



Clinical trial results:

A PHASE 2, MULTICENTER, RANDOMIZED, DOUBLEBLIND, PLACEBO-CONTROLLED STUDY TO EVALUATE THE EFFICACY AND SAFETY OF CC-220 IN SUBJECTS WITH ACTIVE SYSTEMIC LUPUS ERYTHEMATOSUS

Summary

EudraCT number	2016-004574-17
Trial protocol	ES HU DE BE FR
Global end of trial date	03 August 2021

Results information

Result version number	v1 (current)
This version publication date	18 August 2022
First version publication date	18 August 2022

Trial information

Trial identification

Sponsor protocol code	CC-220-SLE-002
-----------------------	----------------

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb
Sponsor organisation address	Chaussée de la Hulpe 185, Brussels, Belgium,
Public contact	Bristol-Myers Squibb International, EU Study Start-Up Unit, Clinical.Trials@bms.com
Scientific contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.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	10 November 2021
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	03 August 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the clinical efficacy of three doses of CC-220 (0.45 mg once per day [QD], 0.3 mg QD or 0.15 mg QD) compared to placebo, for the treatment of active systemic lupus erythematosus (SLE) using the SLE Responder Index at Week 24

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 July 2017
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	Belgium: 1
Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	Hungary: 22
Country: Number of subjects enrolled	Poland: 30
Country: Number of subjects enrolled	Serbia: 24
Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	United States: 58
Country: Number of subjects enrolled	Russian Federation: 15
Country: Number of subjects enrolled	Mexico: 54
Country: Number of subjects enrolled	Brazil: 6
Country: Number of subjects enrolled	Colombia: 40
Country: Number of subjects enrolled	Argentina: 23
Worldwide total number of subjects	288
EEA total number of subjects	63

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)	270
From 65 to 84 years	18
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Placebo-controlled phase: 289 participants were randomized and 288 treated

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

Arms

Are arms mutually exclusive?	Yes
------------------------------	-----

Arm title	PBO QD
------------------	--------

Arm description:

Placebo-matching treatment once a day

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

size #4 matching placebo identical in appearance to CC-220

0.15 mg, and 0.3 mg, and size #3 matching placebo identical in appearance to CC-220 0.45 mg formulated capsules

Arm title	0.45 mg QD
------------------	------------

Arm description:

Participants dosed with CC-220 at 0.45 mg once a day

Arm type	Experimental
Investigational medicinal product name	CC-220
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

0.45 mg (size#3) formulated capsules

Arm title	0.15 mg QD
------------------	------------

Arm description:

Participants dosed with CC-220 at 0.15 mg once a day

Arm type	Experimental
Investigational medicinal product name	CC-220
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:
0.15 mg (size #4) formulated capsules

Arm title	0.30 mg QD
Arm description: Participants dosed with CC-220 at 0.30 mg once a day	
Arm type	Experimental
Investigational medicinal product name	CC-220
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:
0.3 mg (size #4) formulated capsules

Number of subjects in period 1	PBO QD	0.45 mg QD	0.15 mg QD
Started	83	81	42
Going to 0.30mg after week 24	36 ^[1]	0 ^[2]	0 ^[3]
going to 0.45mg after week 24	36 ^[4]	0 ^[5]	0 ^[6]
Staying on Placebo after week 24	11 ^[7]	0 ^[8]	0 ^[9]
Completed	73	73	39
Not completed	10	8	3
Adverse event, serious fatal	1	-	-
Consent withdrawn by subject	2	5	2
Adverse event, non-fatal	5	2	1
Pregnancy	1	-	-
Other reasons	1	1	-
Lost to follow-up	-	-	-
Lack of efficacy	-	-	-
Protocol deviation	-	-	-

Number of subjects in period 1	0.30 mg QD
Started	82
Going to 0.30mg after week 24	0 ^[10]
going to 0.45mg after week 24	0 ^[11]
Staying on Placebo after week 24	0 ^[12]
Completed	62
Not completed	20
Adverse event, serious fatal	-

Consent withdrawn by subject	6
Adverse event, non-fatal	11
Pregnancy	-
Other reasons	-
Lost to follow-up	1
Lack of efficacy	1
Protocol deviation	1

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: 36 Subjects entered the .30mg dosing after week 24

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: 36 Subjects entered the 0.45mg dosing after week 24

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: 0 Subjects entered the 0.15mg dosing after week 24

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: 36 Subjects entered the .30mg and 0.45mg dosing after week 24

[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: 36 Subjects entered the 0.45mg dosing after week 24

[6] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: 0 Subjects entered the 0.15mg dosing after week 24

[7] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: 36 Subjects entered the .30mg and 0.45mg dosing after week 24

[8] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: 36 Subjects entered the 0.45mg dosing after week 24

[9] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: 0 Subjects entered the 0.15mg dosing after week 24

[10] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: 36 Subjects entered the .30mg dosing after week 24

[11] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: 36 Subjects entered the 0.30mg dosing after week 24

[12] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: 36 Subjects entered the .30mg dosing after week 24

Baseline characteristics

Reporting groups

Reporting group title	PBO QD
Reporting group description:	
Placebo-matching treatment once a day	
Reporting group title	0.45 mg QD
Reporting group description:	
Participants dosed with CC-220 at 0.45 mg once a day	
Reporting group title	0.15 mg QD
Reporting group description:	
Participants dosed with CC-220 at 0.15 mg once a day	
Reporting group title	0.30 mg QD
Reporting group description:	
Participants dosed with CC-220 at 0.30 mg once a day	

Reporting group values	PBO QD	0.45 mg QD	0.15 mg QD
Number of subjects	83	81	42
Age Categorical			
Units: Participants			
< 40 years old	33	24	15
>= 40 to <= 50	26	28	15
> 50 to < 65	19	24	10
>= 65	5	5	2
Age Continuous			
Units: Years			
arithmetic mean	43.4	46.4	43.8
standard deviation	± 13.3	± 11.2	± 13.0
Sex: Female, Male			
Units: Participants			
Female	81	79	41
Male	2	2	1
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	41	33	21
Not Hispanic or Latino	42	48	21
Unknown or Not Reported	0	0	0
Race/Ethnicity, Customized			
Units: Subjects			
American Indian or Alaska Native	2	5	5
Asian	0	0	0
Black or African American	7	5	3
Native Hawaiian or Other Pacific Islander	0	0	0
White	60	60	29
Not collected or reported	0	0	0
Other	14	11	5

Reporting group values	0.30 mg QD	Total	
------------------------	------------	-------	--

Number of subjects	82	288	
Age Categorical			
Units: Participants			
< 40 years old	31	103	
>= 40 to <= 50	21	90	
> 50 to < 65	24	77	
>= 65	6	18	
Age Continuous			
Units: Years			
arithmetic mean	44.7		
standard deviation	± 13.7	-	
Sex: Female, Male			
Units: Participants			
Female	77	278	
Male	5	10	
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	46	141	
Not Hispanic or Latino	36	147	
Unknown or Not Reported	0	0	
Race/Ethnicity, Customized			
Units: Subjects			
American Indian or Alaska Native	1	13	
Asian	1	1	
Black or African American	6	21	
Native Hawaiian or Other Pacific Islander	0	0	
White	59	208	
Not collected or reported	0	0	
Other	15	45	

End points

End points reporting groups

Reporting group title	PBO QD
Reporting group description: Placebo-matching treatment once a day	
Reporting group title	0.45 mg QD
Reporting group description: Participants dosed with CC-220 at 0.45 mg once a day	
Reporting group title	0.15 mg QD
Reporting group description: Participants dosed with CC-220 at 0.15 mg once a day	
Reporting group title	0.30 mg QD
Reporting group description: Participants dosed with CC-220 at 0.30 mg once a day	

Primary: Number of participants who achieve SLE Responder Index (SRI) (4) response

End point title	Number of participants who achieve SLE Responder Index (SRI) (4) response
End point description: The primary objective is to evaluate the clinical efficacy of three doses of CC-220 (0.45 mg once per day [QD], 0.3 mg QD or 0.15 mg QD) compared to placebo, for the treatment of active systemic lupus erythematosus (SLE) using the SLE Responder Index at Week 24 Composite endpoint SRI(4), defined by the following criteria: - Reduction from Baseline of ≥ 4 points in the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) 2K score and - No new one or more British Isles Lupus Assessment Group (BILAG) A or new (excludes A to B) 2 or more BILAG B items compared to Baseline using BILAG 2004 Index and - No worsening from Baseline defined by an increase of < 0.30 points from Baseline on a Physician's Global Assessment (PGA) visual analog scale (VAS) from 0-3	
End point type	Primary
End point timeframe: Week 24	

End point values	PBO QD	0.45 mg QD	0.15 mg QD	0.30 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	83	81	42	82
Units: Number of participants	29	44	20	33

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	PBO QD v 0.15 mg QD

Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.214
Method	Cochran-Mantel-Haenszel
Parameter estimate	Stratified difference
Point estimate	11.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.57
upper limit	29

Statistical analysis title	Statistical Analysis
Comparison groups	PBO QD v 0.45 mg QD
Number of subjects included in analysis	164
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.011
Method	Cochran-Mantel-Haenszel
Parameter estimate	Stratified difference
Point estimate	19.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.12
upper limit	33.42

Statistical analysis title	Statistical Analysis
Comparison groups	PBO QD v 0.30 mg QD
Number of subjects included in analysis	165
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.512
Method	Cochran-Mantel-Haenszel
Parameter estimate	Stratified difference
Point estimate	5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.77
upper limit	19.48

Secondary: Number of participants with SLEDAI 2K score improvement of ≥ 4 points

from Baseline

End point title	Number of participants with SLEDAI 2K score improvement of ≥ 4 points from Baseline
-----------------	--

End point description:

The SLEDAI 2K score measures disease activity through assessment of 24 lupus manifestations using a weighted score of 1 to 8 points. A manifestation is recorded if it is present over the previous 30 days regardless of severity or whether it has improved or worsened. A SLEDAI 2K score of 3 to 4 points is representative of active disease and a decrease of 1 to 2 points is considered clinically meaningful.

End point type	Secondary
----------------	-----------

End point timeframe:

Week 24

End point values	PBO QD	0.45 mg QD	0.15 mg QD	0.30 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	83	81	42	82
Units: Number of participants	30	45	20	35

Statistical analyses

Statistical analysis title	Placebo vs 0.15mg
Comparison groups	PBO QD v 0.15 mg QD
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.264
Method	Cochran-Mantel-Haenszel
Parameter estimate	Stratified difference
Point estimate	10.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.66
upper limit	27.97

Statistical analysis title	Placebo vs 0.45mg
Comparison groups	PBO QD v 0.45 mg QD
Number of subjects included in analysis	164
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.012
Method	Cochran-Mantel-Haenszel
Parameter estimate	Stratified difference
Point estimate	19.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	4.01
upper limit	33.36

Statistical analysis title	Placebo vs 0.30mg
Comparison groups	PBO QD v 0.30 mg QD
Number of subjects included in analysis	165
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.399
Method	Cochran-Mantel-Haenszel
Parameter estimate	Stratified difference
Point estimate	6.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.45
upper limit	21

Secondary: Number of participants with a $\geq 50\%$ reduction in Cutaneous Lupus Area and Severity Index (CLASI) activity score from Baseline, in participants with Baseline CLASI activity score ≥ 10

End point title	Number of participants with a $\geq 50\%$ reduction in Cutaneous Lupus Area and Severity Index (CLASI) activity score from Baseline, in participants with Baseline CLASI activity score ≥ 10
-----------------	---

End point description:

The CLASI Activity Score ranges from 0 to 70. To generate the activity score erythema is scored on a scale of 0 (absent) to 3 (dark red; purple/violaceous/crusted/hemorrhagic) and scale/hypertrophy are scored on a scale of 0 (absent) to 2 (verrucous/hypertrophic). Both the erythema and scale/hypertrophy scores are assessed in 13 different anatomical locations. In addition, the presence of mucous membrane lesions is scored on a scale of 0 (absent) to 1 (lesion or ulceration), the occurrence of recent hair loss is captured (1=yes; 0=no) and non-scarring alopecia is scored on a scale of 0 (absent) to 3 (focal or patchy in more than one quadrant). To calculate the activity score, all scores for erythema, scale/hypertrophy, mucous membrane lesions and alopecia are added together.

End point type	Secondary
End point timeframe:	
Week 24	

End point values	PBO QD	0.45 mg QD	0.15 mg QD	0.30 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	19	11	18
Units: Number of participants	8	13	8	8

Statistical analyses

Statistical analysis title	Placebo vs 0.15mg
Comparison groups	PBO QD v 0.15 mg QD
Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.446
Method	Cochran-Mantel-Haenszel
Parameter estimate	Stratified difference
Point estimate	24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.38
upper limit	53.11

Statistical analysis title	Placebo vs 0.45mg
Comparison groups	PBO QD v 0.45 mg QD
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.488
Method	Cochran-Mantel-Haenszel
Parameter estimate	Stratified difference
Point estimate	14.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.54
upper limit	44.48

Statistical analysis title	Placebo vs 0.30mg
Comparison groups	PBO QD v 0.30 mg QD

Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	
P-value	> 0.999
Method	Cochran-Mantel-Haenszel
Parameter estimate	Stratified difference
Point estimate	5.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-27.64
upper limit	39.38

Secondary: Number of participants with no new organ system affected as defined by 1 or more BILAG A or new (excludes A to B) 2 or more BILAG B items compared to Baseline using BILAG 2004 Index

End point title	Number of participants with no new organ system affected as defined by 1 or more BILAG A or new (excludes A to B) 2 or more BILAG B items compared to Baseline using BILAG 2004 Index
End point description:	The BILAG 2004 is a composite index that is based on the Classic BILAG index. It is a clinical measure of lupus disease activity. This tool assesses the changing severity of clinical manifestations of SLE using an ordinal scale scoring system that contain 9 systems (constitutional, mucocutaneous, neuropsychiatric, musculoskeletal, cardiorespiratory, gastrointestinal, ophthalmic, renal and hematological). Activity in each organ system is scored as: A=most active disease; B=intermediate activity; C=mild, stable disease; D=previous involvement, currently inactive; E=no previous activity.
End point type	Secondary
End point timeframe:	
Week 24	

End point values	PBO QD	0.45 mg QD	0.15 mg QD	0.30 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	83	81	42	82
Units: Number of participants	65	70	38	59

Statistical analyses

Statistical analysis title	Placebo vs 0.15mg
Comparison groups	PBO QD v 0.15 mg QD

Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.092
Method	Cochran-Mantel-Haenszel
Parameter estimate	Stratified difference
Point estimate	12.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.74
upper limit	24.07

Statistical analysis title	Placebo vs 0.45mg
Comparison groups	PBO QD v 0.45 mg QD
Number of subjects included in analysis	164
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.182
Method	Cochran-Mantel-Haenszel
Parameter estimate	Stratified difference
Point estimate	8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.88
upper limit	19.65

Statistical analysis title	Placebo vs 0.30mg
Comparison groups	PBO QD v 0.30 mg QD
Number of subjects included in analysis	165
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.434
Method	Cochran-Mantel-Haenszel
Parameter estimate	Stratified difference
Point estimate	-5.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.43
upper limit	8.06

Secondary: Percentage of participants with no worsening (increase of < 0.30 points

from Baseline) in PGA compared to Baseline

End point title	Percentage of participants with no worsening (increase of < 0.30 points from Baseline) in PGA compared to Baseline
End point description: The PGA uses a visual analog scale with scores between 0 and 3 to indicate worsening of disease. The scoring is as follows: 0 = none, 1 = mild disease, 2 = moderate disease, and 3 = severe disease.	
End point type	Secondary
End point timeframe: Week 24	

End point values	PBO QD	0.45 mg QD	0.15 mg QD	0.30 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	83	81	42	82
Units: Percentage of participants				
number (not applicable)	78.3	85.2	90.5	73.2

Statistical analyses

Statistical analysis title	Placebo vs 0.15mg
Comparison groups	PBO QD v 0.15 mg QD
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.098
Method	Cochran-Mantel-Haenszel
Parameter estimate	Stratified difference
Point estimate	12.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.98
upper limit	23.78

Statistical analysis title	Placebo vs 0.30mg
Comparison groups	PBO QD v 0.30 mg QD
Number of subjects included in analysis	165
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.521
Method	Cochran-Mantel-Haenszel
Parameter estimate	Stratified difference
Point estimate	-4.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.36
upper limit	8.92

Statistical analysis title	Placebo vs 0.45mg
Comparison groups	PBO QD v 0.45 mg QD
Number of subjects included in analysis	164
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.267
Method	Cochran-Mantel-Haenszel
Parameter estimate	Stratified difference
Point estimate	6.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.24
upper limit	18.55

Secondary: Mean change from Baseline in swollen joint count in participants with ≥ 2 swollen joints at Baseline

End point title	Mean change from Baseline in swollen joint count in participants with ≥ 2 swollen joints at Baseline
End point description:	
Joint tenderness and swelling will be noted as "present" or "absent," with no quantitation of severity using a 28- joint count. Note: Data presented is Adjusted mean data.	
End point type	Secondary
End point timeframe:	
Week 24	

End point values	PBO QD	0.45 mg QD	0.15 mg QD	0.30 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	62	56	33	54
Units: swollen joints				
arithmetic mean (confidence interval 95%)	-6.7 (-7.2 to -6.2)	-6.6 (-7.1 to -6.1)	-6.0 (-6.7 to -5.3)	-6.0 (-6.7 to -5.2)

Statistical analyses

Statistical analysis title	Placebo vs 0.15mg
Comparison groups	PBO QD v 0.15 mg QD
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.116
Method	longitudinal data analysis model
Parameter estimate	Difference in adjusted mean
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	1.5

Statistical analysis title	Placebo vs 0.30mg
Comparison groups	PBO QD v 0.30 mg QD
Number of subjects included in analysis	116
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.094
Method	longitudinal data analysis model
Parameter estimate	Difference in adjusted mean
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	1.6

Statistical analysis title	Placebo vs 0.45mg
Comparison groups	PBO QD v 0.45 mg QD
Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.881
Method	longitudinal data analysis model
Parameter estimate	Difference in adjusted mean
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	0.8

Secondary: Mean change from Baseline in tender joint count in participants with ≥ 2 tender joints at Baseline

End point title	Mean change from Baseline in tender joint count in participants with ≥ 2 tender joints at Baseline
-----------------	---

End point description:

Joint tenderness and swelling will be noted as "present" or "absent," with no quantitation of severity using a 28- joint count. Note: Data presented is Adjusted mean data.

End point type	Secondary
----------------	-----------

End point timeframe:

Week 24

End point values	PBO QD	0.45 mg QD	0.15 mg QD	0.30 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	62	56	33	54
Units: tender joints				
arithmetic mean (confidence interval 95%)	-7.9 (-8.8 to -7.0)	-7.6 (-8.5 to -6.7)	-6.8 (-8.1 to -5.6)	-6.7 (-7.7 to -5.6)

Statistical analyses

Statistical analysis title	Placebo vs 0.15mg
Comparison groups	PBO QD v 0.15 mg QD
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.16
Method	longitudinal data analysis model
Parameter estimate	Difference in adjusted mean
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	2.6

Statistical analysis title	Placebo vs 0.45mg
Comparison groups	PBO QD v 0.45 mg QD

Number of subjects included in analysis	118
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.621
Method	longitudinal data analysis model
Parameter estimate	Difference in adjusted mean
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	1.6

Statistical analysis title	Placebo vs 0.30mg
Comparison groups	PBO QD v 0.30 mg QD
Number of subjects included in analysis	116
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.056
Method	longitudinal data analysis model
Parameter estimate	Difference in adjusted mean
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	2.6

Secondary: Mean change from Baseline in PGA score

End point title	Mean change from Baseline in PGA score
End point description:	The PGA uses a visual analog scale with scores between 0 and 3 to indicate worsening of disease. The scoring is as follows: 0 = none, 1 = mild disease, 2 = moderate disease, and 3 = severe disease.
End point type	Secondary
End point timeframe:	
Week 24	

End point values	PBO QD	0.45 mg QD	0.15 mg QD	0.30 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	66	70	38	63
Units: scores on a scale				
arithmetic mean (standard deviation)	-0.803 (± 0.605)	-0.883 (± 0.546)	-0.805 (± 0.528)	-0.819 (± 0.629)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue score

End point title	Change from Baseline in Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue score
End point description: The FACIT-Fatigue scale is a 13-item self-administered questionnaire that assesses both the physical and functional consequences of fatigue. Each question is answered on a 5-point scale, where 0 means "not at all," and 4 means "very much." The total FACIT-Fatigue score ranges from 0 to 52. Note: Data presented is Adjusted mean data.	
End point type	Secondary
End point timeframe: Week 24	

End point values	PBO QD	0.45 mg QD	0.15 mg QD	0.30 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	67	69	38	60
Units: scores on a scale				
arithmetic mean (confidence interval 95%)	3.8 (1.6 to 6.0)	5.2 (3.0 to 7.4)	2.7 (-0.3 to 5.6)	3.1 (0.9 to 5.4)

Statistical analyses

Statistical analysis title	Placebo vs 0.15mg
Comparison groups	PBO QD v 0.15 mg QD
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.546
Method	longitudinal data analysis model
Parameter estimate	Difference in adjusted mean
Point estimate	-1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.7
upper limit	2.5

Statistical analysis title	Placebo vs 0.45mg
Comparison groups	PBO QD v 0.45 mg QD
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.35
Method	longitudinal data analysis model
Parameter estimate	Difference in adjusted mean
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	4.4

Statistical analysis title	Placebo vs 0.30mg
Comparison groups	PBO QD v 0.30 mg QD
Number of subjects included in analysis	127
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.681
Method	longitudinal data analysis model
Parameter estimate	Difference in adjusted mean
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.7
upper limit	2.4

Secondary: Percentage of participants with Corticosteroid Reduction

End point title	Percentage of participants with Corticosteroid Reduction
End point description:	
<p>- The percentage of participants with a prednisone or equivalent dose of ≥ 10 mg/day at Baseline whose prednisone or equivalent dose has been reduced to ≤ 7.5 mg/day by Week 16 and maintained through Week 24 with no flares between Week 16 and Week 24</p> <p>- The percentage of participants with a prednisone or equivalent dose of ≥ 10 mg/day at Baseline whose prednisone or equivalent dose has been reduced to < 10 mg/day by Week 16 and maintained through Week 24 with no flares between Week 16 and Week 24</p>	
End point type	Secondary
End point timeframe:	
Week 24	

End point values	PBO QD	0.45 mg QD	0.15 mg QD	0.30 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	32	17	30
Units: Percentage of participants				
number (not applicable)				
Week 24, ≤ 7.5 mg/day	3.2	0.0	0.0	3.3
Week 24, < 10 mg/day	6.5	0.0	0.0	3.3

Statistical analyses

Statistical analysis title	Placebo vs 0.30mg in < 10 mg/day
Comparison groups	PBO QD v 0.30 mg QD
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	
P-value	> 0.999
Method	longitudinal data analysis model
Parameter estimate	Stratified difference
Point estimate	-3.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.74
upper limit	13

Statistical analysis title	Placebo vs 0.30mg in ≤ 7.5 mg/day
Comparison groups	PBO QD v 0.30 mg QD
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	
P-value	> 0.999
Method	longitudinal data analysis model
Parameter estimate	Stratified difference
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.13
upper limit	15.91

Secondary: Percent change from Baseline in Corticosteroid Reduction

End point title	Percent change from Baseline in Corticosteroid Reduction
End point description: Percent change from Baseline in oral corticosteroid (OCS) dose in subjects with prednisone or equivalent ≥ 10 mg/day at Baseline Note: Data presented is Adjusted mean data.	
End point type	Secondary
End point timeframe: Week 24	

End point values	PBO QD	0.45 mg QD	0.15 mg QD	0.30 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	26	30	17	25
Units: percent change from baseline				
arithmetic mean (confidence interval 95%)	-7.9 (-13.6 to -2.2)	-1.4 (-6.4 to 3.6)	-5.1 (-11.9 to 1.6)	-3.8 (-9.5 to 2.0)

Statistical analyses

Statistical analysis title	Placebo vs 0.15mg
Comparison groups	PBO QD v 0.15 mg QD
Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.535
Method	longitudinal data analysis model
Parameter estimate	Difference in adjusted means
Point estimate	2.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6
upper limit	11.6

Statistical analysis title	Placebo vs 0.30mg
Comparison groups	PBO QD v 0.30 mg QD
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.309
Method	longitudinal data analysis model
Parameter estimate	Difference in adjusted means
Point estimate	4.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.9
upper limit	12.2

Statistical analysis title	Placebo vs 0.45mg
Comparison groups	PBO QD v 0.45 mg QD
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.091
Method	longitudinal data analysis model
Parameter estimate	Difference in adjusted means
Point estimate	6.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	14.1

Secondary: The total corticosteroid dose from Baseline through Week 24

End point title	The total corticosteroid dose from Baseline through Week 24
End point description:	
Standardized total oral corticosteroid (OCS) dose.	
End point type	Secondary
End point timeframe:	
Through Week 24	

End point values	PBO QD	0.45 mg QD	0.15 mg QD	0.30 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	83	81	42	82
Units: mg				
arithmetic mean (standard deviation)	1139.7 (± 916.9)	1105.5 (± 969.3)	1101.9 (± 827.1)	1071.8 (± 965.0)

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with Treatment-Emergent Adverse Events

(TEAEs)

End point title	Number of participants with Treatment-Emergent Adverse Events (TEAEs)
End point description: Number of participants who experienced a TEAE during the course of the study	
End point type	Secondary
End point timeframe: from first dose to 28 days post-last dose through Week 24 (placebo-controlled phase), approximately 28 weeks total	

End point values	PBO QD	0.45 mg QD	0.15 mg QD	0.30 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	83	81	42	82
Units: Number of participants				
Any TEAE	54	63	31	64
Any Drug-related TEAE	24	32	14	36
Any Serious TEAE	7	6	3	4
Any Severe TEAE	5	1	3	4
Any TEAE Leading to Drug Interruption	15	23	10	14
Any TEAE Leading to Drug Withdrawal	6	4	2	11
Any TEAE Leading to Death	1	0	0	0

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Cause Mortality: Approximately up to 51 months and 1 week

Serious Adverse Events and Other (Not Including Serious) Adverse Events: Approximately up to 48 months

Adverse event reporting additional description:

The number at Risk for All-Cause Mortality represents all Randomized Participants; From date of randomization to 100 days post last dose.

The number at Risk for Serious Adverse Events and Other (Not Including Serious) Adverse Events represents all participants that received at least 1 dose of study medication; 28 days post last dose.

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	24.0
--------------------	------

Reporting groups

Reporting group title	0.15 mg QD throughout the study
-----------------------	---------------------------------

Reporting group description:

Participants dosed with CC-220 at 0.15 mg once a day

Reporting group title	0.30 mg QD throughout the study
-----------------------	---------------------------------

Reporting group description:

Participants dosed with CC-220 at 0.30 mg once a day

Reporting group title	0.45 mg QD throughout the study
-----------------------	---------------------------------

Reporting group description:

Participants dosed with CC-220 at 0.45 mg once a day

Reporting group title	Placebo
-----------------------	---------

Reporting group description:

Placebo-matching treatment once a day

Reporting group title	Placebo up to W24 and then 0.30 mg
-----------------------	------------------------------------

Reporting group description:

Placebo-matching treatment once a day up to week 24, then started 0.30mg once a day

Reporting group title	Placebo up to W24 and then 0.45 mg
-----------------------	------------------------------------

Reporting group description:

Placebo-matching treatment once a day up to week 24, then started 0.45mg once a day

Serious adverse events	0.15 mg QD throughout the study	0.30 mg QD throughout the study	0.45 mg QD throughout the study
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 42 (14.29%)	10 / 82 (12.20%)	14 / 81 (17.28%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events			
Vascular disorders			
Deep vein thrombosis			

subjects affected / exposed	0 / 42 (0.00%)	3 / 82 (3.66%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	0 / 42 (0.00%)	1 / 82 (1.22%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Implant site pain			
subjects affected / exposed	1 / 42 (2.38%)	0 / 82 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza like illness			
subjects affected / exposed	0 / 42 (0.00%)	0 / 82 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Endometriosis			
subjects affected / exposed	0 / 42 (0.00%)	0 / 82 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abnormal uterine bleeding			
subjects affected / exposed	1 / 42 (2.38%)	0 / 82 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine haemorrhage			
subjects affected / exposed	0 / 42 (0.00%)	0 / 82 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			

subjects affected / exposed	0 / 42 (0.00%)	0 / 82 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 42 (0.00%)	1 / 82 (1.22%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	0 / 42 (0.00%)	0 / 82 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngeal oedema			
subjects affected / exposed	0 / 42 (0.00%)	0 / 82 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 42 (0.00%)	0 / 82 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Panic attack			
subjects affected / exposed	0 / 42 (0.00%)	1 / 82 (1.22%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Acetabulum fracture			
subjects affected / exposed	0 / 42 (0.00%)	1 / 82 (1.22%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Forearm fracture			
subjects affected / exposed	0 / 42 (0.00%)	0 / 82 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Joint injury			
subjects affected / exposed	0 / 42 (0.00%)	0 / 82 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ligament rupture			
subjects affected / exposed	0 / 42 (0.00%)	0 / 82 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	0 / 42 (0.00%)	0 / 82 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic fracture			
subjects affected / exposed	1 / 42 (2.38%)	0 / 82 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suture related complication			
subjects affected / exposed	1 / 42 (2.38%)	0 / 82 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	0 / 42 (0.00%)	0 / 82 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac tamponade			
subjects affected / exposed	1 / 42 (2.38%)	0 / 82 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis			
subjects affected / exposed	1 / 42 (2.38%)	0 / 82 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			

Brain stem infarction			
subjects affected / exposed	0 / 42 (0.00%)	1 / 82 (1.22%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalopathy			
subjects affected / exposed	0 / 42 (0.00%)	0 / 82 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	1 / 42 (2.38%)	0 / 82 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiparesis			
subjects affected / exposed	0 / 42 (0.00%)	1 / 82 (1.22%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polyneuropathy			
subjects affected / exposed	0 / 42 (0.00%)	0 / 82 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	1 / 42 (2.38%)	0 / 82 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 42 (2.38%)	0 / 82 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 42 (0.00%)	0 / 82 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastrointestinal disorders			
Diverticular perforation			
subjects affected / exposed	0 / 42 (0.00%)	0 / 82 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	1 / 42 (2.38%)	0 / 82 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	1 / 42 (2.38%)	0 / 82 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 42 (0.00%)	0 / 82 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urticaria			
subjects affected / exposed	0 / 42 (0.00%)	0 / 82 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 42 (2.38%)	0 / 82 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrotic syndrome			
subjects affected / exposed	0 / 42 (0.00%)	1 / 82 (1.22%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Proteinuria			

subjects affected / exposed	0 / 42 (0.00%)	0 / 82 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Joint instability			
subjects affected / exposed	0 / 42 (0.00%)	0 / 82 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Systemic lupus erythematosus			
subjects affected / exposed	0 / 42 (0.00%)	0 / 82 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abscess limb			
subjects affected / exposed	0 / 42 (0.00%)	0 / 82 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 42 (0.00%)	1 / 82 (1.22%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19 pneumonia			
subjects affected / exposed	0 / 42 (0.00%)	0 / 82 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia urinary tract infection			
subjects affected / exposed	0 / 42 (0.00%)	0 / 82 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 42 (0.00%)	0 / 82 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastroenteritis viral			
subjects affected / exposed	0 / 42 (0.00%)	0 / 82 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 42 (0.00%)	0 / 82 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 42 (0.00%)	1 / 82 (1.22%)	3 / 81 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	1 / 42 (2.38%)	0 / 82 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection enterococcal			
subjects affected / exposed	0 / 42 (0.00%)	0 / 82 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicella zoster pneumonia			
subjects affected / exposed	0 / 42 (0.00%)	0 / 82 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo	Placebo up to W24 and then 0.30 mg	Placebo up to W24 and then 0.45 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 11 (45.45%)	4 / 36 (11.11%)	3 / 36 (8.33%)
number of deaths (all causes)	1	1	0
number of deaths resulting from adverse events			
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 36 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hypertensive crisis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 36 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Implant site pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 36 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza like illness			
subjects affected / exposed	0 / 11 (0.00%)	0 / 36 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Endometriosis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 36 (2.78%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abnormal uterine bleeding			
subjects affected / exposed	0 / 11 (0.00%)	0 / 36 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine haemorrhage			
subjects affected / exposed	0 / 11 (0.00%)	0 / 36 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 11 (0.00%)	0 / 36 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			

subjects affected / exposed	0 / 11 (0.00%)	0 / 36 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 36 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngeal oedema			
subjects affected / exposed	1 / 11 (9.09%)	0 / 36 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 11 (9.09%)	0 / 36 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Psychiatric disorders			
Panic attack			
subjects affected / exposed	0 / 11 (0.00%)	0 / 36 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Acetabulum fracture			
subjects affected / exposed	0 / 11 (0.00%)	0 / 36 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Forearm fracture			
subjects affected / exposed	0 / 11 (0.00%)	0 / 36 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint injury			
subjects affected / exposed	0 / 11 (0.00%)	0 / 36 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Ligament rupture			
subjects affected / exposed	0 / 11 (0.00%)	0 / 36 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	0 / 11 (0.00%)	0 / 36 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic fracture			
subjects affected / exposed	0 / 11 (0.00%)	0 / 36 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suture related complication			
subjects affected / exposed	0 / 11 (0.00%)	0 / 36 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	0 / 11 (0.00%)	1 / 36 (2.78%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cardiac tamponade			
subjects affected / exposed	0 / 11 (0.00%)	0 / 36 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 36 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Brain stem infarction			
subjects affected / exposed	0 / 11 (0.00%)	0 / 36 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Encephalopathy			
subjects affected / exposed	1 / 11 (9.09%)	0 / 36 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 11 (0.00%)	0 / 36 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiparesis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 36 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polyneuropathy			
subjects affected / exposed	0 / 11 (0.00%)	0 / 36 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	0 / 11 (0.00%)	0 / 36 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 36 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 11 (0.00%)	0 / 36 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Diverticular perforation			

subjects affected / exposed	0 / 11 (0.00%)	1 / 36 (2.78%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 36 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 36 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 11 (0.00%)	0 / 36 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urticaria			
subjects affected / exposed	0 / 11 (0.00%)	0 / 36 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 11 (0.00%)	0 / 36 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrotic syndrome			
subjects affected / exposed	0 / 11 (0.00%)	0 / 36 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Proteinuria			
subjects affected / exposed	0 / 11 (0.00%)	0 / 36 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Musculoskeletal and connective tissue disorders			
Joint instability			
subjects affected / exposed	0 / 11 (0.00%)	0 / 36 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Systemic lupus erythematosus			
subjects affected / exposed	3 / 11 (27.27%)	0 / 36 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abscess limb			
subjects affected / exposed	0 / 11 (0.00%)	0 / 36 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 36 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19 pneumonia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 36 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia urinary tract infection			
subjects affected / exposed	1 / 11 (9.09%)	0 / 36 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 36 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	0 / 11 (0.00%)	0 / 36 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Lower respiratory tract infection subjects affected / exposed	0 / 11 (0.00%)	0 / 36 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia subjects affected / exposed	0 / 11 (0.00%)	0 / 36 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock subjects affected / exposed	0 / 11 (0.00%)	0 / 36 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection enterococcal subjects affected / exposed	1 / 11 (9.09%)	0 / 36 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicella zoster pneumonia subjects affected / exposed	0 / 11 (0.00%)	1 / 36 (2.78%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	0.15 mg QD throughout the study	0.30 mg QD throughout the study	0.45 mg QD throughout the study
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 42 (76.19%)	66 / 82 (80.49%)	63 / 81 (77.78%)
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 42 (4.76%)	4 / 82 (4.88%)	5 / 81 (6.17%)
occurrences (all)	3	5	5
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 42 (0.00%)	0 / 82 (0.00%)	1 / 81 (1.23%)
occurrences (all)	0	0	1

Gait disturbance subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0	0 / 82 (0.00%) 0	0 / 81 (0.00%) 0
Discomfort subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0	1 / 82 (1.22%) 1	0 / 81 (0.00%) 0
Pyrexia subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 3	1 / 82 (1.22%) 1	3 / 81 (3.70%) 3
Respiratory, thoracic and mediastinal disorders			
Dyspnoea subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0	0 / 82 (0.00%) 0	2 / 81 (2.47%) 2
Oropharyngeal pain subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1	0 / 82 (0.00%) 0	1 / 81 (1.23%) 1
Investigations			
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1	4 / 82 (4.88%) 4	2 / 81 (2.47%) 2
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1	2 / 82 (2.44%) 2	1 / 81 (1.23%) 1
Injury, poisoning and procedural complications			
Limb injury subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0	1 / 82 (1.22%) 1	2 / 81 (2.47%) 2
Nervous system disorders			
Headache subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 4	3 / 82 (3.66%) 3	4 / 81 (4.94%) 5
Dysgeusia subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1	0 / 82 (0.00%) 0	0 / 81 (0.00%) 0
Dizziness			

subjects affected / exposed	0 / 42 (0.00%)	4 / 82 (4.88%)	0 / 81 (0.00%)
occurrences (all)	0	4	0
Hypoaesthesia			
subjects affected / exposed	0 / 42 (0.00%)	1 / 82 (1.22%)	1 / 81 (1.23%)
occurrences (all)	0	1	1
Migraine			
subjects affected / exposed	0 / 42 (0.00%)	3 / 82 (3.66%)	2 / 81 (2.47%)
occurrences (all)	0	3	2
Optic neuritis			
subjects affected / exposed	0 / 42 (0.00%)	0 / 82 (0.00%)	0 / 81 (0.00%)
occurrences (all)	0	0	0
Paraesthesia			
subjects affected / exposed	1 / 42 (2.38%)	1 / 82 (1.22%)	2 / 81 (2.47%)
occurrences (all)	1	1	2
Parosmia			
subjects affected / exposed	0 / 42 (0.00%)	0 / 82 (0.00%)	0 / 81 (0.00%)
occurrences (all)	0	0	0
Restless legs syndrome			
subjects affected / exposed	0 / 42 (0.00%)	0 / 82 (0.00%)	0 / 81 (0.00%)
occurrences (all)	0	0	0
Tension headache			
subjects affected / exposed	1 / 42 (2.38%)	0 / 82 (0.00%)	1 / 81 (1.23%)
occurrences (all)	1	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 42 (7.14%)	5 / 82 (6.10%)	6 / 81 (7.41%)
occurrences (all)	6	6	9
Leukopenia			
subjects affected / exposed	3 / 42 (7.14%)	3 / 82 (3.66%)	10 / 81 (12.35%)
occurrences (all)	4	5	14
Lymphopenia			
subjects affected / exposed	0 / 42 (0.00%)	1 / 82 (1.22%)	4 / 81 (4.94%)
occurrences (all)	0	1	5
Neutropenia			
subjects affected / exposed	2 / 42 (4.76%)	8 / 82 (9.76%)	16 / 81 (19.75%)
occurrences (all)	2	13	28

Ear and labyrinth disorders Tinnitus subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0	1 / 82 (1.22%) 1	1 / 81 (1.23%) 2
Eye disorders Lacrimation increased subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0	0 / 82 (0.00%) 0	0 / 81 (0.00%) 0
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	6 / 42 (14.29%) 10	5 / 82 (6.10%) 6	8 / 81 (9.88%) 9
Abdominal pain upper subjects affected / exposed occurrences (all)	2 / 42 (4.76%) 2	2 / 82 (2.44%) 3	1 / 81 (1.23%) 1
Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0	1 / 82 (1.22%) 1	1 / 81 (1.23%) 1
Gastritis subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0	4 / 82 (4.88%) 4	1 / 81 (1.23%) 1
Nausea subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 4	4 / 82 (4.88%) 4	5 / 81 (6.17%) 6
Vomiting subjects affected / exposed occurrences (all)	6 / 42 (14.29%) 9	5 / 82 (6.10%) 5	3 / 81 (3.70%) 3
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1	1 / 82 (1.22%) 1	4 / 81 (4.94%) 5
Renal and urinary disorders Proteinuria subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1	0 / 82 (0.00%) 0	1 / 81 (1.23%) 2
Nephrolithiasis			

subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0	0 / 82 (0.00%) 0	1 / 81 (1.23%) 1
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 42 (4.76%)	4 / 82 (4.88%)	5 / 81 (6.17%)
occurrences (all)	2	4	6
Osteoarthritis			
subjects affected / exposed	1 / 42 (2.38%)	1 / 82 (1.22%)	0 / 81 (0.00%)
occurrences (all)	1	1	0
Pain in extremity			
subjects affected / exposed	0 / 42 (0.00%)	1 / 82 (1.22%)	4 / 81 (4.94%)
occurrences (all)	0	1	4
Spinal pain			
subjects affected / exposed	0 / 42 (0.00%)	0 / 82 (0.00%)	0 / 81 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	4 / 42 (9.52%)	6 / 82 (7.32%)	5 / 81 (6.17%)
occurrences (all)	4	6	8
COVID-19			
subjects affected / exposed	0 / 42 (0.00%)	2 / 82 (2.44%)	3 / 81 (3.70%)
occurrences (all)	0	2	3
Cystitis			
subjects affected / exposed	2 / 42 (4.76%)	0 / 82 (0.00%)	4 / 81 (4.94%)
occurrences (all)	2	0	5
Cellulitis			
subjects affected / exposed	0 / 42 (0.00%)	1 / 82 (1.22%)	1 / 81 (1.23%)
occurrences (all)	0	1	1
Gastroenteritis			
subjects affected / exposed	0 / 42 (0.00%)	3 / 82 (3.66%)	3 / 81 (3.70%)
occurrences (all)	0	4	4
Herpes zoster			
subjects affected / exposed	1 / 42 (2.38%)	2 / 82 (2.44%)	1 / 81 (1.23%)
occurrences (all)	1	2	1
Infected skin ulcer			

subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0	0 / 82 (0.00%) 0	0 / 81 (0.00%) 0
Nasopharyngitis subjects affected / exposed occurrences (all)	5 / 42 (11.90%) 8	7 / 82 (8.54%) 7	10 / 81 (12.35%) 11
Influenza subjects affected / exposed occurrences (all)	4 / 42 (9.52%) 4	5 / 82 (6.10%) 8	8 / 81 (9.88%) 15
Oral herpes subjects affected / exposed occurrences (all)	4 / 42 (9.52%) 5	1 / 82 (1.22%) 1	2 / 81 (2.47%) 2
Pharyngitis subjects affected / exposed occurrences (all)	5 / 42 (11.90%) 5	6 / 82 (7.32%) 7	4 / 81 (4.94%) 5
Sinusitis subjects affected / exposed occurrences (all)	1 / 42 (2.38%) 1	5 / 82 (6.10%) 5	5 / 81 (6.17%) 6
Urinary tract infection subjects affected / exposed occurrences (all)	7 / 42 (16.67%) 10	24 / 82 (29.27%) 37	15 / 81 (18.52%) 21
Upper respiratory tract infection subjects affected / exposed occurrences (all)	6 / 42 (14.29%) 7	11 / 82 (13.41%) 16	15 / 81 (18.52%) 27
Wound infection subjects affected / exposed occurrences (all)	0 / 42 (0.00%) 0	0 / 82 (0.00%) 0	0 / 81 (0.00%) 0
Metabolism and nutrition disorders Hypertriglyceridaemia subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 6	3 / 82 (3.66%) 3	2 / 81 (2.47%) 3

Non-serious adverse events	Placebo	Placebo up to W24 and then 0.30 mg	Placebo up to W24 and then 0.45 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 11 (90.91%)	23 / 36 (63.89%)	27 / 36 (75.00%)
Vascular disorders			

Hypertension subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	2 / 36 (5.56%) 2	3 / 36 (8.33%) 4
General disorders and administration site conditions			
Asthenia subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	2 / 36 (5.56%) 2	0 / 36 (0.00%) 0
Gait disturbance subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 36 (0.00%) 0	0 / 36 (0.00%) 0
Discomfort subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 36 (0.00%) 0	0 / 36 (0.00%) 0
Pyrexia subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	0 / 36 (0.00%) 0	0 / 36 (0.00%) 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	2 / 36 (5.56%) 2	0 / 36 (0.00%) 0
Oropharyngeal pain subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	2 / 36 (5.56%) 2	2 / 36 (5.56%) 2
Investigations			
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 36 (0.00%) 0	0 / 36 (0.00%) 0
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 36 (0.00%) 0	0 / 36 (0.00%) 0
Injury, poisoning and procedural complications			
Limb injury subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	1 / 36 (2.78%) 1	2 / 36 (5.56%) 2
Nervous system disorders			

Headache			
subjects affected / exposed	1 / 11 (9.09%)	3 / 36 (8.33%)	3 / 36 (8.33%)
occurrences (all)	1	4	4
Dysgeusia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 36 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Dizziness			
subjects affected / exposed	0 / 11 (0.00%)	2 / 36 (5.56%)	4 / 36 (11.11%)
occurrences (all)	0	2	4
Hypoaesthesia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 36 (2.78%)	4 / 36 (11.11%)
occurrences (all)	0	2	4
Migraine			
subjects affected / exposed	1 / 11 (9.09%)	0 / 36 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Optic neuritis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 36 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Paraesthesia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 36 (0.00%)	1 / 36 (2.78%)
occurrences (all)	1	0	1
Parosmia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 36 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Restless legs syndrome			
subjects affected / exposed	1 / 11 (9.09%)	0 / 36 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Tension headache			
subjects affected / exposed	0 / 11 (0.00%)	0 / 36 (0.00%)	2 / 36 (5.56%)
occurrences (all)	0	0	2
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 11 (0.00%)	3 / 36 (8.33%)	2 / 36 (5.56%)
occurrences (all)	0	6	3
Leukopenia			

subjects affected / exposed	0 / 11 (0.00%)	5 / 36 (13.89%)	1 / 36 (2.78%)
occurrences (all)	0	12	1
Lymphopenia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 36 (0.00%)	3 / 36 (8.33%)
occurrences (all)	0	0	3
Neutropenia			
subjects affected / exposed	1 / 11 (9.09%)	2 / 36 (5.56%)	4 / 36 (11.11%)
occurrences (all)	1	4	10
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	0 / 11 (0.00%)	2 / 36 (5.56%)	1 / 36 (2.78%)
occurrences (all)	0	2	1
Eye disorders			
Lacrimation increased			
subjects affected / exposed	1 / 11 (9.09%)	0 / 36 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 11 (0.00%)	0 / 36 (0.00%)	2 / 36 (5.56%)
occurrences (all)	0	0	2
Abdominal pain upper			
subjects affected / exposed	0 / 11 (0.00%)	3 / 36 (8.33%)	3 / 36 (8.33%)
occurrences (all)	0	3	3
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 11 (0.00%)	2 / 36 (5.56%)	1 / 36 (2.78%)
occurrences (all)	0	2	1
Gastritis			
subjects affected / exposed	0 / 11 (0.00%)	3 / 36 (8.33%)	0 / 36 (0.00%)
occurrences (all)	0	3	0
Nausea			
subjects affected / exposed	1 / 11 (9.09%)	1 / 36 (2.78%)	1 / 36 (2.78%)
occurrences (all)	1	1	2
Vomiting			
subjects affected / exposed	1 / 11 (9.09%)	1 / 36 (2.78%)	2 / 36 (5.56%)
occurrences (all)	1	1	2
Skin and subcutaneous tissue disorders			

Pruritus subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	2 / 36 (5.56%) 2	0 / 36 (0.00%) 0
Renal and urinary disorders Proteinuria subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 36 (0.00%) 0	0 / 36 (0.00%) 0
Nephrolithiasis subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 36 (0.00%) 0	0 / 36 (0.00%) 0
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	0 / 36 (0.00%) 0	1 / 36 (2.78%) 1
Osteoarthritis subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	3 / 36 (8.33%) 3	1 / 36 (2.78%) 2
Pain in extremity subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	0 / 36 (0.00%) 0	1 / 36 (2.78%) 1
Spinal pain subjects affected / exposed occurrences (all)	1 / 11 (9.09%) 1	1 / 36 (2.78%) 2	0 / 36 (0.00%) 0
Infections and infestations Bronchitis subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	4 / 36 (11.11%) 4	1 / 36 (2.78%) 2
COVID-19 subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	2 / 36 (5.56%) 2	1 / 36 (2.78%) 1
Cystitis subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	2 / 36 (5.56%) 5	0 / 36 (0.00%) 0
Cellulitis subjects affected / exposed occurrences (all)	0 / 11 (0.00%) 0	2 / 36 (5.56%) 2	0 / 36 (0.00%) 0

Gastroenteritis			
subjects affected / exposed	0 / 11 (0.00%)	2 / 36 (5.56%)	1 / 36 (2.78%)
occurrences (all)	0	2	1
Herpes zoster			
subjects affected / exposed	2 / 11 (18.18%)	2 / 36 (5.56%)	1 / 36 (2.78%)
occurrences (all)	2	2	1
Infected skin ulcer			
subjects affected / exposed	1 / 11 (9.09%)	0 / 36 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	1 / 11 (9.09%)	4 / 36 (11.11%)	3 / 36 (8.33%)
occurrences (all)	1	4	3
Influenza			
subjects affected / exposed	0 / 11 (0.00%)	3 / 36 (8.33%)	3 / 36 (8.33%)
occurrences (all)	0	4	7
Oral herpes			
subjects affected / exposed	0 / 11 (0.00%)	0 / 36 (0.00%)	0 / 36 (0.00%)
occurrences (all)	0	0	0
Pharyngitis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 36 (2.78%)	1 / 36 (2.78%)
occurrences (all)	0	2	1
Sinusitis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 36 (2.78%)	1 / 36 (2.78%)
occurrences (all)	0	1	2
Urinary tract infection			
subjects affected / exposed	0 / 11 (0.00%)	4 / 36 (11.11%)	6 / 36 (16.67%)
occurrences (all)	0	14	6
Upper respiratory tract infection			
subjects affected / exposed	1 / 11 (9.09%)	3 / 36 (8.33%)	8 / 36 (22.22%)
occurrences (all)	1	4	10
Wound infection			
subjects affected / exposed	0 / 11 (0.00%)	2 / 36 (5.56%)	0 / 36 (0.00%)
occurrences (all)	0	3	0
Metabolism and nutrition disorders			
Hypertriglyceridaemia			

subjects affected / exposed	0 / 11 (0.00%)	2 / 36 (5.56%)	0 / 36 (0.00%)
occurrences (all)	0	2	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 February 2017	Protocol Amendment 1 contains changes to the study based on the implementation of an Urgent Safety Measure regarding thromboembolic risk and prophylaxis. These changes were in line with recommendations from the Study Advisory and Data Monitoring (DMC) Committees.
03 April 2018	Protocol Amendment 1 has been written to implement changes to the study for all participating sites. The overall intent of the amendment is to provide an option for extended treatment with CC-220 for additional one year, address changes in regards to study eligibility criteria and improve protocol clarity.
15 August 2018	Protocol Amendment 2 has been written to implement changes to the study for all participating sites. The overall intent of the amendment is to provide an option for extended treatment with CC-220 for additional 52 weeks, address changes in regards to study eligibility criteria and improve protocol clarity.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported