



Clinical trial results:

A Multicenter, Randomized, Double-blind, Chronic-dosing, Parallel-group, Placebo-controlled Phase 3 Study to Evaluate the Efficacy and Safety of Benralizumab 100 mg in Patients with Moderate to Very Severe Chronic Obstructive Pulmonary Disease (COPD) with a History of Frequent COPD Exacerbations and Elevated Peripheral Blood Eosinophils.

Summary

EudraCT number	2019-001800-39
Trial protocol	DK PL HU CZ DE AT ES GB NL BE GR IT
Global end of trial date	28 July 2025

Results information

Result version number	v1 (current)
This version publication date	13 August 2026
First version publication date	13 August 2026

Trial information

Trial identification

Sponsor protocol code	D3251C00014
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	AstraZeneca
Sponsor organisation address	151 85, Sodertalje, Sweden,
Public contact	Global Clinical Lead, AstraZeneca, 1 877-240-9479, information.center@astrazeneca.com
Scientific contact	Global Clinical Lead, AstraZeneca, 1 877-240-9479, information.center@astrazeneca.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	05 September 2025
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 July 2025
Global end of trial reached?	Yes
Global end of trial date	28 July 2025
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the effect of benralizumab 100 mg on COPD exacerbations in patients with moderate to very severe COPD

Protection of trial subjects:

Participants were maintained on triple (ICS/LABA/LAMA) background therapy, from enrolment throughout the run-in and treatment periods. Background inhaled medications may be provided/reimbursed by AstraZeneca (also referred to as 'AZ' or sponsor), based on local regulations on participant participation in research studies and medication access.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 August 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 55
Country: Number of subjects enrolled	United Kingdom: 30
Country: Number of subjects enrolled	Greece: 25
Country: Number of subjects enrolled	Spain: 25
Country: Number of subjects enrolled	Türkiye: 21
Country: Number of subjects enrolled	Denmark: 19
Country: Number of subjects enrolled	Austria: 18
Country: Number of subjects enrolled	Italy: 17
Country: Number of subjects enrolled	Sweden: 5
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	Argentina: 48
Country: Number of subjects enrolled	Brazil: 34
Country: Number of subjects enrolled	Colombia: 23
Country: Number of subjects enrolled	Chile: 17
Country: Number of subjects enrolled	New Zealand: 15
Country: Number of subjects enrolled	Australia: 7
Country: Number of subjects enrolled	China: 59
Country: Number of subjects enrolled	Korea, Republic of: 23

Country: Number of subjects enrolled	Japan: 22
Country: Number of subjects enrolled	Viet Nam: 13
Country: Number of subjects enrolled	Philippines: 9
Country: Number of subjects enrolled	India: 8
Country: Number of subjects enrolled	United States: 68
Country: Number of subjects enrolled	Canada: 15
Country: Number of subjects enrolled	Mexico: 8
Country: Number of subjects enrolled	Hungary: 39
Country: Number of subjects enrolled	Poland: 23
Country: Number of subjects enrolled	Czechia: 13
Country: Number of subjects enrolled	Bulgaria: 11
Worldwide total number of subjects	676
EEA total number of subjects	256

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)	258
From 65 to 84 years	416
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

A total of 2,026 participants were enrolled.

Pre-assignment

Screening details:

1,337 participants are not randomized due to screen failure or other reasons. The rest 689 participants were randomized. 13 of which were removed from analyses due to GCP non-compliance before study unblinding. Remaining 676 participants, benralizumab arm (331 participants) or placebo arm (345 participants), were included in the analysis.

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, Monitor, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Benralizumab 100 mg

Arm description:

Administered by subcutaneous (SC) injection every 4 weeks for the first 3 doses and then every 8 weeks thereafter (Q8W)

Arm type	Experimental
Investigational medicinal product name	Benralizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Benralizumab 100 mg every 4 weeks for the first 3 doses and then every 8 weeks thereafter (Q8W)

Arm title	Placebo
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Arm description:

Administered by SC injection every 4 weeks for the first 3 doses and then Q8W

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Matching placebo every 4 weeks for the first 3 doses and then every 8 weeks thereafter (Q8W)

Number of subjects in period 1	Benralizumab 100 mg	Placebo
Started	331	345
Completed	226	218
Not completed	105	127
Adverse event, serious fatal	28	33
Consent withdrawn by subject	58	65
Physician decision	5	4
Adverse event, non-fatal	4	10
Other reasons	9	14
Lost to follow-up	1	1

Baseline characteristics

Reporting groups

Reporting group title	Benralizumab 100 mg
Reporting group description:	
Administered by subcutaneous (SC) injection every 4 weeks for the first 3 doses and then every 8 weeks thereafter (Q8W)	
Reporting group title	Placebo
Reporting group description:	
Administered by SC injection every 4 weeks for the first 3 doses and then Q8W	

Reporting group values	Benralizumab 100 mg	Placebo	Total
Number of subjects	331	345	676
Age Categorical			
Units: Participants			
Between 18 and 65 years	122	136	258
>=65 years	209	209	418
Age Continuous			
Units: Years			
arithmetic mean	67.0	66.8	
standard deviation	± 7.72	± 7.28	-
Sex: Female, Male			
Units: Participants			
Female	101	111	212
Male	230	234	464
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	61	62	123
Not Hispanic or Latino	270	283	553
Race/Ethnicity, Customized			
Units: Subjects			
White	244	250	494
Black or African American	1	4	5
Asian	66	72	138
Other	20	19	39

End points

End points reporting groups

Reporting group title	Benralizumab 100 mg
Reporting group description:	
Administered by subcutaneous (SC) injection every 4 weeks for the first 3 doses and then every 8 weeks thereafter (Q8W)	
Reporting group title	Placebo
Reporting group description:	
Administered by SC injection every 4 weeks for the first 3 doses and then Q8W	

Primary: Annualized rate of moderate or severe COPD exacerbations of participants with ≥ 3 exacerbations in the previous year.

End point title	Annualized rate of moderate or severe COPD exacerbations of participants with ≥ 3 exacerbations in the previous year.
End point description:	
Moderate or severe COPD exacerbation is defined by symptomatic worsening of COPD requiring:	
Use of systemic corticosteroids for at least 3 days; and/or	
Use of antibiotics; and/or	
An inpatient hospitalization or death due to COPD.	
Annualized Exacerbation Rate = $365.25 \times \text{Total Number of Exacerbations} / \text{Total time at risk within the treatment group (days)}$	
End point type	Primary
End point timeframe:	
up to Week 56	

End point values	Benralizumab 100 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	241	249		
Units: Annualized exacerbation rate				
least squares mean (confidence interval 95%)	2.04 (1.69 to 2.46)	2.46 (2.05 to 2.95)		

Statistical analyses

Statistical analysis title	Negative binomial model
Statistical analysis description:	
Null hypothesis: Rate ratio (benralizumab vs Placebo) = 1	
Comparison groups	Benralizumab 100 mg v Placebo

Number of subjects included in analysis	490
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1172
Method	Negative binomial model
Parameter estimate	Rate ratio
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	1.05

Primary: Annualized rate of moderate or severe COPD exacerbations of participants with ≥ 2 exacerbations in the previous year

End point title	Annualized rate of moderate or severe COPD exacerbations of participants with ≥ 2 exacerbations in the previous year
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End point description:

Moderate or severe COPD exacerbation is defined by symptomatic worsening of COPD requiring:
 Use of systemic corticosteroids for at least 3 days; and/or
 Use of antibiotics; and/or
 An inpatient hospitalization or death due to COPD.

Annualized Exacerbation Rate = $365.25 \times \text{Total Number of Exacerbations} / \text{Total time at risk within the treatment group (days)}$

End point type	Primary
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End point timeframe:

up to Week 56

End point values	Benralizumab 100 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	331	345		
Units: Annualized exacerbation rate				
least squares mean (confidence interval 95%)	1.86 (1.58 to 2.20)	2.05 (1.75 to 2.41)		

Statistical analyses

Statistical analysis title	Negative binomial model
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Statistical analysis description:

Null hypothesis: Rate ratio (benralizumab vs Placebo) = 1

Comparison groups	Benralizumab 100 mg v Placebo
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Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3367
Method	Negative binomial model
Parameter estimate	Rate ratio
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.74
upper limit	1.11

Secondary: Key secondary endpoint: Annualized rate of severe COPD exacerbations of participants with ≥ 3 exacerbations in the previous year

End point title	Key secondary endpoint: Annualized rate of severe COPD exacerbations of participants with ≥ 3 exacerbations in the previous year
End point description: Severe COPD exacerbation is defined by symptomatic worsening of COPD requiring an inpatient hospitalization or results in death due to COPD. Annualized Exacerbation Rate = $365.25 \times \text{Total Number of Exacerbations} / \text{Total time at risk within the treatment group (days)}$	
End point type	Secondary
End point timeframe: Through end of treatment	

End point values	Benralizumab 100 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	241	249		
Units: Annualized exacerbation rate				
least squares mean (confidence interval 95%)	0.37 (0.28 to 0.49)	0.39 (0.30 to 0.52)		

Statistical analyses

Statistical analysis title	Negative binomial model
Statistical analysis description: Null hypothesis: Rate ratio (benralizumab vs Placebo) = 1	
Comparison groups	Benralizumab 100 mg v Placebo

Number of subjects included in analysis	490
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.7644
Method	Negative binomial model
Parameter estimate	Rate ratio
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	1.35

Secondary: Key secondary endpoint: Annualized rate of severe COPD exacerbations of participants with ≥ 2 exacerbations in the previous year

End point title	Key secondary endpoint: Annualized rate of severe COPD exacerbations of participants with ≥ 2 exacerbations in the previous year
End point description: Severe COPD exacerbation is defined by symptomatic worsening of COPD requiring an inpatient hospitalization or results in death due to COPD. Annualized Exacerbation Rate = $365.25 \times \text{Total Number of Exacerbations} / \text{Total time at risk within the treatment group (days)}$	
End point type	Secondary
End point timeframe: Through end of treatment	

End point values	Benralizumab 100 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	331	345		
Units: Annualized exacerbation rate				
least squares mean (confidence interval 95%)	0.37 (0.30 to 0.47)	0.33 (0.26 to 0.42)		

Statistical analyses

Statistical analysis title	Negative binomial model
Statistical analysis description: Null hypothesis: Rate ratio (benralizumab vs Placebo) = 1	
Comparison groups	Benralizumab 100 mg v Placebo

Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4328
Method	Negative binomial model
Parameter estimate	Rate ratio
Point estimate	1.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1.53

Secondary: Key secondary endpoint: Change from baseline in SGRQ total and domain scores at Week 56 of participants with ≥ 3 exacerbations in the previous year

End point title	Key secondary endpoint: Change from baseline in SGRQ total and domain scores at Week 56 of participants with ≥ 3 exacerbations in the previous year
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End point description:

The St. George's Respiratory Questionnaire (SGRQ) is a 50-item PRO instrument developed to measure the health status of patients with airway obstruction diseases. The questionnaire is divided into 2 parts: part 1 consists of 8 items pertaining to the severity of respiratory symptoms in the preceding 4 weeks; and part 2 consists of 42 items related to the daily activity and psychosocial impacts of the individual's respiratory condition. The SGRQ yields a total score and 3 domain scores (symptoms, activity, and impacts). The total score indicates the impact of disease on overall health status. This total score is expressed as a percentage of overall impairment, in which 100 represents the worst possible health status and 0 indicates the best possible health status. Likewise, the domain scores range from 0 to 100, with higher scores indicative of greater impairment.

End point type	Secondary
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End point timeframe:

up to Week 56

End point values	Benralizumab 100 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	241	249		
Units: Score				
arithmetic mean (standard deviation)				
Total Score	-7.06 ($\pm$ 16.804)	-4.95 ($\pm$ 16.915)		
Symptoms	-7.16 ($\pm$ 18.495)	-5.46 ($\pm$ 16.822)		
Activity	-8.34 ($\pm$ 19.958)	-6.81 ($\pm$ 18.663)		
Impacts	-6.37 ($\pm$ 20.335)	-3.75 ($\pm$ 21.387)		

Statistical analyses

Statistical analysis title	Repeated measures model
Statistical analysis description:	
Null Hypothesis: Difference in mean change from baseline in SGRQ total score at Week 56 (tezepelumab minus placebo) = 0	
Comparison groups	Benralizumab 100 mg v Placebo
Number of subjects included in analysis	490
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1686
Method	Mixed models analysis
Parameter estimate	Difference in Least Squares Means
Point estimate	-2.092
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.072
upper limit	0.889

Secondary: Key secondary endpoint: Change from baseline in SGRQ total and domain scores at Week 56 of participants with ≥ 2 exacerbations in the previous year

End point title	Key secondary endpoint: Change from baseline in SGRQ total and domain scores at Week 56 of participants with ≥ 2 exacerbations in the previous year
End point description:	
The St. George's Respiratory Questionnaire (SGRQ) is a 50-item PRO instrument developed to measure the health status of patients with airway obstruction diseases. The questionnaire is divided into 2 parts: part 1 consists of 8 items pertaining to the severity of respiratory symptoms in the preceding 4 weeks; and part 2 consists of 42 items related to the daily activity and psychosocial impacts of the individual's respiratory condition. The SGRQ yields a total score and 3 domain scores (symptoms, activity, and impacts). The total score indicates the impact of disease on overall health status. This total score is expressed as a percentage of overall impairment, in which 100 represents the worst possible health status and 0 indicates the best possible health status. Likewise, the domain scores range from 0 to 100, with higher scores indicative of greater impairment.	
End point type	Secondary
End point timeframe:	
up to Week 56	

End point values	Benralizumab 100 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	331	345		
Units: Score				
arithmetic mean (standard deviation)				
Total Score	-5.80 ($\pm$ 16.185)	-3.89 ($\pm$ 16.141)		
Symptoms	-6.10 ($\pm$ 18.104)	-4.97 ($\pm$ 16.768)		

Activity	-6.81 ($\pm$ 19.381)	-4.96 ($\pm$ 17.618)		
Impacts	-5.20 ($\pm$ 19.685)	-2.95 ($\pm$ 20.592)		

Statistical analyses

Statistical analysis title	Repeated measures model
Statistical analysis description:	
Null Hypothesis: Difference in mean change from baseline in SGRQ total score at Week 56 (tezepelumab minus placebo) = 0	
Comparison groups	Benralizumab 100 mg v Placebo
Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1013
Method	Mixed models analysis
Parameter estimate	Difference in Least Squares Means
Point estimate	-2.014
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.424
upper limit	0.396

Secondary: Key secondary endpoint: Change from baseline in pre-bronchodilator FEV1 (mL) at Week 56 of participants with ≥ 3 exacerbations in the previous year

End point title	Key secondary endpoint: Change from baseline in pre-bronchodilator FEV1 (mL) at Week 56 of participants with ≥ 3 exacerbations in the previous year
End point description:	
Pre-bronchodilator forced expiratory volume in 1 second (FEV1) is defined as the volume of air exhaled from the lungs in the first second of forced expiration.	
End point type	Secondary
End point timeframe:	
up to Week 56	

End point values	Benralizumab 100 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	241	249		
Units: mL				
arithmetic mean (standard error)	10.8 ($\pm$ 268.48)	17.3 ($\pm$ 285.39)		

Statistical analyses

Statistical analysis title	Repeated measures model
Statistical analysis description:	
Null Hypothesis: Difference in mean change from baseline in pre-bronchodilator FEV1 at 56 weeks (Benralizumab minus placebo) = 0	
Comparison groups	Benralizumab 100 mg v Placebo
Number of subjects included in analysis	490
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.9729
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.882
Confidence interval	
level	95 %
sides	2-sided
lower limit	-50.081
upper limit	51.844

Secondary: Key secondary endpoint: Change from baseline in pre-bronchodilator FEV1 (mL) at Week 56 of participants with ≥ 2 exacerbations in the previous year

End point title	Key secondary endpoint: Change from baseline in pre-bronchodilator FEV1 (mL) at Week 56 of participants with ≥ 2 exacerbations in the previous year
End point description:	
Pre-bronchodilator forced expiratory volume in 1 second (FEV1) is defined as the volume of air exhaled from the lungs in the first second of forced expiration.	
End point type	Secondary
End point timeframe:	
up to Week 56	

End point values	Benralizumab 100 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	331	345		
Units: mL				
arithmetic mean (standard error)	18.3 ($\pm$ 252.20)	3.8 ($\pm$ 259.60)		

Statistical analyses

Statistical analysis title	Repeated measures model
Statistical analysis description: Null Hypothesis: Difference in mean change from baseline in pre-bronchodilator FEV1 at 56 weeks (Benralizumab minus placebo) = 0	
Comparison groups	Benralizumab 100 mg v Placebo
Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2816
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	21.965
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.062
upper limit	61.992

Secondary: Annualized rate of COPD exacerbations that are associated with an emergency room/emergency department visit or a hospitalization due to COPD of participants with ≥ 3 exacerbations in the previous year

End point title	Annualized rate of COPD exacerbations that are associated with an emergency room/emergency department visit or a hospitalization due to COPD of participants with ≥ 3 exacerbations in the previous year
End point description: The annualized rate of COPD exacerbations that are associated with an emergency room/emergency department (ER) or a hospitalization due to COPD through EOT are calculated similarly to the primary efficacy endpoint. The emergence room/emergence department (ER) and hospitalization due to COPD exacerbation are collected in COPDEX eCRF. Annualized Exacerbation Rate = $365.25 \times \text{Total Number of Exacerbations} / \text{Total time at risk within the treatment group (days)}$	
End point type	Secondary
End point timeframe: Through end of treatment	

End point values	Benralizumab 100 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	241	249		
Units: Annualized exacerbation rate				
least squares mean (confidence interval 95%)	0.50 (0.39 to 0.64)	0.60 (0.47 to 0.76)		

Statistical analyses

Statistical analysis title	Negative binomial model
Statistical analysis description:	
Null hypothesis: Rate ratio (benralizumab vs Placebo) = 1	
Comparison groups	Benralizumab 100 mg v Placebo
Number of subjects included in analysis	490
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2589
Method	Negative binomial model
Parameter estimate	Rate ratio
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	1.14

Secondary: Annualized rate of COPD exacerbations that are associated with an emergency room/emergency department visit or a hospitalization due to COPD of participants with ≥ 2 exacerbations in the previous year

End point title	Annualized rate of COPD exacerbations that are associated with an emergency room/emergency department visit or a hospitalization due to COPD of participants with ≥ 2 exacerbations in the previous year
End point description:	
The annualized rate of COPD exacerbations that are associated with an emergency room/emergency department (ER) or a hospitalization due to COPD through EOT are calculated similarly to the primary efficacy endpoint. The emergency room/emergency department (ER) and hospitalization due to COPD exacerbation are collected in COPDEX eCRF.	
Annualized Exacerbation Rate = $365.25 \times \text{Total Number of Exacerbations} / \text{Total time at risk within the treatment group (days)}$	
End point type	Secondary
End point timeframe:	
Through end of treatment	

End point values	Benralizumab 100 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	331	345		
Units: Annualized exacerbation rate				
least squares mean (confidence interval 95%)	0.48 (0.39 to 0.59)	0.50 (0.41 to 0.61)		

Statistical analyses

Statistical analysis title	Negative binomial model
Statistical analysis description:	
Null hypothesis: Rate ratio (benralizumab vs Placebo) = 1	
Comparison groups	Benralizumab 100 mg v Placebo
Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.7971
Method	Negative binomial model
Parameter estimate	Rate ratio
Point estimate	0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.74
upper limit	1.26

Secondary: Time from randomization to the first moderate or severe COPD exacerbation up to Week 56 of participants with ≥ 3 exacerbations in the previous year

End point title	Time from randomization to the first moderate or severe COPD exacerbation up to Week 56 of participants with ≥ 3 exacerbations in the previous year
End point description:	
Time from randomization to the first moderate or severe COPD exacerbation = Start Date of first COPD exacerbation – Date of Randomization + 1.	
The time to first moderate or severe COPD exacerbation for patients who did experience a moderate or severe COPD exacerbation up to Week 56 were censored at Week 56, and for patients who discontinued or are lost-to-follow-up prior to Week 56, at the last time point after which an exacerbation could not be assessed.	
End point type	Secondary
End point timeframe:	
up to Week 56	

End point values	Benralizumab 100 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	241	249		
Units: Weeks				
median (confidence interval 95%)	31.7 (24.1 to 40.4)	26.1 (21.1 to 31.1)		

Statistical analyses

Statistical analysis title	Proportional hazards regression model
Statistical analysis description:	
Null hypothesis: Hazard ratio (benralizumab vs Placebo) = 1	
Comparison groups	Benralizumab 100 mg v Placebo
Number of subjects included in analysis	490
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1331
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	1.03

Secondary: Time from randomization to the first moderate or severe COPD exacerbation up to Week 56 of participants with ≥ 2 exacerbations in the previous year

End point title	Time from randomization to the first moderate or severe COPD exacerbation up to Week 56 of participants with ≥ 2 exacerbations in the previous year
End point description:	
Time from randomization to the first moderate or severe COPD exacerbation = Start Date of first COPD exacerbation – Date of Randomization + 1.	
The time to first moderate or severe COPD exacerbation for patients who did experience a moderate or severe COPD exacerbation up to Week 56 were censored at Week 56, and for patients who discontinued or are lost-to-follow-up prior to Week 56, at the last time point after which an exacerbation could not be assessed.	
End point type	Secondary
End point timeframe:	
up to Week 56	

End point values	Benralizumab 100 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	331	345		
Units: Weeks				
median (confidence interval 95%)	33.0 (26.6 to 44.1)	29.1 (25.6 to 33.0)		

Statistical analyses

Statistical analysis title	Proportional hazards regression model
Statistical analysis description:	
Null hypothesis: Hazard ratio (benralizumab vs Placebo) = 1	
Comparison groups	Benralizumab 100 mg v Placebo
Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2465
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	1.06

Secondary: Time from randomization to the first severe COPD exacerbation of participants with ≥ 3 exacerbations in the previous year

End point title	Time from randomization to the first severe COPD exacerbation of participants with ≥ 3 exacerbations in the previous year
End point description:	
Time from randomization to the first severe COPD exacerbation = Start Date of first COPD exacerbation – Date of Randomization + 1.	
The time to first severe COPD exacerbation for patients who did experience a severe COPD exacerbation through EOT were censored at EOT, and for patients who discontinue or are lost-to-follow-up prior to EOT, at the last time point after which an exacerbation could not be assessed.	
End point type	Secondary
End point timeframe:	
through end of treatment	

End point values	Benralizumab 100 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	241	249		
Units: Weeks				
median (confidence interval 95%)	255.0 (157.1 to 9999)	194.6 (124.1 to 9999)		

Statistical analyses

Statistical analysis title	Proportional hazards regression model
Statistical analysis description:	
Null hypothesis: Hazard ratio (benralizumab vs Placebo) = 1	
Comparison groups	Benralizumab 100 mg v Placebo
Number of subjects included in analysis	490
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3566
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.63
upper limit	1.19

Secondary: Time from randomization to the first severe COPD exacerbation of participants with ≥ 2 exacerbations in the previous year

End point title	Time from randomization to the first severe COPD exacerbation of participants with ≥ 2 exacerbations in the previous year
End point description:	
Time from randomization to the first severe COPD exacerbation = Start Date of first COPD exacerbation – Date of Randomization + 1.	
The time to first severe COPD exacerbation for patients who did experience a severe COPD exacerbation through EOT were censored at EOT, and for patients who discontinue or are lost-to-follow-up prior to EOT, at the last time point after which an exacerbation could not be assessed.	
End point type	Secondary
End point timeframe:	
through end of treatment	

End point values	Benralizumab 100 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	331	345		
Units: Weeks				
median (confidence interval 95%)	255.0 (190.0 to 9999)	0 (0 to 9999)		

Statistical analyses

Statistical analysis title	Proportional hazards regression model
Statistical analysis description:	
Null hypothesis: Hazard ratio (benralizumab vs Placebo) = 1	
Comparison groups	Benralizumab 100 mg v Placebo
Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.8201
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	1.32

Secondary: Change from baseline in COPD assessment tool (CAT) total score up to Week 56 of participants with ≥ 3 exacerbations in the previous year.

End point title	Change from baseline in COPD assessment tool (CAT) total score up to Week 56 of participants with ≥ 3 exacerbations in the previous year.
End point description:	
The CAT is an 8-item PRO developed to measure the impact of COPD on health status. The instrument uses semantic differential 6-point response scales, which are defined by contrasting objectives to capture the impact of COPD. Content includes items related to cough, phlegm, chest tightness, breathlessness going up hills/stairs, activity limitation at home, confidence leaving home, sleep, and energy. The CAT total score is the sum of all item responses. Scores range from 0 to 40 with higher scores indicative of greater COPD impact on health status. A score cannot be calculated if >2 responses are missing; when one or two items are missing, their scores can be set to the average of the non-missing item scores.	
End point type	Secondary
End point timeframe:	
up to Week 56	

End point values	Benralizumab 100 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	241	249		
Units: Score				
least squares mean (confidence interval 95%)	-4.264 (-5.136 to -3.391)	-2.391 (-3.260 to -1.523)		

Statistical analyses

Statistical analysis title	Repeated measures model
Statistical analysis description:	
Null Hypothesis: Difference in CAT total score change from baseline at 56 weeks (Benralizumab minus placebo) = 0	
Comparison groups	Benralizumab 100 mg v Placebo
Number of subjects included in analysis	490
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.003
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.872
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.104
upper limit	-0.641

Secondary: Change from baseline in COPD assessment tool (CAT) total score up to Week 56 of participants with ≥ 2 exacerbations in the previous year.

End point title	Change from baseline in COPD assessment tool (CAT) total score up to Week 56 of participants with ≥ 2 exacerbations in the previous year.
End point description:	
The CAT is an 8-item PRO developed to measure the impact of COPD on health status. The instrument uses semantic differential 6-point response scales, which are defined by contrasting objectives to capture the impact of COPD. Content includes items related to cough, phlegm, chest tightness, breathlessness going up hills/stairs, activity limitation at home, confidence leaving home, sleep, and energy. The CAT total score is the sum of all item responses. Scores range from 0 to 40 with higher scores indicative of greater COPD impact on health status. A score cannot be calculated if >2 responses are missing; when one or two items are missing, their scores can be set to the average of the non-missing item scores.	
End point type	Secondary
End point timeframe:	
up to Week 56	

End point values	Benralizumab 100 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	331	345		
Units: Score				
least squares mean (confidence interval 95%)	-4.021 (-4.761 to -3.281)	-2.178 (-2.909 to -1.447)		

Statistical analyses

Statistical analysis title	Repeated measures model
Statistical analysis description:	
Null Hypothesis: Difference in CAT total score change from baseline at 56 weeks (Benralizumab minus placebo) = 0	
Comparison groups	Benralizumab 100 mg v Placebo
Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0005
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.843
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.883
upper limit	-0.802

Secondary: Change from baseline in Evaluating Respiratory Symptoms in Chronic Obstructive Pulmonary Disease (E-RS: COPD) total and domain scores at week 56 of participants with ≥ 3 exacerbations in the previous year.

End point title	Change from baseline in Evaluating Respiratory Symptoms in Chronic Obstructive Pulmonary Disease (E-RS: COPD) total and domain scores at week 56 of participants with ≥ 3 exacerbations in the previous year.
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End point description:

The E-RS: COPD is an 11-item PRO developed to evaluate the severity of respiratory symptoms of COPD. The E-RS: COPD is a subset of items from the EXACT-PRO. The E-RS: COPD was designed to be captured as part of the daily EXACT-PRO assessment. Summation of E-RS: COPD item responses produces a total score ranging from 0 to 40, with higher scores indicating greater severity. In addition to the total score, symptom domain scores can be calculated for breathlessness (5 items; score range: 0–17), cough and sputum (3 items; score range: 0–11) and chest symptoms (3 items; score range: 0–12) by summing the responses of items within a respective domain. As with the total score, higher domain scores indicate greater severity.

End point type	Secondary
End point timeframe:	
up to Week 56	

End point values	Benralizumab 100 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	241	249		
Units: Score				
arithmetic mean (standard deviation)				
Total Score	-2.32 (± 6.602)	-1.49 (± 5.343)		
Breathlessness	-0.76 (± 3.409)	-0.41 (± 2.839)		
Cough and Sputum	-0.77 (± 1.836)	-0.60 (± 1.593)		
Chest Symptoms	-0.78 (± 2.224)	-0.48 (± 1.850)		

Statistical analyses

Statistical analysis title	Repeated measures model
Statistical analysis description:	
Null Hypothesis: Difference in mean change from baseline in E-RS: COPD total score at Week 56 (tezepelumab minus placebo) = 0	
Comparison groups	Benralizumab 100 mg v Placebo
Number of subjects included in analysis	490
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1285
Method	Mixed models analysis
Parameter estimate	Difference in Least Squares Means
Point estimate	-0.795
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.822
upper limit	0.231

Secondary: Change from baseline in Evaluating Respiratory Symptoms in Chronic Obstructive Pulmonary Disease (E-RS: COPD) total and domain scores at week 56 of participants with ≥2 exacerbations in the previous year.

End point title	Change from baseline in Evaluating Respiratory Symptoms in Chronic Obstructive Pulmonary Disease (E-RS: COPD) total and domain scores at week 56 of participants with ≥2 exacerbations in the previous year.
End point description:	
The E-RS: COPD is an 11-item PRO developed to evaluate the severity of respiratory symptoms of COPD. The E-RS: COPD is a subset of items from the EXACT-PRO. The E-RS: COPD was designed to be captured as part of the daily EXACT-PRO assessment. Summation of E-RS: COPD item responses produces a total score ranging from 0 to 40, with higher scores indicating greater severity. In addition to the total score, symptom domain scores can be calculated for breathlessness (5 items; score range: 0–17), cough and sputum (3 items; score range: 0–11) and chest symptoms (3 items; score range: 0–12) by summing the responses of items within a respective domain. As with the total score, higher domain scores indicate greater severity.	
End point type	Secondary

End point timeframe:
up to Week 56

End point values	Benralizumab 100 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	331	345		
Units: Score				
arithmetic mean (standard deviation)				
Total Score	-1.95 (± 6.218)	-1.20 (± 5.245)		
Breathlessness	-0.57 (± 3.196)	-0.29 (± 2.691)		
Cough and Sputum	-0.67 (± 1.736)	-0.52 (± 1.576)		
Chest Symptoms	-0.70 (± 2.071)	-0.39 (± 1.849)		

Statistical analyses

Statistical analysis title	Repeated measures model
Statistical analysis description:	
Null Hypothesis: Difference in mean change from baseline in E-RS: COPD total score at Week 56 (tezepelumab minus placebo) = 0	
Comparison groups	Benralizumab 100 mg v Placebo
Number of subjects included in analysis	676
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0931
Method	Mixed models analysis
Parameter estimate	Difference in Least Squares Means
Point estimate	-0.722
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.565
upper limit	0.121

Secondary: All-cause and respiratory-related mortality of participants with ≥ 3 exacerbations in the previous year.

End point title	All-cause and respiratory-related mortality of participants with ≥ 3 exacerbations in the previous year.
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End point description:

Respiratory related causes of death are summarised based on the SOC = Respiratory, thoracic and mediastinal disorders.

Exposure adjusted incidence rate (EAIR) of mortality is compared between treatment groups.

EAIR per 100 patient-years is defined as number of subjects with a mortality divided by the total

number of days at risk for mortality across all subjects in given treatment group, multiplied by 365.25 and then multiplied by 100. Total number of days at risk for death is defined as the duration from the first dose of IP to the date of death, or the duration from the first dose of IP to last visit for subjects without death.

End point type	Secondary
End point timeframe:	
Through end of treatment	

End point values	Benralizumab 100 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	241	249		
Units: Exposure adjusted incidence rate				
number (not applicable)				
All causes mortality	3.00	5.05		
Respiratory-related mortality	1.80	2.32		

Statistical analyses

No statistical analyses for this end point

Secondary: All-cause and respiratory-related mortality of participants with ≥ 2 exacerbations in the previous year.

End point title	All-cause and respiratory-related mortality of participants with ≥ 2 exacerbations in the previous year.
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End point description:

Respiratory related causes of death are summarised based on the SOC = Respiratory, thoracic and mediastinal disorders.

Exposure adjusted incidence rate (EAIR) of mortality is compared between treatment groups. EAIR per 100 patient-years is defined as number of subjects with a mortality divided by the total number of days at risk for mortality across all subjects in given treatment group, multiplied by 365.25 and then multiplied by 100. Total number of days at risk for death is defined as the duration from the first dose of IP to the date of death, or the duration from the first dose of IP to last visit for subjects without death.

End point type	Secondary
End point timeframe:	
Through end of treatment	

End point values	Benralizumab 100 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	331	345		
Units: Exposure adjusted incidence rate				
number (not applicable)				
All causes mortality	3.72	4.62		
Respiratory-related mortality	2.13	2.31		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug until last study visit

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	28.0
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Reporting groups

Reporting group title	Placebo
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Reporting group description: -

Reporting group title	Benralizumab 100 mg
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Reporting group description: -

Serious adverse events	Placebo	Benralizumab 100 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	186 / 345 (53.91%)	155 / 331 (46.83%)	
number of deaths (all causes)	34	28	
number of deaths resulting from adverse events	34	28	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma pancreas			
subjects affected / exposed	0 / 345 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
B-cell lymphoma			
subjects affected / exposed	0 / 345 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign gastrointestinal neoplasm			

subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive ductal breast carcinoma			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic neoplasm			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal carcinoma			
subjects affected / exposed	0 / 345 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangiocarcinoma			
subjects affected / exposed	0 / 345 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign small intestinal neoplasm			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	2 / 345 (0.58%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Lung neoplasm			

subjects affected / exposed	2 / 345 (0.58%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung cancer metastatic			
subjects affected / exposed	2 / 345 (0.58%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lung adenocarcinoma			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lip squamous cell carcinoma			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive lobular breast carcinoma			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma stage 0			
subjects affected / exposed	0 / 345 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal adenoma			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	0 / 345 (0.00%)	4 / 331 (1.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic carcinoma			

subjects affected / exposed	1 / 345 (0.29%)	2 / 331 (0.60%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal carcinoma			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small cell lung cancer			
subjects affected / exposed	2 / 345 (0.58%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of lung			
subjects affected / exposed	2 / 345 (0.58%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	1 / 345 (0.29%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional cell carcinoma			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung carcinoma cell type unspecified stage I			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma stage IV			

subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
High-grade B-cell lymphoma			
subjects affected / exposed	0 / 345 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung carcinoma cell type unspecified stage II			
subjects affected / exposed	0 / 345 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung squamous cell carcinoma stage I			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 345 (0.29%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive emergency			
subjects affected / exposed	0 / 345 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	2 / 345 (0.58%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic			

subjects affected / exposed	0 / 345 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery thrombosis			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery occlusion			
subjects affected / exposed	0 / 345 (0.00%)	2 / 331 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 345 (0.29%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Chest discomfort			
subjects affected / exposed	0 / 345 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 345 (0.29%)	2 / 331 (0.60%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Non-cardiac chest pain			

subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 345 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 345 (0.29%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 345 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scrotal oedema			
subjects affected / exposed	0 / 345 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic respiratory failure			
subjects affected / exposed	0 / 345 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	103 / 345 (29.86%)	87 / 331 (26.28%)	
occurrences causally related to treatment / all	0 / 157	0 / 170	
deaths causally related to treatment / all	0 / 6	0 / 8	
Bronchospasm			

subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute respiratory failure			
subjects affected / exposed	2 / 345 (0.58%)	7 / 331 (2.11%)	
occurrences causally related to treatment / all	0 / 2	0 / 8	
deaths causally related to treatment / all	0 / 1	0 / 1	
Dyspnoea			
subjects affected / exposed	1 / 345 (0.29%)	3 / 331 (0.91%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 345 (0.29%)	3 / 331 (0.91%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasal polyps			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 345 (0.29%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercapnia			
subjects affected / exposed	1 / 345 (0.29%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			

subjects affected / exposed	2 / 345 (0.58%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	4 / 345 (1.16%)	3 / 331 (0.91%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory failure			
subjects affected / exposed	8 / 345 (2.32%)	4 / 331 (1.21%)	
occurrences causally related to treatment / all	0 / 9	0 / 4	
deaths causally related to treatment / all	0 / 4	0 / 2	
Pulmonary mass			
subjects affected / exposed	1 / 345 (0.29%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Psychotic disorder			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			
subjects affected / exposed	0 / 345 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Weight decreased			
subjects affected / exposed	0 / 345 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram T wave peaked			

subjects affected / exposed	0 / 345 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Compression fracture			
subjects affected / exposed	1 / 345 (0.29%)	2 / 331 (0.60%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	0 / 345 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 345 (0.00%)	2 / 331 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	1 / 345 (0.29%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 345 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foreign body			
subjects affected / exposed	0 / 345 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	2 / 345 (0.58%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Rib fracture			

subjects affected / exposed	3 / 345 (0.87%)	3 / 331 (0.91%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound complication			
subjects affected / exposed	1 / 345 (0.29%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Patella fracture			
subjects affected / exposed	0 / 345 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 345 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin laceration			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue injury			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic injury			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			

subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic haemothorax			
subjects affected / exposed	0 / 345 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	4 / 345 (1.16%)	5 / 331 (1.51%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 1	
Angina unstable			
subjects affected / exposed	0 / 345 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 345 (0.29%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	0 / 345 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			

subjects affected / exposed	0 / 345 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	2 / 345 (0.58%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 0	
Cardiac failure			
subjects affected / exposed	4 / 345 (1.16%)	2 / 331 (0.60%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 1	
Angina pectoris			
subjects affected / exposed	2 / 345 (0.58%)	3 / 331 (0.91%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	0 / 345 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	1 / 345 (0.29%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 345 (0.29%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Coronary artery stenosis			
subjects affected / exposed	0 / 345 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiomyopathy			

subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cor pulmonale			
subjects affected / exposed	0 / 345 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	0 / 345 (0.00%)	2 / 331 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	4 / 345 (1.16%)	2 / 331 (0.60%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 4	0 / 1	
Right ventricular failure			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus node dysfunction			
subjects affected / exposed	0 / 345 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 345 (0.29%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Left ventricular failure			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heart failure with reduced ejection fraction			

subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	0 / 345 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachyarrhythmia			
subjects affected / exposed	0 / 345 (0.00%)	2 / 331 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachyarrhythmia			
subjects affected / exposed	0 / 345 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Acquired syringomyelia			
subjects affected / exposed	0 / 345 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain hypoxia			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	0 / 345 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 345 (0.29%)	2 / 331 (0.60%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			

subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 345 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 345 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thalamus haemorrhage			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Guillain-Barre syndrome			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Blood loss anaemia			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	2 / 345 (0.58%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypereosinophilic syndrome			

subjects affected / exposed	0 / 345 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Immune thrombocytopenia			
subjects affected / exposed	0 / 345 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy mediastinal			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	0 / 345 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo			
subjects affected / exposed	0 / 345 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	1 / 345 (0.29%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Optic neuropathy			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Macular hole			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glaucoma			

subjects affected / exposed	0 / 345 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epiretinal membrane			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cataract cortical			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vision blurred			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastric ulcer			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral hernia incarcerated			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	3 / 345 (0.87%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal adhesions			
subjects affected / exposed	0 / 345 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			

subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incarcerated inguinal hernia			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoperitoneum			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal angiodysplasia			
subjects affected / exposed	0 / 345 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	2 / 345 (0.58%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 345 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Ischaemic hepatitis			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			

subjects affected / exposed	2 / 345 (0.58%)	3 / 331 (0.91%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	2 / 345 (0.58%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary colic			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	4 / 345 (1.16%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	0 / 345 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal injury			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 345 (0.29%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Renal artery stenosis			

subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator cuff syndrome			
subjects affected / exposed	0 / 345 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoporotic fracture			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoporosis			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteitis			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			

subjects affected / exposed	1 / 345 (0.29%)	2 / 331 (0.60%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Anal abscess			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal infection			
subjects affected / exposed	0 / 345 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess sweat gland			
subjects affected / exposed	0 / 345 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis infective			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 345 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			

subjects affected / exposed	2 / 345 (0.58%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related bacteraemia			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 345 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	6 / 345 (1.74%)	7 / 331 (2.11%)	
occurrences causally related to treatment / all	0 / 6	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	21 / 345 (6.09%)	29 / 331 (8.76%)	
occurrences causally related to treatment / all	0 / 31	0 / 35	
deaths causally related to treatment / all	0 / 1	0 / 1	
Helicobacter gastritis			
subjects affected / exposed	0 / 345 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Focal peritonitis			

subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 345 (0.29%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	0 / 345 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia parainfluenzae viral			
subjects affected / exposed	0 / 345 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia haemophilus			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	9 / 345 (2.61%)	3 / 331 (0.91%)	
occurrences causally related to treatment / all	0 / 10	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Pneumonia acinetobacter			
subjects affected / exposed	0 / 345 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	21 / 345 (6.09%)	23 / 331 (6.95%)	
occurrences causally related to treatment / all	0 / 28	0 / 29	
deaths causally related to treatment / all	0 / 1	0 / 2	
Osteomyelitis			

subjects affected / exposed	0 / 345 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pneumococcal			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 345 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pseudomonal			
subjects affected / exposed	0 / 345 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia proteus			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia respiratory syncytial viral			
subjects affected / exposed	0 / 345 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	1 / 345 (0.29%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia streptococcal			
subjects affected / exposed	0 / 345 (0.00%)	2 / 331 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia staphylococcal			

subjects affected / exposed	0 / 345 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural pneumonia			
subjects affected / exposed	2 / 345 (0.58%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sepsis			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	2 / 345 (0.58%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection viral			
subjects affected / exposed	0 / 345 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	5 / 345 (1.45%)	2 / 331 (0.60%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Septic shock			
subjects affected / exposed	4 / 345 (1.16%)	3 / 331 (0.91%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 2	0 / 2	
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 345 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			

subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheobronchitis bacterial			
subjects affected / exposed	0 / 345 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	3 / 345 (0.87%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethritis			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 345 (0.29%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	6 / 345 (1.74%)	3 / 331 (0.91%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
COVID-19			

subjects affected / exposed	5 / 345 (1.45%)	6 / 331 (1.81%)	
occurrences causally related to treatment / all	0 / 5	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	0 / 345 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 345 (0.29%)	0 / 331 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypervolaemia			
subjects affected / exposed	0 / 345 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 345 (0.00%)	1 / 331 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	2 / 345 (0.58%)	2 / 331 (0.60%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Benralizumab 100 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	193 / 345 (55.94%)	175 / 331 (52.87%)	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	35 / 345 (10.14%)	15 / 331 (4.53%)	
occurrences (all)	39	17	
Vascular disorders			
Hypertension			
subjects affected / exposed	18 / 345 (5.22%)	22 / 331 (6.65%)	
occurrences (all)	23	25	
Nervous system disorders			
Headache			
subjects affected / exposed	20 / 345 (5.80%)	20 / 331 (6.04%)	
occurrences (all)	25	28	
General disorders and administration site conditions			
Influenza like illness			
subjects affected / exposed	18 / 345 (5.22%)	14 / 331 (4.23%)	
occurrences (all)	21	18	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	16 / 345 (4.64%)	26 / 331 (7.85%)	
occurrences (all)	17	32	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	19 / 345 (5.51%)	10 / 331 (3.02%)	
occurrences (all)	19	10	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	20 / 345 (5.80%)	26 / 331 (7.85%)	
occurrences (all)	23	28	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	59 / 345 (17.10%)	44 / 331 (13.29%)	
occurrences (all)	99	82	
Pneumonia			

subjects affected / exposed	25 / 345 (7.25%)	22 / 331 (6.65%)	
occurrences (all)	31	28	
Upper respiratory tract infection			
subjects affected / exposed	43 / 345 (12.46%)	31 / 331 (9.37%)	
occurrences (all)	56	77	
Urinary tract infection			
subjects affected / exposed	26 / 345 (7.54%)	23 / 331 (6.95%)	
occurrences (all)	37	28	
COVID-19			
subjects affected / exposed	47 / 345 (13.62%)	48 / 331 (14.50%)	
occurrences (all)	56	51	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 December 2019	Added an optional mechanistic sub-study, including serum biomarker assessments. An exploratory objective for this study to evaluate the effect of benralizumab 100 mg on rescue medication use was added. The inclusion and exclusion criteria were updated. The duration that patients must abstain from donating blood, plasma, or platelets after last dose of IP was changed. Multiplicity testing strategy was modified to strongly control for type 1 error rate at 0.05 level.
29 July 2020	The primary rationale for this amendment is to add study mitigation language which will provide sites with measures that may be implemented if a participant is not able to visit a study site to ensure that the clinical trial can continue whilst minimizing risk to the participant, maintaining compliance with GCP, and minimizing risks to the study integrity.
19 January 2021	The primary rationale for this amendment is to introduce optional self-administration of IP after week 56 and to update the requirement on the duration of inhaled triple (ICS/LABA/LAMA) therapy prior to enrolment (inclusion criterion #7).
21 June 2022	The primary rationale for this amendment is to address various impacts on the study as a result of the ongoing effects of the global COVID-19 pandemic. In addition to making recruitment more challenging, real-world evidence databases have demonstrated that the global response to the COVID pandemic has substantially impacted the expected rate of severe exacerbations. With the lower expected severe exacerbation rate, the original sample size justification to observe a treatment effect on the secondary endpoint of severe exacerbations is no longer valid. The study's sample size has been revised to be dependent on the primary endpoint only (moderate and severe exacerbations), and the multiplicity testing strategy has been changed as a result. In the mechanistic sub-study, the pandemic-imposed challenges to the recruitment of the sub-study with no patient randomized to date, have led to the removal of the sub-study. Additional protocol modifications were added for clarification, simplification, and to reduce the patient's burden.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported