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Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Icenticaftor

Trial Indication(s)

Chronic Obstructive Pulmonary Disease (COPD)

Protocol Number

CQBW251B2202

Protocol Title

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)

Clinical Trial Phase

Phase 2

Phase of Drug Development

Phase 2

Study Start/End Dates

Study Start Date: September 10, 2020 (Actual)
Primary Completion Date: September 13, 2022 (Actual)
Study Completion Date: September 20, 2022 (Actual)

Reason for Termination (If applicable)

The study was prematurely terminated based on Novartis strategic business decision to discontinue work on QBW251 clinical studies supporting the COPD indication, which was not related to safety concerns.

Study Design/Methodology

This was a randomized, participant and investigator blinded, parallel-group, placebo-controlled study investigating the mode of action and preliminary efficacy and safety of QBW251 administered orally b.i.d. for 12 weeks in participants with moderate to severe COPD (GOLD 2-3).

The study consisted of the following periods: Screening, Baseline / Day 1, Treatment, and End of the Study followed by an additional post-treatment safety follow-up phone call. The total duration for each participant in the study was approximately 19 weeks. Approximately 100 participants were to be randomized in a 1:1 ratio to receive either QBW251 or placebo treatment.

Centers

12 centers in 4 countries: Germany(6), United Kingdom(2), Austria(1), Switzerland(3)

Objectives:

Primary:

- To assess the effect of QBW251 compared to placebo after 12 weeks of treatment on fibrinogen plasma concentration.

Secondary:

- To assess the effect of QBW251 compared to placebo after 12 weeks of treatment on sputum bacterial load.
- To assess the effect of QBW251 compared to placebo after 12 weeks of treatment on airway structure and function.
- To assess the effect of QBW251 compared to placebo after 12 weeks of treatment on COPD participant's symptom burden changes.
- To assess the effect of QBW251 compared to placebo after 12 weeks of treatment on health status.

- To assess the effect of QBW251 compared to placebo after 12 weeks of treatment on changes in health-related quality of life.
- To assess the effect of QBW251 compared to placebo after 12 weeks of treatment on COPD exacerbations.
- To assess the effect of QBW251 compared to placebo after 12 weeks of treatment on clinical symptoms, cough and sputum.
- To assess the safety and tolerability of QBW251 in participants with COPD.
- To assess QBW251 pharmacokinetics (PK) during and after 12 weeks of treatment.
- To assess the effect of QBW251 compared to placebo after 12 weeks of treatment on spirometry.

Test Product (s), Dose(s), and Mode(s) of Administration

Participants received oral dose twice daily of QBW251 300 mg or placebo.

Statistical Methods

Primary Analysis:

The primary analysis (Change from baseline in fibrinogen plasma concentration) was performed using a one-sided test at alpha=0.1 (two-sided 80% CI) and estimated treatment difference (QBW251-placebo) at Week 12 was reported along with associated 80% CI. Hypothesis:

- Null hypothesis (H0): There is no reduction in fibrinogen from baseline after 12 weeks of treatment in QBW251 compared to placebo.
- H1: There is a reduction in fibrinogen from baseline after 12 weeks of treatment in favor of QBW251 compared to placebo.

The change from baseline in fibrinogen was assumed normally distributed. A Mixed-effect linear Model for Repeated Measures (MMRM) was fitted to the changes from baseline in fibrinogen for all time points until Day 84, including the fixed factors and covariates, which include but are not limited to the following: treatment group, visit/time, treatment group by visit/time interaction, smoking status, and baseline fibrinogen value by visit/time interaction.

Secondary Analyses:

For change from baseline in the logarithm of total number of CFU/mL of potentially pathogenic microorganisms in spontaneous sputum after 12 weeks of treatment: the bacterial load included all available data from participants in the PD analysis set and was analyzed similarly to the primary analysis (MMRM). The bacterial load samples taken within 2 weeks after exacerbation or during or after last dose of antibiotics were set to missing if a valid unscheduled assessment did not happen at that time point for the primary analysis.

Other secondary efficacy endpoints were analyzed using the same model (MMRM) as for the primary variable of interest. Contrasts for treatment differences were provided together with two-sided 80% CIs.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

1. Patients who have signed an Informed Consent Form prior to initiation of any study-related procedure.
2. Male and female adults aged ≥40 years at screening.
3. Patients with stable COPD, stages GOLD 2-3, according to the current GOLD strategy (GOLD 2019) at screening.
Patients with a post-bronchodilator FEV1/FVC < 0.70 at screening
4. Patients with airflow limitation indicated by a post-bronchodilator FEV1 ≥ 30% and FEV1 < 80% of the predicted normal at Screening who must have had at least 2 documented moderate or at least 1 documented severe exacerbation(s) between January 2019 to study screening.
5. Patients with sputum positive (>0 CFU) for at least one strain of potentially pathogenic microorganism at screening (H influenzae, H parainfluenzae, P aeruginosa, S pneumoniae, S aureus, Moraxella catarrhalis, Enterobacteriaceae, Stenotrophomonas maltophilia, Burkholderia species, and Achromobacter species or any potential pathogenic bacteria measured by dilution/outgrowth. Any organism that is to be included and that is not included in the list of the protocol defined pathogens will be discussed case by case). Sputum samples may be re collected and re-tested once during the screening period.
6. Patients who have been treated with a combination of LABA/LAMA or LABA/ICS or LABA/LAMA/ICS at a stable dose for the last 3 months prior to screening.
COPD patients are allowed to stay on macrolides as background therapy if they have bronchiectasis as a secondary diagnosis and if they are treated with them at a stable dose 3 months before screening.
7. Patients with plasma fibrinogen level ≥ 320 mg/dL at screening.
Fibrinogen may be re-tested once during the screening period.
8. A COPD Assessment Test (CAT) score of at least 10 at screening.

9. Current or ex-smokers who have a smoking history of at least 10 pack years (e.g. 10 pack years = 1 pack/day x 10 years, or 0.5 pack/day x 20 years) at screening.
10. Patients featuring chronic bronchitis, defined as productive cough that occurs on most days (defined as >50% of days) during at least 3 consecutive months in the year prior to screening, as assessed by documentation of patient recollection (anamnesis) or documented in patients' records.
11. Able to communicate well with the investigator, to understand and comply with the requirements of the study.

Exclusion Criteria:
1. Patients with a history of long-QT syndrome or whose QTcF interval at screening (Fridericia method) is prolonged (QTcF >450 ms in males, >460 ms in females).
2. Patients who have a clinically significant* ECG abnormality before randomization. Note: Clinically significant abnormalities may include but are not limited to the following: left bundle branch block, Wolff-Parkinson-White syndrome, clinically significant arrhythmias (e.g., atrial fibrillation, ventricular tachycardia).
3. Clinical laboratory values abnormalities (including Gamma GT, AST, ALT, total bilirubin or creatinine) considered as clinically significant in the opinion of the Investigator at screening. For additional guidance on hepatic parameters see exclusion criterion #5.
4. Patients who have clinically significant renal, cardiovascular (such as but not limited to unstable ischemic heart disease, NYHA Class III/IV left ventricular failure, myocardial infarction), neurological, endocrine, immunological, psychiatric, gastrointestinal, or hematological abnormalities, which could interfere with the assessment of the efficacy and safety of the study treatment, or patients with uncontrolled Type II diabetes.
5. Patients with a history or current treatment for hepatic disease including but not limited to acute hepatitis, cirrhosis or hepatic failure.
• Patients with stable chronic hepatitis may be included in the study by agreement with Novartis Medical Expert on a case-by-case basis.
• A history of resolved Hepatitis A is not exclusionary.
• Patients with prothrombin time international normalized ratio (PT/INR) of more than 1.5xULN at screening. Patients excluded for the PT/INR of more than 1.5xULN can be re-screened when the values have returned to normal.
6. Patients with a history of malignancy of any organ system, treated or untreated, within the past 5 years whether or not there is evidence of local recurrence or metastases, with the exception of localized basal cell carcinoma of the skin. Patients with a history of cancer and 5 years or more disease free survival time may be included in the study by agreement with Novartis Medical Monitor on a case-by-case basis.
7. Patients who develop a COPD exacerbation that required treatment with antibiotics and/or oral corticosteroids and/or hospitalization during screening. Re-screening is permitted after a minimum of 2 weeks after the resolution of the COPD exacerbation (i.e 2 weeks after the stop of SOC therapy for exacerbation).

8. Patients who have had a respiratory tract infection within 4 weeks prior to screening. If a respiratory tract infection occurs during screening, patients can be re-screened after a minimum of 2 weeks after resolution of the respiratory tract infection.
9. Patients with history of asthma or any other clinically relevant lung diseases..
10. Patients with suspected active pulmonary tuberculosis or currently being treatment for active pulmonary tuberculosis.
Note: Patients with a history of pulmonary tuberculosis can be enrolled if they meet the following requirements: history of appropriate drug treatment followed by negative imaging results within 12 months prior to screening suggesting low probability of recurrent active tuberculosis.
11. Patients with pulmonary lobectomy, lung volume reduction surgery, bronchoscopic lung volume reductions, or lung transplantation.
12. Patients participating in or planning to participate in the active phase of a supervised pulmonary rehabilitation program during the trial. Participation in a maintenance program is permitted. Note: the supervised pulmonary rehabilitation program as a maintenance program has to be ongoing for at least 3 months at the time of enrollment.
13. Patients with a body mass index (BMI) of more than 40 kg/m2.
14. Patients receiving any medications in the classes listed in Table 6-5.
15. Patients receiving any COPD related medications in the classes specified in Table 6-6, unless they undergo the required washout period prior to screening and follow the adjustment to treatment program.
16. Patients receiving medications in the classes listed in Table 6-2 should be excluded unless the medication has been stabilized for the specified period and the stated conditions have been met.
17. Use of other investigational drugs (approved or unapproved) within 30 days or 5 half-lives prior to screening, or until the expected pharmacodynamic effect has returned to baseline (e.g., biologics), whichever is longer; or longer if required by local regulations.
18. Pregnant or nursing (lactating) women, where pregnancy was defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test.
19. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using acceptable effective methods of contraception during study participation.
20. Patients who have not achieved an acceptable spirometry result at screening in accordance with American Thoracic Society (ATS)/ European Respiratory Society (ERS) criteria for acceptability and repeatability.

Participant Flow Table

Overall Study

	QBW251 300mg	Placebo	Total

Arm/Group Description	QBW251 300 mg oral dose, one capsule twice daily	Placebo oral dose, one capsule twice daily	
Started	26	28	54
Completed	24	28	52
Not Completed	2	0	2
Adverse Event	1	0	1
Participant Decision	1	0	1

Baseline Characteristics

	QBW251 300mg	Placebo	Total
Arm/Group Description	QBW251 300 mg oral dose, one capsule twice daily	Placebo oral dose, one capsule twice daily	
Number of Participants [units: participants]	26	28	54
Baseline Analysis Population Description			
Age Continuous (units: years) Analysis Population Type: Participants Mean ± Standard Deviation			
	65.7±7.13	67.3±8.37	66.5±7.77
Sex: Female, Male (units: participants) Analysis Population Type: Participants Count of Participants (Not Applicable)			
Female	16	11	27
Male	10	17	27

Race/Ethnicity, Customized (units: participants) Analysis Population Type: Participants Count of Participants (Not Applicable)			
White	26	28	54

Primary Outcome Result(s)

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

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.
Time Frame	Baseline, week 12.
Analysis Population Description	Pharmacodynamic (PD) analysis set. Participants were analyzed according to the study treatment received. The PD analysis set included all participants with PD data at both baseline and at least one post-baseline assessment which were not affected by any protocol deviations.

	QBW251 300mg	**Placebo**
Arm/Group Description	QBW251 300 mg oral dose, one capsule twice daily	Placebo oral dose, one capsule twice daily
Number of Participants Analyzed [units: participants]	26	28
Change from baseline in fibrinogen plasma concentrations after 12 weeks of treatment (units: g/L)	**Least Squares Mean ± Standard Error**	**Least Squares Mean ± Standard Error**
Week 12	-0.086 ± 0.1374	0.117 ± 0.1365

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Statistical Analysis

Groups	QBW251 300mg, Placebo	
Type of Statistical Test	Superiority	
P Value	0.298	
Method	Other Mixed effects Model for Repeated Measure	
Other Least Squares mean	-0.203	Treatment difference (QBW251-placebo)
Standard Error of the mean	0.1938	
80 % Confidence Interval 2-Sided	-0.524 to 0.119	

Secondary Outcome Result(s)

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

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.
Time Frame	Baseline, week 12.
Analysis Population Description	Pharmacodynamic (PD) analysis set. Participants were analyzed according to the study treatment received. The PD analysis set included all participants with PD data at both baseline and at least one post-baseline assessment which were not affected by any protocol deviations.

	QBW251 300mg	Placebo
Arm/Group Description	QBW251 300 mg oral dose, one capsule twice daily	Placebo oral dose, one capsule twice daily

Number of Participants Analyzed [units: participants]	26	28
Change from baseline in total bacteria load of log10 colony forming units (CFU) after 12 weeks of treatment (units: log10 CFU/mL)	**Least Squares Mean ± Standard Error**	**Least Squares Mean ± Standard Error**
Week 12	-0.2 ± 0.30	0.0 ± 0.32

Statistical Analysis

Groups	QBW251 300mg, Placebo	
Type of Statistical Test	Superiority	
P Value	0.651	
Method	Other Mixed effects Model for Repeated Measure	
Other Least Squares mean	-0.2	Treatment difference (QBW251-placebo)
Standard Error of the mean	0.44	
80 % Confidence Interval 2-Sided	-0.9 to 0.5	

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

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.
Time Frame	Baseline, week 12.
Analysis Population Description	Pharmacodynamic (PD) analysis set. Participants were analyzed according to the study treatment received. The PD analysis set included all participants with PD data at both baseline and at least one post-baseline assessment which were not affected by any protocol deviations.

	QBW251 300mg	Placebo
Arm/Group Description	QBW251 300 mg oral dose, one capsule twice daily	Placebo oral dose, one capsule twice daily
Number of Participants Analyzed [units: participants]	26	28
Change from baseline in COPD Assessment Test (CAT) questionnaire after 12 weeks of treatment (units: Score on a scale)	**Least Squares Mean ± Standard Error**	**Least Squares Mean ± Standard Error**
Week 12	-3.55 ± 0.947	-2.16 ± 0.874

Statistical Analysis

Groups	QBW251 300mg, Placebo	
Type of Statistical Test	Superiority	
P Value	0.288	
Method	Other Mixed effects Model for Repeated Measure	
Other Least Squares mean	-1.39	Treatment difference (QBW251-placebo)
Standard Error of the mean	1.290	
80 % Confidence Interval 2-Sided	-3.55 to 0.78	

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

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).
Time Frame	Baseline, week 12.

Analysis Population Description	Pharmacodynamic (PD) analysis set. Participants were analyzed according to the study treatment received. The PD analysis set included all participants with PD data at both baseline and at least one post-baseline assessment which were not affected by any protocol deviations.

	QBW251 300mg	Placebo
Arm/Group Description	QBW251 300 mg oral dose, one capsule twice daily	Placebo oral dose, one capsule twice daily
Number of Participants Analyzed [units: participants]	26	28
Change from baseline in Euro Quality of Life-5 Dimensions-3 Level (EQ-5D-3L) questionnaire after 12 weeks of treatment (units: Score on a scale)	**Least Squares Mean ± Standard Error**	**Least Squares Mean ± Standard Error**
Week 12	7.63 ± 3.116	3.43 ± 2.854

Statistical Analysis

Groups	QBW251 300mg, Placebo	
Type of Statistical Test	Superiority	
P Value	0.338	
Method	Other Mixed effects Model for Repeated Measure	
Other Least Squares mean	4.20	Treatment difference (QBW251-placebo)
Standard Error of the mean	4.336	
80 % Confidence Interval 2-Sided	-3.09 to 11.48	

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

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.
Time Frame	Baseline, week 12.
Analysis Population Description	Pharmacodynamic (PD) analysis set. Participants were analyzed according to the study treatment received. The PD analysis set included all participants with PD data at both baseline and at least one post-baseline assessment which were not affected by any protocol deviations.

	QBW251 300mg	**Placebo**
Arm/Group Description	QBW251 300 mg oral dose, one capsule twice daily	Placebo oral dose, one capsule twice daily
Number of Participants Analyzed [units: participants]	26	28
Change from baseline in St. George's Respiratory Questionnaire (SGRQ) total and domain scores after 12 weeks of treatment (units: Score on a scale)	**Least Squares Mean ± Standard Error**	**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 Analysis

Groups	QBW251 300mg, Placebo	Total score
Type of Statistical Test	Superiority	
P Value	0.795	

Method	Other Mixed effects Model for Repeated Measure	
Other Least Squares mean	-0.82	Treatment difference (QBW251-placebo)
Standard Error of the mean	3.147	
80 % Confidence Interval 2-Sided	-6.05 to 4.42	

Statistical Analysis

Groups	QBW251 300mg, Placebo	Symptoms score
Type of Statistical Test	Superiority	
P Value	0.170	
Method	Other Mixed effects Model for Repeated Measure	
Other Least Squares mean	5.75	Treatment difference (QBW251-placebo)
Standard Error of the mean	4.155	
80 % Confidence Interval 2-Sided	-1.16 to 12.66	

Statistical Analysis

Groups	QBW251 300mg, Placebo	Activity score
Type of Statistical Test	Superiority	
P Value	0.851	
Method	Other Mixed effects Model for Repeated Measure	

Other Least Squares mean	-0.61	Treatment difference (QBW251-placebo)
Standard Error of the mean	3.259	
80 % Confidence Interval 2-Sided	-6.02 to 4.80	

Statistical Analysis

Groups	QBW251 300mg, Placebo	Impact score
Type of Statistical Test	Superiority	
P Value	0.610	
Method	Other Mixed effects Model for Repeated Measure	
Other Least Squares mean	-2.07	Treatment difference (QBW251-placebo)
Standard Error of the mean	4.035	
80 % Confidence Interval 2-Sided	-8.78 to 4.65	

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

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.
Time Frame	Baseline, week 12.
Analysis Population Description	Pharmacodynamic (PD) analysis set. Participants were analyzed according to the study treatment received. The PD analysis set included all participants with PD data at both baseline and at least one post-baseline assessment which were not affected by any protocol deviations.

	QBW251 300mg	Placebo
Arm/Group Description	QBW251 300 mg oral dose, one capsule twice daily	Placebo oral dose, one capsule twice daily
Number of Participants Analyzed [units: participants]	26	28
Change from baseline in Cough and Sputum Assessment Questionnaire (CASA-Q) after 12 weeks of treatment (units: Score on a scale)	**Least Squares Mean ± Standard Error**	**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 Analysis

Groups	QBW251 300mg, Placebo	Cough symptom score
Type of Statistical Test	Superiority	
P Value	0.956	
Method	Other Mixed effects Model for Repeated Measure	
Other Least Squares mean	0.25	Treatment difference (QBW251-placebo)
Standard Error of the mean	4.557	
80 % Confidence Interval 2-Sided	-7.30 to 7.80	

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Statistical Analysis

Groups	QBW251 300mg, Placebo	Sputum symptom score
Type of Statistical Test	Superiority	
P Value	0.369	
Method	Other Mixed effects Model for Repeated Measure	
Other Least Squares mean	4.22	Treatment difference (QBW251-placebo)
Standard Error of the mean	4.671	
80 % Confidence Interval 2-Sided	-3.55 to 11.99	

Statistical Analysis

Groups	QBW251 300mg, Placebo	Cough impact score
Type of Statistical Test	Superiority	
P Value	0.613	
Method	Other Mixed effects Model for Repeated Measure	
Other Least Squares mean	2.03	Treatment difference (QBW251-placebo)
Standard Error of the mean	4.001	
80 % Confidence Interval 2-Sided	-4.61 to 8.68	

Statistical Analysis

Groups	QBW251 300mg, Placebo	Sputum impact score
Type of Statistical Test	Superiority	
P Value	0.835	
Method	Other Mixed effects Model for Repeated Measure	
Other Least Squares mean	0.94	Treatment difference (QBW251-placebo)
Standard Error of the mean	4.518	
80 % Confidence Interval 2-Sided	-6.58 to 8.47	

Pre-dose trough concentration (Ctrough) of QBW251

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 (LLOQ) was reported as zero. The Number of Subjects Analyzed differs as stated on the first column for each row.
Time Frame	Day 1, Day 28, Day 56 and Day 84
Analysis Population Description	The PK analysis set included all participants with at least one available valid (i.e., not flagged for exclusion) PK concentration measurement, who received QBW251 and experienced no protocol deviations with relevant impact on PK data.

	QBW251 300mg
Arm/Group Description	QBW251 300 mg oral dose, one capsule twice daily
Number of Participants Analyzed [units: participants]	26
Pre-dose trough concentration (Ctrough) of QBW251 (units: ng/mL)	**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

Change from baseline in trough FEV1 after 12 weeks of treatment

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.
Time Frame	Baseline, week 12.
Analysis Population Description	Pharmacodynamic (PD) analysis set. Participants were analyzed according to the study treatment received. The PD analysis set included all participants with PD data at both baseline and at least one post-baseline assessment which were not affected by any protocol deviations.

	QBW251 300mg	**Placebo**
Arm/Group Description	QBW251 300 mg oral dose, one capsule twice daily	Placebo oral dose, one capsule twice daily
Number of Participants Analyzed [units: participants]	26	28
Change from baseline in trough FEV1 after 12 weeks of treatment (units: liters (L))	**Least Squares Mean ± Standard Error**	**Least Squares Mean ± Standard Error**
Week 12	0.0 ± 0.03	-0.1 ± 0.03

Statistical Analysis

Groups	QBW251 300mg, Placebo
Type of Statistical Test	Superiority
P Value	0.335

Method	Other Mixed effects Model for Repeated Measure	
Other Least Squares Mean	0.0	Treatment difference (QBW251-placebo)
Standard Error of the mean	0.04	
80 % Confidence Interval 2-Sided	0.0 to 0.1	

Change from baseline in FVC after 12 weeks of treatment

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.
Time Frame	Baseline, week 12
Analysis Population Description	Pharmacodynamic (PD) analysis set. Participants were analyzed according to the study treatment received. The PD analysis set included all participants with PD data at both baseline and at least one post-baseline assessment which were not affected by any protocol deviations.

	QBW251 300mg	**Placebo**
Arm/Group Description	QBW251 300 mg oral dose, one capsule twice daily	Placebo oral dose, one capsule twice daily
Number of Participants Analyzed [units: participants]	26	28
Change from baseline in FVC after 12 weeks of treatment (units: liters (L))	**Least Squares Mean** **± Standard Error**	**Least Squares Mean** **± Standard Error**
Week 12	-0.1 ± 0.05	-0.1 ± 0.05

Statistical Analysis

Groups	QBW251 300mg, Placebo
Type of Statistical Test	Superiority

P Value	0.645	
Method	Other Mixed effects Model for Repeated Measure	
Other Least Squares mean	0.0	Treatment difference (QBW251-placebo)
Standard Error of the mean	0.07	
80 % Confidence Interval 2-Sided	-0.1 to 0.1	

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

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).
Time Frame	Baseline, week 12.
Analysis Population Description	Pharmacodynamic (PD) analysis set. Participants were analyzed according to the study treatment received. The PD analysis set included all participants with PD data at both baseline and at least one post-baseline assessment which were not affected by any protocol deviations.

	QBW251 300mg	**Placebo**
Arm/Group Description	QBW251 300 mg oral dose, one capsule twice daily	Placebo oral dose, one capsule twice daily
Number of Participants Analyzed [units: participants]	26	28
Change from baseline in FEV1/FVC after 12 weeks of treatment (units: percent)	**Least Squares Mean ± Standard Error**	**Least Squares Mean ± Standard Error**
Week 12	1.7 ± 0.58	-0.3 ± 0.55

Statistical Analysis

Groups	QBW251 300mg, Placebo

Type of Statistical Test	Superiority	
P Value	0.010	
Method	Other Mixed effects Model for Repeated Measure	
Other Least Squares mean	2.1	Treatment difference (QBW251-placebo)
Standard Error of the mean	0.80	
80 % Confidence Interval 2-Sided	0.8 to 3.4	

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

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.
Time Frame	Pre dose, Post dose (1, 2, 3, 4, 6, and 8 hours) at Day 1 and Day 28.
Analysis Population Description	The PK analysis set included all participants with at least one available valid (i.e., not flagged for exclusion) PK concentration measurement, who received QBW251 and experienced no protocol deviations with relevant impact on PK data. The analysis was performed on a subset of the PK analysis set for participants where serial plasma PK concentrations were sampled.

	QBW251 300mg
Arm/Group Description	QBW251 300 mg oral dose, one capsule twice daily
Number of Participants Analyzed [units: participants]	12
Maximum observed plasma concentrations (Cmax) of QBW251 in a subset of patient population (units: ng/mL)	**Mean** **± Standard Deviation**
Day 1	1000 ± 608
Day 28	1580 ± 866

Maximum observed plasma concentrations (Cmax) of QBW251

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.
Time Frame	Post-dose (3 hours) at Day 56 and Day 84.
Analysis Population Description	The PK analysis set included all participants with at least one available valid (i.e., not flagged for exclusion) PK concentration measurement, who received QBW251 and experienced no protocol deviations with relevant impact on PK data.

	QBW251 300mg
Arm/Group Description	QBW251 300 mg oral dose, one capsule twice daily
Number of Participants Analyzed [units: participants]	21
Maximum observed plasma concentrations (Cmax) of QBW251 (units: ng/mL)	**Mean ± Standard Deviation**
Day 56 (n=20)	903 ± 648
Day 84 (n=21)	997 ± 497

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

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.
Time Frame	Pre dose, Post dose (1, 2, 3, 4, 6, and 8 hours) at Day 1 and Day 28
Analysis Population Description	The PK analysis set included all participants with at least one available valid (i.e., not flagged for exclusion) PK concentration measurement, who received QBW251 and experienced no protocol deviations with relevant impact on PK data.

	QBW251 300mg
Arm/Group Description	QBW251 300 mg oral dose, one capsule twice daily
Number of Participants Analyzed [units: participants]	12
Area under plasma concentration-time curve from time zero to the last measurable concentration sampling time (AUClast) of QBW251 (units: h*ng/mL)	**Mean ± Standard Deviation**
Day 1	4290 ± 3630
Day 28	7320 ± 5950

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

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.
Time Frame	Baseline, week 12.
Analysis Population Description	No patients analyzed as there was not a sufficient number of exacerbations to carry out the time to event analysis.

	QBW251 300mg	Placebo
Arm/Group Description	QBW251 300 mg oral dose, one capsule twice daily	Placebo oral dose, one capsule twice daily
Number of Participants Analyzed [units: participants]	0	0
On-treatment analysis of time to first COPD exacerbation using Cox regression model (units: days)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**

Proportion of patients (percentage) with exacerbations

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.
Time Frame	From first dose of study treatment until last dose of study treatment plus 7 days, up to a maximum duration of 99 days
Analysis Population Description	Due to study termination with fewer enrollment of subjects, and shorter treatment duration (i.e., 12 weeks), statistical summaries were not performed as unlikely to provide meaningful values.

	QBW251 300mg	**Placebo**
Arm/Group Description	QBW251 300 mg oral dose, one capsule twice daily	Placebo oral dose, one capsule twice daily
Number of Participants Analyzed [units: participants]	26	28
Proportion of patients (percentage) with exacerbations (units: participants)	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**
Week 12	3 (11.54%)	3 (10.71%)

Annualized rate of EXACT-PRO-defined exacerbations

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.
Time Frame	From first dose of study treatment until last dose of study treatment plus 7 days, up to a maximum duration of 99 days
Analysis Population Description	Pharmacodynamic (PD) analysis set. Participants were analyzed according to the study treatment received. The PD analysis set included all participants with PD data at both baseline and at least one post-baseline assessment which were not affected by any protocol deviations.

	QBW251 300mg	Placebo
Arm/Group Description	QBW251 300 mg oral dose, one capsule twice daily	Placebo oral dose, one capsule twice daily
Number of Participants Analyzed [units: participants]	24	28
Annualized rate of EXACT-PRO-defined exacerbations (units: exacerbations per participant per year)	**Number (80% Confidence Interval)**	**Number (80% Confidence Interval)**
	1.22 (0.74 to 2.03)	1.01 (0.61 to 1.67)

Change from baseline in airway wall and lumen

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 first column for each row.
Time Frame	Baseline, week 12.
Analysis Population Description	Pharmacodynamic (PD) analysis set. Participants were analyzed according to the study treatment received. The PD analysis set included all participants with PD data at both baseline and at least one post-baseline assessment which were not affected by any protocol deviations.

	QBW251 300mg	Placebo
Arm/Group Description	QBW251 300 mg oral dose, one capsule twice daily	Placebo oral dose, one capsule twice daily
Number of Participants Analyzed [units: participants]	21	18
Change from baseline in airway wall and lumen (units: mm)	**Mean ± Standard Deviation**	**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 (n=19,18)	0.08 ± 0.378	-0.03 ± 0.149
Lung, Right, Middle Lobe, Lateral Segment (n=20,17)	0.00 ± 0.145	-0.06 ± 0.105

Lung, Right, Superior Lobe, Apical Segment (n=21,18)	-0.02 ± 0.128	0.02 ± 0.092

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

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).
Time Frame	Baseline, week 12.
Analysis Population Description	Pharmacodynamic (PD) analysis set. Participants were analyzed according to the study treatment received. The PD analysis set included all participants with PD data at both baseline and at least one post-baseline assessment which were not affected by any protocol deviations.

	QBW251 300mg	**Placebo**
Arm/Group Description	QBW251 300 mg oral dose, one capsule twice daily	Placebo oral dose, one capsule twice daily
Number of Participants Analyzed [units: participants]	19	18
Change from baseline in percent global and regional air trapping after 12 weeks of treatment (units: percent air trapping)	**Mean ± Standard Deviation**	**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

Safety Results

Time Frame	Adverse events were reported from first dose of study treatment until last dose of study treatment plus 30 days, up to a maximum duration of 122 days.
Source Vocabulary for Table Default	MedDRA (25.1)
Collection Approach for Table Default	Systematic Assessment

All-Cause Mortality

	QBW251 300 mg b.i.d N = 26	**Placebo N = 28**	**Total N = 54**
Arm/Group Description	QBW251 300 mg b.i.d	Placebo	Total
Total Number Affected	0	0	0
Total Number At Risk	26	28	54

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Serious Adverse Events

	QBW251 300 mg b.i.d N = 26	Placebo N = 28	Total N = 54
Arm/Group Description	QBW251 300 mg b.i.d	Placebo	Total
Total # Affected by any Serious Adverse Event	2	0	2
Total # at Risk by any Serious Adverse Event	26	28	54
Cardiac disorders			
Arrhythmia supraventricular	1 (3.85%)	0 (0.00%)	1 (1.85%)
Infections and infestations			
Pneumonia	1 (3.85%)	0 (0.00%)	1 (1.85%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung neoplasm malignant	1 (3.85%)	0 (0.00%)	1 (1.85%)

Other (Not Including Serious) Adverse Events

Frequent Event Reporting Threshold 5%

	QBW251 300 mg b.i.d N = 26	Placebo N = 28	Total N = 54
Arm/Group Description	QBW251 300 mg b.i.d	Placebo	Total
Total # Affected by any Other Adverse Event	12	5	17
Total # at Risk by any Other Adverse Event	26	28	54

Gastrointestinal disorders			
Diarrhoea	4 (15.38%)	0 (0.00%)	4 (7.41%)
Infections and infestations			
COVID-19	1 (3.85%)	2 (7.14%)	3 (5.56%)
Nasopharyngitis	3 (11.54%)	1 (3.57%)	4 (7.41%)
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease	4 (15.38%)	3 (10.71%)	7 (12.96%)
Pulmonary mass	3 (11.54%)	1 (3.57%)	4 (7.41%)

Conclusion:

Though several endpoints trended toward improvement in participants treated with QBW251 300 mg twice daily, the efficacy results could not be interpreted as the study was prematurely terminated due to Novartis strategic decision to discontinue work on this study. Overall, QBW251 300 mg twice daily was well tolerated and had an acceptable safety profile.

Date of Clinical Trial Report

14-Aug-2023