



## Clinical trial results:

**A randomized, subject- and investigator-blinded, placebo-controlled, parallel group study to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of QBW251 in patients with bronchiectasis**

### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2019-002840-26 |
| Trial protocol           | GB DE          |
| Global end of trial date | 21 June 2023   |

### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1           |
| This version publication date  | 07 July 2024 |
| First version publication date | 07 July 2024 |

### Trial information

#### Trial identification

|                       |               |
|-----------------------|---------------|
| Sponsor protocol code | CQBW251C12201 |
|-----------------------|---------------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT04396366 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Novartis Pharma AG  |
| Sponsor organisation address | Novartis Campus, Basel, Switzerland,  |
| Public contact               | Clinical Disclosure Office , Novartis Pharma AG , 41 613241111, novartis.email@novartis.com |
| Scientific contact           | Clinical Disclosure Office , Novartis Pharma AG , 41 613241111, novartis.email@novartis.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                       | 21 June 2023 |
| Is this the analysis of the primary completion data? | No           |
| Global end of trial reached?                         | Yes          |
| Global end of trial date                             | 21 June 2023 |
| Was the trial ended prematurely?                     | Yes          |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective was to assess the change on sputum bacterial colonization.

Note: Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use <https://www.novctrd.com/CtrdWeb/home.nov> for complete trial results.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 02 February 2021 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | Yes              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United Kingdom: 14 |
| Country: Number of subjects enrolled | Germany: 4         |
| Country: Number of subjects enrolled | Spain: 3           |
| Country: Number of subjects enrolled | China: 21          |
| Worldwide total number of subjects   | 42                 |
| EEA total number of subjects         | 7                  |

Notes:

### Subjects enrolled per age group

|   |   |
|---|---|
| In utero                                  | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days)                      | 0 |
| Infants and toddlers (28 days-23 months)  | 0 |
| Children (2-11 years)                     | 0 |
| Adolescents (12-17 years)                 | 0 |

|                      |    |
|----------------------|----|
| Adults (18-64 years) | 28 |
| From 65 to 84 years  | 14 |
| 85 years and over    | 0  |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

All inclusion and exclusion criteria were checked at screening.

### Period 1

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

### Arms

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

|                  |                     |
|------------------|---------------------|
| <b>Arm title</b> | QBW251 300 mg b.i.d |
|------------------|---------------------|

Arm description:

Participants received QBW251 300 mg orally, twice daily (b.i.d.), for 12 weeks.

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | QBW251       |
| Investigational medicinal product code |              |
| Other name                             |              |
| Pharmaceutical forms                   | Capsule      |
| Routes of administration               | Oral use     |

Dosage and administration details:

Participants received QBW251 300 mg orally, twice daily (b.i.d.), for 12 weeks.

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

Arm description:

Participants received matching placebo, b.i.d., for 12 weeks.

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

Dosage and administration details:

Participants received matching placebo, b.i.d., for 12 weeks.

| Number of subjects in period 1 | QBW251 300 mg b.i.d | Placebo |
|--------------------------------|---------------------|---------|
| Started                        | 21                  | 21      |
| Completed                      | 20                  | 21      |
| Not completed                  | 1                   | 0       |
| Adverse event, non-fatal       | 1                   | -       |



## Baseline characteristics

### Reporting groups

|   |                     |
|---|---------------------|
| Reporting group title   | QBW251 300 mg b.i.d |
| Reporting group description:  |                     |
| Participants received QBW251 300 mg orally, twice daily (b.i.d.), for 12 weeks. |                     |
| Reporting group title   | Placebo             |
| Reporting group description:  |                     |
| Participants received matching placebo, b.i.d., for 12 weeks.                   |                     |

| Reporting group values                                | QBW251 300 mg<br>b.i.d | Placebo | Total |
|---|------------------------|---------|-------|
| Number of subjects                                    | 21                     | 21      | 42    |
| Age categorical<br>Units: Subjects                    |                        |         |       |
| In utero  | 0                      | 0       | 0     |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0                      | 0       | 0     |
| Newborns (0-27 days)                                  | 0                      | 0       | 0     |
| Infants and toddlers (28 days-23<br>months)           | 0                      | 0       | 0     |
| Children (2-11 years)                                 | 0                      | 0       | 0     |
| Adolescents (12-17 years)                             | 0                      | 0       | 0     |
| Adults (18-64 years)                                  | 14                     | 14      | 28    |
| From 65-84 years                                      | 7                      | 7       | 14    |
| 85 years and over                                     | 0                      | 0       | 0     |
| Age Continuous<br>Units: years                        |                        |         |       |
| arithmetic mean                                       | 52.8                   | 56.2    |       |
| standard deviation                                    | ± 15.80                | ± 12.96 | -     |
| Sex: Female, Male<br>Units: participants              |                        |         |       |
| Female  | 11                     | 10      | 21    |
| Male  | 10                     | 11      | 21    |
| Race/Ethnicity, Customized<br>Units: Subjects         |                        |         |       |
| Asian   | 11                     | 10      | 21    |
| White   | 10                     | 11      | 21    |

## End points

### End points reporting groups

|   |                     |
|---|---------------------|
| Reporting group title   | QBW251 300 mg b.i.d |
| Reporting group description:<br>Participants received QBW251 300 mg orally, twice daily (b.i.d.), for 12 weeks. |                     |
| Reporting group title   | Placebo             |
| Reporting group description:<br>Participants received matching placebo, b.i.d., for 12 weeks.                   |                     |

### Primary: Change from Baseline In Bacterial Load Colony-forming Units of Potentially Pathogenic Microorganisms in Sputum at Week 12

|   |  |
|---|--|
| End point title   | Change from Baseline In Bacterial Load Colony-forming Units of Potentially Pathogenic Microorganisms in Sputum at Week 12 <sup>[1]</sup> |
| End point description:<br>No statistical analysis was planned for this primary outcome. |  |
| End point type  | Primary  |
| End point timeframe:<br>Baseline, 12 weeks  |  |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned for this primary outcome measure.

| End point values                     | QBW251 300 mg b.i.d | Placebo          |  |  |
|--------------------------------------|---------------------|------------------|--|--|
| Subject group type                   | Reporting group     | Reporting group  |  |  |
| Number of subjects analysed          | 13                  | 19               |  |  |
| Units: CFU/mL                        |                     |                  |  |  |
| arithmetic mean (standard deviation) | -0.192 (± 1.4621)   | 0.340 (± 1.6476) |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Proportion of Participants with Absence of any Colony-forming Units of Potentially Pathogenic Bacteria Sputum

|  |   |
|--|---|
| End point title                            | Proportion of Participants with Absence of any Colony-forming Units of Potentially Pathogenic Bacteria Sputum |
| End point description:                     |   |
| End point type                             | Secondary   |
| End point timeframe:<br>Baseline, 12 weeks |   |

| End point values            | QBW251 300 mg b.i.d | Placebo         |  |  |
|-----------------------------|---------------------|-----------------|--|--|
| Subject group type          | Reporting group     | Reporting group |  |  |
| Number of subjects analysed | 21                  | 21              |  |  |
| Units: participants         | 0                   | 0               |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in Fibrinogen Plasma Concentration

|                        |   |
|------------------------|---|
| End point title        | Change from Baseline in Fibrinogen Plasma Concentration |
| End point description: |   |
| End point type         | Secondary   |
| End point timeframe:   |   |
| Baseline, 12 weeks     |   |

| End point values                     | QBW251 300 mg b.i.d    | Placebo                |  |  |
|--------------------------------------|------------------------|------------------------|--|--|
| Subject group type                   | Reporting group        | Reporting group        |  |  |
| Number of subjects analysed          | 19                     | 19                     |  |  |
| Units: g/L                           |                        |                        |  |  |
| arithmetic mean (standard deviation) | -0.193 ( $\pm$ 0.6278) | -0.127 ( $\pm$ 0.4828) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from baseline in Quality of Life Questionnaire for Bronchiectasis (QOL-B) (Respiratory Symptoms Domain)

|                 |  |
|-----------------|--|
| End point title | Change from baseline in Quality of Life Questionnaire for Bronchiectasis (QOL-B) (Respiratory Symptoms Domain) |
|-----------------|--|

End point description:

The Quality of Life Questionnaire for Bronchiectasis (QOL-B) is a disease-specific questionnaire developed for non-cystic fibrosis bronchiectasis. It covers 8 dimensions: physical functioning, role functioning, emotional functioning, social functioning, vitality, treatment burden, health perceptions, and respiratory symptoms. Each dimension is scored separately on a scale of 0 to 100, and higher scores represent better outcomes. Only the respiratory symptoms domain score will be reported for this outcome measure. Errors have been identified for the Quality of Life Questionnaire for Bronchiectasis (QOL-B) outcome measure in the final CSR, which don't allow us to report results at this time. The CSR is currently being amended, and results will be provided by November 2024.



|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Baseline, 12 weeks   |           |

|                                      |                     |                  |  |  |
|--------------------------------------|---------------------|------------------|--|--|
| <b>End point values</b>              | QBW251 300 mg b.i.d | Placebo          |  |  |
| Subject group type                   | Reporting group     | Reporting group  |  |  |
| Number of subjects analysed          | 0 <sup>[2]</sup>    | 0 <sup>[3]</sup> |  |  |
| Units: score                         |                     |                  |  |  |
| arithmetic mean (standard deviation) | ()                  | ()               |  |  |

Notes:

[2] - Data to be provided by November 2024.

[3] - Data to be provided by November 2024.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline in Rescue Medication Use (Salbutamol/Albuterol)

|                 |  |
|-----------------|--|
| End point title | Change from Baseline in Rescue Medication Use (Salbutamol/Albuterol) |
|-----------------|--|

End point description:

Data were collected as the number of puffs taken at every 12-hour window. The first 12 hours of the day were categorized as "Morning" and the next 12 hours as "Evening". Total daily number of puffs was derived for each 24-hour window (per day), which was then used to calculate weekly and monthly average number of puffs taken. Baseline rescue medication use was defined as the average number of puffs per day in the screening period and the morning record at Day 1.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Baseline, 12 weeks   |           |

|                                      |                     |                 |  |  |
|--------------------------------------|---------------------|-----------------|--|--|
| <b>End point values</b>              | QBW251 300 mg b.i.d | Placebo         |  |  |
| Subject group type                   | Reporting group     | Reporting group |  |  |
| Number of subjects analysed          | 16                  | 20              |  |  |
| Units: number of puffs               |                     |                 |  |  |
| arithmetic mean (standard deviation) | -0.37 (± 1.069)     | 0.14 (± 0.895)  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline in Pre-bronchodilator Forced Exploratory Volume in the First Second (FEV1)

|                 |   |
|-----------------|---|
| End point title | Change from Baseline in Pre-bronchodilator Forced Exploratory Volume in the First Second (FEV1) |
|-----------------|---|

End point description:

Errors have been identified for the Quality of Life Questionnaire for Bronchiectasis (QOL-B) outcome measure in the final CSR, which don't allow us to report results at this time. The CSR is currently being amended, and results will be provided by November 2024.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Baseline, 12 weeks   |           |

|                                      |                     |                  |  |  |
|--------------------------------------|---------------------|------------------|--|--|
| <b>End point values</b>              | QBW251 300 mg b.i.d | Placebo          |  |  |
| Subject group type                   | Reporting group     | Reporting group  |  |  |
| Number of subjects analysed          | 0 <sup>[4]</sup>    | 0 <sup>[5]</sup> |  |  |
| Units: liters                        |                     |                  |  |  |
| arithmetic mean (standard deviation) | ( )                 | ( )              |  |  |

Notes:

[4] - Data to be provided by November 2024.

[5] - Data to be provided by November 2024.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline in Pre-bronchodilator Forced Vital Capacity (FVC)

|                 |  |
|-----------------|--|
| End point title | Change from Baseline in Pre-bronchodilator Forced Vital Capacity (FVC) |
|-----------------|--|

End point description:

Errors have been identified for the Quality of Life Questionnaire for Bronchiectasis (QOL-B) outcome measure in the final CSR, which don't allow us to report results at this time. The CSR is currently being amended, and results will be provided by November 2024.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Baseline, 12 weeks   |           |

|                                      |                     |                  |  |  |
|--------------------------------------|---------------------|------------------|--|--|
| <b>End point values</b>              | QBW251 300 mg b.i.d | Placebo          |  |  |
| Subject group type                   | Reporting group     | Reporting group  |  |  |
| Number of subjects analysed          | 0 <sup>[6]</sup>    | 0 <sup>[7]</sup> |  |  |
| Units: liters                        |                     |                  |  |  |
| arithmetic mean (standard deviation) | ( )                 | ( )              |  |  |

Notes:

[6] - Data to be provided by November 2024.

[7] - Data to be provided by November 2024.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline in Bronchus Area with Perimeter of 10 Millimeters

|                 |  |
|-----------------|--|
| End point title | Change from Baseline in Bronchus Area with Perimeter of 10 |
|-----------------|--|

|  |             |
|--|-------------|
|  | Millimeters |
| End point description:                                 |             |
| Measured by high resolution computed tomography (HRCT) |             |
| End point type   | Secondary   |
| End point timeframe:                                   |             |
| Baseline, 12 weeks                                     |             |

| End point values                                   | QBW251 300 mg b.i.d | Placebo           |  |  |
|--|---------------------|-------------------|--|--|
| Subject group type                                 | Reporting group     | Reporting group   |  |  |
| Number of subjects analysed                        | 21                  | 21                |  |  |
| Units: mm  |                     |                   |  |  |
| arithmetic mean (standard deviation)               |                     |                   |  |  |
| Left Inferior Lobe Posterior Basal Segment n=21,21 | -0.072 (± 0.3592)   | -0.029 (± 1456)   |  |  |
| Left Superior Lobe Apical Segment n=16,18          | -0.063 (± 0.4140)   | 0.029 (± 0.1600)  |  |  |
| Right Inferior Lobe Post. Basal Segment n=14,18    | 0.001 (± 0.1999)    | -0.015 (± 0.1071) |  |  |
| Right Middle Lobe Lateral Segment n=16,19          | 0.074 (± 0.1867)    | 0.039 (± 0.1471)  |  |  |
| Right Superior Lobe Apical Segment n=15,19         | -0.037 (± 0.1990)   | -0.026 (± 0.0991) |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline in Mucus Score

|                        |                                     |
|------------------------|-------------------------------------|
| End point title        | Change from Baseline in Mucus Score |
| End point description: |                                     |
| Measured by HRCT       |                                     |
| End point type         | Secondary                           |
| End point timeframe:   |                                     |
| Baseline, 12 weeks     |                                     |

| End point values                     | QBW251 300 mg b.i.d | Placebo         |  |  |
|--------------------------------------|---------------------|-----------------|--|--|
| Subject group type                   | Reporting group     | Reporting group |  |  |
| Number of subjects analysed          | 21                  | 21              |  |  |
| Units: score                         |                     |                 |  |  |
| arithmetic mean (standard deviation) |                     |                 |  |  |
| Lower Lobe Bronchus, Left n=15,17    | -0.9 (± 3.13)       | -0.8 (± 1.68)   |  |  |
| Lung, Left Upper Lobe n=15,18        | -0.9 (± 3.13)       | -0.8 (± 1.63)   |  |  |
| Lung, Right Lower Lobe n=16,19       | -0.9 (± 3.03)       | -1.6 (± 3.83)   |  |  |
| Lung, Right Upper Lobe n=16,19       | -0.9 (± 3.03)       | -1.6 (± 3.83)   |  |  |

|   |               |               |  |  |
|---|---------------|---------------|--|--|
| Lung, Right, Middle Lobe, Lateral Segment n=16,19 | -0.9 (± 3.03) | -1.6 (± 3.83) |  |  |
| Lung, Right, Middle Lobe, Medial Segment n=16,19  | -0.9 (± 3.03) | -1.6 (± 3.83) |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline in Region Percent Below or Equal to -856 Hounsfield units (HU)

|                 |   |
|-----------------|---|
| End point title | Change from Baseline in Region Percent Below or Equal to -856 Hounsfield units (HU) |
|-----------------|---|

End point description:

The region percent below or equal to -856 HU represents air trapping, which was evaluated by HRCT in the whole lung and in the regions (thirds, lobes).

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

End point timeframe:

Baseline, 12 weeks

| End point values                                | QBW251 300 mg b.i.d | Placebo            |  |  |
|---|---------------------|--------------------|--|--|
| Subject group type                              | Reporting group     | Reporting group    |  |  |
| Number of subjects analysed                     | 21                  | 21                 |  |  |
| Units: change from baseline in % $\leq$ -856 HU |                     |                    |  |  |
| arithmetic mean (standard deviation)            |                     |                    |  |  |
| Lung n=15,17                                    | -0.284 (± 9.2755)   | -1.074 (± 8.7794)  |  |  |
| Lung, Left n=15,17                              | -1.659 (± 8.5613)   | -1.095 (± 7.2200)  |  |  |
| Lung, Left Lower Lobe n=15,17                   | -3.582 (± 8.4976)   | -2.975 (± 7.8007)  |  |  |
| Lung, Left Upper Lobe n=15,17                   | 0.002 (± 10.3698)   | 1.946 (± 10.7307)  |  |  |
| Lung, Right n=15,17                             | 1.410 (± 10.8421)   | -1.552 (± 10.1631) |  |  |
| Lung, Right Lower Lobe n=15,17                  | 0.303 (± 7.9933)    | -2.193 (± 10.7784) |  |  |
| Lung, Right Middle Lobe n=15,17                 | 2.877 (± 10.3635)   | 0.502 (± 9.3885)   |  |  |
| Lung, Right Upper Lobe n=15,17                  | 1.513 (± 13.1404)   | -2.105 (± 11.4788) |  |  |
| Thirds, Left Lower n=15,17                      | -2.726 (± 9.4063)   | -1.109 (± 4.8754)  |  |  |
| Thirds, Left Middle n=15,17                     | -2.319 (± 8.3145)   | -0.892 (± 8.0664)  |  |  |
| Thirds, Left Upper n=15,17                      | 0.940 (± 10.8083)   | -1.056 (± 9.7966)  |  |  |
| Thirds, Right Lower n=15,17                     | 0.394 (± 9.2444)    | -2.214 (± 9.6626)  |  |  |
| Thirds, Right Middle n=15,17                    | 1.563 (± 11.7119)   | -0.804 (± 10.4909) |  |  |

|                             |                      |                       |  |  |
|-----------------------------|----------------------|-----------------------|--|--|
| Thirds, Right Upper n=15,17 | 1.905 (±<br>12.7615) | -2.052 (±<br>11.7677) |  |  |
|-----------------------------|----------------------|-----------------------|--|--|

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in Region Air Volume

|                        |   |
|------------------------|---|
| End point title        | Change from Baseline in Region Air Volume |
| End point description: |   |
| Measured by HRCT       |   |
| End point type         | Secondary                                 |
| End point timeframe:   |   |
| Baseline, 12 weeks     |   |

| End point values                     | QBW251 300<br>mg b.i.d | Placebo                |  |  |
|--------------------------------------|------------------------|------------------------|--|--|
| Subject group type                   | Reporting group        | Reporting group        |  |  |
| Number of subjects analysed          | 21                     | 21                     |  |  |
| Units: liters                        |                        |                        |  |  |
| arithmetic mean (standard deviation) |                        |                        |  |  |
| Lung n=16,19                         | 7.588 (±<br>362.231)   | -4.667 (±<br>323.292)  |  |  |
| Lung, Left n=16,19                   | 6.719 (±<br>188.304)   | -7.304 (±<br>144.047)  |  |  |
| Lung, Left Lower Lobe n=15,19        | 22.142 (±<br>125.643)  | -14.848 (±<br>84.4328) |  |  |
| Lung, Left Upper Lobe n=16,19        | -14.039 (±<br>82.9500) | 7.545 (±<br>69.1768)   |  |  |
| Lung, Right n=16,19                  | 0.869 (±<br>179.912)   | 2.637 (±<br>190.892)   |  |  |
| Lung, Right Lower Lobe n=16,19       | 9.886 (±<br>95.0629)   | -5.435 (±<br>105.079)  |  |  |
| Lung, Right Middle Lobe n=16,19      | -3.233 (±<br>20.4193)  | 1.242 (±<br>13.5834)   |  |  |
| Lung, Right Upper Lobe n=16,19       | -5.784 (±<br>78.3195)  | 6.830 (±<br>81.4095)   |  |  |
| Thirds, Left Lower n=16,19           | -3.409 (±<br>82.0621)  | -5.155 (±<br>50.2945)  |  |  |
| Thirds, Left Middle n=16,19          | -1.319 (±<br>76.6437)  | -1.992 (±<br>63.8795)  |  |  |
| Thirds, Left Upper n=16,19           | 11.444 (±<br>73.0426)  | -0.432 (±<br>41.7288)  |  |  |
| Thirds, Right Lower n=16,19          | -20.490 (±<br>122.493) | -7.548 (±<br>76.9902)  |  |  |
| Thirds, Right Middle n=16,19         | 8.762 (±<br>98.3416)   | 2.994 (±<br>93.2434)   |  |  |
| Thirds, Right Upper n=16,19          | 12.574 (±<br>84.6939)  | 5.327 (±<br>60.5143)   |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline in Segment Average Inner Area

|                 |  |
|-----------------|--|
| End point title | Change from Baseline in Segment Average Inner Area |
|-----------------|--|

End point description:

Measured by HRCT

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

End point timeframe:

Baseline, 12 weeks

| End point values                                     | QBW251 300<br>mg b.i.d | Placebo               |  |  |
|--|------------------------|-----------------------|--|--|
| Subject group type                                   | Reporting group        | Reporting group       |  |  |
| Number of subjects analysed                          | 21                     | 21                    |  |  |
| Units: mm <sup>2</sup>                               |                        |                       |  |  |
| arithmetic mean (standard deviation)                 |                        |                       |  |  |
| Lower Lobe Bronchus, Left n=15,17                    | 2.009 (±<br>10.4977)   | -1.376 (±<br>6.5410)  |  |  |
| Lung, Left Upper Lobe n=15,18                        | 1.106 (±<br>11.1387)   | 1.506 (±<br>7.5668)   |  |  |
| Lung, Right Lower Lobe n=16,19                       | -0.677 (±<br>7.9904)   | -2.119 (±<br>6.7263)  |  |  |
| Lung, Right Upper Lobe n=16,19                       | 0.667 (±<br>4.9950)    | -2.653 (±<br>14.9922) |  |  |
| Lung, Right, Middle Lobe, Lateral<br>Segment n=16,19 | 0.138 (±<br>4.8198)    | -0.379 (±<br>2.8929)  |  |  |
| Lung, Right, Middle Lobe, Medial<br>Segment n=16,19  | -0.502 (±<br>5.2215)   | 1.828 (±<br>5.5992)   |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline in Segment Average Major Inner Diameter

|                 |  |
|-----------------|--|
| End point title | Change from Baseline in Segment Average Major Inner Diameter |
|-----------------|--|

End point description:

Measured by HRCT

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

End point timeframe:

Baseline, 12 weeks

| End point values                                  | QBW251 300 mg b.i.d | Placebo           |  |  |
|---|---------------------|-------------------|--|--|
| Subject group type                                | Reporting group     | Reporting group   |  |  |
| Number of subjects analysed                       | 21                  | 21                |  |  |
| Units: mm   |                     |                   |  |  |
| arithmetic mean (standard deviation)              |                     |                   |  |  |
| Lower Lobe Bronchus, Left n=15,17                 | 0.364 (± 1.0234)    | -0.128 (± 0.5242) |  |  |
| Lung, Left Upper Lobe n=15,18                     | -0.095 (± 0.7972)   | -0.116 (± 0.7192) |  |  |
| Lung, Right Lower Lobe n=16,19                    | -0.040 (± 0.7883)   | -0.207 (± 0.7876) |  |  |
| Lung, Right Upper Lobe n=16,19                    | 0.081 (± 0.7149)    | -0.525 (± 1.9690) |  |  |
| Lung, Right, Middle Lobe, Lateral Segment n=16,19 | 0.075 (± 0.9001)    | -0.066 (± 0.5419) |  |  |
| Lung, Right, Middle Lobe, Medial Segment n=16,19  | 0.046 (± 0.8759)    | 0.336 (± 1.2354)  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline in Segment Average Minor Inner Diameter

|                        |  |
|------------------------|--|
| End point title        | Change from Baseline in Segment Average Minor Inner Diameter |
| End point description: |  |
| Measured by HRCT       |  |
| End point type         | Secondary  |
| End point timeframe:   |  |
| Baseline, 12 weeks     |  |

| End point values                     | QBW251 300 mg b.i.d | Placebo           |  |  |
|--------------------------------------|---------------------|-------------------|--|--|
| Subject group type                   | Reporting group     | Reporting group   |  |  |
| Number of subjects analysed          | 21                  | 21                |  |  |
| Units: mm                            |                     |                   |  |  |
| arithmetic mean (standard deviation) |                     |                   |  |  |
| Lower Lobe Bronchus, Left n=15,17    | 0.080 (± 0.8100)    | -0.204 (± 0.7995) |  |  |
| Lung, Left Upper Lobe n=15,18        | 0.160 (± 0.7449)    | 0.120 (± 0.5935)  |  |  |
| Lung, Right Lower Lobe n=16,19       | -0.011 (± 0.6186)   | -0.220 (± 0.6556) |  |  |

|   |                   |                   |  |  |
|---|-------------------|-------------------|--|--|
| Lung, Right Upper Lobe n=16,19                    | 0.034 (± 0.4546)  | 0.127 (± 0.5699)  |  |  |
| Lung, Right, Middle Lobe, Lateral Segment n=16,19 | -0.037 (± 0.5225) | -0.058 (± 0.4702) |  |  |
| Lung, Right, Middle Lobe, Medial Segment n=16,19  | -0.309 (± 0.7621) | 0.065 (± 0.5016)  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in Segment Average Outer Area

|  |  |
|--|--|
| End point title                            | Change from Baseline in Segment Average Outer Area |
| End point description:<br>Measured by HRCT |  |
| End point type                             | Secondary  |
| End point timeframe:<br>Baseline, 12 weeks |  |

| End point values                                  | QBW251 300 mg b.i.d | Placebo            |  |  |
|---|---------------------|--------------------|--|--|
| Subject group type                                | Reporting group     | Reporting group    |  |  |
| Number of subjects analysed                       | 21                  | 21                 |  |  |
| Units: mm <sup>2</sup>                            |                     |                    |  |  |
| arithmetic mean (standard deviation)              |                     |                    |  |  |
| Lower Lobe Bronchus, Left n=15,17                 | 3.805 (± 15.3509)   | -3.575 (± 9.6603)  |  |  |
| Lung, Left Upper Lobe n=15,18                     | 2.527 (± 25.2783)   | 6.387 (± 15.1487)  |  |  |
| Lung, Right Lower Lobe n=16,19                    | -0.887 (± 13.2296)  | -2.439 (± 10.4313) |  |  |
| Lung, Right Upper Lobe n=16,19                    | 3.054 (± 11.6503)   | -6.171 (± 35.7465) |  |  |
| Lung, Right, Middle Lobe, Lateral Segment n=16,19 | 0.011 (± 8.9779)    | -0.574 (± 6.6601)  |  |  |
| Lung, Right, Middle Lobe, Medial Segment n=16,19  | -1.929 (± 12.3065)  | 3.655 (± 9.0492)   |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in Segment Average Wall Area Fraction

|  |  |
|--|--|
| End point title                            | Change from Baseline in Segment Average Wall Area Fraction |
| End point description:<br>Measured by HRCT |  |
| End point type                             | Secondary  |



End point timeframe:

Baseline, 12 weeks

| End point values                                  | QBW251 300 mg b.i.d | Placebo           |  |  |
|---|---------------------|-------------------|--|--|
| Subject group type                                | Reporting group     | Reporting group   |  |  |
| Number of subjects analysed                       | 21                  | 21                |  |  |
| Units: percent                                    |                     |                   |  |  |
| arithmetic mean (standard deviation)              |                     |                   |  |  |
| Lower Lobe Bronchus, Left n=15,17                 | -0.009 (± 0.0515)   | -0.002 (± 0.0310) |  |  |
| Lung, Left Upper Lobe n=15,18                     | 0.002 (± 0.0553)    | 0.013 (± 0.0436)  |  |  |
| Lung, Right Lower Lobe n=16,19                    | 0.001 (± 0.0377)    | 0.011 (± 0.0277)  |  |  |
| Lung, Right Upper Lobe n=16,19                    | 0.007 (± 0.0392)    | 0.001 (± 0.0347)  |  |  |
| Lung, Right, Middle Lobe, Lateral Segment n=16,19 | -0.002 (± 0.0414)   | 0.006 (± 0.0262)  |  |  |
| Lung, Right, Middle Lobe, Medial Segment n=16,19  | 0.007 (± 0.0281)    | 0.002 (± 0.0347)  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline in Segment Average Wall Thickness

|                        |  |
|------------------------|--|
| End point title        | Change from Baseline in Segment Average Wall Thickness |
| End point description: |  |
| Measured by HRCT       |  |
| End point type         | Secondary  |
| End point timeframe:   |  |
| Baseline, 12 weeks     |  |

| End point values                     | QBW251 300 mg b.i.d | Placebo           |  |  |
|--------------------------------------|---------------------|-------------------|--|--|
| Subject group type                   | Reporting group     | Reporting group   |  |  |
| Number of subjects analysed          | 21                  | 21                |  |  |
| Units: mm                            |                     |                   |  |  |
| arithmetic mean (standard deviation) |                     |                   |  |  |
| Lower Lobe Bronchus, Left n=15,17    | 0.001 (± 0.1680)    | -0.042 (± 0.0987) |  |  |
| Lung, Left Upper Lobe n=15,18        | 0.014 (± 0.3422)    | 0.081 (± 0.2417)  |  |  |
| Lung, Right Lower Lobe n=16,19       | 0.001 (± 0.1691)    | 0.021 (± 0.0900)  |  |  |

|   |                   |                   |  |  |
|---|-------------------|-------------------|--|--|
| Lung, Right Upper Lobe n=16,19                    | 0.054 (± 0.2231)  | -0.030 (± 0.2941) |  |  |
| Lung, Right, Middle Lobe, Lateral Segment n=16,19 | -0.014 (± 0.0828) | -0.004 (± 0.0968) |  |  |
| Lung, Right, Middle Lobe, Medial Segment n=16,19  | -0.040 (± 0.1606) | 0.057 (± 0.0766)  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline in Segment Wall Area Percent

|                        |   |
|------------------------|---|
| End point title        | Change from Baseline in Segment Wall Area Percent |
| End point description: |   |
| Measured by HRCT       |   |
| End point type         | Secondary   |
| End point timeframe:   |   |
| Baseline, 12 weeks     |   |

| End point values                                  | QBW251 300 mg b.i.d | Placebo           |  |  |
|---|---------------------|-------------------|--|--|
| Subject group type                                | Reporting group     | Reporting group   |  |  |
| Number of subjects analysed                       | 21                  | 21                |  |  |
| Units: percent                                    |                     |                   |  |  |
| arithmetic mean (standard deviation)              |                     |                   |  |  |
| Lower Lobe Bronchus, Left n=15,17                 | -0.009 (± 0.0515)   | -0.002 (± 0.0305) |  |  |
| Lung, Left Upper Lobe n=15,18                     | 0.002 (± 0.0553)    | 0.013 (± 0.0437)  |  |  |
| Lung, Right Lower Lobe n=16,19                    | 0.001 (± 0.0376)    | 0.011 (± 0.0276)  |  |  |
| Lung, Right Upper Lobe n=16,19                    | 0.007 (± 0.0394)    | 0.002 (± 0.0337)  |  |  |
| Lung, Right, Middle Lobe, Lateral Segment n=16,19 | -0.003 (± 0.0411)   | 0.006 (± 0.0261)  |  |  |
| Lung, Right, Middle Lobe, Medial Segment n=16,19  | 0.007 (± 0.0282)    | 0.002 (± 0.0347)  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline in Segment Wall Area

|                        |   |
|------------------------|---|
| End point title        | Change from Baseline in Segment Wall Area |
| End point description: |   |
| Measured by HRCT       |   |
| End point type         | Secondary                                 |

End point timeframe:

Baseline, 12 weeks

| End point values                                  | QBW251 300 mg b.i.d | Placebo            |  |  |
|---|---------------------|--------------------|--|--|
| Subject group type                                | Reporting group     | Reporting group    |  |  |
| Number of subjects analysed                       | 21                  | 21                 |  |  |
| Units: mm <sup>2</sup>                            |                     |                    |  |  |
| arithmetic mean (standard deviation)              |                     |                    |  |  |
| Lower Lobe Bronchus, Left n=15,17                 | 1.796 (± 6.6301)    | -2.199 (± 4.3938)  |  |  |
| Lung, Left Upper Lobe n=15,18                     | 1.421 (± 18.5698)   | 4.881 (± 12.4380)  |  |  |
| Lung, Right Lower Lobe n=16,19                    | -0.209 (± 6.9730)   | -0.320 (± 4.5446)  |  |  |
| Lung, Right Upper Lobe n=16,19                    | 2.388 (± 9.7223)    | -3.518 (± 21.8864) |  |  |
| Lung, Right, Middle Lobe, Lateral Segment n=16,19 | -0.127 (± 4.6312)   | -0.194 (± 4.0452)  |  |  |
| Lung, Right, Middle Lobe, Medial Segment n=16,19  | -1.427 (± 7.3051)   | 1.827 (± 3.8885)   |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Cmax of QBW251

|   |                               |
|---|-------------------------------|
| End point title   | Cmax of QBW251 <sup>[8]</sup> |
| End point description:  |                               |
| Maximum (peak) plasma concentration of QBW251   |                               |
| End point type  | Secondary                     |
| End point timeframe:  |                               |
| 1h, 2h, 3h, 4h, 6h and 8h post-dose on Days 1 and 28, and 3h post-dose on Day 56 and Day 84 |                               |

Notes:

[8] - 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: Pharmacokinetic parameters were only analyzed for the QBW251 arm.

| End point values                     | QBW251 300 mg b.i.d |  |  |  |
|--------------------------------------|---------------------|--|--|--|
| Subject group type                   | Reporting group     |  |  |  |
| Number of subjects analysed          | 21                  |  |  |  |
| Units: ng/mL                         |                     |  |  |  |
| arithmetic mean (standard deviation) |                     |  |  |  |
| Day 1 n=19                           | 1120 (± 913)        |  |  |  |
| Day 28 n=19                          | 1520 (± 951)        |  |  |  |
| Day 56 n=19                          | 1190 (± 578)        |  |  |  |
| Day 84 n=18                          | 1460 (± 947)        |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Ctrough of QBW251

|                 |                                  |
|-----------------|----------------------------------|
| End point title | Ctrough of QBW251 <sup>[9]</sup> |
|-----------------|----------------------------------|

End point description:

Trough (pre-dose) plasma concentration of QBW251

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

End point timeframe:

Pre-dose Day 1, Day 28, Day 56, Day 84

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: Pharmacokinetic parameters were only analyzed for the QBW251 arm.

| End point values                     | QBW251 300 mg b.i.d |  |  |  |
|--------------------------------------|---------------------|--|--|--|
| Subject group type                   | Reporting group     |  |  |  |
| Number of subjects analysed          | 21                  |  |  |  |
| Units: ng/mL                         |                     |  |  |  |
| arithmetic mean (standard deviation) |                     |  |  |  |
| Day 1 n=21                           | 0.00 (± 0.00)       |  |  |  |
| Day 28 n=20                          | 489 (± 371)         |  |  |  |
| Day 56 n=19                          | 483 (± 395)         |  |  |  |
| Day 84 n=18                          | 498 (± 416)         |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Ctrough of QBW251 for a Serial PK Set

|                 |   |
|-----------------|---|
| End point title | Ctrough of QBW251 for a Serial PK Set <sup>[10]</sup> |
|-----------------|---|

End point description:

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

End point timeframe:

Pre-dose, 1h, 2h, 3h, 4h, 6h and 8h post-dose on Day 1 and Day 28

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: Pharmacokinetic parameters were only analyzed for the QBW251 arm.

|                                      |                     |  |  |  |
|--------------------------------------|---------------------|--|--|--|
| <b>End point values</b>              | QBW251 300 mg b.i.d |  |  |  |
| Subject group type                   | Reporting group     |  |  |  |
| Number of subjects analysed          | 3                   |  |  |  |
| Units: ng/mL                         |                     |  |  |  |
| arithmetic mean (standard deviation) |                     |  |  |  |
| Day 1                                | 0.00 (± 0.00)       |  |  |  |
| Day 28                               | 603 (± 142)         |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Cmax of QBW251 for a Serial PK Set

|                 |  |
|-----------------|--|
| End point title | Cmax of QBW251 for a Serial PK Set <sup>[11]</sup> |
|-----------------|--|

End point description:

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

End point timeframe:

Pre-dose, 1h, 2h, 3h, 4h, 6h and 8h post-dose on Day 1 and Day 28

Notes:

[11] - 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: Pharmacokinetic parameters were only analyzed for the QBW251 arm.

|                                      |                     |  |  |  |
|--------------------------------------|---------------------|--|--|--|
| <b>End point values</b>              | QBW251 300 mg b.i.d |  |  |  |
| Subject group type                   | Reporting group     |  |  |  |
| Number of subjects analysed          | 3                   |  |  |  |
| Units: ng/mL                         |                     |  |  |  |
| arithmetic mean (standard deviation) |                     |  |  |  |
| Day 1                                | 2470 (± 787)        |  |  |  |
| Day 28                               | 3000 (± 1390)       |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: AUClast of QBW251 for a Serial PK Set

|                 |   |
|-----------------|---|
| End point title | AUClast of QBW251 for a Serial PK Set <sup>[12]</sup> |
|-----------------|---|

End point description:

Area under the concentration-time curve up to the last measurable concentration of QBW251 (AUClast)

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

End point timeframe:

Pre-dose, 1h, 2h, 3h, 4h, 6h and 8h post-dose on Day 1 and Day 28

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: Pharmacokinetic parameters were only analyzed for the QBW251 arm.

|                                      |                     |  |  |  |
|--------------------------------------|---------------------|--|--|--|
| <b>End point values</b>              | QBW251 300 mg b.i.d |  |  |  |
| Subject group type                   | Reporting group     |  |  |  |
| Number of subjects analysed          | 3                   |  |  |  |
| Units: h*ng/mL                       |                     |  |  |  |
| arithmetic mean (standard deviation) |                     |  |  |  |
| Day 1                                | 6100 (± 2340)       |  |  |  |
| Day 28                               | 10300 (± 3100)      |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Tmax of QBW251 for a Serial PK Set

|  |  |
|--|--|
| End point title  | Tmax of QBW251 for a Serial PK Set <sup>[13]</sup> |
| End point description:   |  |
| Time to reach maximum (peak) plasma concentration after single-dose administration |  |
| End point type   | Secondary  |
| End point timeframe:   |  |
| Pre-dose, 1h, 2h, 3h, 4h, 6h and 8h post-dose on Day 1 and Day 28                  |  |

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: Pharmacokinetic parameters were only analyzed for the QBW251 arm.

|                               |                     |  |  |  |
|-------------------------------|---------------------|--|--|--|
| <b>End point values</b>       | QBW251 300 mg b.i.d |  |  |  |
| Subject group type            | Reporting group     |  |  |  |
| Number of subjects analysed   | 3                   |  |  |  |
| Units: hours                  |                     |  |  |  |
| median (full range (min-max)) |                     |  |  |  |
| Day 1                         | 1.00 (1.00 to 4.00) |  |  |  |
| Day 28                        | 2.00 (1.00 to 3.08) |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: AUC0-12h of QBW251 for a Serial PK Set

|                 |  |
|-----------------|--|
| End point title | AUC0-12h of QBW251 for a Serial PK Set <sup>[14]</sup> |
|-----------------|--|

|   |           |
|---|-----------|
| End point description:  |           |
| Twelve-hour AUC   |           |
| End point type  | Secondary |
| End point timeframe:  |           |
| Pre-dose, 1h, 2h, 3h, 4h, 6h and 8h post-dose on Day 1 and Day 28 |           |

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: Pharmacokinetic parameters were only analyzed for the QBW251 arm.

|                                      |                     |  |  |  |
|--------------------------------------|---------------------|--|--|--|
| <b>End point values</b>              | QBW251 300 mg b.i.d |  |  |  |
| Subject group type                   | Reporting group     |  |  |  |
| Number of subjects analysed          | 3                   |  |  |  |
| Units: h*ng/mL                       |                     |  |  |  |
| arithmetic mean (standard deviation) |                     |  |  |  |
| Day 1 n=2                            | 5260 (± 1780)       |  |  |  |
| Day 28 n=1                           | 15400 (± 999)       |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Tlast of QBW251 for a Serial PK Set

|   |   |
|---|---|
| End point title   | Tlast of QBW251 for a Serial PK Set <sup>[15]</sup> |
| End point description:  |   |
| Tlast is the last measurable concentration sampling time.         |   |
| End point type  | Secondary   |
| End point timeframe:  |   |
| Pre-dose, 1h, 2h, 3h, 4h, 6h and 8h post-dose on Day 1 and Day 28 |   |

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: Pharmacokinetic parameters were only analyzed for the QBW251 arm.

|                                      |                     |  |  |  |
|--------------------------------------|---------------------|--|--|--|
| <b>End point values</b>              | QBW251 300 mg b.i.d |  |  |  |
| Subject group type                   | Reporting group     |  |  |  |
| Number of subjects analysed          | 3                   |  |  |  |
| Units: hours                         |                     |  |  |  |
| arithmetic mean (standard deviation) |                     |  |  |  |
| Day 1                                | 7.99 (± 0.00962)    |  |  |  |
| Day 28                               | 8.00 (± 0.00)       |  |  |  |

## Statistical analyses





## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 25.1 |
|--------------------|------|

### Reporting groups

|                       |                     |
|-----------------------|---------------------|
| Reporting group title | QBW251 300 mg b.i.d |
|-----------------------|---------------------|

Reporting group description:

QBW251 300 mg b.i.d

|                       |       |
|-----------------------|-------|
| Reporting group title | Total |
|-----------------------|-------|

Reporting group description:

Total

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

Reporting group description:

Placebo

| Serious adverse events                            | QBW251 300 mg b.i.d | Total          | Placebo        |
|---|---------------------|----------------|----------------|
| Total subjects affected by serious adverse events |                     |                |                |
| subjects affected / exposed                       | 2 / 21 (9.52%)      | 2 / 42 (4.76%) | 0 / 21 (0.00%) |
| number of deaths (all causes)                     | 0                   | 0              | 0              |
| number of deaths resulting from adverse events    | 0                   | 0              | 0              |
| Renal and urinary disorders                       |                     |                |                |
| Tubulointerstitial nephritis                      |                     |                |                |
| subjects affected / exposed                       | 1 / 21 (4.76%)      | 1 / 42 (2.38%) | 0 / 21 (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          |
| Infections and infestations                       |                     |                |                |
| Infective exacerbation of bronchiectasis          |                     |                |                |
| subjects affected / exposed                       | 1 / 21 (4.76%)      | 1 / 42 (2.38%) | 0 / 21 (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          |

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

| <b>Non-serious adverse events</b>                     | QBW251 300 mg<br>b.i.d | Total            | Placebo          |
|---|------------------------|------------------|------------------|
| Total subjects affected by non-serious adverse events |                        |                  |                  |
| subjects affected / exposed                           | 14 / 21 (66.67%)       | 27 / 42 (64.29%) | 13 / 21 (61.90%) |
| Nervous system disorders                              |                        |                  |                  |
| Dizziness   |                        |                  |                  |
| subjects affected / exposed                           | 3 / 21 (14.29%)        | 3 / 42 (7.14%)   | 0 / 21 (0.00%)   |
| occurrences (all)                                     | 3                      | 3                | 0                |
| Headache  |                        |                  |                  |
| subjects affected / exposed                           | 2 / 21 (9.52%)         | 4 / 42 (9.52%)   | 2 / 21 (9.52%)   |
| occurrences (all)                                     | 2                      | 4                | 2                |
| General disorders and administration site conditions  |                        |                  |                  |
| Fatigue   |                        |                  |                  |
| subjects affected / exposed                           | 3 / 21 (14.29%)        | 8 / 42 (19.05%)  | 5 / 21 (23.81%)  |
| occurrences (all)                                     | 3                      | 8                | 5                |
| Peripheral swelling                                   |                        |                  |                  |
| subjects affected / exposed                           | 0 / 21 (0.00%)         | 2 / 42 (4.76%)   | 2 / 21 (9.52%)   |
| occurrences (all)                                     | 0                      | 2                | 2                |
| Pyrexia   |                        |                  |                  |
| subjects affected / exposed                           | 3 / 21 (14.29%)        | 4 / 42 (9.52%)   | 1 / 21 (4.76%)   |
| occurrences (all)                                     | 3                      | 4                | 1                |
| Gastrointestinal disorders                            |                        |                  |                  |
| Gastrooesophageal reflux disease                      |                        |                  |                  |
| subjects affected / exposed                           | 0 / 21 (0.00%)         | 2 / 42 (4.76%)   | 2 / 21 (9.52%)   |
| occurrences (all)                                     | 0                      | 2                | 2                |
| Respiratory, thoracic and mediastinal disorders       |                        |                  |                  |
| Bronchiectasis  |                        |                  |                  |
| subjects affected / exposed                           | 8 / 21 (38.10%)        | 12 / 42 (28.57%) | 4 / 21 (19.05%)  |
| occurrences (all)                                     | 8                      | 12               | 4                |
| Cough   |                        |                  |                  |
| subjects affected / exposed                           | 0 / 21 (0.00%)         | 2 / 42 (4.76%)   | 2 / 21 (9.52%)   |
| occurrences (all)                                     | 0                      | 2                | 2                |
| Oropharyngeal pain                                    |                        |                  |                  |
| subjects affected / exposed                           | 0 / 21 (0.00%)         | 2 / 42 (4.76%)   | 2 / 21 (9.52%)   |
| occurrences (all)                                     | 0                      | 3                | 3                |
| Rhinorrhoea   |                        |                  |                  |

|   |                      |                     |                     |
|---|----------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all)  | 1 / 21 (4.76%)<br>1  | 3 / 42 (7.14%)<br>3 | 2 / 21 (9.52%)<br>2 |
| Infections and infestations<br>COVID-19<br>subjects affected / exposed<br>occurrences (all) | 3 / 21 (14.29%)<br>3 | 4 / 42 (9.52%)<br>4 | 1 / 21 (4.76%)<br>1 |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)       | 2 / 21 (9.52%)<br>2  | 4 / 42 (9.52%)<br>4 | 2 / 21 (9.52%)<br>2 |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment   |
|------------------|---|
| 01 March 2021    | This protocol amendment: Clarified that the dose to be used in the study was 300 mg b.i.d, as well as the respective dose rationale; Removed the requirement for the serious adverse reactions to be similar in nature as a pre-requisite to put the study on hold; Included a statement that any restart following a temporary hold due to stopping rules being met would require the competent authorities and ethic committees' approval; Clarified the primary analysis strategy.   |
| 04 November 2021 | This protocol amendment addressed the following changes: two inclusion and one exclusion criteria were amended to improve study feasibility and recruitment. These changes expanded the number of eligible participants but did not change the overall patient profile for the study.   |
| 02 December 2022 | This protocol amendment: Removed the stopping rules for NOAEL threshold limits; Discontinued the DMC involvement in the trial; Clarified the requirement of participant's completion of the exacerbations of COPD Tool - Patient Reported Outcome (EXACT-PRO) during screening/baseline period for the purpose of EXACT-PRO baseline score calculation to correctly set up EXACT-PRO alert after patient's being randomized; Updated the exploratory objective and endpoints related to mucus burden to be more specific; Reduced the number of ECGs to one per visit; Updated the co-medication lists to include the most updated drug-drug interaction (DDI) information based on clinical DDI study (CQBW251A2107) and in vitro data; Clarified the inclusion/exclusion criteria, allowing patients with primary ciliary dyskinesia (PCD) to participate; Clarified inclusion criteria, including the use of screening HRCT to satisfy inclusion in the study and clarified that Haemophilus parainfluenzae alone was not permitted for inclusion as a pathogenic organism; Introduced flexibility in the number of attempts for spontaneous sputum collection for each visit before attempting induced sputum collection; Allowed participants at selected sites, upon approval of the sponsor, to forgo HRCT scanning. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use <https://www.novctrd.com/CtrdWeb/home.nov> for complete trial results.

Notes: