



## Clinical trial results:

### A randomised double-blind placebo-controlled trial of Brensocatib (INS1007) in patients with severe COVID-19

#### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2020-001643-13   |
| Trial protocol           | GB               |
| Global end of trial date | 28 February 2021 |

#### Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1 (current)  |
| This version publication date  | 28 March 2023 |
| First version publication date | 28 March 2023 |

#### Trial information

##### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | 01.01.20 |
|-----------------------|----------|

##### Additional study identifiers

|                                    |                |
|------------------------------------|----------------|
| ISRCTN number                      | ISRCTN30564012 |
| ClinicalTrials.gov id (NCT number) | NCT04817332    |
| WHO universal trial number (UTN)   | -              |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | University of Dundee  |
| Sponsor organisation address | Ninewells Hospital and Medical School, Dundee, United Kingdom, DD1 9SY          |
| Public contact               | James Chalmers, University of Dundee, +44 01382 383642, j.chalmers@dundee.ac.uk |
| Scientific contact           | James Chalmers, University of Dundee, +44 01382 383642, j.chalmers@dundee.ac.uk |

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                       | 02 November 2021 |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 28 February 2021 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

The overall objective of the study is to evaluate the clinical efficacy of Brensocatib compared to placebo on top of standard care in adult patients hospitalized with COVID-19

Protection of trial subjects:

Participants (or legally authorized representative) were required to provide written informed consent. Participants were excluded if alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) > 5 times the upper limit of normal, history of severe liver disease, absolute neutrophil count  $<1.0 \times 10^9$  cells/L, were currently treated with Itraconazole, Ketoconazole, diltiazem or verapamil, were pregnant or breast feeding.

Background therapy:

Patients in both arms received all other therapies required to manage their condition (standard of care) with the exception of other investigational products. Where participants had been enrolled into the RECOVERY (Randomised Evaluation of COVID-19 Therapy) trial and had been randomised to the standard care arm, co-enrolment to the STOP-COVID19 trial was allowed. Co-enrolment into RECOVERY RS (Respiratory support) a non-CTIMP intervention trial was allowed. Co-enrolment to other CTIMPs or non-CTIMP intervention trials was not be allowed.

Evidence for comparator:

Neutrophil serine proteases (NSPs) are involved in the pathogenesis of severe COVID-19 infection and are increased in severe and fatal infection (Seren, 2021). Neutrophil elastase, proteinase-3 and cathepsin-G are activated during neutrophil maturation in the bone marrow through dipeptidyl peptidase 1 (DPP1; also known as cathepsin C), which removes the N-terminal dipeptide sequence of neutrophil serine proteases allowing active enzymes to be packaged into granules prior to release of neutrophils into the circulation.(Palmer et al., 2018) Brensocatib (INS1007, formerly AZD7986) is an orally delivered selective, competitive, and reversible inhibitor of DPP1. Brensocatib has been shown to inhibit neutrophil serine protease activity in blood in both animal models and healthy volunteers.(Palmer et al., 2018) We recently conducted a large phase 2 study of Brensocatib in patients with bronchiectasis designed to test if treatment with Brensocatib could reduce infective exacerbations and reduce neutrophil elastase activity in the lung in bronchiectasis patients. The study met its primary endpoint of time to first exacerbation and key secondary endpoint of the frequency of exacerbations as well as showing marked reductions in neutrophil elastase concentrations in sputum (Chalmers, 2020).

|   |             |
|---|-------------|
| Actual start date of recruitment                          | 11 May 2020 |
| Long term follow-up planned                               | No          |
| Independent data monitoring committee (IDMC) involvement? | Yes         |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                     |
|--------------------------------------|---------------------|
| Country: Number of subjects enrolled | United Kingdom: 404 |
|--------------------------------------|---------------------|

|                                    |     |
|------------------------------------|-----|
| Worldwide total number of subjects | 404 |
| EEA total number of subjects       | 0   |

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)                      | 226 |
| From 65 to 84 years                       | 158 |
| 85 years and over                         | 20  |

## Subject disposition

### Recruitment

Recruitment details:

A total of 406 participants were randomised into the study across the 14 participating UK centres. Participants were recruited between 05th June 2020 and 25th January 2021.

### Pre-assignment

Screening details:

Patients were screened for eligibility up to 24 hours prior to randomization and patients meeting the eligibility criteria were randomized within 96 hours of admission to hospital for COVID-19. 406 participants were randomised. There were two post-randomisation exclusions due to ineligibility in the Brensocatib arm.

### Period 1

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

Blinding implementation details:

Double-blind, placebo-controlled. Participants were allocated via the randomisation system to receive either active treatment or matching placebo. The active treatment/placebo were packaged and labelled so as to not identify the contents. Trial staff and participants were blind to the allocation received. The final unblinding of the treatment allocation occurred after the creation of a final locked database.

### Arms

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

Arm description:

Brensocatib 25mg once daily for 28 days

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | INS1007      |
| Investigational medicinal product code |              |
| Other name                             | Brensocatib  |
| Pharmaceutical forms                   | Tablet       |
| Routes of administration               | Oral use     |

Dosage and administration details:

Brensocatib is an oral tablet with a strength dose of 25mg, administered once a day.

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

Arm description:

Oral placebo tablet

|  |                    |
|--|--------------------|
| Arm type                               | Placebo            |
| Investigational medicinal product name | Placebo            |
| Investigational medicinal product code |                    |
| Other name                             |                    |
| Pharmaceutical forms                   | Film-coated tablet |
| Routes of administration               | Oral use           |

Dosage and administration details:

Placebo tablet contains microcrystalline cellulose and sodium fumarate and is coated. Dosage is 25mg once daily

| <b>Number of subjects in period 1</b> | Brensocatib | Placebo |
|---------------------------------------|-------------|---------|
| Started                               | 190         | 214     |
| Completed                             | 187         | 211     |
| Not completed                         | 3           | 3       |
| Lost to follow-up                     | 3           | 3       |

## Baseline characteristics

### Reporting groups

|   |             |
|---|-------------|
| Reporting group title   | Brensocatib |
| Reporting group description:<br>Brensocatib 25mg once daily for 28 days |             |
| Reporting group title   | Placebo     |
| Reporting group description:<br>Oral placebo tablet                     |             |

| Reporting group values                             | Brensocatib | Placebo | Total |
|--|-------------|---------|-------|
| Number of subjects                                 | 190         | 214     | 404   |
| Age categorical                                    |             |         |       |
| Age (years)  |             |         |       |
| Units: Subjects                                    |             |         |       |
| In utero   | 0           | 0       | 0     |
| Preterm newborn infants (gestational age < 37 wks) | 0           | 0       | 0     |
| Newborns (0-27 days)                               | 0           | 0       | 0     |
| Infants and toddlers (28 days-23 months)           | 0           | 0       | 0     |
| Children (2-11 years)                              | 0           | 0       | 0     |
| Adolescents (12-17 years)                          | 0           | 0       | 0     |
| Adults (18-64 years)                               | 104         | 122     | 226   |
| From 65-84 years                                   | 80          | 78      | 158   |
| 85 years and over                                  | 6           | 14      | 20    |
| Age continuous                                     |             |         |       |
| Age, years (standard deviation)                    |             |         |       |
| Units: years                                       |             |         |       |
| arithmetic mean                                    | 62.3        | 62.0    |       |
| standard deviation                                 | ± 12.5      | ± 14.9  | -     |
| Gender categorical                                 |             |         |       |
| Sex: male, female                                  |             |         |       |
| Units: Subjects                                    |             |         |       |
| Female   | 65          | 87      | 152   |
| Male   | 125         | 127     | 252   |
| Ethnicity  |             |         |       |
| Ethnicity  |             |         |       |
| Units: Subjects                                    |             |         |       |
| White British                                      | 167         | 189     | 356   |
| Irish  | 2           | 1       | 3     |
| Any other White background                         | 6           | 5       | 11    |
| White and Black Caribbean                          | 0           | 1       | 1     |
| White and Black African                            | 0           | 1       | 1     |
| Any other Mixed/Multiple ethnic background         | 0           | 1       | 1     |
| Indian   | 1           | 5       | 6     |
| Pakistan   | 4           | 3       | 7     |
| Bangladeshi  | 0           | 1       | 1     |
| Any other Asian background                         | 4           | 2       | 6     |

