



## Clinical trial results:

### A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy, Safety, and Tolerability of Brensocatib Administered Once Daily for 52 Weeks in Subjects With Non-Cystic Fibrosis Bronchiectasis - The ASPEN Study

#### Summary

|                          |  |
|--------------------------|--|
| EudraCT number           | 2020-003688-25                                     |
| Trial protocol           | DE PT DK NL IE HU GR PL BG LT SK AT FR EE BE IT ES |
| Global end of trial date | 28 October 2024                                    |

#### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 11 May 2025  |
| First version publication date | 11 May 2025  |

#### Trial information

##### Trial identification

|                       |             |
|-----------------------|-------------|
| Sponsor protocol code | INS1007-301 |
|-----------------------|-------------|

##### Additional study identifiers

|                                    |                             |
|------------------------------------|-----------------------------|
| ISRCTN number                      | -                           |
| ClinicalTrials.gov id (NCT number) | NCT04594369                 |
| WHO universal trial number (UTN)   | -                           |
| Other trial identifiers            | jRCT Number: jRCT2031210048 |

Notes:

##### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Insmmed Incorporated  |
| Sponsor organisation address | 700 US Highway 202/206, Bridgewater, United States, 08807-1704                                      |
| Public contact               | Insmmed Medical Information, Insmmed Incorporated, +1 1-844-446-7633, medicalinformation@insmed.com |
| Scientific contact           | Insmmed Medical Information, Insmmed Incorporated, +1 1-844-446-7633, medicalinformation@insmed.com |

Notes:

##### Paediatric regulatory details

|  |                     |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP)       | Yes                 |
| EMA paediatric investigation plan number(s)                          | EMA-002905-PIP01-20 |
| 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                       | 28 October 2024 |
| Is this the analysis of the primary completion data? | No              |

|                                  |                 |
|----------------------------------|-----------------|
| Global end of trial reached?     | Yes             |
| Global end of trial date         | 28 October 2024 |
| Was the trial ended prematurely? | No              |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the effect of brensocaticib at 10 milligram (mg) and 25 mg compared with placebo on the rate of pulmonary exacerbations (PEs) over the 52-week treatment period.

Protection of trial subjects:

This trial was performed in compliance with Good Clinical Practice (GCP), including the archiving of essential documents, the International Council for Harmonisation (ICH) Guidelines, and is consistent with the ethical principles of the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 01 December 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 | Australia: 90          |
| Country: Number of subjects enrolled | Argentina: 258         |
| Country: Number of subjects enrolled | Austria: 2             |
| Country: Number of subjects enrolled | Belgium: 25            |
| Country: Number of subjects enrolled | Brazil: 45             |
| Country: Number of subjects enrolled | Bulgaria: 85           |
| Country: Number of subjects enrolled | Canada: 7              |
| Country: Number of subjects enrolled | Chile: 78              |
| Country: Number of subjects enrolled | Colombia: 19           |
| Country: Number of subjects enrolled | Denmark: 48            |
| Country: Number of subjects enrolled | France: 34             |
| Country: Number of subjects enrolled | Germany: 75            |
| Country: Number of subjects enrolled | Greece: 10             |
| Country: Number of subjects enrolled | Hungary: 1             |
| Country: Number of subjects enrolled | Ireland: 4             |
| Country: Number of subjects enrolled | Israel: 84             |
| Country: Number of subjects enrolled | Italy: 57              |
| Country: Number of subjects enrolled | Japan: 87              |
| Country: Number of subjects enrolled | Korea, Republic of: 45 |

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Latvia: 2          |
| Country: Number of subjects enrolled | Malaysia: 11       |
| Country: Number of subjects enrolled | Mexico: 47         |
| Country: Number of subjects enrolled | Netherlands: 19    |
| Country: Number of subjects enrolled | New Zealand: 46    |
| Country: Number of subjects enrolled | Peru: 41           |
| Country: Number of subjects enrolled | Poland: 61         |
| Country: Number of subjects enrolled | Portugal: 9        |
| Country: Number of subjects enrolled | Serbia: 17         |
| Country: Number of subjects enrolled | Slovakia: 3        |
| Country: Number of subjects enrolled | Spain: 55          |
| Country: Number of subjects enrolled | Taiwan: 27         |
| Country: Number of subjects enrolled | Thailand: 6        |
| Country: Number of subjects enrolled | Türkiye: 36        |
| Country: Number of subjects enrolled | United Kingdom: 46 |
| Country: Number of subjects enrolled | United States: 241 |
| Worldwide total number of subjects   | 1721               |
| EEA total number of subjects         | 490                |

Notes:

### Subjects enrolled per age group

|   |     |
|---|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 41  |
| Adults (18-64 years)                      | 841 |
| From 65 to 84 years                       | 832 |
| 85 years and over                         | 7   |

## Subject disposition

### Recruitment

Recruitment details:

Participants took part in the study at 373 sites in 36 countries from 01 Dec 2020 to 28 Oct 2024.

### Pre-assignment

Screening details:

A total of 2296 participants were screened, 1767 participants with non-cystic fibrosis bronchiectasis were enrolled in the study. Due to the war in Ukraine, 44 participants from Ukraine were not analysed, 2 additional participants were not analysed due to serious GCP non-compliance.

### Period 1

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

### Arms

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

|                  |                   |
|------------------|-------------------|
| <b>Arm title</b> | Brensocatib 10 mg |
|------------------|-------------------|

Arm description:

Participants received brensocatib 10 mg tablets, orally, once daily, for 52 weeks.

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

Dosage and administration details:

Participants received 10 mg tablets, once daily, for 52 weeks.

|                  |                   |
|------------------|-------------------|
| <b>Arm title</b> | Brensocatib 25 mg |
|------------------|-------------------|

Arm description:

Participants received brensocatib 25 mg tablets, orally, once daily, for 52 weeks.

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

Dosage and administration details:

Participants received 25 mg tablets, once daily, for 52 weeks.

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

Arm description:

Participants received a brensocatib matching placebo tablets orally, once daily, for 52 weeks.

|          |         |
|----------|---------|
| 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:

Participants received brensocatib matching placebo tablets, once daily, for 52 weeks.

| <b>Number of subjects in period 1</b> | Brensocatib 10 mg | Brensocatib 25 mg | Placebo |
|---------------------------------------|-------------------|-------------------|---------|
| Started                               | 583               | 575               | 563     |
| Completed                             | 458               | 466               | 457     |
| Not completed                         | 125               | 109               | 106     |
| Adverse event, serious fatal          | 2                 | 4                 | 8       |
| Other than specified above            | 60                | 56                | 43      |
| Physician decision                    | 2                 | 2                 | 3       |
| Consent withdrawn by subject          | 40                | 32                | 37      |
| Adverse event, non-fatal              | 10                | 10                | 9       |
| Lost to follow-up                     | 10                | 2                 | 4       |
| Protocol deviation                    | 1                 | 3                 | 2       |

## Baseline characteristics

| Reporting groups   |                   |
|--|-------------------|
| Reporting group title  | Brensocatib 10 mg |
| Reporting group description:   |                   |
| Participants received brensocatib 10 mg tablets, orally, once daily, for 52 weeks.             |                   |
| Reporting group title  | Brensocatib 25 mg |
| Reporting group description:   |                   |
| Participants received brensocatib 25 mg tablets, orally, once daily, for 52 weeks.             |                   |
| Reporting group title  | Placebo           |
| Reporting group description:   |                   |
| Participants received a brensocatib matching placebo tablets orally, once daily, for 52 weeks. |                   |

| Reporting group values | Brensocatib 10 mg | Brensocatib 25 mg | Placebo |
|------------------------|-------------------|-------------------|---------|
| Number of subjects     | 583               | 575               | 563     |
| Age Categorical        |                   |                   |         |
| Units: Subjects        |                   |                   |         |

|   |         |         |         |
|---|---------|---------|---------|
| Age continuous                            |         |         |         |
| Units: Years                              |         |         |         |
| arithmetic mean                           | 59.8    | 60.6    | 60.0    |
| standard deviation                        | ± 15.92 | ± 15.78 | ± 15.44 |
| Gender categorical                        |         |         |         |
| Units: Subjects                           |         |         |         |
| Female                                    | 385     | 360     | 362     |
| Male                                      | 198     | 215     | 201     |
| Ethnicity                                 |         |         |         |
| Units: Subjects                           |         |         |         |
| Not Hispanic or Latino                    | 391     | 397     | 373     |
| Hispanic or Latino                        | 177     | 164     | 170     |
| Not Reported                              | 13      | 13      | 17      |
| Unknown                                   | 2       | 1       | 3       |
| Race                                      |         |         |         |
| Units: Subjects                           |         |         |         |
| American Indian or Alaska Native          | 8       | 6       | 9       |
| Asian                                     | 63      | 64      | 64      |
| Black or African American                 | 2       | 5       | 3       |
| Native Hawaiian or Other Pacific Islander | 1       | 0       | 1       |
| White                                     | 431     | 430     | 405     |
| Other                                     | 15      | 13      | 11      |
| Unknown                                   | 18      | 13      | 14      |
| Not Reported                              | 30      | 33      | 45      |
| Multiple                                  | 15      | 11      | 11      |

| Reporting group values | Total |  |  |
|------------------------|-------|--|--|
| Number of subjects     | 1721  |  |  |

|   |      |  |  |
|---|------|--|--|
| Age Categorical<br>Units: Subjects                                      |      |  |  |
| Age continuous<br>Units: Years<br>arithmetic mean<br>standard deviation | -    |  |  |
| Gender categorical<br>Units: Subjects                                   |      |  |  |
| Female  | 1107 |  |  |
| Male  | 614  |  |  |
| Ethnicity<br>Units: Subjects  |      |  |  |
| Not Hispanic or Latino  | 1161 |  |  |
| Hispanic or Latino  | 511  |  |  |
| Not Reported  | 43   |  |  |
| Unknown   | 6    |  |  |
| Race<br>Units: Subjects   |      |  |  |
| American Indian or Alaska Native  | 23   |  |  |
| Asian   | 191  |  |  |
| Black or African American   | 10   |  |  |
| Native Hawaiian or Other Pacific Islander                               | 2    |  |  |
| White   | 1266 |  |  |
| Other   | 39   |  |  |
| Unknown   | 45   |  |  |
| Not Reported  | 108  |  |  |
| Multiple  | 37   |  |  |

## End points

### End points reporting groups

|  |                   |
|--|-------------------|
| Reporting group title  | Brensocatib 10 mg |
| Reporting group description:<br>Participants received brensocatib 10 mg tablets, orally, once daily, for 52 weeks.             |                   |
| Reporting group title  | Brensocatib 25 mg |
| Reporting group description:<br>Participants received brensocatib 25 mg tablets, orally, once daily, for 52 weeks.             |                   |
| Reporting group title  | Placebo           |
| Reporting group description:<br>Participants received a brensocatib matching placebo tablets orally, once daily, for 52 weeks. |                   |

### Primary: Annualized Rate of Pulmonary Exacerbations (PEs)

|  |  |
|--|--|
| End point title  | Annualized Rate of Pulmonary Exacerbations (PEs) |
| End point description:<br>Pulmonary exacerbation was defined as having 3 or more of these symptoms for at least 48 hours resulting in a physician's decision to prescribe antibiotics: 1. Increased cough 2. Increased sputum volume or change in sputum consistency 3. Increased sputum purulence 4. Increased breathlessness and/or decreased exercise tolerance 5. Fatigue and/or malaise 6. Hemoptysis. A severe pulmonary exacerbation was that required IV antibacterial drug treatment and/or hospitalization. A minimum of 14 days must have occurred between one exacerbation onset and the next. Any exacerbation that occurred less than 14 days from the prior exacerbation was not considered a new exacerbation. Independent adjudication committee with pulmonary physicians will adjudicate reported PE events to see if they fulfil the protocol definition. The rate of PE was analysed using the negative binomial model. The Intent-to-Treat (ITT) analysis set included all participants who were randomised. |  |
| End point type   | Primary  |
| End point timeframe:<br>Up to Week 52  |  |

| End point values                     | Brensocatib 10 mg      | Brensocatib 25 mg      | Placebo                |  |
|--------------------------------------|------------------------|------------------------|------------------------|--|
| Subject group type                   | Reporting group        | Reporting group        | Reporting group        |  |
| Number of subjects analysed          | 583                    | 575                    | 563                    |  |
| Units: exacerbation per patient-year |                        |                        |                        |  |
| number (confidence interval 95%)     | 1.015 (0.910 to 1.132) | 1.036 (0.927 to 1.157) | 1.286 (1.158 to 1.428) |  |

### Statistical analyses

|   |                              |
|---|------------------------------|
| Statistical analysis title  | Brensocatib 25 mg vs Placebo |
| Statistical analysis description:<br>Model treatment & randomization stratification factor=geographic region, sputum sample ( <i>Pseudomonas aeruginosa</i> ) at start & PE last 12 months, age group (fixed effects) & time at risk (log scale) as offset variable. Robust sandwich covariance estimator used. |                              |
| Comparison groups   | Brensocatib 25 mg v Placebo  |



|   |                              |
|---|------------------------------|
| Number of subjects included in analysis | 1138                         |
| Analysis specification                  | Pre-specified                |
| Analysis type                           | superiority                  |
| P-value                                 | = 0.0046 <sup>[1]</sup>      |
| Method                                  | Negative binomial regression |
| Parameter estimate                      | Rate ratio                   |
| Point estimate                          | 0.806                        |
| Confidence interval                     |                              |
| level                                   | 95 %                         |
| sides                                   | 2-sided                      |
| lower limit                             | 0.694                        |
| upper limit                             | 0.936                        |

Notes:

[1] - Adjusted p-value = 0.0048. The enhanced mixture-based gatekeeping procedure was used to control the overall type I error rate. Multiplicity adjusted p-value for the primary endpoint was tested at two-sided alpha = 0.01.

|                                   |                              |
|-----------------------------------|------------------------------|
| <b>Statistical analysis title</b> | Brensocatic 10 mg vs Placebo |
|-----------------------------------|------------------------------|

Statistical analysis description:

Model treatment & randomization stratification factor=geographic region, sputum sample (*Pseudomonas aeruginosa*) at start & PE last 12 months, age group (fixed effects) & time at risk (log scale) as offset variable. Robust sandwich covariance estimator used.

|   |                              |
|---|------------------------------|
| Comparison groups                       | Brensocatic 10 mg v Placebo  |
| Number of subjects included in analysis | 1146                         |
| Analysis specification                  | Pre-specified                |
| Analysis type                           | superiority                  |
| P-value                                 | = 0.0019 <sup>[2]</sup>      |
| Method                                  | Negative binomial regression |
| Parameter estimate                      | Rate ratio                   |
| Point estimate                          | 0.789                        |
| Confidence interval                     |                              |
| level                                   | 95 %                         |
| sides                                   | 2-sided                      |
| lower limit                             | 0.68                         |
| upper limit                             | 0.916                        |

Notes:

[2] - Adjusted p-value = 0.0038. The enhanced mixture-based gatekeeping procedure was used to control the overall type I error rate. Multiplicity adjusted p-value for the primary endpoint was tested at two-sided alpha = 0.01.

## Secondary: Time to First PE

|                 |                  |
|-----------------|------------------|
| End point title | Time to First PE |
|-----------------|------------------|

End point description:

PE was defined as 3 or more of these symptoms for at least 48 hours & physician's choice to prescribe antibiotics: 1. Increased cough 2. Increased sputum volume or change in sputum consistency 3. Increased sputum purulence 4. Increased breathlessness and/or decreased exercise tolerance 5. Fatigue and/or malaise 6. Hemoptysis. Severe PE=IV antibacterial drug treatment and/or hospitalization. Minimum 14 days between one exacerbation onset and next. Any PE in less than 14 days from prior exacerbation was not considered new. Time to first PE=randomisation date to onset date of first exacerbation. Participants with no exacerbation at end of 52-week treatment were censored at Week 52. Independent adjudication committee with pulmonary physicians will adjudicate reported PE events to see if they fulfil the protocol definition. 9999=upper limit of confidence interval was not computable. The ITT analysis set included all participants who were randomised.

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

End point timeframe:

Up to Week 52

| End point values                 | Brensocatib 10 mg       | Brensocatib 25 mg       | Placebo                   |  |
|----------------------------------|-------------------------|-------------------------|---------------------------|--|
| Subject group type               | Reporting group         | Reporting group         | Reporting group           |  |
| Number of subjects analysed      | 583                     | 575                     | 563                       |  |
| Units: weeks                     |                         |                         |                           |  |
| median (confidence interval 95%) | 49.000 (40.000 to 9999) | 50.714 (37.571 to 9999) | 36.714 (31.143 to 41.429) |  |

## Statistical analyses

| Statistical analysis title   | Brensocatib 25 mg vs placebo |
|--|------------------------------|
| Statistical analysis description:  |                              |
| Estimate of Cox proportional hazard model=effect for treatment, sputum sample for Pseudomonas aeruginosa at screening and PE [ $<3$ or $\geq 3$ ] in last 12 months, stratification region and age group. Robust sandwich covariance estimator used. |                              |
| Comparison groups  | Brensocatib 25 mg v Placebo  |
| Number of subjects included in analysis  | 1138                         |
| Analysis specification   | Pre-specified                |
| Analysis type  | superiority                  |
| P-value  | = 0.0182 <sup>[3]</sup>      |
| Method   | Cox proportional hazard      |
| Parameter estimate   | Hazard ratio (HR)            |
| Point estimate   | 0.825                        |
| Confidence interval  |                              |
| level  | 95 %                         |
| sides  | 2-sided                      |
| lower limit  | 0.703                        |
| upper limit  | 0.968                        |

Notes:

[3] - Adjusted p-value = 0.0364. The enhanced mixture-based gatekeeping procedure was used to control the overall type I error rate. Multiplicity adjusted p-value for the secondary endpoints were tested at two-sided alpha = 0.05.

| Statistical analysis title   | Brensocatib 10 mg vs placebo |
|--|------------------------------|
| Statistical analysis description:  |                              |
| Estimate of Cox proportional hazard model=effect for treatment, sputum sample for Pseudomonas aeruginosa at screening and PE [ $<3$ or $\geq 3$ ] in last 12 months, stratification region and age group. Robust sandwich covariance estimator used. |                              |
| Comparison groups  | Brensocatib 10 mg v Placebo  |
| Number of subjects included in analysis  | 1146                         |
| Analysis specification   | Pre-specified                |
| Analysis type  | superiority                  |
| P-value  | = 0.01 <sup>[4]</sup>        |
| Method   | Cox proportional hazard      |
| Parameter estimate   | Hazard ratio (HR)            |
| Point estimate   | 0.813                        |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 0.695   |
| upper limit         | 0.952   |

Notes:

[4] - Adjusted p-value = 0.0200. The enhanced mixture-based gatekeeping procedure was used to control the overall type I error rate. Multiplicity adjusted p-value for the secondary endpoints were tested at two-sided alpha = 0.05.

## Secondary: Responder Status for Exacerbation-Free Over the 52-Week Treatment Period

|                 |  |
|-----------------|--|
| End point title | Responder Status for Exacerbation-Free Over the 52-Week Treatment Period |
|-----------------|--|

End point description:

Responder status was based on percentage of participants who were exacerbation free over 52-weeks of treatment period. PE was defined as having 3 or more of these symptoms for at least 48 hours with physician's decision to prescribe antibiotics: 1. Increased cough 2. Increased sputum volume or change in sputum consistency 3. Increased sputum purulence 4. Increased breathlessness and/or decreased exercise tolerance 5. Fatigue and/or malaise 6. Hemoptysis. Minimum of 14 days must have occurred between one PE onset and the next. Any PE in less than 14 days from prior exacerbation was not considered new exacerbation. Independent adjudication committee of pulmonary physicians will adjudicate reported PE events to see if they fulfill protocol definition. For discontinuation prior to Week 52 without having experienced a confirmed PE, responder status imputed by multiple imputation. The ITT analysis set included all participants who were randomised.

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

End point timeframe:

Up to Week 52

| End point values                  | Brensocatib 10 mg | Brensocatib 25 mg | Placebo         |  |
|-----------------------------------|-------------------|-------------------|-----------------|--|
| Subject group type                | Reporting group   | Reporting group   | Reporting group |  |
| Number of subjects analysed       | 583               | 575               | 563             |  |
| Units: percentage of participants |                   |                   |                 |  |
| number (not applicable)           | 48.5              | 48.5              | 40.3            |  |

## Statistical analyses

|                            |                              |
|----------------------------|------------------------------|
| Statistical analysis title | Brensocatib 25 mg vs Placebo |
|----------------------------|------------------------------|

Statistical analysis description:

Missing responder status was imputed 100 times. Dataset was analyzed via logistic regression with treatment group, sputum P. aeruginosa status, prior PEs (<3/≥3), region, and age group as fixed effects. Results were then combined using Rubin's rules.

|   |                             |
|---|-----------------------------|
| Comparison groups                       | Brensocatib 25 mg v Placebo |
| Number of subjects included in analysis | 1138                        |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority                 |
| P-value                                 | = 0.0074 <sup>[5]</sup>     |
| Method                                  | Logistic Regression         |
| Parameter estimate                      | Odds ratio (OR)             |
| Point estimate                          | 1.4                         |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 1.095   |
| upper limit         | 1.792   |

Notes:

[5] - Adjusted p-value = 0.0364. The enhanced mixture-based gatekeeping procedure was used to control the overall type I error rate. Multiplicity adjusted p-value for the secondary endpoints were tested at two-sided alpha = 0.05.

|                                   |                              |
|-----------------------------------|------------------------------|
| <b>Statistical analysis title</b> | Brensocatic 10 mg vs Placebo |
|-----------------------------------|------------------------------|

Statistical analysis description:

Missing responder status was imputed 100 times. Dataset was analyzed via logistic regression with treatment group, sputum P. aeruginosa status, prior PEs (<3/≥3), region, and age group as fixed effects. Results were then combined using Rubin's rules.

|   |                             |
|---|-----------------------------|
| Comparison groups                       | Brensocatic 10 mg v Placebo |
| Number of subjects included in analysis | 1146                        |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority                 |
| P-value                                 | = 0.0059 <sup>[6]</sup>     |
| Method                                  | Logistic Regression         |
| Parameter estimate                      | Odds ratio (OR)             |
| Point estimate                          | 1.412                       |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | 1.105                       |
| upper limit                             | 1.806                       |

Notes:

[6] - Adjusted p-value = 0.0200. The enhanced mixture-based gatekeeping procedure was used to control the overall type I error rate. Multiplicity adjusted p-value for the secondary endpoints were tested at two-sided alpha = 0.05.

## **Secondary: Change From Baseline at Week 52 in Postbronchodilator Forced Expiratory Volume in 1 Second (FEV1)**

|                 |   |
|-----------------|---|
| End point title | Change From Baseline at Week 52 in Postbronchodilator Forced Expiratory Volume in 1 Second (FEV1) |
|-----------------|---|

End point description:

FEV1 was used to assess lung function and is the maximum amount of air that can be exhaled from the lungs in the first second after taking a forced expiration as measured by spirometer. Postbronchodilator FEV1 tests included spirometry tests performed referred to the spirometry performed within 30 minutes after administration of bronchodilator (4 puffs of salbutamol/albuterol, terbutaline or ipratropium). The ITT analysis set included all participants who were randomised. 'Number of subjects analysed' indicates the number of participants with data available for analyses. Baseline was the most recent non-missing assessment determined as best effort prior to the first dose of the investigational product.

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

End point timeframe:

Baseline, Week 52

| End point values                    | Brensocatib 10 mg      | Brensocatib 25 mg      | Placebo                |  |
|-------------------------------------|------------------------|------------------------|------------------------|--|
| Subject group type                  | Reporting group        | Reporting group        | Reporting group        |  |
| Number of subjects analysed         | 564                    | 551                    | 539                    |  |
| Units: liter (L)                    |                        |                        |                        |  |
| least squares mean (standard error) | -0.050 ( $\pm$ 0.0093) | -0.024 ( $\pm$ 0.0099) | -0.062 ( $\pm$ 0.0094) |  |

## Statistical analyses

| Statistical analysis title | Brensocatib 25 mg vs placebo |
|----------------------------|------------------------------|
|----------------------------|------------------------------|

Statistical analysis description:

Analysis on linear repeated measure model=treatment visit, sputum sample for Pseudomonas aeruginosa at start, PE [ $<3$  or  $\geq 3$ ] last 12 months, stratification region, age group (fixed effect) & baseline (covariate). Robust sandwich covariance estimator used.

|   |                                |
|---|--------------------------------|
| Comparison groups                       | Brensocatib 25 mg v Placebo    |
| Number of subjects included in analysis | 1090                           |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority                    |
| P-value                                 | = 0.0054 <sup>[7]</sup>        |
| Method                                  | Linear repeated measures model |
| Parameter estimate                      | Difference in LS Mean          |
| Point estimate                          | 0.038                          |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | 0.011                          |
| upper limit                             | 0.065                          |
| Variability estimate                    | Standard error of the mean     |
| Dispersion value                        | 0.0136                         |

Notes:

[7] - Adjusted p-value = 0.0364. The enhanced mixture-based gatekeeping procedure was used to control the overall type I error rate. Multiplicity adjusted p-value for the secondary endpoints were tested at two-sided alpha = 0.05.

| Statistical analysis title | Brensocatib 10 mg vs placebo |
|----------------------------|------------------------------|
|----------------------------|------------------------------|

Statistical analysis description:

Analysis on linear repeated measure model=treatment visit, sputum sample for Pseudomonas aeruginosa at start, PE [ $<3$  or  $\geq 3$ ] last 12 months, stratification region, age group (fixed effect) & baseline (covariate). Robust sandwich covariance estimator used.

|   |                                |
|---|--------------------------------|
| Comparison groups                       | Brensocatib 10 mg v Placebo    |
| Number of subjects included in analysis | 1103                           |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority                    |
| P-value                                 | = 0.3841 <sup>[8]</sup>        |
| Method                                  | Linear repeated measures model |
| Parameter estimate                      | Difference in LS Mean          |
| Point estimate                          | 0.011                          |

|                      |                            |
|----------------------|----------------------------|
| Confidence interval  |                            |
| level                | 95 %                       |
| sides                | 2-sided                    |
| lower limit          | -0.014                     |
| upper limit          | 0.037                      |
| Variability estimate | Standard error of the mean |
| Dispersion value     | 0.0132                     |

Notes:

[8] - Adjusted p-value = 0.3841. The enhanced mixture-based gatekeeping procedure was used to control the overall type I error rate. Multiplicity adjusted p-value for the secondary endpoints were tested at two-sided alpha = 0.05.

### Secondary: Annualized Rate of Severe PEs

|                 |                               |
|-----------------|-------------------------------|
| End point title | Annualized Rate of Severe PEs |
|-----------------|-------------------------------|

End point description:

Pulmonary exacerbation was defined as having 3 or more of these symptoms for at least 48 hours resulting in a physician's decision to prescribe antibiotics: 1. Increased cough 2. Increased sputum volume or change in sputum consistency 3. Increased sputum purulence 4. Increased breathlessness and/or decreased exercise tolerance 5. Fatigue and/or malaise 6. Hemoptysis. A severe PE was defined as those requiring IV antibacterial drug treatment and/or hospitalization. A minimum of 14 days must have occurred between one exacerbation onset and the next. Any exacerbation that occurred less than 14 days from the prior exacerbation was not considered a new exacerbation. Independent adjudication committee with pulmonary physicians will adjudicate reported PE events to see if they fulfil the protocol definition. The rate of PE will be analysed using the negative binomial model. The ITT analysis set included all participants who were randomised.

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

End point timeframe:

Up to Week 52

| End point values                     | Brensocatib 10 mg      | Brensocatib 25 mg      | Placebo                |  |
|--------------------------------------|------------------------|------------------------|------------------------|--|
| Subject group type                   | Reporting group        | Reporting group        | Reporting group        |  |
| Number of subjects analysed          | 583                    | 575                    | 563                    |  |
| Units: exacerbation per patient-year |                        |                        |                        |  |
| number (confidence interval 95%)     | 0.137 (0.103 to 0.182) | 0.137 (0.105 to 0.179) | 0.185 (0.142 to 0.242) |  |

### Statistical analyses

|                            |                              |
|----------------------------|------------------------------|
| Statistical analysis title | Brensocatib 10 mg vs placebo |
|----------------------------|------------------------------|

Statistical analysis description:

Analysis based on a negative binomial model including treatment, sputum sample for *Pseudomonas aeruginosa* at screening, PE [ $<3$  or  $\geq 3$ ] in previous 12 months, stratification region and age group. Robust sandwich covariance estimator used.

|                   |                             |
|-------------------|-----------------------------|
| Comparison groups | Brensocatib 10 mg v Placebo |
|-------------------|-----------------------------|

|   |                              |
|---|------------------------------|
| Number of subjects included in analysis | 1146                         |
| Analysis specification                  | Pre-specified                |
| Analysis type                           | superiority                  |
| P-value                                 | = 0.1277 <sup>[9]</sup>      |
| Method                                  | Negative binomial regression |
| Parameter estimate                      | Rate ratio                   |
| Point estimate                          | 0.742                        |
| Confidence interval                     |                              |
| level                                   | 95 %                         |
| sides                                   | 2-sided                      |
| lower limit                             | 0.505                        |
| upper limit                             | 1.089                        |

Notes:

[9] - Adjusted p-value = 0.3841. The enhanced mixture-based gatekeeping procedure was used to control the overall type I error rate. Multiplicity adjusted p-value for the secondary endpoints were tested at two-sided alpha = 0.05.

|                                   |                              |
|-----------------------------------|------------------------------|
| <b>Statistical analysis title</b> | Brensocatic 25 mg vs placebo |
|-----------------------------------|------------------------------|

Statistical analysis description:

Analysis based on a negative binomial model including treatment, sputum sample for *Pseudomonas aeruginosa* at screening, PE [ $<3$  or  $\geq 3$ ] in previous 12 months, stratification region and age group. Robust sandwich covariance estimator used.

|   |                              |
|---|------------------------------|
| Comparison groups                       | Brensocatic 25 mg v Placebo  |
| Number of subjects included in analysis | 1138                         |
| Analysis specification                  | Pre-specified                |
| Analysis type                           | superiority                  |
| P-value                                 | = 0.1025 <sup>[10]</sup>     |
| Method                                  | Negative binomial regression |
| Parameter estimate                      | Rate ratio                   |
| Point estimate                          | 0.74                         |
| Confidence interval                     |                              |
| level                                   | 95 %                         |
| sides                                   | 2-sided                      |
| lower limit                             | 0.515                        |
| upper limit                             | 1.062                        |

Notes:

[10] - Adjusted p-value = 0.2050. The enhanced mixture-based gatekeeping procedure was used to control the overall type I error rate. Multiplicity adjusted p-value for the secondary endpoints were tested at two-sided alpha = 0.05.

### **Secondary: Change from Baseline at Week 52 in Quality of Life Questionnaire - Bronchiectasis (QOL-B) Respiratory Symptoms Domain Score in Adult Participants**

|                 |   |
|-----------------|---|
| End point title | Change from Baseline at Week 52 in Quality of Life Questionnaire - Bronchiectasis (QOL-B) Respiratory Symptoms Domain Score in Adult Participants |
|-----------------|---|

End point description:

QOL-B is validated, self-administered patient-reported outcome (PRO) assessing symptoms, functioning, and health-related quality of life in participants with non-cystic fibrosis bronchiectasis (NCFBE). It includes 37 items across 8 domains: Respiratory Symptoms, Physical Functioning, Role Functioning, Emotional Functioning, Social Functioning, Vitality, Health Perceptions, and Treatment Burden. Each item is scored from 1 to 4, with domain scores standardized on 0-100 scale, where higher scores represent fewer symptoms or better functioning. Positive change from Baseline indicates improvement in symptoms. For this outcome, change in respiratory symptoms domain score from Baseline is reported. Baseline refers to most recent assessment on or before study day 1. ITT analysis set included all randomised adult participants, with 'Number of subjects analysed' is number of adult participants with data available for analyses.

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

End point timeframe:

Baseline, Week 52

| End point values                    | Brensocatib 10 mg     | Brensocatib 25 mg     | Placebo               |  |
|-------------------------------------|-----------------------|-----------------------|-----------------------|--|
| Subject group type                  | Reporting group       | Reporting group       | Reporting group       |  |
| Number of subjects analysed         | 487                   | 495                   | 486                   |  |
| Units: score on scale               |                       |                       |                       |  |
| least squares mean (standard error) | 6.841 ( $\pm$ 0.7706) | 8.575 ( $\pm$ 0.7556) | 4.809 ( $\pm$ 0.7500) |  |

## Statistical analyses

| Statistical analysis title   | Brensocatib 25 mg vs placebo   |
|--|--------------------------------|
| Statistical analysis description:<br>Analysis based on a linear repeated measures model with treatment group, visit, sputum sample for Pseudomonas aeruginosa at screening, pulmonary exacerbations [ $<3$ or $\geq 3$ ] in previous 12 months, stratification region fixed effect, baseline as covariate. |                                |
| Comparison groups  | Brensocatib 25 mg v Placebo    |
| Number of subjects included in analysis  | 981                            |
| Analysis specification   | Pre-specified                  |
| Analysis type  | superiority                    |
| P-value  | = 0.0004 <sup>[11]</sup>       |
| Method   | linear repeated measures model |
| Parameter estimate   | LS mean difference             |
| Point estimate   | 3.766                          |
| Confidence interval  |                                |
| level  | 95 %                           |
| sides  | 2-sided                        |
| lower limit  | 1.68                           |
| upper limit  | 5.852                          |
| Variability estimate   | Standard error of the mean     |
| Dispersion value   | 1.0642                         |

Notes:

[11] - Adjusted p-value = 0.2050. The enhanced mixture-based gatekeeping procedure was used to control the overall type I error rate. Multiplicity adjusted p-value for the secondary endpoints were tested at two-sided alpha = 0.05.

| Statistical analysis title   | Brensocatib 10 mg vs placebo |
|--|------------------------------|
| Statistical analysis description:<br>Analysis based on a linear repeated measures model with treatment group, visit, sputum sample for Pseudomonas aeruginosa at screening, pulmonary exacerbations [ $<3$ or $\geq 3$ ] in previous 12 months, stratification region fixed effect, baseline as covariate. |                              |
| Comparison groups  | Brensocatib 10 mg v Placebo  |



|   |                                |
|---|--------------------------------|
| Number of subjects included in analysis | 973                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority                    |
| P-value                                 | = 0.0594 <sup>[12]</sup>       |
| Method                                  | linear repeated measures model |
| Parameter estimate                      | LS mean difference             |
| Point estimate                          | 2.031                          |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -0.081                         |
| upper limit                             | 4.143                          |
| Variability estimate                    | Standard error of the mean     |
| Dispersion value                        | 1.0775                         |

Notes:

[12] - Adjusted p-value = 0.3841. The enhanced mixture-based gatekeeping procedure was used to control the overall type I error rate. Multiplicity adjusted p-value for the secondary endpoints were tested at two-sided alpha = 0.05.

### Secondary: Number of Participants who Experienced at Least one Treatment-Emergent Adverse Events (TEAEs)

|                 |   |
|-----------------|---|
| End point title | Number of Participants who Experienced at Least one Treatment-Emergent Adverse Events (TEAEs) |
|-----------------|---|

End point description:

An adverse event (AE) was defined as any untoward medical occurrence in a clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. TEAEs are AEs that occurred on or after the date of first dose of study drugs and within 28 days after the end of treatment. The safety analysis set included all participants who were randomised and received at least 1 dose of brensocatib or placebo.

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

End point timeframe:

Up to Week 56

| End point values            | Brensocatib 10 mg | Brensocatib 25 mg | Placebo         |  |
|-----------------------------|-------------------|-------------------|-----------------|--|
| Subject group type          | Reporting group   | Reporting group   | Reporting group |  |
| Number of subjects analysed | 582               | 574               | 563             |  |
| Units: participants         | 452               | 440               | 448             |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Plasma Concentration of Brensocatib in Adults (Main Study)

|                 |  |
|-----------------|--|
| End point title | Plasma Concentration of Brensocatib in Adults (Main Study) <sup>[13]</sup> |
|-----------------|--|

End point description:

Pharmacokinetics (PK) Concentration Analysis Set included adult participants who consented to

participate in the main study in adult's cohort, received at least 1 dose of brensocaticib, and had at least 1 postdose plasma concentration of brensocaticib. 'Subjects analysed' included those adult participants who were evaluable for this endpoint. Here, 'n' signifies number of adult participants analysed for this endpoint.

|  |           |
|--|-----------|
| End point type   | Secondary |
| End point timeframe:   |           |
| 2 hours (h) post-dose on Day 1; Pre-dose and 2 h post-dose at Week 28; Pre-dose and 2 h post-dose at Weeks 4 and 40; Pre-dose at Weeks 16 and 52 |           |

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: As per planned analysis, pharmacokinetic endpoints were assessed only in drug arm groups. Thus, data is reported only for the drug arm groups of the baseline period in this endpoint.

| End point values                                    | Brensocaticib 10 mg | Brensocaticib 25 mg |  |  |
|---|---------------------|---------------------|--|--|
| Subject group type                                  | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed                         | 194                 | 208                 |  |  |
| Units: nanograms per milliliter (ng/ml)             |                     |                     |  |  |
| geometric mean (geometric coefficient of variation) |                     |                     |  |  |
| Day 1: 2 h post-dose (n=18,24)                      | 40.52 (± 69.1)      | 134.9 (± 51.4)      |  |  |
| Week 4: Pre-dose (n=56,63)                          | 52.60 (± 68.7)      | 157.4 (± 70.8)      |  |  |
| Week 4: 2 h post-dose (n=20,25)                     | 100.5 (± 32.8)      | 293.6 (± 35.1)      |  |  |
| Week 16: Pre-dose (n=94,105)                        | 45.19 (± 55.0)      | 131.6 (± 69.0)      |  |  |
| Pre-dose at Week 28 (n=120,130)                     | 49.30 (± 63.9)      | 143.0 (± 64.6)      |  |  |
| Week 28: 2 h post-dose (n=40,36)                    | 91.79 (± 45.3)      | 323.7 (± 40.1)      |  |  |
| Week 40: Pre-dose (n=164,176)                       | 45.71 (± 54.2)      | 136.8 (± 63.4)      |  |  |
| Week 40: 2 h post-dose (n=47,43)                    | 107.3 (± 45.0)      | 302.6 (± 40.7)      |  |  |
| Week 52: Pre-dose (n=194,208)                       | 45.78 (± 61.7)      | 135.4 (± 60.3)      |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Plasma Concentration of Brensocaticib in Adults (PK Substudy)

|  |   |
|--|---|
| End point title  | Plasma Concentration of Brensocaticib in Adults (PK |
| End point description:   |   |
| PK Concentration Analysis Set included adult participants who consented to participate in the PK substudy and received at least 1 dose of brensocaticib, and had at least 1 postdose plasma concentration of brensocaticib. 'Subjects analysed' included those adult participants who were evaluable for this endpoint. Here, 'n' signifies number of adult participants analysed for this endpoint. |   |
| End point type   | Secondary   |

End point timeframe:

0.5 h, 2 h, and 4 to 8 h post-dose on Day 1 and at Week 28; Pre-dose and 2 h post-dose at Weeks 4 and 48; Pre-dose at Weeks 16 and 52

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: As per planned analysis, pharmacokinetic endpoints were assessed only in drug arm groups. Thus, data is reported only for the drug arm groups of the baseline period in this endpoint.

| End point values                                    | Brensocatic 10 mg | Brensocatic 25 mg |  |  |
|---|-------------------|-------------------|--|--|
| Subject group type                                  | Reporting group   | Reporting group   |  |  |
| Number of subjects analysed                         | 62                | 64                |  |  |
| Units: ng/ml  |                   |                   |  |  |
| geometric mean (geometric coefficient of variation) |                   |                   |  |  |
| Day 1: 0.5 h post-dose (n=62,64)                    | 34.51 (± 97.9)    | 85.13 (± 103.5)   |  |  |
| Day 1: 2 h post-dose (n=62,64)                      | 44.52 (± 55.0)    | 120.0 (± 56.2)    |  |  |
| Day 1: 4-8 h post-dose (n=61,64)                    | 38.13 (± 52.9)    | 108.5 (± 46.9)    |  |  |
| Week 4: Pre-dose (n=60,60)                          | 57.53 (± 53.4)    | 131.3 (± 60.2)    |  |  |
| Week 4: 2 h post-dose (n=59,61)                     | 100.3 (± 44.1)    | 286.7 (± 38.4)    |  |  |
| Week 16: Pre-dose (n=61,58)                         | 50.24 (± 58.1)    | 138.0 (± 64.5)    |  |  |
| Week 28: Pre-dose (n=61,59)                         | 50.33 (± 54.7)    | 124.6 (± 59.8)    |  |  |
| Week 28: 0.5 h post-dose (n=56,55)                  | 89.75 (± 46.0)    | 235.5 (± 53.3)    |  |  |
| Week 28: 2 h post-dose (n=58,58)                    | 95.33 (± 35.3)    | 271.9 (± 46.0)    |  |  |
| Week 28: 4-8 h post-dose (n=56,53)                  | 86.27 (± 40.7)    | 246.4 (± 43.7)    |  |  |
| Week 40: Pre-dose (n=58,55)                         | 51.80 (± 54.4)    | 119.3 (± 51.3)    |  |  |
| Week 40: 2 h post-dose (n=57,56)                    | 93.74 (± 32.1)    | 271.2 (± 45.0)    |  |  |
| Week 52: Pre-dose (n=52,50)                         | 49.93 (± 72.2)    | 131.6 (± 56.5)    |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Plasma Concentration of Brensocatic in Adolescents (Main Study)

|                 |   |
|-----------------|---|
| End point title | Plasma Concentration of Brensocatic in Adolescents (Main Study) <sup>[15]</sup> |
|-----------------|---|

End point description:

PK Concentration Analysis Set included adolescent participants who consented to participate in the main study and received at least 1 dose of brensocatic, and had at least 1 postdose plasma concentration of brensocatic. 'Subjects analysed' included those adolescent participants who were evaluable for this endpoint. Here, 'n' signifies number of adolescent participants analysed for this endpoint.

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

End point timeframe:

0.5 h, 2 h, and 4 to 8 h post-dose on Day 1 and at Week 28; Pre-dose and 2 h post-dose at Weeks 4 and 48; Pre-dose at Weeks 16 and 52

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: As per planned analysis, pharmacokinetic endpoints were assessed only in drug arm groups. Thus, data is reported only for the drug arm groups of the baseline period in this endpoint.

| End point values                                    | Brensocatic 10 mg | Brensocatic 25 mg |  |  |
|---|-------------------|-------------------|--|--|
| Subject group type                                  | Reporting group   | Reporting group   |  |  |
| Number of subjects analysed                         | 14                | 16                |  |  |
| Units: ng/ml  |                   |                   |  |  |
| geometric mean (geometric coefficient of variation) |                   |                   |  |  |
| Day 1: 0.5 h post-dose (n=12,14)                    | 63.20 (± 51.7)    | 109.3 (± 139.1)   |  |  |

|                                    |                |                 |  |  |
|------------------------------------|----------------|-----------------|--|--|
| Day 1: 2 h post-dose (n=13,14)     | 68.33 (± 32.5) | 202.5 (± 50.7)  |  |  |
| Day 1: 4-8 h post-dose (n=12,14)   | 56.07 (± 24.1) | 196.1 (± 52.4)  |  |  |
| Week 4: Pre-dose (n=14,16)         | 44.10 (± 64.2) | 126.6 (± 90.4)  |  |  |
| Week 4: 2 h post-dose (n=13,16)    | 134.9 (± 52.8) | 432.9 (± 44.3)  |  |  |
| Week 16: Pre-dose (n=14,15)        | 40.62 (± 51.6) | 158.1 (± 95.7)  |  |  |
| Week 28: Pre-dose (n=14,11)        | 43.74 (± 57.2) | 132.9 (± 96.3)  |  |  |
| Week 28: 0.5 h post-dose (n=11,10) | 123.4 (± 49.1) | 321.6 (± 93.8)  |  |  |
| Week 28: 2 h post-dose (n=13,10)   | 118.5 (± 30.5) | 336.9 (± 77.7)  |  |  |
| Week 28: 4-8 h post-dose (n=11,10) | 115.4 (± 27.7) | 309.9 (± 48.0)  |  |  |
| Week 40: Pre-dose (n=10,7)         | 37.30 (± 52.5) | 84.39 (± 102.3) |  |  |
| Week 40: 2 h post-dose (n=10,7)    | 110.4 (± 43.9) | 262.8 (± 77.6)  |  |  |
| Week 52: Pre-dose (n=6,7)          | 43.02 (± 64.8) | 104.0 (± 57.8)  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to Week 56

Adverse event reporting additional description:

The safety analysis set included all participants who were randomised and received at least 1 dose of brensocatib or placebo.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 27.0 |
|--------------------|------|

### Reporting groups

|                       |                   |
|-----------------------|-------------------|
| Reporting group title | Brensocatib 10 mg |
|-----------------------|-------------------|

Reporting group description:

Participants received brensocatib 10 mg tablets, orally, once daily, for 52 weeks.

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

Reporting group description:

Participants received a brensocatib matching placebo tablets orally, once daily, for 52 weeks.

|                       |                   |
|-----------------------|-------------------|
| Reporting group title | Brensocatib 25 mg |
|-----------------------|-------------------|

Reporting group description:

Participants received brensocatib 25 mg tablets, orally, once daily, for 52 weeks.

| Serious adverse events  | Brensocatib 10 mg  | Placebo            | Brensocatib 25 mg |
|---|--------------------|--------------------|-------------------|
| Total subjects affected by serious adverse events                   |                    |                    |                   |
| subjects affected / exposed   | 101 / 582 (17.35%) | 108 / 563 (19.18%) | 97 / 574 (16.90%) |
| number of deaths (all causes)                                       | 2                  | 8                  | 4                 |
| number of deaths resulting from adverse events                      | 0                  | 0                  | 0                 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                    |                    |                   |
| Anal squamous cell carcinoma  |                    |                    |                   |
| subjects affected / exposed   | 1 / 582 (0.17%)    | 0 / 563 (0.00%)    | 0 / 574 (0.00%)   |
| occurrences causally related to treatment / all                     | 0 / 1              | 0 / 0              | 0 / 0             |
| deaths causally related to treatment / all                          | 0 / 0              | 0 / 0              | 0 / 0             |
| Malignant melanoma in situ  |                    |                    |                   |
| subjects affected / exposed   | 1 / 582 (0.17%)    | 0 / 563 (0.00%)    | 0 / 574 (0.00%)   |
| occurrences causally related to treatment / all                     | 0 / 1              | 0 / 0              | 0 / 0             |
| deaths causally related to treatment / all                          | 0 / 0              | 0 / 0              | 0 / 0             |
| Brain neoplasm  |                    |                    |                   |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 582 (0.00%) | 1 / 563 (0.18%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Colon cancer                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 582 (0.17%) | 0 / 563 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Colorectal cancer                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 0 / 563 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Lung neoplasm malignant                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 1 / 563 (0.18%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Malignant melanoma                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 0 / 563 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Benign salivary gland neoplasm                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 582 (0.17%) | 0 / 563 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Mantle cell lymphoma                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 582 (0.17%) | 0 / 563 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Papillary thyroid cancer                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 0 / 563 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Prostate cancer                                 |                 |                 |                 |

|  |                 |                 |                 |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed                          | 1 / 582 (0.17%) | 0 / 563 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Transitional cell carcinoma                          |                 |                 |                 |
| subjects affected / exposed                          | 0 / 582 (0.00%) | 0 / 563 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Uterine leiomyoma                                    |                 |                 |                 |
| subjects affected / exposed                          | 1 / 582 (0.17%) | 0 / 563 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Vascular disorders                                   |                 |                 |                 |
| Hypotension  |                 |                 |                 |
| subjects affected / exposed                          | 0 / 582 (0.00%) | 1 / 563 (0.18%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypertension   |                 |                 |                 |
| subjects affected / exposed                          | 0 / 582 (0.00%) | 1 / 563 (0.18%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypertensive crisis                                  |                 |                 |                 |
| subjects affected / exposed                          | 0 / 582 (0.00%) | 1 / 563 (0.18%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| General disorders and administration site conditions |                 |                 |                 |
| Pyrexia  |                 |                 |                 |
| subjects affected / exposed                          | 0 / 582 (0.00%) | 0 / 563 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Generalised oedema                                   |                 |                 |                 |
| subjects affected / exposed                          | 0 / 582 (0.00%) | 0 / 563 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |

|  |                  |                   |                  |
|--|------------------|-------------------|------------------|
| General physical health deterioration<br>subjects affected / exposed | 0 / 582 (0.00%)  | 0 / 563 (0.00%)   | 1 / 574 (0.17%)  |
| occurrences causally related to<br>treatment / all                   | 0 / 0            | 0 / 0             | 0 / 1            |
| deaths causally related to<br>treatment / all                        | 0 / 0            | 0 / 0             | 0 / 1            |
| Immune system disorders  |                  |                   |                  |
| Drug hypersensitivity<br>subjects affected / exposed                 | 1 / 582 (0.17%)  | 0 / 563 (0.00%)   | 0 / 574 (0.00%)  |
| occurrences causally related to<br>treatment / all                   | 0 / 1            | 0 / 0             | 0 / 0            |
| deaths causally related to<br>treatment / all                        | 0 / 0            | 0 / 0             | 0 / 0            |
| Reproductive system and breast<br>disorders                          |                  |                   |                  |
| Benign prostatic hyperplasia<br>subjects affected / exposed          | 1 / 582 (0.17%)  | 0 / 563 (0.00%)   | 0 / 574 (0.00%)  |
| occurrences causally related to<br>treatment / all                   | 0 / 1            | 0 / 0             | 0 / 0            |
| deaths causally related to<br>treatment / all                        | 0 / 0            | 0 / 0             | 0 / 0            |
| Ovarian cyst<br>subjects affected / exposed                          | 1 / 582 (0.17%)  | 0 / 563 (0.00%)   | 1 / 574 (0.17%)  |
| occurrences causally related to<br>treatment / all                   | 0 / 1            | 0 / 0             | 0 / 1            |
| deaths causally related to<br>treatment / all                        | 0 / 0            | 0 / 0             | 0 / 0            |
| Pelvic organ prolapse<br>subjects affected / exposed                 | 1 / 582 (0.17%)  | 0 / 563 (0.00%)   | 0 / 574 (0.00%)  |
| occurrences causally related to<br>treatment / all                   | 0 / 1            | 0 / 0             | 0 / 0            |
| deaths causally related to<br>treatment / all                        | 0 / 0            | 0 / 0             | 0 / 0            |
| Uterovaginal prolapse<br>subjects affected / exposed                 | 1 / 582 (0.17%)  | 0 / 563 (0.00%)   | 0 / 574 (0.00%)  |
| occurrences causally related to<br>treatment / all                   | 0 / 1            | 0 / 0             | 0 / 0            |
| deaths causally related to<br>treatment / all                        | 0 / 0            | 0 / 0             | 0 / 0            |
| Respiratory, thoracic and mediastinal<br>disorders                   |                  |                   |                  |
| Bronchiectasis<br>subjects affected / exposed                        | 47 / 582 (8.08%) | 67 / 563 (11.90%) | 48 / 574 (8.36%) |
| occurrences causally related to<br>treatment / all                   | 0 / 69           | 1 / 107           | 0 / 65           |
| deaths causally related to<br>treatment / all                        | 0 / 1            | 0 / 1             | 0 / 0            |
| Acute respiratory failure  |                  |                   |                  |



|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 2 / 582 (0.34%) | 2 / 563 (0.36%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           | 0 / 0           |
| Dyspnoea  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 1 / 563 (0.18%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Eosinophilic pneumonia                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 0 / 563 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Haemoptysis                                     |                 |                 |                 |
| subjects affected / exposed                     | 3 / 582 (0.52%) | 6 / 563 (1.07%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 7           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| Hypoxia   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 582 (0.17%) | 0 / 563 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Lung opacity                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 582 (0.17%) | 0 / 563 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Respiratory failure                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 1 / 563 (0.18%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pneumothorax spontaneous                        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 582 (0.17%) | 0 / 563 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pulmonary arterial hypertension                 |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 582 (0.17%) | 0 / 563 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pulmonary embolism                              |                 |                 |                 |
| subjects affected / exposed                     | 2 / 582 (0.34%) | 2 / 563 (0.36%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pulmonary fibrosis                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 1 / 563 (0.18%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Nasal polyps                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 0 / 563 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Product issues                                  |                 |                 |                 |
| Device dislocation                              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 582 (0.17%) | 0 / 563 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Device malfunction                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 1 / 563 (0.18%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Investigations                                  |                 |                 |                 |
| Alanine aminotransferase increased              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 0 / 563 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Aspartate aminotransferase increased            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 0 / 563 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|  |                 |                 |                 |
|--|-----------------|-----------------|-----------------|
| Urinary sediment abnormal<br>subjects affected / exposed   | 0 / 582 (0.00%) | 1 / 563 (0.18%) | 0 / 574 (0.00%) |
| occurrences causally related to<br>treatment / all         | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to<br>treatment / all              | 0 / 0           | 0 / 0           | 0 / 0           |
| Weight decreased<br>subjects affected / exposed            | 0 / 582 (0.00%) | 0 / 563 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to<br>treatment / all         | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to<br>treatment / all              | 0 / 0           | 0 / 0           | 0 / 0           |
| Injury, poisoning and procedural<br>complications          |                 |                 |                 |
| Alcohol poisoning<br>subjects affected / exposed           | 1 / 582 (0.17%) | 1 / 563 (0.18%) | 0 / 574 (0.00%) |
| occurrences causally related to<br>treatment / all         | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to<br>treatment / all              | 0 / 0           | 0 / 0           | 0 / 0           |
| Ankle fracture<br>subjects affected / exposed              | 1 / 582 (0.17%) | 0 / 563 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to<br>treatment / all         | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all              | 0 / 0           | 0 / 0           | 0 / 0           |
| Cervical vertebral fracture<br>subjects affected / exposed | 0 / 582 (0.00%) | 1 / 563 (0.18%) | 0 / 574 (0.00%) |
| occurrences causally related to<br>treatment / all         | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to<br>treatment / all              | 0 / 0           | 0 / 1           | 0 / 0           |
| Clavicle fracture<br>subjects affected / exposed           | 0 / 582 (0.00%) | 1 / 563 (0.18%) | 0 / 574 (0.00%) |
| occurrences causally related to<br>treatment / all         | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to<br>treatment / all              | 0 / 0           | 0 / 0           | 0 / 0           |
| Fall<br>subjects affected / exposed                        | 1 / 582 (0.17%) | 0 / 563 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to<br>treatment / all         | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all              | 0 / 0           | 0 / 0           | 0 / 0           |
| Femur fracture<br>subjects affected / exposed              | 0 / 582 (0.00%) | 1 / 563 (0.18%) | 0 / 574 (0.00%) |
| occurrences causally related to<br>treatment / all         | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to<br>treatment / all              | 0 / 0           | 0 / 0           | 0 / 0           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Fibula fracture                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 582 (0.17%) | 0 / 563 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Foreign body in throat                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 0 / 563 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hip fracture                                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 582 (0.17%) | 0 / 563 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Joint dislocation                               |                 |                 |                 |
| subjects affected / exposed                     | 2 / 582 (0.34%) | 0 / 563 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Joint injury                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 0 / 563 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Limb traumatic amputation                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 1 / 563 (0.18%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Lower limb fracture                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 1 / 563 (0.18%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Meniscus injury                                 |                 |                 |                 |
| subjects affected / exposed                     | 2 / 582 (0.34%) | 0 / 563 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Patella fracture                                |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 582 (0.17%) | 0 / 563 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pelvic fracture                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 1 / 563 (0.18%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Rib fracture                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 1 / 563 (0.18%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Road traffic accident                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 582 (0.17%) | 0 / 563 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| Upper limb fracture                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 0 / 563 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Wrist fracture                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 1 / 563 (0.18%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Radius fracture                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 582 (0.17%) | 0 / 563 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac disorders                               |                 |                 |                 |
| Acute myocardial infarction                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 0 / 563 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Atrial fibrillation                             |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 2 / 582 (0.34%) | 4 / 563 (0.71%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 4           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Aortic valve stenosis                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 0 / 563 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac failure acute                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 582 (0.17%) | 0 / 563 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac failure congestive                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 1 / 563 (0.18%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac failure                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 0 / 563 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac arrest                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 1 / 563 (0.18%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| Cardio-respiratory arrest                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 1 / 563 (0.18%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| Atrioventricular block                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 0 / 563 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Atrioventricular block complete                 |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 582 (0.00%) | 1 / 563 (0.18%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pericardial effusion                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 582 (0.17%) | 0 / 563 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Myocardial infarction                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 582 (0.17%) | 0 / 563 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| Cardiomyopathy                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 582 (0.17%) | 0 / 563 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Coronary artery disease                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 1 / 563 (0.18%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Diastolic dysfunction                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 582 (0.17%) | 0 / 563 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ischaemic cardiomyopathy                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 1 / 563 (0.18%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Nervous system disorders                        |                 |                 |                 |
| Ischaemic stroke                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 1 / 563 (0.18%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Loss of consciousness                           |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 582 (0.17%) | 0 / 563 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Presyncope                                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 582 (0.17%) | 0 / 563 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Sciatica  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 582 (0.17%) | 0 / 563 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Transient ischaemic attack                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 0 / 563 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Dizziness                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 1 / 563 (0.18%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Blood and lymphatic system disorders            |                 |                 |                 |
| Anaemia   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 1 / 563 (0.18%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Eye disorders                                   |                 |                 |                 |
| Retinal detachment                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 1 / 563 (0.18%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Macular hole                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 1 / 563 (0.18%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Glaucoma  |                 |                 |                 |



|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 582 (0.00%) | 0 / 563 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cataract nuclear                                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 1 / 563 (0.18%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cataract  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 582 (0.17%) | 3 / 563 (0.53%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 4           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Blindness transient                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 582 (0.17%) | 0 / 563 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Vitreous haemorrhage                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 0 / 563 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Vitreoretinal traction syndrome                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 1 / 563 (0.18%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastrointestinal disorders                      |                 |                 |                 |
| Rectal haemorrhage                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 0 / 563 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pancreatitis acute                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 2 / 563 (0.36%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Mechanical ileus                                |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 582 (0.00%) | 1 / 563 (0.18%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Malabsorption                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 1 / 563 (0.18%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Intestinal obstruction                          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 582 (0.17%) | 0 / 563 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Upper gastrointestinal haemorrhage              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 0 / 563 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Enteritis                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 582 (0.17%) | 0 / 563 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Dysphagia                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 1 / 563 (0.18%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Femoral hernia incarcerated                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 1 / 563 (0.18%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hepatobiliary disorders                         |                 |                 |                 |
| Cholelithiasis                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 0 / 563 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cholangitis                                     |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 582 (0.00%) | 0 / 563 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Biliary cyst                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 0 / 563 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hepatic function abnormal                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 0 / 563 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hepatic steatosis                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 0 / 563 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Skin and subcutaneous tissue disorders          |                 |                 |                 |
| Actinic keratosis                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 582 (0.17%) | 0 / 563 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Skin ulcer                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 1 / 563 (0.18%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Urticaria                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 0 / 563 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Renal and urinary disorders                     |                 |                 |                 |
| Acute kidney injury                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 1 / 563 (0.18%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hydronephrosis                                  |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 582 (0.00%) | 0 / 563 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Nephrolithiasis                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 0 / 563 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Renal colic                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 0 / 563 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Renal failure                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 1 / 563 (0.18%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Musculoskeletal and connective tissue disorders |                 |                 |                 |
| Arthralgia                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 1 / 563 (0.18%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Myalgia   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 0 / 563 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Intervertebral disc disorder                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 0 / 563 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Joint range of motion decreased                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 1 / 563 (0.18%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Mobility decreased                              |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 582 (0.17%) | 0 / 563 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Muscle spasms                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 0 / 563 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Arthropathy                                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 582 (0.17%) | 0 / 563 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Osteoarthritis                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 1 / 563 (0.18%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Polymyalgia rheumatica                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 0 / 563 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Spondylolisthesis                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 582 (0.17%) | 0 / 563 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Synovitis                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 582 (0.17%) | 0 / 563 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Infections and infestations                     |                 |                 |                 |
| Aspergillus infection                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 582 (0.17%) | 0 / 563 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| Appendicitis                                    |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 2 / 582 (0.34%) | 1 / 563 (0.18%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Abscess neck                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 0 / 563 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Bacterial infection                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 582 (0.17%) | 0 / 563 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Bronchitis fungal                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 582 (0.17%) | 0 / 563 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Herpes zoster                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 1 / 563 (0.18%) | 2 / 574 (0.35%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastroenteritis cryptosporidial                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 582 (0.17%) | 0 / 563 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Endophthalmitis                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 0 / 563 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Empyema   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 1 / 563 (0.18%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Diverticulitis                                  |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 582 (0.00%) | 0 / 563 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Coronavirus infection                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 582 (0.17%) | 1 / 563 (0.18%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cellulitis                                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 582 (0.17%) | 0 / 563 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| COVID-19 pneumonia                              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 582 (0.17%) | 1 / 563 (0.18%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| COVID-19  |                 |                 |                 |
| subjects affected / exposed                     | 4 / 582 (0.69%) | 6 / 563 (1.07%) | 9 / 574 (1.57%) |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 6           | 0 / 9           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Burkholderia gladioli infection                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 0 / 563 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Influenza                                       |                 |                 |                 |
| subjects affected / exposed                     | 2 / 582 (0.34%) | 1 / 563 (0.18%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Periorbital cellulitis                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 1 / 563 (0.18%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pneumonia                                       |                 |                 |                 |

|   |                  |                  |                  |
|---|------------------|------------------|------------------|
| subjects affected / exposed                     | 11 / 582 (1.89%) | 16 / 563 (2.84%) | 13 / 574 (2.26%) |
| occurrences causally related to treatment / all | 0 / 13           | 0 / 19           | 0 / 14           |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            | 0 / 1            |
| Pneumonia aspiration                            |                  |                  |                  |
| subjects affected / exposed                     | 0 / 582 (0.00%)  | 2 / 563 (0.36%)  | 0 / 574 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Pneumonia bacterial                             |                  |                  |                  |
| subjects affected / exposed                     | 0 / 582 (0.00%)  | 1 / 563 (0.18%)  | 1 / 574 (0.17%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Pneumonia necrotising                           |                  |                  |                  |
| subjects affected / exposed                     | 0 / 582 (0.00%)  | 0 / 563 (0.00%)  | 1 / 574 (0.17%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Mastitis  |                  |                  |                  |
| subjects affected / exposed                     | 0 / 582 (0.00%)  | 0 / 563 (0.00%)  | 1 / 574 (0.17%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Lung abscess                                    |                  |                  |                  |
| subjects affected / exposed                     | 0 / 582 (0.00%)  | 1 / 563 (0.18%)  | 2 / 574 (0.35%)  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 3            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Lower respiratory tract infection               |                  |                  |                  |
| subjects affected / exposed                     | 1 / 582 (0.17%)  | 0 / 563 (0.00%)  | 1 / 574 (0.17%)  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 1            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Large intestine infection                       |                  |                  |                  |
| subjects affected / exposed                     | 1 / 582 (0.17%)  | 0 / 563 (0.00%)  | 0 / 574 (0.00%)  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            | 0 / 0            |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0            |
| Klebsiella infection                            |                  |                  |                  |



|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 582 (0.00%) | 0 / 563 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pneumonia influenzal                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 1 / 563 (0.18%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Scrub typhus                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 1 / 563 (0.18%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Sepsis  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 582 (0.17%) | 1 / 563 (0.18%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Sinusitis                                       |                 |                 |                 |
| subjects affected / exposed                     | 2 / 582 (0.34%) | 0 / 563 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Tuberculosis                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 1 / 563 (0.18%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Urinary tract infection                         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 582 (0.17%) | 1 / 563 (0.18%) | 2 / 574 (0.35%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Viral infection                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 0 / 563 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pneumonia pneumococcal                          |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 582 (0.00%) | 1 / 563 (0.18%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pneumonia pseudomonal                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 0 / 563 (0.00%) | 1 / 574 (0.17%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Postoperative wound infection                   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 582 (0.17%) | 0 / 563 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pseudomonas infection                           |                 |                 |                 |
| subjects affected / exposed                     | 2 / 582 (0.34%) | 2 / 563 (0.36%) | 2 / 574 (0.35%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pyelonephritis chronic                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 1 / 563 (0.18%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Viral pharyngitis                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 582 (0.17%) | 0 / 563 (0.00%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Metabolism and nutrition disorders              |                 |                 |                 |
| Hyponatraemia                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 582 (0.00%) | 1 / 563 (0.18%) | 0 / 574 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

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

| <b>Non-serious adverse events</b>                     | Brensocatib 10 mg  | Placebo            | Brensocatib 25 mg  |
|---|--------------------|--------------------|--------------------|
| Total subjects affected by non-serious adverse events |                    |                    |                    |
| subjects affected / exposed                           | 197 / 582 (33.85%) | 203 / 563 (36.06%) | 213 / 574 (37.11%) |
| Nervous system disorders                              |                    |                    |                    |
| Headache  |                    |                    |                    |
| subjects affected / exposed                           | 39 / 582 (6.70%)   | 39 / 563 (6.93%)   | 49 / 574 (8.54%)   |
| occurrences (all)                                     | 99                 | 41                 | 91                 |
| Respiratory, thoracic and mediastinal disorders       |                    |                    |                    |
| Cough   |                    |                    |                    |
| subjects affected / exposed                           | 41 / 582 (7.04%)   | 36 / 563 (6.39%)   | 35 / 574 (6.10%)   |
| occurrences (all)                                     | 55                 | 39                 | 41                 |
| Musculoskeletal and connective tissue disorders       |                    |                    |                    |
| Back pain   |                    |                    |                    |
| subjects affected / exposed                           | 13 / 582 (2.23%)   | 35 / 563 (6.22%)   | 17 / 574 (2.96%)   |
| occurrences (all)                                     | 14                 | 35                 | 17                 |
| Infections and infestations                           |                    |                    |                    |
| COVID-19  |                    |                    |                    |
| subjects affected / exposed                           | 89 / 582 (15.29%)  | 83 / 563 (14.74%)  | 113 / 574 (19.69%) |
| occurrences (all)                                     | 93                 | 88                 | 119                |
| Nasopharyngitis                                       |                    |                    |                    |
| subjects affected / exposed                           | 45 / 582 (7.73%)   | 43 / 563 (7.64%)   | 36 / 574 (6.27%)   |
| occurrences (all)                                     | 53                 | 54                 | 52                 |
| Urinary tract infection                               |                    |                    |                    |
| subjects affected / exposed                           | 27 / 582 (4.64%)   | 33 / 563 (5.86%)   | 30 / 574 (5.23%)   |
| occurrences (all)                                     | 29                 | 43                 | 40                 |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 12 March 2021    | <p>The following changes were made as per amendment 01:</p> <ul style="list-style-type: none"> <li>• Inclusion criteria: CT scan should be high-resolution; require males to use condoms; define "highly effective contraception" and clarify role of Investigator and designee in explaining contraception to participant.</li> <li>• Exclusion criteria: add CDC definition of "current smoker"; add exceptions to chronic use of oral steroids; clarify compliance with eDiary entries during Screening; exclude participants with hypersensitivity to brensocatib or its excipients.</li> <li>• Dosing may be interrupted for safety reasons.</li> </ul>   |
| 07 December 2021 | <p>The following changes were made as per amendment 02:</p> <ul style="list-style-type: none"> <li>• Randomize approximately 40 adolescents (<math>\geq 12</math> to <math>&lt; 18</math> years of age) in a 2:2:1 ratio to brensocatib 10 mg, brensocatib 25 mg, or placebo (no stratification applied); add supportive toxicology and dose justification information, entry criteria, and pregnancy testing requirements for adolescents; add adolescents not required to provide sputum sample at any time during study if unable; add collection of blood PK and sputum PD samples from all adolescents.</li> <li>• Secondary objectives and/or endpoints: <ul style="list-style-type: none"> <li>o Change from baseline in post-bronchodilator FEV1 is at Week 52</li> <li>o Rate of severe PEs is based on adjudicated events</li> <li>o QOL-B is assessed in adults only</li> <li>o Remove physical exam as a safety endpoint parameter</li> <li>o Add evaluation of brensocatib exposure in adults and adolescents</li> </ul> </li> <li>• Revise, combine, remove, and add exploratory objectives and/or endpoints, including addition of PGI-S and PGI-C in adults and QOL-PCD in adolescents.</li> <li>• Expand randomization enforcement criteria to restrict the percentage of participants with eosinophil count <math>&gt; 300/\text{mm}^3</math> and COPD comorbidity; add regional enrollment targets.</li> <li>• Inclusion criteria: clarify BMI threshold is for adults.</li> <li>• Exclusion criteria: clarify chronic antibiotic treatment of at least 3 months is before Screening; clarify PO steroids for any reason are prohibited; modify LFT thresholds to exclude Child-Pugh class C and remove separate criterion for Child-Pugh class B or C; clarify exclusion of attenuated vaccine is within 4 weeks before Screening; clarify participants currently treated for periodontal disease are excluded; clarify eDiary compliance assessment is for adults and as determined by the Investigator.</li> <li>• Independent adjudication committee adjudicates all PEs.</li> <li>• Clarify BEST completed by adults and EQ-5D-5L completed by adults and adolescents.</li> <li>• Protocol-defined PEs reported as AEs only if they fulfill a seriousness criterion; PEs do not fall under the other infection AESI category.</li> </ul> |
| 09 August 2022   | <p>The following change was made as per Amendment 03:</p> <ul style="list-style-type: none"> <li>• Add estimand framework.</li> <li>• Replace participants from Ukraine whose data will be listed and not included in formal efficacy and safety analyses.</li> <li>• Add PK sample collections from all adults enrolled in the study and sputum PD samples collections from all newly enrolled adults.</li> <li>• Exclude participants receiving cyclic antibiotics from PK/PD substudy.</li> <li>• Adjust criteria by which randomization is enforced.</li> <li>• Adjust enrollment targets and percentage of overall randomized population that any given country may contribute (Protocol Memorandum, 19 September 2022).</li> </ul>   |

|                  |  |
|------------------|--|
| 13 February 2024 | <p>The following changes were made as per Amendment 04:</p> <ul style="list-style-type: none"><li>• Updated the interval duration for defining a separate PE (ie, at least 2 weeks [14 days] must occur between the end date of an earlier PE and the start date of the next PE).</li><li>• Update multiplicity analysis methods for primary and secondary endpoints.</li><li>• Clarify analysis for adult-only subgroup.</li><li>• Add age group (adult, adolescent) as potential covariate in primary analysis model for primary endpoint.</li><li>• Remove safety estimand (analysis unchanged).</li><li>• Increase upper limit of enrollment target for North America, Western Europe Asia Pacific, and Latin America and enrollment cap for any single country (except the US).</li></ul> |
|------------------|--|

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported