Clinical trial results:
A phase III, randomized, double-blind, placebo-controlled, multicentre, clinical trial to assess the efficacy and safety of VPM1002 in reducing hospital admissions and/or severe respiratory infectious diseases in elderly in the SARS-CoV-2 pandemic by modulating the immune system

Summary

EudraCT number	2020-001675-33
Trial protocol	DE
Global end of trial date	12 October 2021

Results information

Result version number	v1 (current)
This version publication date	01 September 2022
First version publication date	01 September 2022

Trial information

Trial identification

Sponsor protocol code	VPM1002-DE-3.07CoV

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Vakzine Projekt Management GmbH
Sponsor organisation address	Mellendorfer Strasse 9, Hannover, Germany, 30625
Public contact	Clinical Trial Information, Vakzine Projekt Management GmbH, +49 5111699080, info@vakzine-manager.de
Scientific contact	Clinical Trial Information, Vakzine Projekt Management GmbH, +49 5111699080, info@vakzine-manager.de

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	18 January 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 October 2021
Global end of trial reached?	Yes
Global end of trial date	12 October 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the reduction of days with severe respiratory infectious diseases at hospital and/or at home in elderly subjects during the pandemic of SARS-CoV-2

Protection of trial subjects:

VPM1002 had been tested in four clinical trials involving healthy adults and newborn infants prior to the VPM1002-DE-3.07CoV trial and was investigated in parallel in larger phase III trials with infants, children and adults. As VPM1002 was shown to be safe and well tolerated, the assessments conducted during this trial were considered appropriate to monitor subject safety and well-being.
After the vaccination with the investigational medicinal product (IMP; VPM1002 or placebo), the subjects were medically monitored at the site under supervision of medical staff for at least 30 minutes. Prior discharge, physical examination and vital signs were repeated when indicated. The subjects were followed up remotely via a web application for 240 days after IMP administration and contacted monthly by clinical trial staff to assess their health status (i.e., they were asked about adverse events [AEs], presence of fever, and concomitant medications). Subjects with confirmed SARS-CoV-2 infection were followed up for at least 6 weeks from the day of the test result. The subjects were encouraged to contact the site in case of AEs and to designate a caregiver who was to provide follow-up data in case of a hospitalization or severe illness of the subject.
An independent data and safety monitoring board (DSMB) was established to monitor the conduct of the trial. Monthly, the DSMB reviewed and discussed unblinded safety data and provided recommendations to the sponsor as to whether there were any safety concerns and whether the trial was to continue without change, be modified, or terminated. The DSMB consisted of 3 voting members who were experts in vaccine and/or infectious diseases and a non-voting statistician.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 June 2020
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	Germany: 2064
Worldwide total number of subjects	2064
EEA total number of subjects	2064

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)	747
From 65 to 84 years	1309
85 years and over	8

Subject disposition

Recruitment

Recruitment details:

Male and female subjects aged 60 years or older were enrolled at 12 centers in Germany. The first subject signed the informed consent form on 18-Jun-2020 and the last on 26-Jan-2021.

Pre-assignment

Screening details:

2064 subjects were screened and enrolled in the trial. 2037 subjects were randomized in a 1:1 ratio to receive a single dose of either VPM1002 or placebo. Twelve of the randomized subjects were not treated, 1013 subjects were vaccinated with VPM1002, and 1012 subjects were vaccinated with placebo.

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	Investigator, Carer, Subject

Blinding implementation details:

The vaccine preparation was done by designated unblinded personnel who did not participate in any of the clinical study evaluations. The administration was done by blinded trial staff. Because the vaccine and the placebo could have distinct appearances, even when drawn into syringes, the syringes were masked with an translucent wrapping before administration.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Subjects received a single dose of placebo injected into the arm.

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

Dosage and administration details:

Subjects received a single dose of placebo (physiological saline) as an intradermal injection of 0.1 mL in the arm over the distal insertion of the deltoid muscle onto the humerus (approximately one third down the upper arm) or lateral to the posterior aspect of the forearm.

Arm title	VPM1002

Arm description:

Subjects received a single dose of VPM1002 injected into the arm.

Arm type	Experimental
Investigational medicinal product name	VPM1002
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Intradermal use

Dosage and administration details:

Subjects received a single dose of VPM1002 reconstituted with 1 mL water for injection as an intradermal injection of 0.1 mL, containing 2-8 x 10E5 colony forming units, in the arm over the distal insertion of the deltoid muscle onto the humerus (approximately one third down the upper arm) or lateral to the posterior aspect of the forearm.

Number of subjects in period 1[1]	Placebo	VPM1002
Started	1012	1013
Completed	997	989
Not completed	15	24
Adverse event, serious fatal	3	6
Consent withdrawn by subject	10	10
Lost to follow-up	2	7
non-compliance	-	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 27 of the enrolled subjects were not randomized to IMP treatment and 12 of the randomized subjects (Placebo: N=5, VPM1002: N=7) were not treated.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects received a single dose of placebo injected into the arm.	
Reporting group title	VPM1002
Reporting group description:	
Subjects received a single dose of VPM1002 injected into the arm.	

Reporting group values	Placebo	VPM1002	Total
Number of subjects	1012	1013	2025
Age categorical Units: Subjects			
Adults (>60 years)	1012	1013	2025
Age continuous Units: years			
median	67	66	
full range (min-max)	60 to 88	60 to 91	-
Gender categorical Units: Subjects			
Female	478	475	953
Male	534	538	1072
Body weight Units: kilogram(s)			
arithmetic mean	83.97	83.74	
standard deviation	± 18.26	± 18.04	-

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Subjects received a single dose of placebo injected into the arm.	
Reporting group title	VPM1002
Reporting group description:	
Subjects received a single dose of VPM1002 injected into the arm.	

Primary: Number of days with severe respiratory disease at hospital and/or home

End point title	Number of days with severe respiratory disease at hospital and/or home

End point description:

Daily in the 1st week and weekly thereafter, subjects had to answer a health status questionnaire (HSQ) with several questions regarding hospitalization, AEs, intensive care unit (ICU) admissions and other secondary endpoints in a web application. They could also document in a paper diary their body temperature, if considered necessary (e.g., if they felt unwell), as well as any AEs or concomitant medications. Entries in HSQ and patient diary as well as data from monthly phone calls were used to calculate the number of days with severe respiratory disease at hospital and/or home.

End point type	Primary

End point timeframe:

From day of vaccination with the IMP (Day 0) until the end of the 240-day follow-up.

End point values	Placebo	VPM1002		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1009[1]	1008[2]		
Units: day				
arithmetic mean (standard deviation)				
All subjects	0.54 (± 4.13)	0.29 (± 2.28)		
Subjects with number of days >0	14.29 (± 16.25)	9.39 (± 9.28)		

Notes:

[1] - Subjects with number of days >0: N=38

[2] - Subjects with number of days >0: N=31

Statistical analyses

Statistical analysis title	Comparison VPM1002 vs placebo - primary model

Statistical analysis description:

The ratio between VPM1002 and placebo in the mean weekly number of days with a severe respiratory disease at the hospital and/or at home (rate ratio) was analyzed using a negative binomial regression model with a random intercept per subject and fixed effects for treatment, sex, site, and observation week.

Comparison groups	Placebo v VPM1002

Number of subjects included in analysis	2017
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.3496 [4]
Method	Negative binomial regression
Parameter estimate	Rate ratio
Point estimate	0.5993
Confidence interval	
level	95.2 %
sides	2-sided
lower limit	0.203
upper limit	1.769

Notes:

[3] - Negative binomial regression model with a random intercept per subject and fixed effects for treatment, sex, site, and observation week. An unstructured covariance matrix was used.
[4] - Significance can be assumed if p-value <0.048 (2-sided).

Statistical analysis title	Comparison VPM1002 vs placebo - secondary model

Statistical analysis description:

The ratio between VPM1002 and placebo in the mean weekly number of days with a severe respiratory disease at the hospital and/or at home (rate ratio) was analyzed using a negative binomial regression model with a random intercept per subject and fixed effects for treatment, sex, treatment*sex, site, and observation week.

Comparison groups	Placebo v VPM1002
Number of subjects included in analysis	2017
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.3546 [6]
Method	Negative binomial regression
Parameter estimate	Rate ratio
Point estimate	0.6023
Confidence interval	
level	95.2 %
sides	2-sided
lower limit	0.2039
upper limit	1.779

Notes:

[5] - Negative binomial regression model with a random intercept per subject and fixed effects for treatment, sex, treatment*sex, site, and observation week. An unstructured covariance matrix was used.
[6] - Significance can be assumed if p-value <0.048 (2-sided).

Secondary: Cumulative incidence of severe respiratory disease at hospital and/or home

End point title	Cumulative incidence of severe respiratory disease at hospital and/or home

End point description:

The cumulative incidence of severe respiratory disease at hospital and/or home was calculated using the life table method. Only subjects with data were included in analysis.

End point type	Secondary

End point timeframe:

From day of vaccination with the IMP (Day 0) until the end of the 240-day follow-up.

End point values	Placebo	VPM1002		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1009	1008		
Units: cumulative incidence over 240 days				
number (not applicable)				
All subjects	0.0385	0.0315		
All subjects (events at home)	0.0304	0.0264		
All subjects (events at hospital)	0.0152	0.0143		

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative incidence of documented SARS-CoV-2 infection

End point title	Cumulative incidence of documented SARS-CoV-2 infection

End point description:

The cumulative incidence of documented SARS-CoV-2 infection was calculated using the life table method based on HSQ and AE entries. Only subjects with data were included in analysis.

End point type	Secondary

End point timeframe:

From day of vaccination with the IMP (Day 0) until the end of the 240-day follow-up.

End point values	Placebo	VPM1002		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1009	1008		
Units: cumulative incidence over 240 days				
number (not applicable)				
All subjects	0.0202	0.0226		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of days with self-reported fever

End point title	Number of days with self-reported fever

End point description:

Data entered in the web based HSQ and paper diary were used to calculate the number of days with self-reported fever (≥38 °C).

End point type	Secondary

End point timeframe:

From day of vaccination with the IMP (Day 0) until the end of the 240-day follow-up.

End point values	Placebo	VPM1002		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1009[7]	1008[8]		
Units: day				
arithmetic mean (standard deviation)				
All subjects	0.14 (± 0.95)	0.05 (± 0.33)		
Subjects with number of days >0	2.75 (± 3.18)	1.88 (± 0.97)		

Notes:

[7] - Subjects with number of days >0: N=53

[8] - Subjects with number of days >0: N=25

Statistical analyses

Statistical analysis title	Comparison VPM1002 vs placebo - primary model

Statistical analysis description:

The ratio between VPM1002 and placebo in the mean weekly number of days with self-reported fever (rate ratio) was analyzed using a negative binomial regression model with a random intercept per subject and fixed effects for treatment, sex, site, and observation week.

Comparison groups	Placebo v VPM1002
Number of subjects included in analysis	2017
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	= 0.001 [10]
Method	Negative binomial regression
Parameter estimate	Rate ratio
Point estimate	0.312
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1554
upper limit	0.6262

Notes:

[9] - Negative binomial regression model with a random intercept per subject and fixed effects for treatment, sex, site, and observation week. An unstructured covariance matrix was used.

[10] - Significance can be assumed if p-value <0.05 (2-sided).

Statistical analysis title	Comparison VPM1002 vs placebo - secondary model

Statistical analysis description:

The ratio between VPM1002 and placebo in the mean weekly number of days with self-reported fever (rate ratio) was analyzed using a negative binomial regression model with a random intercept per subject and fixed effects for treatment, sex, treatment*sex, site, and observation week.

Comparison groups	VPM1002 v Placebo

Number of subjects included in analysis	2017
Analysis specification	Pre-specified
Analysis type	other[11]
P-value	= 0.0007 [12]
Method	Negative binomial regression
Parameter estimate	Rate ratio
Point estimate	0.2964
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1467
upper limit	0.5989

Notes:

[11] - Negative binomial regression model with a random intercept per subject and fixed effects for treatment, sex, treatment*sex, site, and observation week. An unstructured covariance matrix was used.

[12] - Significance can be assumed if p-value <0.05 (2-sided).

Secondary: Number of days with self-reported acute respiratory symptoms

End point title	Number of days with self-reported acute respiratory symptoms

End point description:

Data entered in the web based HSQ and paper diary were used to calculate the number of days with self-reported acute respiratory symptoms.

End point type	Secondary

End point timeframe:

From day of vaccination with the IMP (Day 0) until the end of the 240-day follow-up.

End point values	Placebo	VPM1002		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1009[13]	1008[14]		
Units: day				
arithmetic mean (standard deviation)				
All subjects	0.52 (± 3.18)	0.72 (± 5.03)		
Subjects with number of days >0	9.70 (± 10.09)	12.75 (± 17.27)		

Notes:

[13] - Subjects with number of days >0: N=54

[14] - Subjects with number of days >0: N=57

Statistical analyses

Statistical analysis title	Comparison VPM1002 vs placebo - primary model

Statistical analysis description:

The ratio between VPM1002 and placebo in the mean weekly number of days with self-reported acute respiratory symptoms (rate ratio) was analyzed using a negative binomial regression model with a random intercept per subject and fixed effects for treatment, sex, site, and observation week.

Comparison groups	Placebo v VPM1002

Number of subjects included in analysis	2017
Analysis specification	Pre-specified
Analysis type	other[15]
P-value	= 0.0064 [16]
Method	Negative binomial regression
Parameter estimate	Rate ratio
Point estimate	0.2452
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.08923
upper limit	0.6739

Notes:

[15] - Negative binomial regression model with a random intercept per subject and fixed effects for treatment, sex, site, and observation week. An unstructured covariance matrix was used.
[16] - Significance can be assumed if p-value <0.05 (2-sided).

Statistical analysis title	Comparison VPM1002 vs placebo - secondary model

Statistical analysis description:

The ratio between VPM1002 and placebo in the mean weekly number of days with self-reported acute respiratory symptoms (rate ratio) was analyzed using a negative binomial regression model with a random intercept per subject and fixed effects for treatment, sex, treatment*sex, site, and observation week.

Comparison groups	Placebo v VPM1002
Number of subjects included in analysis	2017
Analysis specification	Pre-specified
Analysis type	other[17]
P-value	= 0.8334 [18]
Method	Negative binomial regression
Parameter estimate	Rate ratio
Point estimate	1.1088
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4236
upper limit	2.9025

Notes:

[17] - Negative binomial regression model with a random intercept per subject and fixed effects for treatment, sex, treatment*sex, site, and observation week. An unstructured covariance matrix was used.
[18] - Significance can be assumed if p-value <0.05 (2-sided).

Secondary: Cumulative incidence of self-reported acute respiratory symptoms

End point title	Cumulative incidence of self-reported acute respiratory symptoms

End point description:

The cumulative incidence of self-reported acute respiratory symptoms was calculated using the life table method. Only subjects with data were included in analysis.

End point type	Secondary

End point timeframe:

From day of vaccination with the IMP (Day 0) until the end of the 240-day follow-up.

End point values	Placebo	VPM1002		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1009	1008		
Units: cumulative incidence over 240 days				
number (not applicable)				
All subjects	0.0544	0.0581		

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative incidence of death for any reason

End point title	Cumulative incidence of death for any reason

End point description:

The cumulative incidence of death for any reason was calculated using the life table method. Only subjects with data were included in analysis.

End point type	Secondary

End point timeframe:

From day of vaccination with the IMP (Day 0) until the end of the 240-day follow-up.

End point values	Placebo	VPM1002		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1009	1008		
Units: cumulative incidence over 240 days				
number (not applicable)				
All subjects	0.0030	0.0061		

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative incidence of death due to documented SARS-CoV-2 infection

End point title	Cumulative incidence of death due to documented SARS-CoV-2 infection

End point description:

The cumulative incidence of death due to documented SARS-CoV-2 infection was calculated using the life table method. Only subjects with data were included in analysis.

End point type	Secondary

End point timeframe:

From day of vaccination with the IMP (Day 0) until the end of the 240-day follow-up.

End point values	Placebo	VPM1002		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1009	1008		
Units: cumulative incidence over 240 days				
number (not applicable)				
All subjects	0.0010	0.0010		

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative incidence of ICU admission for any reason

End point title	Cumulative incidence of ICU admission for any reason

End point description:

The cumulative incidence of ICU admission for any reason was calculated using the life table method. Only subjects with data were included in analysis.

End point type	Secondary

End point timeframe:

From day of vaccination with the IMP (Day 0) until the end of the 240-day follow-up.

End point values	Placebo	VPM1002		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1009	1008		
Units: cumulative incidence over 240 days				
number (not applicable)				
All subjects	0.0142	0.0102		

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative incidence of ICU admission due to documented SARS-CoV-2 infection

End point title	Cumulative incidence of ICU admission due to documented SARS-CoV-2 infection

End point description:

The cumulative incidence of ICU admission due to documented SARS-CoV-2 infection was calculated using the life table method. Only subjects with data were included in analysis.

End point type	Secondary

End point timeframe:

From day of vaccination with the IMP (Day 0) until the end of the 240-day follow-up.

End point values	Placebo	VPM1002		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1009	1008		
Units: cumulative incidence over 240 days				
number (not applicable)				
All subjects	0.0051	0.0010		

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative incidence of hospital admissions

End point title	Cumulative incidence of hospital admissions

End point description:

The cumulative incidence of hospital admissions for any reason using the life table method. Only subjects with data were included in analysis.

End point type	Secondary

End point timeframe:

From day of vaccination with the IMP (Day 0) until the end of the 240-day follow-up.

End point values	Placebo	VPM1002		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1009	1008		
Units: cumulative incidence over 240 days				
number (not applicable)				
All subjects	0.1173	0.1075		

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative incidence of hospital admission due to documented SARS-CoV-2 infection

End point title	Cumulative incidence of hospital admission due to documented SARS-CoV-2 infection

End point description:

The cumulative incidence of hospital admission due to documented SARS-CoV-2 infection was calculated

using the life table method. Only subjects with data were included in analysis.

End point type	Secondary

End point timeframe:

From day of vaccination with the IMP (Day 0) until the end of the 240-day follow-up.

End point values	Placebo	VPM1002		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1009	1008		
Units: cumulative incidence over 240 days				
number (not applicable)				
All subjects	0.0081	0.0020		

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative incidence of self-reported fever

End point title	Cumulative incidence of self-reported fever

End point description:

The cumulative incidence of self-reported fever was calculated using the life table method. Only subjects with data were included in analysis.

End point type	Secondary

End point timeframe:

From day of vaccination with the IMP (Day 0) until the end of the 240-day follow-up.

End point values	Placebo	VPM1002		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1009	1008		
Units: cumulative incidence over 240 days				
number (not applicable)				
All subjects	0.0539	0.0257		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were recorded from the informed consent signature until the end of the 240-day follow-up. Treatment-emergent AEs (TEAEs) started after vaccination with the IMP (Day 0).

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Subjects received a single dose of placebo injected into the arm.

Reporting group title	VPM1002

Reporting group description:

Subjects received a single dose of VPM1002 injected into the arm.

Serious adverse events	Placebo	VPM1002	
Total subjects affected by serious adverse events			
subjects affected / exposed	94 / 1012 (9.29%)	79 / 1013 (7.80%)	
number of deaths (all causes)	3	6	
number of deaths resulting from adverse events	3	6	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	0 / 1012 (0.00%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angioimmunoblastic T-cell lymphoma			
subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign pancreatic neoplasm			
subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer			

subjects affected / exposed	0 / 1012 (0.00%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	0 / 1012 (0.00%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial carcinoma			
subjects affected / exposed	2 / 1012 (0.20%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Central nervous system lymphoma			
subjects affected / exposed	0 / 1012 (0.00%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular carcinoma			
subjects affected / exposed	0 / 1012 (0.00%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to lung			
subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal adenocarcinoma			
subjects affected / exposed	0 / 1012 (0.00%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic carcinoma			
subjects affected / exposed	0 / 1012 (0.00%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papillary renal cell carcinoma			

subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer metastatic			
subjects affected / exposed	0 / 1012 (0.00%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cancer			
subjects affected / exposed	0 / 1012 (0.00%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular disorders			
Aortic dissection			
subjects affected / exposed	0 / 1012 (0.00%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive emergency			
subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery occlusion			
subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicose vein			
subjects affected / exposed	0 / 1012 (0.00%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			

Arteriovenous fistula operation			
subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary arterial stent insertion			
subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hernia diaphragmatic repair			
subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip arthroplasty			
subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Portal shunt procedure			
subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	0 / 1012 (0.00%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complication associated with device			
subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 1012 (0.00%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Pyrexia			
subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sensation of foreign body			
subjects affected / exposed	0 / 1012 (0.00%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden cardiac death			
subjects affected / exposed	0 / 1012 (0.00%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular stent stenosis			
subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cyst			
subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal prolapse			
subjects affected / exposed	0 / 1012 (0.00%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			

subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 1012 (0.00%)	2 / 1013 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 1012 (0.20%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pickwickian syndrome			
subjects affected / exposed	0 / 1012 (0.00%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 1012 (0.10%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 1012 (0.10%)	3 / 1013 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rheumatoid lung			
subjects affected / exposed	0 / 1012 (0.00%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Alcohol abuse			

subjects affected / exposed	1 / 1012 (0.10%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	1 / 1012 (0.10%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device leakage			
subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Glycosylated haemoglobin increased			
subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intraocular pressure increased			
subjects affected / exposed	0 / 1012 (0.00%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Biliary anastomosis complication			
subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	2 / 1012 (0.20%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Fall			
subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	0 / 1012 (0.00%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 1012 (0.10%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus injury			
subjects affected / exposed	0 / 1012 (0.00%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	0 / 1012 (0.00%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound complication			
subjects affected / exposed	0 / 1012 (0.00%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			

subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skull fracture			
subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			
subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	0 / 1012 (0.00%)	2 / 1013 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	1 / 1012 (0.10%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Hypertrophic cardiomyopathy			
subjects affected / exposed	0 / 1012 (0.00%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 1012 (0.10%)	2 / 1013 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Angina pectoris			
subjects affected / exposed	1 / 1012 (0.10%)	2 / 1013 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	0 / 1012 (0.00%)	2 / 1013 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	1 / 1012 (0.10%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis coronary artery			
subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	7 / 1012 (0.69%)	3 / 1013 (0.30%)	
occurrences causally related to treatment / all	0 / 7	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	2 / 1012 (0.20%)	4 / 1013 (0.39%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 2	
Cardiorenal syndrome			
subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiovascular disorder			

subjects affected / exposed	0 / 1012 (0.00%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	3 / 1012 (0.30%)	2 / 1013 (0.20%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	1 / 1012 (0.10%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extrasystoles			
subjects affected / exposed	0 / 1012 (0.00%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive heart disease			
subjects affected / exposed	0 / 1012 (0.00%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve incompetence			
subjects affected / exposed	0 / 1012 (0.00%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 1012 (0.00%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Brain stem stroke			
subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (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	1 / 1012 (0.10%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carpal tunnel syndrome			
subjects affected / exposed	0 / 1012 (0.00%)	1 / 1013 (0.10%)	
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	1 / 1012 (0.10%)	0 / 1013 (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	0 / 1012 (0.00%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dementia Alzheimer's type			
subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nystagmus			
subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Restless legs syndrome			
subjects affected / exposed	0 / 1012 (0.00%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			

subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Deafness neurosensory			
subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo			
subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Dermatochalasis			
subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lagophthalmos			
subjects affected / exposed	0 / 1012 (0.00%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal artery occlusion			
subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 1012 (0.00%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastric ulcer			
subjects affected / exposed	0 / 1012 (0.00%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 1012 (0.00%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiatus hernia			
subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive pancreatitis			
subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal food impaction			
subjects affected / exposed	0 / 1012 (0.00%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngo-oesophageal diverticulum			

subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal prolapse			
subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal haemorrhage			
subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (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 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 1012 (0.00%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cirrhosis			
subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	0 / 1012 (0.00%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	1 / 1012 (0.10%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder tamponade			
subjects affected / exposed	0 / 1012 (0.00%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus urinary			
subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Thyroid mass			
subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (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			
Back pain			
subjects affected / exposed	1 / 1012 (0.10%)	2 / 1013 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis			
subjects affected / exposed	0 / 1012 (0.00%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot deformity			
subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Intervertebral disc protrusion			
subjects affected / exposed	0 / 1012 (0.00%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	0 / 1012 (0.00%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	5 / 1012 (0.49%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteochondrosis			
subjects affected / exposed	0 / 1012 (0.00%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator cuff syndrome			
subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal osteoarthritis			
subjects affected / exposed	0 / 1012 (0.00%)	3 / 1013 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal stenosis			
subjects affected / exposed	1 / 1012 (0.10%)	2 / 1013 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendonitis			
subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			

Appendicitis			
subjects affected / exposed	0 / 1012 (0.00%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis bacterial			
subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	6 / 1012 (0.59%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
COVID-19 pneumonia			
subjects affected / exposed	2 / 1012 (0.20%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	2 / 1012 (0.20%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	2 / 1012 (0.20%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 1012 (0.00%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterobacter bacteraemia			

subjects affected / exposed	0 / 1012 (0.00%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epididymitis			
subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 1012 (0.00%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected dermal cyst			
subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 1012 (0.00%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	0 / 1012 (0.00%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrotising fasciitis			
subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral candidiasis			
subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	1 / 1012 (0.10%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative abscess			
subjects affected / exposed	0 / 1012 (0.00%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Septic shock			
subjects affected / exposed	2 / 1012 (0.20%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Sinusitis aspergillus			
subjects affected / exposed	0 / 1012 (0.00%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 1012 (0.00%)	2 / 1013 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			

subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 1012 (0.00%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 1012 (0.10%)	0 / 1013 (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	1 / 1012 (0.10%)	0 / 1013 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock hypoglycaemic			
subjects affected / exposed	0 / 1012 (0.00%)	1 / 1013 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Placebo	VPM1002	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	520 / 1012 (51.38%)	727 / 1013 (71.77%)	
Injury, poisoning and procedural complications			
Vaccination complication			
subjects affected / exposed	143 / 1012 (14.13%)	134 / 1013 (13.23%)	
occurrences (all)	277	260	
Nervous system disorders			
Headache			
subjects affected / exposed	97 / 1012 (9.58%)	95 / 1013 (9.38%)	
occurrences (all)	141	129	

General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	8 / 1012 (0.79%)	367 / 1013 (36.23%)	
occurrences (all)	8	382	
Injection site induration			
subjects affected / exposed	3 / 1012 (0.30%)	71 / 1013 (7.01%)	
occurrences (all)	3	71	
Injection site inflammation			
subjects affected / exposed	0 / 1012 (0.00%)	61 / 1013 (6.02%)	
occurrences (all)	0	62	
Injection site pain			
subjects affected / exposed	17 / 1012 (1.68%)	83 / 1013 (8.19%)	
occurrences (all)	19	85	
Injection site pruritus			
subjects affected / exposed	5 / 1012 (0.49%)	92 / 1013 (9.08%)	
occurrences (all)	5	94	
Injection site swelling			
subjects affected / exposed	4 / 1012 (0.40%)	209 / 1013 (20.63%)	
occurrences (all)	4	214	
Vaccination site pain			
subjects affected / exposed	53 / 1012 (5.24%)	49 / 1013 (4.84%)	
occurrences (all)	64	60	
Injection site scab			
subjects affected / exposed	0 / 1012 (0.00%)	34 / 1013 (3.36%)	
occurrences (all)	0	34	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	46 / 1012 (4.55%)	32 / 1013 (3.16%)	
occurrences (all)	53	49	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	29 / 1012 (2.87%)	34 / 1013 (3.36%)	
occurrences (all)	37	45	
Oropharyngeal pain			

subjects affected / exposed	33 / 1012 (3.26%)	30 / 1013 (2.96%)	
occurrences (all)	40	35	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	28 / 1012 (2.77%)	32 / 1013 (3.16%)	
occurrences (all)	36	34	
Infections and infestations			
Injection site abscess			
subjects affected / exposed	0 / 1012 (0.00%)	72 / 1013 (7.11%)	
occurrences (all)	0	72	
Injection site pustule			
subjects affected / exposed	2 / 1012 (0.20%)	69 / 1013 (6.81%)	
occurrences (all)	2	73	
Nasopharyngitis			
subjects affected / exposed	80 / 1012 (7.91%)	76 / 1013 (7.50%)	
occurrences (all)	92	97	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 October 2020	Protocol Version 4.0 with following main changes to Version 3.0 (first protocol version under which subjects were included and treated): - Exclusion criterion 4 was changed from "Expected vaccination during the study period; vaccinations against influenza and pneumococcal disease are allowed" to "Expected vaccination during the study period; vaccinations against influenza and pneumococcal disease are allowed with ≥4 weeks between these vaccinations and the trial vaccination". - Exclusion criterion 5 was changed from "Participation in another study within 30 days before screening and during this study" to "Participation in another interventional study within 30 days before screening and during this study". - Exclusion criterion 8 was changed from "Active solid or non-solid malignancy or lymphoma in the past 5 years" to "History of malignancies, unless the subject has been free of the disease for ≥2 years; exception: subjects with adequately treated basal or squamous cell cancer or other localized non-melanoma skin cancer and adequately treated carcinoma in situ of the cervix may participate in the trial". - It was clarified that the subjects were "encouraged" to name a caregiver, but they did not need to. - It was added that subjects who dropped out before application of the trial intervention were to be replaced and subjects who dropped out after application of the trial intervention were not to be replaced. - The completion of a paper diary became optional. - The per-protocol set was introduced for the sensitivity analysis of the primary endpoint.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported