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Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Canakinumab/ACZ885

Trial Indication(s)

Reduction in risk of major adverse cardiac events (MACE) in patients with prior myocardial infarction (MI) with inflammatory atherosclerosis.

Protocol Number

CACZ885M2301

Protocol Title

A randomized, double-blind, placebo-controlled, event-driven trial of quarterly subcutaneous canakinumab in the prevention of recurrent cardiovascular events among stable post-myocardial infarction patients with elevated hsCRP

Clinical Trial Phase

Phase 3

Phase of Drug Development

Phase III

Study Start/End Dates

Study Start Date: April 2011 (Actual)
Primary Completion Date: March 2017 (Actual)
Study Completion Date: April 2019 (Actual)

Reason for Termination (If applicable)

The Core phase of the study completed as planned. The Extension phase of the study was terminated. In addition, the two sub-studies CACZ885M2301S1 and CACZ885M2301S2 terminated prior to data collection, and hence, no data are shown.

Study Design/Methodology

This Phase 3, multi-center, global study consisted of a double-blind Core phase, including the primary study endpoint, and an open-label Extension phase.

Core phase: The randomized, parallel group, placebo-controlled, double-blind, event-driven Core phase of the study was designed to evaluate the effect of quarterly subcutaneous doses of 50 mg, 150 mg and 300 mg (300 mg included an induction dose) canakinumab compared to placebo in patients with a prior MI with an elevated inflammatory burden (hsCRP ≥ 2 mg/L) receiving standard of care therapy. Patients were randomized at least 30 days following their index MI. Standard of care included post-MI background therapies as defined by local guidelines. Patients were also instructed to follow a heart healthy (low fat) diet and a regular exercise program. The study included pre-screening and screening periods. A key component of inclusion into the study was to ensure that all enrolled patients had a central laboratory confirmed hsCRP assessment of ≥ 2mg/L within 60 days prior to their randomization. Randomization was stratified by time since most recent index MI (30 days to < 6 months and ≥ 6 months) and by trial part. Patients who met all eligibility criteria then entered a double-blind treatment period. The study was event driven and designed to complete when a total of 1400 patients had experienced a primary CV endpoint.

Extension phase: Following the completion of the Core phase, every patient who continued to be eligible to receive study drug was to be offered the option to continue into the Extension phase. The Extension phase was designed to obtain additional long-term safety data specifically in cardiovascular risk reduction (CVRR) patients receiving canakinumab. For all patients who were not classified as “pre-diabetic”, the Extension phase was composed of a double-blind treatment period (applicable for patients who started treatment before the final open-label canakinumab dose was chosen) and the main open-label treatment period with canakinumab 150 mg. For the subset of patients classified as “pre-diabetic” (i.e. with pre-

diabetes at both randomization and Core phase EOS), the Extension phase was composed additionally of an initial 6 month study drug washout period, followed by the above described double-blind (if applicable) and open-label treatment periods.

Centers

1214 centers in 39 countries: South Africa(11), United States(357), Taiwan(13), Turkey(8), Sweden(17), Slovakia (Slovak Republic)(34), Russia(54), Romania(33), Poland(16), Peru(4), Norway(16), Netherlands(25), Mexico(7), Latvia(6), Lithuania(14), Korea, Republic of(13), Japan(42), Italy(41), Iceland(3), India(50), Hungary(22), Guatemala(11), Greece(13), United Kingdom(34), Estonia(10), Germany(88), Czech Republic(33), Colombia(17), Canada(38), Brazil(34), Bulgaria(14), Belgium(13), Austria(7), Australia(12), Argentina(53), China(34), Serbia(4), Croatia(10), Slovenia(3)

Objectives:

Core phase:

The primary objective of this study was to demonstrate the superiority of at least one dose of canakinumab compared to placebo in reducing the risk of recurrent major cardiovascular events (cardiovascular death, non-fatal MI and non-fatal stroke) in a population of clinically stable patients with prior MI with elevated hsCRP receiving standard of care.
The key secondary objectives were:

- To demonstrate superiority of canakinumab compared to placebo on the composite endpoint of CV death, non-fatal MI, non-fatal stroke, and hospitalization for unstable angina requiring unplanned revascularizations.
- To demonstrate superiority of canakinumab compared to placebo on the endpoint of new onset type 2 diabetes among those with pre-diabetes at randomization

The other secondary objectives were:

- To demonstrate superiority of canakinumab compared to placebo on the composite endpoint of all-cause mortality, non-fatal MI, and non-fatal stroke.
- To demonstrate superiority of canakinumab as compared to placebo on the endpoint of all-cause mortality
- To evaluate the long-term safety of canakinumab therapy in a placebo (standard of care) - controlled setting

Extension phase:

No primary objective was defined for the Extension phase.

The secondary objective was:

- To obtain further follow-up information on long-term safety on continued exposure to canakinumab in trial participants.

Test Product (s), Dose(s), and Mode(s) of Administration

Two canakinumab strengths and respective corresponding matching placebos were supplied:

- Canakinumab 50 mg in 0.5 mL solution for injection and one placebo formulation matching to this active drug formulation.
- Canakinumab 150 mg in 1 mL solution for injection and one placebo formulation matching to this active drug formulation.

Core phase: The study treatment was administered as subcutaneous injections at randomization, week 2 (month 0.5) for the 300 mg dose only, and then quarterly beginning at week 12 (month 3).

Extension phase: During the double-blind treatment period (if applicable) patients remained on their blinded Core phase treatment, i.e. canakinumab 300 mg, 150 mg, 50 mg or placebo. During the main open-label treatment period all patients received open-label canakinumab 150 mg.

Statistical Methods

Core phase:

All time-to-event analyses were based on events occurring during the double-blind phase. Data on patients who did not reach the primary endpoint by the study end date were censored at the latest date they were known to be at risk or their EOS visit or the study analysis cut off, whichever came first.
The primary statistical null hypotheses were:

- H11: The hazard rate of first adjudication committee confirmed MACE in the canakinumab 300 mg dose group is greater than or equal to the hazard rate of the placebo group
- H21: The hazard rate of first adjudication committee confirmed MACE in the canakinumab 150 mg dose group is greater than or equal to the hazard rate of the placebo group

- H31: The hazard rate of first adjudication committee confirmed MACE in the canakinumab 50 mg dose group is greater than or equal to the hazard rate of the placebo group.

Each null hypothesis was tested against the one-sided alternative that the hazard rate was smaller for the respective active dose group than for the placebo group. These hypotheses were tested by comparing each dose to placebo with a log-rank test stratified by time since index MI (< 6 months and ≥ 6 months) and trial part on the FAS according to the intent-to-treat principle. The family-wise error rate was controlled at the two efficacy interim analyses and the final analysis using the closed testing procedure based on the graphical method of Bretz et al; however, in intersection null hypotheses involving the primary null hypotheses for the 300 mg, 150 mg or 50 mg doses, these primary null hypotheses were tested using a weighted version of Dunnett's test.
Two efficacy interim analyses, at which the trial could have been stopped for demonstrated efficacy, or one or more active arms could have been stopped for futility, were performed respectively after 50% and 75% of the target number of 1,400 patients had experienced a primary endpoint. A fixed Bonferroni split of the one-sided significance level was used to account for the two efficacy interim analyses and the final analysis, with a one-sided significance level of 0.01% for the first and 0.04% for the second efficacy interim analysis, and a one-sided significance level of 2.45% at the final analysis. Thus, the familywise type I error rate for this study was controlled at the overall one-sided significance level α=2.5% level.
The hazard ratios and their associated confidence intervals were estimated with a Cox proportional hazards model stratified by time since index MI (< 6 months, ≥ 6 months) and trial part (trial part 1, trial part 2) using treatment (canakinumab doses and placebo) as a factor in the model.
The following hypotheses were tested with respect to the key secondary variables for the canakinumab 300 mg dose versus placebo

- H12: The hazard rate of first adjudication committee confirmed secondary composite CV endpoint in the canakinumab 300 mg dose group was greater than or equal to the hazard rate of the placebo group
- H13: The hazard rate of adjudication committee confirmed new onset of diabetes for prediabetic patients in the canakinumab 300 mg dose group was greater than or equal to the hazard rate of the placebo group

Each null hypothesis was tested against the one-sided alternative that the hazard rate was smaller for the canakinumab 300 mg dose group than for the placebo group. The corresponding hypotheses for the comparison of the canakinumab 150 mg dose versus placebo were H22 for the secondary composite CV endpoint and H23 for the new onset of diabetes endpoint. For the 50 mg dose they were H32 for the secondary composite CV endpoint and H33 for the new onset of diabetes endpoint.
All key secondary efficacy variables were analyzed with a log-rank test stratified by time since index MI and trial part. The hazard ratios were estimated using a Cox regression model stratified by time since index MI and trial part.
Safety data was summarized, by treatment, across the two trial parts and the two randomization plans in trial part 2.

Time to first event was compared between canakinumab treatment groups and placebo for selected safety events of special interest, using a Cox regression model with treatment as fixed effect, stratified by time since index MI and trial part. Summary statistics including events per 100 patient-years of follow-up were reported.
Changes from baseline in continuous safety parameters were plotted over time based on both trial parts using repeated measures mixed model.
The variables listed below were analyzed on the log-scale and results were back-transformed to report geometric means and ratios of geometric means of canakinumab dose versus placebo:

- Urine albumin/creatinine ratio, urine albumin, urine creatinine
- ALT (SGPT), AST (SGOT), total bilirubin, direct bilirubin, alkaline phosphatase
- Triglycerides, HDL, LDL, VLDL
- hsCRP

All other safety variables were analyzed without any transformation and were summarized by the arithmetic mean and differences in arithmetic means of canakinumab dose versus placebo.

Extension phase:

Safety data were evaluated based on the Ext SAF and the WOS as applicable. The number and percentage of patients reporting AEs (by SOC, PT and treatment as well as by severity), study-drug related AEs, SAEs, AEs leading to study drug discontinuation and AEs leading to treatment interruption were summarized in the Ext SAF. Investigator reported causes of death were reported as rates per 100 patient-years and grouped into CV deaths (including death of unknown cause) and non-CV deaths. Frequencies of adverse events of special interest (AESIs), including infections, opportunistic infections, malignancy, neutropenia, thrombocytopenia, disorders of lipoprotein metabolism, immunogenicity/ allergenicity and other safety topics of interest, were also summarized in the Ext SAF. For vital signs, the frequency and percentage of patients with newly occurring clinically notable values as well as descriptive summary statistics for the change from baseline to each post-baseline visit were presented in the Ext SAF. Laboratory (hematology and clinical chemistry) and ECG evaluations were performed for the WOS, presenting clinically notable post-baseline results (with baseline values not notably abnormal) as well as changes from baseline to the End of Pre-diabetes washout visit.

Study Population: Key Inclusion/Exclusion Criteria

Main Study Inclusion Criteria:
-Written informed consent
-Male, or Female of non-child-bearing potential
-Age ≥ 18 years.
-Spontaneous MI at least 30 days before randomization.
hsCRP ≥ 2 mg/L
Substudy 1 Inclusion:
- All Inclusion from Main Study
- Acquisition of evaluable baseline MRI images of bilateral carotid arteries by the imaging core laboratory
Substudy 2 Inclusion:
- All inclusion from Main Study
- T2D at baseline per Main protocol criteria and be on a stable anti-hyperglycemic medication for at least 4 weeks prior to the baseline OGTT test
- Willing to have the OGTT assessment started before 10 am

Main Study Exclusion Criteria:
-Pregnant or nursing (lactating) women
-Women of child-bearing potential
-Any of the following concomitant diseases
-Planned coronary revascularization (PCI or CABG)
-Major non-cardiac surgical or endoscopic procedure within past 6 months
-Multi-vessel CABG surgery within the past 3 years
-Symptomatic patients with Class IV heart failure (HF) (New York Heart Association [NYHA].
-Uncontrolled hypertension
-Uncontrolled diabetes
-History or evidence of active tuberculosis (TB) infection
Substudy 1 Exclusion
- All Main exclusion
- Patients with prior history of carotid angioplasty, stenting, or carotid atherectomy
- Patients with contraindications to MRI examination (brain aneurysm clip, implanted neural stimulator, implanted cardiac pacemaker, pacemaker wires or defibrillator, prosthetic heart valves, cochlear implant, ocular foreign body or other implanted body, tattoos, implanted insulin pump, metal shrapnel or bullet)
- Patients prone to claustrophobia or known anxiety disorders
- BMI > 40 kg/m2
Substudy 2 Exclusion

- This sub-study does not have any additional exclusion criteria.

Participant Flow Table

Core Phase

	Group I	Group II	Group III	Group IV	Total
Arm/Group Description	Core phase: Blinded Canakinumab 300 mg quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	Core phase: Blinded Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	Core phase: Blinded Canakinumab 50 mg quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	Core phase: Blinded matching placebo quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	
Started	2263	2284	2170	3344	10061
Completed	2235	2252	2144	3311	9942
Not Completed	28	32	26	33	119
Subject decision (vital status: missing)	1	2	2	1	6
Subject decision	0	0	3	3	6

(vital stat: unkn)					
Subject decision (vital stat: dead)	1	3	4	4	12
Subject decision (vital stat: alive)	23	24	13	20	80
Lost to Follow-up	3	3	4	5	15

Extension Phase

	Group I	Group II	Group III	Group IV	Total
Arm/Group Description	Core phase: Blinded Canakinumab 300 mg quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	Core phase: Blinded Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	Core phase: Blinded Canakinumab 50 mg quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	Core phase: Blinded matching placebo quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	
Started	1267	1287	1279	1944	5777

Stopped/discontinued study at washout	127	97	137	178	539
Completed treatment period	41	45	49	60	195
Details missing	0	1	1	0	2
Completed	168	143	187	238	736
Not Completed	1099	1144	1092	1706	5041
Study terminated by sponsor	1073	1124	1067	1660	4924
Withdrawal by Subject	20	13	19	37	89
Lost to Follow-up	4	3	4	7	18
Technical Problems	2	4	2	2	10

Baseline Characteristics

	Group I	**Group II**	**Group III**	**Group IV**	**Total**
Arm/Group Description	Core phase: Blinded Canakinumab 300 mg quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg	Core phase: Blinded Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg	Core phase: Blinded Canakinumab 50 mg quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg	Core phase: Blinded matching placebo quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg	

	quarterly subcutaneous + standard of care (SoC) therapy	quarterly subcutaneous + standard of care (SoC) therapy	quarterly subcutaneous + standard of care (SoC) therapy	quarterly subcutaneous + standard of care (SoC) therapy	
Number of Participants [units: participants]	2263	2284	2170	3344	10061
Age, Customized (units:) Count of Participants (Not Applicable)					
< 65	1424	1428	1350	2089	6291
>= 65	839	856	820	1255	3770
< 75	2056	2066	1968	3045	9135
>= 75	207	218	202	299	926
Sex: Female, Male (units: Participants) Count of Participants (Not Applicable)					
Female	606	575	541	865	2587
Male	1657	1709	1629	2479	7474
Race/Ethnicity, Customized (units:) Count of Participants (Not Applicable)					
Caucasian	1804	1808	1772	2652	8036
Black	84	67	61	106	318
Asian	265	278	232	388	1163
Native American	47	49	41	82	219
Pacific Islander	0	0	1	1	2
Unknown	3	3	1	3	10
Other	60	79	62	112	313

Summary of Efficacy

Primary Outcome Result(s)

Analysis of Core phase First CEC Confirmed Major Adverse Cardiovascular Events (MACE) and its components

(Time Frame: From randomization, to end of treatment plus 30 days, up to approximately 6 years)

	Group I	Group II	Group III	Group IV
Arm/Group Description	Core phase: Blinded Canakinumab 300 mg quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	Core phase: Blinded Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	Core phase: Blinded Canakinumab 50 mg quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	Core phase: Blinded matching placebo quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy
Number of Participants Analyzed [units: participants]	2263	2284	2170	3344
Analysis of Core phase First CEC Confirmed Major Adverse Cardiovascular Events (MACE) and its components (units: Participants)				
MACE	322	320	313	535
CV death	151	144	137	235

MI (fatal and non-fatal)	174	159	169	292
MI (non-fatal)	171	158	168	291
Stroke (fatal and non-fatal)	51	63	58	92
Stroke (non-fatal)	51	63	58	91

Statistical Analysis

Groups	Group I, Group IV	H11: The hazard rate of first adjudication committee confirmed MACE in the canakinumab 300 mg dose group is greater than or equal to the hazard rate of the placebo group
Non-Inferiority/Equivalence Test	Superiority	A HR < 1 favors Canakinumab
P Value	0.0648	1-sided adjusted for multiplicity using weighted Dunnett test. [significance level 0.0245]
Method	Log Rank	
Cox Proportional Hazard	0.86	MACE
95 % Confidence Interval 2-Sided	0.75 to 0.99	

Statistical Analysis

Groups	Group II, Group IV	H21: The hazard rate of first adjudication committee confirmed MACE in the canakinumab 150 mg dose group is greater than or equal to

		the hazard rate of the placebo group
Non-Inferiority/Equivalence Test	Superiority	A HR < 1 favors Canakinumab
P Value	0.0241	1-sided adjusted for multiplicity using weighted Dunnett test. [significance level 0.0245]
Method	Log Rank	
Cox Proportional Hazard	0.85	MACE
95 % Confidence Interval 2-Sided	0.74 to 0.98	

Statistical Analysis

Groups	Group III, Group IV	H31: The hazard rate of first adjudication committee confirmed MACE in the canakinumab 50 mg dose group is greater than or equal to the hazard rate of the placebo group.
Non-Inferiority/Equivalence Test	Superiority	A HR < 1 favors Canakinumab
P Value	0.1895	1-sided adjusted for multiplicity using weighted Dunnett test. [significance level 0.0245]
Method	Log Rank	
Cox Proportional Hazard	0.93	MACE

95 % Confidence Interval 2-Sided	0.80 to 1.07	

Statistical Analysis

Groups	Group I, Group IV	
Non-Inferiority/Equivalence Test	Superiority	A HR < 1 favors Canakinumab
P Value	0.572	2-sided unadjusted p-value
Method	Regression, Cox	
Hazard Ratio (HR)	0.94	CV death
95 % Confidence Interval 2-Sided	0.77 to 1.16	

Statistical Analysis

Groups	Group II, Group IV	
Non-Inferiority/Equivalence Test	Superiority	A HR < 1 favors Canakinumab
P Value	0.296	2-sided unadjusted p-value
Method	Regression, Cox	
Hazard Ratio (HR)	0.90	CV death
95 % Confidence Interval 2-Sided	0.73 to 1.10	

Statistical Analysis

Groups	Group III, Group IV	
Non-Inferiority/Equivalence Test	Superiority	A HR < 1 favors Canakinumab
P Value	0.369	2-sided unadjusted p-value
Method	Regression, Cox	
Hazard Ratio (HR)	0.91	CV death
95 % Confidence Interval 2-Sided	0.73 to 1.12	

Statistical Analysis

Groups	Group I, Group IV	
Non-Inferiority/Equivalence Test	Superiority	A HR < 1 favors Canakinumab
P Value	0.067	2-sided unadjusted p-value
Method	Regression, Cox	
Hazard Ratio (HR)	0.84	MI (fatal and non-fatal)
95 % Confidence Interval 2-Sided	0.69 to 1.01	

Statistical Analysis

Groups	Group II, Group IV	
Non-Inferiority/Equivalence Test	Superiority	A HR < 1 favors Canakinumab
P Value	0.006	2-sided unadjusted p-value

Method	Regression, Cox	
Hazard Ratio (HR)	0.76	MI (fatal and non-fatal)
95 % Confidence Interval 2-Sided	0.63 to 0.92	

Statistical Analysis

Groups	Group III, Group IV	
Non-Inferiority/Equivalence Test	Superiority	A HR < 1 favors Canakinumab
P Value	0.542	2-sided unadjusted p-value
Method	Regression, Cox	
Hazard Ratio (HR)	0.94	MI (fatal and non-fatal)
95 % Confidence Interval 2-Sided	0.78 to 1.14	

Statistical Analysis

Groups	Group I, Group IV	
Non-Inferiority/Equivalence Test	Other	A HR < 1 favors Canakinumab
Hazard Ratio (HR)	0.83	MI (non-fatal)
95 % Confidence Interval 2-Sided	0.68 to 1.00	

Statistical Analysis

Groups	Group II, Group IV	
Non-Inferiority/Equivalence Test	Other	A HR < 1 favors Canakinumab
Hazard Ratio (HR)	0.76	MI (non-fatal)
95 % Confidence Interval 2-Sided	0.62 to 0.92	

Statistical Analysis

Groups	Group III, Group IV	
Non-Inferiority/Equivalence Test	Other	A HR < 1 favors Canakinumab
Hazard Ratio (HR)	0.94	MI (non-fatal)
95 % Confidence Interval 2-Sided	0.78 to 1.14	

Statistical Analysis

Groups	Group I, Group IV	
Non-Inferiority/Equivalence Test	Superiority	A HR < 1 favors Canakinumab
P Value	0.190	2-sided unadjusted p-value
Method	Regression, Cox	
Hazard Ratio (HR)	0.80	Stroke (fatal and non-fatal)
95 % Confidence Interval 2-Sided	0.56 to 1.12	

Statistical Analysis

Groups	Group II, Group IV	
Non-Inferiority/Equivalence Test	Superiority	A HR < 1 favors Canakinumab
P Value	0.912	2-sided unadjusted p-value
Method	Regression, Cox	
Hazard Ratio (HR)	0.98	Stroke (fatal and non-fatal)
95 % Confidence Interval 2-Sided	0.71 to 1.35	

Statistical Analysis

Groups	Group III, Group IV	
Non-Inferiority/Equivalence Test	Superiority	A HR < 1 favors Canakinumab
P Value	0.871	2-sided unadjusted p-value
Method	Regression, Cox	
Hazard Ratio (HR)	1.03	Stroke (fatal and non-fatal)
95 % Confidence Interval 2-Sided	0.74 to 1.43	

Statistical Analysis

Groups	Group I, Group IV	
Non-Inferiority/Equivalence Test	Other	A HR < 1 favors Canakinumab

Hazard Ratio (HR)	0.80	Stroke (nonfatal)
95 % Confidence Interval 2-Sided	0.57 to 1.13	

Statistical Analysis

Groups	Group II, Group IV	
Non-Inferiority/Equivalence Test	Other	A HR < 1 favors Canakinumab
Hazard Ratio (HR)	0.99	Stroke (nonfatal)
95 % Confidence Interval 2-Sided	0.72 to 1.37	

Statistical Analysis

Groups	Group III, Group IV	
Non-Inferiority/Equivalence Test	Other	A HR < 1 favors Canakinumab
Hazard Ratio (HR)	1.04	Stroke (nonfatal)
95 % Confidence Interval 2-Sided	0.75 to 1.45	

Substudy 1 (Core phase): Change from baseline in carotid plaque burden in the bifurcation region of the index carotid artery

(Time Frame: 24 months)

	Group I	**Group II**	**Group III**	**Group IV**
Arm/Group Description	Core phase: Blinded Canakinumab	Core phase: Blinded Canakinumab	Core phase: Blinded Canakinumab	Core phase: Blinded matching

	300 mg quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	150 mg quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	50 mg quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	placebo quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy
Number of Participants Analyzed [units: participants]	0	0	0	0
Substudy 1 (Core phase): Change from baseline in carotid plaque burden in the bifurcation region of the index carotid artery (units: carotid plaque burden)				

Substudy 2 (Core phase): Change from baseline of the insulin secretion rate (ISR) relative to glucose 0-30 min defined as Φ30 = AUCISR 0-30 / AUCGluc 0-30 averaged across the year 3, 4, 5 visits

(Time Frame: From randomization up to approximately 6 years)

	Group I	Group II	Group III	Group IV
Arm/Group Description	Core phase: Blinded	Core phase: Blinded	Core phase: Blinded	Core phase: Blinded

	Canakinumab 300 mg quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	Canakinumab 50 mg quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	matching placebo quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy
Number of Participants Analyzed [units: participants]	0	0	0	0
Substudy 2 (Core phase): Change from baseline of the insulin secretion rate (ISR) relative to glucose 0-30 min defined as Φ30 = AUCISR 0-30 / AUCGluc 0-30 averaged across the year 3, 4, 5 visits (units: change in ISR to glucose)				

Secondary Outcome Result(s)

Patients with Core phase CEC confirmed CV death, non-fatal MI, non-fatal stroke, or hospitalization for unstable angina requiring unplanned revascularization

(Time Frame: From randomization, to end of treatment pus 30 days, up to approximately 6 years)

	Group I	Group II	Group III	Group IV
Arm/Group Description	Core phase: Blinded Canakinumab 300 mg quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	Core phase: Blinded Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	Core phase: Blinded Canakinumab 50 mg quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	Core phase: Blinded matching placebo quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy
Number of Participants Analyzed [units: participants]	2263	2284	2170	3344
Patients with Core phase CEC confirmed CV death, non-fatal MI, non-fatal stroke, or hospitalization for unstable angina requiring unplanned revascularization (units: Participants)				
MACE or unstable angina	348	352	344	601
Unstable angina	34	38	38	85

Statistical Analysis

Groups	Group I, Group IV	
Non-Inferiority/Equivalence Test	Superiority	A HR < 1 favors Canakinumab
P Value	0.0648	1-sided adjusted for multiplicity using weighted Dunnett test. [significance level 0.0245]
Method	Log Rank	
Hazard Ratio (HR)	0.82	MACE or unstable angina
95 % Confidence Interval 2-Sided	0.72 to 0.94	

Statistical Analysis

Groups	Group II, Group IV	
Non-Inferiority/Equivalence Test	Superiority	A HR < 1 favors Canakinumab
P Value	0.0241	1-sided adjusted for multiplicity using weighted Dunnett test. [significance level 0.0245]
Method	Log Rank	
Hazard Ratio (HR)	0.83	MACE or unstable angina
95 % Confidence Interval 2-Sided	0.73 to 0.95	

Statistical Analysis

Groups	Group III, Group IV	
Non-Inferiority/Equivalence Test	Superiority	A HR < 1 favors Canakinumab
P Value	0.1895	1-sided adjusted for multiplicity using weighted Dunnett test. [significance level 0.0245]
Method	Log Rank	
Hazard Ratio (HR)	0.90	MACE or unstable angina
95 % Confidence Interval 2-Sided	0.79 to 1.03	

Statistical Analysis

Groups	Group I, Group IV	
Non-Inferiority/Equivalence Test	Superiority	A HR < 1 favors Canakinumab
P Value	0.007	2-sided unadjusted p-value
Method	Regression, Cox	
Hazard Ratio (HR)	0.58	unstable angina
95 % Confidence Interval 2-Sided	0.39 to 0.86	

Statistical Analysis

Groups	Group II, Group IV

Non-Inferiority/Equivalence Test	Superiority	A HR < 1 favors Canakinumab
P Value	0.022	2-sided unadjusted p-value
Method	Regression, Cox	
Hazard Ratio (HR)	0.64	unstable angina
95 % Confidence Interval 2-Sided	0.44 to 0.94	

Statistical Analysis

Groups	Group III, Group IV	
Non-Inferiority/Equivalence Test	Superiority	A HR < 1 favors Canakinumab
P Value	0.086	2-sided unadjusted p-value
Method	Regression, Cox	
Hazard Ratio (HR)	0.71	unstable angina
95 % Confidence Interval 2-Sided	0.48 to 1.05	

Core phase all-cause mortality, non-fatal MI, or non-fatal stroke

(Time Frame: From randomization, to end of treatment plus 30 days, up to approximately 6 years)

	Group I	**Group II**	**Group III**	**Group IV**
Arm/Group Description	Core phase: Blinded Canakinumab 300 mg quarterly subcutaneous	Core phase: Blinded Canakinumab 150 mg quarterly subcutaneous	Core phase: Blinded Canakinumab 50 mg quarterly subcutaneous	Core phase: Blinded matching placebo quarterly subcutaneous

	+ standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	+ standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	+ standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	+ standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy
Number of Participants Analyzed [units: participants]	2263	2284	2170	3344
Core phase all-cause mortality, non-fatal MI, or non-fatal stroke (units: Participants)				
	403	395	394	661

Statistical Analysis

Groups	Group I, Group IV	
P Value	0.028	2-sided unadjusted p-value
Method	Regression, Cox	
Hazard Ratio (HR)	0.87	All-cause mortality or MI or Stroke
95 % Confidence Interval 2-Sided	0.77 to 0.99	

Statistical Analysis

Groups	Group II, Group IV	
P Value	0.011	2-sided unadjusted p-value
Method	Regression, Cox	
Hazard Ratio (HR)	0.85	All-cause mortality or MI or Stroke
95 % Confidence Interval 2-Sided	0.75 to 0.96	

Statistical Analysis

Groups	Group III, Group IV	
P Value	0.377	2-sided unadjusted p-value
Method	Regression, Cox	
Hazard Ratio (HR)	0.94	All-cause mortality or MI or Stroke
95 % Confidence Interval 2-Sided	0.83 to 1.07	

Core phase all-cause mortality

(Time Frame: From randomization, to end of treatment plus 30 days, up to approximately 6 years)

	Group I	Group II	Group III	Group IV
Arm/Group Description	Core phase: Blinded Canakinumab 300 mg quarterly subcutaneous + standard of	Core phase: Blinded Canakinumab 150 mg quarterly subcutaneous + standard of	Core phase: Blinded Canakinumab 50 mg quarterly subcutaneous + standard of	Core phase: Blinded matching placebo quarterly subcutaneous + standard of

	care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy
Number of Participants Analyzed [units: participants]	2263	2284	2170	3344
Core phase all-cause mortality (units: Participants)				
	239	238	228	375

Statistical Analysis

Groups	Group I, Group IV	
Non-Inferiority/Equivalence Test	Superiority	A HR < 1 favors Canakinumab
P Value	0.406	2-sided unadjusted p-value
Method	Regression, Cox	
Hazard Ratio (HR)	0.93	All-cause mortality
95 % Confidence Interval 2-Sided	0.79 to 1.10	

Statistical Analysis

Groups	Group II, Group IV	
Non-Inferiority/Equivalence Test	Superiority	A HR < 1 favors Canakinumab
P Value	0.329	2-sided unadjusted p-value
Method	Regression, Cox	
Hazard Ratio (HR)	0.92	All-cause mortality
95 % Confidence Interval 2-Sided	0.78 to 1.09	

Statistical Analysis

Groups	Group III, Group IV	
Non-Inferiority/Equivalence Test	Superiority	A HR < 1 favors Canakinumab
P Value	0.597	2-sided unadjusted p-value
Method	Regression, Cox	
Hazard Ratio (HR)	0.96	All-cause mortality
95 % Confidence Interval 2-Sided	0.81 to 1.13	

Substudy 1 (Core phase): Change from baseline of the total vessel wall area at month 3 in the bifurcation region of the Index Carotid Artery

(Time Frame: 3 months)

	Group I	Group II	Group III	Group IV

Arm/Group Description	Core phase: Blinded Canakinumab 300 mg quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	Core phase: Blinded Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	Core phase: Blinded Canakinumab 50 mg quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	Core phase: Blinded matching placebo quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy
Number of Participants Analyzed [units: participants]	0	0	0	0
Substudy 1 (Core phase): Change from baseline of the total vessel wall area at month 3 in the bifurcation region of the Index Carotid Artery (units: area)				

Substudy 1 (Core phase): Mean total vessel wall area across the left and right carotid artery at Month 3 and Month 24

(Time Frame: 24 months)

	Group I	Group II	Group III	Group IV

Arm/Group Description	Core phase: Blinded Canakinumab 300 mg quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	Core phase: Blinded Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	Core phase: Blinded Canakinumab 50 mg quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	Core phase: Blinded matching placebo quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy
Number of Participants Analyzed [units: participants]	0	0	0	0
Substudy 1 (Core phase): Mean total vessel wall area across the left and right carotid artery at Month 3 and Month 24 (units: Mean area)				

Substudy 1 (Core phase): Change from baseline in corresponding total vessel wall area in the left and right carotid arteries

(Time Frame: 24 months)

	Group I	Group II	Group III	Group IV

Arm/Group Description	Core phase: Blinded Canakinumab 300 mg quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	Core phase: Blinded Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	Core phase: Blinded Canakinumab 50 mg quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	Core phase: Blinded matching placebo quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy
Number of Participants Analyzed [units: participants]	0	0	0	0
Substudy 1 (Core phase): Change from baseline in corresponding total vessel wall area in the left and right carotid arteries (units: area)				

Substudy 1 (Core phase): The existence of a baseline total vessel wall area by treatment interaction as well as the consistency of the treatment effect across subgroups

(Time Frame: 24 months)

	Group I	Group II	Group III	Group IV
Arm/Group Description	Core phase: Blinded Canakinumab 300 mg quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	Core phase: Blinded Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	Core phase: Blinded Canakinumab 50 mg quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	Core phase: Blinded matching placebo quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy
Number of Participants Analyzed [units: participants]	0	0	0	0
Substudy 1 (Core phase): The existence of a baseline total vessel wall area by treatment interaction as well as the consistency of the treatment effect across subgroups (units: area)				

Patients with Core phase new onset type 2 diabetes among patients with pre-diabetes at randomization

(Time Frame: From randomization up to approximately 6 years)

	Group I	Group II	Group III	Group IV
Arm/Group Description	Core phase: Blinded Canakinumab 300 mg quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	Core phase: Blinded Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	Core phase: Blinded Canakinumab 50 mg quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	Core phase: Blinded matching placebo quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy
Number of Participants Analyzed [units: participants]	1132	1094	1089	1645
Patients with Core phase new onset type 2 diabetes among patients with pre-diabetes at randomization (units: Participants)				
	169	171	161	246

Statistical Analysis

Groups	Group I, Group IV	
Non-Inferiority/Equivalence Test	Superiority	A HR < 1 favors Canakinumab
P Value	0.8456	1-sided adjusted for multiplicity using weighted Dunnett test. [significance level 0.0245]
Method	Log Rank	
Hazard Ratio (HR)	1.01	
95 % Confidence Interval 2-Sided	0.83 to 1.23	

Statistical Analysis

Groups	Group II, Group IV	
Non-Inferiority/Equivalence Test	Superiority	A HR < 1 favors Canakinumab
P Value	0.8456	1-sided adjusted for multiplicity using weighted Dunnett test. [significance level 0.0245]
Method	Log Rank	
Hazard Ratio (HR)	1.06	
95 % Confidence Interval 2-Sided	0.87 to 1.29	

Statistical Analysis

Groups	Group III, Group IV	
Non-Inferiority/Equivalence Test	Superiority	A HR < 1 favors Canakinumab
P Value	0.6541	1-sided adjusted for multiplicity using weighted Dunnett test. [significance level 0.0245]
Method	Log Rank	
Hazard Ratio (HR)	0.98	
95 % Confidence Interval 2-Sided	0.80 to 1.20	

Summary of Adverse Events (Core phase)

(Time Frame: From randomization, to end of treatment plus 30 days, up to approximately 6 years)

	Group I	Group II	Group III	Group IV
Arm/Group Description	Core phase: Blinded Canakinumab 300 mg quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of	Core phase: Blinded Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of	Core phase: Blinded Canakinumab 50 mg quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of	Core phase: Blinded matching placebo quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of

	care (SoC) therapy	care (SoC) therapy	care (SoC) therapy	care (SoC) therapy
Number of Participants Analyzed [units: participants]	2263	2285	2170	3348
Summary of Adverse Events (Core phase) (units: Participants)				
Patients with at least one AE	1987	1970	1872	2915
AEs suspected to be related tostudy drug	355	350	267	474
Patients with at least one SAE	836	812	741	1204
Discontinued due to SAEs	135	130	117	198
Discontinued due to non-seriousAEs	40	34	26	47
AEs leading to study treatmentinterruption	268	270	228	399

Summary of Adverse Events (Extension phase)

(Time Frame: From start of Extension phase, to end of treatment plus 30 days, up to approximately 2 years)

	Group I	**Group II**	**Group III**	**Group IV**
Arm/Group Description	Core phase: Blinded Canakinumab 300 mg quarterly subcutaneous + standard of care (SoC) therapy Extension phase:	Core phase: Blinded Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy Extension phase:	Core phase: Blinded Canakinumab 50 mg quarterly subcutaneous + standard of care (SoC) therapy Extension phase:	Core phase: Blinded matching placebo quarterly subcutaneous + standard of care (SoC) therapy Extension phase:

	Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy
Number of Participants Analyzed [units: participants]	1267	1287	1279	1944
Summary of Adverse Events (Extension phase) (units: Participants)				
Patients with at least one AE	788	845	793	1250
AEs suspected to be related tostudy drug	40	34	43	65
Patients with at least one SAE	310	326	322	465
Discontinued due to SAEs	67	71	71	98
Discontinued due to non-seriousAEs	8	6	12	8
AEs leading to study treatmentinterruption	59	72	62	100

Substudy 2 (Core phase): Change from baseline in insulin sensitivity index

(Time Frame: From randomization up to approximately 6 years)

	Group I	Group II	Group III	Group IV
Arm/Group Description	Core phase: Blinded Canakinumab 300 mg	Core phase: Blinded Canakinumab 150 mg	Core phase: Blinded Canakinumab 50 mg	Core phase: Blinded matching placebo

	quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy
Number of Participants Analyzed [units: participants]	0	0	0	0
Substudy 2 (Core phase): Change from baseline in insulin sensitivity index (units: Insulin sensitivity index)				

Substudy 2 (Core phase): Change from baseline in OGTT stimulated area under curve (AUC) 0-120 min of glucose concentration, insulin concentration, pro-insulin concentration, and Insulin Concentration/glucose Concentration Ratio

(Time Frame: From randomization up to approximately 6 years)

	Group I	Group II	Group III	Group IV
Arm/Group Description	Core phase: Blinded Canakinumab 300 mg quarterly	Core phase: Blinded Canakinumab 150 mg quarterly	Core phase: Blinded Canakinumab 50 mg quarterly	Core phase: Blinded matching placebo quarterly

	subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy
Number of Participants Analyzed [units: participants]	0	0	0	0
Substudy 2 (Core phase): Change from baseline in OGTT stimulated area under curve (AUC) 0-120 min of glucose concentration, insulin concentration, pro-insulin concentration, and Insulin Concentration/glucose Concentration Ratio (units: AUC)				

Substudy 2 (Core phase): Change from Baseline in Fasting Pro-Insulin Concentration/Insulin Concentration Ratio

(Time Frame: From randomization up to approximately 6 years)

	Group I	Group II	Group III	Group IV

Arm/Group Description	Core phase: Blinded Canakinumab 300 mg quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	Core phase: Blinded Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	Core phase: Blinded Canakinumab 50 mg quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	Core phase: Blinded matching placebo quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy
Number of Participants Analyzed [units: participants]	0	0	0	0
Substudy 2 (Core phase): Change from Baseline in Fasting Pro-Insulin Concentration/Insulin Concentration Ratio (units: Ratio)				

Substudy 2 (Core phase): Change from baseline in OGTT stimulated area under the curve (AUC) 0-120 min of C-peptide Concentration

(Time Frame: From randomization up to approximately 6 years)

	Group I	Group II	Group III	Group IV

Arm/Group Description	Core phase: Blinded Canakinumab 300 mg quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	Core phase: Blinded Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	Core phase: Blinded Canakinumab 50 mg quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	Core phase: Blinded matching placebo quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy
Number of Participants Analyzed [units: participants]	0	0	0	0
Substudy 2 (Core phase): Change from baseline in OGTT stimulated area under the curve (AUC) 0-120 min of C-peptide Concentration (units: AUC)				

Summary of Safety

Safety Results

Time Frame	Core phase: From randomization to end of treatment plus 30 days; up to approximately 6 years; Extension phase: From start of Extension phase, to end of treatment plus 30 days, up to approximately 2 years.
Additional Description	AEs/SAEs are any signs or symptoms that occur during the study treatment. Groups I to IV show AE/SAEs during the Core phase; Group V shows AE/SAEs during the Extension phase. During the Core phase, CV events being study endpoints were exempt from AE/SAE reporting; in contrast, during the Extension phase, all CV events were reported as AEs/SAEs.
Source Vocabulary for Table Default	MedDRA 20.0/21.1
Assessment Type for Table Default	SYSTEMATIC ASSESSMENT

All-Cause Mortality

Group I N = 2263	Group II N = 2285	Group III N = 2170	Group IV N = 3348	Group V N = 5777

Arm/Group Description	Core phase: Blinded Canakinumab 300 mg quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	Core phase: Blinded Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	Core phase: Blinded Canakinumab 50 mg quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	Core phase: Blinded matching placebo quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy.
Total participants affected	239 (10.56%)	240 (10.50%)	228 (10.51%)	378 (11.29%)	211 (3.65%)

Serious Adverse Events by System Organ Class

	Group I N = 2263	**Group II N = 2285**	**Group III N = 2170**	**Group IV N = 3348**	**Group V N = 5777**
Arm/Group Description	Core phase: Blinded Canakinumab 300 mg quarterly subcutaneous + standard of care (SoC) therapy	Core phase: Blinded Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	Core phase: Blinded Canakinumab 50 mg quarterly subcutaneous + standard of care (SoC) therapy	Core phase: Blinded matching placebo quarterly subcutaneous + standard of care (SoC) therapy	Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of

	Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	care (SoC) therapy.
Total participants affected	759 (33.54%)	743 (32.52%)	686 (31.61%)	1099 (32.83%)	1216 (21.05%)
Blood and lymphatic system disorders					
Abnormal clotting factor[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Anaemia[1]	15 (0.66%)	10 (0.44%)	4 (0.18%)	14 (0.42%)	10 (0.17%)
Bone marrow oedema[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Coagulopathy[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Disseminated intravascular coagulation[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Febrile neutropenia[1]	0 (0.00%)	1 (0.04%)	1 (0.05%)	0 (0.00%)	1 (0.02%)
Haemorrhagic anaemia[1]	4 (0.18%)	2 (0.09%)	5 (0.23%)	1 (0.03%)	1 (0.02%)
Heparin-induced thrombocytopenia[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hilar lymphadenopathy[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Histiocytosis haematophagic[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Hypochromic anaemia[1]	0 (0.00%)	1 (0.04%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Immune thrombocytopenic purpura[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Iron deficiency anaemia[1]	0 (0.00%)	1 (0.04%)	1 (0.05%)	3 (0.09%)	1 (0.02%)
Leukocytosis[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	1 (0.03%)	0 (0.00%)

Leukopenia[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (0.06%)	0 (0.00%)
Lymphadenitis[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Lymphadenopathy[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Lymphadenopathy mediastinal[1]	1 (0.04%)	0 (0.00%)	1 (0.05%)	1 (0.03%)	0 (0.00%)
Microcytic anaemia[1]	1 (0.04%)	1 (0.04%)	1 (0.05%)	0 (0.00%)	1 (0.02%)
Monoclonal B-cell lymphocytosis[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Normochromic normocytic anaemia[1]	1 (0.04%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Normocytic anaemia[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Pancytopenia[1]	1 (0.04%)	2 (0.09%)	0 (0.00%)	3 (0.09%)	1 (0.02%)
Polycythaemia[1]	2 (0.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Splenic infarction[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Splenomegaly[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Thrombocytopenia[1]	5 (0.22%)	0 (0.00%)	3 (0.14%)	3 (0.09%)	0 (0.00%)
Thrombocytopenic purpura[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (0.06%)	0 (0.00%)
Cardiac disorders					
Acute coronary syndrome[1]	6 (0.27%)	1 (0.04%)	4 (0.18%)	4 (0.12%)	14 (0.24%)
Acute left ventricular failure[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	1 (0.03%)	2 (0.03%)
Acute myocardial infarction[1]	2 (0.09%)	2 (0.09%)	2 (0.09%)	7 (0.21%)	71 (1.23%)
Adams-Stokes syndrome[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Angina pectoris[1]	42 (1.86%)	41 (1.79%)	37 (1.71%)	76 (2.27%)	66 (1.14%)
Angina unstable[1]	39 (1.72%)	34 (1.49%)	37 (1.71%)	63 (1.88%)	56 (0.97%)
Aortic valve incompetence[1]	1 (0.04%)	1 (0.04%)	0 (0.00%)	1 (0.03%)	0 (0.00%)

Aortic valve stenosis[1]	3 (0.13%)	2 (0.09%)	2 (0.09%)	3 (0.09%)	2 (0.03%)
Arrhythmia[1]	4 (0.18%)	0 (0.00%)	1 (0.05%)	3 (0.09%)	0 (0.00%)
Arrhythmia supraventricular[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Arteriosclerosis coronary artery[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (0.09%)	2 (0.03%)
Arteriospasm coronary[1]	1 (0.04%)	1 (0.04%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Atrial fibrillation[1]	3 (0.13%)	6 (0.26%)	4 (0.18%)	4 (0.12%)	49 (0.85%)
Atrial flutter[1]	2 (0.09%)	0 (0.00%)	1 (0.05%)	1 (0.03%)	6 (0.10%)
Atrial tachycardia[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	1 (0.02%)
Atrial thrombosis[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Atrioventricular block[1]	0 (0.00%)	1 (0.04%)	1 (0.05%)	2 (0.06%)	1 (0.02%)
Atrioventricular block complete[1]	1 (0.04%)	1 (0.04%)	2 (0.09%)	4 (0.12%)	4 (0.07%)
Atrioventricular block first degree[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Atrioventricular block second degree[1]	1 (0.04%)	4 (0.18%)	2 (0.09%)	4 (0.12%)	2 (0.03%)
Bradyarrhythmia[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Bradycardia[1]	4 (0.18%)	2 (0.09%)	3 (0.14%)	10 (0.30%)	6 (0.10%)
Cardiac aneurysm[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Cardiac arrest[1]	2 (0.09%)	7 (0.31%)	7 (0.32%)	15 (0.45%)	9 (0.16%)
Cardiac discomfort[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	1 (0.02%)
Cardiac failure[1]	5 (0.22%)	4 (0.18%)	7 (0.32%)	4 (0.12%)	43 (0.74%)
Cardiac failure acute[1]	2 (0.09%)	2 (0.09%)	0 (0.00%)	0 (0.00%)	16 (0.28%)
Cardiac failure chronic[1]	5 (0.22%)	2 (0.09%)	2 (0.09%)	2 (0.06%)	15 (0.26%)
Cardiac failure congestive[1]	4 (0.18%)	2 (0.09%)	0 (0.00%)	0 (0.00%)	30 (0.52%)
Cardiac fibrillation[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)

Cardiac pseudoaneurysm[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Cardiac tamponade[1]	2 (0.09%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Cardiac ventricular thrombosis[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Cardiogenic shock[1]	1 (0.04%)	3 (0.13%)	3 (0.14%)	7 (0.21%)	9 (0.16%)
Cardiomegaly[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Cardiomyopathy[1]	1 (0.04%)	1 (0.04%)	1 (0.05%)	1 (0.03%)	0 (0.00%)
Cardiopulmonary failure[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Cardio-respiratory arrest[1]	2 (0.09%)	2 (0.09%)	3 (0.14%)	1 (0.03%)	6 (0.10%)
Conduction disorder[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Congestive cardiomyopathy[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Cor pulmonale[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Coronary artery disease[1]	9 (0.40%)	10 (0.44%)	5 (0.23%)	20 (0.60%)	27 (0.47%)
Coronary artery insufficiency[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Coronary artery occlusion[1]	1 (0.04%)	1 (0.04%)	0 (0.00%)	1 (0.03%)	3 (0.05%)
Coronary artery stenosis[1]	2 (0.09%)	1 (0.04%)	0 (0.00%)	2 (0.06%)	14 (0.24%)
Hypertensive heart disease[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Intracardiac thrombus[1]	1 (0.04%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Ischaemic cardiomyopathy[1]	3 (0.13%)	5 (0.22%)	2 (0.09%)	4 (0.12%)	6 (0.10%)
Left ventricular dysfunction[1]	2 (0.09%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	3 (0.05%)
Left ventricular failure[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Left ventricular hypertrophy[1]	0 (0.00%)	1 (0.04%)	1 (0.05%)	0 (0.00%)	0 (0.00%)

Microvascular coronary artery disease[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Mitral valve incompetence[1]	5 (0.22%)	3 (0.13%)	0 (0.00%)	1 (0.03%)	3 (0.05%)
Myocardial infarction[1]	4 (0.18%)	2 (0.09%)	5 (0.23%)	2 (0.06%)	42 (0.73%)
Myocardial ischaemia[1]	6 (0.27%)	3 (0.13%)	5 (0.23%)	6 (0.18%)	10 (0.17%)
Nodal arrhythmia[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	1 (0.02%)
Palpitations[1]	3 (0.13%)	2 (0.09%)	2 (0.09%)	1 (0.03%)	1 (0.02%)
Pericardial effusion[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Pericarditis[1]	2 (0.09%)	1 (0.04%)	0 (0.00%)	2 (0.06%)	0 (0.00%)
Prinzmetal angina[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (0.03%)
Pulseless electrical activity[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Right ventricular dysfunction[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Right ventricular failure[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (0.03%)
Silent myocardial infarction[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Sinus arrest[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Sinus bradycardia[1]	3 (0.13%)	0 (0.00%)	2 (0.09%)	2 (0.06%)	1 (0.02%)
Sinus node dysfunction[1]	4 (0.18%)	2 (0.09%)	5 (0.23%)	4 (0.12%)	6 (0.10%)
Sinus tachycardia[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Stress cardiomyopathy[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	1 (0.02%)
Supraventricular tachycardia[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (0.03%)
Tachyarrhythmia[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Tachycardia[1]	3 (0.13%)	1 (0.04%)	1 (0.05%)	2 (0.06%)	1 (0.02%)
Torsade de pointes[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)

Tricuspid valve incompetence[1]	1 (0.04%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Trifascicular block[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Ventricular arrhythmia[1]	1 (0.04%)	0 (0.00%)	1 (0.05%)	2 (0.06%)	1 (0.02%)
Ventricular extrasystoles[1]	1 (0.04%)	0 (0.00%)	2 (0.09%)	2 (0.06%)	1 (0.02%)
Ventricular fibrillation[1]	4 (0.18%)	9 (0.39%)	3 (0.14%)	7 (0.21%)	7 (0.12%)
Ventricular tachyarrhythmia[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Ventricular tachycardia[1]	10 (0.44%)	5 (0.22%)	9 (0.41%)	16 (0.48%)	18 (0.31%)
Congenital, familial and genetic disorders					
Atrial septal defect[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Branchial cyst[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Cerebrovascular arteriovenous malformation[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Haemorrhagic arteriovenous malformation[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Hereditary haemochromatosis[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Hydrocele[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	1 (0.02%)
Nonketotic hyperglycinaemia[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Phimosis[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pyloric stenosis[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Tracheo-oesophageal fistula[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Ear and labyrinth disorders					

Cerumen impaction[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Ear pain[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Hypoacusis[1]	0 (0.00%)	2 (0.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Meniere's disease[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Otosclerosis[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Presbyacusis[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Sudden hearing loss[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	1 (0.03%)	0 (0.00%)
Tympanic membrane perforation[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Vertigo[1]	3 (0.13%)	5 (0.22%)	4 (0.18%)	4 (0.12%)	4 (0.07%)
Vertigo positional[1]	2 (0.09%)	2 (0.09%)	3 (0.14%)	2 (0.06%)	2 (0.03%)
Endocrine disorders					
Goitre[1]	1 (0.04%)	0 (0.00%)	1 (0.05%)	2 (0.06%)	0 (0.00%)
Hyperparathyroidism primary[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Hyperthyroidism[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Hypopituitarism[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Hypothyroidism[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	1 (0.03%)	1 (0.02%)
Inappropriate antidiuretic hormone secretion[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Primary hyperaldosteronism[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Toxic goitre[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Eye disorders					
Amaurosis fugax[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Angle closure glaucoma[1]	1 (0.04%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Blindness[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	1 (0.03%)	0 (0.00%)

Blindness transient[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Blindness unilateral[1]	0 (0.00%)	2 (0.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Cataract[1]	4 (0.18%)	8 (0.35%)	5 (0.23%)	12 (0.36%)	8 (0.14%)
Cataract cortical[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Cataract diabetic[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Cataract nuclear[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Corneal degeneration[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Corneal infiltrates[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Dacryostenosis acquired[1]	2 (0.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Diabetic retinopathy[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (0.06%)	1 (0.02%)
Eye haemorrhage[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Eyelid ptosis[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Glaucoma[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Iridocyclitis[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (0.06%)	0 (0.00%)
Lens dislocation[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Macular degeneration[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Macular fibrosis[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Macular hole[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Macular oedema[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Neovascular age-related macular degeneration[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Ocular ischaemic syndrome[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Papilloedema[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Retinal artery thrombosis[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Retinal detachment[1]	2 (0.09%)	2 (0.09%)	0 (0.00%)	2 (0.06%)	2 (0.03%)
Retinal haemorrhage[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Retinal vein occlusion[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Retinal vein thrombosis[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Vitreous haemorrhage[1]	1 (0.04%)	0 (0.00%)	1 (0.05%)	1 (0.03%)	2 (0.03%)
Gastrointestinal disorders					
Abdominal adhesions[1]	0 (0.00%)	0 (0.00%)	2 (0.09%)	1 (0.03%)	1 (0.02%)
Abdominal discomfort[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (0.06%)	0 (0.00%)
Abdominal distension[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Abdominal hernia[1]	3 (0.13%)	1 (0.04%)	2 (0.09%)	0 (0.00%)	0 (0.00%)
Abdominal pain[1]	7 (0.31%)	4 (0.18%)	10 (0.46%)	10 (0.30%)	6 (0.10%)
Abdominal pain lower[1]	0 (0.00%)	1 (0.04%)	2 (0.09%)	0 (0.00%)	0 (0.00%)
Abdominal pain upper[1]	6 (0.27%)	2 (0.09%)	3 (0.14%)	2 (0.06%)	4 (0.07%)
Acute abdomen[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	1 (0.03%)	0 (0.00%)
Alcoholic pancreatitis[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Anal fissure[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Anal haemorrhage[1]	0 (0.00%)	1 (0.04%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Anal skin tags[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Anal ulcer[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Anal ulcer haemorrhage[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Anorectal disorder[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Appendiceal mucocoele[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Appendix disorder[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Ascites[1]	0 (0.00%)	2 (0.09%)	1 (0.05%)	1 (0.03%)	0 (0.00%)
Change of bowel habit[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Chronic gastritis[1]	0 (0.00%)	2 (0.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Colitis[1]	3 (0.13%)	3 (0.13%)	2 (0.09%)	3 (0.09%)	4 (0.07%)
Colitis ischaemic[1]	1 (0.04%)	1 (0.04%)	2 (0.09%)	1 (0.03%)	1 (0.02%)

Colitis microscopic[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	1 (0.02%)
Colitis ulcerative[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	3 (0.09%)	0 (0.00%)
Colonic fistula[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Constipation[1]	4 (0.18%)	2 (0.09%)	1 (0.05%)	4 (0.12%)	3 (0.05%)
Crohn's disease[1]	1 (0.04%)	3 (0.13%)	1 (0.05%)	2 (0.06%)	0 (0.00%)
Dental caries[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Diabetic gastroenteropathy[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Diarrhoea[1]	3 (0.13%)	5 (0.22%)	4 (0.18%)	2 (0.06%)	3 (0.05%)
Dieulafoy's vascular malformation[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Diverticulum[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	1 (0.03%)	2 (0.03%)
Diverticulum intestinal[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	1 (0.02%)
Diverticulum intestinal haemorrhagic[1]	0 (0.00%)	1 (0.04%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Duodenal stenosis[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Duodenal ulcer[1]	1 (0.04%)	1 (0.04%)	1 (0.05%)	1 (0.03%)	2 (0.03%)
Duodenal ulcer haemorrhage[1]	2 (0.09%)	0 (0.00%)	0 (0.00%)	2 (0.06%)	0 (0.00%)
Duodenal ulcer perforation[1]	2 (0.09%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Duodenitis[1]	2 (0.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Dyspepsia[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Dysphagia[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	2 (0.06%)	2 (0.03%)
Enteritis[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	1 (0.03%)	1 (0.02%)
Enterocolitis[1]	0 (0.00%)	2 (0.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Enterovesical fistula[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Epigastric discomfort[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Erosive duodenitis[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Erosive oesophagitis[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Faecaloma[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	1 (0.02%)
Faeces discoloured[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Flatulence[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Food poisoning[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Gallstone ileus[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Gastric haemorrhage[1]	0 (0.00%)	1 (0.04%)	1 (0.05%)	2 (0.06%)	0 (0.00%)
Gastric ulcer[1]	7 (0.31%)	6 (0.26%)	0 (0.00%)	1 (0.03%)	2 (0.03%)
Gastric ulcer haemorrhage[1]	2 (0.09%)	1 (0.04%)	1 (0.05%)	2 (0.06%)	0 (0.00%)
Gastric ulcer perforation[1]	0 (0.00%)	1 (0.04%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Gastric volvulus[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Gastritis[1]	4 (0.18%)	1 (0.04%)	4 (0.18%)	6 (0.18%)	4 (0.07%)
Gastritis erosive[1]	1 (0.04%)	1 (0.04%)	0 (0.00%)	1 (0.03%)	1 (0.02%)
Gastritis haemorrhagic[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Gastroduodenitis[1]	1 (0.04%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Gastrointestinal angiodysplasia[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Gastrointestinal disorder[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	2 (0.06%)	0 (0.00%)
Gastrointestinal erosion[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Gastrointestinal haemorrhage[1]	13 (0.57%)	16 (0.70%)	14 (0.65%)	13 (0.39%)	5 (0.09%)
Gastrointestinal necrosis[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Gastrointestinal pain[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Gastrointestinal perforation[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Gastrointestinal ulcer[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Gastrointestinal vascular malformation[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Gastrooesophageal reflux disease[1]	1 (0.04%)	5 (0.22%)	1 (0.05%)	4 (0.12%)	4 (0.07%)
Haematemesis[1]	1 (0.04%)	1 (0.04%)	2 (0.09%)	2 (0.06%)	3 (0.05%)
Haematochezia[1]	1 (0.04%)	3 (0.13%)	1 (0.05%)	2 (0.06%)	0 (0.00%)
Haemorrhagic necrotic pancreatitis[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Haemorrhoidal haemorrhage[1]	2 (0.09%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Haemorrhoids[1]	2 (0.09%)	3 (0.13%)	1 (0.05%)	2 (0.06%)	1 (0.02%)
Haemorrhoids thrombosed[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hiatus hernia[1]	0 (0.00%)	1 (0.04%)	1 (0.05%)	1 (0.03%)	2 (0.03%)
Ileal ulcer[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	1 (0.02%)
Ileus[1]	3 (0.13%)	1 (0.04%)	2 (0.09%)	3 (0.09%)	2 (0.03%)
Ileus paralytic[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	1 (0.03%)	1 (0.02%)
Impaired gastric emptying[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	3 (0.09%)	0 (0.00%)
Incarcerated inguinal hernia[1]	1 (0.04%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	1 (0.02%)
Incarcerated umbilical hernia[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Inflammatory bowel disease[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	2 (0.03%)
Inguinal hernia[1]	8 (0.35%)	5 (0.22%)	7 (0.32%)	7 (0.21%)	8 (0.14%)
Inguinal hernia strangulated[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Intestinal fistula[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Intestinal haemorrhage[1]	1 (0.04%)	1 (0.04%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Intestinal infarction[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)

Intestinal ischaemia[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	2 (0.03%)
Intestinal mass[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Intestinal obstruction[1]	2 (0.09%)	1 (0.04%)	3 (0.14%)	2 (0.06%)	2 (0.03%)
Intestinal perforation[1]	2 (0.09%)	1 (0.04%)	1 (0.05%)	1 (0.03%)	0 (0.00%)
Intestinal ulcer[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Irritable bowel syndrome[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	2 (0.06%)	0 (0.00%)
Ischaemic enteritis[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Large intestinal obstruction[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Large intestinal stenosis[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Large intestine perforation[1]	0 (0.00%)	2 (0.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Large intestine polyp[1]	3 (0.13%)	4 (0.18%)	2 (0.09%)	12 (0.36%)	6 (0.10%)
Lower gastrointestinal haemorrhage[1]	1 (0.04%)	4 (0.18%)	1 (0.05%)	0 (0.00%)	2 (0.03%)
Mallory-Weiss syndrome[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	2 (0.06%)	1 (0.02%)
Melaena[1]	2 (0.09%)	1 (0.04%)	0 (0.00%)	2 (0.06%)	3 (0.05%)
Mesenteric artery stenosis[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	1 (0.02%)
Mesenteric artery thrombosis[1]	1 (0.04%)	1 (0.04%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Mesenteric vascular insufficiency[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Mouth cyst[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Mouth ulceration[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Narcotic bowel syndrome[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Nausea[1]	4 (0.18%)	3 (0.13%)	2 (0.09%)	4 (0.12%)	0 (0.00%)
Obstruction gastric[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Odynophagia[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Oesophageal obstruction[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)

Oesophageal perforation[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Oesophageal rupture[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Oesophageal stenosis[1]	0 (0.00%)	1 (0.04%)	1 (0.05%)	0 (0.00%)	1 (0.02%)
Oesophageal ulcer[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Oesophageal varices haemorrhage[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Oesophagitis[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	2 (0.06%)	1 (0.02%)
Pancreatic cyst[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pancreatic disorder[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Pancreatic duct dilatation[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Pancreatic mass[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Pancreatic pseudocyst[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pancreatitis[1]	6 (0.27%)	6 (0.26%)	3 (0.14%)	11 (0.33%)	3 (0.05%)
Pancreatitis acute[1]	3 (0.13%)	6 (0.26%)	2 (0.09%)	3 (0.09%)	6 (0.10%)
Pancreatitis chronic[1]	0 (0.00%)	2 (0.09%)	1 (0.05%)	1 (0.03%)	2 (0.03%)
Pancreatitis necrotising[1]	2 (0.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Peptic ulcer[1]	2 (0.09%)	0 (0.00%)	0 (0.00%)	3 (0.09%)	0 (0.00%)
Peptic ulcer haemorrhage[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	1 (0.03%)	0 (0.00%)
Peritoneal haemorrhage[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Pneumatosis intestinalis[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Pneumoperitoneum[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Proctalgia[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Proctitis[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Ranula[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Rectal haemorrhage[1]	1 (0.04%)	6 (0.26%)	1 (0.05%)	1 (0.03%)	3 (0.05%)
Rectal lesion[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)

Rectal perforation[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Rectal polyp[1]	1 (0.04%)	2 (0.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Retroperitoneal haematoma[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Retroperitoneal haemorrhage[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Salivary gland calculus[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Small intestinal haemorrhage[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Small intestinal obstruction[1]	2 (0.09%)	1 (0.04%)	2 (0.09%)	1 (0.03%)	9 (0.16%)
Small intestinal perforation[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (0.03%)
Small intestine ulcer[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (0.03%)
Subileus[1]	1 (0.04%)	1 (0.04%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Thrombosis mesenteric vessel[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Umbilical hernia[1]	1 (0.04%)	4 (0.18%)	2 (0.09%)	4 (0.12%)	0 (0.00%)
Upper gastrointestinal haemorrhage[1]	3 (0.13%)	8 (0.35%)	8 (0.37%)	8 (0.24%)	3 (0.05%)
Vomiting[1]	5 (0.22%)	4 (0.18%)	2 (0.09%)	4 (0.12%)	0 (0.00%)
General disorders and administration site conditions					
Adverse drug reaction[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Asthenia[1]	4 (0.18%)	2 (0.09%)	1 (0.05%)	3 (0.09%)	3 (0.05%)
Cardiac death[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (0.07%)
Chest discomfort[1]	2 (0.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Chest pain[1]	3 (0.13%)	12 (0.53%)	2 (0.09%)	9 (0.27%)	9 (0.16%)
Chills[1]	1 (0.04%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Complication associated with device[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	1 (0.03%)	0 (0.00%)
Death[1]	1 (0.04%)	0 (0.00%)	1 (0.05%)	4 (0.12%)	12 (0.21%)
Drowning[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Drug intolerance[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Exercise tolerance decreased[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Facial pain[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Fatigue[1]	2 (0.09%)	2 (0.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Gait disturbance[1]	1 (0.04%)	1 (0.04%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
General physical health deterioration[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	2 (0.06%)	2 (0.03%)
Generalised oedema[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Hernia[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (0.03%)
Heteroplasia[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Hyperplasia[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Hypothermia[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Impaired healing[1]	0 (0.00%)	1 (0.04%)	1 (0.05%)	2 (0.06%)	0 (0.00%)
Implant site irritation[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Incarcerated hernia[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Inflammation[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Influenza like illness[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Injection site reaction[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Ischaemic ulcer[1]	0 (0.00%)	1 (0.04%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Local swelling[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Malaise[1]	1 (0.04%)	1 (0.04%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Mass[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Multiple organ dysfunction syndrome[1]	3 (0.13%)	2 (0.09%)	0 (0.00%)	3 (0.09%)	6 (0.10%)
Necrosis[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Non-cardiac chest pain[1]	44 (1.94%)	48 (2.10%)	39 (1.80%)	75 (2.24%)	35 (0.61%)
Oedema peripheral[1]	2 (0.09%)	0 (0.00%)	1 (0.05%)	3 (0.09%)	1 (0.02%)
Pacemaker syndrome[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Pain[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Polyp[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Pseudocyst[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Pyrexia[1]	4 (0.18%)	4 (0.18%)	6 (0.28%)	5 (0.15%)	3 (0.05%)
Stent-graft endoleak[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	1 (0.03%)	1 (0.02%)
Sudden cardiac death[1]	0 (0.00%)	1 (0.04%)	1 (0.05%)	0 (0.00%)	11 (0.19%)
Sudden death[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	7 (0.12%)
Surgical failure[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Systemic inflammatory response syndrome[1]	1 (0.04%)	0 (0.00%)	3 (0.14%)	2 (0.06%)	0 (0.00%)
Vascular stent restenosis[1]	2 (0.09%)	2 (0.09%)	1 (0.05%)	1 (0.03%)	0 (0.00%)
Vascular stent stenosis[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	3 (0.05%)
Vascular stent thrombosis[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Vessel puncture site haemorrhage[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Hepatobiliary disorders					
Acute hepatic failure[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (0.06%)	0 (0.00%)
Alcoholic liver disease[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	1 (0.03%)	0 (0.00%)
Autoimmune hepatitis[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Bile duct stenosis[1]	0 (0.00%)	2 (0.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Bile duct stone[1]	4 (0.18%)	0 (0.00%)	1 (0.05%)	2 (0.06%)	1 (0.02%)

Biliary cirrhosis[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Biliary colic[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Biliary dilatation[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	1 (0.02%)
Biliary fistula[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Cholangitis[1]	2 (0.09%)	2 (0.09%)	4 (0.18%)	0 (0.00%)	0 (0.00%)
Cholangitis acute[1]	1 (0.04%)	1 (0.04%)	0 (0.00%)	1 (0.03%)	1 (0.02%)
Cholecystitis[1]	11 (0.49%)	4 (0.18%)	8 (0.37%)	9 (0.27%)	7 (0.12%)
Cholecystitis acute[1]	5 (0.22%)	7 (0.31%)	4 (0.18%)	7 (0.21%)	5 (0.09%)
Cholelithiasis[1]	8 (0.35%)	8 (0.35%)	8 (0.37%)	18 (0.54%)	4 (0.07%)
Cholestasis[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (0.06%)	0 (0.00%)
Drug-induced liver injury[1]	0 (0.00%)	1 (0.04%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Gallbladder polyp[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Haemorrhagic hepatic cyst[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hepatic cirrhosis[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	4 (0.07%)
Hepatic congestion[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Hepatic failure[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Hepatic function abnormal[1]	1 (0.04%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Hepatic steatosis[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	1 (0.03%)	0 (0.00%)
Hepatic vein thrombosis[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hepatitis[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Hepatitis toxic[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	1 (0.03%)	0 (0.00%)
Hepatomegaly[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hepatorenal failure[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Hepatosplenomegaly[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hydrocholecystis[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Ischaemic hepatitis[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Jaundice cholestatic[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	1 (0.03%)	2 (0.03%)
Liver disorder[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Liver injury[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	1 (0.02%)
Non-alcoholic fatty liver[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Non-alcoholic steatohepatitis[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Portal vein thrombosis[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Steatohepatitis[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Immune system disorders					
Allergy to arthropod sting[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Anaphylactic reaction[1]	1 (0.04%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Anaphylactic shock[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	1 (0.03%)	2 (0.03%)
Contrast media allergy[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Drug hypersensitivity[1]	0 (0.00%)	0 (0.00%)	2 (0.09%)	0 (0.00%)	0 (0.00%)
Hypersensitivity[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Infections and infestations					
Abdominal abscess[1]	2 (0.09%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Abdominal infection[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Abdominal sepsis[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (0.06%)	0 (0.00%)
Abscess intestinal[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Abscess jaw[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Abscess limb[1]	4 (0.18%)	1 (0.04%)	3 (0.14%)	3 (0.09%)	0 (0.00%)
Abscess neck[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	2 (0.06%)	0 (0.00%)
Abscess oral[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)

Abscess soft tissue[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Acute hepatitis B[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Acute sinusitis[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Anal abscess[1]	1 (0.04%)	1 (0.04%)	1 (0.05%)	2 (0.06%)	2 (0.03%)
Appendicitis[1]	3 (0.13%)	4 (0.18%)	6 (0.28%)	4 (0.12%)	3 (0.05%)
Appendicitis perforated[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	1 (0.02%)
Arthritis bacterial[1]	1 (0.04%)	1 (0.04%)	0 (0.00%)	1 (0.03%)	1 (0.02%)
Arthritis infective[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	3 (0.09%)	1 (0.02%)
Atypical pneumonia[1]	0 (0.00%)	2 (0.09%)	0 (0.00%)	2 (0.06%)	0 (0.00%)
Bacteraemia[1]	3 (0.13%)	1 (0.04%)	1 (0.05%)	1 (0.03%)	2 (0.03%)
Bacterial disease carrier[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Bacterial pyelonephritis[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	1 (0.02%)
Bacterial sepsis[1]	1 (0.04%)	2 (0.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Bacteroides infection[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Bartholin's abscess[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Beta haemolytic streptococcal infection[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Bone abscess[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Bronchitis[1]	10 (0.44%)	9 (0.39%)	6 (0.28%)	14 (0.42%)	10 (0.17%)
Bronchitis bacterial[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	2 (0.06%)	0 (0.00%)
Bursitis infective[1]	0 (0.00%)	1 (0.04%)	1 (0.05%)	1 (0.03%)	1 (0.02%)
Bursitis infective staphylococcal[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Campylobacter gastroenteritis[1]	2 (0.09%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Campylobacter infection[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Candida infection[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)