|   |         |         |     |
|---|---------|---------|-----|
| African   | 1       | 0       | 1   |
| Any other Black/African/Caribbean background      | 0       | 1       | 1   |
| Arab  | 1       | 1       | 2   |
| Any other ethnic group                            | 2       | 3       | 5   |
| Unknown   | 2       | 0       | 2   |
| Smoking Status                                    |         |         |     |
| Smoking Status at enrolment                       |         |         |     |
| Units: Subjects                                   |         |         |     |
| Current smoker                                    | 9       | 12      | 21  |
| Never smoked                                      | 93      | 98      | 191 |
| Former smoker                                     | 67      | 72      | 139 |
| Unknown   | 21      | 32      | 53  |
| Clinical status                                   |         |         |     |
| Clinical status at randomisation                  |         |         |     |
| Units: Subjects                                   |         |         |     |
| Hospitalized, not requiring supplemental oxygen   | 42      | 50      | 92  |
| Hospitalized, requiring supplemental oxygen       | 128     | 140     | 268 |
| Hospitalized, on non-invasive ventilation or high | 20      | 24      | 44  |
| SARS-CoV-2 PCR status                             |         |         |     |
| SARS-CoV-2 PCR status                             |         |         |     |
| Units: Subjects                                   |         |         |     |
| Confirmed positive SARS CoV-2 PCR test            | 186     | 204     | 390 |
| Clinically suspected without confirmed SARS-CoV-2 | 4       | 10      | 14  |
| Duration of symptoms                              |         |         |     |
| Median duration of symptoms (25th, 75th centile)  |         |         |     |
| Units: days                                       |         |         |     |
| median  | 9       | 8       |     |
| inter-quartile range (Q1-Q3)                      | 6 to 12 | 6 to 11 | -   |

## End points

### End points reporting groups

|   |             |
|---|-------------|
| Reporting group title   | Brensocatib |
| Reporting group description:<br>Brensocatib 25mg once daily for 28 days |             |
| Reporting group title   | Placebo     |
| Reporting group description:<br>Oral placebo tablet                     |             |

### Primary: 1. Comparison of participant clinical status between treatment arms

|  |   |
|--|---|
| End point title  | 1. Comparison of participant clinical status between treatment arms |
| End point description:<br>To determine the participant clinical status on a 7-point ordinal scale:<br>1. Not hospitalised, no limitations on activities<br>2. Not hospitalised, limitation on activities;<br>3. Hospitalised, not requiring supplemental oxygen;<br>4. Hospitalised, requiring supplemental oxygen;<br>5. Hospitalised, on non-invasive ventilation or high flow oxygen devices;<br>6. Hospitalised, on invasive mechanical ventilation or Extracorporeal membrane oxygenation (ECMO)<br>7. Death. |   |
| End point type   | Primary   |
| End point timeframe:<br>Up to 29 days  |   |

| End point values                                   | Brensocatib     | Placebo         |  |  |
|--|-----------------|-----------------|--|--|
| Subject group type                                 | Reporting group | Reporting group |  |  |
| Number of subjects analysed                        | 190             | 214             |  |  |
| Units: Participants                                |                 |                 |  |  |
| Not hospitalised, no limitations on activities     | 28              | 40              |  |  |
| Not hospitalised, limitation on activities         | 112             | 129             |  |  |
| Hospitalised, not requiring supplemental oxygen    | 7               | 11              |  |  |
| Hospitalised, requiring supplemental oxygen        | 6               | 1               |  |  |
| Hospitalised, on non-invasive ventilation or high  | 0               | 1               |  |  |
| Hospitalised, on invasive mechanical ventilation o | 5               | 6               |  |  |
| Death  | 29              | 23              |  |  |

## Statistical analyses



|   |  |
|---|--|
| <b>Statistical analysis title</b>   | Ordinal logistic regression- primary outcome |
| Statistical analysis description:<br>Ordinal logistic regression- primary outcome |  |
| Comparison groups   | Brensocatib v Placebo                        |
| Number of subjects included in analysis   | 404  |
| Analysis specification  | Pre-specified                                |
| Analysis type   | superiority                                  |
| P-value   | = 0.008                                      |
| Method  | Regression, Logistic                         |
| Parameter estimate  | Odds ratio (OR)                              |
| Point estimate  | 0.72   |
| Confidence interval   |  |
| level   | 95 %   |
| sides   | 2-sided                                      |
| lower limit   | 0.57   |
| upper limit   | 0.92   |

## Secondary: 2. Time to an Improvement of One Category From Admission Using 7-point Ordinal Scale

|  |  |
|--|--|
| End point title  | 2. Time to an Improvement of One Category From Admission Using 7-point Ordinal Scale |
| End point description:<br>Evaluation of the clinical efficacy of Brensocatib relative to standard care: 7-point ordinal scale. |  |
| End point type   | Secondary  |
| End point timeframe:<br>Up to 29 days  |  |

| End point values            | Brensocatib     | Placebo         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 190             | 214             |  |  |
| Units: Participants         | 159             | 186             |  |  |

## Statistical analyses

|   |                                     |
|---|-------------------------------------|
| <b>Statistical analysis title</b>   | Regression, cox - secondary outcome |
| Statistical analysis description:<br>Baseline CSTAT compared to follow-up CSTAT. Days to improvement derived as<br>1.days from randomization to first follow-up day where CSTAT improved<br>2.those who died before improvement were censored at date of death<br>3.those who withdrew or were loss to follow-up before improvement, if their day 29 status was unknown, they were censored at the date of loss to follow-up/withdrawal<br>4.other participants were censored at day 29 from randomisation in study time if there were no improvement |                                     |
| Comparison groups   | Placebo v Brensocatib               |

|   |                        |
|---|------------------------|
| Number of subjects included in analysis | 404                    |
| Analysis specification                  | Pre-specified          |
| Analysis type                           | superiority            |
| P-value                                 | = 0.058 <sup>[1]</sup> |
| Method                                  | Regression, Cox        |
| Parameter estimate                      | Hazard ratio (HR)      |
| Point estimate                          | 0.87                   |
| Confidence interval                     |                        |
| level                                   | 95 %                   |
| sides                                   | 2-sided                |
| lower limit                             | 0.76                   |
| upper limit                             | 1                      |

Notes:

[1] - Adjusted hazard ratio

### Secondary: 3. Participant Clinical Status on 7-point Ordinal Scale

|                        |   |
|------------------------|---|
| End point title        | 3. Participant Clinical Status on 7-point Ordinal Scale   |
| End point description: | Evaluation of the clinical efficacy of Brensocatib relative to standard care: 7-point ordinal scale |
| End point type         | Secondary   |
| End point timeframe:   | Up to 29 days   |

| End point values                                   | Brensocatib     | Placebo         |  |  |
|--|-----------------|-----------------|--|--|
| Subject group type                                 | Reporting group | Reporting group |  |  |
| Number of subjects analysed                        | 190             | 214             |  |  |
| Units: Participants                                |                 |                 |  |  |
| Not hospitalised, no limitations on activities     | 22              | 26              |  |  |
| Not hospitalised, limitations on activities        | 103             | 124             |  |  |
| Hospitalised, not requiring supplemental oxygen    | 12              | 19              |  |  |
| Hospitalised, requiring supplemental oxygen        | 16              | 13              |  |  |
| Hospitalised, on non-invasive ventilation or high  | 3               | 5               |  |  |
| Hospitalised, on invasive mechanical ventilation o | 9               | 6               |  |  |
| Death  | 20              | 18              |  |  |
| Missing  | 5               | 3               |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: 4. Mean Change in the 7-point Ordinal Scale

|                 |   |
|-----------------|---|
| End point title | 4. Mean Change in the 7-point Ordinal Scale |
|-----------------|---|

|  |           |
|--|-----------|
| End point description:   |           |
| Evaluation of the clinical efficacy of Brensocatib relative to standard care: 7-point ordinal scale. |           |
| End point type   | Secondary |
| End point timeframe:   |           |
| Baseline to days 3, 5, 8, 11, 15 and 29  |           |

| End point values                     | Brensocatib      | Placebo          |  |  |
|--------------------------------------|------------------|------------------|--|--|
| Subject group type                   | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed          | 187              | 211              |  |  |
| Units: Units on WHO Scale            |                  |                  |  |  |
| arithmetic mean (standard deviation) | 1.0 ( $\pm$ 2.0) | 1.3 ( $\pm$ 2.0) |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: 5. Time to Discharge or to a National Early Warning Score (NEWS) of $\leq 2$ and Maintained for 24 Hours, Whichever Occurs First

|  |  |
|--|--|
| End point title  | 5. Time to Discharge or to a National Early Warning Score (NEWS) of $\leq 2$ and Maintained for 24 Hours, Whichever Occurs First |
| End point description:   |  |
| Evaluation of the clinical efficacy of Brensocatib relative to standard care: National Early Warning Score |  |
| End point type   | Secondary  |
| End point timeframe:   |  |
| Up to 29 days  |  |

| End point values            | Brensocatib     | Placebo         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 190             | 195             |  |  |
| Units: Participants         | 172             | 195             |  |  |

### Statistical analyses

|   |                                 |
|---|---------------------------------|
| Statistical analysis title  | Hazard ratio -secondary outcome |
| Statistical analysis description:   |                                 |
| Time to discharge or NEWS of $\leq 2$ was calculated as days from randomization to date of discharged or NEWS of $\leq 2$ , whichever occurs first. Some patients had multiple admission during the study period and the first date of discharged was used for this analysis. |                                 |
| Comparison groups   | Brensocatib v Placebo           |

|   |                            |
|---|----------------------------|
| Number of subjects included in analysis | 385                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority <sup>[2]</sup> |
| P-value                                 | = 0.75                     |
| Method                                  | Regression, Cox            |
| Parameter estimate                      | Hazard ratio (HR)          |
| Point estimate                          | 0.98                       |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | 0.84                       |
| upper limit                             | 1.13                       |

Notes:

[2] - Adjusted hazard ratio

## Secondary: 6. Change From Baseline of National Early Warning Score (NEWS)

|                 |  |
|-----------------|--|
| End point title | 6. Change From Baseline of National Early Warning Score (NEWS) |
|-----------------|--|

End point description:

Evaluation of the clinical efficacy of Brensocatib relative to standard care: National Early Warning Score. Minimum value 0, maximum value 20. Higher scores mean worse outcome.

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

End point timeframe:

Days 8, 15 and 29

| End point values            | Brensocatib     | Placebo         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 190             | 214             |  |  |
| Units: Participants         |                 |                 |  |  |
| -11                         | 1               | 0               |  |  |
| -9                          | 2               | 0               |  |  |
| -8                          | 0               | 1               |  |  |
| -7                          | 1               | 0               |  |  |
| -6                          | 0               | 2               |  |  |
| -5                          | 1               | 0               |  |  |
| -4                          | 1               | 3               |  |  |
| -3                          | 4               | 1               |  |  |
| -2                          | 1               | 1               |  |  |
| -1                          | 3               | 3               |  |  |
| 0.0                         | 15              | 24              |  |  |
| 1.0                         | 22              | 24              |  |  |
| 2.0                         | 36              | 34              |  |  |
| 3.0                         | 28              | 36              |  |  |
| 4.0                         | 21              | 28              |  |  |
| 5.0                         | 10              | 14              |  |  |
| 6.0                         | 11              | 6               |  |  |
| 7.0                         | 3               | 4               |  |  |
| 8.0                         | 1               | 4               |  |  |

|         |    |    |  |  |
|---------|----|----|--|--|
| 9.0     | 0  | 2  |  |  |
| 10.0    | 0  | 1  |  |  |
| Missing | 29 | 26 |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: 7. Number of Oxygen Therapy Free Days

|   |                                       |
|---|---------------------------------------|
| End point title   | 7. Number of Oxygen Therapy Free Days |
| End point description:  |                                       |
| Evaluation of the clinical efficacy of Brensocatib relative to standard care: oxygenation |                                       |
| End point type  | Secondary                             |
| End point timeframe:  |                                       |
| Up to day 29  |                                       |

| End point values                      | Brensocatib     | Placebo         |  |  |
|---------------------------------------|-----------------|-----------------|--|--|
| Subject group type                    | Reporting group | Reporting group |  |  |
| Number of subjects analysed           | 190             | 214             |  |  |
| Units: days                           |                 |                 |  |  |
| median (inter-quartile range (Q1-Q3)) | 24 (11 to 27)   | 24.5 (17 to 27) |  |  |

## Statistical analyses

|  |                              |
|--|------------------------------|
| Statistical analysis title   | Negative binomial regression |
| Statistical analysis description:  |                              |
| Number of days free from oxygen support (CSTAT = 1, 2, 3) were compared between the treatment arms using negative binomial regression, results are expressed as incidence rate ratios (with 95% confidence intervals). |                              |
| Comparison groups  | Brensocatib v Placebo        |
| Number of subjects included in analysis  | 404                          |
| Analysis specification   | Pre-specified                |
| Analysis type  | superiority                  |
| P-value  | = 0.027                      |
| Method   | Rate ratio                   |
| Parameter estimate   | Rate ratio                   |
| Point estimate   | 0.93                         |
| Confidence interval  |                              |
| level  | 95 %                         |
| sides  | 2-sided                      |
| lower limit  | 0.87                         |
| upper limit  | 0.99                         |

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**Secondary: 8. Incidence and Duration of New Oxygen Therapy Use During the Trial**

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|                 |  |
|-----------------|--|
| End point title | 8. Incidence and Duration of New Oxygen Therapy Use During the Trial |
|-----------------|--|

End point description:

Evaluation of the clinical efficacy of Brensocatib relative to standard care: oxygenation

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

End point timeframe:

Up to day 29

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| End point values                      | Brensocatib     | Placebo         |  |  |
|---------------------------------------|-----------------|-----------------|--|--|
| Subject group type                    | Reporting group | Reporting group |  |  |
| Number of subjects analysed           | 190             | 214             |  |  |
| Units: Days                           |                 |                 |  |  |
| median (inter-quartile range (Q1-Q3)) | 0 (0 to 2)      | 0 (0 to 1)      |  |  |

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**Statistical analyses**

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|                            |  |
|----------------------------|--|
| Statistical analysis title | Incidence and Duration of New Oxygen Therapy Use |
|----------------------------|--|

Statistical analysis description:

Evaluation of the clinical efficacy of Brensocatib relative to standard care: oxygenation

|                   |                       |
|-------------------|-----------------------|
| Comparison groups | Brensocatib v Placebo |
|-------------------|-----------------------|

|   |     |
|---|-----|
| Number of subjects included in analysis | 404 |
|---|-----|

|                        |               |
|------------------------|---------------|
| Analysis specification | Pre-specified |
|------------------------|---------------|

|               |             |
|---------------|-------------|
| Analysis type | superiority |
|---------------|-------------|

|         |         |
|---------|---------|
| P-value | = 0.058 |
|---------|---------|

|        |            |
|--------|------------|
| Method | Rate ratio |
|--------|------------|

|                    |            |
|--------------------|------------|
| Parameter estimate | Rate ratio |
|--------------------|------------|

|                |      |
|----------------|------|
| Point estimate | 1.13 |
|----------------|------|

Confidence interval

|       |      |
|-------|------|
| level | 95 % |
|-------|------|

|       |         |
|-------|---------|
| sides | 2-sided |
|-------|---------|

|             |      |
|-------------|------|
| lower limit | 0.73 |
|-------------|------|

|             |      |
|-------------|------|
| upper limit | 1.74 |
|-------------|------|

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**Secondary: 9. Number of Mechanical Ventilator Free Days**

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|                 |  |
|-----------------|--|
| End point title | 9. Number of Mechanical Ventilator Free Days |
|-----------------|--|

End point description:

Evaluation of the clinical efficacy of Brensocatib relative to standard care: Mechanical ventilation

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

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End point timeframe:

Up to day 29

| End point values                      | Brensocatib     | Placebo         |  |  |
|---------------------------------------|-----------------|-----------------|--|--|
| Subject group type                    | Reporting group | Reporting group |  |  |
| Number of subjects analysed           | 190             | 214             |  |  |
| Units: Days                           |                 |                 |  |  |
| median (inter-quartile range (Q1-Q3)) | 28 (22 to 28)   | 28 (26 to 28)   |  |  |

## Statistical analyses

| Statistical analysis title | Negative binomial regression |
|----------------------------|------------------------------|
|----------------------------|------------------------------|

Statistical analysis description:

Number of days free from ventilator (CSTAT = 1, 2, 3, 4) were compared between the treatment arms using negative binomial regression results are expressed as incidence rate ratios (with 95% confidence intervals).

|   |                       |
|---|-----------------------|
| Comparison groups                       | Brensocatib v Placebo |
| Number of subjects included in analysis | 404                   |
| Analysis specification                  | Pre-specified         |
| Analysis type                           | superiority           |
| P-value                                 | = 0.021               |
| Method                                  | Rate ratio            |
| Parameter estimate                      | Rate ratio            |
| Point estimate                          | 0.95                  |
| Confidence interval                     |                       |
| level                                   | 95 %                  |
| sides                                   | 2-sided               |
| lower limit                             | 0.91                  |
| upper limit                             | 0.99                  |

## Secondary: 10. Incidence and Duration of New Mechanical Ventilation Use During the Trial

|                 |   |
|-----------------|---|
| End point title | 10. Incidence and Duration of New Mechanical Ventilation Use During the Trial |
|-----------------|---|

End point description:

Evaluation of the clinical efficacy of Brensocatib relative to standard care: Mechanical ventilation

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

End point timeframe:

Up to day 29

| End point values                      | Brensocatib     | Placebo         |  |  |
|---------------------------------------|-----------------|-----------------|--|--|
| Subject group type                    | Reporting group | Reporting group |  |  |
| Number of subjects analysed           | 190             | 214             |  |  |
| Units: Days                           |                 |                 |  |  |
| median (inter-quartile range (Q1-Q3)) | 0 (0 to 0)      | 0 (0 to 0)      |  |  |

## Statistical analyses

| Statistical analysis title              | Negative binomial regression |
|---|------------------------------|
| Comparison groups                       | Brensocatib v Placebo        |
| Number of subjects included in analysis | 404                          |
| Analysis specification                  | Pre-specified                |
| Analysis type                           | superiority                  |
| P-value                                 | = 0.018                      |
| Method                                  | Rate ratio                   |
| Parameter estimate                      | Rate ratio                   |
| Point estimate                          | 1.68                         |
| Confidence interval                     |                              |
| level                                   | 95 %                         |
| sides                                   | 2-sided                      |
| lower limit                             | 1.09                         |
| upper limit                             | 2.58                         |

## Secondary: 11. Duration of Hospitalisation

|  |   |
|--|---|
| End point title  | 11. Duration of Hospitalisation   |
| End point description:   |   |
| n:   | Evaluation of the clinical efficacy of Brensocatib relative to standard care: hospitalisation |
| End point type   | Secondary   |
| End point timeframe:   |   |
| Duration between date of admission and discharge assessed up to 29 days. |   |

| End point values                     | Brensocatib      | Placebo          |  |  |
|--------------------------------------|------------------|------------------|--|--|
| Subject group type                   | Reporting group  | Reporting group  |  |  |
| Number of subjects analysed          | 190              | 214              |  |  |
| Units: Days                          |                  |                  |  |  |
| arithmetic mean (standard deviation) | 8.4 ( $\pm$ 8.3) | 8.2 ( $\pm$ 8.3) |  |  |

## Statistical analyses



|  |                              |
|--|------------------------------|
| <b>Statistical analysis title</b>  | Negative binomial regression |
| Statistical analysis description:  |                              |
| Duration of hospitalisation was calculated from date of randomisation to date of discharged. If a participant had more than one admission during the study period, the total duration of hospitalisation was calculated. Participants who died in the hospital and participants who withdrew and date of discharged were not recorded were excluded in the analysis. |                              |
| Comparison groups  | Brensocatib v Placebo        |
| Number of subjects included in analysis  | 404                          |
| Analysis specification   | Pre-specified                |
| Analysis type  | superiority                  |
| P-value  | = 0.602                      |
| Method   | Rate ratio                   |
| Parameter estimate   | Rate ratio                   |
| Point estimate   | 1.03                         |
| Confidence interval  |                              |
| level  | 95 %                         |
| sides  | 2-sided                      |
| lower limit  | 0.92                         |
| upper limit  | 1.15                         |

## Secondary: 12. 28-day Mortality

|   |                      |
|---|----------------------|
| End point title   | 12. 28-day Mortality |
| End point description:  |                      |
| Evaluation of the clinical efficacy of Brensocatib relative to standard care: mortality |                      |
| End point type  | Secondary            |
| End point timeframe:  |                      |
| Date of death up to 20 days   |                      |

| End point values            | Brensocatib     | Placebo         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 190             | 214             |  |  |
| Units: Participants         | 29              | 23              |  |  |

## Statistical analyses

|  |                       |
|--|-----------------------|
| <b>Statistical analysis title</b>  | Regression, cox       |
| Statistical analysis description:  |                       |
| Survival analysis was used to compare 28-day mortality between the treatment arms. Participants who did not die will be censored on the last study day. Those who withdrew or were loss to follow-up and their day 29 status was unknown were censored at the date of loss to follow-up/withdrawal. Other participants were censored 28 days from randomisation in study time. |                       |
| Comparison groups  | Brensocatib v Placebo |

|   |                   |
|---|-------------------|
| Number of subjects included in analysis | 404               |
| Analysis specification                  | Pre-specified     |
| Analysis type                           | superiority       |
| P-value                                 | = 0.017           |
| Method                                  | Regression, Cox   |
| Parameter estimate                      | Hazard ratio (HR) |
| Point estimate                          | 1.44              |
| Confidence interval                     |                   |
| level                                   | 95 %              |
| sides                                   | 2-sided           |
| lower limit                             | 1.06              |
| upper limit                             | 1.88              |

### Secondary: 13. Cumulative Incidence of Serious Adverse Events (SAEs)

|  |   |
|--|---|
| End point title  | 13. Cumulative Incidence of Serious Adverse Events (SAEs) |
| End point description:   |   |
| Evaluation of the safety of the intervention through 29 days of follow-up as compared to the control arm |   |
| End point type   | Secondary   |
| End point timeframe:   |   |
| 1-29 days  |   |

| End point values            | Brensocatib     | Placebo         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 190             | 214             |  |  |
| Units: Participants         | 40              | 35              |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: 14. Discontinuation or Temporary Suspension of Treatment

|  |  |
|--|--|
| End point title  | 14. Discontinuation or Temporary Suspension of Treatment |
| End point description:   |  |
| Evaluation of the safety of the intervention through 28 days of follow-up as compared to the control arm |  |
| End point type   | Secondary  |
| End point timeframe:   |  |
| 1-29 days  |  |

| End point values            | Brensocatib     | Placebo         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 190             | 214             |  |  |
| Units: Participants         | 13              | 12              |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: 15. Changes in White 15. Cell Count (x10<sup>9</sup>/L) Over Time (Hospitalised Participants Only)

|  |  |
|--|--|
| End point title  | 15. Changes in White 15. Cell Count (x10 <sup>9</sup> /L) Over Time (Hospitalised Participants Only) |
| End point description:   |  |
| Evaluation of the safety of the intervention through 28 days of follow-up as compared to the control arm |  |
| End point type   | Secondary  |
| End point timeframe:   |  |
| Days 0/1, 3, 5, 8, 11, 15, 29  |  |

| End point values                     | Brensocatib     | Placebo         |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 14              | 18              |  |  |
| Units: cells/millilitre              |                 |                 |  |  |
| arithmetic mean (standard deviation) | 8.9 (± 4.7)     | 8.5 (± 3.1)     |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: 16. Changes in Haemoglobin (g/L) Over Time (Hospitalised Participants Only)

|  |   |
|--|---|
| End point title  | 16. Changes in Haemoglobin (g/L) Over Time (Hospitalised Participants Only) |
| End point description:   |   |
| Evaluation of the safety of the intervention through 28 days of follow-up as compared to the control arm |   |
| End point type   | Secondary   |
| End point timeframe:   |   |
| Days 0/1, 3, 5, 8, 11, 15, 29  |   |

| End point values                     | Brensocatic     | Placebo         |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 14              | 18              |  |  |
| Units: g/L                           |                 |                 |  |  |
| arithmetic mean (standard deviation) | 195.4 (± 264)   | 105.5 (± 21.7)  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: 17. Changes in Platelets (x10<sup>9</sup>/L) Over Time (Hospitalised Participants Only)

|  |   |
|--|---|
| End point title  | 17. Changes in Platelets (x10 <sup>9</sup> /L) Over Time (Hospitalised Participants Only) |
| End point description:   |   |
| Evaluation of the safety of the intervention through 28 days of follow-up as compared to the control arm |   |
| End point type   | Secondary   |
| End point timeframe:   |   |
| Days 0/1, 3, 5, 8, 11, 15, 29  |   |

| End point values                     | Brensocatic     | Placebo         |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 14              | 18              |  |  |
| Units: x10(7) cell/L                 |                 |                 |  |  |
| arithmetic mean (standard deviation) | 270 (± 94.3)    | 269 (± 117)     |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: 18. Changes in Creatinine (Umol/L) Over Time (Hospitalised Participants Only)

|  |   |
|--|---|
| End point title  | 18. Changes in Creatinine (Umol/L) Over Time (Hospitalised Participants Only) |
| End point description:   |   |
| Evaluation of the safety of the intervention through 28 days of follow-up as compared to the control arm |   |
| End point type   | Secondary   |
| End point timeframe:   |   |
| Days 0/1, 3, 5, 8, 11, 15, 29  |   |

| End point values                     | Brensocatib     | Placebo         |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 14              | 19              |  |  |
| Units: umol/L                        |                 |                 |  |  |
| arithmetic mean (standard deviation) | 84.9 (± 39)     | 84.1 (± 52)     |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: 19. Changes in Total Bilirubin (Umol/L) Over Time (Hospitalised Participants Only)

|                 |  |
|-----------------|--|
| End point title | 19. Changes in Total Bilirubin (Umol/L) Over Time (Hospitalised Participants Only) |
|-----------------|--|

End point description:

Evaluation of the safety of the intervention through 28 days of follow-up as compared to the control arm

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

End point timeframe:

Days 0/1, 3, 5, 8, 11, 15, 29

| End point values                     | Brensocatib     | Placebo         |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 14              | 16              |  |  |
| Units: umol/L                        |                 |                 |  |  |
| arithmetic mean (standard deviation) | 8.4 (± 3.9)     | 9.3 (± 9.8)     |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: 20. Changes in Alanine Aminotransferase (U/L) Over Time (Hospitalised Participants Only)

|                 |  |
|-----------------|--|
| End point title | 20. Changes in Alanine Aminotransferase (U/L) Over Time (Hospitalised Participants Only) |
|-----------------|--|

End point description:

Evaluation of the safety of the intervention through 28 days of follow-up as compared to the control arm

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

End point timeframe:

Days 0/1, 3, 5, 8, 11, 15, 29

| End point values                     | Brensocatib     | Placebo         |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 14              | 15              |  |  |
| Units: U/L                           |                 |                 |  |  |
| arithmetic mean (standard deviation) | 62.8 (± 43.2)   | 52.3 (± 92.8)   |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: 21. Changes in Aspartate Aminotransferase U/L Over Time (Hospitalised Participants Only)

|  |  |
|--|--|
| End point title  | 21. Changes in Aspartate Aminotransferase U/L Over Time (Hospitalised Participants Only) |
| End point description:   |  |
| Evaluation of the safety of the intervention through 28 days of follow-up as compared to the control arm |  |
| End point type   | Secondary  |
| End point timeframe:   |  |
| Days 0/1, 3, 5, 8, 11, 15, 29  |  |

| End point values                     | Brensocatib     | Placebo         |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 3               | 4               |  |  |
| Units: U/L                           |                 |                 |  |  |
| arithmetic mean (standard deviation) | 22 (± 11.4)     | 28.8 (± 14.9)   |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: 22. Adverse Events of Special Interest- Hyperkeratosis, Infections and Dental Complications

|  |   |
|--|---|
| End point title  | 22. Adverse Events of Special Interest- Hyperkeratosis, Infections and Dental Complications |
| End point description:   |   |
| Evaluation of the safety of the intervention through 29 days of follow-up as compared to the control arm |   |
| End point type   | Secondary   |
| End point timeframe:   |   |
| 1-29 days  |   |

| <b>End point values</b>     | Brensocatib     | Placebo         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 190             | 214             |  |  |
| Units: Participants         |                 |                 |  |  |
| Hyperkeratosis              | 0               | 0               |  |  |
| Dental complications        | 0               | 1               |  |  |
| Secondary infections        | 6               | 7               |  |  |

## Statistical analyses

---

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

29 days

Adverse event reporting additional description:

Adverse events were reported by the participant, site principal investigators or delegated staff responsible for detecting documenting and recording events that met the definition of an adverse event. Participants discharged from hospital before the end of the trial were given a diary to record adverse events up to day 28. Site principal investigator

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 13.0 |
|--------------------|------|

### Reporting groups

|                       |             |
|-----------------------|-------------|
| Reporting group title | Brensocatib |
|-----------------------|-------------|

Reporting group description:

Brensocatib 25mg once daily for 28 days

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

Reporting group description:

Oral placebo tablet

| Serious adverse events  | Brensocatib       | Placebo           |  |
|---|-------------------|-------------------|--|
| Total subjects affected by serious adverse events                   |                   |                   |  |
| subjects affected / exposed   | 40 / 190 (21.05%) | 35 / 214 (16.36%) |  |
| number of deaths (all causes)                                       | 29                | 23                |  |
| number of deaths resulting from adverse events                      |                   |                   |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                   |                   |  |
| Metastases to liver   |                   |                   |  |
| subjects affected / exposed   | 0 / 190 (0.00%)   | 1 / 214 (0.47%)   |  |
| occurrences causally related to treatment / all                     | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all                          | 0 / 0             | 0 / 1             |  |
| Vascular disorders  |                   |                   |  |
| Cerebellar infarction   |                   |                   |  |
| subjects affected / exposed   | 1 / 190 (0.53%)   | 0 / 214 (0.00%)   |  |
| occurrences causally related to treatment / all                     | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all                          | 0 / 1             | 0 / 0             |  |
| Pulmonary embolism  |                   |                   |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 3 / 190 (1.58%) | 2 / 214 (0.93%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Thrombosis                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 190 (0.00%) | 1 / 214 (0.47%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Peripheral ischaemia                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 190 (0.53%) | 0 / 214 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nervous system disorders                        |                 |                 |  |
| Cerebrovascular accident                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 190 (0.53%) | 0 / 214 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Subarachnoid haemorrhage                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 190 (0.53%) | 0 / 214 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Syncope   |                 |                 |  |
| subjects affected / exposed                     | 0 / 190 (0.00%) | 2 / 214 (0.93%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cerebral infarction                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 190 (0.53%) | 0 / 214 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Blood and lymphatic system disorders            |                 |                 |  |
| Deep vein thrombosis                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 190 (0.00%) | 1 / 214 (0.47%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| General disorders and administration            |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| site conditions                                 |                 |                 |  |
| Multiple organ dysfunction syndrome             |                 |                 |  |
| subjects affected / exposed                     | 1 / 190 (0.53%) | 0 / 214 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Gastrointestinal disorders                      |                 |                 |  |
| Abdominal pain                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 190 (0.00%) | 1 / 214 (0.47%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Oesophagitis                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 190 (0.00%) | 1 / 214 (0.47%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pancreatic cyst                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 190 (0.00%) | 1 / 214 (0.47%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intestinal ischaemia                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 190 (0.53%) | 0 / 214 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Respiratory, thoracic and mediastinal disorders |                 |                 |  |
| Interstitial lung disease                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 190 (0.00%) | 1 / 214 (0.47%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Hypoxia   |                 |                 |  |
| subjects affected / exposed                     | 1 / 190 (0.53%) | 0 / 214 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumothorax                                    |                 |                 |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 190 (0.53%)  | 1 / 214 (0.47%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pneumothorax spontaneous                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 190 (0.53%)  | 0 / 214 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Skin and subcutaneous tissue disorders          |                  |                  |  |
| Urticaria                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 190 (0.53%)  | 0 / 214 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Drug eruption                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 190 (0.53%)  | 0 / 214 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Renal and urinary disorders                     |                  |                  |  |
| Acute kidney injury                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 190 (0.00%)  | 1 / 214 (0.47%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Psychiatric disorders                           |                  |                  |  |
| Delirium  |                  |                  |  |
| subjects affected / exposed                     | 0 / 190 (0.00%)  | 2 / 214 (0.93%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Infections and infestations                     |                  |                  |  |
| COVID-19  |                  |                  |  |
| subjects affected / exposed                     | 14 / 190 (7.37%) | 17 / 214 (7.94%) |  |
| occurrences causally related to treatment / all | 0 / 14           | 0 / 17           |  |
| deaths causally related to treatment / all      | 0 / 13           | 0 / 17           |  |
| Lower respiratory tract infection               |                  |                  |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 190 (0.00%) | 1 / 214 (0.47%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 1 / 1           |  |
| Diverticulitis intestinal haemorrhagic          |                 |                 |  |
| subjects affected / exposed                     | 0 / 190 (0.00%) | 1 / 214 (0.47%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Arthritis bacterial                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 190 (0.53%) | 0 / 214 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinary tract infection                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 190 (0.53%) | 0 / 214 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 190 (0.53%) | 1 / 214 (0.47%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           |  |
| COVID-19 pneumonia                              |                 |                 |  |
| subjects affected / exposed                     | 9 / 190 (4.74%) | 3 / 214 (1.40%) |  |
| occurrences causally related to treatment / all | 0 / 9           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 9           | 0 / 2           |  |
| Urosepsis                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 190 (0.00%) | 1 / 214 (0.47%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

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

| <b>Non-serious adverse events</b>                                   | Brensocaticib     | Placebo           |  |
|---|-------------------|-------------------|--|
| Total subjects affected by non-serious adverse events               |                   |                   |  |
| subjects affected / exposed   | 86 / 190 (45.26%) | 99 / 214 (46.26%) |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                   |                   |  |
| Chronic lymphocytic leukaemia                                       |                   |                   |  |
| subjects affected / exposed   | 1 / 190 (0.53%)   | 0 / 214 (0.00%)   |  |
| occurrences (all)   | 1                 | 0                 |  |
| Vascular disorders  |                   |                   |  |
| Peripheral ischaemia  |                   |                   |  |
| subjects affected / exposed   | 1 / 190 (0.53%)   | 0 / 214 (0.00%)   |  |
| occurrences (all)   | 1                 | 0                 |  |
| General disorders and administration site conditions                |                   |                   |  |
| Chest pain  |                   |                   |  |
| subjects affected / exposed   | 0 / 190 (0.00%)   | 3 / 214 (1.40%)   |  |
| occurrences (all)   | 0                 | 3                 |  |
| Cold sweat  |                   |                   |  |
| subjects affected / exposed   | 0 / 190 (0.00%)   | 1 / 214 (0.47%)   |  |
| occurrences (all)   | 0                 | 1                 |  |
| Chest discomfort  |                   |                   |  |
| subjects affected / exposed   | 2 / 190 (1.05%)   | 0 / 214 (0.00%)   |  |
| occurrences (all)   | 2                 | 0                 |  |
| Non-cardiac chest pain  |                   |                   |  |
| subjects affected / exposed   | 0 / 190 (0.00%)   | 1 / 214 (0.47%)   |  |
| occurrences (all)   | 0                 | 1                 |  |
| Swelling face   |                   |                   |  |
| subjects affected / exposed   | 1 / 190 (0.53%)   | 0 / 214 (0.00%)   |  |
| occurrences (all)   | 1                 | 0                 |  |
| Oedema peripheral   |                   |                   |  |
| subjects affected / exposed   | 1 / 190 (0.53%)   | 1 / 214 (0.47%)   |  |
| occurrences (all)   | 1                 | 1                 |  |
| Extravasation   |                   |                   |  |
| subjects affected / exposed   | 1 / 190 (0.53%)   | 0 / 214 (0.00%)   |  |
| occurrences (all)   | 1                 | 0                 |  |
| Malaise   |                   |                   |  |
| subjects affected / exposed   | 0 / 190 (0.00%)   | 1 / 214 (0.47%)   |  |
| occurrences (all)   | 0                 | 1                 |  |

|   |                      |                      |  |
|---|----------------------|----------------------|--|
| Feeling hot<br>subjects affected / exposed<br>occurrences (all)           | 0 / 190 (0.00%)<br>0 | 1 / 214 (0.47%)<br>1 |  |
| Peripheral swelling<br>subjects affected / exposed<br>occurrences (all)   | 2 / 190 (1.05%)<br>2 | 0 / 214 (0.00%)<br>0 |  |
| Respiratory, thoracic and mediastinal disorders                           |                      |                      |  |
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)              | 1 / 190 (0.53%)<br>1 | 4 / 214 (1.87%)<br>4 |  |
| Hiccups<br>subjects affected / exposed<br>occurrences (all)               | 2 / 190 (1.05%)<br>2 | 1 / 214 (0.47%)<br>1 |  |
| Pneumothorax<br>subjects affected / exposed<br>occurrences (all)          | 1 / 190 (0.53%)<br>1 | 0 / 214 (0.00%)<br>0 |  |
| Epistaxis<br>subjects affected / exposed<br>occurrences (all)             | 3 / 190 (1.58%)<br>3 | 0 / 214 (0.00%)<br>0 |  |
| Rhinorrhoea<br>subjects affected / exposed<br>occurrences (all)           | 1 / 190 (0.53%)<br>1 | 0 / 214 (0.00%)<br>0 |  |
| Pulmonary embolism<br>subjects affected / exposed<br>occurrences (all)    | 1 / 190 (0.53%)<br>1 | 3 / 214 (1.40%)<br>3 |  |
| Psychiatric disorders   |                      |                      |  |
| Hallucination, visual<br>subjects affected / exposed<br>occurrences (all) | 1 / 190 (0.53%)<br>1 | 0 / 214 (0.00%)<br>0 |  |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)              | 0 / 190 (0.00%)<br>0 | 2 / 214 (0.93%)<br>2 |  |
| Delirium<br>subjects affected / exposed<br>occurrences (all)              | 0 / 190 (0.00%)<br>0 | 1 / 214 (0.47%)<br>1 |  |
| Nightmare   |                      |                      |  |

|  |                      |                      |  |
|--|----------------------|----------------------|--|
| subjects affected / exposed<br>occurrences (all)                                       | 1 / 190 (0.53%)<br>1 | 0 / 214 (0.00%)<br>0 |  |
| Suicidal ideation<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 190 (0.00%)<br>0 | 1 / 214 (0.47%)<br>1 |  |
| Investigations   |                      |                      |  |
| Electrocardiogram abnormal<br>subjects affected / exposed<br>occurrences (all)         | 0 / 190 (0.00%)<br>0 | 1 / 214 (0.47%)<br>1 |  |
| Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all) | 2 / 190 (1.05%)<br>2 | 2 / 214 (0.93%)<br>4 |  |
| Liver function test abnormal<br>subjects affected / exposed<br>occurrences (all)       | 1 / 190 (0.53%)<br>1 | 0 / 214 (0.00%)<br>0 |  |
| Glycosylated haemoglobin increased<br>subjects affected / exposed<br>occurrences (all) | 1 / 190 (0.53%)<br>1 | 0 / 214 (0.00%)<br>0 |  |
| Blood glucose abnormal<br>subjects affected / exposed<br>occurrences (all)             | 1 / 190 (0.53%)<br>1 | 1 / 214 (0.47%)<br>1 |  |
| Blood glucose increased<br>subjects affected / exposed<br>occurrences (all)            | 0 / 190 (0.00%)<br>0 | 1 / 214 (0.47%)<br>1 |  |
| Transaminases increased<br>subjects affected / exposed<br>occurrences (all)            | 1 / 190 (0.53%)<br>1 | 0 / 214 (0.00%)<br>0 |  |
| Injury, poisoning and procedural complications   |                      |                      |  |
| Fall<br>subjects affected / exposed<br>occurrences (all)                               | 1 / 190 (0.53%)<br>1 | 0 / 214 (0.00%)<br>0 |  |
| Cardiac disorders  |                      |                      |  |
| Bradycardia<br>subjects affected / exposed<br>occurrences (all)                        | 1 / 190 (0.53%)<br>1 | 1 / 214 (0.47%)<br>1 |  |
| Palpitations   |                      |                      |  |

|                              |                 |                 |  |
|------------------------------|-----------------|-----------------|--|
| subjects affected / exposed  | 2 / 190 (1.05%) | 0 / 214 (0.00%) |  |
| occurrences (all)            | 2               | 0               |  |
| Atrial fibrillation          |                 |                 |  |
| subjects affected / exposed  | 0 / 190 (0.00%) | 2 / 214 (0.93%) |  |
| occurrences (all)            | 0               | 2               |  |
| Tachyarrhythmia              |                 |                 |  |
| subjects affected / exposed  | 1 / 190 (0.53%) | 0 / 214 (0.00%) |  |
| occurrences (all)            | 1               | 0               |  |
| Acute coronary syndrome      |                 |                 |  |
| subjects affected / exposed  | 1 / 190 (0.53%) | 0 / 214 (0.00%) |  |
| occurrences (all)            | 1               | 0               |  |
| Supraventricular tachycardia |                 |                 |  |
| subjects affected / exposed  | 1 / 190 (0.53%) | 0 / 214 (0.00%) |  |
| occurrences (all)            | 1               | 0               |  |
| Sinus bradycardia            |                 |                 |  |
| subjects affected / exposed  | 1 / 190 (0.53%) | 0 / 214 (0.00%) |  |
| occurrences (all)            | 1               | 0               |  |
| Nervous system disorders     |                 |                 |  |
| Dizziness                    |                 |                 |  |
| subjects affected / exposed  | 3 / 190 (1.58%) | 5 / 214 (2.34%) |  |
| occurrences (all)            | 3               | 5               |  |
| Headache                     |                 |                 |  |
| subjects affected / exposed  | 2 / 190 (1.05%) | 2 / 214 (0.93%) |  |
| occurrences (all)            | 2               | 2               |  |
| Memory impairment            |                 |                 |  |
| subjects affected / exposed  | 1 / 190 (0.53%) | 0 / 214 (0.00%) |  |
| occurrences (all)            | 1               | 0               |  |
| Syncope                      |                 |                 |  |
| subjects affected / exposed  | 0 / 190 (0.00%) | 1 / 214 (0.47%) |  |
| occurrences (all)            | 0               | 1               |  |
| Hypoaesthesia                |                 |                 |  |
| subjects affected / exposed  | 0 / 190 (0.00%) | 1 / 214 (0.47%) |  |
| occurrences (all)            | 0               | 1               |  |
| Dysarthria                   |                 |                 |  |
| subjects affected / exposed  | 0 / 190 (0.00%) | 1 / 214 (0.47%) |  |
| occurrences (all)            | 0               | 1               |  |



|   |  |  |  |
|---|--|--|--|
| Paraesthesia<br>subjects affected / exposed<br>occurrences (all)  | 1 / 190 (0.53%)<br>1   | 0 / 214 (0.00%)<br>0   |  |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all)   | 0 / 190 (0.00%)<br>0   | 1 / 214 (0.47%)<br>1   |  |
| Eye disorders<br>Vision blurred<br>subjects affected / exposed<br>occurrences (all)<br><br>Eye pruritus<br>subjects affected / exposed<br>occurrences (all)   | 2 / 190 (1.05%)<br>2<br><br>0 / 190 (0.00%)<br>0   | 1 / 214 (0.47%)<br>1<br><br>1 / 214 (0.47%)<br>1   |  |
| Gastrointestinal disorders<br>Abdominal pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Dyspepsia<br>subjects affected / exposed<br>occurrences (all)<br><br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all)<br><br>Dry mouth<br>subjects affected / exposed<br>occurrences (all)<br><br>Nausea<br>subjects affected / exposed<br>occurrences (all)<br><br>Vomiting<br>subjects affected / exposed<br>occurrences (all)<br><br>Constipation<br>subjects affected / exposed<br>occurrences (all)<br><br>Flatulence | 0 / 190 (0.00%)<br>0<br><br>3 / 190 (1.58%)<br>3<br><br>0 / 190 (0.00%)<br>0<br><br>1 / 190 (0.53%)<br>1<br><br>3 / 190 (1.58%)<br>3<br><br>1 / 190 (0.53%)<br>1<br><br>1 / 190 (0.53%)<br>1 | 4 / 214 (1.87%)<br>4<br><br>4 / 214 (1.87%)<br>4<br><br>2 / 214 (0.93%)<br>2<br><br>2 / 214 (0.93%)<br>2<br><br>3 / 214 (1.40%)<br>3<br><br>4 / 214 (1.87%)<br>4<br><br>4 / 214 (1.87%)<br>4 |  |

|                                    |                 |                 |
|------------------------------------|-----------------|-----------------|
| subjects affected / exposed        | 0 / 190 (0.00%) | 1 / 214 (0.47%) |
| occurrences (all)                  | 0               | 1               |
| Lower gastrointestinal haemorrhage |                 |                 |
| subjects affected / exposed        | 0 / 190 (0.00%) | 1 / 214 (0.47%) |
| occurrences (all)                  | 0               | 1               |
| Rectal haemorrhage                 |                 |                 |
| subjects affected / exposed        | 0 / 190 (0.00%) | 1 / 214 (0.47%) |
| occurrences (all)                  | 0               | 1               |
| Gastritis erosive                  |                 |                 |
| subjects affected / exposed        | 1 / 190 (0.53%) | 0 / 214 (0.00%) |
| occurrences (all)                  | 1               | 0               |
| Gastrooesophageal reflux disease   |                 |                 |
| subjects affected / exposed        | 1 / 190 (0.53%) | 1 / 214 (0.47%) |
| occurrences (all)                  | 1               | 1               |
| Oral mucosal eruption              |                 |                 |
| subjects affected / exposed        | 0 / 190 (0.00%) | 1 / 214 (0.47%) |
| occurrences (all)                  | 0               | 1               |
| Gingival bleeding                  |                 |                 |
| subjects affected / exposed        | 1 / 190 (0.53%) | 0 / 214 (0.00%) |
| occurrences (all)                  | 1               | 0               |
| Glossodynia                        |                 |                 |
| subjects affected / exposed        | 1 / 190 (0.53%) | 1 / 214 (0.47%) |
| occurrences (all)                  | 1               | 1               |
| Tongue blistering                  |                 |                 |
| subjects affected / exposed        | 0 / 190 (0.00%) | 1 / 214 (0.47%) |
| occurrences (all)                  | 0               | 1               |
| Oral mucosal blistering            |                 |                 |
| subjects affected / exposed        | 0 / 190 (0.00%) | 1 / 214 (0.47%) |
| occurrences (all)                  | 0               | 1               |
| Swollen tongue                     |                 |                 |
| subjects affected / exposed        | 1 / 190 (0.53%) | 1 / 214 (0.47%) |
| occurrences (all)                  | 1               | 1               |
| Oral pain                          |                 |                 |
| subjects affected / exposed        | 0 / 190 (0.00%) | 1 / 214 (0.47%) |
| occurrences (all)                  | 0               | 1               |
| Hypoaesthesia oral                 |                 |                 |

|  |  |                 |  |
|--|--|-----------------|--|
| subjects affected / exposed            | 1 / 190 (0.53%)                                    | 0 / 214 (0.00%) |  |
| occurrences (all)                      | 1  | 0               |  |
| Gingival pain                          |  |                 |  |
| subjects affected / exposed            | 0 / 190 (0.00%)                                    | 1 / 214 (0.47%) |  |
| occurrences (all)                      | 0  | 1               |  |
| Lip pain                               |  |                 |  |
| subjects affected / exposed            | 1 / 190 (0.53%)                                    | 0 / 214 (0.00%) |  |
| occurrences (all)                      | 1  | 0               |  |
| Lip swelling                           |  |                 |  |
| subjects affected / exposed            | 0 / 190 (0.00%)                                    | 1 / 214 (0.47%) |  |
| occurrences (all)                      | 0  | 1               |  |
| Paraesthesia oral                      |  |                 |  |
| subjects affected / exposed            | 0 / 190 (0.00%)                                    | 1 / 214 (0.47%) |  |
| occurrences (all)                      | 0  | 1               |  |
| Tongue erythema                        |  |                 |  |
| subjects affected / exposed            | 0 / 190 (0.00%)                                    | 1 / 214 (0.47%) |  |
| occurrences (all)                      | 0  | 1               |  |
| Toothache                              |  |                 |  |
| subjects affected / exposed            | 0 / 190 (0.00%)                                    | 1 / 214 (0.47%) |  |
| occurrences (all)                      | 0  | 1               |  |
| Tongue discolouration                  |  |                 |  |
| subjects affected / exposed            | 0 / 190 (0.00%)                                    | 1 / 214 (0.47%) |  |
| occurrences (all)                      | 0  | 1               |  |
| Hepatobiliary disorders                |  |                 |  |
| Hepatic function abnormal              |  |                 |  |
| subjects affected / exposed            | 1 / 190 (0.53%)                                    | 0 / 214 (0.00%) |  |
| occurrences (all)                      | 1  | 0               |  |
| Skin and subcutaneous tissue disorders |  |                 |  |
| Rash macular                           |  |                 |  |
| subjects affected / exposed            | 0 / 190 (0.00%)                                    | 1 / 214 (0.47%) |  |
| occurrences (all)                      | 0  | 1               |  |
| Pruritus                               | Additional description: Pruritis soles of feet     |                 |  |
| subjects affected / exposed            | 1 / 190 (0.53%)                                    | 1 / 214 (0.47%) |  |
| occurrences (all)                      | 1  | 1               |  |
| Rash pustular                          | Additional description: Pustules on palms of hands |                 |  |

|  |   |                      |  |
|--|---|----------------------|--|
| subjects affected / exposed<br>occurrences (all)   | 0 / 190 (0.00%)<br>0  | 1 / 214 (0.47%)<br>1 |  |
| Rash<br>subjects affected / exposed<br>occurrences (all)   | 5 / 190 (2.63%)<br>5  | 7 / 214 (3.27%)<br>7 |  |
| Eczema<br>subjects affected / exposed<br>occurrences (all)   | 0 / 190 (0.00%)<br>0  | 1 / 214 (0.47%)<br>1 |  |
| Mouth ulceration<br>subjects affected / exposed<br>occurrences (all)                                   | 2 / 190 (1.05%)<br>2  | 1 / 214 (0.47%)<br>1 |  |
| Night sweats<br>subjects affected / exposed<br>occurrences (all)                                       | 0 / 190 (0.00%)<br>0  | 1 / 214 (0.47%)<br>1 |  |
| Subcutaneous emphysema   | Additional description: Widespread surgical emphysema in arms and neck, shown in CXR. |                      |  |
| subjects affected / exposed<br>occurrences (all)   | 1 / 190 (0.53%)<br>1  | 0 / 214 (0.00%)<br>0 |  |
| Dry skin<br>subjects affected / exposed<br>occurrences (all)   | 2 / 190 (1.05%)<br>2  | 1 / 214 (0.47%)<br>1 |  |
| Rash pruritic<br>subjects affected / exposed<br>occurrences (all)                                      | 1 / 190 (0.53%)<br>1  | 1 / 214 (0.47%)<br>1 |  |
| Acne<br>subjects affected / exposed<br>occurrences (all)   | 0 / 190 (0.00%)<br>0  | 1 / 214 (0.47%)<br>1 |  |
| Hyperhidrosis<br>subjects affected / exposed<br>occurrences (all)                                      | 0 / 190 (0.00%)<br>0  | 1 / 214 (0.47%)<br>1 |  |
| Renal and urinary disorders<br>Acute kidney injury<br>subjects affected / exposed<br>occurrences (all) | 2 / 190 (1.05%)<br>2  | 0 / 214 (0.00%)<br>0 |  |
| Cholelithiasis   |   |                      |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 190 (0.00%) | 1 / 214 (0.47%) |  |
| occurrences (all)                               | 0               | 1               |  |
| Pollakiuria                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 190 (0.00%) | 2 / 214 (0.93%) |  |
| occurrences (all)                               | 0               | 2               |  |
| Dysuria   |                 |                 |  |
| subjects affected / exposed                     | 0 / 190 (0.00%) | 1 / 214 (0.47%) |  |
| occurrences (all)                               | 0               | 1               |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |
| Arthralgia                                      |                 |                 |  |
| subjects affected / exposed                     | 2 / 190 (1.05%) | 4 / 214 (1.87%) |  |
| occurrences (all)                               | 2               | 4               |  |
| Plantar fasciitis                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 190 (0.00%) | 1 / 214 (0.47%) |  |
| occurrences (all)                               | 0               | 1               |  |
| Back pain                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 190 (0.53%) | 0 / 214 (0.00%) |  |
| occurrences (all)                               | 1               | 0               |  |
| Musculoskeletal pain                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 190 (0.00%) | 1 / 214 (0.47%) |  |
| occurrences (all)                               | 0               | 1               |  |
| Neck pain                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 190 (0.00%) | 1 / 214 (0.47%) |  |
| occurrences (all)                               | 0               | 1               |  |
| Muscle spasms                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 190 (0.53%) | 0 / 214 (0.00%) |  |
| occurrences (all)                               | 1               | 0               |  |
| Pain in jaw                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 190 (0.00%) | 1 / 214 (0.47%) |  |
| occurrences (all)                               | 0               | 1               |  |
| Infections and infestations                     |                 |                 |  |
| Clostridium difficile colitis                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 190 (0.53%) | 0 / 214 (0.00%) |  |
| occurrences (all)                               | 1               | 0               |  |
| Respiratory tract infection                     |                 |                 |  |

|                                    |   |                 |  |
|------------------------------------|---|-----------------|--|
| subjects affected / exposed        | 2 / 190 (1.05%)   | 2 / 214 (0.93%) |  |
| occurrences (all)                  | 2   | 2               |  |
| Oral candidiasis                   |   |                 |  |
| subjects affected / exposed        | 0 / 190 (0.00%)   | 3 / 214 (1.40%) |  |
| occurrences (all)                  | 0   | 3               |  |
| Candida infection                  |   |                 |  |
| subjects affected / exposed        | 1 / 190 (0.53%)   | 0 / 214 (0.00%) |  |
| occurrences (all)                  | 1   | 0               |  |
| Pneumonia                          |   |                 |  |
| subjects affected / exposed        | 1 / 190 (0.53%)   | 0 / 214 (0.00%) |  |
| occurrences (all)                  | 1   | 0               |  |
| Vulvovaginal candidiasis           |   |                 |  |
| subjects affected / exposed        | 0 / 190 (0.00%)   | 2 / 214 (0.93%) |  |
| occurrences (all)                  | 0   | 2               |  |
| Urinary tract infection            |   |                 |  |
| subjects affected / exposed        | 1 / 190 (0.53%)   | 1 / 214 (0.47%) |  |
| occurrences (all)                  | 1   | 1               |  |
| Pharyngitis                        |   |                 |  |
| subjects affected / exposed        | 0 / 190 (0.00%)   | 1 / 214 (0.47%) |  |
| occurrences (all)                  | 0   | 1               |  |
| Staphylococcal bacteraemia         |   |                 |  |
| subjects affected / exposed        | 1 / 190 (0.53%)   | 0 / 214 (0.00%) |  |
| occurrences (all)                  | 1   | 0               |  |
| Serratia infection                 |   |                 |  |
| subjects affected / exposed        | 1 / 190 (0.53%)   | 0 / 214 (0.00%) |  |
| occurrences (all)                  | 1   | 0               |  |
| Metabolism and nutrition disorders |   |                 |  |
| Hyperglycaemia                     |   |                 |  |
| subjects affected / exposed        | 4 / 190 (2.11%)   | 2 / 214 (0.93%) |  |
| occurrences (all)                  | 4   | 2               |  |
| Gout                               |   |                 |  |
| subjects affected / exposed        | 0 / 190 (0.00%)   | 1 / 214 (0.47%) |  |
| occurrences (all)                  | 0   | 1               |  |
| Steroid diabetes                   | Additional description: Undiagnosed Diabetes (new presentation) - steroid induced |                 |  |

|                             |                 |                 |  |
|-----------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 190 (0.00%) | 1 / 214 (0.47%) |  |
| occurrences (all)           | 0               | 1               |  |
| Hypomagnesaemia             |                 |                 |  |
| subjects affected / exposed | 0 / 190 (0.00%) | 1 / 214 (0.47%) |  |
| occurrences (all)           | 0               | 1               |  |
| Hypokalaemia                |                 |                 |  |
| subjects affected / exposed | 1 / 190 (0.53%) | 0 / 214 (0.00%) |  |
| occurrences (all)           | 1               | 0               |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported