# Clinical trial results:
# A randomized, subjects and investigator blinded, placebo controlled parallel group study to assess the mode of action of QBW251 in patients with Chronic Obstructive Pulmonary Disease (COPD)

## Summary

| | |
|---|---|
| EudraCT number | 2019-000325-49 |
| Trial protocol | DE GB |
| Global end of trial date | 20 September 2022 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 24 September 2023 |
| First version publication date | 24 September 2023 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | CQBW251B2202 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT04268823 |
| 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 | 20 September 2022 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 20 September 2022 |
| Was the trial ended prematurely? | Yes |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of the study was to assess the change in fibrinogen plasma concentration levels from baseline after 12 weeks of treatment with QBW251 compared to placebo.

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 | 10 September 2020 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Austria: 12 |
| Country: Number of subjects enrolled | Germany: 30 |
| Country: Number of subjects enrolled | United Kingdom: 4 |
| Country: Number of subjects enrolled | Switzerland: 8 |
| Worldwide total number of subjects | 54 |
| EEA total number of subjects | 42 |

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) | 23 |

| | |
|---|---|
| From 65 to 84 years | 31 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Participants took part in 12 investigative sites in 4 countries.

### Pre-assignment

Screening details:

Informed consent was obtained from each participant in writing at screening before any study specific procedure was performed. The study was explained to the participant by the investigator or designee, who answered any questions, and written information was also
provided.

### 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 | Investigator, Subject |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | QBW251 300mg |

Arm description:

QBW251 300 mg oral dose, one capsule twice daily

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

QBW251 300 mg oral twice daily

| | |
|---|---|
| **Arm title** | Placebo |

Arm description:

Placebo oral dose, one capsule twice daily

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

Dosage and administration details:

Placebo oral twice daily

| **Number of subjects in period 1** | QBW251 300mg | Placebo |
|---|---|---|
| Started | 26 | 28 |
| Completed | 24 | 28 |
| Not completed | 2 | 0 |
| Participant Decision | 1 | - |
| Adverse Event | 1 | - |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | QBW251 300mg |
| Reporting group description: | |
| QBW251 300 mg oral dose, one capsule twice daily | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Placebo oral dose, one capsule twice daily | |

| Reporting group values | QBW251 300mg | Placebo | Total |
|---|---|---|---|
| Number of subjects | 26 | 28 | 54 |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 12 | 11 | 23 |
| From 65-84 years | 14 | 17 | 31 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous<br>Units: years | | | |
| arithmetic mean | 65.7 | 67.3 | |
| standard deviation | ± 7.13 | ± 8.37 | - |
| Sex: Female, Male<br>Units: participants | | | |
| Female | 16 | 11 | 27 |
| Male | 10 | 17 | 27 |
| Race/Ethnicity, Customized<br>Units: Subjects | | | |
| White | 26 | 28 | 54 |

## End points

| End points reporting groups | |
|---|---|
| Reporting group title | QBW251 300mg |
| Reporting group description: | |
| QBW251 300 mg oral dose, one capsule twice daily | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Placebo oral dose, one capsule twice daily | |

### Primary: Change from baseline in fibrinogen plasma concentrations after 12 weeks of treatment

| End point title | Change from baseline in fibrinogen plasma concentrations after 12 weeks of treatment |
|---|---|
| End point description: | |
| To assess the effect of QBW251 compared to placebo after 12 weeks of treatment on fibrinogen. The least-squares means for change from baseline in fibrinogen plasma concentrations after 12 weeks visits for each individual dose group were obtained from a linear mixed effects model for repeated measures (MMRM). A MMRM was fitted to the changes from baseline in fibrinogen for all time points until Day 84. A decrease in fibrinogen plasma concentration indicates improvement. | |
| End point type | Primary |
| End point timeframe: | |
| Baseline, week 12. | |

| End point values | QBW251 300mg | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 26 | 28 | | |
| Units: g/L | | | | |
| least squares mean (standard error) | -0.086 (± 0.1374) | 0.117 (± 0.1365) | | |

### Statistical analyses

| Statistical analysis title | Fibrinogen |
|---|---|
| Comparison groups | QBW251 300mg v Placebo |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.298 |
| Method | Mixed effects Model for Repeated Measure |
| Parameter estimate | Least Squares mean |
| Point estimate | -0.203 |

| | |
|---|---|
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | -0.524 |
| upper limit | 0.119 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.1938 |

## Secondary: Change from baseline in total bacteria load of log10 colony forming units (CFU) after 12 weeks of treatment

| | |
|---|---|
| End point title | Change from baseline in total bacteria load of log10 colony forming units (CFU) after 12 weeks of treatment |

End point description:

Change from baseline in total bacteria load of colony forming units of potentially pathogenic microorganisms in sputum. A decrease in airway bacterial colonization as detected in the sputum is considered improvement.

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

End point timeframe:

Baseline, week 12.

| End point values | QBW251 300mg | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 26 | 28 | | |
| Units: log10 CFU/mL | | | | |
| least squares mean (standard error) | -0.2 (± 0.30) | 0.0 (± 0.32) | | |

### Statistical analyses

| Statistical analysis title | Colony forming units |
|---|---|
| Comparison groups | QBW251 300mg v Placebo |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.651 |
| Method | Mixed effects Model for Repeated Measure |
| Parameter estimate | Least Squares mean |
| Point estimate | -0.2 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | -0.9 |
| upper limit | 0.5 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.44 |

## Secondary: Change from baseline in Euro Quality of Life-5 Dimensions-3 Level (EQ-5D-3L) questionnaire after 12 weeks of treatment

| End point title | Change from baseline in Euro Quality of Life-5 Dimensions-3 Level (EQ-5D-3L) questionnaire after 12 weeks of treatment |
|---|---|

End point description:

The EQ-5D-3L questionnaire is a general health status and health utility measure which captures 5 dimensions of health state: mobility, self-care, usual activities, pain/discomfort and anxiety/depression and visual analog has a scale 0 to 100 (0=worst imaginable health state, 100=best imaginable health state).

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

End point timeframe:

Baseline, week 12.

| **End point values** | QBW251 300mg | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 26 | 28 | | |
| Units: Score on a scale | | | | |
| least squares mean (standard error) | 7.63 (± 3.116) | 3.43 (± 2.854) | | |

### Statistical analyses

| **Statistical analysis title** | Euro Quality of Life-5 Dimensions-3 Level |
|---|---|
| Comparison groups | QBW251 300mg v Placebo |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.338 |
| Method | Mixed effects Model for Repeated Measure |
| Parameter estimate | Least Squares mean |
| Point estimate | 4.2 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | -3.09 |
| upper limit | 11.48 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 4.336 |

## Secondary: Change from baseline in COPD Assessment Test (CAT) questionnaire after 12 weeks of treatment

| End point title | Change from baseline in COPD Assessment Test (CAT) |
|---|---|

| | |
|---|---|
| | questionnaire after 12 weeks of treatment |

End point description:

The COPD assessment test (CAT) is a short instrument which was used to quantify the symptom burden of COPD and disease severity of participants in this study. The CAT consists of 8 items, each presented as a semantic 6-point differential scale (0-5), providing a total range from 0 to 40. A higher score indicates a worse health status.

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

End point timeframe:

Baseline, week 12.

| **End point values** | QBW251 300mg | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 26 | 28 | | |
| Units: Score on a scale | | | | |
| least squares mean (standard error) | -3.55 (± 0.947) | -2.16 (± 0.874) | | |

**Statistical analyses**

| **Statistical analysis title** | COPD Assessment Test |
|---|---|
| Comparison groups | QBW251 300mg v Placebo |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.288 |
| Method | Mixed effects Model for Repeated Measure |
| Parameter estimate | Least Squares mean |
| Point estimate | -1.39 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | -3.55 |
| upper limit | 0.78 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 1.29 |

## Secondary: Change from baseline in St. George's Respiratory Questionnaire (SGRQ) total and domain scores after 12 weeks of treatment

| | |
|---|---|
| End point title | Change from baseline in St. George's Respiratory Questionnaire (SGRQ) total and domain scores after 12 weeks of treatment |

End point description:

The St. George's Respiratory questionnaire (SGRQ) was used to provide the health status measurements. The SGRQ contains 50 items divided into two parts covering three aspects of health related to COPD: Part I covers “Symptoms”, Part II covers “Activity” and “Impacts”. A score is calculated for each of these three subscales including the "Total" score. In each case the lowest possible value is zero and the highest 100. Higher values correspond to greater impairment of health status.

| | |
|---|---|
| End point type | Secondary |
| End point timeframe:<br>Baseline, week 12. | |

| **End point values** | QBW251 300mg | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 26 | 28 | | |
| Units: Score on a scale | | | | |
| least squares mean (standard error) | | | | |
| Week 12- total score | -2.99 (± 2.297) | -2.17 (± 2.111) | | |
| Week 12- Symptoms score | -0.98 (± 3.052) | -6.73 (± 2.806) | | |
| Week 12- Activity score | -1.96 (± 2.388) | -1.35 (± 2.194) | | |
| Week 12- Impact score | -3.72 (± 2.944) | -1.65 (± 2.705) | | |

## Statistical analyses

| **Statistical analysis title** | St. George's Respiratory questionnaire |
|---|---|
| Statistical analysis description:<br>Total score | |
| Comparison groups | QBW251 300mg v Placebo |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.795 |
| Method | Mixed effects Model for Repeated Measure |
| Parameter estimate | Least Squares mean |
| Point estimate | -0.82 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | -6.05 |
| upper limit | 4.42 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 3.147 |

| **Statistical analysis title** | St. George's Respiratory questionnaire |
|---|---|
| Statistical analysis description:<br>Activity score | |
| Comparison groups | QBW251 300mg v Placebo |

| | |
|---|---|
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.851 |
| Method | Mixed effects Model for Repeated Measure |
| Parameter estimate | Least Squares mean |
| Point estimate | -0.61 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | -6.02 |
| upper limit | 4.8 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 3.259 |

| **Statistical analysis title** | St. George's Respiratory questionnaire |
|---|---|
| Statistical analysis description: | |
| Impact score | |
| Comparison groups | QBW251 300mg v Placebo |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.61 |
| Method | Mixed effects Model for Repeated Measure |
| Parameter estimate | Least Squares mean |
| Point estimate | -2.07 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | -8.78 |
| upper limit | 4.65 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 4.035 |

| **Statistical analysis title** | St. George's Respiratory questionnaire |
|---|---|
| Statistical analysis description: | |
| Symptoms score | |
| Comparison groups | QBW251 300mg v Placebo |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.17 |
| Method | Mixed effects Model for Repeated Measure |
| Parameter estimate | Least Squares mean |
| Point estimate | 5.75 |

| | |
|---|---|
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | -1.16 |
| upper limit | 12.66 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 4.155 |

## Secondary: Change from baseline in Cough and Sputum Assessment Questionnaire (CASA-Q) after 12 weeks of treatment

| | |
|---|---|
| End point title | Change from baseline in Cough and Sputum Assessment Questionnaire (CASA-Q) after 12 weeks of treatment |

End point description:

The CASA-Q is a validated questionnaire used to measure cough and sputum production, and their impact in patients with COPD and/or chronic bronchitis. There are only domain scores and no overall score. The scores in each domain range from 0 to 100, with lower scores indicating more severe symptoms or a higher impact.

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

End point timeframe:

Baseline, week 12.

| End point values | QBW251 300mg | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 26 | 28 | | |
| Units: Score on a scale | | | | |
| least squares mean (standard error) | | | | |
| Week 12 - cough symptom score | 4.36 (± 3.339) | 4.11 (± 3.083) | | |
| Week 12 - sputum symptom score | 5.00 (± 3.401) | 0.78 (± 3.121) | | |
| Week 12 - cough impact score | 4.64 (± 2.936) | 2.60 (± 2.697) | | |
| Week 12 - sputum impact score | 3.22 (± 3.298) | 2.28 (± 3.017) | | |

### Statistical analyses

| Statistical analysis title | Cough and Sputum Assessment Questionnaire |
|---|---|

Statistical analysis description:

Cough symptom score

| | |
|---|---|
| Comparison groups | QBW251 300mg v Placebo |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.956 |
| Method | Mixed effects Model for Repeated Measure |
| Parameter estimate | Least Squares mean |
| Point estimate | 0.25 |

| | |
|---|---|
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | -7.3 |
| upper limit | 7.8 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 4.557 |

| **Statistical analysis title** | Cough and Sputum Assessment Questionnaire |
|---|---|
| Statistical analysis description: Sputum impact score | |
| Comparison groups | QBW251 300mg v Placebo |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.835 |
| Method | Mixed effects Model for Repeated Measure |
| Parameter estimate | Least Squares mean |
| Point estimate | 0.94 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | -6.58 |
| upper limit | 8.47 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 4.518 |

| **Statistical analysis title** | Cough and Sputum Assessment Questionnaire |
|---|---|
| Statistical analysis description: Cough impact score | |
| Comparison groups | QBW251 300mg v Placebo |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.613 |
| Method | Mixed effects Model for Repeated Measure |
| Parameter estimate | Least Squares mean |
| Point estimate | 2.03 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | -4.61 |
| upper limit | 8.68 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 4.001 |

| **Statistical analysis title** | Cough and Sputum Assessment Questionnaire |
|---|---|
| Statistical analysis description:<br>Sputum symptom score | |
| Comparison groups | QBW251 300mg v Placebo |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.369 |
| Method | Mixed effects Model for Repeated Measure |
| Parameter estimate | Least Squares mean |
| Point estimate | 4.22 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | -3.55 |
| upper limit | 11.99 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 4.671 |

| **Secondary: Pre-dose trough concentration (Ctrough) of QBW251** | |
|---|---|
| End point title | Pre-dose trough concentration (Ctrough) of QBW251[1] |
| End point description:<br>Pharmacokinetic blood samples were collected and evaluated in all participants exposed to QBW251. QBW251 was analyzed by a validated Liquid Chromatography with tandem Mass Spectrometry. Concentration below the lower limit of quantification (LLOQ) was reported as zero.<br>The Number of Subjects Analyzed differs as stated on the first column for each row. | |
| End point type | Secondary |
| End point timeframe:<br>Day 1, Day 28, Day 56 and Day 84 | |

Notes:

[1] - 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: PK was not analyzed for participants receiving Placebo.

| **End point values** | QBW251 300mg | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 26 | | | |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 1 (n=23) | 0.00 (± 0.00) | | | |
| Day 28 (n=22) | 526 (± 735) | | | |
| Day 56 (n=23) | 489 (± 540) | | | |
| Day 84 (n=24) | 567 (± 883) | | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change from baseline in trough FEV1 after 12 weeks of treatment

| End point title | Change from baseline in trough FEV1 after 12 weeks of treatment |
|---|---|

End point description:

FEV1 (forced expiratory volume in one second) is the amount of air which can be forcibly exhaled from the lungs in the first second of a forced exhalation, measured through spirometry testing. The least-squares means for change from baseline in FEV1 to assess the effect of QBW251 compared to placebo after 12 weeks were obtained from a linear mixed effects model for repeated measures (MMRM). A positive change from baseline in pre-dose FEV1 is considered a favourable outcome.

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

End point timeframe:

Baseline, week 12.

| End point values | QBW251 300mg | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 26 | 28 | | |
| Units: liters (L) | | | | |
| least squares mean (standard error) | 0.0 (± 0.03) | -0.1 (± 0.03) | | |

### Statistical analyses

| Statistical analysis title | Forced Expiratory Volume in one second |
|---|---|
| Comparison groups | QBW251 300mg v Placebo |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.335 |
| Method | Mixed effects Model for Repeated Measure |
| Parameter estimate | Least Squares Mean |
| Point estimate | 0 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | 0 |
| upper limit | 0.1 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.04 |

## Secondary: Change from baseline in FVC after 12 weeks of treatment

| End point title | Change from baseline in FVC after 12 weeks of treatment |
|---|---|

End point description:

To assess the effect of QBW251 compared to placebo after 12 weeks of treatment on spirometry (Forced Vital Capacity). Forced Vital Capacity (FVC) is the amount of air which can be forcibly exhaled from the lungs after taking the deepest breath possible.

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

End point timeframe:

Baseline, week 12

| End point values | QBW251 300mg | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 26 | 28 | | |
| Units: liters (L) | | | | |
| least squares mean (standard error) | -0.1 (± 0.05) | -0.1 (± 0.05) | | |

### Statistical analyses

| Statistical analysis title | Forced Vital Capacity |
|---|---|
| Comparison groups | QBW251 300mg v Placebo |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.645 |
| Method | Mixed effects Model for Repeated Measure |
| Parameter estimate | Least Squares mean |
| Point estimate | 0 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | -0.1 |
| upper limit | 0.1 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.07 |

## Secondary: Change from baseline in FEV1/FVC after 12 weeks of treatment

| End point title | Change from baseline in FEV1/FVC after 12 weeks of treatment |
|---|---|

End point description:

To assess the effect of QBW251 compared to placebo after 12 weeks of treatment on spirometry. FEV1/FVC is the percent of a person's vital capacity that they are able to expire in the first second of forced expiration (FEV1) to the full, forced vital capacity (FVC).

| | |
|---|---|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, week 12. | |

| **End point values** | QBW251 300mg | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 26 | 28 | | |
| Units: percent | | | | |
| least squares mean (standard error) | 1.7 (± 0.58) | -0.3 (± 0.55) | | |

**Statistical analyses**

| **Statistical analysis title** | FEV1/FVC |
|---|---|
| Comparison groups | QBW251 300mg v Placebo |
| Number of subjects included in analysis | 54 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.01 |
| Method | Mixed effects Model for Repeated Measure |
| Parameter estimate | Least Squares mean |
| Point estimate | 2.1 |
| Confidence interval | |
| level | Other: 80 % |
| sides | 2-sided |
| lower limit | 0.8 |
| upper limit | 3.4 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.8 |

**Secondary: Area under plasma concentration-time curve from time zero to the last measurable concentration sampling time (AUClast) of QBW251**

| End point title | Area under plasma concentration-time curve from time zero to the last measurable concentration sampling time (AUClast) of QBW251[2] |
|---|---|
| End point description: | |
| Pharmacokinetic blood samples were collected and evaluated in all participants exposed to QBW251. QBW251 was analyzed by a validated Liquid Chromatography with tandem Mass Spectrometry. Concentration below the lower limit of quantification was reported as zero. AUClast is the area under the plasma concentration-time curve from time zero to the time of last quantifiable concentration (tlast) of QBW251. | |
| End point type | Secondary |
| End point timeframe: | |
| Pre dose, Post dose (1, 2, 3, 4, 6, and 8 hours) at Day 1 and Day 28 | |

Notes:

[2] - 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: PK was not analyzed for participants receiving Placebo.

| **End point values** | QBW251 300mg | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 12 | | | |
| Units: h*ng/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 1 | 4290 (± 3630) | | | |
| Day 28 | 7320 (± 5950) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Maximum observed plasma concentrations (Cmax) of QBW251

| End point title | Maximum observed plasma concentrations (Cmax) of |
|---|---|

End point description:

Cmax is the maximum (peak) observed plasma concentration of QBW251 after dose administration. QBW251 was analyzed by a validated Liquid Chromatography with tandem Mass Spectrometry. Concentration below the lower limit of quantification was reported as zero.
On Day 56 and Day 84 pre-dose and 3 hour post dose sparse samples were collected from all participants. The Number of Subjects Analyzed differs as stated on the first column for each row.

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

End point timeframe:

Post-dose (3 hours) at Day 56 and Day 84.

Notes:

[3] - 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: PK was not analyzed for participants receiving Placebo.

| **End point values** | QBW251 300mg | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 21 | | | |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 56 (n=20) | 903 (± 648) | | | |
| Day 84 (n=21) | 997 (± 497) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Maximum observed plasma concentrations (Cmax) of QBW251 in a subset of patient population

| End point title | Maximum observed plasma concentrations (Cmax) of QBW251 in a subset of patient population[4] |
|---|---|

End point description:

Cmax is the maximum (peak) observed plasma concentration of QBW251 after dose administration. QBW251 was analyzed by a validated Liquid Chromatography with tandem Mass Spectrometry. Concentration below the lower limit of quantification was reported as zero.
Serial plasma PK concentrations were sampled on Day 1 and Day 28 up to 8 hours post dose in a subset of the patient population.

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

End point timeframe:

Pre dose, Post dose (1, 2, 3, 4, 6, and 8 hours) at Day 1 and Day 28.

Notes:

[4] - 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: PK was not analyzed for participants receiving Placebo.

| **End point values** | QBW251 300mg | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 12 | | | |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 1 | 1000 (± 608) | | | |
| Day 28 | 1580 (± 866) | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Annualized rate of EXACT-PRO-defined exacerbations

| End point title | Annualized rate of EXACT-PRO-defined exacerbations |
|---|---|

End point description:

The Exacerbations of COPD Tool-Patient Reported Outcome (EXACT-PRO) is a validated 14-item electronic questionnaire designed to detect the frequency, severity, and duration of exacerbations in participants with COPD. Minimum score is 0 and Maximum score is 40 (higher scores indicate worsening indicative of an exacerbation). EXACT-PRO-defined exacerbations are defined as a persistent increase from baseline in total EXACT-PRO score of ≥9 points for 3 days or ≥12 points for 2 days. Annualized rate of exacerbations was analyzed using a generalized linear model assuming a negative binomial distribution.

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

End point timeframe:

From first dose of study treatment until last dose of study treatment plus 7 days, up to a maximum duration of 99 days

| **End point values** | QBW251 300mg | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 24 | 28 | | |
| Units: exacerbations per participant per year | | | | |
| number (confidence interval 80%) | 1.22 (0.74 to | 1.01 (0.61 to | | |

| | |
|---|---|
| 2.03) | 1.67) |

### Statistical analyses

No statistical analyses for this end point

## Secondary: On-treatment analysis of time to first COPD exacerbation using Cox regression model

| End point title | On-treatment analysis of time to first COPD exacerbation using Cox regression model |
|---|---|

End point description:

To assess the effect of QBW251 compared to placebo after 12 weeks of treatment on COPD exacerbations, exacerbations defined by EXACT-PRO questionnaire. The protocol defined that the time-to-event analyses were to be carried out only upon sufficient number of exacerbation events occur during the study to estimate the median in either of the treatment groups.

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

End point timeframe:

Baseline, week 12.

| End point values | QBW251 300mg | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0[5] | 0[6] | | |
| Units: days | | | | |
| arithmetic mean (standard deviation) | () | () | | |

Notes:

[5] - The number of exacerbations were insufficient.

[6] - The number of exacerbations were insufficient.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Proportion of patients (percentage) with exacerbations

| End point title | Proportion of patients (percentage) with exacerbations |
|---|---|

End point description:

The EXACT-PRO is a validated 14-item electronic questionnaire designed to detect the frequency, severity, and duration of exacerbations in participants with COPD. Minimum score is 0 and Maximum score is 40 (higher scores indicate worsening indicative of an exacerbation). EXACT-PRO-defined exacerbations are defined as a persistent increase from baseline in total EXACT-PRO score of ≥9 points for 3 days or ≥12 points for 2 days.

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

End point timeframe:

From first dose of study treatment until last dose of study treatment plus 7 days, up to a maximum duration of 99 days

| End point values | QBW251 300mg | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 26 | 28 | | |
| Units: participants | 3 | 3 | | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change from baseline in airway wall and lumen

| End point title | Change from baseline in airway wall and lumen |
|---|---|

End point description:

To assess the effect of QBW251 compared to placebo after 12 weeks of treatment on airway structure and function, measured by High Resolution Computed Tomography (HRCT). The Number of Subjects Analyzed differs as stated on the comment field for each column, in case of difference from Number of subjects that started the Arm.

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

End point timeframe:

Baseline, week 12.

| End point values | QBW251 300mg | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 21[7] | 18[8] | | |
| Units: mm | | | | |
| arithmetic mean (standard deviation) | | | | |
| Lung, Left, Inferior Lobe, Posterior Basal Segment | 0.01 (± 0.201) | 0.02 (± 0.155) | | |
| Lung, Left, Superior Lobe, Apical Segment | -0.01 (± 0.150) | 0.06 (± 0.134) | | |
| Lung,Right,Inferior Lobe,Posterior Basal Segment | 0.08 (± 0.378) | -0.03 (± 0.149) | | |
| Lung, Right, Middle Lobe, Lateral Segment | 0.00 (± 0.145) | -0.06 (± 0.105) | | |
| Lung, Right, Superior Lobe, Apical Segment | -0.02 (± 0.128) | 0.02 (± 0.092) | | |

Notes:

[7] - n=19(Lung,Right,Inferior Lobe,Posterior Basal Segment);n=20(Lung,Right, Middle Lobe,Lateral Segment)
[8] - n=17(Lung,Right, Middle Lobe,Lateral Segment)

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change from baseline in percent global and regional air trapping after 12 weeks of treatment

| End point title | Change from baseline in percent global and regional air trapping after 12 weeks of treatment |
|---|---|

End point description:

To assess the effect of QBW251 compared to placebo after 12 weeks of treatment on airway structure and functions, measured by High Resolution Computed Tomography (HRCT). Air trapping is defined as the percentage of lung voxels with mean attenuation below -856 Hounsfield units (HU).

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

End point timeframe:

Baseline, week 12.

| End point values | QBW251 300mg | Placebo | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 19 | 18 | | |
| Units: percent air trapping | | | | |
| arithmetic mean (standard deviation) | | | | |
| Lung | -3.53 (± 7.534) | -0.95 (± 7.733) | | |
| Lung, Left | -3.93 (± 7.176) | -0.89 (± 7.248) | | |
| Lung, Left Lower Lobe | -4.27 (± 9.708) | -1.55 (± 7.486) | | |
| Lung, Left Upper Lobe | -3.83 (± 7.220) | -0.78 (± 7.910) | | |
| Lung, Right | -3.24 (± 8.280) | -0.98 (± 9.032) | | |
| Lung, Right Lower Lobe | -3.57 (± 9.896) | -1.90 (± 11.666) | | |
| Lung, Right Middle Lobe | -1.98 (± 10.362) | -0.80 (± 8.480) | | |
| Lung, Right Upper Lobe | -2.09 (± 8.500) | 0.27 (± 8.934) | | |
| Thirds, Left Lower | -5.40 (± 10.613) | -1.90 (± 8.111) | | |
| Thirds, Left Middle | -3.56 (± 6.803) | -0.76 (± 6.659) | | |
| Thirds, Left Upper | -2.84 (± 7.597) | -0.11 (± 9.272) | | |
| Thirds, Right Lower | -4.52 (± 8.545) | -1.70 (± 10.890) | | |
| Thirds, Right Middle | -3.28 (± 9.116) | -1.09 (± 8.218) | | |
| Thirds, Right Upper | -1.84 (± 8.956) | 0.18 (± 10.107) | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from first dose of study treatment until last dose of study treatment plus 7 days, up to a maximum duration of 99 days.

| | |
|---|---|
| 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 / 26 (7.69%) | 2 / 54 (3.70%) | 0 / 28 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Lung neoplasm malignant | | | |
| subjects affected / exposed | 1 / 26 (3.85%) | 1 / 54 (1.85%) | 0 / 28 (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 |
| Cardiac disorders | | | |
| Arrhythmia supraventricular | | | |
| subjects affected / exposed | 1 / 26 (3.85%) | 1 / 54 (1.85%) | 0 / 28 (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 | | | |
| Pneumonia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 26 (3.85%) | 1 / 54 (1.85%) | 0 / 28 (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 |

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

| **Non-serious adverse events** | QBW251 300 mg b.i.d | Total | Placebo |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 12 / 26 (46.15%) | 17 / 54 (31.48%) | 5 / 28 (17.86%) |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 4 / 26 (15.38%) | 4 / 54 (7.41%) | 0 / 28 (0.00%) |
| occurrences (all) | 4 | 4 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pulmonary mass | | | |
| subjects affected / exposed | 3 / 26 (11.54%) | 4 / 54 (7.41%) | 1 / 28 (3.57%) |
| occurrences (all) | 4 | 5 | 1 |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 4 / 26 (15.38%) | 7 / 54 (12.96%) | 3 / 28 (10.71%) |
| occurrences (all) | 4 | 7 | 3 |
| Infections and infestations | | | |
| COVID-19 | | | |
| subjects affected / exposed | 1 / 26 (3.85%) | 3 / 54 (5.56%) | 2 / 28 (7.14%) |
| occurrences (all) | 1 | 3 | 2 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 3 / 26 (11.54%) | 4 / 54 (7.41%) | 1 / 28 (3.57%) |
| occurrences (all) | 3 | 4 | 1 |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 21 April 2021 | The protocol was amended:<br>1. to clarify that the dose to be used in the study is 300 mg and the respective dose rationale,<br>2. to update and clarification to the inclusion and exclusion criteria to enable recruitment more aligned with clinical expectations of this subject population, 3. to permit subjects with documented 2 moderate exacerbations or 1 severe exacerbation between January 2019 and study screening, 4. to remove GOLD Stage 4 criteria from the inclusion criteria, 5. to include a statement that any restart following a temporary hold due to stopping rules being met will require the Competent Authorities and Ethic Committees approval, as required per country regulations, 6. On section 8.4.4 COPD Exacerbation - to update to reflect the instructions provided in the<br>Note to File given to sites 17Dec2020 on what assessments are needed for COPD exacerbations. |
| 25 August 2021 | The protocol was amended to change the requirement for screening sputum samples from having a minimum of 80,000 CFU pathogenic bacteria, to require screening sputum samples to be positive for any pathogenic bacteria at any level >0. This amendment removes mucolytics from the prohibited medication list. The study drug has a different mechanism of action compared to mucolytics, so use of mucolytics is permitted as it will not interfere with assessment of the study drug. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported