



## Clinical trial results:

**A Phase 2, single-center, randomised, double-blind, placebo-controlled, cross-over, cold challenge study investigating the effect of C21 on cold-induced vasoconstriction in subjects with Raynaud's Phenomenon (RP) secondary to systemic sclerosis (SSc)**

### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2019-003203-35   |
| Trial protocol           | GB               |
| Global end of trial date | 14 December 2020 |

### Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1 (current)    |
| This version publication date  | 11 January 2022 |
| First version publication date | 11 January 2022 |

### Trial information

#### Trial identification

|                       |            |
|-----------------------|------------|
| Sponsor protocol code | VP-C21-004 |
|-----------------------|------------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT04388176 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Vicore Pharma AB   |
| Sponsor organisation address | Kronhusgatan 11, Göteborg, Sweden, SE-411 05   |
| Public contact               | Anne Katrine Cohrt, Vicore Pharma AB, +45 20111391, anne-katrine.cohrt@vicorepharma.com      |
| Scientific contact           | Carl-Johan Dalsgaard, Vicore Pharma AB, +46 709759863, carl-johan.dalsgaard@vicorepharma.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                       | 30 March 2021    |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 14 December 2020 |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 14 December 2020 |
| Was the trial ended prematurely?                     | Yes              |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the effect of a single dose C21 200 mg o.d. on cold-induced vasoconstriction in subjects with Raynaud's Phenomenon (RP) secondary to systemic sclerosis (SSc).

Protection of trial subjects:

None

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 04 November 2019 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | No               |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United Kingdom: 20 |
| Worldwide total number of subjects   | 20                 |
| EEA total number of subjects         | 0                  |

Notes:

### Subjects enrolled per age group

|   |    |
|---|----|
| In utero                                  | 0  |
| Preterm newborn - gestational age < 37 wk | 0  |
| Newborns (0-27 days)                      | 0  |
| Infants and toddlers (28 days-23 months)  | 0  |
| Children (2-11 years)                     | 0  |
| Adolescents (12-17 years)                 | 0  |
| Adults (18-64 years)                      | 15 |
| From 65 to 84 years                       | 5  |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

The trial planned to include 16 subjects, however as recruitment was challenging during the COVID-19 pandemic, enrolment was stopped prematurely when 12 subjects were randomised. This ensured that trial results could be available in a timely manner.

### Pre-assignment

Screening details:

A total of 20 unique subjects provided informed consent and were enrolled in the trial. Seven of these were screening failures. In addition, 2 subjects were not randomised; 1 subject due to the COVID-19 pandemic and 1 subject due technical issues with the Holter ECG. The latter subject was re-screened. A total of 12 subjects were randomised.

### Pre-assignment period milestones

|                              |    |
|------------------------------|----|
| Number of subjects started   | 20 |
| Number of subjects completed | 12 |

### Pre-assignment subject non-completion reasons

|                            |  |
|----------------------------|--|
| Reason: Number of subjects | Consent withdrawn by subject: 1            |
| Reason: Number of subjects | Physician decision: 1                      |
| Reason: Number of subjects | Sponsor decision: 1                        |
| Reason: Number of subjects | Did not fulfill eligibility criteria: 4    |
| Reason: Number of subjects | Not randomised due to COVID-19 pandemic: 1 |

### Period 1

|                              |                              |
|------------------------------|------------------------------|
| Period 1 title               | Baseline period              |
| Is this the baseline period? | Yes                          |
| Allocation method            | Randomised - controlled      |
| Blinding used                | Double blind                 |
| Roles blinded                | Subject, Investigator, Carer |

### Arms

|                              |         |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes     |
| <b>Arm title</b>             | PLA-C21 |

Arm description:

Placebo followed by C21

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | C21          |
| Investigational medicinal product code |              |
| Other name                             |              |
| Pharmaceutical forms                   | Capsule      |
| Routes of administration               | Oral use     |

Dosage and administration details:

A single oral dose of 200 mg

|  |                               |
|--|-------------------------------|
| Investigational medicinal product name | Reference treatment (placebo) |
| Investigational medicinal product code |                               |
| Other name                             |                               |
| Pharmaceutical forms                   | Capsule                       |
| Routes of administration               | Oral use                      |

Dosage and administration details:

A single oral dose

|   |              |
|---|--------------|
| <b>Arm title</b>                            | C21-PLA      |
| Arm description:<br>C21 followed by placebo |              |
| Arm type                                    | Experimental |
| Investigational medicinal product name      | C21          |
| Investigational medicinal product code      |              |
| Other name                                  |              |
| Pharmaceutical forms                        | Capsule      |
| Routes of administration                    | Oral use     |

Dosage and administration details:

A single oral dose of 200 mg

|  |                               |
|--|-------------------------------|
| Investigational medicinal product name | Reference treatment (placebo) |
| Investigational medicinal product code |                               |
| Other name                             |                               |
| Pharmaceutical forms                   | Capsule                       |
| Routes of administration               | Oral use                      |

Dosage and administration details:

A single oral dose

| <b>Number of subjects in period 1<sup>[1]</sup></b> | PLA-C21 | C21-PLA |
|---|---------|---------|
| Started   | 6       | 6       |
| Completed   | 6       | 6       |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: A total of 20 subjects provided informed consent and were enrolled in the trial. 12 of these subjects completed the pre-assignment period, were included in the baseline period and were randomised to treatment.

## Period 2

|                              |                              |
|------------------------------|------------------------------|
| Period 2 title               | Treatment period             |
| Is this the baseline period? | No                           |
| Allocation method            | Randomised - controlled      |
| Blinding used                | Double blind                 |
| Roles blinded                | Subject, Investigator, Carer |

## Arms

|                              |    |
|------------------------------|----|
| Are arms mutually exclusive? | No |
|------------------------------|----|

|  |                               |
|--|-------------------------------|
| <b>Arm title</b>   | C21 200 mg                    |
| Arm description:<br>200 mg C21                                     |                               |
| Arm type   | Experimental                  |
| Investigational medicinal product name                             | C21                           |
| Investigational medicinal product code                             |                               |
| Other name   |                               |
| Pharmaceutical forms   | Capsule                       |
| Routes of administration   | Oral use                      |
| Dosage and administration details:<br>A single oral dose of 200 mg |                               |
| <b>Arm title</b>   | Placebo                       |
| Arm description:<br>Placebo  |                               |
| Arm type   | Placebo                       |
| Investigational medicinal product name                             | Reference treatment (placebo) |
| Investigational medicinal product code                             |                               |
| Other name   |                               |
| Pharmaceutical forms   | Capsule                       |
| Routes of administration   | Oral use                      |
| Dosage and administration details:<br>A single oral dose           |                               |

| <b>Number of subjects in period 2</b> | C21 200 mg | Placebo |
|---------------------------------------|------------|---------|
| Started                               | 12         | 12      |
| Completed                             | 12         | 12      |

## Baseline characteristics

### Reporting groups

|   |         |
|---|---------|
| Reporting group title                                   | PLA-C21 |
| Reporting group description:<br>Placebo followed by C21 |         |
| Reporting group title                                   | C21-PLA |
| Reporting group description:<br>C21 followed by placebo |         |

| Reporting group values                                | PLA-C21        | C21-PLA        | Total |
|---|----------------|----------------|-------|
| Number of subjects                                    | 6              | 6              | 12    |
| Age categorical<br>Units: Subjects                    |                |                |       |
| In utero  | 0              | 0              | 0     |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0              | 0              | 0     |
| Newborns (0-27 days)                                  | 0              | 0              | 0     |
| Infants and toddlers (28 days-23<br>months)           | 0              | 0              | 0     |
| Children (2-11 years)                                 | 0              | 0              | 0     |
| Adolescents (12-17 years)                             | 0              | 0              | 0     |
| Adults (18-64 years)                                  | 5              | 4              | 9     |
| From 65-84 years                                      | 1              | 2              | 3     |
| 85 years and over                                     | 0              | 0              | 0     |
| Age continuous<br>Units: years                        |                |                |       |
| arithmetic mean                                       | 51.5           | 59.5           |       |
| full range (min-max)                                  | 35 to 67       | 46 to 69       | -     |
| Gender categorical<br>Units: Subjects                 |                |                |       |
| Female  | 6              | 6              | 12    |
| Male  | 0              | 0              | 0     |
| Race<br>Units: Subjects                               |                |                |       |
| White   | 6              | 6              | 12    |
| Ethnicity<br>Units: Subjects                          |                |                |       |
| Not hispanic or latino                                | 6              | 6              | 12    |
| Height<br>Units: cm                                   |                |                |       |
| arithmetic mean                                       | 164.25         | 163.07         |       |
| full range (min-max)                                  | 155.0 to 171.5 | 154.0 to 180.0 | -     |
| Weight<br>Units: kg                                   |                |                |       |
| arithmetic mean                                       | 64.92          | 68.32          |       |
| full range (min-max)                                  | 54.0 to 79.8   | 50.8 to 90.0   | -     |
| BMI<br>Units: kg/m2                                   |                |                |       |

|                      |              |              |   |
|----------------------|--------------|--------------|---|
| arithmetic mean      | 24.2         | 25.6         |   |
| full range (min-max) | 19.2 to 29.3 | 20.2 to 29.0 | - |

## End points

### End points reporting groups

|  |                 |
|--|-----------------|
| Reporting group title  | PLA-C21         |
| Reporting group description:<br>Placebo followed by C21  |                 |
| Reporting group title  | C21-PLA         |
| Reporting group description:<br>C21 followed by placebo  |                 |
| Reporting group title  | C21 200 mg      |
| Reporting group description:<br>200 mg C21   |                 |
| Reporting group title  | Placebo         |
| Reporting group description:<br>Placebo  |                 |
| Subject analysis set title   | FAS             |
| Subject analysis set type  | Full analysis   |
| Subject analysis set description:<br>The full analysis set (FAS) consisted of all subjects/subjects who were randomised and received at least 1 dose of IMP and who had at least one post-baseline assessment of efficacy data allowing endpoint computation from each of the 2 treatment periods.           |                 |
| Subject analysis set title   | PPAS            |
| Subject analysis set type  | Per protocol    |
| Subject analysis set description:<br>The per protocol analysis set (PPAS) was a subset of FAS and consisted of all subjects who were randomised and completed the trial without any major protocol deviations that were judged to compromise the analysis of the data. In this trial, PPAS was equal to FAS. |                 |
| Subject analysis set title   | SAS             |
| Subject analysis set type  | Safety analysis |
| Subject analysis set description:<br>The safety analysis set (SAS) consisted of all subjects who were randomised and received at least 1 dose of IMP.  |                 |

### Primary: Area under the curve for rewarming of each finger after cold challenge (AUC) as measured by thermography

|   |  |
|---|--|
| End point title   | Area under the curve for rewarming of each finger after cold challenge (AUC) as measured by thermography |
| End point description:  |  |
| End point type  | Primary  |
| End point timeframe:  |  |
| For 15 minutes after cold challenge (40-55 minutes after a single dose of C21 or placebo) |  |

| End point values                                    | C21 200 mg             | Placebo                |  |  |
|---|------------------------|------------------------|--|--|
| Subject group type                                  | Reporting group        | Reporting group        |  |  |
| Number of subjects analysed                         | 12                     | 12                     |  |  |
| Units: C*sec  |                        |                        |  |  |
| geometric mean (geometric coefficient of variation) | 20045.96 ( $\pm$ 7.68) | 19558.43 ( $\pm$ 4.36) |  |  |

### Statistical analyses

|   |                              |
|---|------------------------------|
| <b>Statistical analysis title</b>       | Analysis of Thermography AUC |
| Comparison groups                       | C21 200 mg v Placebo         |
| Number of subjects included in analysis | 24                           |
| Analysis specification                  | Pre-specified                |
| Analysis type                           | equivalence                  |
| P-value                                 | = 0.3801                     |
| Method                                  | ANCOVA                       |
| Parameter estimate                      | Ratio in least-square means  |
| Point estimate                          | 1.0146                       |
| Confidence interval                     |                              |
| level                                   | 90 %                         |
| sides                                   | 2-sided                      |
| lower limit                             | 0.9859                       |
| upper limit                             | 1.0442                       |

### Secondary: Maximum skin temperature after rewarming (MAX)

|  |  |
|--|--|
| End point title  | Maximum skin temperature after rewarming (MAX) |
| End point description:   |  |
| End point type   | Secondary                                      |
| End point timeframe:   |  |
| For 15 min after cold challenge (40-55 min after IMP administration) |  |

|   |                  |                  |  |  |
|---|------------------|------------------|--|--|
| <b>End point values</b>                             | C21 200 mg       | Placebo          |  |  |
| Subject group type                                  | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed                         | 12               | 12               |  |  |
| Units: °C   |                  |                  |  |  |
| geometric mean (geometric coefficient of variation) | 23.5336 (± 8.49) | 22.5043 (± 3.73) |  |  |

### Statistical analyses

|                                   |                              |
|-----------------------------------|------------------------------|
| <b>Statistical analysis title</b> | Analysis of thermography MAX |
| Comparison groups                 | C21 200 mg v Placebo         |

|   |                              |
|---|------------------------------|
| Number of subjects included in analysis | 24                           |
| Analysis specification                  | Pre-specified                |
| Analysis type                           | equivalence                  |
| P-value                                 | = 0.0356                     |
| Method                                  | ANCOVA                       |
| Parameter estimate                      | Ratio for least square means |
| Point estimate                          | 1.0346                       |
| Confidence interval                     |                              |
| level                                   | 90 %                         |
| sides                                   | 2-sided                      |
| lower limit                             | 1.0086                       |
| upper limit                             | 1.0613                       |

### Secondary: The distal dorsal difference, defined as the difference in temperature between the dorsum and the finger (DDD)

|  |  |
|--|--|
| End point title  | The distal dorsal difference, defined as the difference in temperature between the dorsum and the finger (DDD) |
| End point description:   |  |
| End point type   | Secondary  |
| End point timeframe:   |  |
| From administration of IMP until before cold challenge (0 to 40 min) |  |

| End point values                 | C21 200 mg         | Placebo            |  |  |
|----------------------------------|--------------------|--------------------|--|--|
| Subject group type               | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed      | 12                 | 12                 |  |  |
| Units: °C                        |                    |                    |  |  |
| arithmetic mean (standard error) |                    |                    |  |  |
| Baseline                         | -2.4215 (± 0.4950) | -2.810 (± 0.3375)  |  |  |
| 10 min                           | -3.395 (± 0.4580)  | -3.2378 (± 0.3045) |  |  |
| 20 min                           | -3.1419 (± 0.4792) | -3.0596 (± 0.2323) |  |  |
| 30 min                           | -3.0347 (± 0.4037) | -3.1005 (± 0.1903) |  |  |
| 40 min                           | -2.9448 (± 0.333)  | -2.7921 (± 0.1918) |  |  |

### Statistical analyses

|                            |  |
|----------------------------|--|
| Statistical analysis title | Analysis of thermography DDD at 10 min |
| Comparison groups          | Placebo v C21 200 mg                   |

|   |                        |
|---|------------------------|
| Number of subjects included in analysis | 24                     |
| Analysis specification                  | Pre-specified          |
| Analysis type                           | equivalence            |
| P-value                                 | = 0.0154               |
| Method                                  | ANCOVA                 |
| Parameter estimate                      | Difference in LS-means |
| Point estimate                          | -0.4991                |
| Confidence interval                     |                        |
| level                                   | 90 %                   |
| sides                                   | 2-sided                |
| lower limit                             | -0.8234                |
| upper limit                             | -0.1749                |

### Secondary: Gradient of rewarming in the first 2 minutes post-cold challenge (GRAD)

|   |   |
|---|---|
| End point title   | Gradient of rewarming in the first 2 minutes post-cold challenge (GRAD) |
| End point description:  |   |
| End point type  | Secondary   |
| End point timeframe:  |   |
| 2 min after cold challenge (40-42 min after IMP administration) |   |

|   |                  |                  |  |  |
|---|------------------|------------------|--|--|
| <b>End point values</b>                             | C21 200 mg       | Placebo          |  |  |
| Subject group type                                  | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed                         | 12               | 12               |  |  |
| Units: °C/min                                       |                  |                  |  |  |
| geometric mean (geometric coefficient of variation) | 0.4482 (± 39.35) | 0.5412 (± 42.26) |  |  |

### Statistical analyses

|   |                               |
|---|-------------------------------|
| <b>Statistical analysis title</b>       | Analysis of thermography GRAD |
| Comparison groups                       | C21 200 mg v Placebo          |
| Number of subjects included in analysis | 24                            |
| Analysis specification                  | Pre-specified                 |
| Analysis type                           | equivalence                   |
| P-value                                 | = 0.282                       |
| Method                                  | ANCOVA                        |
| Parameter estimate                      | Least square mean ratio       |
| Point estimate                          | 0.8301                        |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 90 %    |
| sides               | 2-sided |
| lower limit         | 0.6206  |
| upper limit         | 1.1102  |

### Other pre-specified: Change in finger temperature from intake of IMP to start of cold challenge

|  |  |
|--|--|
| End point title  | Change in finger temperature from intake of IMP to start of cold challenge |
| End point description:                                   |  |
| End point type   | Other pre-specified  |
| End point timeframe:                                     |  |
| From intake of IMP to start of cold challenge (0-40 min) |  |

| End point values                 | C21 200 mg       | Placebo          |  |  |
|----------------------------------|------------------|------------------|--|--|
| Subject group type               | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed      | 12               | 12               |  |  |
| Units: °C                        |                  |                  |  |  |
| arithmetic mean (standard error) | -1.347 (± 0.343) | -0.697 (± 0.471) |  |  |

### Statistical analyses

|   |  |
|---|--|
| Statistical analysis title              | Analysis of change in finger temperature |
| Comparison groups                       | C21 200 mg v Placebo                     |
| Number of subjects included in analysis | 24                                       |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | equivalence                              |
| P-value                                 | = 0.3722                                 |
| Method                                  | ANCOVA                                   |
| Parameter estimate                      | Difference in least square means         |
| Point estimate                          | -0.3989                                  |
| Confidence interval                     |  |
| level                                   | 90 %                                     |
| sides                                   | 2-sided                                  |
| lower limit                             | -1.1718                                  |
| upper limit                             | 0.3739                                   |

### Other pre-specified: Nailfold capillaroscopy

|                 |                         |
|-----------------|-------------------------|
| End point title | Nailfold capillaroscopy |
|-----------------|-------------------------|

End point description:

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Before cold challenge (at 40 min) and post-recovery (at 55 min)

| End point values                 | C21 200 mg      | Placebo         |  |  |
|----------------------------------|-----------------|-----------------|--|--|
| Subject group type               | Reporting group | Reporting group |  |  |
| Number of subjects analysed      | 12              | 12              |  |  |
| Units: mm/sec                    |                 |                 |  |  |
| arithmetic mean (standard error) |                 |                 |  |  |
| Baseline                         | 0.369 (± 0.193) | 0.122 (± 0.042) |  |  |
| Before cold                      | 0.207 (± 0.054) | 0.302 (± 0.175) |  |  |
| Post recovery                    | 0.323 (± 0.149) | 0.318 (± 0.140) |  |  |

### Statistical analyses

| Statistical analysis title              | Analysis of capillaroscopy, before cold |
|---|---|
| Comparison groups                       | C21 200 mg v Placebo                    |
| Number of subjects included in analysis | 24                                      |
| Analysis specification                  | Pre-specified                           |
| Analysis type                           | equivalence                             |
| P-value                                 | = 0.4982                                |
| Method                                  | ANCOVA                                  |
| Parameter estimate                      | Difference in least square means        |
| Point estimate                          | -0.109                                  |
| Confidence interval                     |   |
| level                                   | 90 %                                    |
| sides                                   | 2-sided                                 |
| lower limit                             | -0.4074                                 |
| upper limit                             | 0.1895                                  |

| Statistical analysis title              | Analysis of capillaroscopy, post recovery |
|---|---|
| Comparison groups                       | C21 200 mg v Placebo                      |
| Number of subjects included in analysis | 24  |
| Analysis specification                  | Pre-specified                             |
| Analysis type                           | equivalence                               |
| P-value                                 | = 0.6219                                  |
| Method                                  | ANCOVA                                    |
| Parameter estimate                      | Difference in least square means          |
| Point estimate                          | -0.0637                                   |

| Confidence interval |         |
|---------------------|---------|
| level               | 90 %    |
| sides               | 2-sided |
| lower limit         | -0.3037 |
| upper limit         | 0.1763  |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From signing of informed consent until end of trial participation

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 22.1 |
|--------------------|------|

### Reporting groups

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

Reporting group description: -

|                       |            |
|-----------------------|------------|
| Reporting group title | C21 200 mg |
|-----------------------|------------|

Reporting group description: -

| Serious adverse events                            | Placebo        | C21 200 mg     |  |
|---|----------------|----------------|--|
| Total subjects affected by serious adverse events |                |                |  |
| subjects affected / exposed                       | 0 / 12 (0.00%) | 0 / 12 (0.00%) |  |
| number of deaths (all causes)                     | 0              | 0              |  |
| number of deaths resulting from adverse events    | 0              | 0              |  |

Frequency threshold for reporting non-serious adverse events: 1 %

| Non-serious adverse events                            | Placebo         | C21 200 mg      |  |
|---|-----------------|-----------------|--|
| Total subjects affected by non-serious adverse events |                 |                 |  |
| subjects affected / exposed                           | 3 / 12 (25.00%) | 5 / 12 (41.67%) |  |
| Vascular disorders                                    |                 |                 |  |
| Flushing  |                 |                 |  |
| subjects affected / exposed                           | 1 / 12 (8.33%)  | 0 / 12 (0.00%)  |  |
| occurrences (all)                                     | 1               | 0               |  |
| Nervous system disorders                              |                 |                 |  |
| Dizziness   |                 |                 |  |
| subjects affected / exposed                           | 1 / 12 (8.33%)  | 0 / 12 (0.00%)  |  |
| occurrences (all)                                     | 1               | 0               |  |
| Headache  |                 |                 |  |
| subjects affected / exposed                           | 1 / 12 (8.33%)  | 0 / 12 (0.00%)  |  |
| occurrences (all)                                     | 1               | 0               |  |
| Hypoaesthesia   |                 |                 |  |

|  |                     |                      |  |
|--|---------------------|----------------------|--|
| subjects affected / exposed<br>occurrences (all)   | 1 / 12 (8.33%)<br>1 | 0 / 12 (0.00%)<br>0  |  |
| Tremor<br>subjects affected / exposed<br>occurrences (all)   | 0 / 12 (0.00%)<br>0 | 1 / 12 (8.33%)<br>1  |  |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all)              | 1 / 12 (8.33%)<br>1 | 0 / 12 (0.00%)<br>0  |  |
| Ear and labyrinth disorders<br>Tinnitus<br>subjects affected / exposed<br>occurrences (all)                      | 0 / 12 (0.00%)<br>0 | 1 / 12 (8.33%)<br>1  |  |
| Gastrointestinal disorders<br>Abdominal pain<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 12 (0.00%)<br>0 | 1 / 12 (8.33%)<br>1  |  |
| Skin and subcutaneous tissue disorders<br>Skin tightness<br>subjects affected / exposed<br>occurrences (all)     | 0 / 12 (0.00%)<br>0 | 1 / 12 (8.33%)<br>1  |  |
| Musculoskeletal and connective tissue disorders<br>Back pain<br>subjects affected / exposed<br>occurrences (all) | 0 / 12 (0.00%)<br>0 | 1 / 12 (8.33%)<br>1  |  |
| Musculoskeletal chest pain<br>subjects affected / exposed<br>occurrences (all)                                   | 0 / 12 (0.00%)<br>0 | 1 / 12 (8.33%)<br>1  |  |
| Infections and infestations<br>Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)       | 0 / 12 (0.00%)<br>0 | 2 / 12 (16.67%)<br>2 |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment  |
|-----------------|--|
| 22 October 2020 | <p>There was 1 protocol amendment during the conduct of the trial (protocol version 4.0, dated 22-Oct-2020). The key changes introduced in the protocol version 4.0 were as follows:</p> <p>Exclusion criteria number 2 with respect to body mass index (BMI) &gt; 30 was changed to BMI &gt; 35 to facilitate completion of recruitment. No subjects were recruited after the approval of this amendment.</p> |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date          | Interruption  | Restart date   |
|---------------|---|----------------|
| 18 March 2020 | The trial was on hold once (from 18-Mar-2020 to 17-Aug-2020) due to lock down in the UK during the COVID-19 pandemic. | 17 August 2020 |

Notes:

### Limitations and caveats

None reported