Carbuncle[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Cellulitis[1]	29 (1.28%)	32 (1.40%)	19 (0.88%)	27 (0.81%)	22 (0.38%)
Cellulitis gangrenous[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Cellulitis of male external genital organ[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Cellulitis staphylococcal[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Central nervous system infection[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Chikungunya virus infection[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (0.06%)	0 (0.00%)
Cholangitis infective[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Cholecystitis infective[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	1 (0.02%)
Chorioretinitis[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Chronic sinusitis[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Chronic tonsillitis[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Clostridial infection[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Clostridium difficile colitis[1]	3 (0.13%)	1 (0.04%)	4 (0.18%)	1 (0.03%)	1 (0.02%)
Clostridium difficile infection[1]	2 (0.09%)	1 (0.04%)	2 (0.09%)	1 (0.03%)	0 (0.00%)
Colonic abscess[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Conjunctivitis[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Corona virus infection[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Creutzfeldt-Jakob disease[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Cystitis[1]	2 (0.09%)	0 (0.00%)	3 (0.14%)	1 (0.03%)	1 (0.02%)
Dengue fever[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Device related infection[1]	0 (0.00%)	1 (0.04%)	2 (0.09%)	4 (0.12%)	1 (0.02%)
Device related sepsis[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	1 (0.03%)	0 (0.00%)
Diabetic foot infection[1]	2 (0.09%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	2 (0.03%)

Diabetic gangrene[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	2 (0.06%)	1 (0.02%)
Diarrhoea infectious[1]	0 (0.00%)	1 (0.04%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Diverticulitis[1]	8 (0.35%)	9 (0.39%)	8 (0.37%)	13 (0.39%)	6 (0.10%)
Ear infection[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Empyema[1]	2 (0.09%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Endocarditis[1]	1 (0.04%)	1 (0.04%)	2 (0.09%)	2 (0.06%)	1 (0.02%)
Endocarditis bacterial[1]	2 (0.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Enteritis infectious[1]	0 (0.00%)	0 (0.00%)	3 (0.14%)	2 (0.06%)	0 (0.00%)
Epididymitis[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	1 (0.02%)
Epiglottitis[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Erysipelas[1]	6 (0.27%)	12 (0.53%)	6 (0.28%)	9 (0.27%)	13 (0.23%)
Escherichia sepsis[1]	0 (0.00%)	1 (0.04%)	2 (0.09%)	3 (0.09%)	0 (0.00%)
Escherichia urinary tract infection[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	1 (0.02%)
External ear cellulitis[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Folliculitis[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Fungal skin infection[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Furuncle[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Gallbladder abscess[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Gallbladder empyema[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Gangrene[1]	1 (0.04%)	1 (0.04%)	5 (0.23%)	0 (0.00%)	2 (0.03%)
Gastritis viral[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Gastroenteritis[1]	6 (0.27%)	5 (0.22%)	6 (0.28%)	8 (0.24%)	4 (0.07%)
Gastroenteritis clostridial[1]	2 (0.09%)	0 (0.00%)	1 (0.05%)	1 (0.03%)	0 (0.00%)
Gastroenteritis rotavirus[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Gastroenteritis salmonella[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	1 (0.02%)

Gastroenteritis viral[1]	2 (0.09%)	0 (0.00%)	2 (0.09%)	1 (0.03%)	0 (0.00%)
Gastrointestinal bacterial infection[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Gastrointestinal infection[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Gastrointestinal viral infection[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Groin infection[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Haematoma infection[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Haemophilus infection[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Haemophilus sepsis[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Haemorrhagic pneumonia[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Helicobacter infection[1]	1 (0.04%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hepatic amoebiasis[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hepatitis viral[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Herpes ophthalmic[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Herpes zoster[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	4 (0.12%)	1 (0.02%)
Human ehrlichiosis[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Hypopyon[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Implant site abscess[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Implant site infection[1]	0 (0.00%)	1 (0.04%)	2 (0.09%)	0 (0.00%)	1 (0.02%)
Incision site cellulitis[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Incision site infection[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Infected bite[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Infected cyst[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Infected skin ulcer[1]	0 (0.00%)	1 (0.04%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Infection[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Infectious colitis[1]	1 (0.04%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Infectious pleural effusion[1]	3 (0.13%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Infective exacerbation of chronic obstructive airways disease[1]	5 (0.22%)	0 (0.00%)	2 (0.09%)	3 (0.09%)	1 (0.02%)
Infective spondylitis[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Influenza[1]	4 (0.18%)	6 (0.26%)	2 (0.09%)	3 (0.09%)	9 (0.16%)
Intervertebral discitis[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Joint abscess[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (0.06%)	0 (0.00%)
Labyrinthitis[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Leptospirosis[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Liver abscess[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Localised infection[1]	2 (0.09%)	2 (0.09%)	3 (0.14%)	5 (0.15%)	4 (0.07%)
Lower respiratory tract infection[1]	3 (0.13%)	2 (0.09%)	4 (0.18%)	4 (0.12%)	4 (0.07%)
Lung abscess[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Lung infection[1]	2 (0.09%)	0 (0.00%)	3 (0.14%)	1 (0.03%)	1 (0.02%)
Lyme disease[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Lymphangitis[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Malaria[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Mastoiditis[1]	2 (0.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Mediastinitis[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Medical device site infection[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Meningitis[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Meningitis bacterial[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Meningococcal sepsis[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Mesenteric abscess[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)

Metapneumovirus infection[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	1 (0.02%)
Muscle abscess[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Mycobacterial infection[1]	1 (0.04%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Mycobacterium avium complex infection[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Necrotising fasciitis[1]	0 (0.00%)	2 (0.09%)	1 (0.05%)	1 (0.03%)	1 (0.02%)
Neutropenic sepsis[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Oesophageal candidiasis[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Orchitis[1]	1 (0.04%)	0 (0.00%)	2 (0.09%)	0 (0.00%)	0 (0.00%)
Osteomyelitis[1]	4 (0.18%)	3 (0.13%)	3 (0.14%)	4 (0.12%)	10 (0.17%)
Osteomyelitis bacterial[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Osteomyelitis blastomyces[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Otitis externa[1]	0 (0.00%)	1 (0.04%)	2 (0.09%)	0 (0.00%)	0 (0.00%)
Otitis media[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Otitis media acute[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Otitis media chronic[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pancreatic abscess[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Parainfluenzae virus infection[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Parametritis[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Paronychia[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Parotitis[1]	1 (0.04%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pelvic abscess[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Perichondritis[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Perineal abscess[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	1 (0.03%)	1 (0.02%)
Periodontitis[1]	1 (0.04%)	1 (0.04%)	0 (0.00%)	2 (0.06%)	0 (0.00%)

Periorbital cellulitis[1]	0 (0.00%)	0 (0.00%)	2 (0.09%)	0 (0.00%)	1 (0.02%)
Perirectal abscess[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Peritoneal abscess[1]	1 (0.04%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Peritonitis[1]	2 (0.09%)	1 (0.04%)	3 (0.14%)	2 (0.06%)	2 (0.03%)
Pharyngeal abscess[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Pharyngitis[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Pharyngitis streptococcal[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Pilonidal cyst[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (0.03%)
Pneumococcal sepsis[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pneumonia[1]	67 (2.96%)	60 (2.63%)	53 (2.44%)	83 (2.48%)	70 (1.21%)
Pneumonia bacterial[1]	1 (0.04%)	1 (0.04%)	0 (0.00%)	3 (0.09%)	1 (0.02%)
Pneumonia escherichia[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Pneumonia haemophilus[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pneumonia klebsiella[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Pneumonia legionella[1]	0 (0.00%)	1 (0.04%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Pneumonia necrotising[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pneumonia pneumococcal[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (0.03%)
Pneumonia pseudomonal[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pneumonia staphylococcal[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (0.06%)	0 (0.00%)
Post procedural cellulitis[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Post procedural infection[1]	1 (0.04%)	2 (0.09%)	0 (0.00%)	0 (0.00%)	4 (0.07%)
Post procedural sepsis[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Postoperative abscess[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Postoperative wound infection[1]	2 (0.09%)	2 (0.09%)	2 (0.09%)	1 (0.03%)	4 (0.07%)
Proctitis infectious[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)

Propionibacterium infection[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pseudomembranous colitis[1]	1 (0.04%)	0 (0.00%)	2 (0.09%)	0 (0.00%)	0 (0.00%)
Pseudomonal bacteraemia[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Pseudomonas bronchitis[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Pseudomonas infection[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	1 (0.03%)	0 (0.00%)
Psoas abscess[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pulmonary sepsis[1]	1 (0.04%)	2 (0.09%)	2 (0.09%)	1 (0.03%)	2 (0.03%)
Pulmonary tuberculosis[1]	1 (0.04%)	2 (0.09%)	1 (0.05%)	1 (0.03%)	0 (0.00%)
Pyelitis[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pyelonephritis[1]	3 (0.13%)	1 (0.04%)	2 (0.09%)	5 (0.15%)	2 (0.03%)
Pyelonephritis acute[1]	1 (0.04%)	5 (0.22%)	1 (0.05%)	3 (0.09%)	0 (0.00%)
Pyoderma[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Pyuria[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Renal abscess[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (0.05%)
Respiratory tract infection[1]	2 (0.09%)	7 (0.31%)	0 (0.00%)	7 (0.21%)	2 (0.03%)
Respiratory tract infection viral[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (0.06%)	0 (0.00%)
Rhinitis[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Rubella[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Salmonellosis[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Scrotal abscess[1]	1 (0.04%)	0 (0.00%)	1 (0.05%)	1 (0.03%)	0 (0.00%)
Scrub typhus[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (0.03%)
Sepsis[1]	19 (0.84%)	25 (1.09%)	15 (0.69%)	19 (0.57%)	22 (0.38%)
Sepsis syndrome[1]	1 (0.04%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Septic embolus[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Septic necrosis[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Septic shock[1]	6 (0.27%)	8 (0.35%)	6 (0.28%)	11 (0.33%)	3 (0.05%)
Sialoadenitis[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Sinusitis[1]	3 (0.13%)	1 (0.04%)	0 (0.00%)	2 (0.06%)	3 (0.05%)
Sinusitis fungal[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Staphylococcal abscess[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Staphylococcal bacteraemia[1]	2 (0.09%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	3 (0.05%)
Staphylococcal infection[1]	1 (0.04%)	1 (0.04%)	2 (0.09%)	1 (0.03%)	2 (0.03%)
Staphylococcal mediastinitis[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Staphylococcal sepsis[1]	1 (0.04%)	0 (0.00%)	1 (0.05%)	2 (0.06%)	0 (0.00%)
Streptococcal bacteraemia[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	2 (0.06%)	0 (0.00%)
Streptococcal sepsis[1]	2 (0.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Subcutaneous abscess[1]	4 (0.18%)	3 (0.13%)	2 (0.09%)	3 (0.09%)	0 (0.00%)
Subdiaphragmatic abscess[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Subdural empyema[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Testicular abscess[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Tetanus[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Tonsillitis[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	1 (0.02%)
Tooth abscess[1]	1 (0.04%)	0 (0.00%)	1 (0.05%)	1 (0.03%)	1 (0.02%)
Tracheobronchitis[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	1 (0.03%)	1 (0.02%)
Tuberculosis[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Upper respiratory tract infection[1]	0 (0.00%)	0 (0.00%)	2 (0.09%)	0 (0.00%)	0 (0.00%)
Urinary tract infection[1]	13 (0.57%)	11 (0.48%)	10 (0.46%)	21 (0.63%)	19 (0.33%)

Urinary tract infection bacterial[1]	3 (0.13%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Urinary tract infection enterococcal[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Urinary tract infection fungal[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Urinary tract infection pseudomonal[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Urosepsis[1]	4 (0.18%)	4 (0.18%)	5 (0.23%)	3 (0.09%)	7 (0.12%)
Vestibular neuronitis[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Viral cardiomyopathy[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Viral diarrhoea[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Viral infection[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	1 (0.02%)
Viral upper respiratory tract infection[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Vulval abscess[1]	0 (0.00%)	1 (0.04%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Wound infection[1]	0 (0.00%)	3 (0.13%)	4 (0.18%)	0 (0.00%)	2 (0.03%)
Wound infection bacterial[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Wound infection staphylococcal[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Wound sepsis[1]	2 (0.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Injury, poisoning and procedural complications					
Abdominal injury[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Accident[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Accidental overdose[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Acetabulum fracture[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Alcohol poisoning[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (0.06%)	0 (0.00%)
Anaemia postoperative[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)

Anastomotic leak[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Animal bite[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Ankle fracture[1]	5 (0.22%)	0 (0.00%)	3 (0.14%)	4 (0.12%)	4 (0.07%)
Arterial injury[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Arthropod sting[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Asbestosis[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Bone contusion[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Brain contusion[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Cardiac function disturbance postoperative[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Central cord syndrome[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Cervical vertebral fracture[1]	1 (0.04%)	1 (0.04%)	1 (0.05%)	2 (0.06%)	2 (0.03%)
Chest injury[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	1 (0.03%)	0 (0.00%)
Clavicle fracture[1]	2 (0.09%)	0 (0.00%)	0 (0.00%)	2 (0.06%)	2 (0.03%)
Closed globe injury[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Comminuted fracture[1]	1 (0.04%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Concussion[1]	1 (0.04%)	1 (0.04%)	1 (0.05%)	1 (0.03%)	1 (0.02%)
Contusion[1]	2 (0.09%)	1 (0.04%)	3 (0.14%)	5 (0.15%)	0 (0.00%)
Coronary artery restenosis[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Craniocerebral injury[1]	1 (0.04%)	0 (0.00%)	1 (0.05%)	1 (0.03%)	0 (0.00%)
Dural tear[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Epicondylitis[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Face injury[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Facial bones fracture[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (0.06%)	0 (0.00%)
Fall[1]	3 (0.13%)	1 (0.04%)	2 (0.09%)	3 (0.09%)	9 (0.16%)
Femoral neck fracture[1]	3 (0.13%)	5 (0.22%)	2 (0.09%)	5 (0.15%)	2 (0.03%)

Femur fracture[1]	1 (0.04%)	3 (0.13%)	2 (0.09%)	5 (0.15%)	4 (0.07%)
Foot fracture[1]	2 (0.09%)	0 (0.00%)	1 (0.05%)	1 (0.03%)	1 (0.02%)
Forearm fracture[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Foreign body[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Fracture displacement[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Gallbladder injury[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Gastrointestinal stoma complication[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Gastrointestinal stoma necrosis[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Gun shot wound[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Hand fracture[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (0.06%)	0 (0.00%)
Head injury[1]	0 (0.00%)	1 (0.04%)	1 (0.05%)	3 (0.09%)	2 (0.03%)
Hip fracture[1]	1 (0.04%)	2 (0.09%)	3 (0.14%)	6 (0.18%)	2 (0.03%)
Humerus fracture[1]	0 (0.00%)	1 (0.04%)	1 (0.05%)	4 (0.12%)	2 (0.03%)
Incision site haemorrhage[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Incision site pain[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Incisional hernia[1]	0 (0.00%)	2 (0.09%)	1 (0.05%)	3 (0.09%)	2 (0.03%)
Incisional hernia, obstructive[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Injury[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	1 (0.03%)	1 (0.02%)
Intentional overdose[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	1 (0.03%)	0 (0.00%)
Intentional product misuse[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Jaw fracture[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Joint dislocation[1]	4 (0.18%)	0 (0.00%)	3 (0.14%)	3 (0.09%)	0 (0.00%)
Joint injury[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Laceration[1]	1 (0.04%)	1 (0.04%)	1 (0.05%)	1 (0.03%)	0 (0.00%)

Ligament injury[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Ligament rupture[1]	0 (0.00%)	0 (0.00%)	2 (0.09%)	0 (0.00%)	1 (0.02%)
Ligament sprain[1]	0 (0.00%)	1 (0.04%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Limb injury[1]	1 (0.04%)	2 (0.09%)	2 (0.09%)	0 (0.00%)	1 (0.02%)
Limb traumatic amputation[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	1 (0.03%)	0 (0.00%)
Lower limb fracture[1]	1 (0.04%)	2 (0.09%)	1 (0.05%)	3 (0.09%)	1 (0.02%)
Lumbar vertebral fracture[1]	2 (0.09%)	1 (0.04%)	0 (0.00%)	3 (0.09%)	2 (0.03%)
Meniscus injury[1]	0 (0.00%)	3 (0.13%)	5 (0.23%)	8 (0.24%)	0 (0.00%)
Multiple fractures[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Multiple injuries[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Muscle contusion[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Muscle rupture[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (0.06%)	0 (0.00%)
Muscle strain[1]	0 (0.00%)	2 (0.09%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Musculoskeletal foreign body[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Nerve injury[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Overdose[1]	2 (0.09%)	1 (0.04%)	2 (0.09%)	2 (0.06%)	0 (0.00%)
Patella fracture[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Pelvic fracture[1]	1 (0.04%)	1 (0.04%)	2 (0.09%)	1 (0.03%)	0 (0.00%)
Peripheral artery restenosis[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Periprosthetic fracture[1]	0 (0.00%)	1 (0.04%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Perirenal haematoma[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pneumoconiosis[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pneumothorax traumatic[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Post procedural complication[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	2 (0.03%)

Post procedural discharge[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Post procedural fever[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Post procedural haematoma[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (0.03%)
Post procedural haemorrhage[1]	3 (0.13%)	1 (0.04%)	0 (0.00%)	3 (0.09%)	0 (0.00%)
Postoperative hernia[1]	1 (0.04%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Postoperative wound complication[1]	1 (0.04%)	0 (0.00%)	2 (0.09%)	0 (0.00%)	0 (0.00%)
Procedural complication[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Procedural intestinal perforation[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Procedural pain[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Pubis fracture[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Radiation mucositis[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Radius fracture[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	3 (0.09%)	1 (0.02%)
Rib fracture[1]	4 (0.18%)	3 (0.13%)	3 (0.14%)	7 (0.21%)	0 (0.00%)
Road traffic accident[1]	4 (0.18%)	1 (0.04%)	2 (0.09%)	3 (0.09%)	3 (0.05%)
Scapula fracture[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Scratch[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Seroma[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Skeletal injury[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Skin laceration[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Skull fracture[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Spinal column injury[1]	1 (0.04%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Spinal compression fracture[1]	0 (0.00%)	2 (0.09%)	0 (0.00%)	5 (0.15%)	1 (0.02%)
Spinal cord injury[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	1 (0.02%)

Spinal cord injury cervical[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Spinal fracture[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Splenic rupture[1]	2 (0.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Stab wound[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Sternal fracture[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Stress fracture[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Subarachnoid haemorrhage[1]	2 (0.09%)	2 (0.09%)	1 (0.05%)	2 (0.06%)	0 (0.00%)
Subdural haematoma[1]	2 (0.09%)	4 (0.18%)	4 (0.18%)	5 (0.15%)	5 (0.09%)
Subdural haemorrhage[1]	2 (0.09%)	1 (0.04%)	1 (0.05%)	0 (0.00%)	1 (0.02%)
Tendon injury[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Tendon rupture[1]	4 (0.18%)	2 (0.09%)	0 (0.00%)	0 (0.00%)	2 (0.03%)
Thermal burn[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Thoracic vertebral fracture[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Tibia fracture[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	3 (0.09%)	2 (0.03%)
Tooth fracture[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Toxicity to various agents[1]	2 (0.09%)	0 (0.00%)	2 (0.09%)	2 (0.06%)	0 (0.00%)
Tracheal haemorrhage[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Traumatic amputation[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Traumatic arthritis[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Traumatic haematoma[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Traumatic haemothorax[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Traumatic intracranial haemorrhage[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Ulna fracture[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Upper limb fracture[1]	1 (0.04%)	1 (0.04%)	2 (0.09%)	3 (0.09%)	2 (0.03%)

Urinary retention postoperative[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Vascular graft complication[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Vascular pseudoaneurysm[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (0.06%)	1 (0.02%)
Vascular pseudoaneurysm ruptured[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Wound dehiscence[1]	1 (0.04%)	1 (0.04%)	1 (0.05%)	1 (0.03%)	0 (0.00%)
Wound secretion[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Wrist fracture[1]	0 (0.00%)	2 (0.09%)	1 (0.05%)	1 (0.03%)	0 (0.00%)
Investigations					
Alanine aminotransferase increased[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Anticoagulation drug level above therapeutic[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Aspartate aminotransferase increased[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Blood creatine phosphokinase increased[1]	1 (0.04%)	1 (0.04%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Blood creatine phosphokinase MB increased[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Blood creatinine increased[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Blood glucose increased[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Blood magnesium decreased[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Blood pressure increased[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Blood urine present[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Body mass index decreased[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Central venous pressure increased[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Chest X-ray abnormal[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (0.06%)	0 (0.00%)
Clostridium test positive[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Ejection fraction decreased[1]	1 (0.04%)	1 (0.04%)	1 (0.05%)	1 (0.03%)	0 (0.00%)
Haemoglobin decreased[1]	2 (0.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hepatic enzyme increased[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (0.09%)	0 (0.00%)
Human metapneumovirus test positive[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Imaging procedure abnormal[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
International normalised ratio decreased[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
International normalised ratio increased[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Liver function test abnormal[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Liver function test increased[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	1 (0.03%)	0 (0.00%)
N-terminal prohormone brain natriuretic peptide increased[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Oxygen saturation decreased[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Platelet count decreased[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Quality of life decreased[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Scan myocardial perfusion abnormal[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (0.03%)

Troponin increased[1]	1 (0.04%)	1 (0.04%)	0 (0.00%)	1 (0.03%)	2 (0.03%)
Troponin T increased[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Volume blood decreased[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Weight decreased[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	2 (0.03%)
Weight increased[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
White blood cell count increased[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Metabolism and nutrition disorders					
Acidosis[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Cachexia[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Dehydration[1]	5 (0.22%)	6 (0.26%)	6 (0.28%)	6 (0.18%)	8 (0.14%)
Diabetes mellitus[1]	3 (0.13%)	10 (0.44%)	1 (0.05%)	11 (0.33%)	8 (0.14%)
Diabetes mellitus inadequate control[1]	2 (0.09%)	1 (0.04%)	7 (0.32%)	3 (0.09%)	1 (0.02%)
Diabetes with hyperosmolarity[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Diabetic complication[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Diabetic ketoacidosis[1]	1 (0.04%)	2 (0.09%)	1 (0.05%)	1 (0.03%)	0 (0.00%)
Diabetic metabolic decompensation[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (0.03%)
Electrolyte imbalance[1]	0 (0.00%)	1 (0.04%)	1 (0.05%)	0 (0.00%)	1 (0.02%)
Fluid overload[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Gout[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	3 (0.09%)	0 (0.00%)
Hyperammonaemia[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Hypercalcaemia[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hyperchloraemia[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hyperglycaemia[1]	3 (0.13%)	4 (0.18%)	3 (0.14%)	6 (0.18%)	4 (0.07%)

Hyperglycaemic hyperosmolar nonketotic syndrome[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	1 (0.02%)
Hyperkalaemia[1]	3 (0.13%)	4 (0.18%)	3 (0.14%)	3 (0.09%)	7 (0.12%)
Hypermagnesaemia[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Hyperuricaemia[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Hypoalbuminaemia[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hypocalcaemia[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Hypoglycaemia[1]	4 (0.18%)	4 (0.18%)	3 (0.14%)	9 (0.27%)	4 (0.07%)
Hypokalaemia[1]	1 (0.04%)	1 (0.04%)	3 (0.14%)	9 (0.27%)	4 (0.07%)
Hypomagnesaemia[1]	2 (0.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hyponatraemia[1]	0 (0.00%)	2 (0.09%)	4 (0.18%)	2 (0.06%)	4 (0.07%)
Hypovolaemia[1]	1 (0.04%)	0 (0.00%)	2 (0.09%)	1 (0.03%)	0 (0.00%)
Insulin resistant diabetes[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Insulin-requiring type 2 diabetes mellitus[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Ketoacidosis[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Lactic acidosis[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Malnutrition[1]	1 (0.04%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Metabolic acidosis[1]	1 (0.04%)	2 (0.09%)	2 (0.09%)	1 (0.03%)	0 (0.00%)
Obesity[1]	5 (0.22%)	1 (0.04%)	1 (0.05%)	2 (0.06%)	4 (0.07%)
Type 1 diabetes mellitus[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Type 2 diabetes mellitus[1]	3 (0.13%)	2 (0.09%)	1 (0.05%)	1 (0.03%)	4 (0.07%)
Musculoskeletal and connective tissue disorders					
Arthralgia[1]	2 (0.09%)	5 (0.22%)	2 (0.09%)	4 (0.12%)	6 (0.10%)
Arthritis[1]	2 (0.09%)	0 (0.00%)	0 (0.00%)	3 (0.09%)	2 (0.03%)

Arthritis reactive[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Arthropathy[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Back pain[1]	4 (0.18%)	8 (0.35%)	5 (0.23%)	7 (0.21%)	6 (0.10%)
Bone pain[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Bursitis[1]	0 (0.00%)	1 (0.04%)	2 (0.09%)	4 (0.12%)	0 (0.00%)
Cervical spinal stenosis[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	3 (0.05%)
Chondromalacia[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Chondropathy[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Compartment syndrome[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	1 (0.02%)
Costochondritis[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Dactylitis[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Dupuytren's contracture[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Exostosis[1]	2 (0.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Fasciitis[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Finger deformity[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Flank pain[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Foot deformity[1]	1 (0.04%)	1 (0.04%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Fracture malunion[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Gouty arthritis[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Gouty tophus[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Groin pain[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Haemarthrosis[1]	1 (0.04%)	2 (0.09%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Immunoglobulin G4 related disease[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Intervertebral disc calcification[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)

Intervertebral disc compression[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Intervertebral disc degeneration[1]	1 (0.04%)	1 (0.04%)	2 (0.09%)	3 (0.09%)	0 (0.00%)
Intervertebral disc disorder[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Intervertebral disc displacement[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Intervertebral disc protrusion[1]	4 (0.18%)	2 (0.09%)	6 (0.28%)	10 (0.30%)	6 (0.10%)
Jaw cyst[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Joint instability[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Joint swelling[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Lumbar spinal stenosis[1]	1 (0.04%)	4 (0.18%)	1 (0.05%)	5 (0.15%)	5 (0.09%)
Meniscal degeneration[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Metatarsalgia[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Muscle atrophy[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Muscle haemorrhage[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Muscle spasms[1]	1 (0.04%)	1 (0.04%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Muscle swelling[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Muscular weakness[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	1 (0.03%)	2 (0.03%)
Musculoskeletal chest pain[1]	3 (0.13%)	3 (0.13%)	5 (0.23%)	5 (0.15%)	2 (0.03%)
Musculoskeletal pain[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	4 (0.12%)	4 (0.07%)
Myalgia[1]	1 (0.04%)	2 (0.09%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Myofascial pain syndrome[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Neck pain[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	2 (0.03%)
Neuropathic arthropathy[1]	0 (0.00%)	1 (0.04%)	1 (0.05%)	0 (0.00%)	0 (0.00%)

Osteitis[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Osteoarthritis[1]	19 (0.84%)	21 (0.92%)	18 (0.83%)	51 (1.52%)	26 (0.45%)
Osteochondrosis[1]	1 (0.04%)	2 (0.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Osteolysis[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Osteonecrosis[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Osteoporosis[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Osteoporotic fracture[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Pain in extremity[1]	5 (0.22%)	1 (0.04%)	1 (0.05%)	2 (0.06%)	0 (0.00%)
Pain in jaw[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pathological fracture[1]	2 (0.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Polyarthritis[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Polymyalgia rheumatica[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Rhabdomyolysis[1]	2 (0.09%)	1 (0.04%)	2 (0.09%)	3 (0.09%)	3 (0.05%)
Rheumatoid arthritis[1]	0 (0.00%)	0 (0.00%)	3 (0.14%)	0 (0.00%)	0 (0.00%)
Rotator cuff syndrome[1]	2 (0.09%)	0 (0.00%)	2 (0.09%)	5 (0.15%)	3 (0.05%)
Shoulder deformity[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Soft tissue mass[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Spinal column stenosis[1]	6 (0.27%)	2 (0.09%)	4 (0.18%)	4 (0.12%)	4 (0.07%)
Spinal deformity[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Spinal osteoarthritis[1]	2 (0.09%)	2 (0.09%)	1 (0.05%)	1 (0.03%)	0 (0.00%)
Spinal pain[1]	3 (0.13%)	2 (0.09%)	3 (0.14%)	5 (0.15%)	3 (0.05%)
Spondylitis[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Spondylolisthesis[1]	0 (0.00%)	0 (0.00%)	2 (0.09%)	2 (0.06%)	1 (0.02%)
Synovial cyst[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Synovitis[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	2 (0.06%)	0 (0.00%)
Tendonitis[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)

Tenosynovitis[1]	0 (0.00%)	0 (0.00%)	2 (0.09%)	0 (0.00%)	1 (0.02%)
Trigger finger[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Vertebral foraminal stenosis[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Vertebral wedging[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)					
Abdominal neoplasm[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	1 (0.02%)
Acute leukaemia[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Acute myeloid leukaemia[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Adenocarcinoma[1]	0 (0.00%)	1 (0.04%)	3 (0.14%)	2 (0.06%)	0 (0.00%)
Adenocarcinoma gastric[1]	0 (0.00%)	2 (0.09%)	2 (0.09%)	3 (0.09%)	0 (0.00%)
Adenocarcinoma of colon[1]	3 (0.13%)	1 (0.04%)	2 (0.09%)	5 (0.15%)	3 (0.05%)
Adenocarcinoma pancreas[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Adenoma benign[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Adenosquamous cell lung cancer[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Adrenal adenoma[1]	1 (0.04%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	1 (0.02%)
Adrenal neoplasm[1]	1 (0.04%)	1 (0.04%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Angiolipoma[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	2 (0.06%)	0 (0.00%)
Angiosarcoma[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Basal cell carcinoma[1]	14 (0.62%)	18 (0.79%)	18 (0.83%)	21 (0.63%)	30 (0.52%)
B-cell lymphoma[1]	2 (0.09%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Benign cardiac neoplasm[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Benign gastric neoplasm[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Benign lung neoplasm[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)

Benign neoplasm[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Benign neoplasm of bladder[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Benign neoplasm of scrotum[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Benign neoplasm of skin[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Benign salivary gland neoplasm[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Benign small intestinal neoplasm[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Benign urinary tract neoplasm[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Bile duct cancer[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Bladder cancer[1]	5 (0.22%)	5 (0.22%)	3 (0.14%)	5 (0.15%)	2 (0.03%)
Bladder neoplasm[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (0.06%)	3 (0.05%)
Bladder papilloma[1]	1 (0.04%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Bladder transitional cell carcinoma[1]	3 (0.13%)	2 (0.09%)	2 (0.09%)	0 (0.00%)	0 (0.00%)
Bone cancer[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Bone cancer metastatic[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Bowen's disease[1]	3 (0.13%)	1 (0.04%)	2 (0.09%)	3 (0.09%)	1 (0.02%)
Brain neoplasm[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Brain neoplasm malignant[1]	0 (0.00%)	2 (0.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Breast cancer[1]	4 (0.18%)	0 (0.00%)	5 (0.23%)	2 (0.06%)	4 (0.07%)
Breast cancer female[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Breast cancer metastatic[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Brenner tumour[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Bronchial carcinoma[1]	1 (0.04%)	1 (0.04%)	0 (0.00%)	3 (0.09%)	3 (0.05%)

Carcinoid tumour of the gastrointestinal tract[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Cervix carcinoma[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Cholangiocarcinoma[1]	0 (0.00%)	2 (0.09%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Chronic lymphocytic leukaemia[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Clear cell renal cell carcinoma[1]	1 (0.04%)	1 (0.04%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Colon adenoma[1]	1 (0.04%)	1 (0.04%)	0 (0.00%)	1 (0.03%)	2 (0.03%)
Colon cancer[1]	3 (0.13%)	4 (0.18%)	5 (0.23%)	6 (0.18%)	3 (0.05%)
Colon neoplasm[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Colorectal adenocarcinoma[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Colorectal cancer[1]	2 (0.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Diffuse large B-cell lymphoma[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	1 (0.02%)
Diffuse large B-cell lymphoma stage IV[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Ductal adenocarcinoma of pancreas[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Endometrial adenocarcinoma[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Endometrial cancer[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Endometrial cancer stage III[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Extranodal marginal zone B-cell lymphoma (MALT type)[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Fibroma[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Fibrous histiocytoma[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Gallbladder adenocarcinoma[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Gastric adenoma[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Gastric cancer[1]	5 (0.22%)	1 (0.04%)	1 (0.05%)	5 (0.15%)	5 (0.09%)
Gastrointestinal carcinoma[1]	1 (0.04%)	0 (0.00%)	2 (0.09%)	0 (0.00%)	0 (0.00%)
Gastrointestinal tract adenoma[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Glioblastoma[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Glioma[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Haemangioma[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Hepatic cancer[1]	0 (0.00%)	1 (0.04%)	1 (0.05%)	0 (0.00%)	1 (0.02%)
Hepatic cancer metastatic[1]	1 (0.04%)	1 (0.04%)	0 (0.00%)	3 (0.09%)	0 (0.00%)
Hepatic cancer stage IV[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hepatic neoplasm[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (0.03%)
Hepatocellular carcinoma[1]	1 (0.04%)	2 (0.09%)	1 (0.05%)	2 (0.06%)	0 (0.00%)
Hodgkin's disease[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hypergammaglobulinaemia benign monoclonal[1]	1 (0.04%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Inflammatory pseudotumour[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Intestinal adenocarcinoma[1]	0 (0.00%)	1 (0.04%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Intraductal proliferative breast lesion[1]	0 (0.00%)	1 (0.04%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Invasive breast carcinoma[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Invasive ductal breast carcinoma[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	2 (0.06%)	0 (0.00%)
Keratoacanthoma[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	3 (0.09%)	0 (0.00%)

Large intestine benign neoplasm[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Laryngeal cancer[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Laryngeal squamous cell carcinoma[1]	1 (0.04%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Lentigo maligna[1]	1 (0.04%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Leukaemia[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Lip and/or oral cavity cancer[1]	0 (0.00%)	2 (0.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Lip squamous cell carcinoma[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Lipoma[1]	2 (0.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Liposarcoma[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Lung adenocarcinoma[1]	0 (0.00%)	3 (0.13%)	3 (0.14%)	7 (0.21%)	1 (0.02%)
Lung adenocarcinoma stage III[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Lung adenocarcinoma stage IV[1]	0 (0.00%)	1 (0.04%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Lung cancer metastatic[1]	0 (0.00%)	2 (0.09%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Lung carcinoma cell type unspecified recurrent[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Lung carcinoma cell type unspecified stage III[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Lung neoplasm[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	2 (0.06%)	2 (0.03%)
Lung neoplasm malignant[1]	4 (0.18%)	9 (0.39%)	9 (0.41%)	25 (0.75%)	14 (0.24%)
Lung squamous cell carcinoma metastatic[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (0.06%)	0 (0.00%)
Lymphoma[1]	1 (0.04%)	2 (0.09%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Lymphoproliferative disorder[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Malignant fibrous histiocytoma[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Malignant mediastinal neoplasm[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Malignant melanoma[1]	2 (0.09%)	5 (0.22%)	3 (0.14%)	2 (0.06%)	4 (0.07%)
Malignant melanoma in situ[1]	2 (0.09%)	0 (0.00%)	2 (0.09%)	0 (0.00%)	1 (0.02%)
Malignant neoplasm of pleura[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Malignant neoplasm of unknown primary site[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Malignant peritoneal neoplasm[1]	0 (0.00%)	1 (0.04%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Malignant pleural effusion[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	2 (0.03%)
Mantle cell lymphoma[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Medullary thyroid cancer[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Meningioma[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	1 (0.02%)
Meningioma benign[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Metastases to adrenals[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Metastases to bone[1]	0 (0.00%)	0 (0.00%)	2 (0.09%)	2 (0.06%)	1 (0.02%)
Metastases to central nervous system[1]	0 (0.00%)	2 (0.09%)	1 (0.05%)	1 (0.03%)	1 (0.02%)
Metastases to kidney[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	1 (0.03%)	0 (0.00%)
Metastases to liver[1]	2 (0.09%)	5 (0.22%)	1 (0.05%)	4 (0.12%)	2 (0.03%)
Metastases to lung[1]	0 (0.00%)	2 (0.09%)	5 (0.23%)	2 (0.06%)	2 (0.03%)
Metastases to lymph nodes[1]	1 (0.04%)	0 (0.00%)	2 (0.09%)	1 (0.03%)	0 (0.00%)
Metastases to pelvis[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Metastases to pleura[1]	1 (0.04%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)

Metastases to rectum[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Metastases to spine[1]	2 (0.09%)	1 (0.04%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Metastatic bronchial carcinoma[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Metastatic malignant melanoma[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Metastatic renal cell carcinoma[1]	0 (0.00%)	2 (0.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Metastatic squamous cell carcinoma[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Monoclonal gammopathy[1]	0 (0.00%)	1 (0.04%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Mucinous adenocarcinoma of appendix[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Mycosis fungoides[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Myelodysplastic syndrome[1]	2 (0.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Myelofibrosis[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Nasal cavity cancer[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Neoplasm malignant[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (0.09%)	0 (0.00%)
Neoplasm skin[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (0.06%)	0 (0.00%)
Neuroendocrine breast tumour[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Neuroendocrine carcinoma[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Non-Hodgkin's lymphoma[1]	1 (0.04%)	0 (0.00%)	1 (0.05%)	3 (0.09%)	0 (0.00%)
Non-Hodgkin's lymphoma refractory[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Non-small cell lung cancer[1]	2 (0.09%)	1 (0.04%)	3 (0.14%)	1 (0.03%)	3 (0.05%)
Non-small cell lung cancer metastatic[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)

Non-small cell lung cancer stage IV[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Oesophageal adenocarcinoma[1]	0 (0.00%)	2 (0.09%)	1 (0.05%)	2 (0.06%)	1 (0.02%)
Oesophageal adenocarcinoma stage II[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Oesophageal cancer metastatic[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Oesophageal carcinoma[1]	1 (0.04%)	0 (0.00%)	4 (0.18%)	2 (0.06%)	2 (0.03%)
Oesophageal neoplasm[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Oesophageal squamous cell carcinoma[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Oligodendroglioma[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Oropharyngeal squamous cell carcinoma[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Ovarian adenoma[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Ovarian cancer[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Ovarian neoplasm[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Pancreatic carcinoma[1]	1 (0.04%)	4 (0.18%)	3 (0.14%)	5 (0.15%)	3 (0.05%)
Pancreatic carcinoma metastatic[1]	2 (0.09%)	1 (0.04%)	0 (0.00%)	3 (0.09%)	0 (0.00%)
Papillary cystadenoma lymphomatosum[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Papillary renal cell carcinoma[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	2 (0.06%)	0 (0.00%)
Papillary thyroid cancer[1]	1 (0.04%)	1 (0.04%)	1 (0.05%)	2 (0.06%)	2 (0.03%)
Parathyroid tumour benign[1]	2 (0.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Penile cancer[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Phaeochromocytoma[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Pharyngeal cancer[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	1 (0.03%)	0 (0.00%)

Pituitary tumour benign[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Plasma cell myeloma[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	2 (0.06%)	0 (0.00%)
Pleomorphic adenoma[1]	1 (0.04%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Polycythaemia vera[1]	1 (0.04%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Prostate cancer[1]	12 (0.53%)	10 (0.44%)	10 (0.46%)	13 (0.39%)	15 (0.26%)
Prostate cancer metastatic[1]	0 (0.00%)	1 (0.04%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Prostate cancer recurrent[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Prostatic adenoma[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	1 (0.03%)	0 (0.00%)
Rectal adenocarcinoma[1]	1 (0.04%)	1 (0.04%)	1 (0.05%)	0 (0.00%)	1 (0.02%)
Rectal adenoma[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Rectal cancer[1]	4 (0.18%)	2 (0.09%)	2 (0.09%)	3 (0.09%)	1 (0.02%)
Rectal cancer metastatic[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Rectosigmoid cancer[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Renal cancer[1]	2 (0.09%)	2 (0.09%)	3 (0.14%)	2 (0.06%)	1 (0.02%)
Renal cancer metastatic[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Renal cell carcinoma[1]	2 (0.09%)	1 (0.04%)	5 (0.23%)	1 (0.03%)	3 (0.05%)
Renal neoplasm[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Renal oncocytoma[1]	0 (0.00%)	1 (0.04%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Rosai-Dorfman syndrome[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Salivary gland adenoma[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Salivary gland neoplasm[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Seborrhoeic keratosis[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Skin cancer[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Small cell lung cancer[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	5 (0.15%)	1 (0.02%)
Small cell lung cancer metastatic[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)

Small intestine adenocarcinoma[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Small intestine carcinoma[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Small intestine carcinoma metastatic[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Squamous cell carcinoma[1]	12 (0.53%)	5 (0.22%)	6 (0.28%)	10 (0.30%)	9 (0.16%)
Squamous cell carcinoma of lung[1]	2 (0.09%)	5 (0.22%)	0 (0.00%)	2 (0.06%)	1 (0.02%)
Squamous cell carcinoma of skin[1]	3 (0.13%)	2 (0.09%)	1 (0.05%)	3 (0.09%)	1 (0.02%)
Squamous cell carcinoma of the hypopharynx[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Squamous cell carcinoma of the tongue[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Superficial spreading melanoma stage II[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Testis cancer[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Throat cancer[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Thyroid cancer[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Thyroid cancer metastatic[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Thyroid neoplasm[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Tongue neoplasm malignant stage unspecified[1]	1 (0.04%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Tonsil cancer metastatic[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Transitional cell carcinoma[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	4 (0.07%)
Transitional cell carcinoma urethra[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Tumour perforation[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)

Uterine cancer[1]	0 (0.00%)	0 (0.00%)	2 (0.09%)	1 (0.03%)	0 (0.00%)
Uterine leiomyoma[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (0.03%)
Nervous system disorders					
Amnesia[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Amyotrophic lateral sclerosis[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Aphasia[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Apraxia[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Ataxia[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Balance disorder[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Brain injury[1]	0 (0.00%)	3 (0.13%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Brain oedema[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Carotid arteriosclerosis[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Carotid artery aneurysm[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Carotid artery disease[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Carotid artery occlusion[1]	0 (0.00%)	1 (0.04%)	1 (0.05%)	1 (0.03%)	0 (0.00%)
Carotid artery stenosis[1]	3 (0.13%)	0 (0.00%)	2 (0.09%)	1 (0.03%)	8 (0.14%)
Carpal tunnel syndrome[1]	1 (0.04%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	3 (0.05%)
Cauda equina syndrome[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Cerebellar infarction[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Cerebellar stroke[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Cerebral arteriosclerosis[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Cerebral haemorrhage[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (0.03%)
Cerebral infarction[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	9 (0.16%)
Cerebral ischaemia[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	3 (0.05%)
Cerebrovascular accident[1]	2 (0.09%)	1 (0.04%)	1 (0.05%)	4 (0.12%)	22 (0.38%)

Cervical myelopathy[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Cervical radiculopathy[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (0.03%)
Cervicobrachial syndrome[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	1 (0.03%)	0 (0.00%)
Cognitive disorder[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Coma[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Dementia[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (0.03%)
Dementia Alzheimer's type[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Dementia with Lewy bodies[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Depressed level of consciousness[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Diabetic coma[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Diabetic neuropathy[1]	2 (0.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Diplegia[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Dizziness[1]	6 (0.27%)	2 (0.09%)	3 (0.14%)	7 (0.21%)	4 (0.07%)
Dysaesthesia[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Dysarthria[1]	2 (0.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Dystonia[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Embolic stroke[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Encephalopathy[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	1 (0.03%)	3 (0.05%)
Epilepsy[1]	2 (0.09%)	2 (0.09%)	1 (0.05%)	1 (0.03%)	2 (0.03%)
Facial paralysis[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Focal dyscognitive seizures[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Generalised tonic-clonic seizure[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Guillain-Barre syndrome[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Haemorrhage intracranial[1]	1 (0.04%)	0 (0.00%)	1 (0.05%)	1 (0.03%)	0 (0.00%)
Haemorrhagic stroke[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Haemorrhagic transformation stroke[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Headache[1]	4 (0.18%)	3 (0.13%)	3 (0.14%)	4 (0.12%)	0 (0.00%)
Hemiparesis[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Hydrocephalus[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Hypersomnia[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hypertensive encephalopathy[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (0.06%)	0 (0.00%)
Hypoaesthesia[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	2 (0.06%)	1 (0.02%)
Hypoglycaemic coma[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Hypoglycaemic encephalopathy[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Hypoxic-ischaemic encephalopathy[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	2 (0.03%)
IIIrd nerve paresis[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Intracranial aneurysm[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Intracranial pressure increased[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Ischaemic stroke[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	16 (0.28%)
Lacunar infarction[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	1 (0.02%)
Lacunar stroke[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Loss of consciousness[1]	1 (0.04%)	3 (0.13%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Lumbar radiculopathy[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (0.03%)
Lumbosacral radiculopathy[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Mental impairment[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)

Metabolic encephalopathy[1]	1 (0.04%)	1 (0.04%)	0 (0.00%)	2 (0.06%)	1 (0.02%)
Migraine[1]	1 (0.04%)	1 (0.04%)	0 (0.00%)	1 (0.03%)	2 (0.03%)
Mixed dementia[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Nerve compression[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Neuralgia[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Neuropathy peripheral[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Normal pressure hydrocephalus[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Optic neuritis[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Orthostatic intolerance[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Paraesthesia[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Paralysis[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Paresis[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Partial seizures[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	1 (0.02%)
Peripheral nerve lesion[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Polyneuropathy[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	1 (0.02%)
Post herpetic neuralgia[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Post stroke seizure[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Presyncope[1]	2 (0.09%)	1 (0.04%)	2 (0.09%)	4 (0.12%)	2 (0.03%)
Restless legs syndrome[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Sciatica[1]	0 (0.00%)	0 (0.00%)	5 (0.23%)	4 (0.12%)	0 (0.00%)
Seizure[1]	3 (0.13%)	2 (0.09%)	1 (0.05%)	4 (0.12%)	2 (0.03%)
Sensory disturbance[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Spinal claudication[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Spinal cord compression[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Spinal cord infarction[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (0.06%)	0 (0.00%)

Spondylitic myelopathy[1]	0 (0.00%)	2 (0.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Status epilepticus[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Stupor[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Subdural hygroma[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Syncope[1]	15 (0.66%)	17 (0.74%)	16 (0.74%)	25 (0.75%)	16 (0.28%)
Tension headache[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Thalamic infarction[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Thrombotic cerebral infarction[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Tonic convulsion[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Toxic encephalopathy[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Transient global amnesia[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Transient ischaemic attack[1]	1 (0.04%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	15 (0.26%)
Trigeminal neuralgia[1]	1 (0.04%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Upper motor neurone lesion[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Vascular dementia[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Vascular encephalopathy[1]	0 (0.00%)	2 (0.09%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Vertebrobasilar insufficiency[1]	1 (0.04%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	1 (0.02%)
VIth nerve paralysis[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Product issues					
Device battery issue[1]	2 (0.09%)	0 (0.00%)	2 (0.09%)	0 (0.00%)	1 (0.02%)
Device dislocation[1]	0 (0.00%)	1 (0.04%)	2 (0.09%)	1 (0.03%)	1 (0.02%)
Device end of service[1]	0 (0.00%)	1 (0.04%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Device failure[1]	1 (0.04%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)

Device inappropriate shock delivery[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Device issue[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Device lead damage[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Device lead issue[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Device loosening[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Device malfunction[1]	1 (0.04%)	2 (0.09%)	1 (0.05%)	3 (0.09%)	0 (0.00%)
Device occlusion[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Device signal detection issue[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Lead dislodgement[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Psychiatric disorders					
Acute stress disorder[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Adjustment disorder[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Affective disorder[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Alcoholic psychosis[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Alcoholism[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (0.03%)
Anxiety[1]	0 (0.00%)	1 (0.04%)	1 (0.05%)	3 (0.09%)	2 (0.03%)
Anxiety disorder[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Anxiety disorder due to a general medical condition[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Bipolar disorder[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Bipolar I disorder[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Burnout syndrome[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Completed suicide[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Confusional state[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	1 (0.03%)	1 (0.02%)
Conversion disorder[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)

Delirium[1]	1 (0.04%)	2 (0.09%)	1 (0.05%)	2 (0.06%)	2 (0.03%)
Delirium tremens[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Depression[1]	7 (0.31%)	4 (0.18%)	2 (0.09%)	4 (0.12%)	2 (0.03%)
Dissociative amnesia[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Drug use disorder[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Generalised anxiety disorder[1]	2 (0.09%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hallucination, visual[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Head banging[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Homicidal ideation[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Insomnia[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Intentional self-injury[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Major depression[1]	2 (0.09%)	1 (0.04%)	1 (0.05%)	1 (0.03%)	0 (0.00%)
Mental status changes[1]	4 (0.18%)	0 (0.00%)	2 (0.09%)	6 (0.18%)	2 (0.03%)
Panic attack[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Personality change[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Psychotic disorder[1]	0 (0.00%)	2 (0.09%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Psychotic disorder due to a general medical condition[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Restlessness[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Schizophrenia[1]	0 (0.00%)	0 (0.00%)	2 (0.09%)	0 (0.00%)	0 (0.00%)
Somnambulism[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Suicidal ideation[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Suicide attempt[1]	1 (0.04%)	1 (0.04%)	1 (0.05%)	2 (0.06%)	0 (0.00%)
Renal and urinary disorders					
Acute kidney injury[1]	20 (0.88%)	30 (1.31%)	16 (0.74%)	27 (0.81%)	22 (0.38%)

Acute prerenal failure[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Anuria[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Azotaemia[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Calculus bladder[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	1 (0.03%)	3 (0.05%)
Calculus urethral[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Calculus urinary[1]	1 (0.04%)	1 (0.04%)	0 (0.00%)	1 (0.03%)	1 (0.02%)
Chronic kidney disease[1]	4 (0.18%)	5 (0.22%)	4 (0.18%)	4 (0.12%)	5 (0.09%)
Diabetic nephropathy[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	2 (0.03%)
Dysuria[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	1 (0.02%)
End stage renal disease[1]	1 (0.04%)	1 (0.04%)	0 (0.00%)	2 (0.06%)	1 (0.02%)
Focal segmental glomerulosclerosis[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Glomerulonephritis membranous[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Haematuria[1]	5 (0.22%)	6 (0.26%)	3 (0.14%)	7 (0.21%)	3 (0.05%)
Hydronephrosis[1]	2 (0.09%)	3 (0.13%)	1 (0.05%)	2 (0.06%)	0 (0.00%)
Hypertensive nephropathy[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Lower urinary tract symptoms[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Nephrolithiasis[1]	3 (0.13%)	2 (0.09%)	4 (0.18%)	7 (0.21%)	3 (0.05%)
Nephrotic syndrome[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Obstructive uropathy[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Pollakiuria[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Polyuria[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Prerenal failure[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	1 (0.02%)
Renal artery stenosis[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	2 (0.06%)	1 (0.02%)
Renal artery thrombosis[1]	0 (0.00%)	1 (0.04%)	1 (0.05%)	0 (0.00%)	0 (0.00%)

Renal colic[1]	1 (0.04%)	2 (0.09%)	0 (0.00%)	2 (0.06%)	0 (0.00%)
Renal cyst[1]	1 (0.04%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	1 (0.02%)
Renal failure[1]	7 (0.31%)	10 (0.44%)	11 (0.51%)	13 (0.39%)	5 (0.09%)
Renal haematoma[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Renal impairment[1]	1 (0.04%)	4 (0.18%)	3 (0.14%)	1 (0.03%)	4 (0.07%)
Renal injury[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Renal mass[1]	1 (0.04%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Renal tubular necrosis[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Stress urinary incontinence[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Tubulointerstitial nephritis[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Ureteric obstruction[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Ureteric stenosis[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Ureterolithiasis[1]	1 (0.04%)	1 (0.04%)	2 (0.09%)	7 (0.21%)	3 (0.05%)
Urethral obstruction[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Urinary bladder haemorrhage[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Urinary bladder polyp[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Urinary incontinence[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	1 (0.03%)	0 (0.00%)
Urinary retention[1]	4 (0.18%)	4 (0.18%)	3 (0.14%)	4 (0.12%)	6 (0.10%)
Urinary tract obstruction[1]	0 (0.00%)	1 (0.04%)	1 (0.05%)	0 (0.00%)	1 (0.02%)
Vesicocutaneous fistula[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Reproductive system and breast disorders					
Balanoposthitis[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Benign prostatic hyperplasia[1]	5 (0.22%)	6 (0.26%)	5 (0.23%)	5 (0.15%)	8 (0.14%)
Cystocele[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Dysmenorrhoea[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Endometrial hyperplasia[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Epididymal cyst[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Erectile dysfunction[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Female genital tract fistula[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Genital atrophy[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Genital prolapse[1]	1 (0.04%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Menorrhagia[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Ovarian cyst[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Pelvic pain[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Postmenopausal haemorrhage[1]	2 (0.09%)	1 (0.04%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Prostatic haemorrhage[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Prostatic mass[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Prostatism[1]	0 (0.00%)	1 (0.04%)	1 (0.05%)	0 (0.00%)	1 (0.02%)
Prostatitis[1]	2 (0.09%)	0 (0.00%)	2 (0.09%)	0 (0.00%)	0 (0.00%)
Prostatomegaly[1]	0 (0.00%)	2 (0.09%)	1 (0.05%)	1 (0.03%)	0 (0.00%)
Rectocele[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Spermatocele[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	1 (0.03%)	0 (0.00%)
Uterine cervix stenosis[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Uterine prolapse[1]	1 (0.04%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Vaginal haemorrhage[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Varicocele[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Varicose veins pelvic[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Respiratory, thoracic and mediastinal disorders					
Acute pulmonary oedema[1]	0 (0.00%)	3 (0.13%)	4 (0.18%)	4 (0.12%)	2 (0.03%)

Acute respiratory distress syndrome[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Acute respiratory failure[1]	10 (0.44%)	7 (0.31%)	11 (0.51%)	13 (0.39%)	21 (0.36%)
Alveolitis[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Alveolitis allergic[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Asphyxia[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Asthma[1]	7 (0.31%)	2 (0.09%)	0 (0.00%)	3 (0.09%)	2 (0.03%)
Atelectasis[1]	3 (0.13%)	0 (0.00%)	0 (0.00%)	3 (0.09%)	0 (0.00%)
Bronchial hyperreactivity[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Bronchial obstruction[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Bronchiectasis[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Bronchitis chronic[1]	2 (0.09%)	1 (0.04%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Bronchospasm[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	2 (0.06%)	1 (0.02%)
Cheyne-Stokes respiration[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Chronic obstructive pulmonary disease[1]	28 (1.24%)	21 (0.92%)	16 (0.74%)	40 (1.19%)	33 (0.57%)
Cough[1]	2 (0.09%)	0 (0.00%)	0 (0.00%)	3 (0.09%)	1 (0.02%)
Dyspnoea[1]	14 (0.62%)	8 (0.35%)	10 (0.46%)	23 (0.69%)	19 (0.33%)
Dyspnoea exertional[1]	2 (0.09%)	1 (0.04%)	1 (0.05%)	1 (0.03%)	1 (0.02%)
Dyspnoea paroxysmal nocturnal[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Emphysema[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	1 (0.03%)	1 (0.02%)
Epistaxis[1]	3 (0.13%)	2 (0.09%)	2 (0.09%)	6 (0.18%)	2 (0.03%)
Haemoptysis[1]	2 (0.09%)	1 (0.04%)	0 (0.00%)	4 (0.12%)	1 (0.02%)
Haemothorax[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Hiccups[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	1 (0.02%)
Hydrothorax[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (0.03%)

Hypopnoea[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hypoxia[1]	3 (0.13%)	1 (0.04%)	1 (0.05%)	3 (0.09%)	5 (0.09%)
Idiopathic interstitial pneumonia[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Idiopathic pneumonia syndrome[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Idiopathic pulmonary fibrosis[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Interstitial lung disease[1]	3 (0.13%)	1 (0.04%)	2 (0.09%)	2 (0.06%)	1 (0.02%)
Laryngeal oedema[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Laryngospasm[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Lung consolidation[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Lung hernia[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Lung infiltration[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	2 (0.06%)	0 (0.00%)
Nasal obstruction[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Nasal polyps[1]	0 (0.00%)	1 (0.04%)	1 (0.05%)	1 (0.03%)	0 (0.00%)
Nasal turbinate hypertrophy[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Obstructive airways disorder[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Organising pneumonia[1]	2 (0.09%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Oropharyngeal pain[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pickwickian syndrome[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pleural adhesion[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pleural effusion[1]	8 (0.35%)	5 (0.22%)	4 (0.18%)	6 (0.18%)	4 (0.07%)
Pleurisy[1]	1 (0.04%)	3 (0.13%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Pleuritic pain[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	1 (0.02%)
Pneumomediastinum[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Pneumonia aspiration[1]	1 (0.04%)	4 (0.18%)	0 (0.00%)	3 (0.09%)	1 (0.02%)
Pneumonitis[1]	1 (0.04%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	1 (0.02%)
Pneumothorax[1]	5 (0.22%)	2 (0.09%)	0 (0.00%)	4 (0.12%)	1 (0.02%)
Pneumothorax spontaneous[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Productive cough[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Pulmonary alveolar haemorrhage[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pulmonary arterial hypertension[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pulmonary congestion[1]	2 (0.09%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	2 (0.03%)
Pulmonary embolism[1]	1 (0.04%)	2 (0.09%)	0 (0.00%)	2 (0.06%)	18 (0.31%)
Pulmonary fibrosis[1]	3 (0.13%)	1 (0.04%)	0 (0.00%)	4 (0.12%)	1 (0.02%)
Pulmonary haematoma[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Pulmonary hypertension[1]	2 (0.09%)	3 (0.13%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pulmonary mass[1]	1 (0.04%)	2 (0.09%)	1 (0.05%)	0 (0.00%)	3 (0.05%)
Pulmonary microemboli[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Pulmonary oedema[1]	4 (0.18%)	4 (0.18%)	1 (0.05%)	2 (0.06%)	5 (0.09%)
Pulmonary sarcoidosis[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Respiratory alkalosis[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Respiratory arrest[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Respiratory distress[1]	0 (0.00%)	2 (0.09%)	0 (0.00%)	0 (0.00%)	3 (0.05%)
Respiratory failure[1]	12 (0.53%)	11 (0.48%)	9 (0.41%)	12 (0.36%)	5 (0.09%)
Respiratory tract inflammation[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Respiratory tract irritation[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Rhinitis allergic[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Sinus congestion[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)

Sinus polyp[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Sleep apnoea syndrome[1]	2 (0.09%)	2 (0.09%)	0 (0.00%)	5 (0.15%)	2 (0.03%)
Status asthmaticus[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Vocal cord leukoplakia[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Wheezing[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (0.03%)
Skin and subcutaneous tissue disorders					
Acne[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Actinic keratosis[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Angioedema[1]	1 (0.04%)	2 (0.09%)	0 (0.00%)	3 (0.09%)	1 (0.02%)
Blister[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Brow ptosis[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Decubitus ulcer[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	2 (0.03%)
Dermatitis[1]	0 (0.00%)	1 (0.04%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Dermatitis allergic[1]	1 (0.04%)	1 (0.04%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Diabetic foot[1]	1 (0.04%)	6 (0.26%)	1 (0.05%)	0 (0.00%)	4 (0.07%)
Eczema[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Erythema[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Hyperhidrosis[1]	0 (0.00%)	2 (0.09%)	0 (0.00%)	2 (0.06%)	0 (0.00%)
Hyperkeratosis[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Hypersensitivity vasculitis[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Neurodermatitis[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Prurigo[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pruritus allergic[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Psoriasis[1]	1 (0.04%)	0 (0.00%)	2 (0.09%)	0 (0.00%)	1 (0.02%)
Rhinophyma[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)

Skin ulcer[1]	0 (0.00%)	5 (0.22%)	5 (0.23%)	3 (0.09%)	1 (0.02%)
Stasis dermatitis[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	2 (0.06%)	0 (0.00%)
Stevens-Johnson syndrome[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Subcutaneous emphysema[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Urticaria[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Social circumstances					
Homicide[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Vascular disorders					
Accelerated hypertension[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	1 (0.02%)
Aneurysm ruptured[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Angiodysplasia[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Aortic aneurysm[1]	8 (0.35%)	4 (0.18%)	6 (0.28%)	6 (0.18%)	12 (0.21%)
Aortic aneurysm rupture[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	3 (0.05%)
Aortic dissection[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	2 (0.03%)
Aortic stenosis[1]	1 (0.04%)	0 (0.00%)	2 (0.09%)	0 (0.00%)	1 (0.02%)
Aortitis[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Arterial haemorrhage[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Arterial insufficiency[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	1 (0.03%)	0 (0.00%)
Arteriosclerosis[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	2 (0.06%)	5 (0.09%)
Arteriovenous fistula[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Arteritis[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Brachiocephalic artery stenosis[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Circulatory collapse[1]	3 (0.13%)	1 (0.04%)	3 (0.14%)	1 (0.03%)	2 (0.03%)

Deep vein thrombosis[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	5 (0.09%)
Embolism[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Embolism arterial[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Embolism venous[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Essential hypertension[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Extremity necrosis[1]	0 (0.00%)	1 (0.04%)	1 (0.05%)	2 (0.06%)	2 (0.03%)
Femoral artery aneurysm[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Femoral artery embolism[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Haematoma[1]	2 (0.09%)	3 (0.13%)	1 (0.05%)	5 (0.15%)	5 (0.09%)
Haemodynamic instability[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Haemorrhage[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hypertension[1]	10 (0.44%)	8 (0.35%)	8 (0.37%)	15 (0.45%)	17 (0.29%)
Hypertensive crisis[1]	7 (0.31%)	5 (0.22%)	2 (0.09%)	11 (0.33%)	5 (0.09%)
Hypertensive emergency[1]	1 (0.04%)	2 (0.09%)	1 (0.05%)	0 (0.00%)	1 (0.02%)
Hypotension[1]	8 (0.35%)	5 (0.22%)	4 (0.18%)	11 (0.33%)	6 (0.10%)
Hypovolaemic shock[1]	2 (0.09%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Intermittent claudication[1]	1 (0.04%)	1 (0.04%)	0 (0.00%)	3 (0.09%)	3 (0.05%)
Internal haemorrhage[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Ischaemic limb pain[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Lymphatic fistula[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Lymphorrhoea[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Malignant hypertension[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Orthostatic hypertension[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Orthostatic hypotension[1]	1 (0.04%)	3 (0.13%)	1 (0.05%)	0 (0.00%)	2 (0.03%)
Pallor[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Peripheral arterial occlusive disease[1]	3 (0.13%)	4 (0.18%)	2 (0.09%)	4 (0.12%)	11 (0.19%)
Peripheral artery aneurysm[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Peripheral artery occlusion[1]	0 (0.00%)	3 (0.13%)	2 (0.09%)	0 (0.00%)	4 (0.07%)
Peripheral artery stenosis[1]	1 (0.04%)	2 (0.09%)	1 (0.05%)	1 (0.03%)	6 (0.10%)
Peripheral artery thrombosis[1]	0 (0.00%)	2 (0.09%)	1 (0.05%)	1 (0.03%)	1 (0.02%)
Peripheral embolism[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Peripheral ischaemia[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	11 (0.19%)
Peripheral vascular disorder[1]	0 (0.00%)	3 (0.13%)	2 (0.09%)	1 (0.03%)	4 (0.07%)
Peripheral venous disease[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Shock[1]	0 (0.00%)	0 (0.00%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Shock haemorrhagic[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	1 (0.02%)
Temporal arteritis[1]	1 (0.04%)	0 (0.00%)	1 (0.05%)	1 (0.03%)	1 (0.02%)
Thrombophlebitis[1]	0 (0.00%)	1 (0.04%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Thrombophlebitis superficial[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Thrombosis[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.02%)
Varicose ulceration[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Varicose vein[1]	0 (0.00%)	1 (0.04%)	1 (0.05%)	0 (0.00%)	0 (0.00%)
Vascular insufficiency[1]	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.03%)	0 (0.00%)
Venous thrombosis limb[1]	1 (0.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

1 MedDRA (21.1)

Other (Not Including Serious) Adverse Events by System Organ Class

Time Frame	Core phase: From randomization to end of treatment plus 30 days; up to approximately 6 years; Extension phase: From start of Extension phase, to end of treatment plus 30 days, up to approximately 2 years.
Additional Description	AEs/SAEs are any signs or symptoms that occur during the study treatment. Groups I to IV show AE/SAEs during the Core phase; Group V shows AE/SAEs during the Extension phase. During the Core phase, CV events being study endpoints were exempt from AE/SAE reporting; in contrast, during the Extension phase, all CV events were reported as AEs/SAEs.
Source Vocabulary for Table Default	MedDRA 20.0/21.1
Assessment Type for Table Default	SYSTEMATIC ASSESSMENT
Frequent Event Reporting Threshold	5%

	Group I N = 2263	**Group II N = 2285**	**Group III N = 2170**	**Group IV N = 3348**	**Group V N = 5777**
Arm/Group Description	Core phase: Blinded Canakinumab 300 mg quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	Core phase: Blinded Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	Core phase: Blinded Canakinumab 50 mg quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	Core phase: Blinded matching placebo quarterly subcutaneous + standard of care (SoC) therapy Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy	Extension phase: Switched to open-label Canakinumab 150 mg quarterly subcutaneous + standard of care (SoC) therapy.
Total participants affected	1271 (56.16%)	1324 (57.94%)	1199 (55.25%)	1905 (56.90%)	1497 (25.91%)

Cardiac disorders					
Angina pectoris[1]	142 (6.27%)	164 (7.18%)	129 (5.94%)	228 (6.81%)	115 (1.99%)
Gastrointestinal disorders					
Diarrhoea[1]	138 (6.10%)	146 (6.39%)	137 (6.31%)	216 (6.45%)	110 (1.90%)
General disorders and administration site conditions					
Fatigue[1]	113 (4.99%)	99 (4.33%)	84 (3.87%)	169 (5.05%)	72 (1.25%)
Non-cardiac chest pain[1]	142 (6.27%)	143 (6.26%)	111 (5.12%)	228 (6.81%)	68 (1.18%)
Oedema peripheral[1]	136 (6.01%)	142 (6.21%)	134 (6.18%)	173 (5.17%)	110 (1.90%)
Infections and infestations					
Bronchitis[1]	131 (5.79%)	162 (7.09%)	114 (5.25%)	234 (6.99%)	160 (2.77%)
Influenza[1]	141 (6.23%)	145 (6.35%)	118 (5.44%)	194 (5.79%)	154 (2.67%)
Upper respiratory tract infection[1]	153 (6.76%)	156 (6.83%)	134 (6.18%)	252 (7.53%)	125 (2.16%)
Urinary tract infection[1]	126 (5.57%)	129 (5.65%)	93 (4.29%)	175 (5.23%)	123 (2.13%)
Viral upper respiratory tract infection[1]	264 (11.67%)	297 (13.00%)	263 (12.12%)	388 (11.59%)	16 (0.28%)
Musculoskeletal and connective tissue disorders					
Arthralgia[1]	165 (7.29%)	181 (7.92%)	144 (6.64%)	252 (7.53%)	184 (3.19%)
Back pain[1]	169 (7.47%)	177 (7.75%)	157 (7.24%)	277 (8.27%)	163 (2.82%)
Pain in extremity[1]	145 (6.41%)	145 (6.35%)	98 (4.52%)	204 (6.09%)	128 (2.22%)
Nervous system disorders					
Dizziness[1]	114 (5.04%)	126 (5.51%)	132 (6.08%)	189 (5.65%)	107 (1.85%)

Headache[1]	133 (5.88%)	111 (4.86%)	120 (5.53%)	178 (5.32%)	72 (1.25%)
Respiratory, thoracic and mediastinal disorders					
Cough[1]	151 (6.67%)	152 (6.65%)	121 (5.58%)	233 (6.96%)	103 (1.78%)
Dyspnoea[1]	126 (5.57%)	123 (5.38%)	110 (5.07%)	193 (5.76%)	112 (1.94%)
Vascular disorders					
Hypertension[1]	198 (8.75%)	216 (9.45%)	208 (9.59%)	309 (9.23%)	241 (4.17%)

1 MedDRA (21.1)

Other Relevant Findings

N/A

Conclusion:

Core phase:

The CANTOS study conclusively demonstrated that IL-1β neutralization by canakinumab (150 mg) significantly reduced the risk of MACE in patients with a prior MI and elevated hsCRP at high risk for major adverse cardiac events who were well-treated on guideline-recommended standard of care.

Canakinumab treatment:

- Reduced the risk of the composite MACE endpoint, primarily driven by the reduction in the risk of non-fatal MI and CV death. Consistent efficacy was observed at both the 150 mg and 300 mg doses.
- Reduced the risk of MACE and hospitalization for unstable angina requiring unplanned revascularization. This was further supported by the reduced risk of all coronary revascularizations.
- Showed a numerically lower incidence in all-cause mortality.

Similarly, the following is concluded in regard to the safety of canakinumab in this population:

- There was a slight increased risk of serious infections as well of fatal infections/sepsis, but the overall incidence remains low.
- There was no increased risk of malignancy in the canakinumab treatment groups as compared to placebo with fewer malignancy deaths for lung cancer, particularly in the canakinumab 300 mg group.

Extension phase:

- The safety results from the Extension phase did not reveal any unexpected safety findings and/or new safety signals. The overall safety profile of canakinumab in patients with prior MI and hsCRP ≥2 mg/L remained consistent with the known safety experience for canakinumab.

Limitations and Caveats:

- During the Core phase, CV events being study endpoints were exempt from AE/SAE reporting; in contrast, during the Extension phase, all CV events were reported as AEs/SAEs. Comparison across groups is no longer feasible in the Extension phase because all patients received canakinumab 150 mg. Beyond the primary endpoint, all p-values for the canakinumab 50 mg and 300 mg groups are to be considered nominal only.

Date of Clinical Trial Report

Core phase: 17-Nov-2017

Close-out final report for Extension phase: 3-Sep-2019