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 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 Units: years			
arithmetic mean	65.7	67.3	
standard deviation	± 7.13	± 8.37	-
Sex: Female, Male Units: participants			
Female	16	11	27
Male	10	17	27
Race/Ethnicity, Customized 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: 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: 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: 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: 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: 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.	
End point type	Secondary
End point timeframe: 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: 1. to clarify that the dose to be used in the study is 300 mg and the respective dose rationale, 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 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