Clinical trial results:
A phase III, multicenter, randomized, double blind, placebo-controlled study evaluating the efficacy and safety of canakinumab versus placebo as adjuvant therapy in adult subjects with stages AJCC/UICC v. 8 II -IIIA and IIIB (T>5cm N2) completely resected (R0) non-small cell lung cancer (NSCLC)

Summary

EudraCT number	2017-004011-39
Trial protocol	DE GR GB FR IT ES NO AT PT CZ PL BG HU SI IS IE RO
Global end of trial date	07 February 2023

Results information

Result version number	v2 (current)
This version publication date	11 February 2024
First version publication date	12 January 2024
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	CACZ885T2301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03447769
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	Novartis Campus, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, novartis.email@novartis.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	07 February 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 February 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary purpose of the study was to compare the efficacy and safety of canakinumab versus placebo as adjuvant therapy in adult subjects with stages II -IIIA according to the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) version 8 criteria and the subset of IIIB (T>5cm N2 disease) completely resected (R0) non-small cell lung cancer (NSCLC).

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 March 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 14
Country: Number of subjects enrolled	Austria: 18
Country: Number of subjects enrolled	Brazil: 14
Country: Number of subjects enrolled	Bulgaria: 8
Country: Number of subjects enrolled	Canada: 7
Country: Number of subjects enrolled	Chile: 9
Country: Number of subjects enrolled	China: 100
Country: Number of subjects enrolled	Colombia: 1
Country: Number of subjects enrolled	Czechia: 5
Country: Number of subjects enrolled	France: 99
Country: Number of subjects enrolled	Georgia: 21
Country: Number of subjects enrolled	Germany: 131
Country: Number of subjects enrolled	Greece: 50
Country: Number of subjects enrolled	Hong Kong: 13
Country: Number of subjects enrolled	Hungary: 10
Country: Number of subjects enrolled	Iceland: 5
Country: Number of subjects enrolled	India: 7
Country: Number of subjects enrolled	Israel: 4

Country: Number of subjects enrolled	Italy: 68
Country: Number of subjects enrolled	Japan: 167
Country: Number of subjects enrolled	Jordan: 3
Country: Number of subjects enrolled	Korea, Republic of: 58
Country: Number of subjects enrolled	Lebanon: 13
Country: Number of subjects enrolled	Malaysia: 19
Country: Number of subjects enrolled	Norway: 13
Country: Number of subjects enrolled	Panama: 4
Country: Number of subjects enrolled	Peru: 3
Country: Number of subjects enrolled	Philippines: 2
Country: Number of subjects enrolled	Poland: 28
Country: Number of subjects enrolled	Portugal: 9
Country: Number of subjects enrolled	Romania: 16
Country: Number of subjects enrolled	Russian Federation: 157
Country: Number of subjects enrolled	Slovenia: 4
Country: Number of subjects enrolled	Spain: 50
Country: Number of subjects enrolled	Switzerland: 11
Country: Number of subjects enrolled	Taiwan: 63
Country: Number of subjects enrolled	Thailand: 39
Country: Number of subjects enrolled	Türkiye: 32
Country: Number of subjects enrolled	United Kingdom: 48
Country: Number of subjects enrolled	United States: 50
Country: Number of subjects enrolled	Viet Nam: 9
Worldwide total number of subjects	1382
EEA total number of subjects	514

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	836
From 65 to 84 years	546
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted across 290 centers in 41 countries. A total of 1830 subjects were screened of which 1382 participants were randomized to treatment on a 1:1 basis.

Pre-assignment

Screening details:

1 participant randomized in the canakinumab arm was never treated due to subject decision.
The numbers in the patient disposition table correspond to the treatment period.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Canakinumab

Arm description:

Participants receive 200mg of canakinumab subcutaneously every 3 weeks for up to 18 cycles (approximately 54 weeks)

Arm type	Experimental
Investigational medicinal product name	Canakinumab
Investigational medicinal product code	ACZ885
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

200 mg of canakinumab administered subcutaneously on day 1 of every 21-day cycle for 18 cycles. Canakinumab solution for injection was provided by Novartis as ready-to-use pre-filled syringes to be administered by study personnel.

Arm title	Placebo

Arm description:

Participants receive canakinumab placebo subcutaneously every 3 weeks for up to 18 cycles (approximately 54 weeks)

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

Dosage and administration details:

Placebo administered subcutaneously on day 1 of every 21-day cycle for 18 cycles. Placebo solution for injection was provided by Novartis as ready-to-use pre-filled syringes to be administered by study personnel

Number of subjects in period 1	Canakinumab	Placebo
Started	693	689
Treated	692	689
Completed	414	420
Not completed	279	269
Adverse event, serious fatal	2	7
Patient decision	27	27
Physician decision	13	5
Study terminated by Sponsor	60	44
Adverse event, non-fatal	34	31
Technical problems	1	-
Protocol deviation	4	6
Progressive disease	138	148
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Canakinumab
Reporting group description:	
Participants receive 200mg of canakinumab subcutaneously every 3 weeks for up to 18 cycles (approximately 54 weeks)	
Reporting group title	Placebo
Reporting group description:	
Participants receive canakinumab placebo subcutaneously every 3 weeks for up to 18 cycles (approximately 54 weeks)	

Reporting group values	Canakinumab	Placebo	Total
Number of subjects	693	689	1382
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	414	422	836
From 65-84 years	279	267	546
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	61.5	61.6	
standard deviation	± 8.90	± 9.00	-
Sex: Female, Male Units: Participants			
Female	263	257	520
Male	430	432	862
Race/Ethnicity, Customized Units: Subjects			
White	393	391	784
Asian	248	236	484
Black or African American	3	4	7
American Indian or Alaska Native	0	5	5
Multiple	0	1	1
Missing	49	52	101

End points

End points reporting groups

Reporting group title	Canakinumab
Reporting group description:	
Participants receive 200mg of canakinumab subcutaneously every 3 weeks for up to 18 cycles (approximately 54 weeks)	
Reporting group title	Placebo
Reporting group description:	
Participants receive canakinumab placebo subcutaneously every 3 weeks for up to 18 cycles (approximately 54 weeks)	

Primary: Disease free survival (DFS) by local investigator

End point title	Disease free survival (DFS) by local investigator
End point description:	
DFS is the time from the date of randomization to the date of the first documented NSCLC disease recurrence as assessed by local investigator radiologically or death due to any cause. Disease recurrence included diagnoses of new primary lung malignancies. Clinical deterioration was not considered as a recurrence of disease. In case of non-conclusive radiological evidence, a biopsy assessment was performed to confirm NSCLC recurrence. The median DFS was estimated using the Kaplan-Meier method. DFS was censored if no DFS event was observed prior to the analysis cut-off date or subjects who received any subsequent anti-neoplastic therapy for NSCLC. The censoring date was the date of last assessment before the cut-off date or NSCLC related anti-neoplastic therapy date. 9999 indicates the value was not estimable	
End point type	Primary
End point timeframe:	
Up to approximately 4 years	

End point values	Canakinumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	693	689		
Units: Months				
median (confidence interval 95%)	35.02 (28.55 to 9999)	29.73 (23.72 to 9999)		

Statistical analyses

Statistical analysis title	DFS: Canakinumab vs Placebo
Comparison groups	Canakinumab v Placebo

Number of subjects included in analysis	1382
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.258 [1]
Method	Stratified log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	1.14

Notes:

[1] - 1-sided p-value

Secondary: Overall Survival (OS) in CD8 subgroups

End point title	Overall Survival (OS) in CD8 subgroups

End point description:

Overall Survival (OS) is the time from the date of randomization to the date of death due to any cause. The OS was censored at the latest date the subject was known to be alive. The OS distribution was estimated using the Kaplan-Meier method, and Kaplan-Meier medians and 95% confidence intervals of the medians were presented for each treatment group. OS analysis was performed by CD8 subgroups with the median of baseline CD8 expression as cut-off.
9999 indicates that the value was not estimable

End point type	Secondary

End point timeframe:

up to approximately 4.3 years

End point values	Canakinumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	429	449		
Units: Months				
median (confidence interval 95%)				
CD8 < median (n= 213 / 225)	46.95 (32.23 to 9999)	9999 (-9999 to 9999)		
CD8 ≥ median (n= 216 / 224)	51.12 (-9999 to 9999)	9999 (-9999 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Overall Survival (OS) is the time from the date of randomization to the date of death due to any cause. The OS was censored at the latest date the subject was known to be alive. The OS distribution was estimated using the Kaplan-Meier method, and Kaplan-Meier medians and 95% confidence intervals of

the medians were presented for each treatment group.
9999 indicates that the value was not estimable

End point type	Secondary

End point timeframe:

Up to approximately 4.3 years

End point values	Canakinumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	693	689		
Units: Months				
median (confidence interval 95%)	51.12 (46.95 to 9999)	9999 (-9999 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) in PD-L1 subgroups

End point title	Overall Survival (OS) in PD-L1 subgroups

End point description:

Overall Survival (OS) is the time from the date of randomization to the date of death due to any cause. The OS was censored at the latest date the subject was known to be alive. The OS distribution was estimated using the Kaplan-Meier method, and Kaplan-Meier curves, medians and 95% confidence intervals of the medians were presented for each treatment group. OS analysis was performed by programmed cell death-ligand 1 (PD-L1) expression status: PD-L1 <1%, PD-L1 ≥1% and <49%, and PD-L1 ≥50%.
9999 indicates that the value was not estimable

End point type	Secondary

End point timeframe:

Up to approximately 4.3 years

End point values	Canakinumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	396	418		
Units: Months				
median (confidence interval 95%)				
PD-L1 <1% (n= 211 / 203)	9999 (-9999 to 9999)	9999 (-9999 to 9999)		
PD-L1 ≥1% and <49% (n=99 / 119)	46.95 (22.11 to 9999)	9999 (-9999 to 9999)		
PD-L1 ≥50% (n=86 / 96)	51.12 (-9999 to 9999)	9999 (-9999 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease free survival (DFS) by local investigator in PD-L1 subgroups

End point title	Disease free survival (DFS) by local investigator in PD-L1 subgroups

End point description:

DFS is the time from the date of randomization to the date of the first documented NSCLC disease recurrence as assessed by local investigator radiologically or death due to any cause. Disease recurrence included diagnoses of new primary lung malignancies. Clinical deterioration was not considered as a recurrence of disease. In case of non-conclusive radiological evidence, a biopsy assessment was performed to confirm NSCLC recurrence.
The median DFS was estimated using the Kaplan-Meier method. DFS was censored if no DFS event was observed prior to the analysis cut-off date or subjects who received any subsequent anti-neoplastic therapy for NSCLC. The censoring date was the date of last assessment before the cut-off date or NSCLC related anti-neoplastic therapy date.
DFS analysis was performed by baseline programmed cell death-ligand 1 (PD-L1) expression status: PD-L1 <1%, PD-L1 ≥1% and <49%, and PD-L1 ≥50%.
9999 indicates that the value was not estimable

End point type	Secondary

End point timeframe:

Up to approximately 4 years

End point values	Canakinumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	396	418		
Units: Months				
median (confidence interval 95%)				
PD-L1 <1% (n= 211 / 203)	30.72 (23.52 to 9999)	9999 (23.03 to 9999)		
PD-L1 ≥1% and <49% (n= 99 / 119)	30.42 (21.42 to 9999)	9999 (17.05 to 9999)		
PD-L1 ≥50% (n = 86 / 96)	46.95 (19.45 to 9999)	9999 (22.31 to 9999)		

Statistical analyses

Statistical analysis title	DFS in PD-L1 subgroups: Canakinumab vs Placebo

Statistical analysis description:

PD-L1 <1%

Comparison groups	Canakinumab v Placebo
Number of subjects included in analysis	814
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.676 [2]
Method	Stratified log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	1.09

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	1.58

Notes:

[2] - 1-sided p-value

Statistical analysis title	DFS in PD-L1 subgroups: Canakinumab vs Placebo
Statistical analysis description:	
PD-L1 ≥50%	
Comparison groups	Canakinumab v Placebo
Number of subjects included in analysis	814
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.823 [3]
Method	Stratified log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	1.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	2.43

Notes:

[3] - 1-sided p-value

Statistical analysis title	DFS in PD-L1 subgroups: Canakinumab vs Placebo
Statistical analysis description:	
PD-L1 ≥1% and <49%	
Comparison groups	Canakinumab v Placebo
Number of subjects included in analysis	814
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.036 [4]
Method	Stratified log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.34
upper limit	1.05

Notes:

[4] - 1-sided p-value

Secondary: Lung Cancer Specific Survival (LCSS)

End point title	Lung Cancer Specific Survival (LCSS)

End point description:

LCSS is defined as the time from date of randomization to the date of death due to lung cancer. The

LCSS distribution was estimated using the Kaplan-Meier method, and Kaplan-Meier medians and 95% confidence intervals of the medians were presented for each treatment group.
9999 indicates that the value was not estimable

End point type	Secondary

End point timeframe:

Up to approximately 4.3 years

End point values	Canakinumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	693	689		
Units: Months				
median (confidence interval 95%)	51.12 (44.71 to 9999)	9999 (-9999 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease free survival (DFS) by local investigator in CD8 subgroups

End point title	Disease free survival (DFS) by local investigator in CD8 subgroups

End point description:

DFS is the time from the date of randomization to the date of the first documented NSCLC disease recurrence as assessed by local investigator radiologically or death due to any cause. Disease recurrence included diagnoses of new primary lung malignancies. Clinical deterioration was not considered as a recurrence of disease. In case of non-conclusive radiological evidence, a biopsy assessment was performed to confirm NSCLC recurrence.
The median DFS was estimated using the Kaplan-Meier method. DFS was censored if no DFS event was observed prior to the analysis cut-off date or subjects who received any subsequent anti-neoplastic therapy for NSCLC. The censoring date was the date of last assessment before the cut-off date or NSCLC related anti-neoplastic therapy date.
DFS analysis was performed by CD8 subgroups with the median of baseline CD8 expression as cut-off.
9999 indicates that the value was not estimable

End point type	Secondary

End point timeframe:

Up to approximately 4 years

End point values	Canakinumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	429	449		
Units: Months				
median (confidence interval 95%)				
CD8 < median (n= 213 / 225)	26.58 (20.67 to 9999)	9999 (25.03 to 9999)		
CD8 ≥ median (n= 216 / 224)	46.95 (28.81 to 9999)	9999 (23.89 to 9999)		

Statistical analyses

Statistical analysis title	DFS in CD8 subgroups: Canakinumab vs Placebo
Statistical analysis description: CD8 ≥ median	
Comparison groups	Canakinumab v Placebo
Number of subjects included in analysis	878
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.303 [5]
Method	Stratified log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	1.33

Notes:
[5] - 1-sided p-value

Statistical analysis title	DFS in CD8 subgroups: Canakinumab vs Placebo
Statistical analysis description: CD8 < median	
Comparison groups	Canakinumab v Placebo
Number of subjects included in analysis	878
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.872 [6]
Method	Stratified log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	1.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	1.72

Notes:
[6] - 1-sided p-value

Secondary: Canakinumab serum concentrations

End point title	Canakinumab serum concentrations[7]

End point description:
Serum concentrations of canakinumab were determined using an ELISA method.

End point type	Secondary

End point timeframe:

Cycle 1 on day 1 (pre-dose), day 8 and 15; Cycle 2, 4, 6, 9 and 12 on day 1 (pre-dose). Cycle=21 days

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only participants who received canakinumab were included in this analysis

End point values	Canakinumab			
Subject group type	Reporting group			
Number of subjects analysed	664			
Units: ug/ml				
arithmetic mean (standard deviation)				
Cycle 1 Day 1 (n= 664)	0 (± 0)			
Cycle 1 Day 8 (n= 569)	18.1 (± 6.53)			
Cycle 1 Day 15 (n= 611)	16.9 (± 5.43)			
Cycle 2 Day 1 (n= 636)	15.0 (± 4.91)			
Cycle 4 Day 1 (n= 611)	29.7 (± 10.3)			
Cycle 6 Day 1 (n= 559)	34.7 (± 13.0)			
Cycle 9 Day 1 (n=530)	37.1 (± 14.5)			
Cycle 12 Day 1 (n=502)	38.6 (± 15.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to definitive 10 point deterioration of global health status/quality of life (QoL), shortness of breath and pain per EORTC QLQ-C30 questionnaire

End point title	Time to definitive 10 point deterioration of global health status/quality of life (QoL), shortness of breath and pain per EORTC QLQ-C30 questionnaire

End point description:

The EORTC QLQ-C30 was a questionnaire developed to assess the health-related quality of life of cancer participants. It assessed 15 domains consisting of 5 functional domains and 9 symptom domains and a global health status/QoL scale. All domain scores ranged from 0 to 100. A high score for the functional or global health status scales indicated a high level of functioning or QoL; a high score for a symptom scale indicated a high level of symptoms.
The time to definitive 10 point deterioration of global health status/QoL, shortness of breath and pain was defined as the time from the date of randomization to the date of event, which was defined as at least 10 points relative to baseline worsening of the score with no later change below this threshold or death due to any cause, whichever occurred earlier.
9999 indicates that the value was not estimable

End point type	Secondary

End point timeframe:

From baseline up to approximately 4 years

End point values	Canakinumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	693	689		
Units: Months				
median (confidence interval 95%)				
Global health status/QoL	34.99 (29.93 to 9999)	35.15 (35.15 to 9999)		
Shortness of breath	9999 (-9999 to 9999)	35.15 (34.99 to 9999)		
Pain	29.93 (28.29 to 35.22)	36.44 (34.99 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Canakinumab ADA incidence

End point title	Canakinumab ADA incidence[8]

End point description:

Canakinumab ADA incidence on-treatment was calculated as the percentage of participants who were treatment-induced ADA positive (post-baseline ADA positive with ADA-negative sample at baseline) and treatment-boosted ADA positive (post-baseline ADA positive with titer that was at least the fold titer change greater than the ADA-positive baseline titer)

End point type	Secondary

End point timeframe:

From baseline up to 130 days after end of treatment, assessed up to approx. 1.5 years

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only participants who received canakinumab were included in this analysis

End point values	Canakinumab			
Subject group type	Reporting group			
Number of subjects analysed	692			
Units: Participants	7			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to definitive 10 point deterioration symptom scores of pain,cough and dyspnea per European Organization for Research and Treatment of Cancer Quality of Life (EORTC QLQ)- Lung cancer (LC) 13 questionnaire

End point title	Time to definitive 10 point deterioration symptom scores of pain,cough and dyspnea per European Organization for Research and Treatment of Cancer Quality of Life (EORTC QLQ)- Lung cancer (LC) 13 questionnaire

End point description:

The Lung Cancer module of the EORTC's quality of life questionnaire (EORTC QLQ-LC13) was used in conjunction with the EORTC QLQ-C30 and provided information on an additional 13 items specifically

related to lung cancer. The lung cancer module incorporated one multi-item scale to assess dyspnea, and 9 single items assessing pain, coughing, sore mouth, dysphagia, peripheral neuropathy, alopecia, and hemoptysis. All of the domain scores ranged from 0 to 100. A high score indicated a high level of symptoms.
The time to definitive 10 point deterioration symptom scores of pain, cough and dyspnea was defined as the time from the date of randomization to the date of event, which was defined as at least 10 points relative to baseline worsening of the EORTC QLQ-LC13 symptom score with no later change below this threshold or death due to any cause, whichever occurred earlier.
9999 indicates that the value was not estimable

End point type	Secondary

End point timeframe:

From baseline up to approximately 4 years

End point values	Canakinumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	693	689		
Units: Months				
median (confidence interval 95%)				
Pain	9999 (35.45 to 9999)	9999 (-9999 to 9999)		
Cough	9999 (35.06 to 9999)	9999 (34.99 to 9999)		
Dyspnea	28.88 (23.10 to 34.96)	34.99 (23.13 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Canakinumab Anti-drug Antibody (ADA) prevalence at baseline

End point title	Canakinumab Anti-drug Antibody (ADA) prevalence at

End point description:

Canakinumab ADA prevalence at baseline was calculated as the percentage of participants who had an ADA positive result at baseline

End point type	Secondary

End point timeframe:

Baseline

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only participants who received canakinumab were included in this analysis

End point values	Canakinumab			
Subject group type	Reporting group			
Number of subjects analysed	692			
Units: Participants	8			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first 10 point deterioration for symptom scores of pain, cough and dyspnea per EORTC QLQ-LC13 questionnaire

End point title	Time to first 10 point deterioration for symptom scores of pain, cough and dyspnea per EORTC QLQ-LC13 questionnaire

End point description:

The Lung Cancer module of the EORTC's quality of life questionnaire (EORTC QLQ-LC13) was used in conjunction with the EORTC QLQ-C30 and provided information on an additional 13 items specifically related to lung cancer. The lung cancer module incorporated one multi-item scale to assess dyspnea, and 9 single items assessing pain, coughing, sore mouth, dysphagia, peripheral neuropathy, alopecia, and hemoptysis. All of the domain scores ranged from 0 to 100. A high score indicated a high level of symptoms.
The time to first 10 point deterioration symptom scores of pain, cough and dyspnea was defined as the time from the date of randomization to the first onset of at least 10 points absolute increase from baseline (worsening) in symptoms scores or death due to any cause, whichever occurred earlier.
9999 indicates that the value was not estimable

End point type	Secondary

End point timeframe:

From baseline up to approximately 4 years

End point values	Canakinumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	693	689		
Units: Months				
median (confidence interval 95%)				
Pain	35.15 (26.58 to 9999)	9999 (23.06 to 9999)		
Cough	15.44 (10.38 to 23.06)	15.01 (9.69 to 9999)		
Dyspnea	4.17 (3.42 to 5.55)	4.86 (3.48 to 6.97)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first 10 point deterioration of global health status/QoL, shortness of breath and pain per EORTC QLQ-C30 questionnaire

End point title	Time to first 10 point deterioration of global health status/QoL, shortness of breath and pain per EORTC QLQ-C30 questionnaire

End point description:

The EORTC QLQ-C30 was a questionnaire developed to assess the health-related quality of life of cancer participants. It assessed 15 domains consisting of 5 functional domains (physical, role, emotional, cognitive, social) and 9 symptom domains (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, financial difficulties) and a global health status/QoL scale. All domain scores ranged from 0 to 100. A high score for the functional or global health status scales indicated a high level of functioning or QoL; a high score for a symptom scale indicated a high level of symptoms.
The time to first 10 point deterioration of global health status/QoL, shortness of breath and pain scores was defined as the time from the date of randomization to the first onset of at least 10 points absolute increase from baseline (worsening) in symptoms scores or death due to any cause, whichever occurred earlier.
9999 indicates that the value was not estimable

End point type	Secondary

End point timeframe:

From baseline up to approximately 4 years

End point values	Canakinumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	693	689		
Units: Months				
median (confidence interval 95%)				
Global health status/QoL	9.23 (7.10 to 11.76)	9.07 (7.62 to 11.76)		
Shortness of breath	29.14 (23.03 to 9999)	9999 (23.13 to 9999)		
Pain	5.49 (4.21 to 6.90)	5.62 (4.17 to 7.62)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in the utility score of the EuroQoL- 5 dimension- 5 level (EQ-5D-5L)

End point title	Change from baseline in the utility score of the EuroQoL- 5 dimension- 5 level (EQ-5D-5L)

End point description:

EQ-5D-5L was a standardized questionnaire that measured health-related QoL. EQ-5D-5L consisted of two components: a health state profile and a visual analogue scale. The health state profile included five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, each with five levels ranging from 1 (no problems) to 5 (extreme problems). The EQ-5D-5L health state profile responses were converted into single index utility score, ranging from -1 to 1, where lower scores representing a higher level of dysfunction. A positive change from baseline indicated improvement. This endpoint was assessed throughout the study, including safety and efficacy follow-up (FU) visits. Safety FU visits: every 4 weeks after end of treatment up to 130 days post-last dose. Efficacy FU visits: at 18, 24, 30, 36 and 48 months post-randomization (if no recurrence observed during treatment or safety FU).
9999 indicates that the value was not estimable

End point type	Secondary

End point timeframe:

Baseline, every 3 weeks for 14 months; end of treatment; every 4 weeks up to 130 days post-treatment; at 18,24,30,36 and 48 months post-randomization (if no recurrence); 7 and 28 days post-disease progression, up to approx. 4 years.

End point values	Canakinumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	643	629		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Week 3 (n= 643 /629)	0.0 (± 0.11)	0.0 (± 0.12)		
Week 6 (n= 626 /614)	0.0 (± 0.13)	0.0 (± 0.12)		
Week 9 (n= 619 /603)	0.0 (± 0.13)	0.0 (± 0.13)		
Week 12 (n= 619 /604)	0.0 (± 0.12)	0.0 (± 0.12)		
Week 15 (n= 581 /572)	0.0 (± 0.13)	0.0 (± 0.12)		
Week 18 (n= 564 /558)	0.0 (± 0.13)	0.0 (± 0.13)		
Week 21 (n= 555 /556)	0.0 (± 0.13)	0.0 (± 0.14)		
Week 24 (n=551 /550)	0.0 (± 0.14)	0.0 (± 0.14)		
Week 27 (n=528/532)	0.0 (± 0.13)	0.0 (± 0.14)		
Week 30 (n=523/504)	0.0 (± 0.13)	0.0 (± 0.14)		
Week 33 (n=509/506)	0.0 (± 0.13)	0.0 (± 0.14)		
Week 36 (n=502/502)	0.0 (± 0.14)	0.0 (± 0.15)		
Week 39 (n=461/471)	0.0 (± 0.15)	0.0 (± 0.13)		
Week 42 (n=451/452)	0.0 (± 0.15)	0.0 (± 0.14)		
Week 45 (440/428)	0.0 (± 0.14)	0.0 (± 0.14)		
Week 48 (n=423/422)	0.0 (± 0.14)	0.0 (± 0.15)		
Week 51 (n=385/406)	0.0 (± 0.13)	0.0 (± 0.14)		
Week 54 (n=17/11)	0.0 (± 0.18)	0.1 (± 0.12)		
Week 57 (n=1/1)	0.0 (± 9999)	-0.1 (± 9999)		
Week 60 (n=1/1)	-0.2 (± 9999)	-0.1 (± 9999)		
Safety FU 1 (n=431/443)	0.0 (± 0.15)	0.0 (± 0.14)		
Safety FU 2 (n=421/432)	0.0 (± 0.14)	0.0 (± 0.14)		
Safety FU 3 (n=420/418)	0.0 (± 0.14)	0.0 (± 0.15)		
Safety FU 4 (n=392/406)	0.0 (± 0.15)	0.0 (± 0.16)		
Safety FU 5 (n=392/397)	0.0 (± 0.15)	0.0 (± 0.14)		
Efficacy FU 1 (n=237/254)	0.0 (± 0.16)	0.0 (± 0.16)		
Efficacy FU 2 (n=179/178)	0.0 (± 0.15)	0.0 (± 0.16)		
Efficacy FU 3 (n=124/116)	0.0 (± 0.14)	0.0 (± 0.15)		
Efficacy FU 4 (n=67/72)	0.0 (± 0.13)	0.0 (± 0.15)		
Efficacy FU 5 (n=15/7)	0.0 (± 0.10)	-0.1 (± 0.17)		
7 days post disease progression (n=29/22)	-0.1 (± 0.16)	-0.1 (± 0.22)		
28 days post disease progression (n=86/79)	-0.1 (± 0.18)	-0.1 (± 0.18)		
Week 63 (n=1/0)	0.0 (± 9999)	9999 (± 9999)		
Week 69 (n= 1/0)	0.0 (± 9999)	9999 (± 9999)		

Statistical analyses

No statistical analyses for this end point

Post-hoc: All collected deaths

End point title	All collected deaths

End point description:

Pre-treatment deaths were collected from day of participant’s informed consent to the day before first dose of study medication.
On-treatment deaths were collected from start of treatment to 130 days after last dose.
Post-treatment follow-up deaths were collected from day 131 after last dose of study treatment to end of study.

End point type	Post-hoc

End point timeframe:

Pre-treatment: Up to 28 days prior to treatment. On-treatment: Up to approx. 1.5 years. Post-treatment follow-up: Up to approx. 4.3 years

End point values	Canakinumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	693	689		
Units: Participants				
Pre-treatment deaths	0	0		
On-treatment deaths	9	17		
Post-treatment follow-up deaths	53	51		
All deaths	62	68		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from first dose of study treatment to 130 days after last dose of study medication (on-treatment), up to approx. 1.5 years.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Placebo

Reporting group title	Canakinumab

Reporting group description:

Canakinumab

Serious adverse events	Placebo	Canakinumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	146 / 689 (21.19%)	141 / 692 (20.38%)	
number of deaths (all causes)	17	9	
number of deaths resulting from adverse events	2	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung adenocarcinoma			
subjects affected / exposed	2 / 689 (0.29%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-small cell lung cancer			
subjects affected / exposed	0 / 689 (0.00%)	2 / 692 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	0 / 689 (0.00%)	1 / 692 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Basal cell carcinoma			
subjects affected / exposed	1 / 689 (0.15%)	3 / 692 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
B-cell lymphoma			
subjects affected / exposed	1 / 689 (0.15%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelodysplastic syndrome			
subjects affected / exposed	1 / 689 (0.15%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm swelling			
subjects affected / exposed	0 / 689 (0.00%)	1 / 692 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric cancer			
subjects affected / exposed	0 / 689 (0.00%)	1 / 692 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional cell carcinoma			
subjects affected / exposed	0 / 689 (0.00%)	2 / 692 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small cell lung cancer			
subjects affected / exposed	1 / 689 (0.15%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal neoplasm			
subjects affected / exposed	1 / 689 (0.15%)	1 / 692 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cancer			

subjects affected / exposed	1 / 689 (0.15%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal cancer stage 0			
subjects affected / exposed	0 / 689 (0.00%)	1 / 692 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	1 / 689 (0.15%)	1 / 692 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papillary thyroid cancer			
subjects affected / exposed	1 / 689 (0.15%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic carcinoma			
subjects affected / exposed	1 / 689 (0.15%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Peripheral ischaemia			
subjects affected / exposed	1 / 689 (0.15%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 689 (0.15%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	0 / 689 (0.00%)	1 / 692 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			

Chest pain			
subjects affected / exposed	2 / 689 (0.29%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	1 / 689 (0.15%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	2 / 689 (0.29%)	2 / 692 (0.29%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 689 (0.15%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 689 (0.15%)	2 / 692 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	1 / 689 (0.15%)	1 / 692 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 689 (0.00%)	1 / 692 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			

subjects affected / exposed	3 / 689 (0.44%)	1 / 692 (0.14%)	
occurrences causally related to treatment / all	2 / 5	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bronchial obstruction			
subjects affected / exposed	1 / 689 (0.15%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	0 / 689 (0.00%)	1 / 692 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sleep apnoea syndrome			
subjects affected / exposed	1 / 689 (0.15%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vocal cord polyp			
subjects affected / exposed	0 / 689 (0.00%)	1 / 692 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary thrombosis			
subjects affected / exposed	0 / 689 (0.00%)	1 / 692 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 689 (0.29%)	2 / 692 (0.29%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 689 (0.00%)	3 / 692 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			

subjects affected / exposed	0 / 689 (0.00%)	3 / 692 (0.43%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	2 / 689 (0.29%)	3 / 692 (0.43%)	
occurrences causally related to treatment / all	0 / 3	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	0 / 689 (0.00%)	1 / 692 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	0 / 689 (0.00%)	2 / 692 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 689 (0.00%)	1 / 692 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 689 (0.15%)	1 / 692 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea exertional			
subjects affected / exposed	1 / 689 (0.15%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 689 (0.29%)	7 / 692 (1.01%)	
occurrences causally related to treatment / all	0 / 2	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			

subjects affected / exposed	1 / 689 (0.15%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 689 (0.15%)	2 / 692 (0.29%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Psychiatric disorders			
Schizophrenia			
subjects affected / exposed	0 / 689 (0.00%)	1 / 692 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 689 (0.15%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 689 (0.15%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-reactive protein increased			
subjects affected / exposed	3 / 689 (0.44%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram T wave amplitude decreased			
subjects affected / exposed	1 / 689 (0.15%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	0 / 689 (0.00%)	1 / 692 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Influenza A virus test positive			
subjects affected / exposed	0 / 689 (0.00%)	1 / 692 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SARS-CoV-2 test positive			
subjects affected / exposed	2 / 689 (0.29%)	3 / 692 (0.43%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Alcohol poisoning			
subjects affected / exposed	1 / 689 (0.15%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Head injury			
subjects affected / exposed	1 / 689 (0.15%)	1 / 692 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 689 (0.15%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament rupture			
subjects affected / exposed	1 / 689 (0.15%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pneumothorax			
subjects affected / exposed	1 / 689 (0.15%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	0 / 689 (0.00%)	1 / 692 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Spinal compression fracture			
subjects affected / exposed	1 / 689 (0.15%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	2 / 689 (0.29%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 689 (0.15%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	2 / 689 (0.29%)	3 / 692 (0.43%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 689 (0.00%)	2 / 692 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 689 (0.15%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 689 (0.00%)	1 / 692 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure			
subjects affected / exposed	1 / 689 (0.15%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			

subjects affected / exposed	0 / 689 (0.00%)	1 / 692 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac ventricular thrombosis			
subjects affected / exposed	1 / 689 (0.15%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiovascular insufficiency			
subjects affected / exposed	1 / 689 (0.15%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 689 (0.15%)	1 / 692 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	4 / 689 (0.58%)	1 / 692 (0.14%)	
occurrences causally related to treatment / all	1 / 4	0 / 1	
deaths causally related to treatment / all	1 / 2	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	2 / 689 (0.29%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pericarditis constrictive			
subjects affected / exposed	1 / 689 (0.15%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 689 (0.00%)	1 / 692 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			

subjects affected / exposed	1 / 689 (0.15%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Epilepsy			
subjects affected / exposed	0 / 689 (0.00%)	1 / 692 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	4 / 689 (0.58%)	4 / 692 (0.58%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebral infarction			
subjects affected / exposed	1 / 689 (0.15%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Carotid artery occlusion			
subjects affected / exposed	1 / 689 (0.15%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aphasia			
subjects affected / exposed	1 / 689 (0.15%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Altered state of consciousness			
subjects affected / exposed	1 / 689 (0.15%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised tonic-clonic seizure			
subjects affected / exposed	1 / 689 (0.15%)	1 / 692 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			

subjects affected / exposed	1 / 689 (0.15%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Partial seizures			
subjects affected / exposed	1 / 689 (0.15%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral nerve palsy			
subjects affected / exposed	0 / 689 (0.00%)	1 / 692 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulnar nerve palsy			
subjects affected / exposed	0 / 689 (0.00%)	1 / 692 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombotic cerebral infarction			
subjects affected / exposed	0 / 689 (0.00%)	1 / 692 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 689 (0.15%)	1 / 692 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Thrombocytosis			
subjects affected / exposed	1 / 689 (0.15%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	1 / 689 (0.15%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			

Vertigo			
subjects affected / exposed	1 / 689 (0.15%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal detachment			
subjects affected / exposed	1 / 689 (0.15%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhegmatogenous retinal detachment			
subjects affected / exposed	0 / 689 (0.00%)	1 / 692 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal tear			
subjects affected / exposed	1 / 689 (0.15%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Rectal haemorrhage			
subjects affected / exposed	1 / 689 (0.15%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal hernia			
subjects affected / exposed	0 / 689 (0.00%)	1 / 692 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	2 / 689 (0.29%)	3 / 692 (0.43%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 689 (0.00%)	1 / 692 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Constipation			
subjects affected / exposed	1 / 689 (0.15%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 689 (0.15%)	1 / 692 (0.14%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	0 / 689 (0.00%)	1 / 692 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	2 / 689 (0.29%)	1 / 692 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal pain			
subjects affected / exposed	1 / 689 (0.15%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	1 / 689 (0.15%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine polyp			
subjects affected / exposed	1 / 689 (0.15%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar hernia			
subjects affected / exposed	0 / 689 (0.00%)	1 / 692 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic cyst			

subjects affected / exposed	0 / 689 (0.00%)	1 / 692 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 689 (0.15%)	1 / 692 (0.14%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 689 (0.15%)	1 / 692 (0.14%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Biliary colic			
subjects affected / exposed	1 / 689 (0.15%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	3 / 689 (0.44%)	1 / 692 (0.14%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 689 (0.15%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder obstruction			
subjects affected / exposed	0 / 689 (0.00%)	1 / 692 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis acute			
subjects affected / exposed	0 / 689 (0.00%)	1 / 692 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			

Dermatitis acneiform			
subjects affected / exposed	1 / 689 (0.15%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	1 / 689 (0.15%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	0 / 689 (0.00%)	1 / 692 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal haemorrhage			
subjects affected / exposed	1 / 689 (0.15%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	2 / 689 (0.29%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	1 / 689 (0.15%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	0 / 689 (0.00%)	1 / 692 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus urinary			
subjects affected / exposed	0 / 689 (0.00%)	1 / 692 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue			

disorders			
Tenosynovitis			
subjects affected / exposed	0 / 689 (0.00%)	1 / 692 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 689 (0.15%)	1 / 692 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	1 / 689 (0.15%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	3 / 689 (0.44%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	0 / 689 (0.00%)	2 / 692 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
COVID-19			
subjects affected / exposed	48 / 689 (6.97%)	48 / 692 (6.94%)	
occurrences causally related to treatment / all	2 / 50	0 / 50	
deaths causally related to treatment / all	0 / 1	0 / 1	
Appendicitis			
subjects affected / exposed	1 / 689 (0.15%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asymptomatic COVID-19			
subjects affected / exposed	0 / 689 (0.00%)	1 / 692 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bronchitis			
subjects affected / exposed	1 / 689 (0.15%)	2 / 692 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	4 / 689 (0.58%)	1 / 692 (0.14%)	
occurrences causally related to treatment / all	1 / 4	0 / 1	
deaths causally related to treatment / all	1 / 2	0 / 0	
Sepsis			
subjects affected / exposed	1 / 689 (0.15%)	1 / 692 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronavirus infection			
subjects affected / exposed	1 / 689 (0.15%)	1 / 692 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 689 (0.15%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			
subjects affected / exposed	0 / 689 (0.00%)	1 / 692 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	1 / 689 (0.15%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 689 (0.15%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection parasitic			

subjects affected / exposed	0 / 689 (0.00%)	1 / 692 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney infection			
subjects affected / exposed	1 / 689 (0.15%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	1 / 689 (0.15%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung abscess			
subjects affected / exposed	0 / 689 (0.00%)	1 / 692 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	2 / 689 (0.29%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	9 / 689 (1.31%)	13 / 692 (1.88%)	
occurrences causally related to treatment / all	2 / 10	1 / 13	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia pseudomonal			
subjects affected / exposed	0 / 689 (0.00%)	1 / 692 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal abscess			
subjects affected / exposed	1 / 689 (0.15%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			

subjects affected / exposed	2 / 689 (0.29%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 689 (0.00%)	1 / 692 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 689 (0.00%)	1 / 692 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Tuberculosis			
subjects affected / exposed	0 / 689 (0.00%)	1 / 692 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 689 (0.15%)	1 / 692 (0.14%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 689 (0.15%)	0 / 692 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 689 (0.15%)	1 / 692 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 689 (0.15%)	1 / 692 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Placebo	Canakinumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	455 / 689 (66.04%)	465 / 692 (67.20%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	49 / 689 (7.11%)	65 / 692 (9.39%)	
occurrences (all)	68	102	
Amylase increased			
subjects affected / exposed	51 / 689 (7.40%)	52 / 692 (7.51%)	
occurrences (all)	70	83	
Lipase increased			
subjects affected / exposed	47 / 689 (6.82%)	47 / 692 (6.79%)	
occurrences (all)	79	68	
Neutrophil count decreased			
subjects affected / exposed	13 / 689 (1.89%)	45 / 692 (6.50%)	
occurrences (all)	23	105	
Weight increased			
subjects affected / exposed	48 / 689 (6.97%)	63 / 692 (9.10%)	
occurrences (all)	68	90	
White blood cell count decreased			
subjects affected / exposed	18 / 689 (2.61%)	35 / 692 (5.06%)	
occurrences (all)	30	93	
Aspartate aminotransferase increased			
subjects affected / exposed	37 / 689 (5.37%)	53 / 692 (7.66%)	
occurrences (all)	45	76	
Vascular disorders			
Hypertension			
subjects affected / exposed	24 / 689 (3.48%)	35 / 692 (5.06%)	
occurrences (all)	27	40	
Nervous system disorders			
Headache			
subjects affected / exposed	60 / 689 (8.71%)	31 / 692 (4.48%)	
occurrences (all)	72	37	
Paraesthesia			

subjects affected / exposed	44 / 689 (6.39%)	29 / 692 (4.19%)	
occurrences (all)	48	32	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	50 / 689 (7.26%)	46 / 692 (6.65%)	
occurrences (all)	56	57	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	43 / 689 (6.24%)	28 / 692 (4.05%)	
occurrences (all)	47	30	
Fatigue			
subjects affected / exposed	60 / 689 (8.71%)	70 / 692 (10.12%)	
occurrences (all)	84	92	
Asthenia			
subjects affected / exposed	33 / 689 (4.79%)	47 / 692 (6.79%)	
occurrences (all)	38	61	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	42 / 689 (6.10%)	34 / 692 (4.91%)	
occurrences (all)	56	38	
Diarrhoea			
subjects affected / exposed	48 / 689 (6.97%)	57 / 692 (8.24%)	
occurrences (all)	66	84	
Nausea			
subjects affected / exposed	51 / 689 (7.40%)	46 / 692 (6.65%)	
occurrences (all)	61	63	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	108 / 689 (15.67%)	89 / 692 (12.86%)	
occurrences (all)	143	117	
Dyspnoea			
subjects affected / exposed	50 / 689 (7.26%)	67 / 692 (9.68%)	
occurrences (all)	55	80	
Skin and subcutaneous tissue disorders			
Pruritus			

subjects affected / exposed	34 / 689 (4.93%)	35 / 692 (5.06%)	
occurrences (all)	37	43	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	88 / 689 (12.77%)	74 / 692 (10.69%)	
occurrences (all)	108	83	
Back pain			
subjects affected / exposed	56 / 689 (8.13%)	61 / 692 (8.82%)	
occurrences (all)	68	64	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	33 / 689 (4.79%)	44 / 692 (6.36%)	
occurrences (all)	38	49	
Upper respiratory tract infection			
subjects affected / exposed	31 / 689 (4.50%)	37 / 692 (5.35%)	
occurrences (all)	36	45	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 December 2018	Included a biomarker sub-study which collected pre- and post- resection surgery blood samples. Central ECG collection was replaced by local ECG at screening and as clinically indicated. Updated dose interruption schedule related to Drug Induced Liver Injury (DILI). Updated the contraception language. Reduced number of C1D2 and C1D3 pharmacokinetics samples. Made clarifications, editorial and typographic changes
05 February 2020	Allowed sites the flexibility to perform hematology, chemistry, and coagulation based on local laboratory results allowed for same-day safety evaluations. The remaining blood specimens collected as part of safety monitoring (e.g., HIV screen, HbsAg, HCV antibody) continued to be performed by central laboratory. Additional minor protocol language clarification updates were made throughout the amendment.
03 February 2022	Second DFS IA removal. Inclusion as a secondary endpoint the comparison between the canakinumab and placebo arms of DFS by investigator local assessment and OS in subgroups defined respectively by PD-L1 and CD8 expression Time to first 10-point deterioration addition for symptoms and global health status/QoL as a secondary patient-reported outcomes variable of interest Disruption proofing language addition

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported