Clinical trial results:
A pivotal, multicentre, randomized, modified double-blind, placebo-controlled phase 3 trial to assess the safety and clinical efficacy of M-001, an influenza vaccine administered intramuscularly twice in older adults and the elderly (50 years of age).

Summary

EudraCT number	2018-000468-27
Trial protocol	HU PL LV BG HR
Global end of trial date	02 July 2020

Results information

Result version number	v1 (current)
This version publication date	02 July 2021
First version publication date	02 July 2021
Summary attachment (see zip file)	CSR Synopsis V1.0_14Jun2021 (CSR Synopsis_V1.0_14Jun2021.pdf)

Trial information

Trial identification

Sponsor protocol code	BVX-010

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03450915
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	BiondVax Pharmaceuticals Ltd.
Sponsor organisation address	Hadassah Ein Kerem, Jerusalem, Israel,
Public contact	Dr Tamar Ben-Yedidia, BiondVax Pharmaceuticals Ltd., 972 89302529 5103, benyedidia@BiondVax.com
Scientific contact	Dr Tamar Ben-Yedidia, BiondVax Pharmaceuticals Ltd., 972 89302529 5103, benyedidia@BiondVax.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	04 June 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 July 2020
Global end of trial reached?	Yes
Global end of trial date	02 July 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Safety: To assess M-001 Safety by solicited local and systemic reactogenicity events occurring within 8 days (day of the vaccination inclusive) following receipt of each of the two doses of M-001 or placebo and to assess SAEs and new-onset of chronic medical illnesses (NOCIs) during period from Day 0 until end of first passive surveillance period in each group. To assess M-001 safety by occurrence of unsolicited AEs from the time of first study vaccination through 22 days after each M-001 vaccination (day of the vaccination inclusive).
Clinical Efficacy: To assess efficacy of M-001 in the prevention of influenza disease by comparing the occurrence of either qRT-PCR or culture confirmed influenza in the M-001 experimental group vs. placebo caused by any influenza A or B virus in association with a protocol defined Influenza Like Illness (ILI).

Protection of trial subjects:

Subjects were informed by the Investigator about the nature of the study, along with the aims, methods, anticipated benefits, potential hazards, and discomfort that participation may have entailed. Written informed consent awas obtained from the subjects. The study protocol and the informed consent form were submitted to the Independent Ethics Committee (IEC) or Institutional
Review Board (IRB) for review and approval before study initiation. The study was conducted in accordance with recognised international scientific and ethical standards, including but not limited to the International Conference on Harmonization Guideline for Good Clinical Practice (ICH GCP) and the original principles embodied in the Declaration of Helsinki.

The pain associated with injection was minimal as thin needles (22G) was used.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 August 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Bulgaria: 3500
Country: Number of subjects enrolled	Hungary: 371
Country: Number of subjects enrolled	Latvia: 541
Country: Number of subjects enrolled	Ukraine: 1896
Country: Number of subjects enrolled	Croatia: 160
Country: Number of subjects enrolled	Georgia: 514
Country: Number of subjects enrolled	Poland: 5476

Worldwide total number of subjects	12458
EEA total number of subjects	10048

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)	6163
From 65 to 84 years	6295
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled during the influenza season 2018/2019 and 2019/2020 in Bulgaria (23 sites), Croatia (7 sites), Georgia (7 sites), Hungary 812 sites), Latvia (4 sites), Poland (33 sites), and Ukraine (24 sites).

Pre-assignment

Screening details:

12462 out of the 12569 screened subjects were enrolled. Four enrolled subjects (2 in the experimental group and 2 in the control group) were excluded from the Intention-to-treat Population as these subjects did not received vaccination due to discontinuation. 12458 subjects were included in the Intention-to-treat Population.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	M-001

Arm description:

Intramuscular administration of two doses at 21 days interval

Arm type	Experimental
Investigational medicinal product name	M-001
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intramuscular use

Dosage and administration details:

1 mg, two doses at 21 days interval.

Arm title	Placebo

Arm description:

Intramuscular administration of two doses at 21 days interval

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.6 ml, two doses at 21 days interval

Number of subjects in period 1	M-001	Placebo
Started	6229	6229
Completed	5827	5855
Not completed	402	374
Consent withdrawn by subject	307	271
Physician decision	6	6
Adverse event, non-fatal	7	14
Deaths, missing, others	-	40
Lost to follow-up	38	43
Death, missing, others	44	-

Baseline characteristics

Reporting groups	
Reporting group title	M-001
Reporting group description: Intramuscular administration of two doses at 21 days interval	
Reporting group title	Placebo
Reporting group description: Intramuscular administration of two doses at 21 days interval	

Reporting group values	M-001	Placebo	Total
Number of subjects	6229	6229	12458
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	3082	3081	6163
From 65-84 years	3147	3148	6295
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	3454	3486	6940
Male	2775	2743	5518

End points

End points reporting groups

Reporting group title	M-001
Reporting group description: Intramuscular administration of two doses at 21 days interval	
Reporting group title	Placebo
Reporting group description: Intramuscular administration of two doses at 21 days interval	

Primary: Occurrence of Serious Adverse Events, New Onset Chronic Illness, and Non-solicited Adverse Events

End point title	Occurrence of Serious Adverse Events, New Onset Chronic Illness, and Non-solicited Adverse Events
End point description: Local and systemic reactogenicity solicited events will be included in the table for unsolicited adverse events with the severity provided by the investigator, which may differ from that given by the subject's diary.	
End point type	Primary
End point timeframe: Day 0 until 30 days after Visit 4 (V4: 180 days after last vaccination day)	

End point values	M-001	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6229	6229		
Units: Number of subjects				
New Onset Chronic Illness	167	166		
Non-solicited Adverse Event	781	760		
Serious Adverse Event	185	177		

Statistical analyses

Statistical analysis title	Safety
Comparison groups	M-001 v Placebo
Number of subjects included in analysis	12458
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05
Method	Fisher exact

Primary: Vaccine Efficacy Assessed by qRT-PCR or Culture-confirmed Influenza-like

Illness

End point title	Vaccine Efficacy Assessed by qRT-PCR or Culture-confirmed Influenza-like Illness

End point description:

Prevention of influenza disease by comparing the occurrence of either qRT-PCR or culture confirmed influenza in the M-001 experimental group vs. placebo caused by any influenza A or B virus in association with a protocol defined Influenza Like Illness.

End point type	Primary

End point timeframe:

From Day 14 post-second vaccination day to end of influenza season

End point values	M-001	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6229	6229		
Units: Number of subjects	160	138		

Statistical analyses

Statistical analysis title	Vaccine Efficacy
Comparison groups	M-001 v Placebo
Number of subjects included in analysis	12458
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05
Method	Clopper-Pearson

Secondary: Culture-confirmed Influenza Incidence

End point title	Culture-confirmed Influenza Incidence

End point description:

Occurrence of culture confirmed influenza in the M-001 experimental group vs. placebo caused by any influenza A or B virus in association with a protocol defined Influenza Like Illness.

End point type	Secondary

End point timeframe:

From Day 14 post-second vaccination day to end of influenza season

End point values	M-001	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6229	6229		
Units: Number of influenza events	111	96		

Statistical analyses

No statistical analyses for this end point

Secondary: Reduction of Severity of qRT-PCR or Culture-confirmed Influenza

End point title	Reduction of Severity of qRT-PCR or Culture-confirmed Influenza

End point description:

Assessed by reduction of severity of either qRT-PCR or culture-confirmed influenza illness by the reduction due to M-001 in the average number of days with respiratory or systemic symptoms during the first laboratory-confirmed influenza illness episode.

End point type	Secondary

End point timeframe:

From Day 14 post-second vaccination day to end of influenza season

End point values	M-001	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6229	6229		
Units: Number of subjects				
< 7 days	19	12		
>= 7 - 14 days	94	71		
>= 14 - 21 days	29	29		
>= 21 days	24	26		

Statistical analyses

No statistical analyses for this end point

Secondary: Influenza-like Illness Symptoms

End point title	Influenza-like Illness Symptoms

End point description:

From Day 14 post-second vaccination day to end of influenza season

End point type	Secondary

End point timeframe:

Assessment of proportion of subjects having ILI symptoms in the experimental or control group

End point values	M-001	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6229	6229		
Units: Number of subjects	1231	1266		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Day 0 until 30 days after Visit 4 (V4: 180 days after last vaccination day)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups	
Reporting group title	M-001
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	M-001	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	185 / 6230 (2.97%)	177 / 6228 (2.84%)	
number of deaths (all causes)	28	30	
number of deaths resulting from adverse events	3	5	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pancreatic carcinoma			
subjects affected / exposed	2 / 6230 (0.03%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Adenocarcinoma of colon			
subjects affected / exposed	1 / 6230 (0.02%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain neoplasm			
subjects affected / exposed	1 / 6230 (0.02%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Breast cancer			
subjects affected / exposed	1 / 6230 (0.02%)	3 / 6228 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Colon cancer			
subjects affected / exposed	1 / 6230 (0.02%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	1 / 6230 (0.02%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Non-small cell lung cancer			
subjects affected / exposed	1 / 6230 (0.02%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectosigmoid cancer			
subjects affected / exposed	1 / 6230 (0.02%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal neoplasm			
subjects affected / exposed	1 / 6230 (0.02%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small cell lung cancer			
subjects affected / exposed	1 / 6230 (0.02%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Tongue neoplasm benign			
subjects affected / exposed	1 / 6230 (0.02%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adrenal adenoma			
subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer			

subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer recurrent			
subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer stage II			
subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysplastic naevus			
subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial cancer			
subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric cancer			
subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal cancer			
subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelofibrosis			
subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cancer			

subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine cancer			
subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 6230 (0.06%)	6 / 6228 (0.10%)	
occurrences causally related to treatment / all	0 / 4	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypertensive crisis			
subjects affected / exposed	4 / 6230 (0.06%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 6230 (0.02%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Steal syndrome			
subjects affected / exposed	1 / 6230 (0.02%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	1 / 6230 (0.02%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bleeding varicose vein			

subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Circulatory collapse			
subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Deep vein thrombosis			
subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phlebitis			
subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular occlusion			
subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			
subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Adverse event			
subjects affected / exposed	3 / 6230 (0.05%)	2 / 6228 (0.03%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 3	0 / 2	
Death			
subjects affected / exposed	2 / 6230 (0.03%)	2 / 6228 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 2	
Sudden death			

subjects affected / exposed	1 / 6230 (0.02%)	3 / 6228 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 3	
Chest pain			
subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial pain			
subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden cardiac death			
subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 6230 (0.02%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial hypertrophy			
subjects affected / exposed	1 / 6230 (0.02%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive tract disorder			

subjects affected / exposed	1 / 6230 (0.02%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine haemorrhage			
subjects affected / exposed	1 / 6230 (0.02%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	27 / 6230 (0.43%)	28 / 6228 (0.45%)	
occurrences causally related to treatment / all	0 / 29	0 / 30	
deaths causally related to treatment / all	0 / 0	0 / 1	
Asthma			
subjects affected / exposed	10 / 6230 (0.16%)	9 / 6228 (0.14%)	
occurrences causally related to treatment / all	0 / 10	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	7 / 6230 (0.11%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 7	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bronchiectasis			
subjects affected / exposed	2 / 6230 (0.03%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	2 / 6230 (0.03%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	2 / 6230 (0.03%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sleep apnoea syndrome			

subjects affected / exposed	2 / 6230 (0.03%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis chronic			
subjects affected / exposed	1 / 6230 (0.02%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic respiratory failure			
subjects affected / exposed	1 / 6230 (0.02%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary fibrosis			
subjects affected / exposed	1 / 6230 (0.02%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Choking			
subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Epistaxis			
subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lung infiltration			

subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 6230 (0.02%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reactive psychosis			
subjects affected / exposed	1 / 6230 (0.02%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Coronary artery restenosis			
subjects affected / exposed	1 / 6230 (0.02%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
subjects affected / exposed	1 / 6230 (0.02%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pubis fracture			
subjects affected / exposed	1 / 6230 (0.02%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	1 / 6230 (0.02%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	1 / 6230 (0.02%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Concussion			
subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 6230 (0.00%)	3 / 6228 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fractured coccyx			
subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus injury			
subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound			
subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Myocardial infarction			
subjects affected / exposed	6 / 6230 (0.10%)	6 / 6228 (0.10%)	
occurrences causally related to treatment / all	0 / 6	0 / 6	
deaths causally related to treatment / all	0 / 1	0 / 3	
Cardiac arrest			
subjects affected / exposed	5 / 6230 (0.08%)	2 / 6228 (0.03%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 5	0 / 2	
Cardiac failure			
subjects affected / exposed	5 / 6230 (0.08%)	2 / 6228 (0.03%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	3 / 6230 (0.05%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	3 / 6230 (0.05%)	3 / 6228 (0.05%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute coronary syndrome			
subjects affected / exposed	2 / 6230 (0.03%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	2 / 6230 (0.03%)	4 / 6228 (0.06%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	2 / 6230 (0.03%)	3 / 6228 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure chronic			

subjects affected / exposed	2 / 6230 (0.03%)	5 / 6228 (0.08%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	2 / 6230 (0.03%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 6230 (0.02%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac valve disease			
subjects affected / exposed	185 / 6230 (2.97%)	177 / 6228 (2.84%)	
occurrences causally related to treatment / all	0 / 218	0 / 211	
deaths causally related to treatment / all	0 / 3	0 / 5	
Cardiovascular insufficiency			
subjects affected / exposed	1 / 6230 (0.02%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Mitral valve incompetence			
subjects affected / exposed	1 / 6230 (0.02%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Arrhythmia			
subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial tachycardia			
subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiovascular disorder			

subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial ischaemia			
subjects affected / exposed	0 / 6230 (0.00%)	4 / 6228 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	2 / 6230 (0.03%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebral infarction			
subjects affected / exposed	2 / 6230 (0.03%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebrospinal fluid circulation disorder			
subjects affected / exposed	2 / 6230 (0.03%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	2 / 6230 (0.03%)	5 / 6228 (0.08%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	
Syncope			
subjects affected / exposed	2 / 6230 (0.03%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			

subjects affected / exposed	2 / 6230 (0.03%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carpal tunnel syndrome			
subjects affected / exposed	1 / 6230 (0.02%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 6230 (0.02%)	3 / 6228 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Cerebrovascular insufficiency			
subjects affected / exposed	1 / 6230 (0.02%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	1 / 6230 (0.02%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			
subjects affected / exposed	1 / 6230 (0.02%)	3 / 6228 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Headache			
subjects affected / exposed	1 / 6230 (0.02%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar radiculopathy			
subjects affected / exposed	1 / 6230 (0.02%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulnar tunnel syndrome			

subjects affected / exposed	1 / 6230 (0.02%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery stenosis			
subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	0 / 6230 (0.00%)	2 / 6228 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiculopathy			
subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertebrobasilar insufficiency			
subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	1 / 6230 (0.02%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			

subjects affected / exposed	1 / 6230 (0.02%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 6230 (0.03%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoacusis			
subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Posterior capsule rupture			
subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Haemorrhoidal haemorrhage			
subjects affected / exposed	1 / 6230 (0.02%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 6230 (0.02%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis necrotising			
subjects affected / exposed	1 / 6230 (0.02%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Umbilical hernia			
subjects affected / exposed	1 / 6230 (0.02%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastritis			
subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal obstruction			
subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Irritable bowel syndrome			
subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal mass			
subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	3 / 6230 (0.05%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct obstruction			
subjects affected / exposed	1 / 6230 (0.02%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	1 / 6230 (0.02%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis chronic			

subjects affected / exposed	1 / 6230 (0.02%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute hepatic failure			
subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary dyskinesia			
subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Diabetic foot			
subjects affected / exposed	1 / 6230 (0.02%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 6230 (0.03%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus urinary			
subjects affected / exposed	1 / 6230 (0.02%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis noninfective			
subjects affected / exposed	1 / 6230 (0.02%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			

subjects affected / exposed	1 / 6230 (0.02%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis			
subjects affected / exposed	1 / 6230 (0.02%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postmenopausal haemorrhage			
subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Thyroiditis subacute			
subjects affected / exposed	1 / 6230 (0.02%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	1 / 6230 (0.02%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteochondrosis			
subjects affected / exposed	1 / 6230 (0.02%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periarthritis			
subjects affected / exposed	1 / 6230 (0.02%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Polymyalgia rheumatica			
subjects affected / exposed	1 / 6230 (0.02%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scleroderma			
subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal disorder			
subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	16 / 6230 (0.26%)	13 / 6228 (0.21%)	
occurrences causally related to treatment / all	0 / 16	0 / 13	
deaths causally related to treatment / all	0 / 1	0 / 1	
Respiratory tract infection			
subjects affected / exposed	3 / 6230 (0.05%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia			
subjects affected / exposed	2 / 6230 (0.03%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	2 / 6230 (0.03%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			

subjects affected / exposed	2 / 6230 (0.03%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 6230 (0.03%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial infection			
subjects affected / exposed	1 / 6230 (0.02%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 6230 (0.02%)	4 / 6228 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Conjunctivitis			
subjects affected / exposed	1 / 6230 (0.02%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Corona virus infection			
subjects affected / exposed	1 / 6230 (0.02%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngitis			
subjects affected / exposed	1 / 6230 (0.02%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parotitis			
subjects affected / exposed	1 / 6230 (0.02%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			

subjects affected / exposed	1 / 6230 (0.02%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pyelonephritis chronic			
subjects affected / exposed	1 / 6230 (0.02%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal abscess			
subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 6230 (0.00%)	2 / 6228 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial pyelonephritis			
subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiolitis			
subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			

subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection bacterial			
subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	2 / 6230 (0.03%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 6230 (0.02%)	0 / 6228 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	0 / 6230 (0.00%)	1 / 6228 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 6230 (0.00%)	3 / 6228 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0.1 %

Non-serious adverse events	M-001	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	781 / 6230 (12.54%)	760 / 6228 (12.20%)	
Investigations			
Blood pressure decreased			
subjects affected / exposed	12 / 6230 (0.19%)	6 / 6228 (0.10%)	
occurrences (all)	14	6	
Blood pressure increased			
subjects affected / exposed	6 / 6230 (0.10%)	11 / 6228 (0.18%)	
occurrences (all)	6	12	
Vascular disorders			
Hypertension			
subjects affected / exposed	26 / 6230 (0.42%)	29 / 6228 (0.47%)	
occurrences (all)	26	30	
Hypertensive crisis			
subjects affected / exposed	8 / 6230 (0.13%)	2 / 6228 (0.03%)	
occurrences (all)	8	2	
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	6 / 6230 (0.10%)	5 / 6228 (0.08%)	
occurrences (all)	6	7	
Myocardial infarction			
subjects affected / exposed	6 / 6230 (0.10%)	6 / 6228 (0.10%)	
occurrences (all)	6	6	
Cardiac failure chronic			
subjects affected / exposed	4 / 6230 (0.06%)	6 / 6228 (0.10%)	
occurrences (all)	4	6	
Myocardial ischemia			
subjects affected / exposed	3 / 6230 (0.05%)	7 / 6228 (0.11%)	
occurrences (all)	3	7	
Nervous system disorders			
Headache			
subjects affected / exposed	106 / 6230 (1.70%)	90 / 6228 (1.45%)	
occurrences (all)	113	99	

Dizziness			
subjects affected / exposed	16 / 6230 (0.26%)	19 / 6228 (0.31%)	
occurrences (all)	17	21	
General disorders and administration site conditions			
Malaise			
subjects affected / exposed	38 / 6230 (0.61%)	33 / 6228 (0.53%)	
occurrences (all)	40	37	
Pyrexia			
subjects affected / exposed	33 / 6230 (0.53%)	19 / 6228 (0.31%)	
occurrences (all)	35	20	
Chills			
subjects affected / exposed	26 / 6230 (0.42%)	20 / 6228 (0.32%)	
occurrences (all)	28	24	
Injection site pain			
subjects affected / exposed	21 / 6230 (0.34%)	3 / 6228 (0.05%)	
occurrences (all)	22	3	
Fatigue			
subjects affected / exposed	17 / 6230 (0.27%)	15 / 6228 (0.24%)	
occurrences (all)	18	16	
Injection site bruising			
subjects affected / exposed	15 / 6230 (0.24%)	13 / 6228 (0.21%)	
occurrences (all)	15	13	
Injection site erythema			
subjects affected / exposed	8 / 6230 (0.13%)	2 / 6228 (0.03%)	
occurrences (all)	8	2	
Asthenia			
subjects affected / exposed	7 / 6230 (0.11%)	9 / 6228 (0.14%)	
occurrences (all)	7	9	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	13 / 6230 (0.21%)	13 / 6228 (0.21%)	
occurrences (all)	13	13	
Nausea			
subjects affected / exposed	8 / 6230 (0.13%)	7 / 6228 (0.11%)	
occurrences (all)	9	7	
Abdominal pain upper			

subjects affected / exposed	7 / 6230 (0.11%)	9 / 6228 (0.14%)	
occurrences (all)	8	10	
Abdominal pain			
subjects affected / exposed	5 / 6230 (0.08%)	10 / 6228 (0.16%)	
occurrences (all)	5	10	
Abdominal discomfort			
subjects affected / exposed	2 / 6230 (0.03%)	6 / 6228 (0.10%)	
occurrences (all)	2	6	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	57 / 6230 (0.91%)	60 / 6228 (0.96%)	
occurrences (all)	60	65	
Rhinorrhoea			
subjects affected / exposed	42 / 6230 (0.67%)	55 / 6228 (0.88%)	
occurrences (all)	50	57	
Oropharyngeal Pain			
subjects affected / exposed	40 / 6230 (0.64%)	41 / 6228 (0.66%)	
occurrences (all)	43	43	
Chronic obstructive pulmonary disease			
subjects affected / exposed	33 / 6230 (0.53%)	39 / 6228 (0.63%)	
occurrences (all)	35	42	
Nasal congestion			
subjects affected / exposed	24 / 6230 (0.39%)	20 / 6228 (0.32%)	
occurrences (all)	25	20	
Dyspnoea			
subjects affected / exposed	20 / 6230 (0.32%)	11 / 6228 (0.18%)	
occurrences (all)	21	11	
Asthma			
subjects affected / exposed	19 / 6230 (0.30%)	13 / 6228 (0.21%)	
occurrences (all)	19	14	
Pulmonary embolism			
subjects affected / exposed	7 / 6230 (0.11%)	0 / 6228 (0.00%)	
occurrences (all)	7	0	
Dysphonia			

subjects affected / exposed	6 / 6230 (0.10%)	5 / 6228 (0.08%)	
occurrences (all)	6	5	
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	26 / 6230 (0.42%)	23 / 6228 (0.37%)	
occurrences (all)	28	26	
Pruritus			
subjects affected / exposed	21 / 6230 (0.34%)	17 / 6228 (0.27%)	
occurrences (all)	21	17	
Erythema			
subjects affected / exposed	7 / 6230 (0.11%)	2 / 6228 (0.03%)	
occurrences (all)	7	2	
Rash			
subjects affected / exposed	7 / 6230 (0.11%)	15 / 6228 (0.24%)	
occurrences (all)	7	15	
Psychiatric disorders			
Irritability			
subjects affected / exposed	15 / 6230 (0.24%)	17 / 6228 (0.27%)	
occurrences (all)	15	18	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	77 / 6230 (1.24%)	54 / 6228 (0.87%)	
occurrences (all)	84	60	
Myalgia			
subjects affected / exposed	28 / 6230 (0.45%)	26 / 6228 (0.42%)	
occurrences (all)	30	28	
Back pain			
subjects affected / exposed	8 / 6230 (0.13%)	11 / 6228 (0.18%)	
occurrences (all)	8	11	
Musculoskeletal pain			
subjects affected / exposed	7 / 6230 (0.11%)	6 / 6228 (0.10%)	
occurrences (all)	7	6	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	25 / 6230 (0.40%)	23 / 6228 (0.37%)	
occurrences (all)	25	24	

Pneumonia			
subjects affected / exposed	19 / 6230 (0.30%)	16 / 6228 (0.26%)	
occurrences (all)	19	16	
Rhinitis			
subjects affected / exposed	16 / 6230 (0.26%)	14 / 6228 (0.22%)	
occurrences (all)	16	14	
Upper respiratory tract infection			
subjects affected / exposed	16 / 6230 (0.26%)	18 / 6228 (0.29%)	
occurrences (all)	16	18	
Bronchitis			
subjects affected / exposed	13 / 6230 (0.21%)	16 / 6228 (0.26%)	
occurrences (all)	13	16	
Respiratory tract infection			
subjects affected / exposed	13 / 6230 (0.21%)	8 / 6228 (0.13%)	
occurrences (all)	13	9	
Urinary tract infection			
subjects affected / exposed	12 / 6230 (0.19%)	6 / 6228 (0.10%)	
occurrences (all)	12	6	
Viral Infection			
subjects affected / exposed	9 / 6230 (0.14%)	7 / 6228 (0.11%)	
occurrences (all)	10	7	
Herpes zoster			
subjects affected / exposed	7 / 6230 (0.11%)	1 / 6228 (0.02%)	
occurrences (all)	7	1	
Conjunctivitis			
subjects affected / exposed	6 / 6230 (0.10%)	4 / 6228 (0.06%)	
occurrences (all)	6	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 March 2018	Revision of inclusion and exclusion criteria
02 June 2018	Revision of primary and secondary endpoint
27 March 2019	Revision of primary and secondary endpoints
08 May 2019	Revision of primary and secondary endpoints

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Not applicable

Notes: