Clinical trial results:
A Multicentre, Double-blind, Randomized, Placebo Controlled, Parallel Group, Phase 3, Safety Extension Study to Evaluate the Safety and Tolerability of Tezepelumab in Adults and Adolescents with Severe Uncontrolled Asthma (DESTINATION)

Summary

EudraCT number	2018-002501-53
Trial protocol	DE FR AT PL
Global end of trial date	30 June 2022

Results information

Result version number	v2 (current)
This version publication date	25 May 2023
First version publication date	15 December 2022
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	D5180C00018

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03706079
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca AB
Sponsor organisation address	151 85, Södertälje, Sweden,
Public contact	Global Clinical Head, AstraZeneca AB, +1 302 885 1180, information.center@astrazeneca.com
Scientific contact	Global Clinical Head, AstraZeneca AB, +1 302 885 1180, information.center@astrazeneca.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	09 December 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 October 2021
Global end of trial reached?	Yes
Global end of trial date	30 June 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the long-term safety and tolerability of Tezepelumab in severe asthma subjects

Protection of trial subjects:

The protocol, protocol amendments, informed consent form (ICF), Investigator Brochure (IB), and other relevant documents (eg, advertisements) were submitted to an Institutional Review Board/Independent Ethics Committee (IRB/IEC) by the Investigator and reviewed and approved by the IRB/IEC before the study was initiated. The Investigator or his/her representative explained the nature of the study to the subject or his/her legally authorised representative and answered all questions regarding the study. Subjects were informed that their participation was voluntary. Subjects were required to sign a statement of informed consent that met the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study centre. The medical record must have included a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must have also signed the ICF. Subjects must have been re-consented to the most current version of the ICF(s) during their participation in the study. A copy of the ICF(s) was provided to the subject.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 January 2019
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	Argentina: 102
Country: Number of subjects enrolled	Australia: 19
Country: Number of subjects enrolled	Austria: 8
Country: Number of subjects enrolled	Brazil: 93
Country: Number of subjects enrolled	Canada: 36
Country: Number of subjects enrolled	France: 41
Country: Number of subjects enrolled	Germany: 132
Country: Number of subjects enrolled	Israel: 47
Country: Number of subjects enrolled	Japan: 97
Country: Number of subjects enrolled	Korea, Republic of: 147
Country: Number of subjects enrolled	Poland: 30
Country: Number of subjects enrolled	Russian Federation: 51
Country: Number of subjects enrolled	Saudi Arabia: 7

Country: Number of subjects enrolled	South Africa: 109
Country: Number of subjects enrolled	Taiwan: 9
Country: Number of subjects enrolled	United States: 203
Country: Number of subjects enrolled	Ukraine: 41
Country: Number of subjects enrolled	Viet Nam: 20
Country: Number of subjects enrolled	Turkey: 17
Worldwide total number of subjects	1209
EEA total number of subjects	211

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)	82
Adults (18-64 years)	927
From 65 to 84 years	200
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants who completed treatment and attended end of treatment visit in predecessor studies NAVIGATOR (NCT03347279) and SOURCE (NCT03406078) were eligible. In the predecessor studies, a total of 1059 and 150 subjects were randomised and dosed in the NAVIGATOR and SOURCE study respectively.

Pre-assignment

Screening details:

In this long-term extension study, 950 subjects were randomised and dosed with tezepelumab or placebo. The patients receiving tezepelumab in the predecessors continued to receive tezepelumab, while patients receiving placebo in the predecessors were re-randomized to either tezepelumab or placebo in the extension study

Period 1

Period 1 title	Predecessor Study
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Subject, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	NAVIGATOR Rand Teze

Arm description:

All subjects randomised to tezepelumab in the NAVIGATOR predecessor and treated with at least one dose in the predecessor, regardless of whether they participated in the DESTINATION study.

Arm type	Experimental
Investigational medicinal product name	Tezepelumab administered every 4 weeks subcutaneously
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

210 mg Q4W

Arm title	NAVIGATOR Rand Pbo

Arm description:

All subjects randomised to placebo in the NAVIGATOR predecessor and treated with at least one dose in the predecessor, regardless of whether they participated in the DESTINATION study and regardless of their treatment assignment in DESTINATION.

Arm type	Placebo
Investigational medicinal product name	Placebo administered every 4 weeks subcutaneously
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Q4W

Arm title	SOURCE Rand Teze

Arm description:

All subjects randomised to tezepelumab in the SOURCE predecessor and treated with at least one dose in the predecessor, regardless of whether they participated in the DESTINATION study.

Arm type	Experimental
Investigational medicinal product name	Tezepelumab administered every 4 weeks subcutaneously
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

210 mg Q4W

Arm title	SOURCE Rand Pbo

Arm description:

All subjects randomised to placebo in the SOURCE predecessor and treated with at least one dose in the predecessor, regardless of whether they participated in the DESTINATION study and regardless of their treatment assignment in DESTINATION.

Arm type	Placebo
Investigational medicinal product name	Placebo administered every 4 weeks subcutaneously
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Q4W

Number of subjects in period 1	NAVIGATOR Rand Teze	NAVIGATOR Rand Pbo	SOURCE Rand Teze
Started	528	531	74
Completed	513	509	68
Not completed	15	22	6
Adverse event, serious fatal	-	2	1
Consent withdrawn by subject	8	15	5
Did not complete safety follow-up visits	2	3	-
Lost to follow-up	5	2	-

Number of subjects in period 1	SOURCE Rand Pbo
Started	76
Completed	73
Not completed	3
Adverse event, serious fatal	-
Consent withdrawn by subject	2
Did not complete safety follow-up visits	-
Lost to follow-up	1

Period 2

Period 2 title	Long Term Extension Study
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	NAVIGATOR Rand Teze

Arm description:

All subjects randomised to tezepelumab in the NAVIGATOR predecessor and treated with at least one dose in the predecessor, regardless of whether they participated in the DESTINATION study.

Arm type	Experimental
Investigational medicinal product name	Tezepelumab administered every 4 weeks subcutaneously
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

210 mg Q4W

Arm title	NAVIGATOR Rand Pbo

Arm description:

All subjects randomised to placebo in the NAVIGATOR predecessor and treated with at least one dose in the predecessor, regardless of whether they participated in the DESTINATION study and regardless of their treatment assignment in DESTINATION.

Arm type	Placebo
Investigational medicinal product name	Placebo administered every 4 weeks subcutaneously
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Q4W

Arm title	SOURCE Rand Teze

Arm description:

All subjects randomised to tezepelumab in the SOURCE predecessor and treated with at least one dose in the predecessor, regardless of whether they participated in the DESTINATION study.

Arm type	Experimental
Investigational medicinal product name	Tezepelumab administered every 4 weeks subcutaneously
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

210 mg Q4W

Arm title	SOURCE Rand Pbo

Arm description:

All subjects randomised to placebo in the SOURCE predecessor and treated with at least one dose in the predecessor, regardless of whether they participated in the DESTINATION study and regardless of their treatment assignment in DESTINATION.

Arm type	Placebo

Investigational medicinal product name	Placebo administered every 4 weeks subcutaneously
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Q4W

Number of subjects in period 2[1]	NAVIGATOR Rand Teze	NAVIGATOR Rand Pbo	SOURCE Rand Teze
Started	415	412	60
Completed	400	398	58
Not completed	15	14	2
Adverse event, serious fatal	8	4	1
Consent withdrawn by subject	3	6	1
Did not complete safety follow-up visits	1	2	-
Pregnancy	1	-	-
Lost to follow-up	2	2	-
Due to COVID-19 pandemic	-	-	-

Number of subjects in period 2[1]	SOURCE Rand Pbo
Started	64
Completed	59
Not completed	5
Adverse event, serious fatal	-
Consent withdrawn by subject	3
Did not complete safety follow-up visits	-
Pregnancy	-
Lost to follow-up	1
Due to COVID-19 pandemic	1

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Not everyone who completed predecessors was eligible or consented to participate in DESTINATION. However all patients randomized in the predecessor studies are included in the analysis.

Baseline characteristics

Reporting groups	
Reporting group title	NAVIGATOR Rand Teze
Reporting group description:	
All subjects randomised to tezepelumab in the NAVIGATOR predecessor and treated with at least one dose in the predecessor, regardless of whether they participated in the DESTINATION study.	
Reporting group title	NAVIGATOR Rand Pbo
Reporting group description:	
All subjects randomised to placebo in the NAVIGATOR predecessor and treated with at least one dose in the predecessor, regardless of whether they participated in the DESTINATION study and regardless of their treatment assignment in DESTINATION.	
Reporting group title	SOURCE Rand Teze
Reporting group description:	
All subjects randomised to tezepelumab in the SOURCE predecessor and treated with at least one dose in the predecessor, regardless of whether they participated in the DESTINATION study.	
Reporting group title	SOURCE Rand Pbo
Reporting group description:	
All subjects randomised to placebo in the SOURCE predecessor and treated with at least one dose in the predecessor, regardless of whether they participated in the DESTINATION study and regardless of their treatment assignment in DESTINATION.	

Reporting group values	NAVIGATOR Rand Teze	NAVIGATOR Rand Pbo	SOURCE Rand Teze
Number of subjects	528	531	74
Age Categorical Units: Participants			
<=18 years	41	41	0
Between 18 and 65 years	391	416	58
>=65 years	96	74	16
Age Continuous Units: Years			
arithmetic mean	49.9	49.0	53.5
standard deviation	± 16.3	± 15.9	± 12.1
Sex: Female, Male Units: Participants			
Female	335	337	49
Male	193	194	25
Race/Ethnicity, Customized Units: Subjects			
Hispanic or Latino	83	81	10
Not Hispanic or Latino	445	450	64
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	0	1	0
Asian	146	149	11
Black of African American	30	31	1
Native Hawaiian or Other Pacific Islander	1	0	0
Other	19	23	0
White	332	327	62

Reporting group values	SOURCE Rand Pbo	Total	
Number of subjects	76	1209	
Age Categorical Units: Participants			
<=18 years	0	82	
Between 18 and 65 years	62	927	
>=65 years	14	200	
Age Continuous Units: Years			
arithmetic mean	53.4		
standard deviation	± 11.9	-	
Sex: Female, Male Units: Participants			
Female	45	766	
Male	31	443	
Race/Ethnicity, Customized Units: Subjects			
Hispanic or Latino	14	188	
Not Hispanic or Latino	62	1021	
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	0	1	
Asian	11	317	
Black of African American	0	62	
Native Hawaiian or Other Pacific Islander	0	1	
Other	1	43	
White	64	785	

End points

End points reporting groups

Reporting group title	NAVIGATOR Rand Teze
Reporting group description:	
All subjects randomised to tezepelumab in the NAVIGATOR predecessor and treated with at least one dose in the predecessor, regardless of whether they participated in the DESTINATION study.	
Reporting group title	NAVIGATOR Rand Pbo
Reporting group description:	
All subjects randomised to placebo in the NAVIGATOR predecessor and treated with at least one dose in the predecessor, regardless of whether they participated in the DESTINATION study and regardless of their treatment assignment in DESTINATION.	
Reporting group title	SOURCE Rand Teze
Reporting group description:	
All subjects randomised to tezepelumab in the SOURCE predecessor and treated with at least one dose in the predecessor, regardless of whether they participated in the DESTINATION study.	
Reporting group title	SOURCE Rand Pbo
Reporting group description:	
All subjects randomised to placebo in the SOURCE predecessor and treated with at least one dose in the predecessor, regardless of whether they participated in the DESTINATION study and regardless of their treatment assignment in DESTINATION.	
Reporting group title	NAVIGATOR Rand Teze
Reporting group description:	
All subjects randomised to tezepelumab in the NAVIGATOR predecessor and treated with at least one dose in the predecessor, regardless of whether they participated in the DESTINATION study.	
Reporting group title	NAVIGATOR Rand Pbo
Reporting group description:	
All subjects randomised to placebo in the NAVIGATOR predecessor and treated with at least one dose in the predecessor, regardless of whether they participated in the DESTINATION study and regardless of their treatment assignment in DESTINATION.	
Reporting group title	SOURCE Rand Teze
Reporting group description:	
All subjects randomised to tezepelumab in the SOURCE predecessor and treated with at least one dose in the predecessor, regardless of whether they participated in the DESTINATION study.	
Reporting group title	SOURCE Rand Pbo
Reporting group description:	
All subjects randomised to placebo in the SOURCE predecessor and treated with at least one dose in the predecessor, regardless of whether they participated in the DESTINATION study and regardless of their treatment assignment in DESTINATION.	

Primary: Exposure adjusted incidence rates of AEs/SAEs

End point title	Exposure adjusted incidence rates of AEs/SAEs[1]
End point description:	
Includes adverse events with an onset date between the date of first dose of IP in the predecessor and minimum (date of last dose of IP + 33 days, date of death, date of study withdrawal, day prior to start of another biologic). The analysis is based on the Safety Analysis Set. Exposure adjusted rates are defined as number of subjects with AEs divided by total time at risk across all subjects, multiplied by 100	
End point type	Primary
End point timeframe:	
Baseline (Week 0 in predecessor study) to Week 104. For subjects switching treatments from placebo in the predecessor to tezepelumab in DESTINATION, all data collected after first dose in the LTE part are excluded.	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Primary analysis was descriptive only, no hypothesis testing per the SAP

End point values	NAVIGATOR Rand Teze	NAVIGATOR Rand Pbo	SOURCE Rand Teze	SOURCE Rand Pbo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	528	531	74	76
Units: Incidence rate (per 100 years)				
number (not applicable)				
Total time at risk in years across all subjects	917.0	699.0	129.4	100.0
Any AE incidence rate	49.62	62.66	47.15	69.97
Any AE with outcome=death incidence rate	0.76	0.14	1.55	0.00
Any SAE incidence rate	7.85	12.45	13.14	17.99
AE leading to discontinuation of IP incidence rate	1.64	3.00	1.55	2.00

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized asthma exacerbation rate (AAER)

End point title	Annualized asthma exacerbation rate (AAER)

End point description:

The annualized exacerbation rate is based on exacerbations reported by the investigator in the eCRF. The analysis is based on the primary population (Full Analysis Set)

End point type	Secondary

End point timeframe:

Baseline (Week 0 in predecessor study) to Week 104. For subjects switching treatments from placebo in the predecessor to tezepelumab in DESTINATION, all data collected after first dose in the LTE part are excluded.

End point values	NAVIGATOR Rand Teze	NAVIGATOR Rand Pbo	SOURCE Rand Teze	SOURCE Rand Pbo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	528	531	74	76
Units: events per year				
least squares mean (confidence interval 95%)	0.82 (0.71 to 0.95)	1.93 (1.70 to 2.20)	1.07 (0.76 to 1.51)	1.76 (1.27 to 2.45)

Statistical analyses

Statistical analysis title	Rand Teze vs Rand Pbo in NAVIGATOR patients
Comparison groups	NAVIGATOR Rand Pbo v NAVIGATOR Rand Teze

Number of subjects included in analysis	1059
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Rate Ratio
Point estimate	0.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.35
upper limit	0.51

Statistical analysis title	Rand Teze vs Rand Pbo in SOURCE patients
Comparison groups	SOURCE Rand Teze v SOURCE Rand Pbo
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Rate Ratio
Point estimate	0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.38
upper limit	0.96

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline (Week 0 in predecessor study) to long-term extension completion (either weeks 104 or 116). Includes AEs with onset date between the date of first dose of IP and and the long-term extension completion or withdrawal date (on-study period)

Adverse event reporting additional description:

For subjects switching treatments from placebo in the predecessor to tezepelumab in DESTINATION, all data collected after first dose in the LTE part are exluded. Note the primary objective in the End Points section presents on-treatment safety as opposed to on-study safety.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	SOURCE Rand Pbo

Reporting group description:

All subjects randomised to placebo in the SOURCE predecessor and treated with at least one dose in the predecessor, regardless of whether they participated in the DESTINATION study and regardless of their treatment assignment in DESTINATION.

Reporting group title	NAVIGATOR Rand Teze

Reporting group description:

All subjects randomised to tezepelumab in the NAVIGATOR predecessor and treated with at least one dose in the predecessor, regardless of whether they participated in the DESTINATION study.

Reporting group title	NAVIGATOR Rand Pbo

Reporting group description:

All subjects randomised to placebo in the NAVIGATOR predecessor and treated with at least one dose in the predecessor, regardless of whether they participated in the DESTINATION study and regardless of their treatment assignment in DESTINATION.

Reporting group title	SOURCE Rand Teze

Reporting group description:

All subjects randomised to tezepelumab in the SOURCE predecessor and treated with at least one dose in the predecessor, regardless of whether they participated in the DESTINATION study.

Serious adverse events	SOURCE Rand Pbo	NAVIGATOR Rand Teze	NAVIGATOR Rand Pbo
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 76 (25.00%)	82 / 528 (15.53%)	94 / 531 (17.70%)
number of deaths (all causes)	0	8	5
number of deaths resulting from adverse events	0	8	5
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	2 / 531 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Benign neoplasm of thyroid gland			

subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon adenoma			
subjects affected / exposed	0 / 76 (0.00%)	0 / 528 (0.00%)	1 / 531 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colorectal cancer			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Endometrial cancer			
subjects affected / exposed	0 / 76 (0.00%)	0 / 528 (0.00%)	1 / 531 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Invasive breast carcinoma			
subjects affected / exposed	0 / 76 (0.00%)	0 / 528 (0.00%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neurilemmoma benign			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma in situ			
subjects affected / exposed	0 / 76 (0.00%)	2 / 528 (0.38%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma			

subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	1 / 531 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of the oral cavity			
subjects affected / exposed	0 / 76 (0.00%)	0 / 528 (0.00%)	1 / 531 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma			
subjects affected / exposed	0 / 76 (0.00%)	0 / 528 (0.00%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer stage IV			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostatic adenoma			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thymoma			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 76 (1.32%)	0 / 528 (0.00%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosis			

subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma			
subjects affected / exposed	0 / 76 (0.00%)	0 / 528 (0.00%)	1 / 531 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cyanosis			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous			
subjects affected / exposed	0 / 76 (0.00%)	2 / 528 (0.38%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	0 / 76 (0.00%)	0 / 528 (0.00%)	1 / 531 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	3 / 531 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 3
Malaise			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 76 (0.00%)	0 / 528 (0.00%)	1 / 531 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug hypersensitivity			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cyst			
subjects affected / exposed	0 / 76 (0.00%)	0 / 528 (0.00%)	1 / 531 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine prolapse			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	8 / 76 (10.53%)	16 / 528 (3.03%)	43 / 531 (8.10%)
occurrences causally related to treatment / all	0 / 12	2 / 20	0 / 91
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchial secretion retention			
subjects affected / exposed	1 / 76 (1.32%)	0 / 528 (0.00%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemothorax			

subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	0 / 76 (0.00%)	0 / 528 (0.00%)	1 / 531 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasal polyps			
subjects affected / exposed	1 / 76 (1.32%)	0 / 528 (0.00%)	1 / 531 (0.19%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	1 / 531 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eosinophilic pneumonia			
subjects affected / exposed	0 / 76 (0.00%)	0 / 528 (0.00%)	1 / 531 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Bipolar disorder			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disruptive mood dysregulation disorder			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 76 (0.00%)	0 / 528 (0.00%)	1 / 531 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Injury, poisoning and procedural complications			
Head injury			
subjects affected / exposed	0 / 76 (0.00%)	0 / 528 (0.00%)	1 / 531 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incisional hernia			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower limb fracture			
subjects affected / exposed	1 / 76 (1.32%)	0 / 528 (0.00%)	1 / 531 (0.19%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ligament sprain			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ligament rupture			
subjects affected / exposed	0 / 76 (0.00%)	3 / 528 (0.57%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar vertebral fracture			
subjects affected / exposed	0 / 76 (0.00%)	0 / 528 (0.00%)	1 / 531 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periprocedural myocardial infarction			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0

Radius fracture			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin laceration			
subjects affected / exposed	0 / 76 (0.00%)	0 / 528 (0.00%)	1 / 531 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			
subjects affected / exposed	1 / 76 (1.32%)	0 / 528 (0.00%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	1 / 76 (1.32%)	0 / 528 (0.00%)	1 / 531 (0.19%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia fracture			
subjects affected / exposed	0 / 76 (0.00%)	0 / 528 (0.00%)	1 / 531 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ulna fracture			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon rupture			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Hypertrophic cardiomyopathy			
subjects affected / exposed	0 / 76 (0.00%)	0 / 528 (0.00%)	1 / 531 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	0 / 76 (0.00%)	0 / 528 (0.00%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prinzmetal angina			
subjects affected / exposed	0 / 76 (0.00%)	0 / 528 (0.00%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	0 / 76 (0.00%)	0 / 528 (0.00%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular extrasystoles			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	0 / 76 (0.00%)	2 / 528 (0.38%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 76 (0.00%)	0 / 528 (0.00%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 76 (0.00%)	0 / 528 (0.00%)	1 / 531 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiac failure congestive			

subjects affected / exposed	0 / 76 (0.00%)	2 / 528 (0.38%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	0 / 76 (0.00%)	2 / 528 (0.38%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery occlusion			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic valve stenosis			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Palpitations			
subjects affected / exposed	0 / 76 (0.00%)	0 / 528 (0.00%)	1 / 531 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cubital tunnel syndrome			
subjects affected / exposed	0 / 76 (0.00%)	0 / 528 (0.00%)	1 / 531 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	1 / 76 (1.32%)	0 / 528 (0.00%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic stroke			

subjects affected / exposed	0 / 76 (0.00%)	0 / 528 (0.00%)	1 / 531 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Migraine			
subjects affected / exposed	1 / 76 (1.32%)	1 / 528 (0.19%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Idiopathic generalised epilepsy			
subjects affected / exposed	0 / 76 (0.00%)	0 / 528 (0.00%)	1 / 531 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myelopathy			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 76 (0.00%)	0 / 528 (0.00%)	1 / 531 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ruptured cerebral aneurysm			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	1 / 531 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	0 / 76 (0.00%)	0 / 528 (0.00%)	1 / 531 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Immune thrombocytopenia			

subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	0 / 76 (0.00%)	0 / 528 (0.00%)	1 / 531 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Cataract			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	2 / 531 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uveitis			
subjects affected / exposed	0 / 76 (0.00%)	0 / 528 (0.00%)	1 / 531 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal fistula			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	1 / 76 (1.32%)	0 / 528 (0.00%)	2 / 531 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticular perforation			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Colitis ischaemic			
subjects affected / exposed	0 / 76 (0.00%)	0 / 528 (0.00%)	1 / 531 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine polyp			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstruction gastric			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	1 / 531 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis necrotising			
subjects affected / exposed	0 / 76 (0.00%)	0 / 528 (0.00%)	1 / 531 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Umbilical hernia			
subjects affected / exposed	1 / 76 (1.32%)	1 / 528 (0.19%)	1 / 531 (0.19%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus paralytic			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal achalasia			

subjects affected / exposed	0 / 76 (0.00%)	0 / 528 (0.00%)	1 / 531 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 76 (1.32%)	0 / 528 (0.00%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 76 (0.00%)	2 / 528 (0.38%)	1 / 531 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug-induced liver injury			
subjects affected / exposed	0 / 76 (0.00%)	0 / 528 (0.00%)	1 / 531 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis chronic			
subjects affected / exposed	0 / 76 (0.00%)	0 / 528 (0.00%)	1 / 531 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dermatitis contact			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash			
subjects affected / exposed	0 / 76 (0.00%)	0 / 528 (0.00%)	1 / 531 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	1 / 531 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Glomerulonephritis membranous			
subjects affected / exposed	0 / 76 (0.00%)	0 / 528 (0.00%)	1 / 531 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	0 / 76 (0.00%)	0 / 528 (0.00%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ureterolithiasis			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Hyperparathyroidism primary			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Amyotrophy			
subjects affected / exposed	1 / 76 (1.32%)	0 / 528 (0.00%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthralgia			
subjects affected / exposed	0 / 76 (0.00%)	0 / 528 (0.00%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone cyst			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis			
subjects affected / exposed	1 / 76 (1.32%)	0 / 528 (0.00%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Intervertebral disc protrusion			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar spinal stenosis			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscle necrosis			
subjects affected / exposed	0 / 76 (0.00%)	0 / 528 (0.00%)	1 / 531 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscle spasms			
subjects affected / exposed	1 / 76 (1.32%)	0 / 528 (0.00%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myositis			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	1 / 531 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polyarthritis			
subjects affected / exposed	0 / 76 (0.00%)	0 / 528 (0.00%)	1 / 531 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal stenosis			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spondylolisthesis			

subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Anal abscess			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 76 (0.00%)	0 / 528 (0.00%)	1 / 531 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial pyelonephritis			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast abscess			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	2 / 531 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis infective			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	2 / 531 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			

subjects affected / exposed	0 / 76 (0.00%)	2 / 528 (0.38%)	1 / 531 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis salmonella			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster oticus			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral discitis			
subjects affected / exposed	0 / 76 (0.00%)	0 / 528 (0.00%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection bacterial			
subjects affected / exposed	0 / 76 (0.00%)	0 / 528 (0.00%)	2 / 531 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 76 (0.00%)	0 / 528 (0.00%)	1 / 531 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung abscess			

subjects affected / exposed	0 / 76 (0.00%)	0 / 528 (0.00%)	1 / 531 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periorbital cellulitis			
subjects affected / exposed	0 / 76 (0.00%)	0 / 528 (0.00%)	1 / 531 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	0 / 76 (0.00%)	3 / 528 (0.57%)	2 / 531 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	2 / 76 (2.63%)	1 / 528 (0.19%)	1 / 531 (0.19%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pneumonia klebsiella			
subjects affected / exposed	0 / 76 (0.00%)	0 / 528 (0.00%)	1 / 531 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia streptococcal			
subjects affected / exposed	0 / 76 (0.00%)	0 / 528 (0.00%)	1 / 531 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia viral			
subjects affected / exposed	0 / 76 (0.00%)	0 / 528 (0.00%)	1 / 531 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			

subjects affected / exposed	0 / 76 (0.00%)	2 / 528 (0.38%)	1 / 531 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 76 (0.00%)	0 / 528 (0.00%)	1 / 531 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	1 / 76 (1.32%)	3 / 528 (0.57%)	2 / 531 (0.38%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
COVID-19 pneumonia			
subjects affected / exposed	0 / 76 (0.00%)	3 / 528 (0.57%)	2 / 531 (0.38%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
H1N1 influenza			
subjects affected / exposed	1 / 76 (1.32%)	0 / 528 (0.00%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis bacterial			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atypical pneumonia			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			

subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia staphylococcal			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 76 (0.00%)	1 / 528 (0.19%)	0 / 531 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Type 1 diabetes mellitus			
subjects affected / exposed	0 / 76 (0.00%)	0 / 528 (0.00%)	1 / 531 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 76 (0.00%)	0 / 528 (0.00%)	1 / 531 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 76 (0.00%)	0 / 528 (0.00%)	1 / 531 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic ketoacidosis			
subjects affected / exposed	0 / 76 (0.00%)	0 / 528 (0.00%)	1 / 531 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gout			
subjects affected / exposed	0 / 76 (0.00%)	0 / 528 (0.00%)	1 / 531 (0.19%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	SOURCE Rand Teze		

Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 74 (24.32%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	2		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Benign neoplasm of thyroid gland			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Colon adenoma			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Colorectal cancer			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endometrial cancer			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Invasive breast carcinoma			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neurilemmoma benign			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Malignant melanoma in situ			

subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Prostate cancer				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Squamous cell carcinoma				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Squamous cell carcinoma of the oral cavity				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Uterine leiomyoma				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Colon cancer stage IV				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Prostatic adenoma				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Thymoma				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Hypertension				

subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Peripheral arterial occlusive disease				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Thrombosis				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haematoma				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cyanosis				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pregnancy, puerperium and perinatal conditions				
Abortion spontaneous				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Chest discomfort				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Death				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Malaise			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Non-cardiac chest pain			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Drug hypersensitivity			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ovarian cyst			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Uterine prolapse			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Asthma			

subjects affected / exposed	5 / 74 (6.76%)			
occurrences causally related to treatment / all	0 / 7			
deaths causally related to treatment / all	0 / 0			
Bronchial secretion retention				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemothorax				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Epistaxis				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nasal polyps				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Eosinophilic pneumonia				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Bipolar disorder				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Disruptive mood dysregulation disorder				

subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Head injury			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hip fracture			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Incisional hernia			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lower limb fracture			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ligament sprain			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ligament rupture			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Lumbar vertebral fracture				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Periprocedural myocardial infarction				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Radius fracture				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin laceration				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Spinal compression fracture				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Road traffic accident				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tibia fracture				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ulna fracture				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Tendon rupture				

subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Hypertrophic cardiomyopathy			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Prinzmetal angina			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Supraventricular tachycardia			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Ventricular extrasystoles			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute myocardial infarction			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atrial flutter			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Cardiac arrest				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Cardiac failure				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac failure congestive				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Coronary artery disease				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Coronary artery occlusion				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Aortic valve stenosis				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Palpitations				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Cerebrovascular accident				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cubital tunnel syndrome				

subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Headache				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haemorrhagic stroke				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Migraine				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Idiopathic generalised epilepsy				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myelopathy				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Seizure				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ruptured cerebral aneurysm				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Transient ischaemic attack				

subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dizziness				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Immune thrombocytopenia				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ear and labyrinth disorders				
Vertigo positional				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Eye disorders				
Cataract				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Uveitis				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Colitis				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Anal fistula				

subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Inguinal hernia				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diverticular perforation				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Colitis ischaemic				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Large intestine polyp				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Obstruction gastric				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancreatitis acute				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancreatitis necrotising				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rectal haemorrhage				

subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Umbilical hernia			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ileus paralytic			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Oesophageal achalasia			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholelithiasis			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Drug-induced liver injury			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholecystitis chronic			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			

Dermatitis contact				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Rash				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Acute kidney injury				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Glomerulonephritis membranous				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nephrolithiasis				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ureterolithiasis				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Endocrine disorders				
Hyperparathyroidism primary				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Amyotrophy				

subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Arthralgia				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bone cyst				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Arthritis				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intervertebral disc protrusion				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lumbar spinal stenosis				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Muscle necrosis				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Muscle spasms				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Myositis				

subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Osteoarthritis				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Polyarthritis				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Spinal stenosis				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Spondylolisthesis				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Anal abscess				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Appendicitis				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bacterial pyelonephritis				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Breast abscess				

subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cholecystitis infective				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diverticulitis				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis salmonella				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis viral				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Herpes zoster oticus				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Influenza				

subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intervertebral discitis				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection bacterial				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lung abscess				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Osteomyelitis				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Periorbital cellulitis				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia bacterial				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				

subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia klebsiella				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia streptococcal				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia viral				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Septic shock				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Upper respiratory tract infection				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Viral upper respiratory tract infection				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
COVID-19				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
COVID-19 pneumonia				

subjects affected / exposed	3 / 74 (4.05%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
H1N1 influenza				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Meningitis bacterial				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atypical pneumonia				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia aspiration				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia staphylococcal				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Type 1 diabetes mellitus				
subjects affected / exposed	0 / 74 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Type 2 diabetes mellitus				

subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diabetic ketoacidosis			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gout			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	SOURCE Rand Pbo	NAVIGATOR Rand Teze	NAVIGATOR Rand Pbo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	56 / 76 (73.68%)	369 / 528 (69.89%)	376 / 531 (70.81%)
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 76 (1.32%)	14 / 528 (2.65%)	9 / 531 (1.69%)
occurrences (all)	1	20	10
Fall			
subjects affected / exposed	4 / 76 (5.26%)	9 / 528 (1.70%)	12 / 531 (2.26%)
occurrences (all)	4	9	12
Vascular disorders			
Hypertension			
subjects affected / exposed	7 / 76 (9.21%)	30 / 528 (5.68%)	26 / 531 (4.90%)
occurrences (all)	7	39	40
Nervous system disorders			

Headache			
subjects affected / exposed	10 / 76 (13.16%)	58 / 528 (10.98%)	54 / 531 (10.17%)
occurrences (all)	12	157	101
General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	6 / 76 (7.89%)	26 / 528 (4.92%)	25 / 531 (4.71%)
occurrences (all)	6	28	29
Eye disorders			
Cataract			
subjects affected / exposed	3 / 76 (3.95%)	7 / 528 (1.33%)	2 / 531 (0.38%)
occurrences (all)	3	8	3
Gastrointestinal disorders			
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 76 (2.63%)	9 / 528 (1.70%)	8 / 531 (1.51%)
occurrences (all)	3	9	9
Nausea			
subjects affected / exposed	1 / 76 (1.32%)	16 / 528 (3.03%)	9 / 531 (1.69%)
occurrences (all)	1	19	10
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	9 / 76 (11.84%)	14 / 528 (2.65%)	25 / 531 (4.71%)
occurrences (all)	16	17	27
Nasal polyps			
subjects affected / exposed	5 / 76 (6.58%)	0 / 528 (0.00%)	4 / 531 (0.75%)
occurrences (all)	7	0	6
Rhinitis allergic			
subjects affected / exposed	0 / 76 (0.00%)	30 / 528 (5.68%)	22 / 531 (4.14%)
occurrences (all)	0	39	31
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 76 (0.00%)	4 / 528 (0.76%)	9 / 531 (1.69%)
occurrences (all)	0	4	12
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 76 (3.95%)	27 / 528 (5.11%)	21 / 531 (3.95%)
occurrences (all)	4	46	23

Back pain			
subjects affected / exposed	2 / 76 (2.63%)	36 / 528 (6.82%)	25 / 531 (4.71%)
occurrences (all)	2	49	30
Myalgia			
subjects affected / exposed	1 / 76 (1.32%)	12 / 528 (2.27%)	11 / 531 (2.07%)
occurrences (all)	2	15	13
Pain in extremity			
subjects affected / exposed	0 / 76 (0.00%)	18 / 528 (3.41%)	11 / 531 (2.07%)
occurrences (all)	0	21	12
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	0 / 76 (0.00%)	16 / 528 (3.03%)	16 / 531 (3.01%)
occurrences (all)	0	23	26
Bronchitis			
subjects affected / exposed	3 / 76 (3.95%)	29 / 528 (5.49%)	39 / 531 (7.34%)
occurrences (all)	3	44	51
Chronic sinusitis			
subjects affected / exposed	4 / 76 (5.26%)	9 / 528 (1.70%)	6 / 531 (1.13%)
occurrences (all)	4	13	8
Bronchitis bacterial			
subjects affected / exposed	7 / 76 (9.21%)	30 / 528 (5.68%)	19 / 531 (3.58%)
occurrences (all)	10	34	24
Gastroenteritis			
subjects affected / exposed	1 / 76 (1.32%)	25 / 528 (4.73%)	16 / 531 (3.01%)
occurrences (all)	1	26	17
Pharyngitis			
subjects affected / exposed	2 / 76 (2.63%)	26 / 528 (4.92%)	23 / 531 (4.33%)
occurrences (all)	2	35	28
Oral candidiasis			
subjects affected / exposed	6 / 76 (7.89%)	12 / 528 (2.27%)	15 / 531 (2.82%)
occurrences (all)	11	16	17
Nasopharyngitis			
subjects affected / exposed	22 / 76 (28.95%)	130 / 528 (24.62%)	124 / 531 (23.35%)
occurrences (all)	38	220	222
Rhinitis			

subjects affected / exposed	2 / 76 (2.63%)	18 / 528 (3.41%)	21 / 531 (3.95%)
occurrences (all)	2	24	42
Upper respiratory tract infection			
subjects affected / exposed	9 / 76 (11.84%)	72 / 528 (13.64%)	91 / 531 (17.14%)
occurrences (all)	9	131	151
Sinusitis bacterial			
subjects affected / exposed	1 / 76 (1.32%)	2 / 528 (0.38%)	1 / 531 (0.19%)
occurrences (all)	1	2	1
Sinusitis			
subjects affected / exposed	5 / 76 (6.58%)	30 / 528 (5.68%)	43 / 531 (8.10%)
occurrences (all)	6	34	64
Urinary tract infection			
subjects affected / exposed	1 / 76 (1.32%)	29 / 528 (5.49%)	29 / 531 (5.46%)
occurrences (all)	2	50	33
Viral upper respiratory tract infection			
subjects affected / exposed	3 / 76 (3.95%)	24 / 528 (4.55%)	17 / 531 (3.20%)
occurrences (all)	3	31	23
COVID-19			
subjects affected / exposed	1 / 76 (1.32%)	7 / 528 (1.33%)	8 / 531 (1.51%)
occurrences (all)	1	8	8
Upper respiratory tract infection bacterial			
subjects affected / exposed	1 / 76 (1.32%)	8 / 528 (1.52%)	2 / 531 (0.38%)
occurrences (all)	1	10	6
Metabolism and nutrition disorders			
Type 2 diabetes mellitus			
subjects affected / exposed	2 / 76 (2.63%)	16 / 528 (3.03%)	8 / 531 (1.51%)
occurrences (all)	2	16	9

Non-serious adverse events	SOURCE Rand Teze		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	51 / 74 (68.92%)		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	3 / 74 (4.05%)		
occurrences (all)	4		
Fall			

subjects affected / exposed occurrences (all)	3 / 74 (4.05%) 3		
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	 5 / 74 (6.76%) 7		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	 9 / 74 (12.16%) 16		
General disorders and administration site conditions Influenza like illness subjects affected / exposed occurrences (all)	 0 / 74 (0.00%) 0		
Eye disorders Cataract subjects affected / exposed occurrences (all)	 2 / 74 (2.70%) 2		
Gastrointestinal disorders Gastrooesophageal reflux disease subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	 3 / 74 (4.05%) 3 1 / 74 (1.35%) 1		
Respiratory, thoracic and mediastinal disorders Asthma subjects affected / exposed occurrences (all) Nasal polyps subjects affected / exposed occurrences (all) Rhinitis allergic subjects affected / exposed occurrences (all)	 6 / 74 (8.11%) 7 1 / 74 (1.35%) 1 0 / 74 (0.00%) 0		
Skin and subcutaneous tissue disorders			

Pruritus			
subjects affected / exposed	3 / 74 (4.05%)		
occurrences (all)	3		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 74 (2.70%)		
occurrences (all)	2		
Back pain			
subjects affected / exposed	3 / 74 (4.05%)		
occurrences (all)	4		
Myalgia			
subjects affected / exposed	5 / 74 (6.76%)		
occurrences (all)	7		
Pain in extremity			
subjects affected / exposed	2 / 74 (2.70%)		
occurrences (all)	2		
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences (all)	0		
Bronchitis			
subjects affected / exposed	9 / 74 (12.16%)		
occurrences (all)	10		
Chronic sinusitis			
subjects affected / exposed	3 / 74 (4.05%)		
occurrences (all)	4		
Bronchitis bacterial			
subjects affected / exposed	8 / 74 (10.81%)		
occurrences (all)	20		
Gastroenteritis			
subjects affected / exposed	2 / 74 (2.70%)		
occurrences (all)	2		
Pharyngitis			
subjects affected / exposed	0 / 74 (0.00%)		
occurrences (all)	0		
Oral candidiasis			

subjects affected / exposed	5 / 74 (6.76%)		
occurrences (all)	6		
Nasopharyngitis			
subjects affected / exposed	18 / 74 (24.32%)		
occurrences (all)	27		
Rhinitis			
subjects affected / exposed	4 / 74 (5.41%)		
occurrences (all)	4		
Upper respiratory tract infection			
subjects affected / exposed	12 / 74 (16.22%)		
occurrences (all)	13		
Sinusitis bacterial			
subjects affected / exposed	5 / 74 (6.76%)		
occurrences (all)	5		
Sinusitis			
subjects affected / exposed	2 / 74 (2.70%)		
occurrences (all)	2		
Urinary tract infection			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences (all)	1		
Viral upper respiratory tract infection			
subjects affected / exposed	2 / 74 (2.70%)		
occurrences (all)	5		
COVID-19			
subjects affected / exposed	5 / 74 (6.76%)		
occurrences (all)	5		
Upper respiratory tract infection bacterial			
subjects affected / exposed	3 / 74 (4.05%)		
occurrences (all)	3		
Metabolism and nutrition disorders			
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 May 2019	Amended Inclusion/ exclusion criteria, clarification on dose preparation/administration, updated randomization and blinding procedures. Additional 'vaping products' added as restricted during the study. Asthma Control Questionnaire removed from visit 2 onwards, in degrees Celsius removed as units of body temperature, updated paternal exposure.
10 January 2020	CSP Version 3.0 was submitted to the FDA but was not implemented due to the identification of aspects needing to be corrected/clarified. The CSP Version 3.0 was not submitted to any other regulatory authorities and/or IRB/IEC. After further update and revision, the CSP changes were fully implemented as CSP Version 4.0. Study phrase 'the extension study' replaced with 'Long Term Extension Study' or 'LTE' throughout the protocol. Schedule of activities, table 1 updated with additional assessments and footnotes. Primary and exploratory objectives updated. Dupilumab added as approved medication for severe asthma with an eosinophilic phenotype. Updated inclusion/exclusion criteria for subjects. Procedures for discontinuation of study treatment updated. Added the maximum amount of blood collected from subjects that are a part of extended follow-up. Updated statistical, safety and other analyses.
06 March 2020	Addition of multiple assessments to correct omission in previous CSP amendment. Addition of 'weight' assessment, '12-lead ECG' assessment and 'urine pregnancy test, dipstick'. Removal of 'serum pregnancy test' assessment. Revised maximum amount of blood collected from subjects a part of extended follow-up.
02 June 2020	Informed consent names changed from 'Addendum to Informed Consent' to 'Addendum for Extended Follow-up to Informed Consent' throughout the protocol for consistency. Added appendix H to describe in more detail the changes made during the COVID-19 pandemic. Inclusion criteria updated, prohibited medications section updated, clarification on restrictions throughout the course of the study for alcohol, tobacco and other. Added reference to Appendix H for guidance on safety assessments during the COVID-19 pandemic. General instructions added to follow the local regulations/guidance during the COVID-19 pandemic. Revised text in Asthma Control Questionnaire and St George's Respiratory Questionnaire.
12 April 2021	Assessment blood RNA transcript profiling, transcriptomics added to further clarify the biomarkers collected during the study. Independent adjudication committee updated to clarify that ER visit, urgent care visit and hospitalization visits will be assessed by independent adjudication committee until completion of follow-up or extended follow-up. Clarification on concomitant therapy and biologics introduction following week 116 provided. Added guidance for COVID-19 vaccination in the study. Revised wording to clarify PK sample analysis process in the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported