



## Clinical trial results:

### A Phase II, Randomized, Double-Blind, Placebo-Controlled, Study to Assess the Efficacy and Safety of Lebrikizumab in Patients with Idiopathic Pulmonary Fibrosis

#### Summary

|                          |                      |
|--------------------------|----------------------|
| EudraCT number           | 2013-001163-24       |
| Trial protocol           | DE IT ES PL GB BE FR |
| Global end of trial date | 06 November 2017     |

#### Results information

|                                |                |
|--------------------------------|----------------|
| Result version number          | v1 (current)   |
| This version publication date  | 09 August 2018 |
| First version publication date | 09 August 2018 |

#### Trial information

##### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | GB28547 |
|-----------------------|---------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01872689 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | F. Hoffmann-La Roche AG  |
| Sponsor organisation address | Grenzacherstrasse 124, Basel, Switzerland, CH-4070   |
| Public contact               | Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, global.trial_information@roche.com |
| Scientific contact           | Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, global.trial_information@roche.com |

Notes:

#### Paediatric regulatory details

|  |    |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

|  |                  |
|--|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 06 November 2017 |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 06 November 2017 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate lebrikizumab compared with placebo as monotherapy or as combination therapy with pirfenidone background compared with placebo in participants with idiopathic pulmonary fibrosis (IPF), as measured by the annualized rate of decline in percentage of predicted forced vital capacity (FVC) over 52 weeks.

Protection of trial subjects:

The study was conducted in accordance with the principles of the "Declaration of Helsinki" and Good Clinical Practice (GCP) according to the regulations and procedures described in the protocol. Approval from the Independent Ethics Committee/Institutional Review Board (IEC/IRB) was obtained before study start and was documented in a letter to the Investigator specifying the date on which the committee met and granted the approval. The Sponsor also obtained approval from the relevant Competent Authority prior to starting the study.

Background therapy: -

Evidence for comparator: -

|   |                 |
|---|-----------------|
| Actual start date of recruitment                          | 13 October 2013 |
| Long term follow-up planned                               | No              |
| Independent data monitoring committee (IDMC) involvement? | Yes             |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United States: 222 |
| Country: Number of subjects enrolled | Belgium: 15        |
| Country: Number of subjects enrolled | Canada: 15         |
| Country: Number of subjects enrolled | Spain: 12          |
| Country: Number of subjects enrolled | France: 17         |
| Country: Number of subjects enrolled | United Kingdom: 25 |
| Country: Number of subjects enrolled | Germany: 31        |
| Country: Number of subjects enrolled | Italy: 12          |
| Country: Number of subjects enrolled | Poland: 43         |
| Country: Number of subjects enrolled | Australia: 44      |
| Country: Number of subjects enrolled | Japan: 49          |
| Country: Number of subjects enrolled | Mexico: 13         |
| Country: Number of subjects enrolled | Peru: 7            |
| Worldwide total number of subjects   | 505                |
| EEA total number of subjects         | 155                |

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|---|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 0   |
| Adults (18-64 years)                      | 120 |
| From 65 to 84 years                       | 382 |
| 85 years and over                         | 3   |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

A total of 505 participants (154 participants in Monotherapy Cohort and 351 participants in Combination Therapy Cohort) were enrolled in the study. Of the monotherapy cohort, 114 participants completed the double-blind period and only 108 of these participants continued into the 52-week open-label lebrikizumab treatment period.

### Period 1

|                              |  |
|------------------------------|--|
| Period 1 title               | Double-Blind/Placebo-Controlled 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>             | Monotherapy (Cohort A): Placebo |

Arm description:

Participants received monotherapy with placebo matched to lebrikizumab administered via subcutaneous (SC) injection once every 4 weeks up to 52 weeks during the placebo-controlled treatment period. Participants were allowed to receive treatment with lebrikizumab at a dose of 250 milligrams (mg) administered via SC injection once every 4 weeks up to additional 52 weeks (that is, up to Week 104) in the open-label period.

|  |  |
|--|--|
| Arm type                               | Placebo                                      |
| Investigational medicinal product name | Placebo                                      |
| Investigational medicinal product code |  |
| Other name                             |  |
| Pharmaceutical forms                   | Solution for injection in pre-filled syringe |
| Routes of administration               | Subcutaneous use                             |

Dosage and administration details:

Placebo matched to lebrikizumab was administered via SC injection once every 4 weeks.

|                  |                                      |
|------------------|--------------------------------------|
| <b>Arm title</b> | Monotherapy (Cohort A): Lebrikizumab |
|------------------|--------------------------------------|

Arm description:

Participants received monotherapy with lebrikizumab at a dose of 250 mg administered via SC injection once every 4 weeks up to 52 weeks during the placebo-controlled treatment period. Participants were allowed to receive treatment with lebrikizumab at a dose of 250 mg administered via SC injection once every 4 weeks up to additional 52 weeks (that is, up to Week 104) in the open-label period.

|  |  |
|--|--|
| Arm type                               | Experimental                                 |
| Investigational medicinal product name | Lebrikizumab                                 |
| Investigational medicinal product code |  |
| Other name                             | RO5490255                                    |
| Pharmaceutical forms                   | Solution for injection in pre-filled syringe |
| Routes of administration               | Subcutaneous use                             |

Dosage and administration details:

Lebrikizumab was administered at a dose of 250 mg via SC injection once every 4 weeks.

|                  |   |
|------------------|---|
| <b>Arm title</b> | Combination Therapy (Cohort B): Placebo + Pirfenidone |
|------------------|---|

Arm description:

Participants received pirfenidone at a stable dose of 2403 mg per day (three 267 mg capsules three times a day [9 capsules daily] for a total of 2403 mg/day) or at maximum tolerated dose (MTD) administered orally along with placebo matched to lebrikizumab administered via SC injection once

every 4 weeks up to 52 weeks during the placebo-controlled treatment period.

|  |  |
|--|--|
| Arm type                               | Placebo                                      |
| Investigational medicinal product name | Placebo                                      |
| Investigational medicinal product code |  |
| Other name                             |  |
| Pharmaceutical forms                   | Solution for injection in pre-filled syringe |
| Routes of administration               | Subcutaneous use                             |

Dosage and administration details:

Placebo matched to lebrikizumab was administered via SC injection once every 4 weeks.

|  |               |
|--|---------------|
| Investigational medicinal product name | Pirfenidone   |
| Investigational medicinal product code |               |
| Other name                             |               |
| Pharmaceutical forms                   | Capsule, hard |
| Routes of administration               | Oral use      |

Dosage and administration details:

Pirfenidone was administered orally at a stable dose of 2403 mg per day or at MTD.

|                  |  |
|------------------|--|
| <b>Arm title</b> | Combination Therapy (Cohort B): Lebrikizumab + Pirfenidone |
|------------------|--|

Arm description:

Participants received pirfenidone at a stable dose of 2403 mg per day (three 267 mg capsules three times a day [9 capsules daily] for a total of 2403 mg/day) or at MTD administered orally along with lebrikizumab at a dose of 250 mg administered via SC injection once every 4 weeks up to 52 weeks during the placebo-controlled treatment period.

|  |  |
|--|--|
| Arm type                               | Experimental                                 |
| Investigational medicinal product name | Lebrikizumab                                 |
| Investigational medicinal product code |  |
| Other name                             | RO5490255                                    |
| Pharmaceutical forms                   | Solution for injection in pre-filled syringe |
| Routes of administration               | Subcutaneous use                             |

Dosage and administration details:

Lebrikizumab was administered at a dose of 250 mg via SC injection once every 4 weeks.

|  |               |
|--|---------------|
| Investigational medicinal product name | Pirfenidone   |
| Investigational medicinal product code |               |
| Other name                             |               |
| Pharmaceutical forms                   | Capsule, hard |
| Routes of administration               | Oral use      |

Dosage and administration details:

Pirfenidone was administered orally at a stable dose of 2403 mg per day or at MTD.

| Number of subjects in period 1 | Monotherapy<br>(Cohort A): Placebo | Monotherapy<br>(Cohort A):<br>Lebrikizumab | Combination<br>Therapy (Cohort B):<br>Placebo +<br>Pirfenidone |
|--------------------------------|------------------------------------|--|--|
|                                |                                    |  |  |
| Started                        | 76                                 | 78   | 177  |
| Completed                      | 56                                 | 58   | 129  |
| Not completed                  | 20                                 | 20   | 48   |
| Consent withdrawn by subject   | 9                                  | 8  | 14   |
| Physician decision             | -                                  | 3  | 3  |
| Adverse Event                  | 6                                  | 3  | 10   |
| Death                          | 3                                  | 4  | 14   |

|                    |   |   |   |
|--------------------|---|---|---|
| Unspecified        | 1 | 1 | 6 |
| Lost to follow-up  | 1 | - | - |
| Lack of efficacy   | - | 1 | - |
| Protocol deviation | - | - | 1 |

| Number of subjects in period 1 | Combination Therapy (Cohort B):<br>Lebrikizumab +<br>Pirfenidone |
|--------------------------------|--|
| Started                        | 174  |
| Completed                      | 136  |
| Not completed                  | 38   |
| Consent withdrawn by subject   | 16   |
| Physician decision             | 1  |
| Adverse Event                  | 7  |
| Death                          | 9  |
| Unspecified                    | 3  |
| Lost to follow-up              | 1  |
| Lack of efficacy               | -  |
| Protocol deviation             | 1  |

## Period 2

|                              |  |
|------------------------------|--|
| Period 2 title               | Open-Label Period (Only For Monotherapy) |
| Is this the baseline period? | No                                       |
| Allocation method            | Randomised - controlled                  |
| Blinding used                | Not blinded                              |

## Arms

|                              |                                 |
|------------------------------|---------------------------------|
| Are arms mutually exclusive? | Yes                             |
| <b>Arm title</b>             | Monotherapy (Cohort A): Placebo |

### Arm description:

Participants received monotherapy with placebo matched to lebrikizumab administered via SC injection once every 4 weeks up to 52 weeks during the placebo-controlled treatment period. Participants were allowed to receive treatment with lebrikizumab at a dose of 250 mg administered via SC injection once every 4 weeks up to additional 52 weeks (that is, up to Week 104) in the open-label period.

|  |  |
|--|--|
| Arm type                               | Placebo                                      |
| Investigational medicinal product name | Lebrikizumab                                 |
| Investigational medicinal product code |  |
| Other name                             | RO5490255                                    |
| Pharmaceutical forms                   | Solution for injection in pre-filled syringe |
| Routes of administration               | Subcutaneous use                             |

### Dosage and administration details:

Lebrikizumab was administered at a dose of 250 mg via SC injection once every 4 weeks.

|                  |                                      |
|------------------|--------------------------------------|
| <b>Arm title</b> | Monotherapy (Cohort A): Lebrikizumab |
|------------------|--------------------------------------|

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**Arm description:**

Participants received monotherapy with lebrikizumab at a dose of 250 mg administered via SC injection once every 4 weeks up to 52 weeks during the placebo-controlled treatment period. Participants were allowed to receive treatment with lebrikizumab at a dose of 250 mg administered via SC injection once every 4 weeks up to additional 52 weeks (that is, up to Week 104) in the open-label period.

|  |  |
|--|--|
| Arm type                               | Experimental                                 |
| Investigational medicinal product name | Lebrikizumab                                 |
| Investigational medicinal product code |  |
| Other name                             | RO5490255                                    |
| Pharmaceutical forms                   | Solution for injection in pre-filled syringe |
| Routes of administration               | Subcutaneous use                             |

**Dosage and administration details:**

Lebrikizumab was administered at a dose of 250 mg via SC injection once every 4 weeks.

| <b>Number of subjects in period 2<sup>[1]</sup></b> | Monotherapy (Cohort A): Placebo | Monotherapy (Cohort A): Lebrikizumab |
|---|---------------------------------|--------------------------------------|
|   |                                 |                                      |
| Started   | 52                              | 56                                   |
| Completed   | 31                              | 33                                   |
| Not completed                                       | 21                              | 23                                   |
| Consent withdrawn by subject                        | 11                              | 12                                   |
| Physician decision                                  | -                               | 1                                    |
| Adverse Event                                       | 2                               | 1                                    |
| Death   | 5                               | 3                                    |
| Unspecified   | 2                               | 3                                    |
| Lost to follow-up                                   | 1                               | 3                                    |

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**Notes:**

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: All participants who completed double-blind placebo-controlled period did not require to continue in the open-label period, so numbers may not match.

## Baseline characteristics

### Reporting groups

|  |  |
|--|--|
| Reporting group title  | Monotherapy (Cohort A): Placebo                            |
| Reporting group description:   |  |
| Participants received monotherapy with placebo matched to lebrikizumab administered via subcutaneous (SC) injection once every 4 weeks up to 52 weeks during the placebo-controlled treatment period. Participants were allowed to receive treatment with lebrikizumab at a dose of 250 milligrams (mg) administered via SC injection once every 4 weeks up to additional 52 weeks (that is, up to Week 104) in the open-label period. |  |
| Reporting group title  | Monotherapy (Cohort A): Lebrikizumab                       |
| Reporting group description:   |  |
| Participants received monotherapy with lebrikizumab at a dose of 250 mg administered via SC injection once every 4 weeks up to 52 weeks during the placebo-controlled treatment period. Participants were allowed to receive treatment with lebrikizumab at a dose of 250 mg administered via SC injection once every 4 weeks up to additional 52 weeks (that is, up to Week 104) in the open-label period.                            |  |
| Reporting group title  | Combination Therapy (Cohort B): Placebo + Pirfenidone      |
| Reporting group description:   |  |
| Participants received pirfenidone at a stable dose of 2403 mg per day (three 267 mg capsules three times a day [9 capsules daily] for a total of 2403 mg/day) or at maximum tolerated dose (MTD) administered orally along with placebo matched to lebrikizumab administered via SC injection once every 4 weeks up to 52 weeks during the placebo-controlled treatment period.  |  |
| Reporting group title  | Combination Therapy (Cohort B): Lebrikizumab + Pirfenidone |
| Reporting group description:   |  |
| Participants received pirfenidone at a stable dose of 2403 mg per day (three 267 mg capsules three times a day [9 capsules daily] for a total of 2403 mg/day) or at MTD administered orally along with lebrikizumab at a dose of 250 mg administered via SC injection once every 4 weeks up to 52 weeks during the placebo-controlled treatment period.  |  |

| Reporting group values                    | Monotherapy (Cohort A): Placebo | Monotherapy (Cohort A): Lebrikizumab | Combination Therapy (Cohort B): Placebo + Pirfenidone |
|---|---------------------------------|--------------------------------------|---|
| Number of subjects                        | 76                              | 78                                   | 177   |
| Age, Customized                           |                                 |                                      |   |
| Units: Subjects                           |                                 |                                      |   |
| From 40 to <55 years                      | 2                               | 1                                    | 6   |
| From 55 to <65 years                      | 18                              | 10                                   | 40  |
| From 65 to <75 years                      | 38                              | 44                                   | 99  |
| >=75 years                                | 18                              | 23                                   | 32  |
| Sex: Female, Male                         |                                 |                                      |   |
| Units: Subjects                           |                                 |                                      |   |
| Female                                    | 13                              | 13                                   | 30  |
| Male                                      | 63                              | 65                                   | 147   |
| Race (NIH/OMB)                            |                                 |                                      |   |
| Units: Subjects                           |                                 |                                      |   |
| American Indian or Alaska Native          | 1                               | 1                                    | 0   |
| Asian                                     | 11                              | 8                                    | 19  |
| Native Hawaiian or Other Pacific Islander | 1                               | 0                                    | 1   |
| Black or African American                 | 0                               | 0                                    | 1   |
| White                                     | 60                              | 66                                   | 149   |
| More than one race                        | 0                               | 1                                    | 0   |
| Unknown or Not Reported                   | 3                               | 2                                    | 7   |

|                         |    |    |     |
|-------------------------|----|----|-----|
| Ethnicity (NIH/OMB)     |    |    |     |
| Units: Subjects         |    |    |     |
| Hispanic or Latino      | 9  | 6  | 13  |
| Not Hispanic or Latino  | 64 | 68 | 160 |
| Unknown or Not Reported | 3  | 4  | 4   |

|  |   |       |  |
|--|---|-------|--|
| <b>Reporting group values</b>                | Combination<br>Therapy (Cohort B):<br>Lebrikizumab +<br>Pirfenidone | Total |  |
| Number of subjects                           | 174   | 505   |  |
| Age, Customized                              |   |       |  |
| Units: Subjects                              |   |       |  |
| From 40 to <55 years                         | 2   | 11    |  |
| From 55 to <65 years                         | 41  | 109   |  |
| From 65 to <75 years                         | 92  | 273   |  |
| >/=75 years                                  | 39  | 112   |  |
| Sex: Female, Male                            |   |       |  |
| Units: Subjects                              |   |       |  |
| Female                                       | 37  | 93    |  |
| Male   | 137   | 412   |  |
| Race (NIH/OMB)                               |   |       |  |
| Units: Subjects                              |   |       |  |
| American Indian or Alaska Native             | 1   | 3     |  |
| Asian  | 15  | 53    |  |
| Native Hawaiian or Other Pacific<br>Islander | 0   | 2     |  |
| Black or African American                    | 1   | 2     |  |
| White  | 151   | 426   |  |
| More than one race                           | 0   | 1     |  |
| Unknown or Not Reported                      | 6   | 18    |  |
| Ethnicity (NIH/OMB)                          |   |       |  |
| Units: Subjects                              |   |       |  |
| Hispanic or Latino                           | 15  | 43    |  |
| Not Hispanic or Latino                       | 155   | 447   |  |
| Unknown or Not Reported                      | 4   | 15    |  |

## End points

### End points reporting groups

|  |  |
|--|--|
| Reporting group title  | Monotherapy (Cohort A): Placebo                            |
| Reporting group description:<br>Participants received monotherapy with placebo matched to lebrikizumab administered via subcutaneous (SC) injection once every 4 weeks up to 52 weeks during the placebo-controlled treatment period. Participants were allowed to receive treatment with lebrikizumab at a dose of 250 milligrams (mg) administered via SC injection once every 4 weeks up to additional 52 weeks (that is, up to Week 104) in the open-label period. |  |
| Reporting group title  | Monotherapy (Cohort A): Lebrikizumab                       |
| Reporting group description:<br>Participants received monotherapy with lebrikizumab at a dose of 250 mg administered via SC injection once every 4 weeks up to 52 weeks during the placebo-controlled treatment period. Participants were allowed to receive treatment with lebrikizumab at a dose of 250 mg administered via SC injection once every 4 weeks up to additional 52 weeks (that is, up to Week 104) in the open-label period.                            |  |
| Reporting group title  | Combination Therapy (Cohort B): Placebo + Pirfenidone      |
| Reporting group description:<br>Participants received pirfenidone at a stable dose of 2403 mg per day (three 267 mg capsules three times a day [9 capsules daily] for a total of 2403 mg/day) or at maximum tolerated dose (MTD) administered orally along with placebo matched to lebrikizumab administered via SC injection once every 4 weeks up to 52 weeks during the placebo-controlled treatment period.  |  |
| Reporting group title  | Combination Therapy (Cohort B): Lebrikizumab + Pirfenidone |
| Reporting group description:<br>Participants received pirfenidone at a stable dose of 2403 mg per day (three 267 mg capsules three times a day [9 capsules daily] for a total of 2403 mg/day) or at MTD administered orally along with lebrikizumab at a dose of 250 mg administered via SC injection once every 4 weeks up to 52 weeks during the placebo-controlled treatment period.  |  |
| Reporting group title  | Monotherapy (Cohort A): Placebo                            |
| Reporting group description:<br>Participants received monotherapy with placebo matched to lebrikizumab administered via SC injection once every 4 weeks up to 52 weeks during the placebo-controlled treatment period. Participants were allowed to receive treatment with lebrikizumab at a dose of 250 mg administered via SC injection once every 4 weeks up to additional 52 weeks (that is, up to Week 104) in the open-label period.                             |  |
| Reporting group title  | Monotherapy (Cohort A): Lebrikizumab                       |
| Reporting group description:<br>Participants received monotherapy with lebrikizumab at a dose of 250 mg administered via SC injection once every 4 weeks up to 52 weeks during the placebo-controlled treatment period. Participants were allowed to receive treatment with lebrikizumab at a dose of 250 mg administered via SC injection once every 4 weeks up to additional 52 weeks (that is, up to Week 104) in the open-label period.                            |  |

### Primary: Annualized Rate of Decrease in Percent Predicted Forced Vital Capacity (FVC) Over 52 Weeks

|   |  |
|---|--|
| End point title   | Annualized Rate of Decrease in Percent Predicted Forced Vital Capacity (FVC) Over 52 Weeks |
| End point description:<br>Annualized rates of decrease (slope throughout time from baseline to Week 52) for percent predicted FVC was assessed and reported. FVC is a standard pulmonary function test. FVC is defined as the volume of air that can forcibly be blown out after full inspiration in the upright position, measured in liters. Predicted FVC is based on sex, age, and height of a person. Percent predicted FVC (in %) = $[(\text{observed FVC})/(\text{predicted FVC})]*100$ . Analysis was performed on Intent-to-Treat (ITT) Population, which included all participants who were randomized in the study, with participants grouped according to the treatment assignment at randomization. Here 'Number of Subjects Analysed' signifies number of participants evaluable for this outcome measure at Week 52. |  |
| End point type  | Primary  |

End point timeframe:

Baseline up to Week 52 (assessed at Baseline, Weeks 1, 4, 12, 24, 36, 44, and 52)

| End point values                  | Monotherapy<br>(Cohort A):<br>Placebo | Monotherapy<br>(Cohort A):<br>Lebrikizumab | Combination<br>Therapy<br>(Cohort B):<br>Placebo +<br>Pirfenidone | Combination<br>Therapy<br>(Cohort B):<br>Lebrikizumab +<br>Pirfenidone |
|-----------------------------------|---------------------------------------|--|---|--|
| Subject group type                | Reporting group                       | Reporting group                            | Reporting group   | Reporting group  |
| Number of subjects analysed       | 53                                    | 56   | 120   | 134  |
| Units: Percent predicted FVC/year |                                       |  |   |  |
| arithmetic mean (standard error)  | -6.1876 ( $\pm$<br>0.92597)           | -5.2065 ( $\pm$<br>0.92758)                | -6.0430 ( $\pm$<br>0.60633)                                       | -5.5430 ( $\pm$<br>0.59507)  |

## Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|
|----------------------------|------------------------|

Statistical analysis description:

Mixed Linear model comparing Lebrikizumab to Placebo, with assessment as the outcome variable; assessment time by treatment as fixed effects; and participant baseline FVC (<50%, 50 to 75%, >75%) and participant by assessment time as random effects with unstructured covariance.

|   |  |
|---|--|
| Comparison groups                       | Monotherapy (Cohort A): Placebo v Monotherapy (Cohort A): Lebrikizumab |
| Number of subjects included in analysis | 109  |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | superiority  |
| P-value                                 | = 0.4555   |
| Method                                  | Mixed models analysis  |
| Parameter estimate                      | Median difference (final values)                                       |
| Point estimate                          | 0.98111  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | -1.61  |
| upper limit                             | 3.57   |
| Variability estimate                    | Standard error of the mean   |
| Dispersion value                        | 1.31064  |

| Statistical analysis title | Statistical Analysis 2 |
|----------------------------|------------------------|
|----------------------------|------------------------|

Statistical analysis description:

Mixed Linear model comparing Lebrikizumab to Placebo, with assessment as the outcome variable; assessment time by treatment as fixed effects; and participant baseline FVC (<50%, 50 to 75%, >75%) and participant by assessment time as random effects with unstructured covariance.

|                   |   |
|-------------------|---|
| Comparison groups | Combination Therapy (Cohort B): Placebo + Pirfenidone v<br>Combination Therapy (Cohort B): Lebrikizumab + Pirfenidone |
|-------------------|---|

|   |                                |
|---|--------------------------------|
| Number of subjects included in analysis | 254                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | superiority                    |
| P-value                                 | = 0.5566                       |
| Method                                  | Mixed models analysis          |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | 0.49998                        |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -1.17                          |
| upper limit                             | 2.17                           |
| Variability estimate                    | Standard error of the mean     |
| Dispersion value                        | 0.84946                        |

### Secondary: Annualized Rate of Decline in 6-Minute Walk Test (6MWT) Distance Over 52 Weeks

|                        |  |
|------------------------|--|
| End point title        | Annualized Rate of Decline in 6-Minute Walk Test (6MWT) Distance Over 52 Weeks   |
| End point description: | Annualized rates of decline (slope throughout time from baseline to Week 52) in 6MWT was assessed and reported. 6MWT was the distance (in meters [m]) that a participant could walk in 6 minutes. Analysis was performed on ITT Population. Here 'Number of Subjects Analysed' signifies number of participants evaluable for this outcome measure at Week 52. |
| End point type         | Secondary  |
| End point timeframe:   | Baseline up to Week 52 (assessed at Baseline, Weeks 1, 4, 12, 24, 36, 44, and 52)  |

| End point values                 | Monotherapy (Cohort A): Placebo | Monotherapy (Cohort A): Lebrikizumab | Combination Therapy (Cohort B): Placebo + Pirfenidone | Combination Therapy (Cohort B): Lebrikizumab + Pirfenidone |
|----------------------------------|---------------------------------|--------------------------------------|---|--|
| Subject group type               | Reporting group                 | Reporting group                      | Reporting group                                       | Reporting group  |
| Number of subjects analysed      | 52                              | 59                                   | 120   | 129  |
| Units: m/year                    |                                 |                                      |   |  |
| arithmetic mean (standard error) | -44.6512 (± 15.97862)           | -22.7209 (± 15.34753)                | -25.5683 (± 12.24923)                                 | -46.9810 (± 11.84199)                                      |

### Statistical analyses

|                                   |   |
|-----------------------------------|---|
| Statistical analysis title        | Statistical Analysis 1  |
| Statistical analysis description: | Mixed Linear model comparing Lebrikizumab to Placebo, with assessment as the outcome variable; assessment time by treatment as fixed effects; and participant baseline FVC (<50%, 50 to 75%, >75%) and participant by assessment time as random effects with unstructured covariance. |
| Comparison groups                 | Monotherapy (Cohort A): Placebo v Monotherapy (Cohort A): Lebrikizumab  |

|   |                                  |
|---|----------------------------------|
| Number of subjects included in analysis | 111                              |
| Analysis specification                  | Pre-specified                    |
| Analysis type                           | superiority                      |
| P-value                                 | = 0.3129                         |
| Method                                  | Mixed models analysis            |
| Parameter estimate                      | Median difference (final values) |
| Point estimate                          | 21.93023                         |
| Confidence interval                     |                                  |
| level                                   | 95 %                             |
| sides                                   | 2-sided                          |
| lower limit                             | -20.97                           |
| upper limit                             | 64.83                            |
| Variability estimate                    | Standard error of the mean       |
| Dispersion value                        | 21.62248                         |

|                                   |                        |
|-----------------------------------|------------------------|
| <b>Statistical analysis title</b> | Statistical Analysis 2 |
|-----------------------------------|------------------------|

Statistical analysis description:

Mixed Linear model comparing Lebrikizumab to Placebo, with assessment as the outcome variable; assessment time by treatment as fixed effects; and participant baseline FVC (<50%, 50 to 75%, >75%) and participant by assessment time as random effects with unstructured covariance.

|   |   |
|---|---|
| Comparison groups                       | Combination Therapy (Cohort B): Placebo + Pirfenidone v<br>Combination Therapy (Cohort B): Lebrikizumab + Pirfenidone |
| Number of subjects included in analysis | 249   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | = 0.2036  |
| Method                                  | Mixed models analysis   |
| Parameter estimate                      | Mean difference (final values)  |
| Point estimate                          | -21.4127  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -54.5   |
| upper limit                             | 11.67   |
| Variability estimate                    | Standard error of the mean  |
| Dispersion value                        | 16.8016   |

## **Secondary: Percentage of Participants with Event of Greater Than or Equal to (>=) 10% Absolute Decline in Percent Predicted FVC or Death from Any Cause**

|                 |  |
|-----------------|--|
| End point title | Percentage of Participants with Event of Greater Than or Equal to (>=) 10% Absolute Decline in Percent Predicted FVC or Death from Any Cause |
|-----------------|--|

End point description:

FVC is defined as the volume of air that can forcibly be blown out after full inspiration in the upright position, measured in liters. Predicted FVC is based on sex, age, and height of a person. Percent predicted FVC (in %) = [(observed FVC)/(predicted FVC)]\*100. Analysis was performed on ITT Population. Here 'Number of Subjects Analysed' signifies number of participants evaluable for this outcome measure.

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

End point timeframe:

Baseline up to the event of  $\geq 10\%$  absolute decline in percent predicted FVC or death from any cause, whichever occurred first (up to Week 122)

| End point values                  | Monotherapy<br>(Cohort A):<br>Placebo | Monotherapy<br>(Cohort A):<br>Lebrikizumab | Combination<br>Therapy<br>(Cohort B):<br>Placebo +<br>Pirfenidone | Combination<br>Therapy<br>(Cohort B):<br>Lebrikizumab +<br>Pirfenidone |
|-----------------------------------|---------------------------------------|--|---|--|
| Subject group type                | Reporting group                       | Reporting group                            | Reporting group   | Reporting group  |
| Number of subjects analysed       | 76                                    | 76   | 175   | 173  |
| Units: percentage of participants |                                       |  |   |  |
| number (not applicable)           | 34.2                                  | 27.6                                       | 30.3  | 26.6   |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to First Occurrence of a $\geq 10\%$ Absolute Decline in Percent Predicted FVC or Death from Any Cause

|                 |   |
|-----------------|---|
| End point title | Time to First Occurrence of a $\geq 10\%$ Absolute Decline in Percent Predicted FVC or Death from Any Cause |
|-----------------|---|

End point description:

FVC is defined as the volume of air that can forcibly be blown out after full inspiration in the upright position, measured in liters. Predicted FVC is based on sex, age, and height of a person. Percent predicted FVC =  $[(\text{observed FVC})/(\text{predicted FVC})]*100$ . Time from randomization to first occurrence of an event of  $\geq 10\%$  absolute decline in percent predicted FVC or death from any cause was reported. Participants without an event were censored at the last assessment during the double-blind treatment period. Any participant who underwent lung transplantation was censored at the date of the transplant. The median time to event was estimated using Kaplan-Meier method and 95% confidence interval (CI) was computed using the method of Brookmeyer and Crowley. Analysis was performed on ITT Population. 'Number of Subjects Analysed' = participants evaluable for this outcome measure.

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

End point timeframe:

Baseline up to the event of  $\geq 10\%$  absolute decline in percent predicted FVC or death from any cause, whichever occurred first (up to Week 122)

| End point values                 | Monotherapy<br>(Cohort A):<br>Placebo | Monotherapy<br>(Cohort A):<br>Lebrikizumab | Combination<br>Therapy<br>(Cohort B):<br>Placebo +<br>Pirfenidone | Combination<br>Therapy<br>(Cohort B):<br>Lebrikizumab +<br>Pirfenidone |
|----------------------------------|---------------------------------------|--|---|--|
| Subject group type               | Reporting group                       | Reporting group                            | Reporting group   | Reporting group  |
| Number of subjects analysed      | 76 <sup>[1]</sup>                     | 76 <sup>[2]</sup>                          | 175 <sup>[3]</sup>  | 173 <sup>[4]</sup>   |
| Units: weeks                     |                                       |  |   |  |
| median (confidence interval 95%) | 53.1 (52.6 to 99999)                  | 99999 (99999 to 99999)                     | 99999 (52.9 to 99999)   | 99999 (99999 to 99999)   |

Notes:

[1] - '99999' = CI could not be estimated due to high number of censored participants.

[2] - '99999' = median and CI could not be estimated due to high number of censored participants.

[3] - '99999' = median and CI could not be estimated due to high number of censored participants.

[4] - '99999' = median and CI could not be estimated due to high number of censored participants.

## Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>                                       | Statistical Analysis 1   |
| Statistical analysis description:                                       |  |
| Stratified Analysis: stratified by baseline FVC (<50%, 50 to 75%, >75%) |  |
| Comparison groups   | Monotherapy (Cohort A): Placebo v Monotherapy (Cohort A): Lebrikizumab |
| Number of subjects included in analysis                                 | 152  |
| Analysis specification  | Pre-specified  |
| Analysis type   | superiority  |
| P-value   | = 0.4299   |
| Method  | Logrank  |
| Parameter estimate  | Hazard ratio (HR)  |
| Point estimate  | 0.79   |
| Confidence interval   |  |
| level   | 95 %   |
| sides   | 2-sided  |
| lower limit   | 0.44   |
| upper limit   | 1.41   |

|   |  |
|---|--|
| <b>Statistical analysis title</b>                                       | Statistical Analysis 2   |
| Statistical analysis description:                                       |  |
| Stratified Analysis: stratified by baseline FVC (<50%, 50 to 75%, >75%) |  |
| Comparison groups   | Combination Therapy (Cohort B): Placebo + Pirfenidone v Combination Therapy (Cohort B): Lebrikizumab + Pirfenidone |
| Number of subjects included in analysis                                 | 348  |
| Analysis specification  | Pre-specified  |
| Analysis type   | superiority  |
| P-value   | = 0.3751   |
| Method  | Logrank  |
| Parameter estimate  | Hazard ratio (HR)  |
| Point estimate  | 0.84   |
| Confidence interval   |  |
| level   | 95 %   |
| sides   | 2-sided  |
| lower limit   | 0.56   |
| upper limit   | 1.24   |

## Secondary: Annualized Rate of Decrease in Diffusion Capacity of the Lung for Carbon Monoxide (DLco) Over 52 Weeks

|                 |   |
|-----------------|---|
| End point title | Annualized Rate of Decrease in Diffusion Capacity of the Lung |
|-----------------|---|

## End point description:

Annualized rates of decrease (slope throughout time from baseline to Week 52) in DLco was assessed and reported. DLco (in milliliters per minute/millimeters of mercury [mL/min/mmHg]) is a measure of the gas transfer. Analysis was performed on ITT Population. Here 'Number of Subjects Analysed' signifies number of participants evaluable for this outcome measure at Week 52.

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

## End point timeframe:

Baseline up to Week 52 (assessed at Baseline, Weeks 1, 4, 12, 24, 36, 44, and 52)

| End point values                 | Monotherapy (Cohort A): Placebo | Monotherapy (Cohort A): Lebrikizumab | Combination Therapy (Cohort B): Placebo + Pirfenidone | Combination Therapy (Cohort B): Lebrikizumab + Pirfenidone |
|----------------------------------|---------------------------------|--------------------------------------|---|--|
| Subject group type               | Reporting group                 | Reporting group                      | Reporting group                                       | Reporting group  |
| Number of subjects analysed      | 50                              | 52                                   | 112   | 122  |
| Units: mL/min/mmHg/year          |                                 |                                      |   |  |
| arithmetic mean (standard error) | -4.7818 ( $\pm$ 0.74479)        | -4.2400 ( $\pm$ 0.73826)             | -5.7552 ( $\pm$ 0.46561)                              | -5.5732 ( $\pm$ 0.45577)                                   |

## Statistical analyses

|                            |                        |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|

## Statistical analysis description:

Mixed Linear model comparing Lebrikizumab to Placebo, with assessment as the outcome variable; assessment time by treatment as fixed effects; and participant baseline FVC (<50%, 50 to 75%, >75%) and participant by assessment time as random effects with unstructured covariance.

|   |  |
|---|--|
| Comparison groups                       | Monotherapy (Cohort A): Placebo v Monotherapy (Cohort A): Lebrikizumab |
| Number of subjects included in analysis | 102  |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | superiority  |
| P-value                                 | = 0.6075   |
| Method                                  | Mixed models analysis  |
| Parameter estimate                      | Median difference (final values)                                       |
| Point estimate                          | 0.54171  |
| Confidence interval                     |  |
| level                                   | 95 %   |
| sides                                   | 2-sided  |
| lower limit                             | -1.54  |
| upper limit                             | 2.62   |
| Variability estimate                    | Standard error of the mean   |
| Dispersion value                        | 1.05201  |

|                            |                        |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 2 |
|----------------------------|------------------------|

**Statistical analysis description:**

Mixed Linear model comparing Lebrikizumab to Placebo, with assessment as the outcome variable; assessment time by treatment as fixed effects; and participant baseline FVC (<50%, 50 to 75%, >75%) and participant by assessment time as random effects with unstructured covariance.

|   |   |
|---|---|
| Comparison groups                       | Combination Therapy (Cohort B): Placebo + Pirfenidone v<br>Combination Therapy (Cohort B): Lebrikizumab + Pirfenidone |
| Number of subjects included in analysis | 234   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | = 0.7803  |
| Method                                  | Mixed models analysis   |
| Parameter estimate                      | Mean difference (final values)  |
| Point estimate                          | 0.18203   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -1.1  |
| upper limit                             | 1.47  |
| Variability estimate                    | Standard error of the mean  |
| Dispersion value                        | 0.65206   |

**Secondary: Percentage of Participants with Event of Death, All Cause Hospitalization, or a Decrease from Baseline of  $\geq 10\%$  in FVC**

|                 |  |
|-----------------|--|
| End point title | Percentage of Participants with Event of Death, All Cause Hospitalization, or a Decrease from Baseline of $\geq 10\%$ in FVC |
|-----------------|--|

**End point description:**

FVC is defined as the volume of air that can forcibly be blown out after full inspiration in the upright position, measured in liters. Predicted FVC is based on sex, age, and height of a person. Percent predicted FVC = [(observed FVC)/(predicted FVC)]\*100. Analysis was performed on ITT Population. Here 'Number of Subjects Analysed' signifies number of participants evaluable for this outcome measure.

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

**End point timeframe:**

Baseline up to the event of death from any cause, all cause hospitalization, or a decrease from baseline of  $\geq 10\%$  in FVC, whichever occurred first (up to Week 122)

| <b>End point values</b>           | Monotherapy<br>(Cohort A):<br>Placebo | Monotherapy<br>(Cohort A):<br>Lebrikizumab | Combination<br>Therapy<br>(Cohort B):<br>Placebo +<br>Pirfenidone | Combination<br>Therapy<br>(Cohort B):<br>Lebrikizumab +<br>Pirfenidone |
|-----------------------------------|---------------------------------------|--|---|--|
| Subject group type                | Reporting group                       | Reporting group                            | Reporting group   | Reporting group  |
| Number of subjects analysed       | 76                                    | 76   | 175   | 173  |
| Units: percentage of participants |                                       |  |   |  |
| number (not applicable)           | 47.4                                  | 32.9                                       | 39.4  | 39.9   |

**Statistical analyses**

**Secondary: Progression-Free Survival (PFS)**

|   |                                 |
|---|---------------------------------|
| End point title   | Progression-Free Survival (PFS) |
| End point description:  |                                 |
| FVC is defined as the volume of air that can forcibly be blown out after full inspiration in the upright position, measured in liters. Predicted FVC is based on sex, age, and height of a person. Percent predicted FVC = [(observed FVC)/(predicted FVC)]*100. PFS was defined as time from randomization to death from any cause, all cause hospitalization, or a decrease from baseline of $\geq 10\%$ in FVC, whichever occurred first. Participants without an event were censored at the last assessment during the double-blind treatment period. Any participant who underwent lung transplantation was censored at the date of the transplant. The median PFS was estimated using Kaplan-Meier method. 95% CI for median was computed using the method of Brookmeyer and Crowley. Analysis was performed on ITT Population. Here 'Number of Subjects Analysed' signifies number of participants evaluable for this outcome measure. |                                 |
| End point type  | Secondary                       |
| End point timeframe:  |                                 |
| Baseline up to the event of death from any cause, all cause hospitalization, or a decrease from baseline of $\geq 10\%$ in FVC, whichever occurred first (up to Week 122)   |                                 |

| End point values                 | Monotherapy (Cohort A): Placebo | Monotherapy (Cohort A): Lebrikizumab | Combination Therapy (Cohort B): Placebo + Pirfenidone | Combination Therapy (Cohort B): Lebrikizumab + Pirfenidone |
|----------------------------------|---------------------------------|--------------------------------------|---|--|
| Subject group type               | Reporting group                 | Reporting group                      | Reporting group                                       | Reporting group  |
| Number of subjects analysed      | 76 <sup>[5]</sup>               | 76 <sup>[6]</sup>                    | 175 <sup>[7]</sup>                                    | 173 <sup>[8]</sup>   |
| Units: weeks                     |                                 |                                      |   |  |
| median (confidence interval 95%) | 52.6 (43.9 to 99999)            | 99999 (99999 to 99999)               | 99999 (99999 to 99999)                                | 99999 (52.3 to 99999)                                      |

Notes:

[5] - '99999' = CI could not be estimated due to high number of censored participants.

[6] - '99999' = median and CI could not be estimated due to high number of censored participants.

[7] - '99999' = median and CI could not be estimated due to high number of censored participants.

[8] - '99999' = median and CI could not be estimated due to high number of censored participants.

**Statistical analyses**

|   |  |
|---|--|
| Statistical analysis title  | Statistical Analysis 1   |
| Statistical analysis description:                                       |  |
| Stratified Analysis: stratified by baseline FVC (<50%, 50 to 75%, >75%) |  |
| Comparison groups   | Monotherapy (Cohort A): Placebo v Monotherapy (Cohort A): Lebrikizumab |
| Number of subjects included in analysis                                 | 152  |
| Analysis specification  | Pre-specified  |
| Analysis type   | superiority  |
| P-value   | = 0.0972   |
| Method  | Logrank  |
| Parameter estimate  | Hazard ratio (HR)  |
| Point estimate  | 0.65   |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 0.39    |
| upper limit         | 1.09    |

|   |   |
|---|---|
| <b>Statistical analysis title</b>                                       | Statistical Analysis 2  |
| Statistical analysis description:                                       |   |
| Stratified Analysis: stratified by baseline FVC (<50%, 50 to 75%, >75%) |   |
| Comparison groups   | Combination Therapy (Cohort B): Placebo + Pirfenidone v<br>Combination Therapy (Cohort B): Lebrikizumab + Pirfenidone |
| Number of subjects included in analysis                                 | 348   |
| Analysis specification  | Pre-specified   |
| Analysis type   | superiority   |
| P-value   | = 0.9344  |
| Method  | Logrank   |
| Parameter estimate  | Hazard ratio (HR)   |
| Point estimate  | 1.01  |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided   |
| lower limit   | 0.72  |
| upper limit   | 1.42  |

### Secondary: Annualized Rate of Decrease in FVC Over 52 Weeks

|   |  |
|---|--|
| End point title   | Annualized Rate of Decrease in FVC Over 52 Weeks |
| End point description:  |  |
| Annualized rates of decrease (slope throughout time from baseline to Week 52) in FVC (in milliliters per year [mL/year]) was assessed and reported. FVC is defined as the volume of air that can forcibly be blown out after full inspiration in the upright position. Analysis was performed on ITT Population. Here 'Number of Subjects Analysed' signifies number of participants evaluable for this outcome measure at Week 52. |  |
| End point type  | Secondary  |
| End point timeframe:  |  |
| Baseline up to Week 52 (assessed at Baseline, Weeks 1, 4, 12, 24, 36, 44, and 52)   |  |

| End point values                 | Monotherapy (Cohort A): Placebo | Monotherapy (Cohort A): Lebrikizumab | Combination Therapy (Cohort B): Placebo + Pirfenidone | Combination Therapy (Cohort B): Lebrikizumab + Pirfenidone |
|----------------------------------|---------------------------------|--------------------------------------|---|--|
| Subject group type               | Reporting group                 | Reporting group                      | Reporting group                                       | Reporting group  |
| Number of subjects analysed      | 53                              | 57                                   | 120   | 134  |
| Units: mL/year                   |                                 |                                      |   |  |
| arithmetic mean (standard error) | -221.029 (± 34.87511)           | -192.906 (± 34.93853)                | -231.167 (± 22.67786)                                 | -209.437 (± 22.25073)                                      |

## Statistical analyses

|  |  |
|--|--|
| <b>Statistical analysis title</b>  | Statistical Analysis 1   |
| Statistical analysis description:<br>Mixed Linear model comparing Lebrikizumab to Placebo, with assessment as the outcome variable; assessment time by treatment as fixed effects; and participant baseline FVC (<50%, 50 to 75%, >75%) and participant by assessment time as random effects with unstructured covariance. |  |
| Comparison groups  | Monotherapy (Cohort A): Placebo v Monotherapy (Cohort A): Lebrikizumab |
| Number of subjects included in analysis  | 110  |
| Analysis specification   | Pre-specified  |
| Analysis type  | superiority  |
| P-value  | = 0.5707   |
| Method   | Mixed models analysis  |
| Parameter estimate   | Median difference (final values)                                       |
| Point estimate   | 28.12302   |
| Confidence interval  |  |
| level  | 95 %   |
| sides  | 2-sided  |
| lower limit  | -69.8  |
| upper limit  | 126.04   |
| Variability estimate   | Standard error of the mean   |
| Dispersion value   | 49.47253   |

|  |  |
|--|--|
| <b>Statistical analysis title</b>  | Statistical Analysis 2   |
| Statistical analysis description:<br>Mixed Linear model comparing Lebrikizumab to Placebo, with assessment as the outcome variable; assessment time by treatment as fixed effects; and participant baseline FVC (<50%, 50 to 75%, >75%) and participant by assessment time as random effects with unstructured covariance. |  |
| Comparison groups  | Combination Therapy (Cohort B): Placebo + Pirfenidone v Combination Therapy (Cohort B): Lebrikizumab + Pirfenidone |
| Number of subjects included in analysis  | 254  |
| Analysis specification   | Pre-specified  |
| Analysis type  | superiority  |
| P-value  | = 0.4934   |
| Method   | Mixed models analysis  |
| Parameter estimate   | Mean difference (final values)   |
| Point estimate   | 21.72972   |
| Confidence interval  |  |
| level  | 95 %   |
| sides  | 2-sided  |
| lower limit  | -40.65   |
| upper limit  | 84.11  |

|                      |                            |
|----------------------|----------------------------|
| Variability estimate | Standard error of the mean |
| Dispersion value     | 31.68767                   |

## Secondary: Annualized Rate of Decrease in A Tool to Assess Quality of Life in IPF (ATAQ-IPF) Questionnaire Total Score Over 52 Weeks

|                 |   |
|-----------------|---|
| End point title | Annualized Rate of Decrease in A Tool to Assess Quality of Life in IPF (ATAQ-IPF) Questionnaire Total Score Over 52 Weeks |
|-----------------|---|

### End point description:

The ATAQ-IPF Version 3 was utilized that included 31 items within 5 domains: cough (6 items), dyspnea (7 items), exhaustion (6 items), emotional well-being (6 items), and independence (6 items). Each item was assessed on a scale ranging from 1 (Strongly disagree) to 4 (Strongly agree). The ATAQ-IPF had a recall specification of 2 weeks. Simple summation scoring was used to derive individual domain scores as well as a total score. ATAQ-IPF total score ranged from 31 to 124 with lower score indicating better quality of life (QoL). Annualized rates of decrease (slope throughout time from baseline to Week 52) in ATAQ-IPF questionnaire total score was assessed and reported. Analysis was performed on ITT Population. Here 'Number of Subjects Analysed' signifies number of participants evaluable for this outcome measure at Week 52.

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

### End point timeframe:

Baseline up to Week 52 (assessed at Baseline, Weeks 1, 4, 12, 24, 36, 44, and 52)

| End point values                 | Monotherapy (Cohort A): Placebo | Monotherapy (Cohort A): Lebrikizumab | Combination Therapy (Cohort B): Placebo + Pirfenidone | Combination Therapy (Cohort B): Lebrikizumab + Pirfenidone |
|----------------------------------|---------------------------------|--------------------------------------|---|--|
| Subject group type               | Reporting group                 | Reporting group                      | Reporting group                                       | Reporting group  |
| Number of subjects analysed      | 58                              | 62                                   | 136   | 144  |
| Units: units on a scale/year     |                                 |                                      |   |  |
| arithmetic mean (standard error) | 6.8907 ( $\pm$ 1.71778)         | 4.7886 ( $\pm$ 1.70370)              | 5.6189 ( $\pm$ 0.99880)                               | 5.4558 ( $\pm$ 0.97793)                                    |

## Statistical analyses

|                            |                        |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|

### Statistical analysis description:

Mixed Linear model comparing Lebrikizumab to Placebo, with assessment as the outcome variable; assessment time by treatment as fixed effects; and participant baseline FVC (<50%, 50 to 75%, >75%) and participant by assessment time as random effects with unstructured covariance.

|   |  |
|---|--|
| Comparison groups                       | Monotherapy (Cohort A): Placebo v Monotherapy (Cohort A): Lebrikizumab |
| Number of subjects included in analysis | 120  |
| Analysis specification                  | Pre-specified  |
| Analysis type                           | superiority  |
| P-value                                 | = 0.3854   |
| Method                                  | Mixed models analysis  |
| Parameter estimate                      | Median difference (final values)                                       |
| Point estimate                          | -2.10204   |

|                      |                            |
|----------------------|----------------------------|
| Confidence interval  |                            |
| level                | 95 %                       |
| sides                | 2-sided                    |
| lower limit          | -6.88                      |
| upper limit          | 2.68                       |
| Variability estimate | Standard error of the mean |
| Dispersion value     | 2.41325                    |

|                                   |                        |
|-----------------------------------|------------------------|
| <b>Statistical analysis title</b> | Statistical Analysis 2 |
|-----------------------------------|------------------------|

Statistical analysis description:

Mixed Linear model comparing Lebrikizumab to Placebo, with assessment as the outcome variable; assessment time by treatment as fixed effects; and participant baseline FVC (<50%, 50 to 75%, >75%) and participant by assessment time as random effects with unstructured covariance.

|   |   |
|---|---|
| Comparison groups                       | Combination Therapy (Cohort B): Placebo + Pirfenidone v<br>Combination Therapy (Cohort B): Lebrikizumab + Pirfenidone |
| Number of subjects included in analysis | 280   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | = 0.9057  |
| Method                                  | Mixed models analysis   |
| Parameter estimate                      | Mean difference (final values)  |
| Point estimate                          | -0.16313  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | -2.87   |
| upper limit                             | 2.55  |
| Variability estimate                    | Standard error of the mean  |
| Dispersion value                        | 1.37698   |

### **Secondary: Percentage of Participants with an Event of St. George's Respiratory Questionnaire (SGRQ) Total Score Worsening or Death from Any Cause**

|                 |  |
|-----------------|--|
| End point title | Percentage of Participants with an Event of St. George's Respiratory Questionnaire (SGRQ) Total Score Worsening or Death from Any Cause <sup>[9]</sup> |
|-----------------|--|

End point description:

The SGRQ is a 50-item health-related QoL instrument that measured health impairment. The questionnaire contains 3 domains: symptoms, activity, and impacts. Items were assessed on various response scales, including a 5-point Likert scale and True/False scale. The SGRQ had a recall specification of 4 weeks. The SGRQ total score (summed weights) ranged from 0 to 100 with a lower score denoting a better health status. Percentage of participants with an event of SGRQ total score worsening (defined as reaching minimal important difference [MID], that is, an increase in total score of  $\geq 7$ ) or death from any cause was reported. Analysis was performed on ITT Population for monotherapy cohort only. Here, 'Number of Subjects Analysed' signifies number of participants evaluable for this outcome measure.

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

End point timeframe:

Baseline up to the event of SGRQ total score worsening or death from any cause, whichever occurred first (up to Week 122)

Notes:

[9] - 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: Reported analysis was planned to be carried out in the indicated arms only.

| End point values                  | Monotherapy<br>(Cohort A):<br>Placebo | Monotherapy<br>(Cohort A):<br>Lebrikizumab |  |  |
|-----------------------------------|---------------------------------------|--|--|--|
| Subject group type                | Reporting group                       | Reporting group                            |  |  |
| Number of subjects analysed       | 76                                    | 76   |  |  |
| Units: percentage of participants |                                       |  |  |  |
| number (not applicable)           | 57.9                                  | 48.7                                       |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to First Occurrence of SGRQ Total Score Worsening or Death from Any Cause

|                 |  |
|-----------------|--|
| End point title | Time to First Occurrence of SGRQ Total Score Worsening or Death from Any Cause <sup>[10]</sup> |
|-----------------|--|

End point description:

The SGRQ is a 50-item health-related QoL instrument that measured health impairment. The questionnaire contains 3 domains: symptoms, activity, and impacts. Items were assessed on various response scales, including a 5-point Likert scale and True/False scale. The SGRQ had a recall specification of 4 weeks. The SGRQ total score (summed weights) ranged from 0 to 100 with a lower score denoting a better health status. Time from randomization to first occurrence of an event of SGRQ total score worsening (defined as reaching minimal important difference [MID], that is, an increase in total score of  $\geq 7$ ) or death from any cause was reported. The median time to event was estimated using Kaplan-Meier method. 95% CI for median was computed using the method of Brookmeyer and Crowley. ITT Population for monotherapy cohort only; 'Number of Subjects Analysed' = number of participants evaluable for this outcome measure.

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

End point timeframe:

Baseline up to the event of SGRQ total score worsening or death from any cause, whichever occurred first (up to Week 122)

Notes:

[10] - 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: Reported analysis was planned to be carried out in the indicated arms only.

| End point values                 | Monotherapy<br>(Cohort A):<br>Placebo | Monotherapy<br>(Cohort A):<br>Lebrikizumab |  |  |
|----------------------------------|---------------------------------------|--|--|--|
| Subject group type               | Reporting group                       | Reporting group                            |  |  |
| Number of subjects analysed      | 76                                    | 76 <sup>[11]</sup>                         |  |  |
| Units: weeks                     |                                       |  |  |  |
| median (confidence interval 95%) | 51.7 (24.1 to 54.6)                   | 52.3 (35.7 to 99999)                       |  |  |

Notes:

[11] - '99999' = upper limit of CI could not be estimated due to high number of censored participants.

## Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>                                       | Statistical Analysis 1   |
| Statistical analysis description:                                       |  |
| Stratified Analysis: stratified by baseline FVC (<50%, 50 to 75%, >75%) |  |
| Comparison groups   | Monotherapy (Cohort A): Placebo v Monotherapy (Cohort A): Lebrikizumab |
| Number of subjects included in analysis                                 | 152  |
| Analysis specification  | Pre-specified  |
| Analysis type   | superiority  |
| P-value   | = 0.4433   |
| Method  | Logrank  |
| Parameter estimate  | Hazard ratio (HR)  |
| Point estimate  | 0.84   |
| Confidence interval   |  |
| level   | 95 %   |
| sides   | 2-sided  |
| lower limit   | 0.54   |
| upper limit   | 1.31   |

## Secondary: Percentage of Participants with an Event of Acute Idiopathic Pulmonary Fibrosis (IPF) Exacerbation

|   |  |
|---|--|
| End point title   | Percentage of Participants with an Event of Acute Idiopathic Pulmonary Fibrosis (IPF) Exacerbation |
| End point description:  |  |
| <p>IPF exacerbation was defined as an event that met all of the following criteria as determined by the investigator: Unexplained worsening or development of dyspnea within the previous 30 days; And radiologic evidence of new bilateral ground-glass abnormality or consolidation, superimposed on a reticular or honeycomb background pattern, that is consistent with usual interstitial pneumonitis; And absence of alternative causes, such as left heart failure, pulmonary embolism, pulmonary infection (on the basis of endotracheal aspirate or bronchoalveolar lavage if available, or investigator judgment), or other events leading to acute lung injury (for example, sepsis, aspiration, trauma, reperfusion pulmonary edema). Analysis was performed on ITT Population. Here 'Number of Subjects Analysed' signifies number of participants evaluable for this outcome measure.</p> |  |
| End point type  | Secondary  |
| End point timeframe:  |  |
| Baseline up to the event of acute IPF exacerbation (up to Week 122)   |  |

| <b>End point values</b>           | Monotherapy (Cohort A): Placebo | Monotherapy (Cohort A): Lebrikizumab | Combination Therapy (Cohort B): Placebo + Pirfenidone | Combination Therapy (Cohort B): Lebrikizumab + Pirfenidone |
|-----------------------------------|---------------------------------|--------------------------------------|---|--|
| Subject group type                | Reporting group                 | Reporting group                      | Reporting group                                       | Reporting group  |
| Number of subjects analysed       | 76                              | 76                                   | 175   | 172  |
| Units: percentage of participants |                                 |                                      |   |  |
| number (not applicable)           | 3.9                             | 3.9                                  | 6.3   | 2.9  |

## Statistical analyses

**Secondary: Time to First Event of Acute IPF Exacerbation**

|   |   |
|---|---|
| End point title   | Time to First Event of Acute IPF Exacerbation |
| End point description:  |   |
| Time from randomization to first occurrence of an event of IPF exacerbation was reported. IPF exacerbation was defined as an event that met all of the following criteria as determined by the investigator: Unexplained worsening or development of dyspnea within the previous 30 days; And radiologic evidence of new bilateral ground-glass abnormality or consolidation, superimposed on a reticular or honeycomb background pattern, that is consistent with usual interstitial pneumonitis; And absence of alternative causes, or other events leading to acute lung injury. The median time to event was estimated using Kaplan-Meier method. 95% CI for median was computed using the method of Brookmeyer and Crowley. Analysis was performed on ITT Population. Here 'Number of Subjects Analysed' signifies number of participants evaluable for this outcome measure. The data '99999' in the results signifies that median and corresponding CI could not be estimated due to high number of censored participants. |   |
| End point type  | Secondary                                     |
| End point timeframe:  |   |
| Baseline up to the event of acute IPF exacerbation (up to Week 122)   |   |

| End point values                 | Monotherapy (Cohort A): Placebo | Monotherapy (Cohort A): Lebrikizumab | Combination Therapy (Cohort B): Placebo + Pirfenidone | Combination Therapy (Cohort B): Lebrikizumab + Pirfenidone |
|----------------------------------|---------------------------------|--------------------------------------|---|--|
| Subject group type               | Reporting group                 | Reporting group                      | Reporting group                                       | Reporting group  |
| Number of subjects analysed      | 76                              | 76                                   | 175   | 172  |
| Units: weeks                     |                                 |                                      |   |  |
| median (confidence interval 95%) | 99999 (99999 to 99999)          | 99999 (99999 to 99999)               | 99999 (99999 to 99999)                                | 99999 (99999 to 99999)                                     |

**Statistical analyses**

|   |  |
|---|--|
| Statistical analysis title  | Statistical Analysis 1   |
| Statistical analysis description:                                       |  |
| Stratified Analysis: stratified by baseline FVC (<50%, 50 to 75%, >75%) |  |
| Comparison groups   | Monotherapy (Cohort A): Placebo v Monotherapy (Cohort A): Lebrikizumab |
| Number of subjects included in analysis                                 | 152  |
| Analysis specification  | Pre-specified  |
| Analysis type   | superiority  |
| P-value   | = 0.9366   |
| Method  | Logrank  |
| Parameter estimate  | Hazard ratio (HR)  |
| Point estimate  | 1.07   |
| Confidence interval   |  |
| level   | 95 %   |
| sides   | 2-sided  |
| lower limit   | 0.21   |
| upper limit   | 5.3  |

|   |   |
|---|---|
| <b>Statistical analysis title</b>                                       | Statistical Analysis 2  |
| Statistical analysis description:                                       |   |
| Stratified Analysis: stratified by baseline FVC (<50%, 50 to 75%, >75%) |   |
| Comparison groups   | Combination Therapy (Cohort B): Placebo + Pirfenidone v<br>Combination Therapy (Cohort B): Lebrikizumab + Pirfenidone |
| Number of subjects included in analysis                                 | 347   |
| Analysis specification  | Pre-specified   |
| Analysis type   | superiority   |
| P-value   | = 0.1346  |
| Method  | Logrank   |
| Parameter estimate  | Hazard ratio (HR)   |
| Point estimate  | 0.45  |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided   |
| lower limit   | 0.16  |
| upper limit   | 1.31  |

## Secondary: Percentage of Participants with Respiratory-Related Hospitalization

|   |   |
|---|---|
| End point title   | Percentage of Participants with Respiratory-Related Hospitalization <sup>[12]</sup> |
| End point description:  |   |
| Analysis was performed on ITT Population for combination therapy cohorts only. Here, 'Number of Subjects Analysed' signifies number of participants evaluable for this outcome measure. |   |
| End point type  | Secondary   |

End point timeframe:

Baseline up to the event of respiratory-related hospitalization (up to Week 122)

Notes:

[12] - 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: Reported analysis was planned to be carried out in the indicated arms only.

| <b>End point values</b>           | Combination Therapy (Cohort B): Placebo + Pirfenidone | Combination Therapy (Cohort B): Lebrikizumab + Pirfenidone |  |  |
|-----------------------------------|---|--|--|--|
| Subject group type                | Reporting group                                       | Reporting group  |  |  |
| Number of subjects analysed       | 175   | 173  |  |  |
| Units: percentage of participants |   |  |  |  |
| number (not applicable)           | 15.4  | 14.5   |  |  |

## Statistical analyses

**Secondary: Time to Respiratory-Related Hospitalization**

|                 |   |
|-----------------|---|
| End point title | Time to Respiratory-Related Hospitalization <sup>[13]</sup> |
|-----------------|---|

End point description:

Time from randomization to first occurrence of an event of respiratory-related hospitalization was reported. Participants without an event were censored at the last known alive day, study Day 368, or the last date during the double-blind period. The median time to event was estimated using Kaplan-Meier method. 95% CI for median was computed using the method of Brookmeyer and Crowley. Analysis was performed on ITT Population for combination therapy cohorts only. Here 'Number of Subjects Analysed' signifies number of participants evaluable for this outcome measure. The data '99999' in the results signifies that median and corresponding CI could not be estimated due to high number of censored participants.

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

End point timeframe:

Baseline up to the event of respiratory-related hospitalization (up to Week 122)

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: Reported analysis was planned to be carried out in the indicated arms only.

| End point values                 | Combination Therapy (Cohort B): Placebo + Pirfenidone | Combination Therapy (Cohort B): Lebrikizumab + Pirfenidone |  |  |
|----------------------------------|---|--|--|--|
| Subject group type               | Reporting group                                       | Reporting group  |  |  |
| Number of subjects analysed      | 175   | 173  |  |  |
| Units: weeks                     |   |  |  |  |
| median (confidence interval 95%) | 99999 (99999 to 99999)                                | 99999 (99999 to 99999)                                     |  |  |

**Statistical analyses**

|                            |                        |
|----------------------------|------------------------|
| Statistical analysis title | Statistical Analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

Stratified Analysis: stratified by baseline FVC (&lt;50%, 50 to 75%, &gt;75%)

|   |   |
|---|---|
| Comparison groups                       | Combination Therapy (Cohort B): Placebo + Pirfenidone v<br>Combination Therapy (Cohort B): Lebrikizumab + Pirfenidone |
| Number of subjects included in analysis | 348   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | = 0.6815  |
| Method                                  | Logrank   |
| Parameter estimate                      | Hazard ratio (HR)   |
| Point estimate                          | 0.89  |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided   |
| lower limit                             | 0.52  |
| upper limit                             | 1.54  |

---

**Secondary: Percentage of Participants with an Event of  $\geq 15\%$  Absolute Decrease in Percentage of Predicted DLco or Death from Any Cause**

---

|                 |   |
|-----------------|---|
| End point title | Percentage of Participants with an Event of $\geq 15\%$ Absolute Decrease in Percentage of Predicted DLco or Death from Any Cause |
|-----------------|---|

End point description:

DLco (in mL/min/mmHg) is a measure of the gas transfer. Predicted DLco is based on sex, age, and height of a person. Percent of predicted DLco (in %) = [(observed DLco)/(predicted DLco)]\*100. Analysis was performed on ITT Population. Here 'Number of Subjects Analysed' signifies number of participants evaluable for this outcome measure.

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

End point timeframe:

Baseline up to the event of  $\geq 15\%$  absolute decrease in percentage of predicted DLco or death from any cause (up to Week 122)

---

| End point values                  | Monotherapy (Cohort A): Placebo | Monotherapy (Cohort A): Lebrikizumab | Combination Therapy (Cohort B): Placebo + Pirfenidone | Combination Therapy (Cohort B): Lebrikizumab + Pirfenidone |
|-----------------------------------|---------------------------------|--------------------------------------|---|--|
| Subject group type                | Reporting group                 | Reporting group                      | Reporting group                                       | Reporting group  |
| Number of subjects analysed       | 76                              | 76                                   | 175   | 173  |
| Units: percentage of participants |                                 |                                      |   |  |
| number (not applicable)           | 9.2                             | 6.6                                  | 14.9  | 11.0   |

---

**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: Time to First Event of  $\geq 15\%$  Absolute Decrease in Percentage of Predicted DLco or Death from Any Cause**

---

|                 |  |
|-----------------|--|
| End point title | Time to First Event of $\geq 15\%$ Absolute Decrease in Percentage of Predicted DLco or Death from Any Cause |
|-----------------|--|

End point description:

DLco is a measure of the gas transfer. Predicted DLco is based on sex, age, and height of a person. Percent of predicted DLco (in %) = [(observed DLco)/(predicted DLco)]\*100. Time from randomization to first occurrence of  $\geq 15\%$  absolute decrease in percentage of predicted DLco or death from any cause was reported. The median time to event was estimated using Kaplan-Meier method. 95% CI for median was computed using the method of Brookmeyer and Crowley. Analysis was performed on ITT Population. Here 'Number of Subjects Analysed' signifies number of participants evaluable for this outcome measure. The data '99999' in the results signifies that median and corresponding CI could not be estimated due to high number of censored participants.

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

End point timeframe:

Baseline up to the event of  $\geq 15\%$  absolute decrease in percentage of predicted DLco or death from any cause (up to Week 122)

---

| <b>End point values</b>          | Monotherapy<br>(Cohort A):<br>Placebo | Monotherapy<br>(Cohort A):<br>Lebrikizumab | Combination<br>Therapy<br>(Cohort B):<br>Placebo +<br>Pirfenidone | Combination<br>Therapy<br>(Cohort B):<br>Lebrikizumab +<br>Pirfenidone |
|----------------------------------|---------------------------------------|--|---|--|
| Subject group type               | Reporting group                       | Reporting group                            | Reporting group   | Reporting group  |
| Number of subjects analysed      | 76                                    | 76   | 175   | 173  |
| Units: weeks                     |                                       |  |   |  |
| median (confidence interval 95%) | 99999 (99999<br>to 99999)             | 99999 (99999<br>to 99999)                  | 99999 (99999<br>to 99999)   | 99999 (99999<br>to 99999)  |

## Statistical analyses

| <b>Statistical analysis title</b>                                       | Statistical Analysis 1   |
|---|--|
| Statistical analysis description:                                       |  |
| Stratified Analysis: stratified by baseline FVC (<50%, 50 to 75%, >75%) |  |
| Comparison groups   | Monotherapy (Cohort A): Placebo v Monotherapy (Cohort A): Lebrikizumab |
| Number of subjects included in analysis                                 | 152  |
| Analysis specification  | Pre-specified  |
| Analysis type   | superiority  |
| P-value   | = 0.5685   |
| Method  | Logrank  |
| Parameter estimate  | Hazard ratio (HR)  |
| Point estimate  | 0.72   |
| Confidence interval   |  |
| level   | 95 %   |
| sides   | 2-sided  |
| lower limit   | 0.23   |
| upper limit   | 2.26   |

| <b>Statistical analysis title</b>                                       | Statistical Analysis 2   |
|---|--|
| Statistical analysis description:                                       |  |
| Stratified Analysis: stratified by baseline FVC (<50%, 50 to 75%, >75%) |  |
| Comparison groups   | Combination Therapy (Cohort B): Placebo + Pirfenidone v Combination Therapy (Cohort B): Lebrikizumab + Pirfenidone |
| Number of subjects included in analysis                                 | 348  |
| Analysis specification  | Pre-specified  |
| Analysis type   | superiority  |
| P-value   | = 0.1976   |
| Method  | Logrank  |
| Parameter estimate  | Hazard ratio (HR)  |
| Point estimate  | 0.68   |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 0.37    |
| upper limit         | 1.23    |

## Secondary: Percentage of Participants with Anti-therapeutic Antibody (ATA) to Lebrikizumab

|                 |   |
|-----------------|---|
| End point title | Percentage of Participants with Anti-therapeutic Antibody (ATA) to Lebrikizumab <sup>[14]</sup> |
|-----------------|---|

End point description:

ATA to lebrikizumab was tested using a validated immunoassay. A positive ATA result was defined as one in which the presence of detectable ATAs could be confirmed by competitive binding with lebrikizumab. Percentage of participants with positive results for ATA at Baseline and at Post-baseline time points were reported. Only participants who received lebrikizumab were included in the analysis. Analysis was performed on Safety Population, which included all participants who received at least one dose of study drug and grouped according to the actual treatment received. Here, 'Number of Subjects Analysed' = participants evaluable for this outcome measure; 'n' = number of participants evaluable at indicated time points.

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

End point timeframe:

Baseline and Post-Baseline (assessed at multiple time points: Weeks 4, 12, 24, 36, 52, 56, 64, 76, and at safety follow-up up to Week 122)

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: Reported analysis was planned to be carried out in the indicated arms only.

| End point values                  | Monotherapy<br>(Cohort A):<br>Lebrikizumab | Combination<br>Therapy<br>(Cohort B):<br>Lebrikizumab +<br>Pirfenidone |  |  |
|-----------------------------------|--|--|--|--|
| Subject group type                | Reporting group                            | Reporting group  |  |  |
| Number of subjects analysed       | 75   | 172  |  |  |
| Units: percentage of participants |  |  |  |  |
| number (not applicable)           |  |  |  |  |
| Baseline (n=75,171)               | 5.3  | 1.8  |  |  |
| Post-Baseline (n=75,172)          | 6.7  | 5.2  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Minimum Observed Serum Concentration (Cmin) of Lebrikizumab at Week 52

|                 |  |
|-----------------|--|
| End point title | Minimum Observed Serum Concentration (Cmin) of Lebrikizumab at Week 52 <sup>[15]</sup> |
|-----------------|--|

End point description:

Participants who received lebrikizumab were only included in the analysis. Analysis was performed on Pharmacokinetic (PK)-Evaluable Population, which included all participants who received at least one

dose of study drug and had at least one non-missing PK observation. Here 'Number of Subjects Analysed' signifies number of participants evaluable for this outcome measure at Week 52.

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

End point timeframe:

Predose (Hour 0) at Week 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: Reported analysis was planned to be carried out in the indicated arms only.

| End point values                          | Monotherapy (Cohort A): Lebrikizumab | Combination Therapy (Cohort B): Lebrikizumab + Pirfenidone |  |  |
|---|--------------------------------------|--|--|--|
| Subject group type                        | Reporting group                      | Reporting group  |  |  |
| Number of subjects analysed               | 62                                   | 137  |  |  |
| Units: micrograms per milliliter (mcg/mL) |                                      |  |  |  |
| arithmetic mean (standard deviation)      | 29.6 (± 14.0)                        | 25.2 (± 12.7)  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Minimum Observed Serum Concentration (Cmin) of Lebrikizumab

|                 |   |
|-----------------|---|
| End point title | Minimum Observed Serum Concentration (Cmin) of Lebrikizumab <sup>[16]</sup> |
|-----------------|---|

End point description:

Participants who received lebrikizumab were only included in the analysis. Analysis was performed on PK-Evaluable Population. Here, 'Number of Subjects Analysed' signifies number of participants evaluable for this outcome measure and 'n' signifies number of participants evaluable at specified time points for different arms, respectively

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

End point timeframe:

Predose (Hour 0) at Weeks 4, 12, 24, and 36

Notes:

[16] - 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: Reported analysis was planned to be carried out in the indicated arms only.

| End point values                     | Monotherapy (Cohort A): Lebrikizumab | Combination Therapy (Cohort B): Lebrikizumab + Pirfenidone |  |  |
|--------------------------------------|--------------------------------------|--|--|--|
| Subject group type                   | Reporting group                      | Reporting group  |  |  |
| Number of subjects analysed          | 78                                   | 174  |  |  |
| Units: mcg/mL                        |                                      |  |  |  |
| arithmetic mean (standard deviation) |                                      |  |  |  |
| Cmin at Week 4 (n=74,170)            | 14.0 (± 4.86)                        | 14.9 (± 5.75)  |  |  |
| Cmin at Week 12 (n=68,165)           | 24.4 (± 9.86)                        | 25.0 (± 11.0)  |  |  |

|                            |               |               |  |  |
|----------------------------|---------------|---------------|--|--|
| Cmin at Week 24 (n=65,153) | 28.5 (± 12.5) | 25.7 (± 12.4) |  |  |
| Cmin at Week 36 (n=61,146) | 29.9 (± 14.1) | 25.6 (± 13.8) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Elimination Half-Life (t1/2) of Lebrikizumab

|                 |  |
|-----------------|--|
| End point title | Elimination Half-Life (t1/2) of Lebrikizumab <sup>[17]</sup> |
|-----------------|--|

End point description:

Elimination half-life is the time measured for the plasma drug concentration to decrease by one-half during the elimination phase of the drug. Analysis was performed on PK-Evaluable Population. Participants who received lebrikizumab were only included in the analysis. Analysis was performed on PK-Evaluable Population. Here, 'Number of Subjects Analysed' signifies number of participants evaluable for this outcome measure.

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

End point timeframe:

Pre-dose (Hour 0) at Weeks 1, 4, 12, 24, 36, 64, 76, 88, 104; and at 4, 12, and 18 weeks post-last dose (last dose = Week 104)

Notes:

[17] - 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: Reported analysis was planned to be carried out in the indicated arms only.

| End point values                     | Monotherapy<br>(Cohort A):<br>Lebrikizumab | Combination<br>Therapy<br>(Cohort B):<br>Lebrikizumab +<br>Pirfenidone |  |  |
|--------------------------------------|--|--|--|--|
| Subject group type                   | Reporting group                            | Reporting group  |  |  |
| Number of subjects analysed          | 35   | 125  |  |  |
| Units: days                          |  |  |  |  |
| arithmetic mean (standard deviation) | 23.5 (± 5.36)                              | 21.9 (± 4.79)  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Baseline up to Week 122

Adverse event reporting additional description:

Safety Population

|                 |                |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 20.1 |
|--------------------|------|

### Reporting groups

|                       |                                 |
|-----------------------|---------------------------------|
| Reporting group title | Monotherapy (Cohort A): Placebo |
|-----------------------|---------------------------------|

Reporting group description:

Participants received monotherapy with placebo matched to lebrikizumab administered via SC injection once every 4 weeks up to 52 weeks during the placebo-controlled treatment period. Participants were allowed to receive treatment with lebrikizumab at a dose of 250 mg administered via SC injection once every 4 weeks up to additional 52 weeks (that is, up to Week 104) in the open-label period.

|                       |                                      |
|-----------------------|--------------------------------------|
| Reporting group title | Monotherapy (Cohort A): Lebrikizumab |
|-----------------------|--------------------------------------|

Reporting group description:

Participants received monotherapy with lebrikizumab at a dose of 250 mg administered via SC injection once every 4 weeks up to 52 weeks during the placebo-controlled treatment period. Participants were allowed to receive treatment with lebrikizumab at a dose of 250 mg administered via SC injection once every 4 weeks up to additional 52 weeks (that is, up to Week 104) in the open-label period.

|                       |   |
|-----------------------|---|
| Reporting group title | Combination Therapy (Cohort B): Placebo + Pirfenidone |
|-----------------------|---|

Reporting group description:

Participants received pirfenidone at a stable dose of 2403 mg per day (three 267 mg capsules three times a day [9 capsules daily] for a total of 2403 mg/day) or at MTD administered orally along with placebo matched to lebrikizumab administered via SC injection once every 4 weeks up to 52 weeks during the placebo-controlled treatment period.

|                       |  |
|-----------------------|--|
| Reporting group title | Combination Therapy (Cohort B): Lebrikizumab + Pirfenidone |
|-----------------------|--|

Reporting group description:

Participants received pirfenidone at a stable dose of 2403 mg per day (three 267 mg capsules three times a day [9 capsules daily] for a total of 2403 mg/day) or at MTD administered orally along with lebrikizumab at a dose of 250 mg administered via SC injection once every 4 weeks up to 52 weeks during the placebo-controlled treatment period.

| Serious adverse events   | Monotherapy<br>(Cohort A): Placebo | Monotherapy<br>(Cohort A):<br>Lebrikizumab | Combination<br>Therapy (Cohort B):<br>Placebo +<br>Pirfenidone |
|--|------------------------------------|--|--|
| Total subjects affected by serious<br>adverse events                   |                                    |  |  |
| subjects affected / exposed  | 19 / 76 (25.00%)                   | 23 / 78 (29.49%)                           | 47 / 177 (26.55%)  |
| number of deaths (all causes)  | 4                                  | 4  | 15   |
| number of deaths resulting from<br>adverse events                      |                                    |  |  |
| Neoplasms benign, malignant and<br>unspecified (incl cysts and polyps) |                                    |  |  |
| Basal cell carcinoma   |                                    |  |  |

|   |                |                |                 |
|---|----------------|----------------|-----------------|
| subjects affected / exposed                     | 0 / 76 (0.00%) | 0 / 78 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Basosquamous carcinoma                          |                |                |                 |
| subjects affected / exposed                     | 1 / 76 (1.32%) | 0 / 78 (0.00%) | 0 / 177 (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           |
| Chondrosarcoma                                  |                |                |                 |
| subjects affected / exposed                     | 1 / 76 (1.32%) | 0 / 78 (0.00%) | 0 / 177 (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           |
| Hepatic cancer                                  |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 0 / 78 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Hepatocellular carcinoma                        |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 1 / 78 (1.28%) | 0 / 177 (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           |
| Lung Adenocarcinoma Stage IV                    |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 0 / 78 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Lung Neoplasm                                   |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 1 / 78 (1.28%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Lung neoplasm malignant                         |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 1 / 78 (1.28%) | 0 / 177 (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           |
| Lung squamous cell carcinoma Stage 0            |                |                |                 |

|   |                |                |                 |
|---|----------------|----------------|-----------------|
| subjects affected / exposed                     | 1 / 76 (1.32%) | 0 / 78 (0.00%) | 0 / 177 (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           |
| Neuroendocrine carcinoma                        |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 1 / 78 (1.28%) | 0 / 177 (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           |
| Pancreatic carcinoma metastatic                 |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 1 / 78 (1.28%) | 0 / 177 (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           |
| Plasma cell myeloma                             |                |                |                 |
| subjects affected / exposed                     | 1 / 76 (1.32%) | 0 / 78 (0.00%) | 0 / 177 (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           |
| Squamous cell carcinoma                         |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 1 / 78 (1.28%) | 3 / 177 (1.69%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Squamous cell carcinoma of skin                 |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 0 / 78 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Vascular disorders                              |                |                |                 |
| Aortic aneurysm                                 |                |                |                 |
| subjects affected / exposed                     | 1 / 76 (1.32%) | 0 / 78 (0.00%) | 0 / 177 (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           |
| Aortic stenosis                                 |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 0 / 78 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Axillary vein thrombosis                        |                |                |                 |

|  |                |                |                 |
|--|----------------|----------------|-----------------|
| subjects affected / exposed                          | 1 / 76 (1.32%) | 0 / 78 (0.00%) | 0 / 177 (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           |
| Hypotension  |                |                |                 |
| subjects affected / exposed                          | 0 / 76 (0.00%) | 0 / 78 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0           |
| Orthostatic hypotension                              |                |                |                 |
| subjects affected / exposed                          | 0 / 76 (0.00%) | 0 / 78 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0           |
| General disorders and administration site conditions |                |                |                 |
| Chest pain   |                |                |                 |
| subjects affected / exposed                          | 1 / 76 (1.32%) | 0 / 78 (0.00%) | 0 / 177 (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           |
| Death  |                |                |                 |
| subjects affected / exposed                          | 0 / 76 (0.00%) | 0 / 78 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0           |
| Multiple organ dysfunction syndrome                  |                |                |                 |
| subjects affected / exposed                          | 0 / 76 (0.00%) | 0 / 78 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0           |
| Sudden death   |                |                |                 |
| subjects affected / exposed                          | 1 / 76 (1.32%) | 0 / 78 (0.00%) | 0 / 177 (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           |
| Immune system disorders                              |                |                |                 |
| Graft versus host disease                            |                |                |                 |
| subjects affected / exposed                          | 0 / 76 (0.00%) | 0 / 78 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0           |

|   |                  |                  |                   |
|---|------------------|------------------|-------------------|
| Respiratory, thoracic and mediastinal disorders |                  |                  |                   |
| Acute respiratory failure                       |                  |                  |                   |
| subjects affected / exposed                     | 2 / 76 (2.63%)   | 1 / 78 (1.28%)   | 1 / 177 (0.56%)   |
| occurrences causally related to treatment / all | 1 / 2            | 0 / 1            | 0 / 1             |
| deaths causally related to treatment / all      | 1 / 2            | 0 / 0            | 0 / 1             |
| Haemoptysis                                     |                  |                  |                   |
| subjects affected / exposed                     | 0 / 76 (0.00%)   | 0 / 78 (0.00%)   | 1 / 177 (0.56%)   |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0             |
| Hyperventilation                                |                  |                  |                   |
| subjects affected / exposed                     | 0 / 76 (0.00%)   | 1 / 78 (1.28%)   | 0 / 177 (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             |
| Hypoxia   |                  |                  |                   |
| subjects affected / exposed                     | 1 / 76 (1.32%)   | 0 / 78 (0.00%)   | 0 / 177 (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             |
| Idiopathic pulmonary fibrosis                   |                  |                  |                   |
| subjects affected / exposed                     | 13 / 76 (17.11%) | 11 / 78 (14.10%) | 22 / 177 (12.43%) |
| occurrences causally related to treatment / all | 2 / 15           | 0 / 15           | 3 / 27            |
| deaths causally related to treatment / all      | 1 / 7            | 0 / 4            | 1 / 11            |
| Oropharyngeal discomfort                        |                  |                  |                   |
| subjects affected / exposed                     | 0 / 76 (0.00%)   | 0 / 78 (0.00%)   | 0 / 177 (0.00%)   |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 0            | 0 / 0             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 0             |
| Pleural effusion                                |                  |                  |                   |
| subjects affected / exposed                     | 0 / 76 (0.00%)   | 1 / 78 (1.28%)   | 1 / 177 (0.56%)   |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            | 0 / 1             |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            | 0 / 1             |
| Pneumomediastinum                               |                  |                  |                   |
| subjects affected / exposed                     | 2 / 76 (2.63%)   | 0 / 78 (0.00%)   | 0 / 177 (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             |

|   |                |                |                 |
|---|----------------|----------------|-----------------|
| Pneumothorax                                    |                |                |                 |
| subjects affected / exposed                     | 2 / 76 (2.63%) | 2 / 78 (2.56%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 2          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Pulmonary arterial hypertension                 |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 0 / 78 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Pulmonary embolism                              |                |                |                 |
| subjects affected / exposed                     | 3 / 76 (3.95%) | 2 / 78 (2.56%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 3          | 1 / 2          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 1 / 1          | 0 / 0           |
| Pulmonary fibrosis                              |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 0 / 78 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1           |
| Pulmonary hypertension                          |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 0 / 78 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Respiratory failure                             |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 0 / 78 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1           |
| Dyspnoea  |                |                |                 |
| subjects affected / exposed                     | 2 / 76 (2.63%) | 1 / 78 (1.28%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1           |
| Psychiatric disorders                           |                |                |                 |
| Delirium  |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 0 / 78 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Investigations                                  |                |                |                 |

|   |                |                |                 |
|---|----------------|----------------|-----------------|
| Blood creatine phosphokinase increased          |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 1 / 78 (1.28%) | 0 / 177 (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           |
| Hepatic enzyme increased                        |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 0 / 78 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Injury, poisoning and procedural complications  |                |                |                 |
| Fall  |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 0 / 78 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Procedural hypotension                          |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 0 / 78 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Procedural pain                                 |                |                |                 |
| subjects affected / exposed                     | 1 / 76 (1.32%) | 0 / 78 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Radius fracture                                 |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 0 / 78 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Spinal fracture                                 |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 0 / 78 (0.00%) | 1 / 177 (0.56%) |
| 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 disorders                               |                |                |                 |
| Acute coronary syndrome                         |                |                |                 |

|   |                |                |                 |
|---|----------------|----------------|-----------------|
| subjects affected / exposed                     | 0 / 76 (0.00%) | 0 / 78 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Acute myocardial infarction                     |                |                |                 |
| subjects affected / exposed                     | 1 / 76 (1.32%) | 1 / 78 (1.28%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0           |
| Angina pectoris                                 |                |                |                 |
| subjects affected / exposed                     | 1 / 76 (1.32%) | 0 / 78 (0.00%) | 0 / 177 (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           |
| Atrial fibrillation                             |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 1 / 78 (1.28%) | 2 / 177 (1.13%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Atrial flutter                                  |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 0 / 78 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Atrioventricular block                          |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 1 / 78 (1.28%) | 0 / 177 (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           |
| Atrioventricular block second degree            |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 1 / 78 (1.28%) | 0 / 177 (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           |
| Bradycardia                                     |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 1 / 78 (1.28%) | 0 / 177 (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 arrest                                  |                |                |                 |

|   |                |                |                 |
|---|----------------|----------------|-----------------|
| subjects affected / exposed                     | 0 / 76 (0.00%) | 1 / 78 (1.28%) | 0 / 177 (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           |
| Cardio-respiratory arrest                       |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 0 / 78 (0.00%) | 1 / 177 (0.56%) |
| 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                                 |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 2 / 78 (2.56%) | 3 / 177 (1.69%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 3          | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Cardiomegaly                                    |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 0 / 78 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Coronary artery disease                         |                |                |                 |
| subjects affected / exposed                     | 2 / 76 (2.63%) | 0 / 78 (0.00%) | 2 / 177 (1.13%) |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0          | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Coronary artery occlusion                       |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 0 / 78 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Myocardial ischaemia                            |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 1 / 78 (1.28%) | 3 / 177 (1.69%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 1 / 3           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Right ventricular failure                       |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 0 / 78 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Tachycardia                                     |                |                |                 |

|   |                |                |                 |
|---|----------------|----------------|-----------------|
| subjects affected / exposed                     | 1 / 76 (1.32%) | 0 / 78 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Nervous system disorders                        |                |                |                 |
| Carotid artery stenosis                         |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 0 / 78 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Cerebrovascular accident                        |                |                |                 |
| subjects affected / exposed                     | 1 / 76 (1.32%) | 0 / 78 (0.00%) | 0 / 177 (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           |
| Epilepsy  |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 0 / 78 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Ischaemic stroke                                |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 0 / 78 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Presyncope                                      |                |                |                 |
| subjects affected / exposed                     | 1 / 76 (1.32%) | 0 / 78 (0.00%) | 0 / 177 (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           |
| Syncope   |                |                |                 |
| subjects affected / exposed                     | 1 / 76 (1.32%) | 1 / 78 (1.28%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Ear and labyrinth disorders                     |                |                |                 |
| Vertigo positional                              |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 0 / 78 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Gastrointestinal disorders                      |                |                |                 |

|   |                |                |                 |
|---|----------------|----------------|-----------------|
| Diarrhoea                                       |                |                |                 |
| subjects affected / exposed                     | 1 / 76 (1.32%) | 0 / 78 (0.00%) | 0 / 177 (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           |
| Diverticulum intestinal haemorrhagic            |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 0 / 78 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Gastritis                                       |                |                |                 |
| subjects affected / exposed                     | 1 / 76 (1.32%) | 0 / 78 (0.00%) | 0 / 177 (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           |
| Gastroesophageal reflux disease                 |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 0 / 78 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Inguinal hernia                                 |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 0 / 78 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Intestinal prolapse                             |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 1 / 78 (1.28%) | 0 / 177 (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           |
| Mesenteric vein thrombosis                      |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 0 / 78 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Nausea  |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 0 / 78 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Pancreatitis                                    |                |                |                 |

|   |                |                |                 |
|---|----------------|----------------|-----------------|
| subjects affected / exposed                     | 0 / 76 (0.00%) | 0 / 78 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Pancreatitis acute                              |                |                |                 |
| subjects affected / exposed                     | 2 / 76 (2.63%) | 0 / 78 (0.00%) | 0 / 177 (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           |
| Toothache                                       |                |                |                 |
| subjects affected / exposed                     | 1 / 76 (1.32%) | 0 / 78 (0.00%) | 0 / 177 (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           |
| Vomiting  |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 0 / 78 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Hepatobiliary disorders                         |                |                |                 |
| Drug-induced liver injury                       |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 0 / 78 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Skin and subcutaneous tissue disorders          |                |                |                 |
| Angioedema                                      |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 0 / 78 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Musculoskeletal and connective tissue disorders |                |                |                 |
| Back pain                                       |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 0 / 78 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Musculoskeletal chest pain                      |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 1 / 78 (1.28%) | 0 / 177 (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 pain                            |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 0 / 78 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Rheumatoid arthritis                            |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 0 / 78 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Infections and infestations                     |                |                |                 |
| Bronchitis                                      |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 1 / 78 (1.28%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Bronchitis bacterial                            |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 0 / 78 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Bronchopulmonary aspergillosis                  |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 0 / 78 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Campylobacter infection                         |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 1 / 78 (1.28%) | 0 / 177 (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                     | 1 / 76 (1.32%) | 0 / 78 (0.00%) | 0 / 177 (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           |
| Erysipelas                                      |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 0 / 78 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Fungal infection                                |                |                |                 |

|   |                |                |                 |
|---|----------------|----------------|-----------------|
| subjects affected / exposed                     | 0 / 76 (0.00%) | 0 / 78 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| H1N1 influenza                                  |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 0 / 78 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Influenza                                       |                |                |                 |
| subjects affected / exposed                     | 1 / 76 (1.32%) | 1 / 78 (1.28%) | 0 / 177 (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           |
| Lower respiratory tract infection               |                |                |                 |
| subjects affected / exposed                     | 1 / 76 (1.32%) | 4 / 78 (5.13%) | 2 / 177 (1.13%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 5          | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0           |
| Lung infection                                  |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 1 / 78 (1.28%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0           |
| Pneumonia                                       |                |                |                 |
| subjects affected / exposed                     | 2 / 76 (2.63%) | 3 / 78 (3.85%) | 7 / 177 (3.95%) |
| occurrences causally related to treatment / all | 0 / 2          | 1 / 3          | 2 / 9           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 2           |
| Pneumonia bacterial                             |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 0 / 78 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Pneumonia haemophilus                           |                |                |                 |
| subjects affected / exposed                     | 1 / 76 (1.32%) | 0 / 78 (0.00%) | 0 / 177 (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           |
| Pneumonia influenzal                            |                |                |                 |

|   |                |                |                 |
|---|----------------|----------------|-----------------|
| subjects affected / exposed                     | 0 / 76 (0.00%) | 1 / 78 (1.28%) | 0 / 177 (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 viral                                 |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 0 / 78 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Postoperative wound infection                   |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 0 / 78 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Respiratory syncytial virus infection           |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 0 / 78 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Respiratory tract infection                     |                |                |                 |
| subjects affected / exposed                     | 1 / 76 (1.32%) | 1 / 78 (1.28%) | 3 / 177 (1.69%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1          | 0 / 3           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Sepsis  |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 0 / 78 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Septic shock                                    |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 1 / 78 (1.28%) | 0 / 177 (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           |
| Urinary tract infection enterococcal            |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 0 / 78 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Wound infection bacterial                       |                |                |                 |

|   |                |                |                 |
|---|----------------|----------------|-----------------|
| subjects affected / exposed                     | 0 / 76 (0.00%) | 0 / 78 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Mycobacterium avium complex infection           |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 0 / 78 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Urinary tract infection                         |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 2 / 78 (2.56%) | 0 / 177 (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           |
| Metabolism and nutrition disorders              |                |                |                 |
| Decreased appetite                              |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 0 / 78 (0.00%) | 1 / 177 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Dehydration                                     |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 0 / 78 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Hypercalcaemia                                  |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 0 / 78 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |
| Hyponatraemia                                   |                |                |                 |
| subjects affected / exposed                     | 0 / 76 (0.00%) | 0 / 78 (0.00%) | 0 / 177 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0           |

|   |  |  |  |
|---|--|--|--|
| <b>Serious adverse events</b>                     | Combination Therapy (Cohort B):<br>Lebrikizumab +<br>Pirfenidone |  |  |
| Total subjects affected by serious adverse events |  |  |  |
| subjects affected / exposed                       | 56 / 174 (32.18%)  |  |  |
| number of deaths (all causes)                     | 7  |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| number of deaths resulting from adverse events                      |                 |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                 |  |  |
| Basal cell carcinoma  |                 |  |  |
| subjects affected / exposed   | 1 / 174 (0.57%) |  |  |
| occurrences causally related to treatment / all                     | 0 / 1           |  |  |
| deaths causally related to treatment / all                          | 0 / 0           |  |  |
| Basosquamous carcinoma  |                 |  |  |
| subjects affected / exposed   | 0 / 174 (0.00%) |  |  |
| occurrences causally related to treatment / all                     | 0 / 0           |  |  |
| deaths causally related to treatment / all                          | 0 / 0           |  |  |
| Chondrosarcoma  |                 |  |  |
| subjects affected / exposed   | 0 / 174 (0.00%) |  |  |
| occurrences causally related to treatment / all                     | 0 / 0           |  |  |
| deaths causally related to treatment / all                          | 0 / 0           |  |  |
| Hepatic cancer  |                 |  |  |
| subjects affected / exposed   | 1 / 174 (0.57%) |  |  |
| occurrences causally related to treatment / all                     | 0 / 1           |  |  |
| deaths causally related to treatment / all                          | 0 / 0           |  |  |
| Hepatocellular carcinoma  |                 |  |  |
| subjects affected / exposed   | 0 / 174 (0.00%) |  |  |
| occurrences causally related to treatment / all                     | 0 / 0           |  |  |
| deaths causally related to treatment / all                          | 0 / 0           |  |  |
| Lung Adenocarcinoma Stage IV  |                 |  |  |
| subjects affected / exposed   | 1 / 174 (0.57%) |  |  |
| occurrences causally related to treatment / all                     | 0 / 1           |  |  |
| deaths causally related to treatment / all                          | 0 / 0           |  |  |
| Lung Neoplasm   |                 |  |  |
| subjects affected / exposed   | 0 / 174 (0.00%) |  |  |
| occurrences causally related to treatment / all                     | 0 / 0           |  |  |
| deaths causally related to treatment / all                          | 0 / 0           |  |  |
| Lung neoplasm malignant   |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 174 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Lung squamous cell carcinoma Stage 0            |                 |  |  |
| subjects affected / exposed                     | 0 / 174 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Neuroendocrine carcinoma                        |                 |  |  |
| subjects affected / exposed                     | 0 / 174 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pancreatic carcinoma metastatic                 |                 |  |  |
| subjects affected / exposed                     | 0 / 174 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Plasma cell myeloma                             |                 |  |  |
| subjects affected / exposed                     | 0 / 174 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Squamous cell carcinoma                         |                 |  |  |
| subjects affected / exposed                     | 1 / 174 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Squamous cell carcinoma of skin                 |                 |  |  |
| subjects affected / exposed                     | 0 / 174 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Vascular disorders                              |                 |  |  |
| Aortic aneurysm                                 |                 |  |  |
| subjects affected / exposed                     | 1 / 174 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Aortic stenosis                                 |                 |  |  |

|  |                 |  |  |
|--|-----------------|--|--|
| subjects affected / exposed                          | 1 / 174 (0.57%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Axillary vein thrombosis                             |                 |  |  |
| subjects affected / exposed                          | 0 / 174 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Hypotension  |                 |  |  |
| subjects affected / exposed                          | 2 / 174 (1.15%) |  |  |
| occurrences causally related to treatment / all      | 0 / 2           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Orthostatic hypotension                              |                 |  |  |
| subjects affected / exposed                          | 1 / 174 (0.57%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| General disorders and administration site conditions |                 |  |  |
| Chest pain   |                 |  |  |
| subjects affected / exposed                          | 1 / 174 (0.57%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Death  |                 |  |  |
| subjects affected / exposed                          | 1 / 174 (0.57%) |  |  |
| occurrences causally related to treatment / all      | 0 / 1           |  |  |
| deaths causally related to treatment / all           | 0 / 1           |  |  |
| Multiple organ dysfunction syndrome                  |                 |  |  |
| subjects affected / exposed                          | 0 / 174 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Sudden death   |                 |  |  |
| subjects affected / exposed                          | 0 / 174 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Immune system disorders                              |                 |  |  |

|   |                  |  |  |
|---|------------------|--|--|
| Graft versus host disease                       |                  |  |  |
| subjects affected / exposed                     | 1 / 174 (0.57%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 1            |  |  |
| Respiratory, thoracic and mediastinal disorders |                  |  |  |
| Acute respiratory failure                       |                  |  |  |
| subjects affected / exposed                     | 1 / 174 (0.57%)  |  |  |
| occurrences causally related to treatment / all | 0 / 2            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Haemoptysis                                     |                  |  |  |
| subjects affected / exposed                     | 0 / 174 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hyperventilation                                |                  |  |  |
| subjects affected / exposed                     | 0 / 174 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Hypoxia   |                  |  |  |
| subjects affected / exposed                     | 3 / 174 (1.72%)  |  |  |
| occurrences causally related to treatment / all | 2 / 4            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Idiopathic pulmonary fibrosis                   |                  |  |  |
| subjects affected / exposed                     | 17 / 174 (9.77%) |  |  |
| occurrences causally related to treatment / all | 0 / 21           |  |  |
| deaths causally related to treatment / all      | 0 / 6            |  |  |
| Oropharyngeal discomfort                        |                  |  |  |
| subjects affected / exposed                     | 1 / 174 (0.57%)  |  |  |
| occurrences causally related to treatment / all | 0 / 1            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |
| Pleural effusion                                |                  |  |  |
| subjects affected / exposed                     | 0 / 174 (0.00%)  |  |  |
| occurrences causally related to treatment / all | 0 / 0            |  |  |
| deaths causally related to treatment / all      | 0 / 0            |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| Pneumomediastinum                               |                 |  |  |
| subjects affected / exposed                     | 1 / 174 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pneumothorax                                    |                 |  |  |
| subjects affected / exposed                     | 1 / 174 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pulmonary arterial hypertension                 |                 |  |  |
| subjects affected / exposed                     | 0 / 174 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pulmonary embolism                              |                 |  |  |
| subjects affected / exposed                     | 2 / 174 (1.15%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pulmonary fibrosis                              |                 |  |  |
| subjects affected / exposed                     | 1 / 174 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pulmonary hypertension                          |                 |  |  |
| subjects affected / exposed                     | 0 / 174 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Respiratory failure                             |                 |  |  |
| subjects affected / exposed                     | 0 / 174 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Dyspnoea  |                 |  |  |
| subjects affected / exposed                     | 1 / 174 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Psychiatric disorders                           |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| Delirium  |                 |  |  |
| subjects affected / exposed                     | 0 / 174 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Investigations                                  |                 |  |  |
| Blood creatine phosphokinase increased          |                 |  |  |
| subjects affected / exposed                     | 0 / 174 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hepatic enzyme increased                        |                 |  |  |
| subjects affected / exposed                     | 1 / 174 (0.57%) |  |  |
| occurrences causally related to treatment / all | 1 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Injury, poisoning and procedural complications  |                 |  |  |
| Fall  |                 |  |  |
| subjects affected / exposed                     | 0 / 174 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Procedural hypotension                          |                 |  |  |
| subjects affected / exposed                     | 1 / 174 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Procedural pain                                 |                 |  |  |
| subjects affected / exposed                     | 0 / 174 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Radius fracture                                 |                 |  |  |
| subjects affected / exposed                     | 1 / 174 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Spinal fracture                                 |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 174 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cardiac disorders                               |                 |  |  |
| Acute coronary syndrome                         |                 |  |  |
| subjects affected / exposed                     | 1 / 174 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Acute myocardial infarction                     |                 |  |  |
| subjects affected / exposed                     | 1 / 174 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Angina pectoris                                 |                 |  |  |
| subjects affected / exposed                     | 1 / 174 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Atrial fibrillation                             |                 |  |  |
| subjects affected / exposed                     | 1 / 174 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Atrial flutter                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 174 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Atrioventricular block                          |                 |  |  |
| subjects affected / exposed                     | 0 / 174 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Atrioventricular block second degree            |                 |  |  |
| subjects affected / exposed                     | 0 / 174 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Bradycardia                                     |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 174 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cardiac arrest                                  |                 |  |  |
| subjects affected / exposed                     | 0 / 174 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cardio-respiratory arrest                       |                 |  |  |
| subjects affected / exposed                     | 0 / 174 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cardiac failure                                 |                 |  |  |
| subjects affected / exposed                     | 1 / 174 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 5           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Cardiomegaly                                    |                 |  |  |
| subjects affected / exposed                     | 1 / 174 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Coronary artery disease                         |                 |  |  |
| subjects affected / exposed                     | 2 / 174 (1.15%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Coronary artery occlusion                       |                 |  |  |
| subjects affected / exposed                     | 0 / 174 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Myocardial ischaemia                            |                 |  |  |
| subjects affected / exposed                     | 0 / 174 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Right ventricular failure                       |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 174 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Tachycardia                                     |                 |  |  |
| subjects affected / exposed                     | 0 / 174 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Nervous system disorders                        |                 |  |  |
| Carotid artery stenosis                         |                 |  |  |
| subjects affected / exposed                     | 0 / 174 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cerebrovascular accident                        |                 |  |  |
| subjects affected / exposed                     | 1 / 174 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Epilepsy  |                 |  |  |
| subjects affected / exposed                     | 0 / 174 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Ischaemic stroke                                |                 |  |  |
| subjects affected / exposed                     | 0 / 174 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Presyncope                                      |                 |  |  |
| subjects affected / exposed                     | 0 / 174 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Syncope   |                 |  |  |
| subjects affected / exposed                     | 1 / 174 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Ear and labyrinth disorders                     |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| Vertigo positional                              |                 |  |  |
| subjects affected / exposed                     | 0 / 174 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Gastrointestinal disorders                      |                 |  |  |
| Diarrhoea                                       |                 |  |  |
| subjects affected / exposed                     | 0 / 174 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Diverticulum intestinal haemorrhagic            |                 |  |  |
| subjects affected / exposed                     | 1 / 174 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Gastritis                                       |                 |  |  |
| subjects affected / exposed                     | 0 / 174 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Gastrooesophageal reflux disease                |                 |  |  |
| subjects affected / exposed                     | 1 / 174 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Inguinal hernia                                 |                 |  |  |
| subjects affected / exposed                     | 1 / 174 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Intestinal prolapse                             |                 |  |  |
| subjects affected / exposed                     | 0 / 174 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Mesenteric vein thrombosis                      |                 |  |  |
| subjects affected / exposed                     | 1 / 174 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Nausea  |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 1 / 174 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pancreatitis                                    |                 |  |  |
| subjects affected / exposed                     | 2 / 174 (1.15%) |  |  |
| occurrences causally related to treatment / all | 1 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pancreatitis acute                              |                 |  |  |
| subjects affected / exposed                     | 0 / 174 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Toothache                                       |                 |  |  |
| subjects affected / exposed                     | 0 / 174 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Vomiting  |                 |  |  |
| subjects affected / exposed                     | 1 / 174 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hepatobiliary disorders                         |                 |  |  |
| Drug-induced liver injury                       |                 |  |  |
| subjects affected / exposed                     | 2 / 174 (1.15%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Skin and subcutaneous tissue disorders          |                 |  |  |
| Angioedema                                      |                 |  |  |
| subjects affected / exposed                     | 0 / 174 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Musculoskeletal and connective tissue disorders |                 |  |  |
| Back pain                                       |                 |  |  |
| subjects affected / exposed                     | 1 / 174 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| Musculoskeletal chest pain                      |                 |  |  |
| subjects affected / exposed                     | 0 / 174 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Musculoskeletal pain                            |                 |  |  |
| subjects affected / exposed                     | 1 / 174 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Rheumatoid arthritis                            |                 |  |  |
| subjects affected / exposed                     | 1 / 174 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Infections and infestations                     |                 |  |  |
| Bronchitis                                      |                 |  |  |
| subjects affected / exposed                     | 0 / 174 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Bronchitis bacterial                            |                 |  |  |
| subjects affected / exposed                     | 0 / 174 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Bronchopulmonary aspergillosis                  |                 |  |  |
| subjects affected / exposed                     | 0 / 174 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Campylobacter infection                         |                 |  |  |
| subjects affected / exposed                     | 0 / 174 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Diverticulitis                                  |                 |  |  |
| subjects affected / exposed                     | 0 / 174 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Erysipelas                                      |                 |  |  |

|   |                 |  |  |  |
|---|-----------------|--|--|--|
| subjects affected / exposed                     | 1 / 174 (0.57%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Fungal infection                                |                 |  |  |  |
| subjects affected / exposed                     | 1 / 174 (0.57%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| H1N1 influenza                                  |                 |  |  |  |
| subjects affected / exposed                     | 1 / 174 (0.57%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Influenza                                       |                 |  |  |  |
| subjects affected / exposed                     | 0 / 174 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Lower respiratory tract infection               |                 |  |  |  |
| subjects affected / exposed                     | 1 / 174 (0.57%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Lung infection                                  |                 |  |  |  |
| subjects affected / exposed                     | 2 / 174 (1.15%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Pneumonia                                       |                 |  |  |  |
| subjects affected / exposed                     | 7 / 174 (4.02%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 7           |  |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |  |
| Pneumonia bacterial                             |                 |  |  |  |
| subjects affected / exposed                     | 1 / 174 (0.57%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Pneumonia haemophilus                           |                 |  |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 174 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pneumonia influenzal                            |                 |  |  |
| subjects affected / exposed                     | 0 / 174 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pneumonia viral                                 |                 |  |  |
| subjects affected / exposed                     | 1 / 174 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Postoperative wound infection                   |                 |  |  |
| subjects affected / exposed                     | 1 / 174 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Respiratory syncytial virus infection           |                 |  |  |
| subjects affected / exposed                     | 1 / 174 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Respiratory tract infection                     |                 |  |  |
| subjects affected / exposed                     | 5 / 174 (2.87%) |  |  |
| occurrences causally related to treatment / all | 0 / 6           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Sepsis  |                 |  |  |
| subjects affected / exposed                     | 1 / 174 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Septic shock                                    |                 |  |  |
| subjects affected / exposed                     | 1 / 174 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 1           |  |  |
| Urinary tract infection enterococcal            |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 174 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Wound infection bacterial                       |                 |  |  |
| subjects affected / exposed                     | 1 / 174 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Mycobacterium avium complex infection           |                 |  |  |
| subjects affected / exposed                     | 1 / 174 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Urinary tract infection                         |                 |  |  |
| subjects affected / exposed                     | 0 / 174 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Metabolism and nutrition disorders              |                 |  |  |
| Decreased appetite                              |                 |  |  |
| subjects affected / exposed                     | 0 / 174 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Dehydration                                     |                 |  |  |
| subjects affected / exposed                     | 1 / 174 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hypercalcaemia                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 174 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hyponatraemia                                   |                 |  |  |
| subjects affected / exposed                     | 1 / 174 (0.57%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

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

| <b>Non-serious adverse events</b>  | <b>Monotherapy<br/>(Cohort A): Placebo</b> | <b>Monotherapy<br/>(Cohort A):<br/>Lebrikizumab</b> | <b>Combination<br/>Therapy (Cohort B):<br/>Placebo +<br/>Pirfenidone</b> |
|--|--|---|--|
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed                                 | 70 / 76 (92.11%)                           | 73 / 78 (93.59%)                                    | 158 / 177 (89.27%)   |
| Vascular disorders<br>Hypertension<br>subjects affected / exposed<br>occurrences (all)                               | 4 / 76 (5.26%)<br>4                        | 4 / 78 (5.13%)<br>4                                 | 4 / 177 (2.26%)<br>4   |
| General disorders and administration site conditions<br>Asthenia<br>subjects affected / exposed<br>occurrences (all) | 2 / 76 (2.63%)<br>2                        | 5 / 78 (6.41%)<br>5                                 | 3 / 177 (1.69%)<br>3   |
| Chest discomfort<br>subjects affected / exposed<br>occurrences (all)   | 5 / 76 (6.58%)<br>9                        | 2 / 78 (2.56%)<br>2                                 | 3 / 177 (1.69%)<br>3   |
| Chest pain<br>subjects affected / exposed<br>occurrences (all)   | 5 / 76 (6.58%)<br>6                        | 7 / 78 (8.97%)<br>8                                 | 7 / 177 (3.95%)<br>7   |
| Fatigue<br>subjects affected / exposed<br>occurrences (all)  | 12 / 76 (15.79%)<br>17                     | 15 / 78 (19.23%)<br>17                              | 22 / 177 (12.43%)<br>24  |
| Injection site erythema<br>subjects affected / exposed<br>occurrences (all)  | 1 / 76 (1.32%)<br>1                        | 4 / 78 (5.13%)<br>18                                | 1 / 177 (0.56%)<br>1   |
| Oedema peripheral<br>subjects affected / exposed<br>occurrences (all)  | 2 / 76 (2.63%)<br>2                        | 4 / 78 (5.13%)<br>5                                 | 4 / 177 (2.26%)<br>4   |
| Pain<br>subjects affected / exposed<br>occurrences (all)   | 2 / 76 (2.63%)<br>3                        | 4 / 78 (5.13%)<br>4                                 | 2 / 177 (1.13%)<br>2   |
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)  | 2 / 76 (2.63%)<br>2                        | 6 / 78 (7.69%)<br>7                                 | 5 / 177 (2.82%)<br>7   |
| Respiratory, thoracic and mediastinal  |  |   |  |

|                                 |                  |                  |                   |
|---------------------------------|------------------|------------------|-------------------|
| disorders                       |                  |                  |                   |
| Cough                           |                  |                  |                   |
| subjects affected / exposed     | 19 / 76 (25.00%) | 21 / 78 (26.92%) | 46 / 177 (25.99%) |
| occurrences (all)               | 22               | 33               | 59                |
| Dysphonia                       |                  |                  |                   |
| subjects affected / exposed     | 0 / 76 (0.00%)   | 4 / 78 (5.13%)   | 1 / 177 (0.56%)   |
| occurrences (all)               | 0                | 4                | 1                 |
| Dyspnoea                        |                  |                  |                   |
| subjects affected / exposed     | 12 / 76 (15.79%) | 14 / 78 (17.95%) | 18 / 177 (10.17%) |
| occurrences (all)               | 19               | 14               | 19                |
| Dyspnoea exertional             |                  |                  |                   |
| subjects affected / exposed     | 4 / 76 (5.26%)   | 6 / 78 (7.69%)   | 4 / 177 (2.26%)   |
| occurrences (all)               | 4                | 6                | 4                 |
| Idiopathic pulmonary fibrosis   |                  |                  |                   |
| subjects affected / exposed     | 13 / 76 (17.11%) | 11 / 78 (14.10%) | 10 / 177 (5.65%)  |
| occurrences (all)               | 14               | 12               | 10                |
| Oropharyngeal pain              |                  |                  |                   |
| subjects affected / exposed     | 7 / 76 (9.21%)   | 4 / 78 (5.13%)   | 5 / 177 (2.82%)   |
| occurrences (all)               | 7                | 6                | 5                 |
| Productive cough                |                  |                  |                   |
| subjects affected / exposed     | 3 / 76 (3.95%)   | 8 / 78 (10.26%)  | 8 / 177 (4.52%)   |
| occurrences (all)               | 3                | 12               | 8                 |
| Sinus congestion                |                  |                  |                   |
| subjects affected / exposed     | 1 / 76 (1.32%)   | 5 / 78 (6.41%)   | 1 / 177 (0.56%)   |
| occurrences (all)               | 1                | 5                | 1                 |
| Psychiatric disorders           |                  |                  |                   |
| Anxiety                         |                  |                  |                   |
| subjects affected / exposed     | 5 / 76 (6.58%)   | 3 / 78 (3.85%)   | 1 / 177 (0.56%)   |
| occurrences (all)               | 6                | 3                | 1                 |
| Insomnia                        |                  |                  |                   |
| subjects affected / exposed     | 3 / 76 (3.95%)   | 7 / 78 (8.97%)   | 4 / 177 (2.26%)   |
| occurrences (all)               | 3                | 7                | 4                 |
| Investigations                  |                  |                  |                   |
| Forced vital capacity decreased |                  |                  |                   |
| subjects affected / exposed     | 4 / 76 (5.26%)   | 11 / 78 (14.10%) | 6 / 177 (3.39%)   |
| occurrences (all)               | 4                | 12               | 6                 |
| Weight decreased                |                  |                  |                   |

|   |   |   |   |
|---|---|---|---|
| subjects affected / exposed<br>occurrences (all)  | 5 / 76 (6.58%)<br>5   | 2 / 78 (2.56%)<br>2   | 9 / 177 (5.08%)<br>9  |
| Injury, poisoning and procedural complications<br>Fall<br>subjects affected / exposed<br>occurrences (all)  | 6 / 76 (7.89%)<br>8   | 4 / 78 (5.13%)<br>5   | 3 / 177 (1.69%)<br>3  |
| Nervous system disorders<br>Dizziness<br>subjects affected / exposed<br>occurrences (all)<br><br>Headache<br>subjects affected / exposed<br>occurrences (all)   | 10 / 76 (13.16%)<br>15<br><br>9 / 76 (11.84%)<br>14   | 14 / 78 (17.95%)<br>18<br><br>10 / 78 (12.82%)<br>12  | 14 / 177 (7.91%)<br>18<br><br>17 / 177 (9.60%)<br>21  |
| Eye disorders<br>Cataract<br>subjects affected / exposed<br>occurrences (all)<br><br>Dry eye<br>subjects affected / exposed<br>occurrences (all)  | 2 / 76 (2.63%)<br>2<br><br>0 / 76 (0.00%)<br>0  | 4 / 78 (5.13%)<br>5<br><br>4 / 78 (5.13%)<br>4  | 7 / 177 (3.95%)<br>8<br><br>1 / 177 (0.56%)<br>1  |
| Gastrointestinal disorders<br>Abdominal discomfort<br>subjects affected / exposed<br>occurrences (all)<br><br>Abdominal pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all)<br><br>Constipation<br>subjects affected / exposed<br>occurrences (all)<br><br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all) | 2 / 76 (2.63%)<br>2<br><br>3 / 76 (3.95%)<br>4<br><br>4 / 76 (5.26%)<br>4<br><br>11 / 76 (14.47%)<br>14<br><br>16 / 76 (21.05%)<br>19 | 4 / 78 (5.13%)<br>4<br><br>4 / 78 (5.13%)<br>4<br><br>4 / 78 (5.13%)<br>5<br><br>11 / 78 (14.10%)<br>14<br><br>17 / 78 (21.79%)<br>25 | 3 / 177 (1.69%)<br>3<br><br>2 / 177 (1.13%)<br>2<br><br>4 / 177 (2.26%)<br>6<br><br>12 / 177 (6.78%)<br>13<br><br>23 / 177 (12.99%)<br>30 |

|  |                        |                        |                         |
|--|------------------------|------------------------|-------------------------|
| Dry mouth<br>subjects affected / exposed<br>occurrences (all)                        | 0 / 76 (0.00%)<br>0    | 6 / 78 (7.69%)<br>6    | 2 / 177 (1.13%)<br>2    |
| Dyspepsia<br>subjects affected / exposed<br>occurrences (all)                        | 2 / 76 (2.63%)<br>2    | 4 / 78 (5.13%)<br>4    | 5 / 177 (2.82%)<br>5    |
| Flatulence<br>subjects affected / exposed<br>occurrences (all)                       | 0 / 76 (0.00%)<br>0    | 4 / 78 (5.13%)<br>4    | 1 / 177 (0.56%)<br>1    |
| Gastrooesophageal reflux disease<br>subjects affected / exposed<br>occurrences (all) | 2 / 76 (2.63%)<br>3    | 3 / 78 (3.85%)<br>4    | 9 / 177 (5.08%)<br>11   |
| Nausea<br>subjects affected / exposed<br>occurrences (all)                           | 10 / 76 (13.16%)<br>15 | 10 / 78 (12.82%)<br>12 | 23 / 177 (12.99%)<br>29 |
| Toothache<br>subjects affected / exposed<br>occurrences (all)                        | 4 / 76 (5.26%)<br>4    | 0 / 78 (0.00%)<br>0    | 2 / 177 (1.13%)<br>2    |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)                         | 6 / 76 (7.89%)<br>11   | 3 / 78 (3.85%)<br>4    | 9 / 177 (5.08%)<br>10   |
| Skin and subcutaneous tissue disorders   |                        |                        |                         |
| Photosensitivity reaction<br>subjects affected / exposed<br>occurrences (all)        | 6 / 76 (7.89%)<br>8    | 3 / 78 (3.85%)<br>4    | 24 / 177 (13.56%)<br>27 |
| Pruritus<br>subjects affected / exposed<br>occurrences (all)                         | 2 / 76 (2.63%)<br>2    | 3 / 78 (3.85%)<br>7    | 12 / 177 (6.78%)<br>12  |
| Rash<br>subjects affected / exposed<br>occurrences (all)                             | 5 / 76 (6.58%)<br>9    | 9 / 78 (11.54%)<br>15  | 21 / 177 (11.86%)<br>24 |
| Musculoskeletal and connective tissue disorders                                      |                        |                        |                         |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)                       | 9 / 76 (11.84%)<br>15  | 9 / 78 (11.54%)<br>9   | 8 / 177 (4.52%)<br>10   |
| Back pain  |                        |                        |                         |

|   |                        |                        |                         |
|---|------------------------|------------------------|-------------------------|
| subjects affected / exposed<br>occurrences (all)                                      | 9 / 76 (11.84%)<br>9   | 12 / 78 (15.38%)<br>15 | 11 / 177 (6.21%)<br>13  |
| Muscle spasms<br>subjects affected / exposed<br>occurrences (all)                     | 5 / 76 (6.58%)<br>5    | 6 / 78 (7.69%)<br>6    | 4 / 177 (2.26%)<br>6    |
| Musculoskeletal chest pain<br>subjects affected / exposed<br>occurrences (all)        | 1 / 76 (1.32%)<br>1    | 5 / 78 (6.41%)<br>5    | 2 / 177 (1.13%)<br>2    |
| Musculoskeletal pain<br>subjects affected / exposed<br>occurrences (all)              | 10 / 76 (13.16%)<br>11 | 5 / 78 (6.41%)<br>6    | 8 / 177 (4.52%)<br>8    |
| <b>Infections and infestations</b>  |                        |                        |                         |
| Bronchitis<br>subjects affected / exposed<br>occurrences (all)                        | 11 / 76 (14.47%)<br>14 | 15 / 78 (19.23%)<br>21 | 11 / 177 (6.21%)<br>17  |
| Influenza<br>subjects affected / exposed<br>occurrences (all)                         | 4 / 76 (5.26%)<br>5    | 5 / 78 (6.41%)<br>5    | 10 / 177 (5.65%)<br>12  |
| Lower respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 5 / 76 (6.58%)<br>9    | 11 / 78 (14.10%)<br>23 | 13 / 177 (7.34%)<br>21  |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)                   | 19 / 76 (25.00%)<br>33 | 17 / 78 (21.79%)<br>28 | 25 / 177 (14.12%)<br>35 |
| Pneumonia<br>subjects affected / exposed<br>occurrences (all)                         | 3 / 76 (3.95%)<br>5    | 1 / 78 (1.28%)<br>1    | 9 / 177 (5.08%)<br>9    |
| Respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)       | 5 / 76 (6.58%)<br>7    | 4 / 78 (5.13%)<br>4    | 9 / 177 (5.08%)<br>16   |
| Rhinitis<br>subjects affected / exposed<br>occurrences (all)                          | 4 / 76 (5.26%)<br>4    | 4 / 78 (5.13%)<br>4    | 7 / 177 (3.95%)<br>9    |
| Sinusitis<br>subjects affected / exposed<br>occurrences (all)                         | 5 / 76 (6.58%)<br>5    | 6 / 78 (7.69%)<br>6    | 9 / 177 (5.08%)<br>10   |

|  |                        |                        |                         |
|--|------------------------|------------------------|-------------------------|
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)                        | 13 / 76 (17.11%)<br>17 | 18 / 78 (23.08%)<br>27 | 38 / 177 (21.47%)<br>47 |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)                                  | 5 / 76 (6.58%)<br>7    | 9 / 78 (11.54%)<br>14  | 11 / 177 (6.21%)<br>14  |
| Metabolism and nutrition disorders<br>Decreased appetite<br>subjects affected / exposed<br>occurrences (all) | 5 / 76 (6.58%)<br>8    | 9 / 78 (11.54%)<br>9   | 22 / 177 (12.43%)<br>22 |

|   |   |  |  |
|---|---|--|--|
| <b>Non-serious adverse events</b>   | Combination<br>Therapy (Cohort B):<br>Lebrikizumab +<br>Pirfenidone |  |  |
| Total subjects affected by non-serious<br>adverse events<br>subjects affected / exposed                                 | 142 / 174 (81.61%)  |  |  |
| Vascular disorders<br>Hypertension<br>subjects affected / exposed<br>occurrences (all)                                  | 7 / 174 (4.02%)<br>7  |  |  |
| General disorders and administration<br>site conditions<br>Asthenia<br>subjects affected / exposed<br>occurrences (all) | 0 / 174 (0.00%)<br>0  |  |  |
| Chest discomfort<br>subjects affected / exposed<br>occurrences (all)  | 3 / 174 (1.72%)<br>3  |  |  |
| Chest pain<br>subjects affected / exposed<br>occurrences (all)  | 10 / 174 (5.75%)<br>12  |  |  |
| Fatigue<br>subjects affected / exposed<br>occurrences (all)   | 28 / 174 (16.09%)<br>32   |  |  |
| Injection site erythema<br>subjects affected / exposed<br>occurrences (all)   | 1 / 174 (0.57%)<br>2  |  |  |
| Oedema peripheral   |   |  |  |

|   |                   |  |  |
|---|-------------------|--|--|
| subjects affected / exposed                     | 3 / 174 (1.72%)   |  |  |
| occurrences (all)                               | 3                 |  |  |
| Pain  |                   |  |  |
| subjects affected / exposed                     | 1 / 174 (0.57%)   |  |  |
| occurrences (all)                               | 1                 |  |  |
| Pyrexia   |                   |  |  |
| subjects affected / exposed                     | 1 / 174 (0.57%)   |  |  |
| occurrences (all)                               | 1                 |  |  |
| Respiratory, thoracic and mediastinal disorders |                   |  |  |
| Cough   |                   |  |  |
| subjects affected / exposed                     | 33 / 174 (18.97%) |  |  |
| occurrences (all)                               | 38                |  |  |
| Dysphonia                                       |                   |  |  |
| subjects affected / exposed                     | 0 / 174 (0.00%)   |  |  |
| occurrences (all)                               | 0                 |  |  |
| Dyspnoea  |                   |  |  |
| subjects affected / exposed                     | 13 / 174 (7.47%)  |  |  |
| occurrences (all)                               | 14                |  |  |
| Dyspnoea exertional                             |                   |  |  |
| subjects affected / exposed                     | 5 / 174 (2.87%)   |  |  |
| occurrences (all)                               | 6                 |  |  |
| Idiopathic pulmonary fibrosis                   |                   |  |  |
| subjects affected / exposed                     | 9 / 174 (5.17%)   |  |  |
| occurrences (all)                               | 9                 |  |  |
| Oropharyngeal pain                              |                   |  |  |
| subjects affected / exposed                     | 2 / 174 (1.15%)   |  |  |
| occurrences (all)                               | 2                 |  |  |
| Productive cough                                |                   |  |  |
| subjects affected / exposed                     | 6 / 174 (3.45%)   |  |  |
| occurrences (all)                               | 6                 |  |  |
| Sinus congestion                                |                   |  |  |
| subjects affected / exposed                     | 2 / 174 (1.15%)   |  |  |
| occurrences (all)                               | 2                 |  |  |
| Psychiatric disorders                           |                   |  |  |

|  |                        |  |  |
|--|------------------------|--|--|
| Anxiety<br>subjects affected / exposed<br>occurrences (all)  | 2 / 174 (1.15%)<br>2   |  |  |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)   | 8 / 174 (4.60%)<br>10  |  |  |
| Investigations<br>Forced vital capacity decreased<br>subjects affected / exposed<br>occurrences (all)      | 6 / 174 (3.45%)<br>6   |  |  |
| Weight decreased<br>subjects affected / exposed<br>occurrences (all)                                       | 11 / 174 (6.32%)<br>12 |  |  |
| Injury, poisoning and procedural complications<br>Fall<br>subjects affected / exposed<br>occurrences (all) | 6 / 174 (3.45%)<br>7   |  |  |
| Nervous system disorders<br>Dizziness<br>subjects affected / exposed<br>occurrences (all)                  | 11 / 174 (6.32%)<br>12 |  |  |
| Headache<br>subjects affected / exposed<br>occurrences (all)   | 11 / 174 (6.32%)<br>17 |  |  |
| Eye disorders<br>Cataract<br>subjects affected / exposed<br>occurrences (all)                              | 4 / 174 (2.30%)<br>5   |  |  |
| Dry eye<br>subjects affected / exposed<br>occurrences (all)  | 3 / 174 (1.72%)<br>3   |  |  |
| Gastrointestinal disorders<br>Abdominal discomfort<br>subjects affected / exposed<br>occurrences (all)     | 3 / 174 (1.72%)<br>3   |  |  |
| Abdominal pain   |                        |  |  |

|  |                   |  |  |
|--|-------------------|--|--|
| subjects affected / exposed            | 1 / 174 (0.57%)   |  |  |
| occurrences (all)                      | 1                 |  |  |
| Abdominal pain upper                   |                   |  |  |
| subjects affected / exposed            | 6 / 174 (3.45%)   |  |  |
| occurrences (all)                      | 9                 |  |  |
| Constipation                           |                   |  |  |
| subjects affected / exposed            | 14 / 174 (8.05%)  |  |  |
| occurrences (all)                      | 15                |  |  |
| Diarrhoea                              |                   |  |  |
| subjects affected / exposed            | 18 / 174 (10.34%) |  |  |
| occurrences (all)                      | 20                |  |  |
| Dry mouth                              |                   |  |  |
| subjects affected / exposed            | 4 / 174 (2.30%)   |  |  |
| occurrences (all)                      | 4                 |  |  |
| Dyspepsia                              |                   |  |  |
| subjects affected / exposed            | 8 / 174 (4.60%)   |  |  |
| occurrences (all)                      | 12                |  |  |
| Flatulence                             |                   |  |  |
| subjects affected / exposed            | 1 / 174 (0.57%)   |  |  |
| occurrences (all)                      | 1                 |  |  |
| Gastrooesophageal reflux disease       |                   |  |  |
| subjects affected / exposed            | 9 / 174 (5.17%)   |  |  |
| occurrences (all)                      | 14                |  |  |
| Nausea                                 |                   |  |  |
| subjects affected / exposed            | 28 / 174 (16.09%) |  |  |
| occurrences (all)                      | 30                |  |  |
| Toothache                              |                   |  |  |
| subjects affected / exposed            | 1 / 174 (0.57%)   |  |  |
| occurrences (all)                      | 1                 |  |  |
| Vomiting                               |                   |  |  |
| subjects affected / exposed            | 8 / 174 (4.60%)   |  |  |
| occurrences (all)                      | 10                |  |  |
| Skin and subcutaneous tissue disorders |                   |  |  |
| Photosensitivity reaction              |                   |  |  |
| subjects affected / exposed            | 7 / 174 (4.02%)   |  |  |
| occurrences (all)                      | 9                 |  |  |

|   |                   |  |  |
|---|-------------------|--|--|
| Pruritus  |                   |  |  |
| subjects affected / exposed                     | 8 / 174 (4.60%)   |  |  |
| occurrences (all)                               | 8                 |  |  |
| Rash  |                   |  |  |
| subjects affected / exposed                     | 18 / 174 (10.34%) |  |  |
| occurrences (all)                               | 24                |  |  |
| Musculoskeletal and connective tissue disorders |                   |  |  |
| Arthralgia                                      |                   |  |  |
| subjects affected / exposed                     | 10 / 174 (5.75%)  |  |  |
| occurrences (all)                               | 11                |  |  |
| Back pain                                       |                   |  |  |
| subjects affected / exposed                     | 11 / 174 (6.32%)  |  |  |
| occurrences (all)                               | 11                |  |  |
| Muscle spasms                                   |                   |  |  |
| subjects affected / exposed                     | 2 / 174 (1.15%)   |  |  |
| occurrences (all)                               | 2                 |  |  |
| Musculoskeletal chest pain                      |                   |  |  |
| subjects affected / exposed                     | 1 / 174 (0.57%)   |  |  |
| occurrences (all)                               | 1                 |  |  |
| Musculoskeletal pain                            |                   |  |  |
| subjects affected / exposed                     | 2 / 174 (1.15%)   |  |  |
| occurrences (all)                               | 2                 |  |  |
| Infections and infestations                     |                   |  |  |
| Bronchitis                                      |                   |  |  |
| subjects affected / exposed                     | 17 / 174 (9.77%)  |  |  |
| occurrences (all)                               | 19                |  |  |
| Influenza                                       |                   |  |  |
| subjects affected / exposed                     | 3 / 174 (1.72%)   |  |  |
| occurrences (all)                               | 3                 |  |  |
| Lower respiratory tract infection               |                   |  |  |
| subjects affected / exposed                     | 10 / 174 (5.75%)  |  |  |
| occurrences (all)                               | 11                |  |  |
| Nasopharyngitis                                 |                   |  |  |
| subjects affected / exposed                     | 31 / 174 (17.82%) |  |  |
| occurrences (all)                               | 38                |  |  |
| Pneumonia                                       |                   |  |  |

|                                    |                   |  |  |
|------------------------------------|-------------------|--|--|
| subjects affected / exposed        | 3 / 174 (1.72%)   |  |  |
| occurrences (all)                  | 3                 |  |  |
| Respiratory tract infection        |                   |  |  |
| subjects affected / exposed        | 8 / 174 (4.60%)   |  |  |
| occurrences (all)                  | 9                 |  |  |
| Rhinitis                           |                   |  |  |
| subjects affected / exposed        | 2 / 174 (1.15%)   |  |  |
| occurrences (all)                  | 2                 |  |  |
| Sinusitis                          |                   |  |  |
| subjects affected / exposed        | 11 / 174 (6.32%)  |  |  |
| occurrences (all)                  | 13                |  |  |
| Upper respiratory tract infection  |                   |  |  |
| subjects affected / exposed        | 31 / 174 (17.82%) |  |  |
| occurrences (all)                  | 43                |  |  |
| Urinary tract infection            |                   |  |  |
| subjects affected / exposed        | 6 / 174 (3.45%)   |  |  |
| occurrences (all)                  | 9                 |  |  |
| Metabolism and nutrition disorders |                   |  |  |
| Decreased appetite                 |                   |  |  |
| subjects affected / exposed        | 17 / 174 (9.77%)  |  |  |
| occurrences (all)                  | 17                |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 02 May 2014      | The IPF diagnostic criteria required for eligibility were expanded to include participants with a diagnosis of definite IPF, probable IPF, possible IPF, or possible high-resolution computed tomography (HRCT) with no surgical lung biopsy (SLB) based on 2011 ATS/ERS/JRS/ALAT guidelines; A Multidisciplinary Discussion of Diagnosis (MDD) based on 2011 ATS/ERS/JRS/ALAT guidelines was utilized to finalize the diagnosis in the event of initial central review outcome results for HRCT and SLB were disparate; Time period for inclusion was extended to 5 years since initial diagnosis of IPF; Historical HRCT scans performed within 12 months of screening Visit 1 were allowed to be used to confirm IPF diagnosis and eligibility; Eligibility was expanded to include participants with minimal or no limitation in lung function indicated by FVC upper limit to 100% predicted. |
| 11 February 2015 | Two cohorts were included of participants to test lebrikizumab as monotherapy (Cohort A) or as combination therapy with pirfenidone (Cohort B); The primary endpoint for each cohort was changed from PFS to the absolute change from baseline to Week 52 in percent predicted FVC; The placebo-controlled study treatment duration was changed from a maximum of 2.5 years to 52 weeks; The statistical analysis considerations and plans were changed based upon the revised target participant populations, treatment duration, and primary endpoint; Open-label treatment (with lebrikizumab) period was added for participants in Cohort A who completed the 52-week placebo-controlled study period; The biosensor substudy was limited to participants who enrolled in the study prior to this version of the protocol.   |
| 27 March 2015    | Clarity was provided with respect to protocol execution to ensure high quality data was captured throughout the study periods in both cohorts.   |
| 02 December 2015 | Number of sites was updated from 110 to 120; The sample size of Cohort B was increased; Stratification for Cohort B was changed to by prior pirfenidone exposure, baseline lung function, and baseline serum periostin concentration; Updates were included to reflect the statistical power of each study cohort, to clarify the time period for the efficacy analysis of Cohort A, and how the missing data was handled for the analysis of primary endpoint.  |
| 23 October 2016  | The objectives, endpoints, and statistical methods were updated; The randomization for Cohort B was modified to be stratified by region, baseline lung function, and baseline serum periostin concentration; The benefit-risk profile for lebrikizumab was updated based on the totality of data from completed studies.   |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported