Units: Subjects			

Geographic Region Units: Subjects			

xx Units: Subjects			

End points

End points reporting groups

Reporting group title	SAXA + DAPA + MET
Reporting group description:	
Saxagliptin 5-mg tablet+Dapagliflozin 10-mg tablet+Placebo capsules matching the sitagliptin 100-mg capsules+Metformin background therapy	
Reporting group title	SITA + MET
Reporting group description:	
Placebo tablet matching the saxagliptin 5-mg tablet +Placebo tablet matching the dapagliflozin 10-mg table+Sitagliptin 100-mg capsules +Metformin background therapy	
Reporting group title	SAXA + DAPA + MET
Reporting group description:	
Saxagliptin 5-mg tablet+Dapagliflozin 10-mg tablet+Placebo capsules matching the sitagliptin 100-mg capsules+Metformin background therapy	
Reporting group title	SITA + MET
Reporting group description:	
Placebo tablet matching the saxagliptin 5-mg tablet +Placebo tablet matching the dapagliflozin 10-mg table+Sitagliptin 100-mg capsules +Metformin background therapy	
Subject analysis set title	SAXA+DAPA+MET
Subject analysis set type	Full analysis
Subject analysis set description:	
Saxagliptin 5-mg tablet +Dapagliflozin 10-mg tablet+Placebo capsules matching the sitagliptin 100-mg capsules+Metformin background therapy	
Subject analysis set title	SITA+MET
Subject analysis set type	Full analysis
Subject analysis set description:	
Placebo tablet matching the saxagliptin 5-mg tablet+Placebo tablet matching the dapagliflozin 10-mg tablet+Sitagliptin 100-mg capsules+Metformin background therapy	

Primary: Mean change in HbA1c

End point title	Mean change in HbA1c
End point description:	
End point type	Primary
End point timeframe:	
From baseline to week 26	

End point values	SAXA+DAPA+MET	SITA+MET		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	224	219		
Units: Percentage (%)				
least squares mean (standard error)	-1.41 (± 0.0696)	-1.07 (± 0.0719)		

Statistical analyses

Statistical analysis title	SAXA + DAPA + MET VS. SITA + MET
Comparison groups	SAXA+DAPA+MET v SITA+MET
Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0008
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.53
upper limit	-0.14
Variability estimate	Standard error of the mean
Dispersion value	0.1001

Secondary: Percent of subjects achieving a therapeutic glycemic response, defined as HbA1c < 7.0%

End point title	Percent of subjects achieving a therapeutic glycemic response, defined as HbA1c < 7.0%
End point description:	
End point type	Secondary
End point timeframe: week 26	

End point values	SAXA+DAPA+MET	SITA+MET		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	224	219		
Units: Percentage				
least squares mean (standard error)	37.3 (± 3.150)	25.1 (± 2.871)		

Statistical analyses

Statistical analysis title	SAXA + DAPA + MET VS. SITA + MET
Comparison groups	SAXA+DAPA+MET v SITA+MET

Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0034
Method	Regression, Logistic
Parameter estimate	Mean difference (final values)
Point estimate	12.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	4
upper limit	20.4
Variability estimate	Standard error of the mean
Dispersion value	4.175

Secondary: Mean change in total body weight	
End point title	Mean change in total body weight
End point description:	
End point type	Secondary
End point timeframe: from baseline to week 26	

End point values	SAXA+DAPA+MET	SITA+MET		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	224	219		
Units: kg				
least squares mean (standard error)	-1.86 (± 0.2010)	-0.51 (± 0.2078)		

Statistical analyses

Statistical analysis title	SAXA + DAPA + MET VS. SITA + MET
Comparison groups	SAXA+DAPA+MET v SITA+MET
Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.35

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.92
upper limit	-0.79
Variability estimate	Standard error of the mean
Dispersion value	0.2891

Secondary: Mean change in FPG	
End point title	Mean change in FPG
End point description:	
End point type	Secondary
End point timeframe: from baseline to week 26	

End point values	SAXA+DAPA+MET	SITA+MET		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	224	219		
Units: mg/dl				
least squares mean (standard error)	-31.9 (± 2.538)	-11.0 (± 2.668)		

Statistical analyses

Statistical analysis title	SAXA + DAPA + MET VS. SITA + MET
Comparison groups	SAXA+DAPA+MET v SITA+MET
Number of subjects included in analysis	443
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-20.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-28.2
upper limit	-13.7
Variability estimate	Standard error of the mean
Dispersion value	3.682

Adverse events

Adverse events information

Timeframe for reporting adverse events:

52 weeks

Adverse event reporting additional description:

including Data After Rescue
Treated Subjects (The Treated Subjects data set consists of all subjects who received at least 1 dose of double-blind study drug)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	SITA + MET

Reporting group description:

Placebo tablet matching the saxagliptin 5-mg tablet+Placebo tablet matching the dapagliflozin 10-mg tablet+Sitagliptin 100-mg capsules+Metformin background therapy

Reporting group title	SAXA + DAPA + MET

Reporting group description:

Saxagliptin 5-mg tablet +Dapagliflozin 10-mg tablet+Placebo capsules matching the sitagliptin 100-mg capsules+Metformin background therapy

Serious adverse events	SITA + MET	SAXA + DAPA + MET	
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 229 (5.68%)	9 / 232 (3.88%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	0 / 229 (0.00%)	1 / 232 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm	Additional description: Meningioma		
subjects affected / exposed	0 / 229 (0.00%)	1 / 232 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Laceration of leg	Additional description: Laceration		

subjects affected / exposed	1 / 229 (0.44%)	0 / 232 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb motor deficit	Additional description: Lower limb fracture		
subjects affected / exposed	1 / 229 (0.44%)	0 / 232 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis	Additional description: Deep vein thrombosis		
subjects affected / exposed	1 / 229 (0.44%)	0 / 232 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral vasoconstriction, necrosis and vascular insufficiency	Additional description: Peripheral Arterial Occlusive Disease		
subjects affected / exposed	0 / 229 (0.00%)	1 / 232 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 229 (0.44%)	0 / 232 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure chronic aggravated			
subjects affected / exposed	1 / 229 (0.44%)	0 / 232 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure (NOS)	Additional description: Cardiac Failure Congestive		
subjects affected / exposed	1 / 229 (0.44%)	0 / 232 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiomyopathy primary	Additional description: congestive cardiomyopathy		
subjects affected / exposed	1 / 229 (0.44%)	0 / 232 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Coronary artery disease NOS			
subjects affected / exposed	0 / 229 (0.00%)	1 / 232 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve disease NOS	Additional description: Mitral valve Prolapse		
subjects affected / exposed	1 / 229 (0.44%)	0 / 232 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heart rate increased	Additional description: Palpitations		
subjects affected / exposed	0 / 229 (0.00%)	1 / 232 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia NOS	Additional description: Tachycardia		
subjects affected / exposed	1 / 229 (0.44%)	0 / 232 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 229 (0.44%)	0 / 232 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar nerve decompression	Additional description: Lumbar Radiculopathy		
subjects affected / exposed	0 / 229 (0.00%)	1 / 232 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity NOS	Additional description: Drug hypersnsitivity		
subjects affected / exposed	1 / 229 (0.44%)	0 / 232 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Dysfunctional uterine haemorrhage	Additional description: Dysfunctional Uterine Bleeding		

subjects affected / exposed	0 / 229 (0.00%)	1 / 232 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometriosis ablation	Additional description: Endometriosis		
subjects affected / exposed	2 / 229 (0.87%)	0 / 232 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal wall disorder	Additional description: Abdominal Pain		
subjects affected / exposed	1 / 229 (0.44%)	0 / 232 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal exam abnormal	Additional description: Anal Fissure		
subjects affected / exposed	1 / 229 (0.44%)	0 / 232 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal junction ulcer	Additional description: Garstrooesophageal Reflux Disease		
subjects affected / exposed	0 / 229 (0.00%)	1 / 232 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting alone	Additional description: Vomiting		
subjects affected / exposed	0 / 229 (0.00%)	1 / 232 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory failures (excl neonatal)	Additional description: Acute Respiratory Failure		
subjects affected / exposed	1 / 229 (0.44%)	0 / 232 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysponesis	Additional description: Dyspnoea		
subjects affected / exposed	1 / 229 (0.44%)	0 / 232 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Psychiatric disorders			
Mental status changes			
subjects affected / exposed	0 / 229 (0.00%)	1 / 232 (0.43%)	
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			
Osteoarthritis aggravated	Additional description: Osteoarthritis		
subjects affected / exposed	2 / 229 (0.87%)	0 / 232 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia viral	Additional description: Pneumonia		
subjects affected / exposed	2 / 229 (0.87%)	0 / 232 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 229 (0.44%)	0 / 232 (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: 2 %

Non-serious adverse events	SITA + MET	SAXA + DAPA + MET	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	131 / 229 (57.21%)	132 / 232 (56.90%)	
Congenital, familial and genetic disorders			
Lipid metabolism disorder	Additional description: dyslipidaemia		
subjects affected / exposed	3 / 229 (1.31%)	5 / 232 (2.16%)	
occurrences (all)	3	5	
Vascular disorders			
hypertension			
subjects affected / exposed	8 / 229 (3.49%)	3 / 232 (1.29%)	
occurrences (all)	10	3	
Cardiac disorders			

Atrial flutter/ fibrillation			
subjects affected / exposed	5 / 229 (2.18%)	1 / 232 (0.43%)	
occurrences (all)	5	1	
Nervous system disorders			
Headache			
subjects affected / exposed	10 / 229 (4.37%)	13 / 232 (5.60%)	
occurrences (all)	11	16	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	7 / 229 (3.06%)	1 / 232 (0.43%)	
occurrences (all)	8	1	
Gastrointestinal disorders			
Diarrhea NOS			
subjects affected / exposed	6 / 229 (2.62%)	2 / 232 (0.86%)	
occurrences (all)	7	2	
Gastritis			
subjects affected / exposed	5 / 229 (2.18%)	1 / 232 (0.43%)	
occurrences (all)	5	1	
Gastrooesophageal junction ulcer	Additional description: Gastrooesophageal Reflux Disease		
subjects affected / exposed	1 / 229 (0.44%)	5 / 232 (2.16%)	
occurrences (all)	1	5	
Respiratory, thoracic and mediastinal disorders			
Cough aggravated	Additional description: cough		
subjects affected / exposed	7 / 229 (3.06%)	3 / 232 (1.29%)	
occurrences (all)	7	3	
Renal and urinary disorders			

Backache	Additional description: back pain		
subjects affected / exposed	9 / 229 (3.93%)	5 / 232 (2.16%)	
occurrences (all)	9	5	
Pain	Additional description: Pain in extremity		
subjects affected / exposed	6 / 229 (2.62%)	3 / 232 (1.29%)	
occurrences (all)	6	3	
Infections and infestations			
Bronchitis NOS			
subjects affected / exposed	2 / 229 (0.87%)	8 / 232 (3.45%)	
occurrences (all)	2	9	
Gastroenteritis			
subjects affected / exposed	5 / 229 (2.18%)	4 / 232 (1.72%)	
occurrences (all)	5	5	
Influenza with other manifestations	Additional description: Influenza		
subjects affected / exposed	11 / 229 (4.80%)	8 / 232 (3.45%)	
occurrences (all)	12	8	
Nasopharyngeal disorder	Additional description: Nasopharygitis		
subjects affected / exposed	12 / 229 (5.24%)	18 / 232 (7.76%)	
occurrences (all)	12	20	
Sinus disorder	Additional description: Sinusitis		
subjects affected / exposed	2 / 229 (0.87%)	5 / 232 (2.16%)	
occurrences (all)	2	6	
Upper respiratory infection	Additional description: Upper respiratory tract infection		
subjects affected / exposed	8 / 229 (3.49%)	7 / 232 (3.02%)	
occurrences (all)	9	8	
Vulvovaginal mycotic infection			
subjects affected / exposed	2 / 229 (0.87%)	5 / 232 (2.16%)	
occurrences (all)	2	7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported