Clinical trial results:
The Precision Hypertension Care study
Summary

EudraCT number	2015-003049-24
Trial protocol	SE
Global end of trial date	11 June 2021

Results information

Result version number	v1 (current)
This version publication date	27 June 2022
First version publication date	27 June 2022

Trial information

Trial identification

Sponsor protocol code	PHY201501

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Uppsala University
Sponsor organisation address	Department of Medical Sciences, Uppsala, Sweden, 75185
Public contact	Department of Medical Sciences, Uppsala University, johan.sundstrom@uu.se
Scientific contact	Department of Medical Sciences, Uppsala University, johan.sundstrom@uu.se

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	02 June 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 June 2021
Global end of trial reached?	Yes
Global end of trial date	11 June 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To establish the potential for precision hypertension care, by investigating if there is a consistent between-person variation in blood pressure response to the common blood pressure-lowering drug classes of a clinically relevant magnitude, given the within-person variation in blood pressure.

Protection of trial subjects:

The investigational medicinal products (IMPs) and therapies used in the study are all well known and were not expected to cause a high risk for the study participants. Evidence-based drug titration and target doses were picked for all of the IMPs. The treatment length, 7-9 weeks per treatment arm, was based on the latest guidelines.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 February 2017
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	Sweden: 280
Worldwide total number of subjects	280
EEA total number of subjects	280

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)	150
From 65 to 84 years	130
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited from the SCAPIS study or via advertisement.

Pre-assignment

Screening details:

391 consenting participants were screened for inclusion/exclusion criteria between February 20, 2017, and May 25, 2020, and 280 participants were randomised.

Pre-assignment period milestones

Number of subjects started	391[1]
Number of subjects completed	280

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Adverse event, non-fatal: 2
Reason: Number of subjects	Physician decision: 3
Reason: Number of subjects	Consent withdrawn by subject: 18
Reason: Number of subjects	Protocol deviation: 1
Reason: Number of subjects	Screen failure: 87

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Enrollment is defined as patients randomised to a treatment arm. Pre-assignment is the screening period prior to randomisation.

Period 1

Period 1 title	Baseline period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

Investigational products were provided to the patient in inconspicuous packaging, labelled with randomization number by clinical staff. Interpretation of 24h blood pressure and ECG measurements, symptom and treatment preference ratings were performed by persons unaware of the treatment allocation.

Arms

Arm title	Total data set
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Candesartan
Investigational medicinal product code	
Other name	Atacand
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Week 1-2: 8 mg administered as 1 x 8 mg capsule
Week 3-8: 16 mg administered as 1 x 16 mg capsule.
For a total treatment period of 7-9 weeks.

Investigational medicinal product name	Lisinopril
Investigational medicinal product code	
Other name	Zestril
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Week 1-2: 10 mg administered as 1 x 10 mg capsule
Week 3-8: 20 mg administered as 1 x 20 mg capsule.
For a total treatment period of 7-9 weeks.

Investigational medicinal product name	Amlodipin
Investigational medicinal product code	
Other name	Norvasc
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Week 1-2: 5 mg administered as 1 x 5 mg capsule
Week 3-8: 10 mg administered as 1 x 10 mg capsule.
For a total treatment period of 7-9 weeks.

Investigational medicinal product name	Hydrochlortiazid
Investigational medicinal product code	
Other name	Hydrochlortiazid Evolan
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Week 1-2: 12,5 mg administered as 1 x 12,5mg capsule
Week 3-8: 25 mg administered as 1 x 25 mg capsule
For a total treatment period of 7-9 weeks.

Number of subjects in period 1	Total data set
Started	280
Completed	280

Period 2

Period 2 title	Overall trial
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

Investigational products were provided to the patient in inconspicuous packaging, labelled with randomization number by clinical staff.

Arms

Are arms mutually exclusive?	No

Arm title	Candesartan
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Candesartan
Investigational medicinal product code	
Other name	Atacand
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Week 1-2: 8 mg administered as 1 x 8 mg capsule
Week 3-8: 16 mg administered as 1 x 16 mg capsule.
For a total treatment period of 7-9 weeks.

Arm title	Lisinopril
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Lisinopril
Investigational medicinal product code	
Other name	Zestril
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Week 1-2: 10 mg administered as 1 x 10 mg capsule
Week 3-8: 20 mg administered as 1 x 20 mg capsule.
For a total treatment period of 7-9 weeks.

Arm title	Amlodipine
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Amlodipin
Investigational medicinal product code	
Other name	Norvasc
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Week 1-2: 5 mg administered as 1 x 5 mg capsule
Week 3-8: 10 mg administered as 1 x 10 mg capsule.
For a total treatment period of 7-9 weeks.

Arm title	Hydrochlortiazid
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Hydrochlortiazid
Investigational medicinal product code	
Other name	Hydrochlortiazid Evolan
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Week 1-2: 12,5 mg administered as 1 x 12,5mg capsule
Week 3-8: 25 mg administered as 1 x 25 mg capsule
For a total treatment period of 7-9 weeks.

Number of subjects in period 2	Candesartan	Lisinopril	Amlodipine
Started	280	280	280
Completed	250	241	244
Not completed	30	39	36
Consent withdrawn by subject	2	4	-
Physician decision	-	1	-
Adverse event, non-fatal	2	1	4
Tachycard every treatmentperiod. Stop after few we	-	-	-
Protocol deviation	26	33	32

Number of subjects in period 2	Hydrochlortiazid
Started	280
Completed	253
Not completed	27
Consent withdrawn by subject	6
Physician decision	-
Adverse event, non-fatal	4
Tachycard every treatmentperiod. Stop after few we	1
Protocol deviation	16

Baseline characteristics

Reporting groups

Reporting group title	Total data set

Reporting group description: -

Reporting group values	Total data set	Total	
Number of subjects	280	280	
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			
median	64		
inter-quartile range (Q1-Q3)	58 to 70	-	
Gender categorical Units: Subjects			
Female	128	128	
Male	152	152	
Daytime systolic blood pressure Units: mmHg			
arithmetic mean	145		
standard deviation	± 11	-	
Daytime diastolic blood pressure Units: mmHg			
arithmetic mean	89		
standard deviation	± 9	-	

End points

End points reporting groups	
Reporting group title	Total data set
Reporting group description: -	
Reporting group title	Candesartan
Reporting group description: -	
Reporting group title	Lisinopril
Reporting group description: -	
Reporting group title	Amlodipine
Reporting group description: -	
Reporting group title	Hydrochlortiazid
Reporting group description: -	

Primary: Daytime systolic blood pressure by treatment	
End point title	Daytime systolic blood pressure by treatment
End point description:	
The primary analysis set consisted of treatment periods with at least 90% adherence and a valid daytime blood pressure measurement.	
End point type	Primary
End point timeframe:	
First treatment period with the investigational product.	

End point values	Candesartan	Lisinopril	Amlodipine	Hydrochlortiazid
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	250	241	244	253
Units: mmHg				
arithmetic mean (standard deviation)	131.8 (± 12.8)	129.7 (± 12.7)	130.9 (± 8.6)	136.1 (± 10.3)

Statistical analyses

Statistical analysis title	Average treatment contrast Lis vs Cand
Statistical analysis description:	
Estimated average treatment contrasts in systolic blood pressure in the trial population. Linear mixed effect model with participant as the only random factor.	
Comparison groups	Candesartan v Lisinopril
Number of subjects included in analysis	491
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0002
Method	Mixed models analysis

Statistical analysis title	Average treatment contrast Aml vs Cand
Statistical analysis description: Estimated average treatment contrasts in systolic blood pressure in the trial population. Linear mixed effect model with participant as the only random factor.	
Comparison groups	Amlodipine v Candesartan
Number of subjects included in analysis	494
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1847
Method	Mixed models analysis

Statistical analysis title	Average treatment contrast Hyd vs Cand
Statistical analysis description: Estimated average treatment contrasts in systolic blood pressure in the trial population. Linear mixed effect model with participant as the only random factor.	
Comparison groups	Candesartan v Hydrochlortiazid
Number of subjects included in analysis	503
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Mixed models analysis

Statistical analysis title	Average treatment contrast Aml vs Lis
Statistical analysis description: Estimated average treatment contrasts in systolic blood pressure in the trial population. Linear mixed effect model with participant as the only random factor.	
Comparison groups	Amlodipine v Lisinopril
Number of subjects included in analysis	485
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0179
Method	Mixed models analysis

Statistical analysis title	Average treatment contrast Hyd vs Lis
Comparison groups	Lisinopril v Hydrochlortiazid

Number of subjects included in analysis	494
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Mixed models analysis

Statistical analysis title	Average treatment contrast Hyd vs Aml

Statistical analysis description:

Estimated average treatment contrasts in systolic blood pressure in the trial population. Linear mixed effect model with participant as the only random factor.

Comparison groups	Amlodipine v Hydrochlortiazid
Number of subjects included in analysis	497
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	Mixed models analysis

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are presented by allocated treatment in the period of onset, defined as onset date after the Visit 4 date of the preceding period (or randomisation date, for Period 1), and up to and including the Visit 4 date for the period in question.

Adverse event reporting additional description:

Throughout the study (until visit 3 in last treatment period), patients had access to an electronic diary for reporting symptoms using a validated questionnaire, PERSYVE (only modified section 2.1 in questionnaire was used in this study).

Assessment type	Systematic

Dictionary used

Dictionary name	ICD
Dictionary version	11

Reporting groups

Reporting group title	Candesartan
Reporting group description: -	
Reporting group title	Lisinopril
Reporting group description: -	
Reporting group title	Amlodipine
Reporting group description: -	
Reporting group title	Hydrochlortiazid
Reporting group description: -	

Serious adverse events	Candesartan	Lisinopril	Amlodipine
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 264 (0.38%)	4 / 263 (1.52%)	2 / 267 (0.75%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Vascular disorders			
BB00.Z: Pulmonary thromboembolism, unspecified			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	1 / 267 (0.37%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BA41.1: Acute non-ST elevation myocardial infarction			
subjects affected / exposed	0 / 264 (0.00%)	0 / 263 (0.00%)	0 / 267 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
DB10.00: Acute appendicitis with generalised peritonitis			

subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	0 / 267 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DC50.Z: Peritonitis			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	0 / 267 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DC70.00: Diverticulitis of small intestine with perforation and abscess			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	0 / 267 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LB15.0: Meckel diverticulum with complication			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	0 / 267 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MD81: Abdominal or pelvic pain			
subjects affected / exposed	0 / 264 (0.00%)	0 / 263 (0.00%)	1 / 267 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ME24.9Z: Gastrointestinal bleeding, unspecified			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	0 / 267 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
EB04: Idiopathic angioedema			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	0 / 267 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
GB54: Tubulo-interstitial nephritis, not specied as acute or chronic			

subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	0 / 267 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GB56.4: Other or unspecified hydronephrosis			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	0 / 267 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GB70.0Z: Calculus of kidney, unspecified			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	0 / 267 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GC00.1: Infectious cystitis			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	0 / 267 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
RA01.0: COVID-19, virus identified			
subjects affected / exposed	0 / 264 (0.00%)	0 / 263 (0.00%)	1 / 267 (0.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Hydrochlortiazid		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 268 (0.37%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Vascular disorders			
BB00.Z: Pulmonary thromboembolism, unspecified			
subjects affected / exposed	0 / 268 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
BA41.1: Acute non-ST elevation myocardial infarction			

subjects affected / exposed	1 / 268 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
DB10.00: Acute appendicitis with generalised peritonitis			
subjects affected / exposed	0 / 268 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
DC50.Z: Peritonitis			
subjects affected / exposed	0 / 268 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
DC70.00: Diverticulitis of small intestine with perforation and abscess			
subjects affected / exposed	0 / 268 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
LB15.0: Meckel diverticulum with complication			
subjects affected / exposed	0 / 268 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
MD81: Abdominal or pelvic pain			
subjects affected / exposed	0 / 268 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
ME24.9Z: Gastrointestinal bleeding, unspecified			
subjects affected / exposed	0 / 268 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
EB04: Idiopathic angioedema			

subjects affected / exposed	0 / 268 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
GB54: Tubulo-interstitial nephritis, not specied as acute or chronic			
subjects affected / exposed	0 / 268 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
GB56.4: Other or unspecified hydronephrosis			
subjects affected / exposed	0 / 268 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
GB70.0Z: Calculus of kidney, unspecified			
subjects affected / exposed	0 / 268 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
GC00.1: Infectious cystitis			
subjects affected / exposed	0 / 268 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
RA01.0: COVID-19, virus identified			
subjects affected / exposed	0 / 268 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Candesartan	Lisinopril	Amlodipine
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 264 (10.61%)	40 / 263 (15.21%)	33 / 267 (12.36%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

2A20.4: Polycythaemia vera			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	0 / 267 (0.00%)
occurrences (all)	1	0	0
2C30.Z: Melanoma of skin, unspecified			
subjects affected / exposed	0 / 264 (0.00%)	0 / 263 (0.00%)	0 / 267 (0.00%)
occurrences (all)	0	0	0
2E80.02: Deep internal or visceral lipoma			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	0 / 267 (0.00%)
occurrences (all)	0	1	0
2E86.0 & XA99N3 & XH1CZ1 : Leiomyoma of uterus			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	0 / 267 (0.00%)
occurrences (all)	1	0	0
2E90.5: Benign neoplasm of oropharynx			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	0 / 267 (0.00%)
occurrences (all)	1	0	0
2F31.1: Benign non-mesenchymal neoplasm of uterus, corpus uteri			
subjects affected / exposed	0 / 264 (0.00%)	0 / 263 (0.00%)	1 / 267 (0.37%)
occurrences (all)	0	0	1
2F90.Y & XA07S: Neoplasm of unknown behaviour of parotid salivary glands			
subjects affected / exposed	0 / 264 (0.00%)	0 / 263 (0.00%)	1 / 267 (0.37%)
occurrences (all)	0	0	1
Vascular disorders			
BD70.2: Thrombophlebitis migrans			
subjects affected / exposed	0 / 264 (0.00%)	0 / 263 (0.00%)	1 / 267 (0.37%)
occurrences (all)	0	0	1
Surgical and medical procedures			
QF01.Y: Other specified acquired absence of organs			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	0 / 267 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
MA10.2: Abnormal level of unspecified serum enzyme			

subjects affected / exposed	0 / 264 (0.00%)	0 / 263 (0.00%)	1 / 267 (0.37%)
occurrences (all)	0	0	1
MA18.4: Low haemoglobin			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	0 / 267 (0.00%)
occurrences (all)	0	1	0
ME86.3: Symptom or complaint of the chest			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	0 / 267 (0.00%)
occurrences (all)	1	0	0
MG29.00: Ankle oedema			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	0 / 267 (0.00%)
occurrences (all)	0	1	0
Immune system disorders			
4A8Z: Allergic or hypersensitivity conditions of unspecified type			
subjects affected / exposed	0 / 264 (0.00%)	0 / 263 (0.00%)	0 / 267 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
GA30.1: Postmenopausal uterine bleeding			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	0 / 267 (0.00%)
occurrences (all)	1	0	0
GA90: Hyperplasia of prostate			
subjects affected / exposed	0 / 264 (0.00%)	0 / 263 (0.00%)	0 / 267 (0.00%)
occurrences (all)	0	0	0
GB23.5: Mastodynia			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	0 / 267 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
MD11.5: Dyspnoea			
subjects affected / exposed	0 / 264 (0.00%)	0 / 263 (0.00%)	1 / 267 (0.37%)
occurrences (all)	0	0	1
MD12: Cough			
subjects affected / exposed	0 / 264 (0.00%)	2 / 263 (0.76%)	1 / 267 (0.37%)
occurrences (all)	0	3	1
MD30.Z: Chest pain, unspecified			

subjects affected / exposed	0 / 264 (0.00%)	0 / 263 (0.00%)	1 / 267 (0.37%)
occurrences (all)	0	0	1
MD36.0: Pain in throat			
subjects affected / exposed	0 / 264 (0.00%)	0 / 263 (0.00%)	1 / 267 (0.37%)
occurrences (all)	0	0	1
CA00: Acute nasopharyngitis			
subjects affected / exposed	3 / 264 (1.14%)	1 / 263 (0.38%)	5 / 267 (1.87%)
occurrences (all)	3	1	5
CA0Y: Other specified upper respiratory tract disorders			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	1 / 267 (0.37%)
occurrences (all)	0	1	1
CA40.Z & XK8G: Pneumonia, organism unspecified [Left]			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	0 / 267 (0.00%)
occurrences (all)	0	1	0
CA40.Z: Pneumonia, organism unspecified			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	0 / 267 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
6B60.0: Dissociative neurological symptom disorder, with visual disturbance			
subjects affected / exposed	0 / 264 (0.00%)	0 / 263 (0.00%)	0 / 267 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
0Z: Injuries to the head, unspecified			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	0 / 267 (0.00%)
occurrences (all)	0	1	0
NB3Z: Injuries to the thorax, unspecified			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	0 / 267 (0.00%)
occurrences (all)	0	1	0
NC32.1 & XA2N25: Fracture of upper end of radius [Radial head]			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	0 / 267 (0.00%)
occurrences (all)	0	1	0
NC32.1: Fracture of upper end of radius			

subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	0 / 267 (0.00%)
occurrences (all)	0	1	0
NC53.3Z & XA88S1: Fracture of other metacarpal bone, unspecified [Fifth metacarpal]			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	0 / 267 (0.00%)
occurrences (all)	0	1	0
NC54.6Z: Strain or sprain of wrist, unspecified			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	0 / 267 (0.00%)
occurrences (all)	0	1	0
NE61: Harmful effects of or exposure to noxious substances, chiefly nonmedicinal as to source, not e			
subjects affected / exposed	0 / 264 (0.00%)	2 / 263 (0.76%)	1 / 267 (0.37%)
occurrences (all)	0	2	1
NF0A.3: Post traumatic wound infection, not elsewhere classified			
subjects affected / exposed	0 / 264 (0.00%)	0 / 263 (0.00%)	1 / 267 (0.37%)
occurrences (all)	0	0	1
Cardiac disorders			
BC81.2Z: Macro reentrant atrial tachycardia, unspecified			
subjects affected / exposed	0 / 264 (0.00%)	0 / 263 (0.00%)	0 / 267 (0.00%)
occurrences (all)	0	0	0
BC81.3Z: Atrial fibrillation, unspecified			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	0 / 267 (0.00%)
occurrences (all)	1	0	0
BD11.Z: Left ventricular failure, unspecified			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	0 / 267 (0.00%)
occurrences (all)	1	0	0
BD50.Z: Aortic aneurysm or dissection, unspecified			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	0 / 267 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
8C10.0: Carpal tunnel syndrome			
subjects affected / exposed	0 / 264 (0.00%)	0 / 263 (0.00%)	1 / 267 (0.37%)
occurrences (all)	0	0	1
8C10.1: Lesion of ulnar nerve			

subjects affected / exposed	0 / 264 (0.00%)	0 / 263 (0.00%)	0 / 267 (0.00%)
occurrences (all)	0	0	0
MB40.3: Anaesthesia of skin			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	1 / 267 (0.37%)
occurrences (all)	0	1	1
MB47.3: Cramp			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	0 / 267 (0.00%)
occurrences (all)	1	0	0
MB48.4: Presyncope			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	0 / 267 (0.00%)
occurrences (all)	0	1	0
MB6Y: Headache, unspecified			
subjects affected / exposed	1 / 264 (0.38%)	1 / 263 (0.38%)	0 / 267 (0.00%)
occurrences (all)	1	1	0
Ear and labyrinth disorders			
AA3Z: Otitis externa, unspecified			
subjects affected / exposed	1 / 264 (0.38%)	1 / 263 (0.38%)	0 / 267 (0.00%)
occurrences (all)	1	1	0
AB31.2: Benign positional paroxysmal vertigo			
subjects affected / exposed	0 / 264 (0.00%)	0 / 263 (0.00%)	0 / 267 (0.00%)
occurrences (all)	0	0	0
AB51.Z & XK9K: Acquired hearing impairment, unspecified [Right]			
subjects affected / exposed	0 / 264 (0.00%)	0 / 263 (0.00%)	0 / 267 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
9B10.Z: Cataract, unspecified			
subjects affected / exposed	0 / 264 (0.00%)	2 / 263 (0.76%)	0 / 267 (0.00%)
occurrences (all)	0	3	0
9B8Y: Other specified disorders of the vitreous body			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	0 / 267 (0.00%)
occurrences (all)	0	1	0
9D90.Z & XK70: Vision impairment including blindness, unspecified [Unilateral, unspecified]			
subjects affected / exposed	0 / 264 (0.00%)	0 / 263 (0.00%)	1 / 267 (0.37%)
occurrences (all)	0	0	1

9E1Z: Diseases of the visual system, unspecified			
subjects affected / exposed	1 / 264 (0.38%)	2 / 263 (0.76%)	2 / 267 (0.75%)
occurrences (all)	1	2	2
Gastrointestinal disorders			
MD81.12: Pain localised to other parts of lower abdomen			
subjects affected / exposed	0 / 264 (0.00%)	0 / 263 (0.00%)	1 / 267 (0.37%)
occurrences (all)	0	0	1
MD90.0: Nausea			
subjects affected / exposed	0 / 264 (0.00%)	2 / 263 (0.76%)	1 / 267 (0.37%)
occurrences (all)	0	2	1
MD95: Heartburn			
subjects affected / exposed	0 / 264 (0.00%)	0 / 263 (0.00%)	1 / 267 (0.37%)
occurrences (all)	0	0	1
DA09.62: Periapical abscess without sinus			
subjects affected / exposed	0 / 264 (0.00%)	0 / 263 (0.00%)	0 / 267 (0.00%)
occurrences (all)	0	0	0
DA60.Z: Gastric ulcer, unspecified			
subjects affected / exposed	0 / 264 (0.00%)	0 / 263 (0.00%)	0 / 267 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
EE13.1: Ingrowing nail			
subjects affected / exposed	0 / 264 (0.00%)	0 / 263 (0.00%)	1 / 267 (0.37%)
occurrences (all)	0	0	1
EA90.42: Palmoplantar pustulosis			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	0 / 267 (0.00%)
occurrences (all)	1	0	0
ME65.1: Itching of skin			
subjects affected / exposed	0 / 264 (0.00%)	0 / 263 (0.00%)	1 / 267 (0.37%)
occurrences (all)	0	0	1
ME66.6Z: Rash, unspecified			
subjects affected / exposed	0 / 264 (0.00%)	2 / 263 (0.76%)	2 / 267 (0.75%)
occurrences (all)	0	2	2
Renal and urinary disorders			
GB70.0Z: Calculus of kidney, unspecified			

subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	1 / 267 (0.37%)
occurrences (all)	2	0	1
GB71.1: Calculus in urethra			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	0 / 267 (0.00%)
occurrences (all)	0	1	0
GC00.1: Infectious cystitis			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	0 / 267 (0.00%)
occurrences (all)	1	0	0
GC40.Z: Pelvic organ prolapse, unspecified			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	0 / 267 (0.00%)
occurrences (all)	0	1	0
MF50.2Z: Urinary incontinence, unspecified			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	0 / 267 (0.00%)
occurrences (all)	0	1	0
Endocrine disorders			
5A00.Z: Hypothyroidism, unspecified			
subjects affected / exposed	0 / 264 (0.00%)	0 / 263 (0.00%)	0 / 267 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
FA01.Z & XK9K: Osteoarthritis of knee, unspecified [Right]			
subjects affected / exposed	0 / 264 (0.00%)	0 / 263 (0.00%)	1 / 267 (0.37%)
occurrences (all)	0	0	1
FA2Z: Inflammatory arthropathies, unspecified			
subjects affected / exposed	0 / 264 (0.00%)	0 / 263 (0.00%)	0 / 267 (0.00%)
occurrences (all)	0	0	0
FA71: Torticollis			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	0 / 267 (0.00%)
occurrences (all)	0	1	0
FA82: Spinal stenosis			
subjects affected / exposed	0 / 264 (0.00%)	0 / 263 (0.00%)	0 / 267 (0.00%)
occurrences (all)	0	0	0
FB50.Z & XK8G: Bursitis, unspecified			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	0 / 267 (0.00%)
occurrences (all)	1	0	0

FB53.0: Adhesive capsulitis of shoulder			
subjects affected / exposed	0 / 264 (0.00%)	0 / 263 (0.00%)	0 / 267 (0.00%)
occurrences (all)	0	0	0
FB55.Z: Enthesopathies, unspecified			
subjects affected / exposed	0 / 264 (0.00%)	0 / 263 (0.00%)	0 / 267 (0.00%)
occurrences (all)	0	0	0
FB56.2: Myalgia			
subjects affected / exposed	0 / 264 (0.00%)	0 / 263 (0.00%)	1 / 267 (0.37%)
occurrences (all)	0	0	1
FB56.4: Pain in limb			
subjects affected / exposed	2 / 264 (0.76%)	0 / 263 (0.00%)	0 / 267 (0.00%)
occurrences (all)	2	0	0
FB56.6: Other specified soft tissue disorders			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	0 / 267 (0.00%)
occurrences (all)	1	0	0
ME82: Pain in joint			
subjects affected / exposed	0 / 264 (0.00%)	0 / 263 (0.00%)	1 / 267 (0.37%)
occurrences (all)	0	0	1
ME84.Z: Spinal pain, unspecified			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	1 / 267 (0.37%)
occurrences (all)	0	1	1
ME85: Stiffness of joint			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	0 / 267 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
1A40.Z: Infectious gastroenteritis or colitis without specification of infectious agent			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	0 / 267 (0.00%)
occurrences (all)	1	0	0
1B72.Z: Impetigo, unspecified			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	0 / 267 (0.00%)
occurrences (all)	0	1	0
1C1G.0: Early cutaneous Lyme borreliosis			
subjects affected / exposed	1 / 264 (0.38%)	1 / 263 (0.38%)	0 / 267 (0.00%)
occurrences (all)	1	1	0

1C1G: Lyme borreliosis			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	0 / 267 (0.00%)
occurrences (all)	1	0	0
1D9Z: Unspecified viral infection of unspecified site			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	0 / 267 (0.00%)
occurrences (all)	0	1	0
1E32: Influenza, virus not identified			
subjects affected / exposed	0 / 264 (0.00%)	0 / 263 (0.00%)	0 / 267 (0.00%)
occurrences (all)	0	0	0
1E91.0: Zoster without complications			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	0 / 267 (0.00%)
occurrences (all)	1	0	0
1E91.Z: Zoster, unspecified			
subjects affected / exposed	0 / 264 (0.00%)	3 / 263 (1.14%)	0 / 267 (0.00%)
occurrences (all)	0	3	0
1F00.Z: Herpes simplex infections, unspecified			
subjects affected / exposed	0 / 264 (0.00%)	1 / 263 (0.38%)	0 / 267 (0.00%)
occurrences (all)	0	1	0
1F23.Z: Candidosis, unspecified			
subjects affected / exposed	0 / 264 (0.00%)	0 / 263 (0.00%)	1 / 267 (0.37%)
occurrences (all)	0	0	1
1F28.Y: Other specified dermatophytosis			
subjects affected / exposed	1 / 264 (0.38%)	0 / 263 (0.00%)	0 / 267 (0.00%)
occurrences (all)	1	0	0
1H0Z: Infection, unspecified			
subjects affected / exposed	0 / 264 (0.00%)	0 / 263 (0.00%)	0 / 267 (0.00%)
occurrences (all)	0	0	0
RA01.0: COVID-19, virus identified			
subjects affected / exposed	1 / 264 (0.38%)	1 / 263 (0.38%)	3 / 267 (1.12%)
occurrences (all)	1	1	3
Metabolism and nutrition disorders			
5C72: Hypo-osmolality or hyponatraemia			
subjects affected / exposed	0 / 264 (0.00%)	0 / 263 (0.00%)	0 / 267 (0.00%)
occurrences (all)	0	0	0

5C77: Hypokalaemia			
subjects affected / exposed	0 / 264 (0.00%)	0 / 263 (0.00%)	1 / 267 (0.37%)
occurrences (all)	0	0	1

Non-serious adverse events	Hydrochlortiazid		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 268 (11.94%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
2A20.4: Polycythaemia vera			
subjects affected / exposed	0 / 268 (0.00%)		
occurrences (all)	0		
2C30.Z: Melanoma of skin, unspecified			
subjects affected / exposed	1 / 268 (0.37%)		
occurrences (all)	1		
2E80.02: Deep internal or visceral lipoma			
subjects affected / exposed	0 / 268 (0.00%)		
occurrences (all)	0		
2E86.0 & XA99N3 & XH1CZ1 : Leiomyoma of uterus			
subjects affected / exposed	0 / 268 (0.00%)		
occurrences (all)	0		
2E90.5: Benign neoplasm of oropharynx			
subjects affected / exposed	0 / 268 (0.00%)		
occurrences (all)	0		
2F31.1: Benign non-mesenchymal neoplasm of uterus, corpus uteri			
subjects affected / exposed	0 / 268 (0.00%)		
occurrences (all)	0		
2F90.Y & XA07S: Neoplasm of unknown behaviour of parotid salivary glands			
subjects affected / exposed	0 / 268 (0.00%)		
occurrences (all)	0		
Vascular disorders			
BD70.2: Thrombophlebitis migrans			
subjects affected / exposed	0 / 268 (0.00%)		
occurrences (all)	0		

Surgical and medical procedures			
QF01.Y: Other specified acquired absence of organs			
subjects affected / exposed	0 / 268 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
MA10.2: Abnormal level of unspecified serum enzyme			
subjects affected / exposed	0 / 268 (0.00%)		
occurrences (all)	0		
MA18.4: Low haemoglobin			
subjects affected / exposed	0 / 268 (0.00%)		
occurrences (all)	0		
ME86.3: Symptom or complaint of the chest			
subjects affected / exposed	0 / 268 (0.00%)		
occurrences (all)	0		
MG29.00: Ankle oedema			
subjects affected / exposed	0 / 268 (0.00%)		
occurrences (all)	0		
Immune system disorders			
4A8Z: Allergic or hypersensitivity conditions of unspecified type			
subjects affected / exposed	1 / 268 (0.37%)		
occurrences (all)	1		
Reproductive system and breast disorders			
GA30.1: Postmenopausal uterine bleeding			
subjects affected / exposed	0 / 268 (0.00%)		
occurrences (all)	0		
GA90: Hyperplasia of prostate			
subjects affected / exposed	1 / 268 (0.37%)		
occurrences (all)	1		
GB23.5: Mastodynia			
subjects affected / exposed	0 / 268 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			

MD11.5: Dyspnoea subjects affected / exposed occurrences (all)	0 / 268 (0.00%) 0		
MD12: Cough subjects affected / exposed occurrences (all)	0 / 268 (0.00%) 0		
MD30.Z: Chest pain, unspecified subjects affected / exposed occurrences (all)	0 / 268 (0.00%) 0		
MD36.0: Pain in throat subjects affected / exposed occurrences (all)	0 / 268 (0.00%) 0		
CA00: Acute nasopharyngitis subjects affected / exposed occurrences (all)	0 / 268 (0.00%) 0		
CA0Y: Other specified upper respiratory tract disorders subjects affected / exposed occurrences (all)	0 / 268 (0.00%) 0		
CA40.Z & XK8G: Pneumonia, organism unspecified [Left] subjects affected / exposed occurrences (all)	0 / 268 (0.00%) 0		
CA40.Z: Pneumonia, organism unspecified subjects affected / exposed occurrences (all)	0 / 268 (0.00%) 0		
Psychiatric disorders 6B60.0: Dissociative neurological symptom disorder, with visual disturbance subjects affected / exposed occurrences (all)	1 / 268 (0.37%) 1		
Injury, poisoning and procedural complications 0Z: Injuries to the head, unspecified subjects affected / exposed occurrences (all)	0 / 268 (0.00%) 0		
NB3Z: Injuries to the thorax, unspecified			

subjects affected / exposed	0 / 268 (0.00%)		
occurrences (all)	0		
NC32.1 & XA2N25: Fracture of upper end of radius [Radial head]			
subjects affected / exposed	0 / 268 (0.00%)		
occurrences (all)	0		
NC32.1: Fracture of upper end of radius			
subjects affected / exposed	0 / 268 (0.00%)		
occurrences (all)	0		
NC53.3Z & XA88S1: Fracture of other metacarpal bone, unspecified [Fifth metacarpal]			
subjects affected / exposed	0 / 268 (0.00%)		
occurrences (all)	0		
NC54.6Z: Strain or sprain of wrist, unspecified			
subjects affected / exposed	0 / 268 (0.00%)		
occurrences (all)	0		
NE61: Harmful effects of or exposure to noxious substances, chiefly nonmedicinal as to source, not e			
subjects affected / exposed	0 / 268 (0.00%)		
occurrences (all)	0		
NF0A.3: Post traumatic wound infection, not elsewhere classified			
subjects affected / exposed	0 / 268 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
BC81.2Z: Macro reentrant atrial tachycardia, unspecified			
subjects affected / exposed	1 / 268 (0.37%)		
occurrences (all)	1		
BC81.3Z: Atrial fibrillation, unspecified			
subjects affected / exposed	2 / 268 (0.75%)		
occurrences (all)	2		
BD11.Z: Left ventricular failure, unspecified			
subjects affected / exposed	0 / 268 (0.00%)		
occurrences (all)	0		
BD50.Z: Aortic aneurysm or			

dissection, unspecified subjects affected / exposed occurrences (all)	0 / 268 (0.00%) 0		
Nervous system disorders 8C10.0: Carpal tunnel syndrome subjects affected / exposed occurrences (all) 8C10.1: Lesion of ulnar nerve subjects affected / exposed occurrences (all) MB40.3: Anaesthesia of skin subjects affected / exposed occurrences (all) MB47.3: Cramp subjects affected / exposed occurrences (all) MB48.4: Presyncope subjects affected / exposed occurrences (all) MB6Y: Headache, unspecified subjects affected / exposed occurrences (all)	0 / 268 (0.00%) 0 1 / 268 (0.37%) 1 1 / 268 (0.37%) 1 0 / 268 (0.00%) 0 0 / 268 (0.00%) 0 1 / 268 (0.37%) 1		
Ear and labyrinth disorders AA3Z: Otitis externa, unspecified subjects affected / exposed occurrences (all) AB31.2: Benign positional paroxysmal vertigo subjects affected / exposed occurrences (all) AB51.Z & XK9K: Acquired hearing impairment, unspecified [Right] subjects affected / exposed occurrences (all)	0 / 268 (0.00%) 0 1 / 268 (0.37%) 1 1 / 268 (0.37%) 1		
Eye disorders 9B10.Z: Cataract, unspecified subjects affected / exposed occurrences (all)	0 / 268 (0.00%) 0		

9B8Y: Other specified disorders of the vitreous body			
subjects affected / exposed	0 / 268 (0.00%)		
occurrences (all)	0		
9D90.Z & XK70: Vision impairment including blindness, unspecified [Unilateral, unspecified]			
subjects affected / exposed	3 / 268 (1.12%)		
occurrences (all)	3		
9E1Z: Diseases of the visual system, unspecified			
subjects affected / exposed	0 / 268 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
MD81.12: Pain localised to other parts of lower abdomen			
subjects affected / exposed	0 / 268 (0.00%)		
occurrences (all)	0		
MD90.0: Nausea			
subjects affected / exposed	0 / 268 (0.00%)		
occurrences (all)	0		
MD95: Heartburn			
subjects affected / exposed	0 / 268 (0.00%)		
occurrences (all)	0		
DA09.62: Periapical abscess without sinus			
subjects affected / exposed	1 / 268 (0.37%)		
occurrences (all)	1		
DA60.Z: Gastric ulcer, unspecified			
subjects affected / exposed	1 / 268 (0.37%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
EE13.1: Ingrowing nail			
subjects affected / exposed	0 / 268 (0.00%)		
occurrences (all)	0		
EA90.42: Palmoplantar pustulosis			
subjects affected / exposed	0 / 268 (0.00%)		
occurrences (all)	0		
ME65.1: Itching of skin			

subjects affected / exposed	1 / 268 (0.37%)		
occurrences (all)	1		
ME66.6Z: Rash, unspecified			
subjects affected / exposed	0 / 268 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
GB70.0Z: Calculus of kidney, unspecified			
subjects affected / exposed	1 / 268 (0.37%)		
occurrences (all)	1		
GB71.1: Calculus in urethra			
subjects affected / exposed	0 / 268 (0.00%)		
occurrences (all)	0		
GC00.1: Infectious cystitis			
subjects affected / exposed	0 / 268 (0.00%)		
occurrences (all)	0		
GC40.Z: Pelvic organ prolapse, unspecified			
subjects affected / exposed	0 / 268 (0.00%)		
occurrences (all)	0		
MF50.2Z: Urinary incontinence, unspecified			
subjects affected / exposed	0 / 268 (0.00%)		
occurrences (all)	0		
Endocrine disorders			
5A00.Z: Hypothyroidism, unspecified			
subjects affected / exposed	1 / 268 (0.37%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
FA01.Z & XK9K: Osteoarthritis of knee, unspecified [Right]			
subjects affected / exposed	0 / 268 (0.00%)		
occurrences (all)	0		
FA2Z: Inflammatory arthropathies, unspecified			
subjects affected / exposed	1 / 268 (0.37%)		
occurrences (all)	1		
FA71: Torticollis			

subjects affected / exposed	0 / 268 (0.00%)		
occurrences (all)	0		
FA82: Spinal stenosis			
subjects affected / exposed	1 / 268 (0.37%)		
occurrences (all)	1		
FB50.Z & XK8G: Bursitis, unspecified			
subjects affected / exposed	0 / 268 (0.00%)		
occurrences (all)	0		
FB53.0: Adhesive capsulitis of shoulder			
subjects affected / exposed	1 / 268 (0.37%)		
occurrences (all)	1		
FB55.Z: Enthesopathies, unspecified			
subjects affected / exposed	2 / 268 (0.75%)		
occurrences (all)	2		
FB56.2: Myalgia			
subjects affected / exposed	0 / 268 (0.00%)		
occurrences (all)	0		
FB56.4: Pain in limb			
subjects affected / exposed	1 / 268 (0.37%)		
occurrences (all)	1		
FB56.6: Other specified soft tissue disorders			
subjects affected / exposed	1 / 268 (0.37%)		
occurrences (all)	1		
ME82: Pain in joint			
subjects affected / exposed	1 / 268 (0.37%)		
occurrences (all)	1		
ME84.Z: Spinal pain, unspecified			
subjects affected / exposed	0 / 268 (0.00%)		
occurrences (all)	0		
ME85: Stiffness of joint			
subjects affected / exposed	0 / 268 (0.00%)		
occurrences (all)	0		
Infections and infestations			

1A40.Z: Infectious gastroenteritis or colitis without specification of infectious agent				
subjects affected / exposed	0 / 268 (0.00%)			
occurrences (all)	0			
1B72.Z: Impetigo, unspecified				
subjects affected / exposed	0 / 268 (0.00%)			
occurrences (all)	0			
1C1G.0: Early cutaneous Lyme borreliosis				
subjects affected / exposed	1 / 268 (0.37%)			
occurrences (all)	1			
1C1G: Lyme borreliosis				
subjects affected / exposed	1 / 268 (0.37%)			
occurrences (all)	1			
1D9Z: Unspecified viral infection of unspecified site				
subjects affected / exposed	0 / 268 (0.00%)			
occurrences (all)	0			
1E32: Influenza, virus not identified				
subjects affected / exposed	1 / 268 (0.37%)			
occurrences (all)	1			
1E91.0: Zoster without complications				
subjects affected / exposed	1 / 268 (0.37%)			
occurrences (all)	1			
1E91.Z: Zoster, unspecified				
subjects affected / exposed	1 / 268 (0.37%)			
occurrences (all)	1			
1F00.Z: Herpes simplex infections, unspecified				
subjects affected / exposed	0 / 268 (0.00%)			
occurrences (all)	0			
1F23.Z: Candidosis, unspecified				
subjects affected / exposed	0 / 268 (0.00%)			
occurrences (all)	0			
1F28.Y: Other specified dermatophytosis				
subjects affected / exposed	0 / 268 (0.00%)			
occurrences (all)	0			

1H0Z: Infection, unspecified subjects affected / exposed occurrences (all) RA01.0: COVID-19, virus identified subjects affected / exposed occurrences (all)	 1 / 268 (0.37%) 1 1 / 268 (0.37%) 1		
Metabolism and nutrition disorders 5C72: Hypo-osmolality or hyponatraemia subjects affected / exposed occurrences (all) 5C77: Hypokalaemia subjects affected / exposed occurrences (all)	 1 / 268 (0.37%) 1 1 / 268 (0.37%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 May 2016	Medical Products Agency requested updates: (1) Analysis of the primary variable was changed to include randomised, instead of treated, patients. (2) A pregnancy test was included in the screening visit. (3) Any contraindications to the investigational products, atrial fibrillation in need of rate control, and heart failure due to left ventricular systolic dysfunction were added to the exclusion criteria.
08 May 2017	(1) Body weight measurement was added to visit 3. (2) Fasting was not required prior to collection of whole blood samples at visit 1.
15 December 2017	(1) Exclusion criteria were clarified: o Gout -> active gout. o Use of concomitant medication -> continuous use of… o Any history of drug reaction -> any history of drug reaction to active or inactive compounds in the investigational product (IP). o Previous enrolment in present study -> Previous randomization… (2) Introduction to reporting symptoms and QoL in an electronic diary was moved from the placebo run-in period to visit 2. (3) At visit 3, the patient was not allowed to keep one capsule of the IP, but had to return all unused IPs. (4) If the patient discontinued the study, he/she was asked to carry out visit 3 and 4.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30265168