Clinical trial results:
Phase 3 multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of canakinumab on cytokine release syndrome in patients with COVID-19-induced pneumonia (CAN-COVID)

Summary

EudraCT number	2020-001370-30
Trial protocol	DE GB FR ES HU IT
Global end of trial date	22 December 2020

Results information

Result version number	v1 (current)
This version publication date	15 August 2021
First version publication date	15 August 2021

Trial information

Trial identification

Sponsor protocol code	CACZ885D2310

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04362813
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharmaceuticals
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, novartis.email@novartis.com
Scientific contact	Study Director, Novartis Pharmaceuticals, 1 862 7788300, novartis.email@novartis.com
Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis PPharma AG, 41 613241111, novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,

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	23 February 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 December 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this trial was to demonstrate the benefit of canakinumab + SOC in increasing chance of survival without ever requiring invasive mechanical ventilation among patients with COVID-19-induced pneumonia and CRS

Protection of trial subjects:

This 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	30 April 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	Russian Federation: 153
Country: Number of subjects enrolled	Spain: 34
Country: Number of subjects enrolled	United Kingdom: 11
Country: Number of subjects enrolled	United States: 253
Worldwide total number of subjects	454
EEA total number of subjects	37

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)	304
From 65 to 84 years	142
85 years and over	8

Subject disposition

Recruitment

Recruitment details:

Participants took part at 39 investigative sites in 6 countries.

While patient flow shows 454 participants enrolled, only 451 randomized. 3 were "mis-randomized" i.e. assigned a randomization number in error and not treated.

Pre-assignment

Screening details:

Participants were screened within 24 hours prior to enrollment.

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

Blinding implementation details:

This was a double-blind, randomized, placebo-controlled trial. Participants, all site staff (including study investigator and study nurse), persons performing the assessments, and clinical trial team remained blinded to the identity of the treatment from the time of randomization until database lock for the primary analysis.

Arms

Are arms mutually exclusive?	Yes
Arm title	Canakinumab

Arm description:

Canakinumab 450 mg for body weight 40-<60 kg, 600 mg for 60-80 kg or 750 mg for >80 kg in 250 mL of 5% dextrose infused IV over 2 hours. Single dose on Day 1.

Arm type	Experimental
Investigational medicinal product name	I.V. infusion
Investigational medicinal product code	ACZ885
Other name	canakinumab
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Canakinumab (450 mg for body weight of 40-<60 kg, 600 mg for 60-80 kg or 750 mg for >80 kg) versus placebo in 250mL of 5% dextrose administered by intravenous infusion over 2 hours.

Arm title	Placebo

Arm description:

250 mL of 5% dextrose infused IV over 2 hours. Single dose on Day 1.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	Placebo
Other name	Dextrose
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

I.V. infusion

Number of subjects in period 1	Canakinumab	Placebo
Started	227	227
Safety set	225	223
Completed	209	202
Not completed	18	25
Adverse event, serious fatal	12	16
Consent withdrawn by subject	3	1
Enrolled but did not receive treatment	2	4
Lost to follow-up	1	1
Protocol deviation	-	3

Baseline characteristics

Reporting groups	
Reporting group title	Canakinumab
Reporting group description:	
Canakinumab 450 mg for body weight 40-<60 kg, 600 mg for 60-80 kg or 750 mg for >80 kg in 250 mL of 5% dextrose infused IV over 2 hours. Single dose on Day 1.	
Reporting group title	Placebo
Reporting group description:	
250 mL of 5% dextrose infused IV over 2 hours. Single dose on Day 1.	

Reporting group values	Canakinumab	Placebo	Total
Number of subjects	227	227	454
Age Categorical			
Units:			
< 18 years	0	0	0
Between 18 and 64 years	149	155	304
>=65 years	78	72	150
Age Continuous			
Units: years			
arithmetic mean	58.5	57.8	
standard deviation	± 14.55	± 13.89	-
Sex: Female, Male			
Units:			
Female	92	95	187
Male	135	132	267
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	3	8	11
Asian	10	9	19
Native Hawaiian or Other Pacific Islander	1	5	6
Black or African American	35	37	72
White	159	156	315
More than one race	0	0	0
Unknown or Not Reported	19	12	31

End points

End points reporting groups

Reporting group title	Canakinumab
Reporting group description:	
Canakinumab 450 mg for body weight 40-<60 kg, 600 mg for 60-80 kg or 750 mg for >80 kg in 250 mL of 5% dextrose infused IV over 2 hours. Single dose on Day 1.	
Reporting group title	Placebo
Reporting group description:	
250 mL of 5% dextrose infused IV over 2 hours. Single dose on Day 1.	

Primary: Participants who survived without requiring invasive mechanical ventilation from Day 3 to Day 29, Primary analysis

End point title	Participants who survived without requiring invasive mechanical ventilation from Day 3 to Day 29, Primary analysis
End point description:	
Number of responders who survived without requiring invasive mechanical ventilation from Day 3 to Day 29. An early dropout without requiring invasive mechanical ventilation is considered as a responder if discharged from hospital with 9-point ordinal scale<=1 or with last 9-point ordinal scale on/after Day 15 better than baseline.	
End point type	Primary
End point timeframe:	
Day 3 to Day 29	

End point values	Canakinumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	223	223		
Units: participants	198	191		

Statistical analyses

Statistical analysis title	Responders who survived without ventilation
Statistical analysis description:	
Odds ratio is based on a Logistic regression model adjusted by treatment, region (North America vs Europe), and baseline 9-point ordinal scale (<=4, >=5).	
Comparison groups	Canakinumab v Placebo
Number of subjects included in analysis	446
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2874
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.39

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	2.54

Secondary: COVID-19-related death after study treatment

End point title	COVID-19-related death after study treatment
End point description:	
Participants with COVID-19 related (as assessed by investigator) death up to Day 29	
End point type	Secondary
End point timeframe:	
29 days	

End point values	Canakinumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	223	222		
Units: participants	11	16		

Statistical analyses

Statistical analysis title	Participants with COVID-19 related death
Statistical analysis description:	
Odds ratio is based on a Logistic regression model adjusted by treatment, region (North America vs Europe), and baseline 9-point ordinal scale (<=4, >=5)	
Comparison groups	Canakinumab v Placebo
Number of subjects included in analysis	445
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3303
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	1.5

Secondary: Geometric Mean Ratio to baseline in the C-reactive protein (CRP)

End point title	Geometric Mean Ratio to baseline in the C-reactive protein

	(CRP)

End point description:

Measurement of C Reactive Protein (mg/L), Serum Or Plasma over time. The level of C-reactive protein (CRP), which can be measured in the blood, increases when there's inflammation in the body. Lower values of ratio to baseline in the CRP indicates less inflammation. The ratio to baseline at each time point (day) for each patient is calculated as the level of a specific biomarker at the time point divided by the baseline level of the biomarker, where baseline is the last non-missing value before study treatment. The geometric mean of ratio to baseline at each time point for each treatment group is calculated by first averaging the logarithms of the ratios to baseline and then take the exponential function of the same base.

End point type	Secondary

End point timeframe:

Over time and up to day 29: Baseline, Day 2, Day 3, Day 5, Day 7, Day 9, Day 11, Day 13, Day 15, Day 17, Day 19, Day 21, Day 23, Day 25, Day 27 and Day 29.

End point values	Canakinumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	227	227		
Units: ratio				
geometric mean (confidence interval 95%)				
Day 2	0.726 (0.671 to 0.786)	0.785 (0.722 to 0.853)		
Day 3	0.479 (0.430 to 0.534)	0.649 (0.578 to 0.729)		
Day 5	0.255 (0.222 to 0.292)	0.384 (0.325 to 0.454)		
Day 7	0.160 (0.129 to 0.198)	0.238 (0.195 to 0.290)		
Day 9	0.131 (0.101 to 0.171)	0.159 (0.126 to 0.201)		
Day 11	0.099 (0.073 to 0.133)	0.133 (0.096 to 0.185)		
Day 13	0.108 (0.072 to 0.162)	0.141 (0.087 to 0.228)		
Day 15	0.133 (0.086 to 0.205)	0.149 (0.088 to 0.252)		
Day 17	0.123 (0.069 to 0.220)	0.289 (0.189 to 0.441)		
Day 19	0.123 (0.059 to 0.255)	0.368 (0.227 to 0.598)		
Day 21	0.115 (0.053 to 0.247)	0.296 (0.164 to 0.533)		
Day 23	0.106 (0.036 to 0.311)	0.400 (0.201 to 0.796)		
Day 25	0.126 (0.024 to 0.633)	0.368 (0.160 to 0.846)		
Day 27	0.175 (0.041 to 0.743)	0.331 (0.152 to 0.720)		
Day 29	0.240 (0.052 to 1.106)	0.258 (0.121 to 0.551)		

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Ratio to baseline in the D-dimer

End point title	Geometric Mean Ratio to baseline in the D-dimer

End point description:

Clinical chemistry measurement D-Dimer (mg/L FEU), Blood in a blood sample over time

D-dimer is one of the protein fragments produced when a blood clot gets dissolved in the body. The ratio to baseline at each time point (day) for each patient is calculated as the level of a specific biomarker at the time point divided by the baseline level of the biomarker, where baseline is the last non-missing value before study treatment. The geometric mean of ratio to baseline at each time point for each treatment group is calculated by first averaging the logarithms of the ratios to baseline and then take the exponential function of the same base.

End point type	Secondary

End point timeframe:

Over time and up to day 29: Baseline, Day 2, Day 3, Day 5, Day 7, Day 9, Day 11, Day 13, Day 15, Day 17, Day 19, Day 21, Day 23, Day 25, Day 27 and Day 29.

End point values	Canakinumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	227	227		
Units: ratio				
geometric mean (confidence interval 95%)				
Day 2	1.032 (0.910 to 1.170)	1.028 (0.948 to 1.114)		
Day 3	0.992 (0.866 to 1.135)	1.188 (1.004 to 1.242)		
Day 5	1.094 (0.971 to 1.233)	1.188 (1.061 to 1.330)		
Day 7	1.038 (0.851 to 1.267)	1.244 (1.088 to 1.422)		
Day 9	1.164 (0.961 to 1.410)	1.184 (1.003 to 1.422)		
Day 11	1.162 (0.929 to 1.453)	1.115 (0.896 to 1.388)		
Day 13	1.135 (0.891 to 1.447)	1.184 (0.927 to 1.513)		
Day 15	1.100 (0.800 to 1.514)	1.078 (0.862 to 1.349)		
Day 17	1.033 (0.698 to 1.528)	1.384 (1.041 to 1.838)		
Day 19	1.520 (0.853 to 2.711)	1.446 (1.005 to 2.081)		
Day 21	1.431 (0.770 to 2.659)	1.443 (0.958 to 2.172)		
Day 23	1.208 (0.495 to 2.950)	1.521 (1.093 to 2.118)		
Day 25	2.670 (0.362 to 3.891)	1.808 (0.969 to 3.371)		
Day 27	1.785 (0.644 to 4.949)	2.262 (1.008 to 5.075)		
Day 29	1.818 (0.627 to 5.270)	2.441 (0.912 to 6.534)		

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Ratio to baseline in Ferritin

End point title	Geometric Mean Ratio to baseline in Ferritin

End point description:

Clinical chemistry measurement for amount of ferritin (ug/L) in Serum. The ratio to baseline at each time point (day) for each patient is calculated as the level of a specific biomarker at the time point divided by the baseline level of the biomarker, where baseline is the last non-missing value before study treatment. The geometric mean of ratio to baseline at each time point for each treatment group is calculated by first averaging the logarithms of the ratios to baseline and then take the exponential function of the same base.

End point type	Secondary

End point timeframe:

Over time and up to day 29: Baseline, Day 2, Day 3, Day 5, Day 7, Day 9, Day 11, Day 13, Day 15, Day 17, Day 19, Day 21, Day 23, Day 25, Day 27 and Day 29.

End point values	Canakinumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	227	227		
Units: ratio				
geometric mean (confidence interval 95%)				
Day 2	0.996 (0.953 to 1.040)	1.014 (0.972 to 1.058)		
Day 3	0.921 (0.870 to 0.976)	1.014 (0.954 to 1.077)		
Day 5	0.825 (0.765 to 0.889)	0.879 (0.810 to 0.953)		
Day 7	0.761 (0.701 to 0.826)	0.815 (0.742 to 0.896)		
Day 9	0.676 (0.609 to 0.751)	0.764 (0.679 to 0.859)		
Day 11	0.618 (0.548 to 0.698)	0.735 (0.637 to 0.849)		
Day 13	0.582 (0.501 to 0.675)	0.684 (0.563 to 0.830)		
Day 15	0.535 (0.448 to 0.638)	0.618 (0.510 to 0.750)		
Day 17	0.534 (0.449 to 0.634)	0.641 (0.495 to 0.832)		
Day 19	0.545 (0.420 to 0.707)	0.644 (0.464 to 0.893)		
Day 21	0.514 (0.377 to 0.700)	0.644 (0.439 to 0.944)		
Day 23	0.469 (0.294 to 0.749)	0.692 (0.432 to 1.109)		

Day 25	0.542 (0.310 to 0.945)	0.745 (0.524 to 1.059)		
Day 27	0.490 (0.299 to 0.802)	0.809 (0.480 to 1.363)		
Day 29	0.543 (0.212 to 1.393)	0.517 (0.298 to 0.896)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with treatment emergent adverse events

End point title	Number of participants with treatment emergent adverse events

End point description:

Number of participants with treatment emergent adverse events, including changes from baseline in vital signs and laboratory results qualifying and reported as adverse events.

Safety was monitored from the canakinumab or placebo dose (Day 1) up to 126 days post-dose (Day 127).

End point type	Secondary

End point timeframe:

Up to day 127

End point values	Canakinumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	225	223		
Units: participants	141	140		

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 until end of study at day 127

Adverse event reporting additional description:

Adverse Events (AEs) are any untoward sign or symptom that occurs during the study treatment. Adverse events and all-cause mortality are evaluated in the Safety Set that includes all participants who received at least one dose of double-blind treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Canakinumab

Reporting group description:

Canakinumab 450 mg for body weight 40-<60 kg, 600 mg for 60-80 kg or 750 mg for >80 kg in 250 mL of 5% dextrose infused IV over 2 hours. Single dose on Day 1.

Reporting group title	Placebo

Reporting group description:

250 mL of 5% dextrose infused IV over 2 hours. Single dose on Day 1.

Serious adverse events	Canakinumab	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	47 / 225 (20.89%)	53 / 223 (23.77%)	
number of deaths (all causes)	22	26	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	1 / 225 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	0 / 225 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to liver			
subjects affected / exposed	1 / 225 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Vascular disorders			
Haemodynamic instability			
subjects affected / exposed	0 / 225 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	2 / 225 (0.89%)	3 / 223 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jugular vein thrombosis			
subjects affected / exposed	0 / 225 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery occlusion			
subjects affected / exposed	0 / 225 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	1 / 225 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral vascular disorder			
subjects affected / exposed	1 / 225 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock			
subjects affected / exposed	1 / 225 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 225 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 225 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	1 / 225 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Haemophagocytic lymphohistiocytosis			
subjects affected / exposed	1 / 225 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	0 / 225 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute lung injury			
subjects affected / exposed	0 / 225 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute pulmonary oedema			
subjects affected / exposed	1 / 225 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory distress syndrome			
subjects affected / exposed	6 / 225 (2.67%)	3 / 223 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			

subjects affected / exposed	12 / 225 (5.33%)	13 / 223 (5.83%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atelectasis			
subjects affected / exposed	0 / 225 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 225 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 225 (0.44%)	3 / 223 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	1 / 225 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemothorax			
subjects affected / exposed	1 / 225 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	2 / 225 (0.89%)	4 / 223 (1.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 225 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumomediastinum			

subjects affected / exposed	1 / 225 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 225 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	2 / 225 (0.89%)	3 / 223 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 225 (0.00%)	2 / 223 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	0 / 225 (0.00%)	2 / 223 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	8 / 225 (3.56%)	8 / 223 (3.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Bipolar disorder			
subjects affected / exposed	1 / 225 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	0 / 225 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			

Wound necrosis			
subjects affected / exposed	1 / 225 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 225 (0.44%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 225 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	0 / 225 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 225 (0.44%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 225 (0.44%)	2 / 223 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	0 / 225 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	1 / 225 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			

subjects affected / exposed	2 / 225 (0.89%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	2 / 225 (0.89%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 225 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 225 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulseless electrical activity			
subjects affected / exposed	0 / 225 (0.00%)	2 / 223 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	0 / 225 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	0 / 225 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	0 / 225 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			

subjects affected / exposed	1 / 225 (0.44%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	1 / 225 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 225 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 225 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 225 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood loss anaemia			
subjects affected / exposed	0 / 225 (0.00%)	2 / 223 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coagulopathy			
subjects affected / exposed	1 / 225 (0.44%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 225 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			

subjects affected / exposed	1 / 225 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	1 / 225 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	2 / 225 (0.89%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 225 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal motility disorder			
subjects affected / exposed	0 / 225 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 225 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 225 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 225 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			

Drug reaction with eosinophilia and systemic symptoms			
subjects affected / exposed	0 / 225 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	3 / 225 (1.33%)	7 / 223 (3.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	1 / 225 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 225 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	0 / 225 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal injury			
subjects affected / exposed	0 / 225 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthritis reactive			
subjects affected / exposed	1 / 225 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			

subjects affected / exposed	0 / 225 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	1 / 225 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess limb			
subjects affected / exposed	1 / 225 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Antibiotic associated colitis			
subjects affected / exposed	2 / 225 (0.89%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial sepsis			
subjects affected / exposed	1 / 225 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	2 / 225 (0.89%)	3 / 223 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	1 / 225 (0.44%)	3 / 223 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Candida infection			
subjects affected / exposed	0 / 225 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			

subjects affected / exposed	0 / 225 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 225 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal bacteraemia			
subjects affected / exposed	1 / 225 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis viral			
subjects affected / exposed	1 / 225 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	1 / 225 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 225 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella infection			
subjects affected / exposed	0 / 225 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 225 (0.89%)	3 / 223 (1.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			

subjects affected / exposed	1 / 225 (0.44%)	2 / 223 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia escherichia			
subjects affected / exposed	0 / 225 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia fungal			
subjects affected / exposed	1 / 225 (0.44%)	0 / 223 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia haemophilus			
subjects affected / exposed	0 / 225 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pseudomonal			
subjects affected / exposed	0 / 225 (0.00%)	2 / 223 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia staphylococcal			
subjects affected / exposed	0 / 225 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	3 / 225 (1.33%)	2 / 223 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	3 / 225 (1.33%)	5 / 223 (2.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			

subjects affected / exposed	0 / 225 (0.00%)	2 / 223 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 225 (0.00%)	1 / 223 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Canakinumab	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 225 (6.67%)	19 / 223 (8.52%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	12 / 225 (5.33%)	10 / 223 (4.48%)	
occurrences (all)	0	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 225 (2.67%)	12 / 223 (5.38%)	
occurrences (all)	0	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 June 2020	1- A clarification on source data verification approaches was included to align with the EMA Guidance on the Management Of Clinical Trials During The COVID-19 (Coronavirus) Pandemic (Version 3, 28APR20); 2- As requested by FDA, inclusion criteria 2 was updated to allow patients ≥ 12 years of age to be included in the trial in the US only (However, no children were ever enrolled. This was an adult trial); 3- Other minor points were also updated or corrected to further optimize the clinical trial protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported