Clinical trial results:
Effectiveness of low molecular weight heparin at increased doses prophylaxis weight-adjusted, compared with lower doses prophylaxis (intermediate or standard), on the onset of venous thromboembolism in coronavirus disease 2019 (COVID-19) hospitalized patients : The randomized multicentric controlled open-label trial COVI-DOSE

Summary

EudraCT number	2020-001709-21
Trial protocol	FR
Global end of trial date	03 May 2022

Results information

Result version number	v1 (current)
This version publication date	22 October 2023
First version publication date	22 October 2023
Summary attachment (see zip file)	COVI-DOSE_Brief Summary (COVI-DOSE_Brief Summary.pdf)

Trial information

Trial identification

Sponsor protocol code	2020PI073

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04373707
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	CHRU Nancy
Sponsor organisation address	Rue du MORVAN, Vandoeuvre les Nancy, France, 54511
Public contact	Direction de la Recherche Clinique , CHRU de Nancy, 33 383 155285, dripromoteur@chru-nancy.fr
Scientific contact	Direction de la Recherche Clinique , CHRU de Nancy, 33 383 155285, dripromoteur@chru-nancy.fr

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	11 May 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 September 2021
Global end of trial reached?	Yes
Global end of trial date	03 May 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effectiveness, during the hospitalization, of low molecular weight heparin at increased doses prophylaxis weight-adjusted, compared with lower doses prophylaxis (intermediate or standard), on the onset of venous thromboembolism, causing death or not, in coronavirus 19 patients hospitalized in medical care units or intensive care units

Protection of trial subjects:

Subjects included:

Subjects able to express their consent and
Subjects unable to express their consent and who are not under legal protection

Background therapy:

Not applicable

Evidence for comparator:

The research involves comparing weight-adjusted prophylactic dose of low-molecular-weight heparin to fixed prophylactic dose

Actual start date of recruitment	13 May 2020
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Ethical reason, Regulatory reason, Scientific research
Long term follow-up duration	2 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 1000
Worldwide total number of subjects	1000
EEA total number of subjects	1000

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	728
From 65 to 84 years	272
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Date of start: 11-May-2022
Date of last visit of last participated patient: 14-Sep-2021
Patients, with COVID-19, were enrolled in medical wards or intensive care units from 20 French hospitals.

Pre-assignment

Screening details:

Hospitalization for an acute respiratory COVID-19 infection
SARS-Cov-2 infection diagnosed by biology (positive PCR for COVID-19 from any specimen and/or serology) and or by a composite criterium associating lung injury on imaging and clinical / biological symptoms suggestive of COVID-19 (eg : dyspnea, cough, fever, biological inflammatory syndrom

Period 1

Period 1 title	Hospital stay maximal duration 28days
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Experimental arm

Arm description:

weight-adjusted inter- mediate dose of low-molecular-weight heparin

Arm type	Experimental
Investigational medicinal product name	low molecular-weight heparin
Investigational medicinal product code	
Other name	LOVENOX, INNOHEP, FRAGMINE, FRAXIPARINE
Pharmaceutical forms	Anticoagulant and preservative solution for blood
Routes of administration	Intravenous use

Dosage and administration details:

patients received an increased weight-adjusted inter- mediate dose of low-molecular-weight heparin ranging from a double standard dose (e.g., enoxaparin 4000 UI twice daily for <50 kg) to a higher dose (e.g., enoxaparin 7000 UI twice daily for > 100 kg)

Arm title	Control arm

Arm description:

fixed-dose of low-molecular-weight heparin

Arm type	Active comparator
Investigational medicinal product name	low molecular-weight heparin
Investigational medicinal product code	
Other name	LOVENOX, INNOHEP, FRAGMINE, FRAXIPARINE
Pharmaceutical forms	Anticoagulant and preservative solution for blood
Routes of administration	Intravenous use

Dosage and administration details:

patients admitted to the medical wards received a fixed standard dose of low-molecular-weight heparin (e.g., enoxaparin 4000 UI once daily), while patients from the intensive care units received a fixed doubled standard dose (e.g., enoxaparin 4000 UI twice daily)

Number of subjects in period 1	Experimental arm	Control arm
Started	502	498
28 days	478	471
Completed	478	471
Not completed	24	27
Adverse event, serious fatal	22	25
Consent withdrawn by subject	2	1
other reason	-	1

Period 2	
Period 2 title	60 days after inclusion
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Experimental arm

Arm description:

weight-adjusted inter- mediate dose of low-molecular-weight heparin

Arm type	Experimental
Investigational medicinal product name	low molecular-weight heparin
Investigational medicinal product code	
Other name	LOVENOX, INNOHEP, FRAGMINE, FRAXIPARINE
Pharmaceutical forms	Anticoagulant and preservative solution for blood
Routes of administration	Intravenous use

Dosage and administration details:

patients received an increased weight-adjusted inter- mediate dose of low-molecular-weight heparin ranging from a double standard dose (e.g., enoxaparin 4000 UI twice daily for <50 kg) to a higher dose (e.g., enoxaparin 7000 UI twice daily for > 100 kg)

Arm title	Control arm

Arm description:

fixed-dose of low-molecular-weight heparin

Arm type	Active comparator
Investigational medicinal product name	low molecular-weight heparin
Investigational medicinal product code	
Other name	LOVENOX, INNOHEP, FRAGMINE, FRAXIPARINE
Pharmaceutical forms	Anticoagulant and preservative solution for blood
Routes of administration	Intravenous use

Dosage and administration details:

patients admitted to the medical wards received a fixed standard dose of low-molecular-weight heparin (e.g., enoxaparin 4000 UI once daily), while patients from the intensive care units received a fixed doubled standard dose (e.g., enoxaparin 4000 UI twice daily)

Number of subjects in period 2	Experimental arm	Control arm
Started	478	471
Completed	449	440
Not completed	29	31
Adverse event, serious fatal	4	6
Consent withdrawn by subject	1	-
other reasons	4	3
Lost to follow-up	20	22

Baseline characteristics

Reporting groups	
Reporting group title	Experimental arm
Reporting group description: weight-adjusted inter- mediate dose of low-molecular-weight heparin	
Reporting group title	Control arm
Reporting group description: fixed-dose of low-molecular-weight heparin	

Reporting group values	Experimental arm	Control arm	Total
Number of subjects	502	498	1000
Age categorical Units: Subjects			
Less than 70 years	368	360	728
70 years or more	134	138	272
Age continuous Units: years			
median	62.2	61.8	
inter-quartile range (Q1-Q3)	53.1 to 70.6	51.6 to 71.0	-
Gender categorical Units: Subjects			
Female	171	163	334
Male	331	335	666
Body weight Units: Subjects			
Less than 50 kg	9	8	17
50-70 kg	95	94	189
70-100 kg	308	317	625
100 kg or more	90	78	168
Not available	0	1	1
Body mass index Units: Subjects			
Less than 30 kg/m²	312	327	639
30 kg/m² or more	184	158	342
Not available	6	13	19
Creatinine clearance (Cockcroft-Gault) Units: Subjects			
Less than 50 mL/min	21	29	50
50–90 mL/min	149	160	309
90 mL/min or more	331	306	637
Not available	1	3	4
Hospitalization in medical wards at inclusion Units: Subjects			
Yes	407	394	801
No	95	104	199
Hypertension Units: Subjects			

Yes	195	204	399
No	297	291	588
Not available	10	3	13
Diabetes mellitus Units: Subjects			
Yes	112	104	216
No	379	391	770
Not available	11	3	14
Hypercholesterolemia Units: Subjects			
Yes	111	112	223
No	380	379	759
Not available	11	7	18
Coronary heart disease Units: Subjects			
Yes	45	33	78
No	450	461	911
Not available	7	4	11
Sleep apnea Units: Subjects			
Yes	44	41	85
No	450	451	901
Not available	8	6	14
Chronic respiratory disease Units: Subjects			
Yes	31	19	50
No	463	475	938
Not available	8	4	12
Active cancer Units: Subjects			
Yes	19	23	42
No	471	466	937
Not available	12	9	21
History of venous thromboembolism Units: Subjects			
Yes	19	26	45
No	476	468	944
Not available	7	4	11
Stroke Units: Subjects			
Yes	18	16	34
No	473	473	946
Not available	11	9	20
Chronic kidney disease Units: Subjects			
Yes	11	10	21
No	484	485	969
Not available	7	3	10
Heart failure Units: Subjects			
Yes	10	12	22

No	484	482	966
Not available	8	4	12
Antiplatelet agent at baseline Units: Subjects			
Yes	97	95	192
No	405	401	806
Not available	0	2	2
Renin-angiotensin system blockers at baseline Units: Subjects			
Yes	138	160	298
No	357	334	691
Not available	7	4	11
Corticosteroid use at baseline (10 mg/day or more) Units: Subjects			
Yes	57	48	105
No	436	447	883
Not available	9	3	12
Dexamethasone			
COVID-19 specific treatments			
Units: Subjects			
Yes	384	390	774
No	89	96	185
Not available	29	12	41
Tocilizumab use			
COVID-19 specific treatments			
Units: Subjects			
Yes	7	9	16
No	461	475	936
Not available	34	14	48
Respiratory support Units: Subjects			
Supplemental oxygen ≤15 L/min	404	401	805
NI ventilation with high flow O2 support> 15 L/min	14	19	33
Invasive mechanical ventilation ± ECMO	14	14	28
No supplemental oxygen therapy	62	57	119
Not available	8	7	15
At least one dose of study drug Units: Subjects			
Yes	481	485	966
No	21	13	34
Full compliance Units: Subjects			
Yes	436	437	873
No	45	48	93
Not available	21	13	34
Body weight Units: kg			
median	83.0	81.7	

inter-quartile range (Q1-Q3)	72.0 to 95.0	72.0 to 93.0	-
Body mass index			
Units: kg/m²			
median	28.3	28.1	
inter-quartile range (Q1-Q3)	24.9 to 32.2	24.8 to 31.3	-

End points

End points reporting groups

Reporting group title	Experimental arm
Reporting group description: weight-adjusted inter- mediate dose of low-molecular-weight heparin	
Reporting group title	Control arm
Reporting group description: fixed-dose of low-molecular-weight heparin	
Reporting group title	Experimental arm
Reporting group description: weight-adjusted inter- mediate dose of low-molecular-weight heparin	
Reporting group title	Control arm
Reporting group description: fixed-dose of low-molecular-weight heparin	

Primary: Symptomatic venous thromboembolism

End point title	Symptomatic venous thromboembolism
End point description:	
End point type	Primary
End point timeframe: Hospital stay maximal duration 28days	

End point values	Experimental arm	Control arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	502	498		
Units: subjects				
Yes	6	10		
No	496	488		

Attachments (see zip file)	Cumulative Event Rates for the Primary Outcome/Fig3-

Statistical analyses

Statistical analysis title	Analysis of primary endpoint
Comparison groups	Experimental arm v Control arm

Number of subjects included in analysis	1000
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Sub Hazard Ratio
Point estimate	0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.22
upper limit	1.63

Secondary: Major bleeding or clinically relevant nonmajor bleeding

End point title	Major bleeding or clinically relevant nonmajor bleeding
End point description:	

End point type	Secondary
End point timeframe:	
Hospital stay maximal duration 28days	

End point values	Experimental arm	Control arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	502	498		
Units: Subjects				
Yes	29	15		
No	473	483		

Statistical analyses

Statistical analysis title	Analysis secondary outcome 2
Comparison groups	Experimental arm v Control arm
Number of subjects included in analysis	1000
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Sub Hazard Ratio
Point estimate	1.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.05
upper limit	3.63

Secondary: Major bleeding

End point title	Major bleeding

End point description:

End point type	Secondary

End point timeframe:

Hospital stay maximal duration 28days

End point values	Experimental arm	Control arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	502	498		
Units: subjects				
Yes	5	6		
No	497	492		

Statistical analyses

Statistical analysis title	Analysis secondary outcome 2
Comparison groups	Experimental arm v Control arm
Number of subjects included in analysis	1000
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Sub Hazard Ratio
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.25
upper limit	2.7

Secondary: Net clinical benefit

End point title	Net clinical benefit

End point description:

End point type	Secondary

End point timeframe:

Hospital stay maximal duration 28days

End point values	Experimental arm	Control arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	502	498		
Units: subjects				
Yes	10	16		
No	492	482		

Statistical analyses

Statistical analysis title	Analysis secondary outcome 3
Comparison groups	Experimental arm v Control arm
Number of subjects included in analysis	1000
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Sub Hazard Ratio
Point estimate	0.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.28
upper limit	1.36

Secondary: Net clinical benefit

End point title	Net clinical benefit

End point description:

End point type	Secondary

End point timeframe:

60 days after inclusion

End point values	Experimental arm	Control arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	478	471		
Units: subjects				
Yes	15	23		
No	463	448		

Statistical analyses

Statistical analysis title	Analysis secondary outcome 4
Comparison groups	Control arm v Experimental arm
Number of subjects included in analysis	949
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Sub Hazard Ratio
Point estimate	0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.34
upper limit	1.23

Secondary: Symptomatic venous thromboses of other sites	
End point title	Symptomatic venous thromboses of other sites
End point description:	
End point type	Secondary
End point timeframe:	
Hospital stay maximal duration 28days	

End point values	Experimental arm	Control arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	502	498		
Units: subjects				
Yes	3	3		
No	499	495		

Statistical analyses

Statistical analysis title	Analysis secondary outcome 5
Comparison groups	Experimental arm v Control arm
Number of subjects included in analysis	1000
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Sub Hazard Ratio
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.2
upper limit	4.89

Secondary: Symptomatic arterial thrombosis

End point title	Symptomatic arterial thrombosis

End point description:

End point type	Secondary

End point timeframe:

Hospital stay maximal duration 28days

End point values	Experimental arm	Control arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	502	498		
Units: subjects				
Yes	1	2		
No	501	496		

Statistical analyses

Statistical analysis title	Analysis secondary outcome 6
Comparison groups	Experimental arm v Control arm
Number of subjects included in analysis	1000
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Sub Hazard Ratio
Point estimate	0.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.04
upper limit	5.41

Secondary: All-cause death

End point title	All-cause death

End point description:

End point type	Secondary

End point timeframe:

Hospital stay maximal duration 28days

End point values	Experimental arm	Control arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	502	498		
Units: subjects				
Yes	22	25		
No	480	473		

Statistical analyses

Statistical analysis title	Analysis secondary outcome 7
Comparison groups	Experimental arm v Control arm
Number of subjects included in analysis	1000
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	1.55

Secondary: All-cause death

End point title	All-cause death

End point description:

End point type	Secondary

End point timeframe:

60 days after inclusion

End point values	Experimental arm	Control arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	478	471		
Units: subjects				
Yes	26	31		
No	452	440		

Statistical analyses

Statistical analysis title	Analysis secondary outcome 8
Comparison groups	Experimental arm v Control arm
Number of subjects included in analysis	949
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	1.4

Adverse events

Adverse events information

Timeframe for reporting adverse events:

SAE were collected and transmitted without undue delay to the sponsor from the enrollment until the end of the study.
AE were collected in the CRF throughout the patient's participation in the study (for 1 month or until discharge whichever is shorter).

Adverse event reporting additional description:

Patients were monitored using the usual patient management parameters COVID-19 during routine inpatient care (medical or intensive care) at the investigator's discretion.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	Experimental arm

Reporting group description:

Adjusted posology

Reporting group title	Control arm

Reporting group description:

Non adjusted posology

Serious adverse events	Experimental arm	Control arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	162 / 502 (32.27%)	147 / 498 (29.52%)	
number of deaths (all causes)	53	58	
number of deaths resulting from adverse events	27	31	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastatic neoplasm			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Naevus haemorrhage			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Arterial thrombosis			

subjects affected / exposed	0 / 502 (0.00%)	2 / 498 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 502 (0.20%)	4 / 498 (0.80%)	
occurrences causally related to treatment / all	0 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	2 / 502 (0.40%)	2 / 498 (0.40%)	
occurrences causally related to treatment / all	1 / 3	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemodynamic instability			
subjects affected / exposed	0 / 502 (0.00%)	3 / 498 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 3	
Haemorrhage			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jugular vein thrombosis			
subjects affected / exposed	5 / 502 (1.00%)	3 / 498 (0.60%)	
occurrences causally related to treatment / all	1 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic venous thrombosis			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery dissection			

subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery thrombosis			
subjects affected / exposed	1 / 502 (0.20%)	3 / 498 (0.60%)	
occurrences causally related to treatment / all	0 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral coldness			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	0 / 502 (0.00%)	2 / 498 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phlebitis			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			
subjects affected / exposed	1 / 502 (0.20%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superficial vein thrombosis			
subjects affected / exposed	1 / 502 (0.20%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vena cava thrombosis			

subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis limb			
subjects affected / exposed	3 / 502 (0.60%)	2 / 498 (0.40%)	
occurrences causally related to treatment / all	0 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Cardiac pacemaker insertion			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileectomy			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung assist device therapy			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palliative care			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheostomy			
subjects affected / exposed	1 / 502 (0.20%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Complication associated with device			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concomitant disease aggravated			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Condition aggravated			
subjects affected / exposed	0 / 502 (0.00%)	3 / 498 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
General physical health deterioration			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Inflammation			
subjects affected / exposed	1 / 502 (0.20%)	2 / 498 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injection site haematoma			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical device site haemorrhage			
subjects affected / exposed	3 / 502 (0.60%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	7 / 502 (1.39%)	6 / 498 (1.20%)	
occurrences causally related to treatment / all	0 / 7	1 / 7	
deaths causally related to treatment / all	0 / 7	1 / 7	
No adverse event			

subjects affected / exposed	21 / 502 (4.18%)	20 / 498 (4.02%)	
occurrences causally related to treatment / all	0 / 21	0 / 20	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Immunosuppression			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (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			
Intermenstrual bleeding			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory distress syndrome			
subjects affected / exposed	3 / 502 (0.60%)	7 / 498 (1.41%)	
occurrences causally related to treatment / all	0 / 3	0 / 7	
deaths causally related to treatment / all	0 / 1	0 / 4	
Acute respiratory failure			
subjects affected / exposed	2 / 502 (0.40%)	3 / 498 (0.60%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 3	
Bronchial haemorrhage			
subjects affected / exposed	1 / 502 (0.20%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Emphysema			

subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	7 / 502 (1.39%)	3 / 498 (0.60%)	
occurrences causally related to treatment / all	6 / 7	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	3 / 502 (0.60%)	4 / 498 (0.80%)	
occurrences causally related to treatment / all	3 / 3	5 / 5	
deaths causally related to treatment / all	0 / 0	1 / 1	
Haemothorax			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	3 / 502 (0.60%)	5 / 498 (1.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 2	0 / 1	
Interstitial lung disease			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal oedema			
subjects affected / exposed	1 / 502 (0.20%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pharyngeal haemorrhage			

subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumomediastinum			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumothorax			
subjects affected / exposed	2 / 502 (0.40%)	0 / 498 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	7 / 502 (1.39%)	10 / 498 (2.01%)	
occurrences causally related to treatment / all	0 / 7	2 / 10	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary fibrosis			
subjects affected / exposed	1 / 502 (0.20%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary infarction			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory disorder			

subjects affected / exposed	2 / 502 (0.40%)	0 / 498 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory distress			
subjects affected / exposed	2 / 502 (0.40%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 0	
Respiratory failure			
subjects affected / exposed	3 / 502 (0.60%)	4 / 498 (0.80%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 2	0 / 3	
Respiratory tract haemorrhage			
subjects affected / exposed	0 / 502 (0.00%)	2 / 498 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Computerised tomogram normal			
subjects affected / exposed	1 / 502 (0.20%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oxygen saturation decreased			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Red blood cell count decreased			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ultrasound Doppler normal			

subjects affected / exposed	1 / 502 (0.20%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	10 / 502 (1.99%)	7 / 498 (1.41%)	
occurrences causally related to treatment / all	0 / 11	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Dose calculation error			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endotracheal intubation complication			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eschar			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product administration error			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product prescribing error			
subjects affected / exposed	33 / 502 (6.57%)	28 / 498 (5.62%)	
occurrences causally related to treatment / all	1 / 36	1 / 29	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous haematoma			

subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheal haemorrhage			
subjects affected / exposed	2 / 502 (0.40%)	0 / 498 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vasoplegia syndrome			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound haematoma			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram abnormal			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 502 (0.00%)	2 / 498 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Arrhythmia			
subjects affected / exposed	0 / 502 (0.00%)	2 / 498 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			

subjects affected / exposed	3 / 502 (0.60%)	5 / 498 (1.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	2 / 502 (0.40%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cardiac failure			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac flutter			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiogenic shock			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardio-respiratory arrest			
subjects affected / exposed	6 / 502 (1.20%)	4 / 498 (0.80%)	
occurrences causally related to treatment / all	0 / 6	0 / 4	
deaths causally related to treatment / all	0 / 6	0 / 4	
Myocardial ischaemia			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocarditis			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			

subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus bradycardia			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular hypokinesia			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebellar stroke			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coma			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Haemorrhagic transformation stroke			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningorrhagia			

subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	9 / 502 (1.79%)	11 / 498 (2.21%)	
occurrences causally related to treatment / all	5 / 9	8 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia macrocytic			
subjects affected / exposed	1 / 502 (0.20%)	2 / 498 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aplastic anaemia			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Microcytic anaemia			
subjects affected / exposed	2 / 502 (0.40%)	0 / 498 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	2 / 502 (0.40%)	0 / 498 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Papilloedema			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vision blurred			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (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 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum intestinal			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gingival bleeding			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	1 / 502 (0.20%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoidal haemorrhage			
subjects affected / exposed	1 / 502 (0.20%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intra-abdominal haematoma			

subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	3 / 502 (0.60%)	4 / 498 (0.80%)	
occurrences causally related to treatment / all	2 / 3	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mouth haemorrhage			
subjects affected / exposed	2 / 502 (0.40%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	5 / 502 (1.00%)	2 / 498 (0.40%)	
occurrences causally related to treatment / all	4 / 5	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic cytolysis			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular injury			

subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Bullous haemorrhagic dermatosis			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Purpura			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin necrosis			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous emphysema			
subjects affected / exposed	1 / 502 (0.20%)	1 / 498 (0.20%)	
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	4 / 502 (0.80%)	4 / 498 (0.80%)	
occurrences causally related to treatment / all	3 / 4	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 1	
Haematuria			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	3 / 502 (0.60%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			

subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal infarct			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Haematoma muscle			
subjects affected / exposed	5 / 502 (1.00%)	3 / 498 (0.60%)	
occurrences causally related to treatment / all	5 / 5	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	2 / 502 (0.40%)	0 / 498 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchopulmonary aspergillosis			
subjects affected / exposed	1 / 502 (0.20%)	2 / 498 (0.40%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 1	1 / 1	
Cellulitis			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (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	7 / 502 (1.39%)	8 / 498 (1.61%)	
occurrences causally related to treatment / all	0 / 7	0 / 8	
deaths causally related to treatment / all	0 / 6	0 / 8	
COVID-19 pneumonia			
subjects affected / exposed	3 / 502 (0.60%)	0 / 498 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 3	0 / 0	

Enterococcal bacteraemia			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Peritonitis			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii infection			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Pneumonia staphylococcal			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sepsis			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sepsis			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (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	1 / 502 (0.20%)	6 / 498 (1.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 4	
Severe acute respiratory syndrome			
subjects affected / exposed	1 / 502 (0.20%)	3 / 498 (0.60%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	1 / 3	
Superinfection bacterial			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Thrombophlebitis septic			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Veillonella infection			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	2 / 502 (0.40%)	3 / 498 (0.60%)	
occurrences causally related to treatment / all	1 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	

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

Non-serious adverse events	Experimental arm	Control arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	225 / 502 (44.82%)	325 / 498 (65.26%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatic neoplasm			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	

Monoclonal gammopathy			
subjects affected / exposed	1 / 502 (0.20%)	1 / 498 (0.20%)	
occurrences (all)	1	1	
Basal cell carcinoma			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences (all)	0	1	
Adrenal neoplasm			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences (all)	0	1	
Renal neoplasm			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences (all)	0	1	
Myelodysplastic syndrome			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences (all)	0	1	
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	
Haemorrhage	Additional description: minor haemorrhage		
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences (all)	0	1	
Haematoma			
subjects affected / exposed	1 / 502 (0.20%)	5 / 498 (1.00%)	
occurrences (all)	1	6	
Hypertension			
subjects affected / exposed	3 / 502 (0.60%)	1 / 498 (0.20%)	
occurrences (all)	3	1	
Hypotension			
subjects affected / exposed	2 / 502 (0.40%)	3 / 498 (0.60%)	
occurrences (all)	2	3	
Thrombosis	Additional description: blood clots		
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences (all)	0	1	
Vascular pain	Additional description: vein inflammation (veinitis)		

subjects affected / exposed	3 / 502 (0.60%)	5 / 498 (1.00%)	
occurrences (all)	3	5	
Venous thrombosis	Additional description: distal venous thrombosis		
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	
Surgical and medical procedures			
Gastrostomy			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences (all)	0	1	
Tracheostomy			
subjects affected / exposed	0 / 502 (0.00%)	2 / 498 (0.40%)	
occurrences (all)	0	2	
General disorders and administration site conditions			
Face oedema			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences (all)	0	1	
Disease progression			
subjects affected / exposed	1 / 502 (0.20%)	4 / 498 (0.80%)	
occurrences (all)	1	4	
Generalised oedema			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	
Hyperthermia			
subjects affected / exposed	3 / 502 (0.60%)	2 / 498 (0.40%)	
occurrences (all)	3	5	
Hypothermia			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences (all)	0	1	
Inflammation	Additional description: biological inflammatory syndrome		
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences (all)	0	1	
Injection site erythema			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	
Injection site inflammation			

subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	
Injection site pain			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	
Malaise			
subjects affected / exposed	0 / 502 (0.00%)	2 / 498 (0.40%)	
occurrences (all)	0	2	
Oedema			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences (all)	0	1	
Oedema peripheral			
subjects affected / exposed	6 / 502 (1.20%)	11 / 498 (2.21%)	
occurrences (all)	7	11	
Physical deconditioning			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences (all)	0	1	
Puncture site haematoma			
subjects affected / exposed	2 / 502 (0.40%)	1 / 498 (0.20%)	
occurrences (all)	2	1	
Puncture site haemorrhage			
subjects affected / exposed	5 / 502 (1.00%)	3 / 498 (0.60%)	
occurrences (all)	6	4	
Pyrexia			
subjects affected / exposed	2 / 502 (0.40%)	1 / 498 (0.20%)	
occurrences (all)	3	1	
Ulcer			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences (all)	0	1	
Weight decreased			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	
Social circumstances			
Loss of personal independence in daily activities			

subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Penile dermatitis			
subjects affected / exposed	1 / 502 (0.20%)	1 / 498 (0.20%)	
occurrences (all)	1	1	
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	1 / 502 (0.20%)	2 / 498 (0.40%)	
occurrences (all)	1	2	
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 502 (0.20%)	1 / 498 (0.20%)	
occurrences (all)	1	1	
Acute respiratory failure			
subjects affected / exposed	1 / 502 (0.20%)	2 / 498 (0.40%)	
occurrences (all)	1	2	
Atelectasis			
subjects affected / exposed	4 / 502 (0.80%)	1 / 498 (0.20%)	
occurrences (all)	4	1	
Bronchitis			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences (all)	0	1	
Chest pain			
subjects affected / exposed	1 / 502 (0.20%)	2 / 498 (0.40%)	
occurrences (all)	2	2	
Cough			
subjects affected / exposed	2 / 502 (0.40%)	1 / 498 (0.20%)	
occurrences (all)	2	1	
Dysphonia			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	
Dyspnoea			
subjects affected / exposed	2 / 502 (0.40%)	2 / 498 (0.40%)	
occurrences (all)	2	2	
Dyspnoea exertional			

subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences (all)	0	1	
Epistaxis			
subjects affected / exposed	13 / 502 (2.59%)	13 / 498 (2.61%)	
occurrences (all)	15	13	
Haemoptysis			
subjects affected / exposed	6 / 502 (1.20%)	9 / 498 (1.81%)	
occurrences (all)	6	9	
Hypercapnia			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences (all)	0	1	
Hypoxia			
subjects affected / exposed	3 / 502 (0.60%)	7 / 498 (1.41%)	
occurrences (all)	3	7	
Laryngeal oedema			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences (all)	0	1	
Oropharyngeal oedema			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences (all)	0	1	
Pneumomediastinum			
subjects affected / exposed	2 / 502 (0.40%)	2 / 498 (0.40%)	
occurrences (all)	2	2	
Pneumothorax			
subjects affected / exposed	1 / 502 (0.20%)	1 / 498 (0.20%)	
occurrences (all)	1	1	
Tachypnoea			
subjects affected / exposed	2 / 502 (0.40%)	1 / 498 (0.20%)	
occurrences (all)	2	2	
Pulmonary embolism	Additional description: suspected but not confirmed pulmonary embolism		
subjects affected / exposed	1 / 502 (0.20%)	2 / 498 (0.40%)	
occurrences (all)	1	2	
Pulmonary mass	Additional description: nodules		
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences (all)	0	1	
Respiratory acidosis			

subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	
Respiratory alkalosis			
subjects affected / exposed	2 / 502 (0.40%)	0 / 498 (0.00%)	
occurrences (all)	2	0	
Respiratory disorder	Additional description: respiratory worsening		
subjects affected / exposed	29 / 502 (5.78%)	26 / 498 (5.22%)	
occurrences (all)	30	26	
Respiratory distress			
subjects affected / exposed	2 / 502 (0.40%)	4 / 498 (0.80%)	
occurrences (all)	2	4	
Respiratory failure			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	
Tracheal haemorrhage			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	
Tracheomalacia			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences (all)	0	1	
Psychiatric disorders			
Depressed mood			
subjects affected / exposed	0 / 502 (0.00%)	2 / 498 (0.40%)	
occurrences (all)	0	2	
Agitation			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	
Anxiety			
subjects affected / exposed	6 / 502 (1.20%)	3 / 498 (0.60%)	
occurrences (all)	6	3	
Brief psychotic disorder without marked stressors			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences (all)	0	1	
Confusional state			

subjects affected / exposed	2 / 502 (0.40%)	2 / 498 (0.40%)	
occurrences (all)	2	2	
Insomnia			
subjects affected / exposed	1 / 502 (0.20%)	1 / 498 (0.20%)	
occurrences (all)	1	1	
Sleep disorder			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	
Investigations			
Antiphospholipid antibodies			
subjects affected / exposed	1 / 502 (0.20%)	1 / 498 (0.20%)	
occurrences (all)	1	1	
Bacterial test positive			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences (all)	0	1	
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences (all)	0	1	
Blood urea increased			
subjects affected / exposed	2 / 502 (0.40%)	2 / 498 (0.40%)	
occurrences (all)	2	2	
Bronchoscopy abnormal			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences (all)	0	1	
Electrocardiogram abnormal			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences (all)	0	1	
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 502 (0.40%)	3 / 498 (0.60%)	
occurrences (all)	2	3	
Sputum culture positive			
subjects affected / exposed	1 / 502 (0.20%)	2 / 498 (0.40%)	
occurrences (all)	1	2	
Injury, poisoning and procedural complications			

Weaning failure			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	
Ear injury			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	
Eschar			
subjects affected / exposed	1 / 502 (0.20%)	2 / 498 (0.40%)	
occurrences (all)	1	2	
Fall			
subjects affected / exposed	0 / 502 (0.00%)	4 / 498 (0.80%)	
occurrences (all)	0	3	
Tooth fracture			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences (all)	0	1	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	6 / 502 (1.20%)	4 / 498 (0.80%)	
occurrences (all)	6	5	
Bradycardia			
subjects affected / exposed	1 / 502 (0.20%)	2 / 498 (0.40%)	
occurrences (all)	1	2	
Cardiac murmur			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences (all)	0	1	
Heart transplant rejection			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	
Myocarditis			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences (all)	0	1	
Palpitations			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	
Tachyarrhythmia			

subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	
Tachycardia			
subjects affected / exposed	2 / 502 (0.40%)	2 / 498 (0.40%)	
occurrences (all)	2	2	
Ventricular extrasystoles			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences (all)	0	1	
Ventricular tachycardia			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Amnesia			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	
Aphasia			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	
Burning sensation			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	
Dizziness			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences (all)	0	1	
Gait disturbance			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	
Generalised tonic-clonic seizure			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	
Hemiparesis			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences (all)	0	1	

Loss of consciousness			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences (all)	0	1	
Migraine			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	
Neuropathy peripheral			
subjects affected / exposed	2 / 502 (0.40%)	0 / 498 (0.00%)	
occurrences (all)	2	0	
Paraesthesia			
subjects affected / exposed	1 / 502 (0.20%)	1 / 498 (0.20%)	
occurrences (all)	1	1	
Polyneuropathy			
subjects affected / exposed	1 / 502 (0.20%)	2 / 498 (0.40%)	
occurrences (all)	1	2	
Presyncope			
subjects affected / exposed	1 / 502 (0.20%)	1 / 498 (0.20%)	
occurrences (all)	1	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 502 (0.80%)	6 / 498 (1.20%)	
occurrences (all)	4	7	
Hyperleukocytosis			
subjects affected / exposed	1 / 502 (0.20%)	2 / 498 (0.40%)	
occurrences (all)	1	2	
Leukocytosis			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences (all)	0	1	
Lymphopenia			
subjects affected / exposed	3 / 502 (0.60%)	3 / 498 (0.60%)	
occurrences (all)	3	3	
Microcytic anaemia			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	
Neutropenia			

subjects affected / exposed	1 / 502 (0.20%)	2 / 498 (0.40%)	
occurrences (all)	1	2	
Neutrophilia			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences (all)	0	1	
Splenomegaly			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences (all)	0	1	
Thrombocytopenia			
subjects affected / exposed	3 / 502 (0.60%)	2 / 498 (0.40%)	
occurrences (all)	3	3	
Thrombocytosis			
subjects affected / exposed	6 / 502 (1.20%)	4 / 498 (0.80%)	
occurrences (all)	6	4	
Eye disorders			
blepharitis			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	
Eye oedema			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	
Vision blurred			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences (all)	0	1	
Anorectal discomfort			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	
Cheilitis			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	
Colitis			

subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	
Constipation			
subjects affected / exposed	2 / 502 (0.40%)	3 / 498 (0.60%)	
occurrences (all)	2	3	
Diarrhoea			
subjects affected / exposed	2 / 502 (0.40%)	7 / 498 (1.41%)	
occurrences (all)	2	7	
Dry mouth			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences (all)	0	1	
Dysphagia			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	
Enteritis			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences (all)	0	1	
Faecaloma			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences (all)	0	1	
Gastric ulcer			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences (all)	0	1	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	
Haematochezia			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences (all)	0	1	
Haemorrhoids			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	
Lip haemorrhage			

subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	
Lip ulceration			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences (all)	0	1	
Macroglossia			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	
Mouth haemorrhage			
subjects affected / exposed	1 / 502 (0.20%)	2 / 498 (0.40%)	
occurrences (all)	1	2	
Nausea			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	
Rectal haemorrhage			
subjects affected / exposed	1 / 502 (0.20%)	1 / 498 (0.20%)	
occurrences (all)	1	1	
Regurgitation			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	
Stomatitis haemorrhagic			
subjects affected / exposed	0 / 502 (0.00%)	2 / 498 (0.40%)	
occurrences (all)	0	2	
Subileus			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	1 / 502 (0.20%)	1 / 498 (0.20%)	
occurrences (all)	1	1	
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences (all)	0	1	

Cholecystitis			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences (all)	0	1	
Cholestasis			
subjects affected / exposed	2 / 502 (0.40%)	0 / 498 (0.00%)	
occurrences (all)	2	0	
Hepatic cytolysis			
subjects affected / exposed	22 / 502 (4.38%)	10 / 498 (2.01%)	
occurrences (all)	22	10	
Hepatitis viral			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences (all)	0	1	
Hypertransaminasaemia			
subjects affected / exposed	3 / 502 (0.60%)	6 / 498 (1.20%)	
occurrences (all)	3	7	
Liver disorder			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
alopecia			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	
Blister			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences (all)	0	1	
Dry skin			
subjects affected / exposed	2 / 502 (0.40%)	1 / 498 (0.20%)	
occurrences (all)	2	1	
Ecchymosis			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences (all)	0	1	
Eczema			
subjects affected / exposed	1 / 502 (0.20%)	1 / 498 (0.20%)	
occurrences (all)	1	1	
Erythema			

subjects affected / exposed	2 / 502 (0.40%)	2 / 498 (0.40%)	
occurrences (all)	2	2	
Rash			
subjects affected / exposed	1 / 502 (0.20%)	1 / 498 (0.20%)	
occurrences (all)	1	1	
Hyperhidrosis			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences (all)	0	1	
Livedo reticularis			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	
Rash macular			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	
Rash maculo-papular			
subjects affected / exposed	1 / 502 (0.20%)	3 / 498 (0.60%)	
occurrences (all)	1	3	
Skin lesion			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences (all)	0	1	
Subcutaneous emphysema			
subjects affected / exposed	1 / 502 (0.20%)	1 / 498 (0.20%)	
occurrences (all)	1	1	
Urticaria			
subjects affected / exposed	1 / 502 (0.20%)	1 / 498 (0.20%)	
occurrences (all)	1	1	
Skin erosion			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	5 / 502 (1.00%)	7 / 498 (1.41%)	
occurrences (all)	5	7	
Cystitis			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	

Dysuria			
subjects affected / exposed	1 / 502 (0.20%)	1 / 498 (0.20%)	
occurrences (all)	1	1	
End stage renal disease			
subjects affected / exposed	2 / 502 (0.40%)	1 / 498 (0.20%)	
occurrences (all)	2	1	
Haematuria			
subjects affected / exposed	2 / 502 (0.40%)	0 / 498 (0.00%)	
occurrences (all)	2	0	
Nephrolithiasis			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	
Oliguria			
subjects affected / exposed	0 / 502 (0.00%)	3 / 498 (0.60%)	
occurrences (all)	0	3	
Polyuria			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	
Renal failure			
subjects affected / exposed	0 / 502 (0.00%)	2 / 498 (0.40%)	
occurrences (all)	0	2	
Urethral haemorrhage			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences (all)	0	1	
Urinary retention			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 502 (0.00%)	3 / 498 (0.60%)	
occurrences (all)	0	3	
Back pain			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	
Muscular weakness			

subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	
Pain in extremity			
subjects affected / exposed	1 / 502 (0.20%)	2 / 498 (0.40%)	
occurrences (all)	1	2	
Pelvic misalignment			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	
Sarcopenia			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences (all)	0	1	
Tendonitis			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Aspergillus infection			
subjects affected / exposed	1 / 502 (0.20%)	1 / 498 (0.20%)	
occurrences (all)	1	1	
Bacteraemia			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences (all)	0	2	
Bronchopulmonary aspergillosis			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	
Candida infection			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences (all)	0	1	
COVID-19			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	
Genital herpes			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	
Herpes virus infection			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences (all)	0	1	

HIV infection			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences (all)	0	1	
Impetigo			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences (all)	0	1	
Infection			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	
Oral herpes			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	
Fungal infection			
subjects affected / exposed	4 / 502 (0.80%)	1 / 498 (0.20%)	
occurrences (all)	4	1	
peritonitis			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences (all)	0	1	
Pneumococcal infection			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences (all)	0	1	
Pneumonia			
subjects affected / exposed	1 / 502 (0.20%)	1 / 498 (0.20%)	
occurrences (all)	1	1	
Pneumonia bacterial			
subjects affected / exposed	8 / 502 (1.59%)	7 / 498 (1.41%)	
occurrences (all)	11	9	
Pneumonitis			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	
Pyelonephritis			
subjects affected / exposed	2 / 502 (0.40%)	3 / 498 (0.60%)	
occurrences (all)	2	3	
Sepsis			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	

Septic shock			
subjects affected / exposed	0 / 502 (0.00%)	2 / 498 (0.40%)	
occurrences (all)	0	2	
Sinusitis			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	
Staphylococcal infection			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences (all)	0	1	
Superinfection			
subjects affected / exposed	3 / 502 (0.60%)	5 / 498 (1.00%)	
occurrences (all)	3	5	
Tooth abscess			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	
Urinary tract infection			
subjects affected / exposed	4 / 502 (0.80%)	4 / 498 (0.80%)	
occurrences (all)	4	4	
Blood creatine phosphokinase BB increased			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences (all)	0	1	
Blood culture positive			
subjects affected / exposed	0 / 502 (0.00%)	3 / 498 (0.60%)	
occurrences (all)	0	3	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	8 / 502 (1.59%)	8 / 498 (1.61%)	
occurrences (all)	8	8	
Diabetes mellitus inadequate control			
subjects affected / exposed	3 / 502 (0.60%)	3 / 498 (0.60%)	
occurrences (all)	3	3	
Hypercalcaemia			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences (all)	0	1	
Hyperkalaemia			

subjects affected / exposed	7 / 502 (1.39%)	7 / 498 (1.41%)	
occurrences (all)	8	9	
Hypernatraemia			
subjects affected / exposed	3 / 502 (0.60%)	2 / 498 (0.40%)	
occurrences (all)	3	2	
Hyperthyroidism			
subjects affected / exposed	1 / 502 (0.20%)	1 / 498 (0.20%)	
occurrences (all)	1	1	
Hypertriglyceridaemia			
subjects affected / exposed	1 / 502 (0.20%)	1 / 498 (0.20%)	
occurrences (all)	1	1	
Hypoalbuminaemia			
subjects affected / exposed	1 / 502 (0.20%)	3 / 498 (0.60%)	
occurrences (all)	1	3	
Hypocalcaemia			
subjects affected / exposed	1 / 502 (0.20%)	3 / 498 (0.60%)	
occurrences (all)	1	4	
Hypoglycaemia			
subjects affected / exposed	2 / 502 (0.40%)	0 / 498 (0.00%)	
occurrences (all)	2	0	
Hypokalaemia			
subjects affected / exposed	9 / 502 (1.79%)	4 / 498 (0.80%)	
occurrences (all)	9	4	
Hyponatraemia			
subjects affected / exposed	4 / 502 (0.80%)	7 / 498 (1.41%)	
occurrences (all)	4	7	
Hypophosphataemia			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	
Hypovitaminosis			
subjects affected / exposed	1 / 502 (0.20%)	0 / 498 (0.00%)	
occurrences (all)	1	0	
Malnutrition			
subjects affected / exposed	3 / 502 (0.60%)	5 / 498 (1.00%)	
occurrences (all)	3	5	
Type 2 diabetes mellitus			

subjects affected / exposed	3 / 502 (0.60%)	0 / 498 (0.00%)	
occurrences (all)	3	0	
Vitamin D deficiency			
subjects affected / exposed	0 / 502 (0.00%)	1 / 498 (0.20%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 June 2020	MS1: New participating centres
03 July 2020	MS2: New participating centres
06 August 2020	MS3: clarification of inclusion criteria + increase in inclusion duration
20 November 2020	MS4: New participating centres
14 January 2021	MS5: New participating centres
15 February 2021	MS6: New participating centres
15 February 2021	MS7: Increase in the number of subjects required from 602 to 1000 subjects.
02 June 2021	MS8: Modification of non-inclusion criteria

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/37350990