



## 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:

| <b>Subjects enrolled per age group</b>    |     |
|-------------------------------------------|-----|
| 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 |
|------------------------------|-----|

|                  |        |
|------------------|--------|
| <b>Arm title</b> | 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

|                  |            |
|------------------|------------|
| <b>Arm title</b> | 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

|                  |            |
|------------------|------------|
| <b>Arm title</b> | 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

|                                                                          |              |
|--------------------------------------------------------------------------|--------------|
| <b>Arm title</b>                                                         | 0.30 mg QD   |
| Arm description:<br>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

| <b>Number of subjects in period 1</b> | PBO QD            | 0.45 mg QD       | 0.15 mg QD       |
|---------------------------------------|-------------------|------------------|------------------|
| Started                               | 83                | 81               | 42               |
| Going to 0.30mg after week 24         | 36 <sup>[1]</sup> | 0 <sup>[2]</sup> | 0 <sup>[3]</sup> |
| going to 0.45mg after week 24         | 36 <sup>[4]</sup> | 0 <sup>[5]</sup> | 0 <sup>[6]</sup> |
| Staying on Placebo after week 24      | 11 <sup>[7]</sup> | 0 <sup>[8]</sup> | 0 <sup>[9]</sup> |
| 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                    | -                 | -                | -                |

| <b>Number of subjects in period 1</b> | 0.30 mg QD        |
|---------------------------------------|-------------------|
| Started                               | 82                |
| Going to 0.30mg after week 24         | 0 <sup>[10]</sup> |
| going to 0.45mg after week 24         | 0 <sup>[11]</sup> |
| Staying on Placebo after week 24      | 0 <sup>[12]</sup> |
| 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  |

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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:<br>Placebo-matching treatment once a day                |            |
| Reporting group title                                                                | 0.45 mg QD |
| Reporting group description:<br>Participants dosed with CC-220 at 0.45 mg once a day |            |
| Reporting group title                                                                | 0.15 mg QD |
| Reporting group description:<br>Participants dosed with CC-220 at 0.15 mg once a day |            |
| Reporting group title                                                                | 0.30 mg QD |
| Reporting group description:<br>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:<br>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 $\geq 4$ 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:<br>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                      |

|                                         |                         |
|-----------------------------------------|-------------------------|
| <b>Statistical analysis title</b>       | 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                   |

|                                         |                         |
|-----------------------------------------|-------------------------|
| <b>Statistical analysis title</b>       | 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                   |

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## Secondary: Number of participants with SLEDAI 2K score improvement of $\geq 4$ points

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**from Baseline**

|                 |                                                                                          |
|-----------------|------------------------------------------------------------------------------------------|
| End point title | Number of participants with SLEDAI 2K score improvement of $\geq 4$ 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**

|                                         |                         |
|-----------------------------------------|-------------------------|
| <b>Statistical analysis title</b>       | 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                   |

|                                         |                         |
|-----------------------------------------|-------------------------|
| <b>Statistical analysis title</b>       | 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   |

|                                         |                         |
|-----------------------------------------|-------------------------|
| <b>Statistical analysis title</b>       | 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  $\geq 10$**

|                 |                                                                                                                                                                                                   |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 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 $\geq 10$ |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

**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              |           |

| <b>End point values</b>       | 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

|                                         |                         |
|-----------------------------------------|-------------------------|
| <b>Statistical analysis title</b>       | 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                   |

|                                         |                         |
|-----------------------------------------|-------------------------|
| <b>Statistical analysis title</b>       | 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                   |

|                                   |                     |
|-----------------------------------|---------------------|
| <b>Statistical analysis title</b> | 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                   |

|                                         |                         |
|-----------------------------------------|-------------------------|
| <b>Statistical analysis title</b>       | 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                   |

|                                         |                         |
|-----------------------------------------|-------------------------|
| <b>Statistical analysis title</b>       | 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:<br>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:<br>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**

|                                         |                         |
|-----------------------------------------|-------------------------|
| <b>Statistical analysis title</b>       | 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                   |

|                                         |                         |
|-----------------------------------------|-------------------------|
| <b>Statistical analysis title</b>       | 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    |

|                                         |                         |
|-----------------------------------------|-------------------------|
| <b>Statistical analysis title</b>       | 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 $\geq 2$ swollen joints at Baseline

|                                                                                                                                                                             |                                                                                                           |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                             | Mean change from Baseline in swollen joint count in participants with $\geq 2$ 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

|                                         |                                  |
|-----------------------------------------|----------------------------------|
| <b>Statistical analysis title</b>       | 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                              |

|                                         |                                  |
|-----------------------------------------|----------------------------------|
| <b>Statistical analysis title</b>       | 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                              |

|                                         |                                  |
|-----------------------------------------|----------------------------------|
| <b>Statistical analysis title</b>       | 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  $\geq 2$  tender joints at Baseline**

|                 |                                                                                                         |
|-----------------|---------------------------------------------------------------------------------------------------------|
| End point title | Mean change from Baseline in tender joint count in participants with $\geq 2$ 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**

|                                         |                                  |
|-----------------------------------------|----------------------------------|
| <b>Statistical analysis title</b>       | 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                              |

|                                   |                     |
|-----------------------------------|---------------------|
| <b>Statistical analysis title</b> | 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                              |

|                                         |                                  |
|-----------------------------------------|----------------------------------|
| <b>Statistical analysis title</b>       | 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                |                                                                                                                                                                                                       |

|                                      |                  |                  |                  |                  |
|--------------------------------------|------------------|------------------|------------------|------------------|
| <b>End point values</b>              | 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:<br>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:<br>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                              |

|                                         |                                  |
|-----------------------------------------|----------------------------------|
| <b>Statistical analysis title</b>       | 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                              |

|                                         |                                  |
|-----------------------------------------|----------------------------------|
| <b>Statistical analysis title</b>       | 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 <math>\geq 10</math> mg/day at Baseline whose prednisone or equivalent dose has been reduced to <math>\leq 7.5</math> 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 <math>\geq 10</math> mg/day at Baseline whose prednisone or equivalent dose has been reduced to <math>&lt; 10</math> 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                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                          |

| <b>End point values</b>           | 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, $\leq 7.5$ 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

|                                         |                                    |
|-----------------------------------------|------------------------------------|
| <b>Statistical analysis title</b>       | 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                                 |

|                                         |                                        |
|-----------------------------------------|----------------------------------------|
| <b>Statistical analysis title</b>       | Placebo vs 0.30mg in $\leq 7.5$ 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:<br>Percent change from Baseline in oral corticosteroid (OCS) dose in subjects with prednisone or equivalent $\geq 10$ mg/day at Baseline Note: Data presented is Adjusted mean data. |                                                          |
| End point type                                                                                                                                                                                              | Secondary                                                |
| End point timeframe:<br>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**

|                                         |                                  |
|-----------------------------------------|----------------------------------|
| <b>Statistical analysis title</b>       | 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                             |

|                                         |                                  |
|-----------------------------------------|----------------------------------|
| <b>Statistical analysis title</b>       | 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    |

|                                         |                                  |
|-----------------------------------------|----------------------------------|
| <b>Statistical analysis title</b>       | 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          |
| <b>Musculoskeletal and connective tissue disorders</b> |                |                |                |
| 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          |
| <b>Infections and infestations</b>                     |                |                |                |
| 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          |

| <b>Serious adverse events</b>                     | 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          |
| <b>Hepatobiliary disorders</b>                  |                |                |                |
| 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          |
| <b>Skin and subcutaneous tissue disorders</b>   |                |                |                |
| 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          |
| <b>Renal and urinary disorders</b>              |                |                |                |
| 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<br>subjects affected / exposed    | 0 / 11 (0.00%) | 0 / 36 (0.00%) | 0 / 36 (0.00%) |
| occurrences causally related to<br>treatment / all                  | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to<br>treatment / all                       | 0 / 0          | 0 / 0          | 0 / 0          |
| Pneumonia<br>subjects affected / exposed                            | 0 / 11 (0.00%) | 0 / 36 (0.00%) | 1 / 36 (2.78%) |
| occurrences causally related to<br>treatment / all                  | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to<br>treatment / all                       | 0 / 0          | 0 / 0          | 0 / 0          |
| Septic shock<br>subjects affected / exposed                         | 0 / 11 (0.00%) | 0 / 36 (0.00%) | 0 / 36 (0.00%) |
| occurrences causally related to<br>treatment / all                  | 0 / 0          | 0 / 0          | 0 / 0          |
| deaths causally related to<br>treatment / all                       | 0 / 0          | 0 / 0          | 0 / 0          |
| Urinary tract infection enterococcal<br>subjects affected / exposed | 1 / 11 (9.09%) | 0 / 36 (0.00%) | 0 / 36 (0.00%) |
| occurrences causally related to<br>treatment / all                  | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to<br>treatment / all                       | 0 / 0          | 0 / 0          | 0 / 0          |
| Varicella zoster pneumonia<br>subjects affected / exposed           | 0 / 11 (0.00%) | 1 / 36 (2.78%) | 0 / 36 (0.00%) |
| occurrences causally related to<br>treatment / all                  | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to<br>treatment / all                       | 0 / 0          | 0 / 0          | 0 / 0          |

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

| <b>Non-serious adverse events</b>                        | 0.15 mg QD<br>throughout the<br>study | 0.30 mg QD<br>throughout the study | 0.45 mg QD<br>throughout the<br>study |
|----------------------------------------------------------|---------------------------------------|------------------------------------|---------------------------------------|
| Total subjects affected by non-serious<br>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<br>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<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 42 (0.00%)<br>0 | 0 / 82 (0.00%)<br>0 | 0 / 81 (0.00%)<br>0 |
| Discomfort<br>subjects affected / exposed<br>occurrences (all)                           | 0 / 42 (0.00%)<br>0 | 1 / 82 (1.22%)<br>1 | 0 / 81 (0.00%)<br>0 |
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)                              | 3 / 42 (7.14%)<br>3 | 1 / 82 (1.22%)<br>1 | 3 / 81 (3.70%)<br>3 |
| Respiratory, thoracic and mediastinal disorders                                          |                     |                     |                     |
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)                             | 0 / 42 (0.00%)<br>0 | 0 / 82 (0.00%)<br>0 | 2 / 81 (2.47%)<br>2 |
| Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all)                   | 1 / 42 (2.38%)<br>1 | 0 / 82 (0.00%)<br>0 | 1 / 81 (1.23%)<br>1 |
| Investigations                                                                           |                     |                     |                     |
| Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)   | 1 / 42 (2.38%)<br>1 | 4 / 82 (4.88%)<br>4 | 2 / 81 (2.47%)<br>2 |
| Aspartate aminotransferase increased<br>subjects affected / exposed<br>occurrences (all) | 1 / 42 (2.38%)<br>1 | 2 / 82 (2.44%)<br>2 | 1 / 81 (1.23%)<br>1 |
| Injury, poisoning and procedural complications                                           |                     |                     |                     |
| Limb injury<br>subjects affected / exposed<br>occurrences (all)                          | 0 / 42 (0.00%)<br>0 | 1 / 82 (1.22%)<br>1 | 2 / 81 (2.47%)<br>2 |
| Nervous system disorders                                                                 |                     |                     |                     |
| Headache<br>subjects affected / exposed<br>occurrences (all)                             | 3 / 42 (7.14%)<br>4 | 3 / 82 (3.66%)<br>3 | 4 / 81 (4.94%)<br>5 |
| Dysgeusia<br>subjects affected / exposed<br>occurrences (all)                            | 1 / 42 (2.38%)<br>1 | 0 / 82 (0.00%)<br>0 | 0 / 81 (0.00%)<br>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<br>Tinnitus<br>subjects affected / exposed<br>occurrences (all)            | 0 / 42 (0.00%)<br>0   | 1 / 82 (1.22%)<br>1 | 1 / 81 (1.23%)<br>2 |
| Eye disorders<br>Lacrimation increased<br>subjects affected / exposed<br>occurrences (all)             | 0 / 42 (0.00%)<br>0   | 0 / 82 (0.00%)<br>0 | 0 / 81 (0.00%)<br>0 |
| Gastrointestinal disorders<br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all)            | 6 / 42 (14.29%)<br>10 | 5 / 82 (6.10%)<br>6 | 8 / 81 (9.88%)<br>9 |
| Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all)                               | 2 / 42 (4.76%)<br>2   | 2 / 82 (2.44%)<br>3 | 1 / 81 (1.23%)<br>1 |
| Gastrooesophageal reflux disease<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 42 (0.00%)<br>0   | 1 / 82 (1.22%)<br>1 | 1 / 81 (1.23%)<br>1 |
| Gastritis<br>subjects affected / exposed<br>occurrences (all)                                          | 0 / 42 (0.00%)<br>0   | 4 / 82 (4.88%)<br>4 | 1 / 81 (1.23%)<br>1 |
| Nausea<br>subjects affected / exposed<br>occurrences (all)                                             | 3 / 42 (7.14%)<br>4   | 4 / 82 (4.88%)<br>4 | 5 / 81 (6.17%)<br>6 |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)                                           | 6 / 42 (14.29%)<br>9  | 5 / 82 (6.10%)<br>5 | 3 / 81 (3.70%)<br>3 |
| Skin and subcutaneous tissue disorders<br>Pruritus<br>subjects affected / exposed<br>occurrences (all) | 1 / 42 (2.38%)<br>1   | 1 / 82 (1.22%)<br>1 | 4 / 81 (4.94%)<br>5 |
| Renal and urinary disorders<br>Proteinuria<br>subjects affected / exposed<br>occurrences (all)         | 1 / 42 (2.38%)<br>1   | 0 / 82 (0.00%)<br>0 | 1 / 81 (1.23%)<br>2 |
| Nephrolithiasis                                                                                        |                       |                     |                     |

|                                                  |                     |                     |                     |
|--------------------------------------------------|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all) | 0 / 42 (0.00%)<br>0 | 0 / 82 (0.00%)<br>0 | 1 / 81 (1.23%)<br>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<br>occurrences (all)                                                                | 0 / 42 (0.00%)<br>0   | 0 / 82 (0.00%)<br>0    | 0 / 81 (0.00%)<br>0    |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)                                             | 5 / 42 (11.90%)<br>8  | 7 / 82 (8.54%)<br>7    | 10 / 81 (12.35%)<br>11 |
| Influenza<br>subjects affected / exposed<br>occurrences (all)                                                   | 4 / 42 (9.52%)<br>4   | 5 / 82 (6.10%)<br>8    | 8 / 81 (9.88%)<br>15   |
| Oral herpes<br>subjects affected / exposed<br>occurrences (all)                                                 | 4 / 42 (9.52%)<br>5   | 1 / 82 (1.22%)<br>1    | 2 / 81 (2.47%)<br>2    |
| Pharyngitis<br>subjects affected / exposed<br>occurrences (all)                                                 | 5 / 42 (11.90%)<br>5  | 6 / 82 (7.32%)<br>7    | 4 / 81 (4.94%)<br>5    |
| Sinusitis<br>subjects affected / exposed<br>occurrences (all)                                                   | 1 / 42 (2.38%)<br>1   | 5 / 82 (6.10%)<br>5    | 5 / 81 (6.17%)<br>6    |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)                                     | 7 / 42 (16.67%)<br>10 | 24 / 82 (29.27%)<br>37 | 15 / 81 (18.52%)<br>21 |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)                           | 6 / 42 (14.29%)<br>7  | 11 / 82 (13.41%)<br>16 | 15 / 81 (18.52%)<br>27 |
| Wound infection<br>subjects affected / exposed<br>occurrences (all)                                             | 0 / 42 (0.00%)<br>0   | 0 / 82 (0.00%)<br>0    | 0 / 81 (0.00%)<br>0    |
| Metabolism and nutrition disorders<br>Hypertriglyceridaemia<br>subjects affected / exposed<br>occurrences (all) | 3 / 42 (7.14%)<br>6   | 3 / 82 (3.66%)<br>3    | 2 / 81 (2.47%)<br>3    |

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

|                                                                                                                                                                                                                                                                                                                                           |                                                                                                      |                                                                                                      |                                                                                                      |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|
| Hypertension<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                                                                          | 1 / 11 (9.09%)<br>1                                                                                  | 2 / 36 (5.56%)<br>2                                                                                  | 3 / 36 (8.33%)<br>4                                                                                  |
| General disorders and administration site conditions<br>Asthenia<br>subjects affected / exposed<br>occurrences (all)<br><br>Gait disturbance<br>subjects affected / exposed<br>occurrences (all)<br><br>Discomfort<br>subjects affected / exposed<br>occurrences (all)<br><br>Pyrexia<br>subjects affected / exposed<br>occurrences (all) | 0 / 11 (0.00%)<br>0<br><br>1 / 11 (9.09%)<br>1<br><br>1 / 11 (9.09%)<br>1<br><br>0 / 11 (0.00%)<br>0 | 2 / 36 (5.56%)<br>2<br><br>0 / 36 (0.00%)<br>0<br><br>0 / 36 (0.00%)<br>0<br><br>0 / 36 (0.00%)<br>0 | 0 / 36 (0.00%)<br>0<br><br>0 / 36 (0.00%)<br>0<br><br>0 / 36 (0.00%)<br>0<br><br>0 / 36 (0.00%)<br>0 |
| Respiratory, thoracic and mediastinal disorders<br>Dyspnoea<br>subjects affected / exposed<br>occurrences (all)<br><br>Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                             | 0 / 11 (0.00%)<br>0<br><br>0 / 11 (0.00%)<br>0                                                       | 2 / 36 (5.56%)<br>2<br><br>2 / 36 (5.56%)<br>2                                                       | 0 / 36 (0.00%)<br>0<br><br>2 / 36 (5.56%)<br>2                                                       |
| Investigations<br>Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)<br><br>Aspartate aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                  | 1 / 11 (9.09%)<br>1<br><br>1 / 11 (9.09%)<br>1                                                       | 0 / 36 (0.00%)<br>0<br><br>0 / 36 (0.00%)<br>0                                                       | 0 / 36 (0.00%)<br>0<br><br>0 / 36 (0.00%)<br>0                                                       |
| Injury, poisoning and procedural complications<br>Limb injury<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                         | 0 / 11 (0.00%)<br>0                                                                                  | 1 / 36 (2.78%)<br>1                                                                                  | 2 / 36 (5.56%)<br>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<br>subjects affected / exposed<br>occurrences (all)                                                     | 0 / 11 (0.00%)<br>0 | 2 / 36 (5.56%)<br>2  | 0 / 36 (0.00%)<br>0 |
| Renal and urinary disorders<br>Proteinuria<br>subjects affected / exposed<br>occurrences (all)                   | 1 / 11 (9.09%)<br>1 | 0 / 36 (0.00%)<br>0  | 0 / 36 (0.00%)<br>0 |
| Nephrolithiasis<br>subjects affected / exposed<br>occurrences (all)                                              | 1 / 11 (9.09%)<br>1 | 0 / 36 (0.00%)<br>0  | 0 / 36 (0.00%)<br>0 |
| Musculoskeletal and connective tissue disorders<br>Back pain<br>subjects affected / exposed<br>occurrences (all) | 0 / 11 (0.00%)<br>0 | 0 / 36 (0.00%)<br>0  | 1 / 36 (2.78%)<br>1 |
| Osteoarthritis<br>subjects affected / exposed<br>occurrences (all)                                               | 0 / 11 (0.00%)<br>0 | 3 / 36 (8.33%)<br>3  | 1 / 36 (2.78%)<br>2 |
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all)                                            | 1 / 11 (9.09%)<br>1 | 0 / 36 (0.00%)<br>0  | 1 / 36 (2.78%)<br>1 |
| Spinal pain<br>subjects affected / exposed<br>occurrences (all)                                                  | 1 / 11 (9.09%)<br>1 | 1 / 36 (2.78%)<br>2  | 0 / 36 (0.00%)<br>0 |
| Infections and infestations<br>Bronchitis<br>subjects affected / exposed<br>occurrences (all)                    | 0 / 11 (0.00%)<br>0 | 4 / 36 (11.11%)<br>4 | 1 / 36 (2.78%)<br>2 |
| COVID-19<br>subjects affected / exposed<br>occurrences (all)                                                     | 0 / 11 (0.00%)<br>0 | 2 / 36 (5.56%)<br>2  | 1 / 36 (2.78%)<br>1 |
| Cystitis<br>subjects affected / exposed<br>occurrences (all)                                                     | 0 / 11 (0.00%)<br>0 | 2 / 36 (5.56%)<br>5  | 0 / 36 (0.00%)<br>0 |
| Cellulitis<br>subjects affected / exposed<br>occurrences (all)                                                   | 0 / 11 (0.00%)<br>0 | 2 / 36 (5.56%)<br>2  | 0 / 36 (0.00%)<br>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:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported