Clinical trial results:
A 24-week multi-center, double-blind, placebo controlled dose-range finding study to investigate the efficacy and safety of oral QBW251 in COPD patients on triple inhaled therapy (LABA / LAMA / ICS)

Summary

EudraCT number	2018-003197-28
Trial protocol	SK NL BE DK FR AT CZ GR HU IT ES GB
Global end of trial date	01 February 2022

Results information

Result version number	v1 (current)
This version publication date	15 February 2023
First version publication date	15 February 2023

Trial information

Trial identification

Sponsor protocol code	CQBW251B2201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04072887
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	01 February 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 February 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To characterize the dose-response relationship of QBW251 administered orally over 12 Weeks on lung function, compared to placebo when added to inhaled triple combination therapy (long-acting β2 agonist/long-acting muscarinic receptor antagonist/inhaled corticosteroid; LABA/LAMA/ICS).

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:

COPD maintenance background therapy: Combination of fluticasone furoate, vilanterol and umeclidinium bromide

Evidence for comparator: -

Actual start date of recruitment	12 September 2019
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	Australia: 17
Country: Number of subjects enrolled	Hong Kong: 2
Country: Number of subjects enrolled	Japan: 83
Country: Number of subjects enrolled	Philippines: 55
Country: Number of subjects enrolled	Thailand: 12
Country: Number of subjects enrolled	Czechia: 48
Country: Number of subjects enrolled	Greece: 20
Country: Number of subjects enrolled	Hungary: 64
Country: Number of subjects enrolled	Poland: 31
Country: Number of subjects enrolled	Slovakia: 50
Country: Number of subjects enrolled	Turkey: 18
Country: Number of subjects enrolled	Argentina: 95
Country: Number of subjects enrolled	Colombia: 2
Country: Number of subjects enrolled	Guatemala: 24
Country: Number of subjects enrolled	Canada: 17
Country: Number of subjects enrolled	United States: 156
Country: Number of subjects enrolled	Austria: 28

Country: Number of subjects enrolled	Belgium: 15
Country: Number of subjects enrolled	Germany: 172
Country: Number of subjects enrolled	Denmark: 17
Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	France: 10
Country: Number of subjects enrolled	United Kingdom: 7
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	Netherlands: 10
Country: Number of subjects enrolled	Korea, Republic of: 6
Worldwide total number of subjects	974
EEA total number of subjects	480

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)	371
From 65 to 84 years	603
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were recruited from 149 sites in 26 countries.

Pre-assignment

Screening details:

Participants underwent a Screening period of up to 1 week. Then, participants entered the run-in period of up to 2 weeks to establish baseline values for symptom assessments, to standardize the COPD background therapy and to complete eligibility assessments.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	QBW251 450 mg

Arm description:

QBW251 was orally administered 450 mg b.i.d for 24 weeks

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

Dosage and administration details:

QBW251 was orally administered 450 mg b.i.d for 24 weeks

Arm title	QBW251 300 mg

Arm description:

QBW251 was orally administered 300 mg b.i.d for 24 weeks

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

Dosage and administration details:

QBW251 was orally administered 300 mg b.i.d for 24 weeks

Arm title	QBW251 150 mg

Arm description:

QBW251 was orally administered 150 mg b.i.d for 24 weeks

Arm type	Experimental

Investigational medicinal product name	QBW251
Investigational medicinal product code	QBW251
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

QBW251 was orally administered 150 mg b.i.d for 24 weeks

Arm title	QBW251 75 mg

Arm description:

QBW251 was orally administered 75 mg b.i.d for 24 weeks

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

Dosage and administration details:

QBW251 was orally administered 75 mg b.i.d for 24 weeks

Arm title	QBW251 25 mg

Arm description:

QBW251 was orally administered 25 mg b.i.d for 24 weeks

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

Dosage and administration details:

QBW251 was orally administered 25 mg b.i.d for 24 weeks

Arm title	Placebo

Arm description:

Placebo was orally administered b.i.d for 24 weeks

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

Dosage and administration details:

Placebo was orally administered b.i.d for 24 weeks

Number of subjects in period 1	QBW251 450 mg	QBW251 300 mg	QBW251 150 mg
Started	99	250	124
Pharmacokinetic (PK) Set	99	250	123
Serial Pharmacokinetic (PK) Set	14 [1]	21 [2]	14 [3]

Completed	91	233	122
Not completed	8	17	2
Adverse event, serious fatal	-	2	-
Consent withdrawn by subject	3	8	1
Physician decision	2	-	-
Adverse event, non-fatal	2	4	1
Lost to follow-up	1	3	-

Number of subjects in period 1	QBW251 75 mg	QBW251 25 mg	Placebo
Started	126	124	251
Pharmacokinetic (PK) Set	126	124	0 [4]
Serial Pharmacokinetic (PK) Set	13 [5]	14 [6]	0 [7]
Completed	117	118	236
Not completed	9	6	15
Adverse event, serious fatal	2	3	-
Consent withdrawn by subject	3	3	13
Physician decision	-	-	1
Adverse event, non-fatal	4	-	1
Lost to follow-up	-	-	-

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: the numbers for the analysis subset are displayed

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: the numbers for the analysis subset are displayed

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: the numbers for the analysis subset are displayed

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: the numbers for the analysis subset are displayed

[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: the numbers for the analysis subset are displayed

[6] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: the numbers for the analysis subset are displayed

[7] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: the numbers for the analysis subset are displayed

Baseline characteristics

Reporting groups	
Reporting group title	QBW251 450 mg
Reporting group description: QBW251 was orally administered 450 mg b.i.d for 24 weeks	
Reporting group title	QBW251 300 mg
Reporting group description: QBW251 was orally administered 300 mg b.i.d for 24 weeks	
Reporting group title	QBW251 150 mg
Reporting group description: QBW251 was orally administered 150 mg b.i.d for 24 weeks	
Reporting group title	QBW251 75 mg
Reporting group description: QBW251 was orally administered 75 mg b.i.d for 24 weeks	
Reporting group title	QBW251 25 mg
Reporting group description: QBW251 was orally administered 25 mg b.i.d for 24 weeks	
Reporting group title	Placebo
Reporting group description: Placebo was orally administered b.i.d for 24 weeks	

Reporting group values	QBW251 450 mg	QBW251 300 mg	QBW251 150 mg
Number of subjects	99	250	124
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)	38	96	40
From 65-84 years	61	154	84
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	66.5	66.6	66.7
standard deviation	± 7.28	± 7.56	± 6.58
Sex: Female, Male Units: Participants			
Female	36	99	47
Male	63	151	77
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	2	10	1
Asian	9	42	27

Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	5	2
White	87	193	94
More than one race	0	0	0
Unknown or Not Reported	0	0	0

Reporting group values	QBW251 75 mg	QBW251 25 mg	Placebo
Number of subjects	126	124	251
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)	59	45	93
From 65-84 years	67	79	158
85 years and over	0	0	0
Age Continuous			
Units: Years			
arithmetic mean	65.7	67.0	66.7
standard deviation	± 8.30	± 7.83	± 7.59
Sex: Female, Male			
Units: Participants			
Female	50	49	92
Male	76	75	159
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	4	4	5
Asian	20	25	43
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	6	2	5
White	96	93	198
More than one race	0	0	0
Unknown or Not Reported	0	0	0

Reporting group values	Total		
Number of subjects	974		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	371		
From 65-84 years	603		
85 years and over	0		
Age Continuous			
Units: Years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male			
Units: Participants			
Female	373		
Male	601		
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	26		
Asian	166		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	21		
White	761		
More than one race	0		
Unknown or Not Reported	0		

End points

End points reporting groups

Reporting group title	QBW251 450 mg
Reporting group description: QBW251 was orally administered 450 mg b.i.d for 24 weeks	
Reporting group title	QBW251 300 mg
Reporting group description: QBW251 was orally administered 300 mg b.i.d for 24 weeks	
Reporting group title	QBW251 150 mg
Reporting group description: QBW251 was orally administered 150 mg b.i.d for 24 weeks	
Reporting group title	QBW251 75 mg
Reporting group description: QBW251 was orally administered 75 mg b.i.d for 24 weeks	
Reporting group title	QBW251 25 mg
Reporting group description: QBW251 was orally administered 25 mg b.i.d for 24 weeks	
Reporting group title	Placebo
Reporting group description: Placebo was orally administered b.i.d for 24 weeks	

Primary: Change From Baseline in Forced Expiratory Volume in One Second (FEV1) at week 12

End point title	Change From Baseline in Forced Expiratory Volume in One Second (FEV1) at week 12

End point description:

The primary efficacy analysis assessed the effect of QBW251 on the absolute change from baseline in trough FEV1 in liters on Week 12. Forced Expiratory Volume in one second (FEV1) is calculated as the volume of air forcibly exhaled in one second as measured by a spirometer. Baseline measurement was defined as the baseline visit pre-bronchodilator spirometry assessment.

Change from baseline in the FEV1 mean scores were analyzed using a Mixed Model for Repeated Measures (MMRM): treatment + baseline score + smoking status at screening + run-in FEV1 + airflow limitation severity + region + time interval + treatment*time interval interaction + baseline score*time interval interaction.

End point type	Primary

End point timeframe:

Baseline and Week 12

End point values	QBW251 450 mg	QBW251 300 mg	QBW251 150 mg	QBW251 75 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	209	111	112
Units: Liter				
least squares mean (standard error)	0.013 (± 0.021)	0.013 (± 0.0103)	0.014 (± 0.0142)	0.021 (± 0.0141)

End point values	QBW251 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	219		
Units: Liter				
least squares mean (standard error)	0.006 (± 0.0144)	0.001 (± 0.0101)		

Statistical analyses

Statistical analysis title	ANCOVA
Comparison groups	QBW251 450 mg v Placebo
Number of subjects included in analysis	261
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.628
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	0.011
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.027
upper limit	0.05
Variability estimate	Standard error of the mean
Dispersion value	0.0235

Statistical analysis title	ANCOVA
Comparison groups	QBW251 300 mg v Placebo
Number of subjects included in analysis	428
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.425
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	0.012
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.012
upper limit	0.035
Variability estimate	Standard error of the mean
Dispersion value	0.0144

Statistical analysis title	ANCOVA
Comparison groups	QBW251 150 mg v Placebo
Number of subjects included in analysis	330
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.463
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	0.013
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.016
upper limit	0.041
Variability estimate	Standard error of the mean
Dispersion value	0.0174

Statistical analysis title	ANCOVA
Comparison groups	QBW251 75 mg v Placebo
Number of subjects included in analysis	331
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.244
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	0.02
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.008
upper limit	0.049
Variability estimate	Standard error of the mean
Dispersion value	0.0173

Statistical analysis title	ANCOVA
Comparison groups	QBW251 25 mg v Placebo
Number of subjects included in analysis	324
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.793
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	0.005

Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.024
upper limit	0.034
Variability estimate	Standard error of the mean
Dispersion value	0.0176

Secondary: Change From Baseline in Forced Expiratory Volume in One Second (FEV1)

End point title	Change From Baseline in Forced Expiratory Volume in One Second (FEV1)

End point description:

The primary efficacy analysis assessed the effect of QBW251 on the absolute change from baseline in trough FEV1 in liters compared to placebo on Weeks 4, 8, 16, 20 and 24. Forced Expiratory Volume in one second (FEV1) is calculated as the volume of air forcibly exhaled in one second as measured by a spirometer. Baseline measurement was defined as the baseline visit pre-bronchodilator spirometry assessment. A positive trend for change from baseline in FEV1 across the dose range is considered a favorable outcome.

End point type	Secondary

End point timeframe:

Baseline, weeks 4, 8, 16, 20 and 24

End point values	QBW251 450 mg	QBW251 300 mg	QBW251 150 mg	QBW251 75 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	99	250	124	126
Units: Liter				
arithmetic mean (standard deviation)				
Week 4	0.007 (± 0.14)	0.007 (± 0.15)	0.009 (± 0.13)	0.000 (± 0.14)
Week 8	0.028 (± 0.14)	0.013 (± 0.16)	-0.002 (± 0.13)	0.002 (± 0.15)
Week 16	0.013 (± 0.18)	0.003 (± 0.16)	0.005 (± 0.14)	0.011 (± 0.15)
Week 20	-0.031 (± 0.20)	0.005 (± 0.18)	0.012 (± 0.13)	0.001 (± 0.16)
Week 24	0.033 (± 0.13)	0.023 (± 0.19)	0.004 (± 0.16)	0.003 (± 0.19)

End point values	QBW251 25 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124	251		
Units: Liter				
arithmetic mean (standard deviation)				
Week 4	0.009 (± 0.14)	0.005 (± 0.13)		
Week 8	0.016 (± 0.16)	0.009 (± 0.15)		
Week 16	0.007 (± 0.17)	-0.011 (± 0.14)		

Week 20	0.003 (± 0.16)	-0.007 (± 0.15)		
Week 24	0.003 (± 0.17)	-0.013 (± 0.16)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Evaluating Respiratory Symptoms (E-RS); Total score

End point title	Change from baseline in Evaluating Respiratory Symptoms (E-RS); Total score[1]

End point description:

The E-RS assesses overall daily respiratory COPD symptoms (Total score) and it is derived as the sum of 11 severity items; a higher scores indicate more severe symptoms. E-RS total score has a range of 0 to 40.

Change from baseline in the E-RS Total weekly mean scores were analyzed using a Mixed Model for Repeated Measures (MMRM): treatment + baseline score + smoking status at screening + run-in E-RS + airflow limitation severity + region + time interval + treatment*time interval interaction + baseline score*time interval interaction.

The mean baseline E-RS Total score was the average of the corresponding daily scores from the run-in period.

A negative change from baseline corresponds to improvement in symptoms severity.

End point type	Secondary

End point timeframe:

Baseline, weeks 12 and 24

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: only descriptive analyses performed

End point values	QBW251 300 mg	QBW251 150 mg	QBW251 75 mg	QBW251 25 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	250	124	126	124
Units: Score on a scale				
least squares mean (standard error)				
Week 12	-1.75 (± 0.234)	-1.26 (± 0.323)	-1.66 (± 0.317)	-1.30 (± 0.324)
Week 24	-2.16 (± 0.239)	-1.37 (± 0.327)	-1.36 (± 0.325)	-1.36 (± 0.333)

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	251			
Units: Score on a scale				
least squares mean (standard error)				

Week 12	-1.41 (± 0.228)			
Week 24	-1.31 (± 0.232)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Evaluating Respiratory Symptoms (E-RS); Cough and Sputum score

End point title	Change from baseline in Evaluating Respiratory Symptoms (E-RS); Cough and Sputum score[2]

End point description:

The E-RS assesses both overall daily respiratory COPD symptoms (Total score) and specific respiratory symptoms using 3 subscales (Breathlessness, Cough & Sputum, and Chest Symptoms). The E-RS comprises 11 severity items and higher scores indicate more severe symptoms. The Cough and Sputum subscale score has a range of 0 to 11 and was derived as the sum of items 2 - 4.

Change from baseline in the E-RS Cough and Sputum weekly mean scores were analyzed using a Mixed Model for Repeated Measures (MMRM): treatment + baseline score + smoking status at screening + run-in E-RS + airflow limitation severity + region + time interval + treatment*time interval interaction + baseline score*time interval interaction.

The mean baseline E-RS Cough & Sputum subscale score was the average of the corresponding daily scores from the run-in period. Lower scores in the change from baseline correspond to lower symptom severity.

End point type	Secondary

End point timeframe:

Baseline, weeks 12 and 24

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: only descriptive analyses performed

End point values	QBW251 300 mg	QBW251 150 mg	QBW251 75 mg	QBW251 25 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	250	124	126	124
Units: Score on a scale				
least squares mean (standard error)				
Week 12	-0.78 (± 0.077)	-0.63 (± 0.105)	-0.52 (± 0.104)	-0.22 (± 0.106)
Week 24	-0.90 (± 0.078)	-0.68 (± 0.107)	-0.51 (± 0.106)	-0.26 (± 0.109)

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	251			
Units: Score on a scale				
least squares mean (standard error)				

Week 12	-0.44 (± 0.074)			
Week 24	-0.50 (± 0.076)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with a "Better" change in the Patient Global Impression of Severity (PGI-S) from baseline

End point title	Number of Participants with a "Better" change in the Patient Global Impression of Severity (PGI-S) from baseline[3]

End point description:

The PGI-S questionnaire is a patient-reported outcomes score that rates the severity of the respiratory symptoms and of cough and mucus. The change in severity scores (Better, No change and Worse) from baseline were reported at weeks 12 and 24. Thus, the number of participants with a Better change in the severity score are reported in the table below.

End point type	Secondary

End point timeframe:

Baseline, weeks 12 and 24

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: only descriptive analyses performed

End point values	QBW251 300 mg	QBW251 150 mg	QBW251 75 mg	QBW251 25 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	250	124	126	124
Units: Participants				
Week 12 - Respiratory Symptoms	66	27	35	33
Week 24 - Respiratory Symptoms	72	28	40	31
Week 12 - Cough and mucus	85	55	54	41
Week 24 - Cough and mucus	104	57	50	37

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	251			
Units: Participants				
Week 12 - Respiratory Symptoms	64			
Week 24 - Respiratory Symptoms	79			
Week 12 - Cough and mucus	78			
Week 24 - Cough and mucus	96			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in the Cough and Sputum Assessment Questionnaire (CASA-Q)

End point title	Change from baseline in the Cough and Sputum Assessment Questionnaire (CASA-Q)[4]

End point description:

The CASA-Q is a validated questionnaire instrument used to measure cough and sputum production, and their impact in patients COPD and/or chronic bronchitis. It contains a total of 20 items on a 5-step scale distributed in 4 domains: Cough symptoms, Cough impact, Sputum symptoms and Sputum impact. All items are rescored from 1-5 to 0-4 and then reverse scored such that better responses have higher scores. The four domains are ranged from 0-100 where higher scores associated with fewer symptoms/less impact due to cough or sputum.

Change from baseline in the CASA-Q cough and symptoms scores were analyzed using a Mixed Model for Repeated Measures (MMRM): treatment + baseline score + smoking status at screening + run-in E-RS + airflow limitation severity + region + time interval + treatment*time interval interaction + baseline score*time interval interaction.

End point type	Secondary

End point timeframe:

Baseline, weeks 12 and 24

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: only descriptive analyses performed

End point values	QBW251 300 mg	QBW251 150 mg	QBW251 75 mg	QBW251 25 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	250	124	126	124
Units: Score on a scale				
least squares mean (standard error)				
Cough symptoms score, week 12	6.06 (± 1.082)	8.82 (± 1.488)	6.68 (± 1.498)	6.73 (± 1.535)
Cough symptoms score, week 24	10.49 (± 1.148)	10.59 (± 1.556)	8.04 (± 1.575)	5.84 (± 1.623)
Cough impact score, week 12	4.97 (± 0.983)	5.94 (± 1.352)	5.89 (± 1.359)	5.03 (± 1.394)
Cough impact score, week 24	7.08 (± 0.983)	8.29 (± 1.334)	7.51 (± 1.349)	4.02 (± 1.391)
Sputum symptoms score, week 12	7.74 (± 1.142)	8.51 (± 1.571)	7.01 (± 1.580)	5.74 (± 1.620)
Sputum symptoms score, week 24	10.52 (± 1.242)	11.34 (± 1.685)	5.81 (± 1.704)	4.64 (± 1.756)
Sputum impact score, week 12	5.88 (± 1.011)	6.58 (± 1.391)	6.98 (± 1.398)	4.35 (± 1.433)
Sputum impact score, week 24	7.14 (± 1.032)	7.66 (± 1.401)	7.75 (± 1.417)	4.40 (± 1.460)

End point values	Placebo			
Subject group type	Reporting group			
Number of subjects analysed	251			
Units: Score on a scale				
least squares mean (standard error)				
Cough symptoms score, week 12	6.06 (± 1.077)			
Cough symptoms score, week 24	7.25 (± 1.118)			
Cough impact score, week 12	5.26 (± 0.978)			
Cough impact score, week 24	7.12 (± 0.958)			
Sputum symptoms score, week 12	6.96 (± 1.136)			

Sputum symptoms score, week 24	9.05 (± 1.211)			
Sputum impact score, week 12	4.72 (± 1.005)			
Sputum impact score, week 24	7.04 (± 1.007)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in St. George's Respiratory Questionnaire (SGRQ)

End point title	Change from baseline in St. George's Respiratory Questionnaire (SGRQ)

End point description:

SGRQ measures health impairment and contains 50 items divided into three components: Symptoms, Activity and Impacts. A score was calculated for each component and a "Total" score was also calculated. In each case the lowest possible value is zero and the highest 100. Higher values correspond to greater impairment of quality of life.

Change from baseline in the SGRQ scores were analyzed using a Mixed Model for Repeated Measures (MMRM): treatment + baseline score + smoking status at screening + baseline SGRQ score + airflow limitation severity + region + time interval + treatment*time interval interaction + baseline score*time interval interaction.

End point type	Secondary

End point timeframe:

Baseline, weeks 12 and 24

End point values	QBW251 450 mg	QBW251 300 mg	QBW251 150 mg	QBW251 75 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	99	250	124	126
Units: Score on a scale				
least squares mean (standard error)				
Week 12 - Total score	-0.34 (± 11.17)	-5.84 (± 14.82)	-3.14 (± 12.67)	-6.78 (± 14.64)
Week 24 - Total score	-2.93 (± 10.58)	-6.48 (± 15.35)	-3.69 (± 12.39)	-6.06 (± 14.88)
Week 12 - Symptoms score	-5.24 (± 21.16)	-8.23 (± 18.73)	-5.70 (± 18.39)	-6.93 (± 19.29)
Week 24 - Symptoms score	-7.90 (± 22.47)	-10.59 (± 21.06)	-7.09 (± 17.02)	-8.42 (± 18.21)
Week 12 - Activity score	-2.00 (± 10.83)	-4.80 (± 17.67)	-4.72 (± 17.35)	-7.27 (± 17.48)
Week 24 - Activity score	-1.25 (± 12.50)	-5.12 (± 17.36)	-3.69 (± 16.37)	-5.80 (± 20.47)
Week 12 - Impacts score	2.03 (± 14.28)	-5.69 (± 17.06)	-1.49 (± 13.88)	-6.42 (± 16.63)
Week 24 - Impacts score	-2.21 (± 8.24)	-6.04 (± 17.455)	-2.63 (± 14.18)	-5.44 (± 16.05)

End point values	QBW251 25	Placebo		

	mg			
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124	251		
Units: Score on a scale				
least squares mean (standard error)				
Week 12 - Total score	-3.85 (± 10.82)	-3.36 (± 13.27)		
Week 24 - Total score	-1.70 (± 10.97)	-4.37 (± 13.00)		
Week 12 - Symptoms score	-5.59 (± 16.52)	-6.07 (± 17.14)		
Week 24 - Symptoms score	-5.16 (± 15.61)	-6.97 (± 17.39)		
Week 12 - Activity score	-4.06 (± 14.68)	-2.40 (± 15.21)		
Week 24 - Activity score	-1.20 (± 14.36)	-4.27 (± 16.07)		
Week 12 - Impacts score	-3.13 (± 13.11)	-3.11 (± 15.90)		
Week 24 - Impacts score	-1.04 (± 13.95)	-3.68 (± 14.95)		

Statistical analyses

No statistical analyses for this end point

Secondary: Minimum plasma concentration (Cmin) for QBW251

End point title	Minimum plasma concentration (Cmin) for QBW251[5]

End point description:

Venous whole blood samples were collected for pharmacokinetics characterization. Cmin was measured pre dose at all visits and was summarized using descriptive statistics. All concentrations below the lower limit of quantification (LLOQ) were treated as zero.

End point type	Secondary

End point timeframe:

Pre-dose on Days 15, 29, 57, 85, 113, 141 and 169

Notes:

[5] - 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: only descriptive analyses performed

End point values	QBW251 450 mg	QBW251 300 mg	QBW251 150 mg	QBW251 75 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	99	250	123	126
Units: ng/mL				
arithmetic mean (standard deviation)				
Day 15	1280 (± 1700)	619 (± 1230)	143 (± 158)	44.0 (± 49.0)
Day 29	951 (± 1050)	571 (± 923)	125 (± 123)	47.8 (± 47.3)
Day 57	1040 (± 1330)	572 (± 833)	116 (± 103)	47.7 (± 62.2)
Day 85	1080 (± 1360)	587 (± 951)	119 (± 147)	49.7 (± 71.2)
Day 113	859 (± 1150)	593 (± 1000)	120 (± 130)	52.7 (± 73.9)
Day 141	1150 (± 1150)	552 (± 923)	118 (± 103)	66.8 (± 226)
Day 169	637 (± 349)	465 (± 618)	128 (± 147)	44.9 (± 61.1)

End point values	QBW251 25 mg			
Subject group type	Reporting group			
Number of subjects analysed	124			
Units: ng/mL				
arithmetic mean (standard deviation)				
Day 15	12.7 (± 15.5)			
Day 29	10.1 (± 10.1)			
Day 57	14.2 (± 25.5)			
Day 85	9.93 (± 10.3)			
Day 113	9.89 (± 9.20)			
Day 141	15.9 (± 45.7)			
Day 169	8.97 (± 8.08)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum plasma concentration (Cmax) for QBW251

End point title	Maximum plasma concentration (Cmax) for QBW251[6]

End point description:

Venous whole blood samples were collected for pharmacokinetics characterization. Cmax was calculated from plasma concentration data using non-compartmental methods and summarized using descriptive statistics. Cmax was measured in the samples taken at 3 hours post-dose with the exception of the participants included in the Serial PK set on Days 1 and 15 for whom all samples (1, 2, 4, 6, and 8 hours post-dose) were taken into consideration for the measurement of Cmax. All concentrations below the lower limit of quantification (LLOQ) were treated as zero.

End point type	Secondary

End point timeframe:

Days 1, 15 and 169

Notes:

[6] - 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: only descriptive analyses performed

End point values	QBW251 450 mg	QBW251 300 mg	QBW251 150 mg	QBW251 75 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	99	250	123	126
Units: ng/mL				
arithmetic mean (standard deviation)				
Day 1	1280 (± 847)	751 (± 598)	251 (± 238)	68.9 (± 64.5)
Day 15	2500 (± 1710)	1320 (± 1030)	411 (± 368)	114 (± 101)
Day 169	2370 (± 1160)	1210 (± 797)	361 (± 303)	104 (± 86.6)

End point values	QBW251 25 mg			
Subject group type	Reporting group			
Number of subjects analysed	124			
Units: ng/mL				
arithmetic mean (standard deviation)				
Day 1	14.4 (± 15.2)			
Day 15	26.1 (± 20.6)			
Day 169	22.5 (± 16.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum plasma concentration (Cmax) for QBW251 in Serial PK set

End point title	Maximum plasma concentration (Cmax) for QBW251 in Serial PK set[7]

End point description:

Venous whole blood samples were collected for pharmacokinetics characterization. Cmax was calculated from plasma concentration data using non-compartmental methods and summarized using descriptive statistics. All concentrations below the lower limit of quantification (LLOQ) were treated as zero.

End point type	Secondary

End point timeframe:

1, 2, 4, 6, and 8 hours post-dose on Days 1 and 15

Notes:

[7] - 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: only descriptive analyses performed

End point values	QBW251 450 mg	QBW251 300 mg	QBW251 150 mg	QBW251 75 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	21	14	13
Units: ng/mL				
arithmetic mean (standard deviation)				
Day 1	1510 (± 928)	1280 (± 622)	478 (± 241)	96.6 (± 72.7)
Day 15	2700 (± 1170)	1870 (± 844)	542 (± 523)	175 (± 127)

End point values	QBW251 25 mg			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: ng/mL				
arithmetic mean (standard deviation)				
Day 1	25.3 (± 29.7)			
Day 15	39.4 (± 27.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the curve from time 0 to 24 hours (AUC0-24h) of QBW251 in Serial PK set

End point title	Area under the curve from time 0 to 24 hours (AUC0-24h) of QBW251 in Serial PK set[8]

End point description:

Venous whole blood samples were collected for pharmacokinetics characterization. AUC0-24h was calculated from plasma concentration-time data using non-compartmental methods and summarized using descriptive statistics. All concentrations below the lower limit of quantification (LLOQ) were treated as zero.

End point type	Secondary

End point timeframe:

1, 2, 4, 6, and 8 hours post-dose on Days 1 and 15

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: only descriptive analyses performed

End point values	QBW251 450 mg	QBW251 300 mg	QBW251 150 mg	QBW251 75 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	14	21	14	13
Units: ng*h/mL				
arithmetic mean (standard deviation)				
Day 1	10900 (± 3740)	8480 (± 3660)	2920 (± 1140)	769 (± 330)
Day 15	30000 (± 22600)	16500 (± 8380)	4740 (± 2390)	1390 (± 679)

End point values	QBW251 25 mg			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: ng*h/mL				
arithmetic mean (standard deviation)				
Day 1	185 (± 107)			
Day 15	333 (± 209)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events were reported from the start of treatment to 30 days after end of treatment, assessed up to maximum duration of 199 days.	
Adverse event reporting additional description:	
Any sign or symptom that occurs during the study treatment plus the 30 days post treatment	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups	
Reporting group title	QBW251 450 mg
Reporting group description:	
QBW251 was orally administered 450 mg b.i.d for 24 weeks	
Reporting group title	QBW251 150 mg
Reporting group description:	
QBW251 was orally administered 150 mg b.i.d for 24 weeks	
Reporting group title	QBW251 300 mg
Reporting group description:	
QBW251 was orally administered 300 mg b.i.d for 24 weeks	
Reporting group title	QBW251 75 mg
Reporting group description:	
QBW251 was orally administered 75 mg b.i.d for 24 weeks	
Reporting group title	QBW251 25 mg
Reporting group description:	
QBW251 was orally administered 25 mg b.i.d for 24 weeks	
Reporting group title	Placebo
Reporting group description:	
Placebo was orally administered b.i.d for 24 weeks	
Reporting group title	Total
Reporting group description:	
Total	

Serious adverse events	QBW251 450 mg	QBW251 150 mg	QBW251 300 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 99 (10.10%)	6 / 124 (4.84%)	33 / 250 (13.20%)
number of deaths (all causes)	0	0	2
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Abdominal neoplasm			

subjects affected / exposed	0 / 99 (0.00%)	0 / 124 (0.00%)	0 / 250 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			
subjects affected / exposed	1 / 99 (1.01%)	0 / 124 (0.00%)	0 / 250 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			
subjects affected / exposed	1 / 99 (1.01%)	0 / 124 (0.00%)	0 / 250 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gallbladder adenocarcinoma			
subjects affected / exposed	0 / 99 (0.00%)	0 / 124 (0.00%)	0 / 250 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic cancer			
subjects affected / exposed	0 / 99 (0.00%)	0 / 124 (0.00%)	0 / 250 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm			
subjects affected / exposed	0 / 99 (0.00%)	0 / 124 (0.00%)	0 / 250 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	1 / 99 (1.01%)	0 / 124 (0.00%)	3 / 250 (1.20%)
occurrences causally related to treatment / all	1 / 1	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to lymph nodes			
subjects affected / exposed	0 / 99 (0.00%)	0 / 124 (0.00%)	0 / 250 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to peritoneum			

subjects affected / exposed	0 / 99 (0.00%)	0 / 124 (0.00%)	0 / 250 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-small cell lung cancer stage IIIA			
subjects affected / exposed	0 / 99 (0.00%)	0 / 124 (0.00%)	0 / 250 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal adenocarcinoma			
subjects affected / exposed	0 / 99 (0.00%)	0 / 124 (0.00%)	0 / 250 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	0 / 99 (0.00%)	0 / 124 (0.00%)	0 / 250 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal neoplasm			
subjects affected / exposed	0 / 99 (0.00%)	0 / 124 (0.00%)	0 / 250 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma			
subjects affected / exposed	1 / 99 (1.01%)	0 / 124 (0.00%)	0 / 250 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 99 (0.00%)	0 / 124 (0.00%)	1 / 250 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Arteriosclerosis			
subjects affected / exposed	0 / 99 (0.00%)	0 / 124 (0.00%)	0 / 250 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive emergency			

subjects affected / exposed	0 / 99 (0.00%)	1 / 124 (0.81%)	0 / 250 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 99 (0.00%)	0 / 124 (0.00%)	0 / 250 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 99 (1.01%)	0 / 124 (0.00%)	0 / 250 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 99 (0.00%)	0 / 124 (0.00%)	0 / 250 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 99 (0.00%)	0 / 124 (0.00%)	1 / 250 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular stent thrombosis			
subjects affected / exposed	0 / 99 (0.00%)	0 / 124 (0.00%)	0 / 250 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 99 (0.00%)	0 / 124 (0.00%)	1 / 250 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			

subjects affected / exposed	0 / 99 (0.00%)	0 / 124 (0.00%)	1 / 250 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Bronchospasm			
subjects affected / exposed	0 / 99 (0.00%)	0 / 124 (0.00%)	0 / 250 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	5 / 99 (5.05%)	1 / 124 (0.81%)	9 / 250 (3.60%)
occurrences causally related to treatment / all	5 / 5	1 / 1	10 / 10
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 99 (0.00%)	1 / 124 (0.81%)	0 / 250 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung consolidation			
subjects affected / exposed	0 / 99 (0.00%)	0 / 124 (0.00%)	0 / 250 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 99 (0.00%)	0 / 124 (0.00%)	1 / 250 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 99 (0.00%)	0 / 124 (0.00%)	0 / 250 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood potassium increased			
subjects affected / exposed	0 / 99 (0.00%)	0 / 124 (0.00%)	1 / 250 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			

Ankle fracture			
subjects affected / exposed	0 / 99 (0.00%)	0 / 124 (0.00%)	1 / 250 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone graft lysis			
subjects affected / exposed	0 / 99 (0.00%)	0 / 124 (0.00%)	1 / 250 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 99 (0.00%)	0 / 124 (0.00%)	1 / 250 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot fracture			
subjects affected / exposed	0 / 99 (0.00%)	0 / 124 (0.00%)	1 / 250 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Limb injury			
subjects affected / exposed	0 / 99 (0.00%)	0 / 124 (0.00%)	0 / 250 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural intestinal perforation			
subjects affected / exposed	0 / 99 (0.00%)	0 / 124 (0.00%)	0 / 250 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia fracture			
subjects affected / exposed	0 / 99 (0.00%)	0 / 124 (0.00%)	0 / 250 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wrist fracture			
subjects affected / exposed	0 / 99 (0.00%)	0 / 124 (0.00%)	1 / 250 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			

Acute myocardial infarction			
subjects affected / exposed	0 / 99 (0.00%)	0 / 124 (0.00%)	0 / 250 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic valve stenosis			
subjects affected / exposed	0 / 99 (0.00%)	0 / 124 (0.00%)	1 / 250 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 99 (0.00%)	0 / 124 (0.00%)	1 / 250 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bundle branch block left			
subjects affected / exposed	0 / 99 (0.00%)	0 / 124 (0.00%)	1 / 250 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 99 (0.00%)	0 / 124 (0.00%)	1 / 250 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiac failure congestive			
subjects affected / exposed	0 / 99 (0.00%)	0 / 124 (0.00%)	0 / 250 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cor pulmonale			
subjects affected / exposed	0 / 99 (0.00%)	1 / 124 (0.81%)	0 / 250 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	0 / 99 (0.00%)	0 / 124 (0.00%)	0 / 250 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery stenosis			

subjects affected / exposed	0 / 99 (0.00%)	0 / 124 (0.00%)	1 / 250 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	1 / 99 (1.01%)	0 / 124 (0.00%)	0 / 250 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular fibrillation			
subjects affected / exposed	0 / 99 (0.00%)	0 / 124 (0.00%)	0 / 250 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Aphasia			
subjects affected / exposed	0 / 99 (0.00%)	1 / 124 (0.81%)	0 / 250 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Embolic stroke			
subjects affected / exposed	0 / 99 (0.00%)	1 / 124 (0.81%)	0 / 250 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoaesthesia			
subjects affected / exposed	1 / 99 (1.01%)	0 / 124 (0.00%)	0 / 250 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polyneuropathy			
subjects affected / exposed	0 / 99 (0.00%)	0 / 124 (0.00%)	0 / 250 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 99 (0.00%)	0 / 124 (0.00%)	1 / 250 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			

Cataract			
subjects affected / exposed	0 / 99 (0.00%)	0 / 124 (0.00%)	1 / 250 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal detachment			
subjects affected / exposed	0 / 99 (0.00%)	0 / 124 (0.00%)	1 / 250 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vitreous haemorrhage			
subjects affected / exposed	0 / 99 (0.00%)	0 / 124 (0.00%)	1 / 250 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 99 (0.00%)	0 / 124 (0.00%)	0 / 250 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	0 / 99 (0.00%)	0 / 124 (0.00%)	0 / 250 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute abdomen			
subjects affected / exposed	0 / 99 (0.00%)	0 / 124 (0.00%)	0 / 250 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis ulcerative			
subjects affected / exposed	0 / 99 (0.00%)	0 / 124 (0.00%)	0 / 250 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer			
subjects affected / exposed	0 / 99 (0.00%)	0 / 124 (0.00%)	0 / 250 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erosive oesophagitis			

subjects affected / exposed	0 / 99 (0.00%)	0 / 124 (0.00%)	0 / 250 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric haemorrhage			
subjects affected / exposed	0 / 99 (0.00%)	1 / 124 (0.81%)	0 / 250 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 99 (0.00%)	0 / 124 (0.00%)	0 / 250 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagitis			
subjects affected / exposed	0 / 99 (0.00%)	0 / 124 (0.00%)	0 / 250 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 99 (0.00%)	0 / 124 (0.00%)	0 / 250 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 99 (0.00%)	1 / 124 (0.81%)	1 / 250 (0.40%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 99 (0.00%)	0 / 124 (0.00%)	0 / 250 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Intervertebral disc disorder			
subjects affected / exposed	0 / 99 (0.00%)	1 / 124 (0.81%)	0 / 250 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Osteoarthritis			
subjects affected / exposed	0 / 99 (0.00%)	0 / 124 (0.00%)	0 / 250 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Plantar fasciitis			
subjects affected / exposed	1 / 99 (1.01%)	0 / 124 (0.00%)	0 / 250 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
COVID-19			
subjects affected / exposed	0 / 99 (0.00%)	0 / 124 (0.00%)	3 / 250 (1.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19 pneumonia			
subjects affected / exposed	0 / 99 (0.00%)	0 / 124 (0.00%)	1 / 250 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Diverticulitis			
subjects affected / exposed	0 / 99 (0.00%)	0 / 124 (0.00%)	0 / 250 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocarditis bacterial			
subjects affected / exposed	0 / 99 (0.00%)	0 / 124 (0.00%)	0 / 250 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	0 / 99 (0.00%)	0 / 124 (0.00%)	1 / 250 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	0 / 99 (0.00%)	0 / 124 (0.00%)	0 / 250 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritoneal abscess			

subjects affected / exposed	0 / 99 (0.00%)	0 / 124 (0.00%)	1 / 250 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 99 (1.01%)	0 / 124 (0.00%)	6 / 250 (2.40%)
occurrences causally related to treatment / all	1 / 1	0 / 0	6 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 99 (0.00%)	0 / 124 (0.00%)	0 / 250 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	QBW251 75 mg	QBW251 25 mg	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 126 (11.11%)	12 / 124 (9.68%)	15 / 251 (5.98%)
number of deaths (all causes)	2	3	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Abdominal neoplasm			
subjects affected / exposed	1 / 126 (0.79%)	0 / 124 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			
subjects affected / exposed	0 / 126 (0.00%)	1 / 124 (0.81%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			
subjects affected / exposed	0 / 126 (0.00%)	0 / 124 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gallbladder adenocarcinoma			
subjects affected / exposed	1 / 126 (0.79%)	0 / 124 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hepatic cancer			
subjects affected / exposed	1 / 126 (0.79%)	0 / 124 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm			
subjects affected / exposed	1 / 126 (0.79%)	0 / 124 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	0 / 126 (0.00%)	0 / 124 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to lymph nodes			
subjects affected / exposed	0 / 126 (0.00%)	0 / 124 (0.00%)	1 / 251 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to peritoneum			
subjects affected / exposed	1 / 126 (0.79%)	0 / 124 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-small cell lung cancer stage IIIA			
subjects affected / exposed	0 / 126 (0.00%)	0 / 124 (0.00%)	1 / 251 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal adenocarcinoma			
subjects affected / exposed	0 / 126 (0.00%)	1 / 124 (0.81%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	0 / 126 (0.00%)	0 / 124 (0.00%)	1 / 251 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal neoplasm			

subjects affected / exposed	0 / 126 (0.00%)	1 / 124 (0.81%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma			
subjects affected / exposed	0 / 126 (0.00%)	0 / 124 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 126 (0.00%)	0 / 124 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Arteriosclerosis			
subjects affected / exposed	0 / 126 (0.00%)	0 / 124 (0.00%)	1 / 251 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive emergency			
subjects affected / exposed	0 / 126 (0.00%)	0 / 124 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	1 / 126 (0.79%)	0 / 124 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 126 (0.00%)	0 / 124 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 126 (0.79%)	0 / 124 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0

Pyrexia			
subjects affected / exposed	0 / 126 (0.00%)	0 / 124 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular stent thrombosis			
subjects affected / exposed	0 / 126 (0.00%)	0 / 124 (0.00%)	1 / 251 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 126 (0.00%)	0 / 124 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 126 (0.79%)	0 / 124 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchospasm			
subjects affected / exposed	0 / 126 (0.00%)	0 / 124 (0.00%)	1 / 251 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	5 / 126 (3.97%)	2 / 124 (1.61%)	5 / 251 (1.99%)
occurrences causally related to treatment / all	5 / 5	2 / 2	5 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 126 (0.00%)	0 / 124 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung consolidation			

subjects affected / exposed	0 / 126 (0.00%)	0 / 124 (0.00%)	1 / 251 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 126 (0.00%)	0 / 124 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 126 (0.00%)	1 / 124 (0.81%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood potassium increased			
subjects affected / exposed	0 / 126 (0.00%)	0 / 124 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 126 (0.00%)	0 / 124 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone graft lysis			
subjects affected / exposed	0 / 126 (0.00%)	0 / 124 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 126 (0.00%)	0 / 124 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot fracture			
subjects affected / exposed	0 / 126 (0.00%)	0 / 124 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Limb injury			
subjects affected / exposed	1 / 126 (0.79%)	0 / 124 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural intestinal perforation			
subjects affected / exposed	0 / 126 (0.00%)	0 / 124 (0.00%)	1 / 251 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia fracture			
subjects affected / exposed	0 / 126 (0.00%)	0 / 124 (0.00%)	1 / 251 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wrist fracture			
subjects affected / exposed	0 / 126 (0.00%)	0 / 124 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 126 (0.79%)	0 / 124 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Aortic valve stenosis			
subjects affected / exposed	0 / 126 (0.00%)	0 / 124 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 126 (0.00%)	0 / 124 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bundle branch block left			
subjects affected / exposed	0 / 126 (0.00%)	0 / 124 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			

subjects affected / exposed	0 / 126 (0.00%)	0 / 124 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	1 / 126 (0.79%)	0 / 124 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cor pulmonale			
subjects affected / exposed	0 / 126 (0.00%)	0 / 124 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	1 / 126 (0.79%)	0 / 124 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Coronary artery stenosis			
subjects affected / exposed	0 / 126 (0.00%)	0 / 124 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	0 / 126 (0.00%)	0 / 124 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular fibrillation			
subjects affected / exposed	1 / 126 (0.79%)	0 / 124 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Nervous system disorders			
Aphasia			
subjects affected / exposed	0 / 126 (0.00%)	0 / 124 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Embolic stroke			

subjects affected / exposed	0 / 126 (0.00%)	0 / 124 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoaesthesia			
subjects affected / exposed	0 / 126 (0.00%)	0 / 124 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polyneuropathy			
subjects affected / exposed	1 / 126 (0.79%)	0 / 124 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 126 (0.00%)	0 / 124 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Cataract			
subjects affected / exposed	0 / 126 (0.00%)	0 / 124 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal detachment			
subjects affected / exposed	0 / 126 (0.00%)	0 / 124 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vitreous haemorrhage			
subjects affected / exposed	0 / 126 (0.00%)	0 / 124 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 126 (0.79%)	0 / 124 (0.00%)	1 / 251 (0.40%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Abdominal pain upper			
subjects affected / exposed	0 / 126 (0.00%)	0 / 124 (0.00%)	1 / 251 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute abdomen			
subjects affected / exposed	0 / 126 (0.00%)	1 / 124 (0.81%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis ulcerative			
subjects affected / exposed	0 / 126 (0.00%)	0 / 124 (0.00%)	1 / 251 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer			
subjects affected / exposed	1 / 126 (0.79%)	0 / 124 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erosive oesophagitis			
subjects affected / exposed	1 / 126 (0.79%)	0 / 124 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric haemorrhage			
subjects affected / exposed	0 / 126 (0.00%)	0 / 124 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoidal haemorrhage			
subjects affected / exposed	0 / 126 (0.00%)	1 / 124 (0.81%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagitis			
subjects affected / exposed	0 / 126 (0.00%)	0 / 124 (0.00%)	1 / 251 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			

subjects affected / exposed	0 / 126 (0.00%)	0 / 124 (0.00%)	1 / 251 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 126 (0.00%)	0 / 124 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 126 (0.79%)	0 / 124 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Intervertebral disc disorder			
subjects affected / exposed	0 / 126 (0.00%)	0 / 124 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 126 (0.00%)	0 / 124 (0.00%)	1 / 251 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Plantar fasciitis			
subjects affected / exposed	0 / 126 (0.00%)	0 / 124 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
COVID-19			
subjects affected / exposed	1 / 126 (0.79%)	2 / 124 (1.61%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	1 / 1	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
COVID-19 pneumonia			
subjects affected / exposed	0 / 126 (0.00%)	1 / 124 (0.81%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0

Diverticulitis			
subjects affected / exposed	1 / 126 (0.79%)	0 / 124 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocarditis bacterial			
subjects affected / exposed	1 / 126 (0.79%)	0 / 124 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	0 / 126 (0.00%)	0 / 124 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	1 / 126 (0.79%)	0 / 124 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritoneal abscess			
subjects affected / exposed	0 / 126 (0.00%)	0 / 124 (0.00%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	3 / 126 (2.38%)	2 / 124 (1.61%)	3 / 251 (1.20%)
occurrences causally related to treatment / all	3 / 3	2 / 2	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 126 (0.00%)	1 / 124 (0.81%)	0 / 251 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Total		
Total subjects affected by serious adverse events			
subjects affected / exposed	90 / 974 (9.24%)		
number of deaths (all causes)	7		
number of deaths resulting from adverse events	0		

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Abdominal neoplasm			
subjects affected / exposed	1 / 974 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Basal cell carcinoma			
subjects affected / exposed	2 / 974 (0.21%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Breast cancer			
subjects affected / exposed	1 / 974 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gallbladder adenocarcinoma			
subjects affected / exposed	1 / 974 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatic cancer			
subjects affected / exposed	1 / 974 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Lung neoplasm			
subjects affected / exposed	1 / 974 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 1		
Lung neoplasm malignant			
subjects affected / exposed	4 / 974 (0.41%)		
occurrences causally related to treatment / all	4 / 4		
deaths causally related to treatment / all	0 / 0		
Metastases to lymph nodes			
subjects affected / exposed	1 / 974 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Metastases to peritoneum				
subjects affected / exposed	1 / 974 (0.10%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Non-small cell lung cancer stage IIIA				
subjects affected / exposed	1 / 974 (0.10%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Oesophageal adenocarcinoma				
subjects affected / exposed	1 / 974 (0.10%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Prostate cancer				
subjects affected / exposed	1 / 974 (0.10%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Renal neoplasm				
subjects affected / exposed	1 / 974 (0.10%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Squamous cell carcinoma				
subjects affected / exposed	1 / 974 (0.10%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Squamous cell carcinoma of skin				
subjects affected / exposed	1 / 974 (0.10%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Arteriosclerosis				
subjects affected / exposed	1 / 974 (0.10%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hypertensive emergency				

subjects affected / exposed	1 / 974 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypotension			
subjects affected / exposed	1 / 974 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 1		
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 974 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 974 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 1		
Pyrexia			
subjects affected / exposed	1 / 974 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular stent thrombosis			
subjects affected / exposed	1 / 974 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 974 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			

subjects affected / exposed	2 / 974 (0.21%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 1			
Bronchospasm				
subjects affected / exposed	1 / 974 (0.10%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Chronic obstructive pulmonary disease				
subjects affected / exposed	27 / 974 (2.77%)			
occurrences causally related to treatment / all	28 / 28			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	1 / 974 (0.10%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Lung consolidation				
subjects affected / exposed	1 / 974 (0.10%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumothorax				
subjects affected / exposed	1 / 974 (0.10%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	1 / 974 (0.10%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				
Blood potassium increased				
subjects affected / exposed	1 / 974 (0.10%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				

Ankle fracture			
subjects affected / exposed	1 / 974 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Bone graft lysis			
subjects affected / exposed	1 / 974 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Fall			
subjects affected / exposed	1 / 974 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Foot fracture			
subjects affected / exposed	1 / 974 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Limb injury			
subjects affected / exposed	1 / 974 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Procedural intestinal perforation			
subjects affected / exposed	1 / 974 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Tibia fracture			
subjects affected / exposed	1 / 974 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Wrist fracture			
subjects affected / exposed	1 / 974 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			

Acute myocardial infarction			
subjects affected / exposed	1 / 974 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 1		
Aortic valve stenosis			
subjects affected / exposed	1 / 974 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Atrial fibrillation			
subjects affected / exposed	1 / 974 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Bundle branch block left			
subjects affected / exposed	1 / 974 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac arrest			
subjects affected / exposed	1 / 974 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 1		
Cardiac failure congestive			
subjects affected / exposed	1 / 974 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cor pulmonale			
subjects affected / exposed	1 / 974 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Coronary artery disease			
subjects affected / exposed	1 / 974 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 1		
Coronary artery stenosis			

subjects affected / exposed	1 / 974 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Supraventricular tachycardia			
subjects affected / exposed	1 / 974 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Ventricular fibrillation			
subjects affected / exposed	1 / 974 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 1		
Nervous system disorders			
Aphasia			
subjects affected / exposed	1 / 974 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Embolic stroke			
subjects affected / exposed	1 / 974 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoaesthesia			
subjects affected / exposed	1 / 974 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Polyneuropathy			
subjects affected / exposed	1 / 974 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 974 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			

Cataract				
subjects affected / exposed	1 / 974 (0.10%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Retinal detachment				
subjects affected / exposed	1 / 974 (0.10%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Vitreous haemorrhage				
subjects affected / exposed	1 / 974 (0.10%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain				
subjects affected / exposed	2 / 974 (0.21%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Abdominal pain upper				
subjects affected / exposed	1 / 974 (0.10%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Acute abdomen				
subjects affected / exposed	1 / 974 (0.10%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Colitis ulcerative				
subjects affected / exposed	1 / 974 (0.10%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Duodenal ulcer				
subjects affected / exposed	1 / 974 (0.10%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Erosive oesophagitis				

subjects affected / exposed	1 / 974 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastric haemorrhage			
subjects affected / exposed	1 / 974 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Haemorrhoidal haemorrhage			
subjects affected / exposed	1 / 974 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Oesophagitis			
subjects affected / exposed	1 / 974 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Small intestinal obstruction			
subjects affected / exposed	1 / 974 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	2 / 974 (0.21%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 974 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Intervertebral disc disorder			
subjects affected / exposed	1 / 974 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Osteoarthritis			
subjects affected / exposed	1 / 974 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Plantar fasciitis			
subjects affected / exposed	1 / 974 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
COVID-19			
subjects affected / exposed	6 / 974 (0.62%)		
occurrences causally related to treatment / all	6 / 6		
deaths causally related to treatment / all	0 / 2		
COVID-19 pneumonia			
subjects affected / exposed	2 / 974 (0.21%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 2		
Diverticulitis			
subjects affected / exposed	1 / 974 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Endocarditis bacterial			
subjects affected / exposed	1 / 974 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Erysipelas			
subjects affected / exposed	1 / 974 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			
subjects affected / exposed	1 / 974 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Peritoneal abscess			

subjects affected / exposed	1 / 974 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	15 / 974 (1.54%)		
occurrences causally related to treatment / all	15 / 15		
deaths causally related to treatment / all	0 / 1		
Respiratory tract infection			
subjects affected / exposed	1 / 974 (0.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	QBW251 450 mg	QBW251 150 mg	QBW251 300 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	48 / 99 (48.48%)	59 / 124 (47.58%)	117 / 250 (46.80%)
Investigations			
C-reactive protein increased			
subjects affected / exposed	1 / 99 (1.01%)	4 / 124 (3.23%)	8 / 250 (3.20%)
occurrences (all)	1	4	8
Gamma-glutamyltransferase increased			
subjects affected / exposed	4 / 99 (4.04%)	4 / 124 (3.23%)	6 / 250 (2.40%)
occurrences (all)	4	5	6
Haemoglobin decreased			
subjects affected / exposed	2 / 99 (2.02%)	0 / 124 (0.00%)	0 / 250 (0.00%)
occurrences (all)	2	0	0
Hepatic enzyme increased			
subjects affected / exposed	2 / 99 (2.02%)	0 / 124 (0.00%)	2 / 250 (0.80%)
occurrences (all)	2	0	2
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 99 (0.00%)	0 / 124 (0.00%)	2 / 250 (0.80%)
occurrences (all)	0	0	2

Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 99 (4.04%)	3 / 124 (2.42%)	8 / 250 (3.20%)
occurrences (all)	4	3	8
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	2 / 99 (2.02%)	2 / 124 (1.61%)	1 / 250 (0.40%)
occurrences (all)	2	2	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 99 (4.04%)	0 / 124 (0.00%)	5 / 250 (2.00%)
occurrences (all)	5	0	5
Headache			
subjects affected / exposed	4 / 99 (4.04%)	4 / 124 (3.23%)	11 / 250 (4.40%)
occurrences (all)	5	5	11
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 99 (0.00%)	3 / 124 (2.42%)	2 / 250 (0.80%)
occurrences (all)	0	3	3
Fatigue			
subjects affected / exposed	2 / 99 (2.02%)	2 / 124 (1.61%)	3 / 250 (1.20%)
occurrences (all)	2	2	3
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	6 / 99 (6.06%)	1 / 124 (0.81%)	7 / 250 (2.80%)
occurrences (all)	6	2	9
Nausea			
subjects affected / exposed	5 / 99 (5.05%)	2 / 124 (1.61%)	4 / 250 (1.60%)
occurrences (all)	5	2	4
Vomiting			
subjects affected / exposed	1 / 99 (1.01%)	0 / 124 (0.00%)	2 / 250 (0.80%)
occurrences (all)	1	0	2
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	16 / 99 (16.16%)	32 / 124 (25.81%)	51 / 250 (20.40%)
occurrences (all)	22	46	69

Cough			
subjects affected / exposed	1 / 99 (1.01%)	0 / 124 (0.00%)	4 / 250 (1.60%)
occurrences (all)	1	0	4
Rhinitis allergic			
subjects affected / exposed	2 / 99 (2.02%)	0 / 124 (0.00%)	1 / 250 (0.40%)
occurrences (all)	2	0	1
Skin and subcutaneous tissue disorders			
Photosensitivity reaction			
subjects affected / exposed	2 / 99 (2.02%)	1 / 124 (0.81%)	0 / 250 (0.00%)
occurrences (all)	3	1	0
Rash			
subjects affected / exposed	3 / 99 (3.03%)	2 / 124 (1.61%)	2 / 250 (0.80%)
occurrences (all)	3	2	2
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 99 (2.02%)	2 / 124 (1.61%)	2 / 250 (0.80%)
occurrences (all)	2	2	2
Back pain			
subjects affected / exposed	2 / 99 (2.02%)	3 / 124 (2.42%)	7 / 250 (2.80%)
occurrences (all)	2	3	7
Myalgia			
subjects affected / exposed	1 / 99 (1.01%)	4 / 124 (3.23%)	1 / 250 (0.40%)
occurrences (all)	1	4	1
Infections and infestations			
Bronchitis			
subjects affected / exposed	4 / 99 (4.04%)	2 / 124 (1.61%)	6 / 250 (2.40%)
occurrences (all)	4	2	7
COVID-19			
subjects affected / exposed	0 / 99 (0.00%)	1 / 124 (0.81%)	4 / 250 (1.60%)
occurrences (all)	0	1	4
Cystitis			
subjects affected / exposed	0 / 99 (0.00%)	2 / 124 (1.61%)	2 / 250 (0.80%)
occurrences (all)	0	2	2
Gastroenteritis			
subjects affected / exposed	4 / 99 (4.04%)	0 / 124 (0.00%)	2 / 250 (0.80%)
occurrences (all)	4	0	2

Influenza			
subjects affected / exposed	2 / 99 (2.02%)	0 / 124 (0.00%)	4 / 250 (1.60%)
occurrences (all)	2	0	4
Lower respiratory tract infection			
subjects affected / exposed	3 / 99 (3.03%)	3 / 124 (2.42%)	3 / 250 (1.20%)
occurrences (all)	3	4	3
Nasopharyngitis			
subjects affected / exposed	4 / 99 (4.04%)	5 / 124 (4.03%)	12 / 250 (4.80%)
occurrences (all)	5	8	14
Pharyngitis			
subjects affected / exposed	2 / 99 (2.02%)	1 / 124 (0.81%)	0 / 250 (0.00%)
occurrences (all)	2	1	0
Pneumonia			
subjects affected / exposed	3 / 99 (3.03%)	1 / 124 (0.81%)	5 / 250 (2.00%)
occurrences (all)	4	1	5
Sinusitis			
subjects affected / exposed	0 / 99 (0.00%)	3 / 124 (2.42%)	1 / 250 (0.40%)
occurrences (all)	0	3	1
Upper respiratory tract infection			
subjects affected / exposed	3 / 99 (3.03%)	5 / 124 (4.03%)	4 / 250 (1.60%)
occurrences (all)	3	5	5
Upper respiratory tract infection bacterial			
subjects affected / exposed	3 / 99 (3.03%)	4 / 124 (3.23%)	12 / 250 (4.80%)
occurrences (all)	3	5	13
Urinary tract infection			
subjects affected / exposed	3 / 99 (3.03%)	3 / 124 (2.42%)	8 / 250 (3.20%)
occurrences (all)	5	3	8
Viral upper respiratory tract infection			
subjects affected / exposed	3 / 99 (3.03%)	3 / 124 (2.42%)	8 / 250 (3.20%)
occurrences (all)	3	3	11
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	2 / 99 (2.02%)	1 / 124 (0.81%)	1 / 250 (0.40%)
occurrences (all)	2	1	1

Non-serious adverse events	QBW251 75 mg	QBW251 25 mg	Placebo

Total subjects affected by non-serious adverse events subjects affected / exposed	55 / 126 (43.65%)	60 / 124 (48.39%)	107 / 251 (42.63%)
Investigations			
C-reactive protein increased			
subjects affected / exposed	0 / 126 (0.00%)	0 / 124 (0.00%)	2 / 251 (0.80%)
occurrences (all)	0	0	2
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 126 (1.59%)	0 / 124 (0.00%)	3 / 251 (1.20%)
occurrences (all)	2	0	3
Haemoglobin decreased			
subjects affected / exposed	0 / 126 (0.00%)	0 / 124 (0.00%)	1 / 251 (0.40%)
occurrences (all)	0	0	1
Hepatic enzyme increased			
subjects affected / exposed	0 / 126 (0.00%)	0 / 124 (0.00%)	2 / 251 (0.80%)
occurrences (all)	0	0	3
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 126 (0.00%)	3 / 124 (2.42%)	1 / 251 (0.40%)
occurrences (all)	0	3	1
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 126 (2.38%)	3 / 124 (2.42%)	4 / 251 (1.59%)
occurrences (all)	3	3	4
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 126 (0.00%)	1 / 124 (0.81%)	3 / 251 (1.20%)
occurrences (all)	0	1	3
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 126 (0.79%)	1 / 124 (0.81%)	1 / 251 (0.40%)
occurrences (all)	1	1	1
Headache			
subjects affected / exposed	4 / 126 (3.17%)	4 / 124 (3.23%)	6 / 251 (2.39%)
occurrences (all)	4	4	6
General disorders and administration site conditions			

Chest pain			
subjects affected / exposed	0 / 126 (0.00%)	1 / 124 (0.81%)	1 / 251 (0.40%)
occurrences (all)	0	1	1
Fatigue			
subjects affected / exposed	1 / 126 (0.79%)	0 / 124 (0.00%)	3 / 251 (1.20%)
occurrences (all)	1	0	3
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 126 (1.59%)	3 / 124 (2.42%)	6 / 251 (2.39%)
occurrences (all)	2	3	6
Nausea			
subjects affected / exposed	3 / 126 (2.38%)	1 / 124 (0.81%)	5 / 251 (1.99%)
occurrences (all)	3	1	5
Vomiting			
subjects affected / exposed	3 / 126 (2.38%)	1 / 124 (0.81%)	4 / 251 (1.59%)
occurrences (all)	3	1	4
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	24 / 126 (19.05%)	34 / 124 (27.42%)	56 / 251 (22.31%)
occurrences (all)	37	44	73
Cough			
subjects affected / exposed	1 / 126 (0.79%)	1 / 124 (0.81%)	6 / 251 (2.39%)
occurrences (all)	1	1	6
Rhinitis allergic			
subjects affected / exposed	0 / 126 (0.00%)	0 / 124 (0.00%)	0 / 251 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Photosensitivity reaction			
subjects affected / exposed	0 / 126 (0.00%)	0 / 124 (0.00%)	0 / 251 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	0 / 126 (0.00%)	0 / 124 (0.00%)	0 / 251 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	1 / 126 (0.79%)	3 / 124 (2.42%)	6 / 251 (2.39%)
occurrences (all)	1	3	6
Back pain			
subjects affected / exposed	3 / 126 (2.38%)	2 / 124 (1.61%)	7 / 251 (2.79%)
occurrences (all)	3	2	7
Myalgia			
subjects affected / exposed	1 / 126 (0.79%)	0 / 124 (0.00%)	3 / 251 (1.20%)
occurrences (all)	1	0	3
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 126 (0.00%)	3 / 124 (2.42%)	2 / 251 (0.80%)
occurrences (all)	0	4	2
COVID-19			
subjects affected / exposed	1 / 126 (0.79%)	6 / 124 (4.84%)	5 / 251 (1.99%)
occurrences (all)	1	6	5
Cystitis			
subjects affected / exposed	3 / 126 (2.38%)	1 / 124 (0.81%)	1 / 251 (0.40%)
occurrences (all)	3	1	2
Gastroenteritis			
subjects affected / exposed	1 / 126 (0.79%)	1 / 124 (0.81%)	1 / 251 (0.40%)
occurrences (all)	1	1	1
Influenza			
subjects affected / exposed	1 / 126 (0.79%)	1 / 124 (0.81%)	2 / 251 (0.80%)
occurrences (all)	1	1	2
Lower respiratory tract infection			
subjects affected / exposed	2 / 126 (1.59%)	4 / 124 (3.23%)	5 / 251 (1.99%)
occurrences (all)	2	4	7
Nasopharyngitis			
subjects affected / exposed	10 / 126 (7.94%)	6 / 124 (4.84%)	10 / 251 (3.98%)
occurrences (all)	15	7	12
Pharyngitis			
subjects affected / exposed	0 / 126 (0.00%)	2 / 124 (1.61%)	3 / 251 (1.20%)
occurrences (all)	0	2	3
Pneumonia			

subjects affected / exposed	1 / 126 (0.79%)	2 / 124 (1.61%)	2 / 251 (0.80%)
occurrences (all)	1	2	3
Sinusitis			
subjects affected / exposed	1 / 126 (0.79%)	0 / 124 (0.00%)	2 / 251 (0.80%)
occurrences (all)	1	0	2
Upper respiratory tract infection			
subjects affected / exposed	0 / 126 (0.00%)	0 / 124 (0.00%)	5 / 251 (1.99%)
occurrences (all)	0	0	5
Upper respiratory tract infection bacterial			
subjects affected / exposed	4 / 126 (3.17%)	4 / 124 (3.23%)	9 / 251 (3.59%)
occurrences (all)	4	4	12
Urinary tract infection			
subjects affected / exposed	5 / 126 (3.97%)	2 / 124 (1.61%)	5 / 251 (1.99%)
occurrences (all)	6	3	5
Viral upper respiratory tract infection			
subjects affected / exposed	3 / 126 (2.38%)	3 / 124 (2.42%)	7 / 251 (2.79%)
occurrences (all)	4	3	9
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 126 (0.00%)	0 / 124 (0.00%)	1 / 251 (0.40%)
occurrences (all)	0	0	1

Non-serious adverse events	Total		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	446 / 974 (45.79%)		
Investigations			
C-reactive protein increased			
subjects affected / exposed	15 / 974 (1.54%)		
occurrences (all)	15		
Gamma-glutamyltransferase increased			
subjects affected / exposed	19 / 974 (1.95%)		
occurrences (all)	20		
Haemoglobin decreased			
subjects affected / exposed	3 / 974 (0.31%)		
occurrences (all)	3		
Hepatic enzyme increased			

subjects affected / exposed	6 / 974 (0.62%)		
occurrences (all)	7		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	6 / 974 (0.62%)		
occurrences (all)	6		
Vascular disorders			
Hypertension			
subjects affected / exposed	25 / 974 (2.57%)		
occurrences (all)	25		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	9 / 974 (0.92%)		
occurrences (all)	9		
Nervous system disorders			
Dizziness			
subjects affected / exposed	12 / 974 (1.23%)		
occurrences (all)	13		
Headache			
subjects affected / exposed	33 / 974 (3.39%)		
occurrences (all)	35		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	7 / 974 (0.72%)		
occurrences (all)	8		
Fatigue			
subjects affected / exposed	11 / 974 (1.13%)		
occurrences (all)	11		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	25 / 974 (2.57%)		
occurrences (all)	28		
Nausea			
subjects affected / exposed	20 / 974 (2.05%)		
occurrences (all)	20		
Vomiting			

subjects affected / exposed	11 / 974 (1.13%)		
occurrences (all)	11		
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	213 / 974 (21.87%)		
occurrences (all)	291		
Cough			
subjects affected / exposed	13 / 974 (1.33%)		
occurrences (all)	13		
Rhinitis allergic			
subjects affected / exposed	3 / 974 (0.31%)		
occurrences (all)	3		
Skin and subcutaneous tissue disorders			
Photosensitivity reaction			
subjects affected / exposed	3 / 974 (0.31%)		
occurrences (all)	4		
Rash			
subjects affected / exposed	7 / 974 (0.72%)		
occurrences (all)	7		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	16 / 974 (1.64%)		
occurrences (all)	16		
Back pain			
subjects affected / exposed	24 / 974 (2.46%)		
occurrences (all)	24		
Myalgia			
subjects affected / exposed	10 / 974 (1.03%)		
occurrences (all)	10		
Infections and infestations			
Bronchitis			
subjects affected / exposed	17 / 974 (1.75%)		
occurrences (all)	19		
COVID-19			

subjects affected / exposed	17 / 974 (1.75%)			
occurrences (all)	17			
Cystitis				
subjects affected / exposed	9 / 974 (0.92%)			
occurrences (all)	10			
Gastroenteritis				
subjects affected / exposed	9 / 974 (0.92%)			
occurrences (all)	9			
Influenza				
subjects affected / exposed	10 / 974 (1.03%)			
occurrences (all)	10			
Lower respiratory tract infection				
subjects affected / exposed	20 / 974 (2.05%)			
occurrences (all)	23			
Nasopharyngitis				
subjects affected / exposed	47 / 974 (4.83%)			
occurrences (all)	61			
Pharyngitis				
subjects affected / exposed	8 / 974 (0.82%)			
occurrences (all)	8			
Pneumonia				
subjects affected / exposed	14 / 974 (1.44%)			
occurrences (all)	16			
Sinusitis				
subjects affected / exposed	7 / 974 (0.72%)			
occurrences (all)	7			
Upper respiratory tract infection				
subjects affected / exposed	17 / 974 (1.75%)			
occurrences (all)	18			
Upper respiratory tract infection bacterial				
subjects affected / exposed	36 / 974 (3.70%)			
occurrences (all)	41			
Urinary tract infection				
subjects affected / exposed	26 / 974 (2.67%)			
occurrences (all)	30			

Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	27 / 974 (2.77%) 33		
Metabolism and nutrition disorders Hypokalaemia subjects affected / exposed occurrences (all)	5 / 974 (0.51%) 5		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 June 2019	The protocol is being amended to implement requested protocol changes and in response to considerations received from health authorities in some countries where the study is planned to be conducted.
24 October 2019	The protocol is being amended to implement requested protocol changes and in response to considerations received from health authorities and ethics committees in countries where the study is planned to be conducted.
10 June 2020	The protocol is being amended in response to both the discontinuation of the 450 mg b.i.d. treatment arm and the impact of the COVID-19 pandemic.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported