Clinical trial results:
A multi-center, randomized, double-blind, placebo controlled, parallel group study to compare cessation versus continuation of long-term mepolizumab treatment in patients with severe eosinophilic asthma (201810)

Summary

EudraCT number	2015-002361-32
Trial protocol	DE NL FR PL Outside EU/EEA
Global end of trial date	24 July 2019

Results information

Result version number	v1 (current)
This version publication date	08 February 2020
First version publication date	08 February 2020

Trial information

Trial identification

Sponsor protocol code	201810

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline
Sponsor organisation address	980 Great West Road, Brentford, Middlesex, United Kingdom,
Public contact	GSK Response Center, GlaxoSmithKline, 1 8664357343, GSKClinicalSupportHD@gsk.com
Scientific contact	GSK Response Center, GlaxoSmithKline, 1 8664357343, GSKClinicalSupportHD@gsk.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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	26 November 2019

Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	24 July 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate whether patients with severe eosinophilic asthma who have received long term treatment with mepolizumab (at least 3 years) need to maintain treatment with mepolizumab to continue to receive benefit.

Protection of trial subjects:

Numbing cream or spray was permitted at the site of injection and rescue medications (salbutamol/albuterol) are available to the participant throughout the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 January 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Ethical reason
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 11
Country: Number of subjects enrolled	Australia: 6
Country: Number of subjects enrolled	Canada: 15
Country: Number of subjects enrolled	France: 22
Country: Number of subjects enrolled	Germany: 35
Country: Number of subjects enrolled	Japan: 21
Country: Number of subjects enrolled	Korea, Republic of: 28
Country: Number of subjects enrolled	Netherlands: 14
Country: Number of subjects enrolled	Poland: 14
Country: Number of subjects enrolled	Romania: 20
Country: Number of subjects enrolled	Russian Federation: 22
Country: Number of subjects enrolled	Spain: 11
Country: Number of subjects enrolled	Ukraine: 41
Country: Number of subjects enrolled	United States: 46
Worldwide total number of subjects	306
EEA total number of subjects	116

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	1
Adults (18-64 years)	234
From 65 to 84 years	71
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A multi-center, randomized, double-blind, placebo controlled, parallel group study to compare cessation versus continuation of long-term mepolizumab treatment. Participants (par.) who completed the Follow Up/Exit Visit or Early Withdrawal Visit from study MEA115666 (NCT01691859) or 201312 (NCT02135692) were eligible to participate in this study.

Pre-assignment

Screening details:

This is a 3 period study including variable open-label (OL) run-in, double-blind (DB) treatment period and open-label treatment switch period. The study was conducted in 75 centers across 14 countries from 07-Jan-2016 to 24-Jul-2019.

Period 1

Period 1 title	PartA(Upto 132W)+PartB(Upto 8W)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Part A/B: Mepolizumab 100mg SC

Arm description:

Participants with less than 3 years of mepolizumab treatment entered variable open-label run-in period-Part A in order to reach 3 years of exposure and received 100 mg of mepolizumab injected subcutaneously (SC) once every 4 weeks (W) up to 132 weeks. Upon achieving 3 years exposure, participants entered Part B. Participants with at least 3 years of mepolizumab treatment directly entered fixed open-label run-in period-Part B and received 100 mg of mepolizumab injected SC once every 4 weeks up to 8 weeks.

Arm type	Experimental
Investigational medicinal product name	Mepolizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Mepolizumab was available as lyophilized cake in sterile vial which was reconstituted using sterile water for injection and was administered 100 mg SC into the upper arm or thigh approximately every 4 weeks

Number of subjects in period 1	Part A/B: Mepolizumab 100mg SC
Started	306
Completed	295
Not completed	11
Physician decision	1
Lack of efficacy	2
Failure to meet continuation criteria	2
Adverse event, non-fatal	1
Consent withdrawn by subject	5

Period 2

Period 2 title	Part C (Up to 52W)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Arms

Are arms mutually exclusive?	Yes
Arm title	Part C: Placebo

Arm description:

Upon completion of the fixed run-in period, participants entered a double-blind study treatment and received placebo SC every 4 weeks up to 52 weeks. Participants who experienced a clinically significant asthma exacerbation were assessed by the investigator to determine if they could continue double-blind treatment or should instead enter OL mepolizumab 100 mg SC every 4 weeks for the remainder of the treatment period (up to 52 weeks after randomization).

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:

Sterile normal saline was administered as Placebo

Arm title	Part C: Mepolizumab 100mg SC

Arm description:

Upon completion of the fixed run-in period, participants entered a double-blind study treatment and received continued mepolizumab 100 mg SC every 4 weeks up to 52 weeks. Participants who experienced a clinically significant asthma exacerbation were assessed by the investigator to determine if they could continue double-blind treatment or should instead enter OL mepolizumab 100 mg SC every 4 weeks for the remainder of the treatment period (up to 52 weeks after randomization).

Arm type	Experimental
Investigational medicinal product name	Mepolizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Mepolizumab was available as lyophilized cake in sterile vial which was reconstituted using sterile water for injection and was administered 100 mg SC into the upper arm or thigh approximately every 4 weeks

Number of subjects in period 2	Part C: Placebo	Part C: Mepolizumab 100mg SC
Started	151	144
Completed	62	96
Not completed	89	48
Switched to Part D treatment	84	45
Lack of efficacy	1	-
Adverse event, serious fatal	1	-
Adverse event, non-fatal	1	1
Consent withdrawn by subject	2	2

Period 3

Period 3 title	PartD (OL mepolizumab Period:Up to 52 W)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Part D: Mepolizumab 100mg SC (Previous Placebo)

Arm description:

Participants who experienced a clinically significant asthma exacerbation were assessed by the investigator to determine if they could continue double-blind treatment or should instead enter OL mepolizumab 100 mg SC every 4 weeks for the remainder of the treatment period (up to 52 weeks after randomization).

Arm type	Experimental
Investigational medicinal product name	Mepolizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Mepolizumab was available as lyophilized cake in sterile vial which was reconstituted using sterile water for injection and was administered 100 mg SC into the upper arm or thigh approximately every 4 weeks

Arm title	Part D: Mepolizumab 100mg SC (Previous Mepolizumab)

Arm description:

Participants who experienced a clinically significant asthma exacerbation were assessed by the investigator to determine if they could continue double-blind treatment or should instead enter OL mepolizumab 100 mg SC every 4 weeks for the remainder of the treatment period (up to 52 weeks after randomization).

Arm type	Experimental
Investigational medicinal product name	Mepolizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Mepolizumab was available as lyophilized cake in sterile vial which was reconstituted using sterile water for injection and was administered 100 mg SC into the upper arm or thigh approximately every 4 weeks

Number of subjects in period 3[1]	Part D: Mepolizumab 100mg SC (Previous Placebo)	Part D: Mepolizumab 100mg SC (Previous Mepolizumab)
Started	84	45
Completed	80	42
Not completed	4	3
Physician decision	2	-
Lack of efficacy	-	1
Adverse event, serious fatal	1	-
Consent withdrawn by subject	1	-
Lost to follow-up	-	2

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: 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.

Baseline characteristics

Reporting groups

Reporting group title	Part A/B: Mepolizumab 100mg SC

Reporting group description:

Participants with less than 3 years of mepolizumab treatment entered variable open-label run-in period-Part A in order to reach 3 years of exposure and received 100 mg of mepolizumab injected subcutaneously (SC) once every 4 weeks (W) up to 132 weeks. Upon achieving 3 years exposure, participants entered Part B. Participants with at least 3 years of mepolizumab treatment directly entered fixed open-label run-in period-Part B and received 100 mg of mepolizumab injected SC once every 4 weeks up to 8 weeks.

Reporting group values	Part A/B: Mepolizumab 100mg SC	Total	
Number of subjects	306	306	
Age categorical Units: Subjects			
Overall Participants	306	306	
Age Continuous Units: Years			
arithmetic mean	55.6		
standard deviation	± 11.74	-	
Sex: Female, Male Units: Participants			
Female	180	180	
Male	126	126	
Race/Ethnicity, Customized Units: Subjects			
ASIAN - CENTRAL/SOUTH ASIAN HERITAGE	1	1	
ASIAN - EAST ASIAN HERITAGE	28	28	
ASIAN - JAPANESE HERITAGE	21	21	
BLACK OR AFRICAN AMERICAN	8	8	
WHITE - ARABIC/NORTH AFRICAN HERITAGE	3	3	
WHITE - WHITE/CAUCASIAN/EUROPEAN HERITAGE	245	245	

Subject analysis sets

Subject analysis set title	Parts A/B: Mepolizumab 100mg SC
Subject analysis set type	Full analysis

Subject analysis set description:

Participants with less than 3 years of mepolizumab treatment entered variable open-label run-in period-Part A in order to reach 3 years of exposure and received 100 mg of mepolizumab injected subcutaneously (SC) once every 4 weeks up to 132 weeks. Upon achieving 3 years exposure, participants entered Part B. Participants with at least 3 years of mepolizumab treatment directly entered fixed open-label run-in period-Part B and received 100 mg of mepolizumab injected SC once every 4 weeks up to 8 weeks.

Subject analysis set title	Part C: Placebo
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Upon completion of the fixed run-in period, participants entered a double-blind study treatment and received placebo SC every 4 weeks up to 52 weeks. Participants who experienced a clinically significant asthma exacerbation were assessed by the investigator to determine if they could continue double-blind treatment or should instead enter OL mepolizumab 100 mg SC every 4 weeks for the remainder of the treatment period (up to 52 weeks after randomization).

Subject analysis set title	Part C: Mepolizumab 100mg SC
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Upon completion of the fixed run-in period, participants entered a double-blind study treatment and received continued mepolizumab 100 mg SC every 4 weeks up to 52 weeks. Participants who experienced a clinically significant asthma exacerbation were assessed by the investigator to determine if they could continue double-blind treatment or should instead enter OL mepolizumab 100 mg SC every 4 weeks for the remainder of the treatment period (up to 52 weeks after randomization).

Reporting group values	Parts A/B: Mepolizumab 100mg SC	Part C: Placebo	Part C: Mepolizumab 100mg SC
Number of subjects	306	151	144
Age categorical Units: Subjects			
Overall Participants			
Age Continuous Units: Years			
arithmetic mean	55.6		
standard deviation	± 11.74	±	±
Sex: Female, Male Units: Participants			
Female	180		
Male	126		
Race/Ethnicity, Customized Units: Subjects			
ASIAN - CENTRAL/SOUTH ASIAN HERITAGE	1	0	0
ASIAN - EAST ASIAN HERITAGE	28	0	0
ASIAN - JAPANESE HERITAGE	21	0	0
BLACK OR AFRICAN AMERICAN	8	0	0
WHITE - ARABIC/NORTH AFRICAN HERITAGE	3	0	0
WHITE - WHITE/CAUCASIAN/EUROPEAN HERITAGE	245	0	0

End points

End points reporting groups

Reporting group title	Part A/B: Mepolizumab 100mg SC

Reporting group description:

Participants with less than 3 years of mepolizumab treatment entered variable open-label run-in period-Part A in order to reach 3 years of exposure and received 100 mg of mepolizumab injected subcutaneously (SC) once every 4 weeks (W) up to 132 weeks. Upon achieving 3 years exposure, participants entered Part B. Participants with at least 3 years of mepolizumab treatment directly entered fixed open-label run-in period-Part B and received 100 mg of mepolizumab injected SC once every 4 weeks up to 8 weeks.

Reporting group title	Part C: Placebo

Reporting group description:

Upon completion of the fixed run-in period, participants entered a double-blind study treatment and received placebo SC every 4 weeks up to 52 weeks. Participants who experienced a clinically significant asthma exacerbation were assessed by the investigator to determine if they could continue double-blind treatment or should instead enter OL mepolizumab 100 mg SC every 4 weeks for the remainder of the treatment period (up to 52 weeks after randomization).

Reporting group title	Part C: Mepolizumab 100mg SC

Reporting group description:

Upon completion of the fixed run-in period, participants entered a double-blind study treatment and received continued mepolizumab 100 mg SC every 4 weeks up to 52 weeks. Participants who experienced a clinically significant asthma exacerbation were assessed by the investigator to determine if they could continue double-blind treatment or should instead enter OL mepolizumab 100 mg SC every 4 weeks for the remainder of the treatment period (up to 52 weeks after randomization).

Reporting group title	Part D: Mepolizumab 100mg SC (Previous Placebo)

Reporting group description:

Participants who experienced a clinically significant asthma exacerbation were assessed by the investigator to determine if they could continue double-blind treatment or should instead enter OL mepolizumab 100 mg SC every 4 weeks for the remainder of the treatment period (up to 52 weeks after randomization).

Reporting group title	Part D: Mepolizumab 100mg SC (Previous Mepolizumab)

Reporting group description:

Participants who experienced a clinically significant asthma exacerbation were assessed by the investigator to determine if they could continue double-blind treatment or should instead enter OL mepolizumab 100 mg SC every 4 weeks for the remainder of the treatment period (up to 52 weeks after randomization).

Subject analysis set title	Parts A/B: Mepolizumab 100mg SC
Subject analysis set type	Full analysis

Subject analysis set description:

Participants with less than 3 years of mepolizumab treatment entered variable open-label run-in period-Part A in order to reach 3 years of exposure and received 100 mg of mepolizumab injected subcutaneously (SC) once every 4 weeks up to 132 weeks. Upon achieving 3 years exposure, participants entered Part B. Participants with at least 3 years of mepolizumab treatment directly entered fixed open-label run-in period-Part B and received 100 mg of mepolizumab injected SC once every 4 weeks up to 8 weeks.

Subject analysis set title	Part C: Placebo
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Upon completion of the fixed run-in period, participants entered a double-blind study treatment and received placebo SC every 4 weeks up to 52 weeks. Participants who experienced a clinically significant asthma exacerbation were assessed by the investigator to determine if they could continue double-blind treatment or should instead enter OL mepolizumab 100 mg SC every 4 weeks for the remainder of the treatment period (up to 52 weeks after randomization).

Subject analysis set title	Part C: Mepolizumab 100mg SC
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Upon completion of the fixed run-in period, participants entered a double-blind study treatment and received continued mepolizumab 100 mg SC every 4 weeks up to 52 weeks. Participants who

experienced a clinically significant asthma exacerbation were assessed by the investigator to determine if they could continue double-blind treatment or should instead enter OL mepolizumab 100 mg SC every 4 weeks for the remainder of the treatment period (up to 52 weeks after randomization).

Primary: Percentage of participants with first clinically significant exacerbation in Part C

End point title	Percentage of participants with first clinically significant exacerbation in Part C

End point description:

Clinically significant exacerbation was defined as worsening of asthma which requires use of systemic corticosteroids (e.g., prednisone) for at least 3 days or a single intramuscular (IM) corticosteroid dose and/or hospitalization and/or emergency department (ED) visits. For participants on maintenance systemic corticosteroids, at least double the existing maintenance dose for at least 3 days is required. Percentage of participants with clinically significant exacerbation over time during the on-treatment period of Part C and 95% confidence interval were estimated using Kaplan-Meier estimates. Intent-to-Treat Population includes all randomized participants who received at least one dose of double-blind study medication within Part C.

End point type	Primary

End point timeframe:

Weeks 12, 24, 36 and 52

End point values	Part C: Placebo	Part C: Mepolizumab 100mg SC		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	151[1]	144[2]		
Units: Percentage of participants				
number (confidence interval 95%)				
Week 12	31.8 (25.0 to 39.9)	20.2 (14.5 to 27.7)		
Week 24	49.3 (41.5 to 57.6)	32.3 (25.3 to 40.7)		
Week 36	56.0 (48.1 to 64.2)	40.3 (32.8 to 48.9)		
Weeks 52	60.7 (52.7 to 68.8)	47.1 (39.2 to 55.7)		

Notes:

[1] - Intent-to-Treat Population.

[2] - Intent-to-Treat Population.

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Treatment comparison between mepolizumab 100 mg SC and placebo using hazards ratio and 95% confidence interval has been presented.

Comparison groups	Part C: Placebo v Part C: Mepolizumab 100mg SC
Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	Cox Proportional Hazards Model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.62

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	0.86

Secondary: Ratio to Baseline in blood eosinophil count in Part C

End point title	Ratio to Baseline in blood eosinophil count in Part C

End point description:

Blood samples were collected at specific time points to measure blood eosinophils level. Baseline was defined as the latest available assessment prior to first dose of double-blind treatment within Part C. Ratio to Baseline is defined as visit value divided by Baseline value and was analyzed using Mixed Model Repeated Measures with covariates of Baseline, region, exacerbations in the year prior to randomization (as an ordinal variable), Baseline maintenance oral corticosteroids (OCS) therapy (OCS vs. no OCS), treatment and visit, plus interaction terms for visit by Baseline and visit by treatment group. The log transformation was applied to blood eosinophil counts prior to analysis. If a blood eosinophil count of zero was reported, a small value was added prior to log transforming the data. The dispersion measure used was log standard error.

End point type	Secondary

End point timeframe:

Baseline and Weeks 12, 24, 36 and 52

End point values	Part C: Placebo	Part C: Mepolizumab 100mg SC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	121[3]	120[4]		
Units: Ratio				
least squares mean (standard error)				
Week 12, n=121, 120	6.03 (± 0.077)	1.16 (± 0.078)		
Week 24, n= 79, 106	6.58 (± 0.095)	1.03 (± 0.084)		
Week 36, n= 65, 99	6.48 (± 0.093)	1.20 (± 0.079)		
Week 52, n=60, 92	6.17 (± 0.091)	1.00 (± 0.077)		

Notes:

[3] - Intent-to-Treat Population.

[4] - Intent-to-Treat Population.

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Treatment comparison between mepolizumab 100 mg SC and placebo using ratio of mepolizumab to placebo and its 95% confidence interval at Week 12 has been presented.

Comparison groups	Part C: Placebo v Part C: Mepolizumab 100mg SC
Number of subjects included in analysis	241
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed model repeated measures
Parameter estimate	Ratio

Point estimate	0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.15
upper limit	0.24

Statistical analysis title	Statistical analysis 2
Statistical analysis description:	
Treatment comparison between mepolizumab 100 mg SC and placebo using ratio of mepolizumab to placebo and its 95% confidence interval at Week 24 has been presented.	
Comparison groups	Part C: Placebo v Part C: Mepolizumab 100mg SC
Number of subjects included in analysis	241
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed model repeated measures
Parameter estimate	Ratio
Point estimate	0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.12
upper limit	0.2

Statistical analysis title	Statistical analysis 3
Statistical analysis description:	
Treatment comparison between mepolizumab 100 mg SC and placebo using ratio of mepolizumab to placebo and its 95% confidence interval at Week 36 has been presented.	
Comparison groups	Part C: Placebo v Part C: Mepolizumab 100mg SC
Number of subjects included in analysis	241
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed model repeated measures
Parameter estimate	Ratio
Point estimate	0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.15
upper limit	0.24

Statistical analysis title	Statistical analysis 4

Statistical analysis description:

Treatment comparison between mepolizumab 100 mg SC and placebo using ratio of mepolizumab to placebo and its 95% confidence interval at Week 52 has been presented.

Comparison groups	Part C: Placebo v Part C: Mepolizumab 100mg SC
Number of subjects included in analysis	241
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed model repeated measures
Parameter estimate	Ratio
Point estimate	0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.13
upper limit	0.2

Secondary: Percentage of participants with 0.5 Point or More Increase in Asthma Control Questionnaire (ACQ)-5 Score from Baseline in Part C

End point title	Percentage of participants with 0.5 Point or More Increase in Asthma Control Questionnaire (ACQ)-5 Score from Baseline in Part C

End point description:

The ACQ-5 is a five-item, self-completed questionnaire. Five questions (concerning nocturnal awakening, waking in the morning, activity limitation, shortness of breath and wheeze) enquire about the frequency and/or severity of symptoms over the previous week. The response ranges from zero (no impairment/limitation) to six (total impairment/ limitation) scale. Increase in score of >= 0.5 units from Baseline indicates decrease in asthma control. Baseline is the latest available assessment prior to first dose of double-blind treatment within Part C. Percentage of participants with a 0.5 point or more increase in ACQ-5 score from Baseline over time during the on-treatment period of Part C and its 95% confidence interval were estimated using Kaplan-Meier estimates.

End point type	Secondary

End point timeframe:

Baseline and Weeks 12, 24, 36 and 52

End point values	Part C: Placebo	Part C: Mepolizumab 100mg SC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	151[5]	144[6]		
Units: Percentage of participants				
number (confidence interval 95%)				
Week 12	44.5 (36.9 to 52.8)	39.3 (31.8 to 47.8)		
Week 24	69.5 (61.6 to 77.1)	49.3 (41.3 to 57.9)		
Week 36	74.9 (67.1 to 82.1)	56.0 (47.8 to 64.6)		
Weeks 52	79.0 (71.3 to 85.7)	63.1 (54.8 to 71.5)		

Notes:

[5] - Intent-to-Treat Population

[6] - Intent-to-Treat Population

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Treatment comparison between mepolizumab 100 mg SC and placebo using hazards ratio and 95% confidence interval has been presented.

Comparison groups	Part C: Placebo v Part C: Mepolizumab 100mg SC
Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005
Method	Cox Proportional Hazards Model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	0.88

Secondary: Percentage of participants with time to first exacerbation requiring hospitalization or ED visit in Part C

End point title	Percentage of participants with time to first exacerbation requiring hospitalization or ED visit in Part C

End point description:

Exacerbations of asthma requiring hospitalization or ED visit were assessed. The analysis was performed from Cox Proportional Hazards Model with covariates of treatment group, region, exacerbations in the year prior to randomization (as an ordinal variable) and Baseline maintenance OCS therapy (OCS vs. no OCS). Kaplan-Meier estimates of the probability of an exacerbation and its 95% confidence interval was expressed as percentage of participants with an exacerbation over time.

End point type	Secondary

End point timeframe:

Weeks 12, 24, 36 and 52

End point values	Part C: Placebo	Part C: Mepolizumab 100mg SC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	151[7]	144[8]		
Units: Percentage of participants				
number (confidence interval 95%)				
Week 12	2.9 (1.1 to 7.5)	2.8 (1.1 to 7.2)		

Week 24	5.7 (2.7 to 11.8)	5.1 (2.4 to 10.3)		
Week 36	5.7 (2.7 to 11.8)	5.9 (3.0 to 11.6)		
Weeks 52	5.7 (2.7 to 11.8)	7.9 (4.3 to 14.3)		

Notes:

[7] - Intent-to-Treat Population

[8] - Intent-to-Treat Population

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Treatment comparison between mepolizumab 100 mg SC and placebo using hazards ratio and 95% confidence interval has been presented.

Comparison groups	Part C: Placebo v Part C: Mepolizumab 100mg SC
Number of subjects included in analysis	295
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.57
Method	Cox Proportional Hazards Model
Parameter estimate	Hazard ratio (HR)
Point estimate	1.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	3.51

Adverse events

Adverse events information

Timeframe for reporting adverse events:

For Part A/B: from first dose of open-label mepolizumab up to 132 weeks, for Part C: from start of double blind treatment up to 52 weeks, and for Part D: from start of first dose of open-label treatment in Part D upto 52 weeks post-randomization in Part C

Adverse event reporting additional description:

AEs and SAEs were collected for As Treated Population which comprised of all participants who received at least one dose of open label mepolizumab for Parts A/B and Part D. Intent-to-Treat (ITT) Population was used for Part C which comprised of all randomized participants who received at least one dose of double-blind study medication.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Part A/B: Mepolizumab 100mg SC

Reporting group description:

Participants with less than 3 years of mepolizumab treatment entered variable open-label run-in period-Part A in order to reach 3 years of exposure and received 100 mg of mepolizumab injected subcutaneously (SC) once every 4 weeks (W) up to 132 weeks. Upon achieving 3 years exposure, participants entered Part B. Participants with at least 3 years of mepolizumab treatment directly entered fixed open-label run-in period-Part B and received 100 mg of mepolizumab injected SC once every 4 weeks up to 8 weeks.

Reporting group title	Part C: Placebo

Reporting group description:

Upon completion of the fixed run-in period, participants entered a double-blind study treatment and received placebo SC every 4 weeks up to 52 weeks. Participants who experienced a clinically significant asthma exacerbation were assessed by the investigator to determine if they could continue double-blind treatment or should instead enter OL mepolizumab 100 mg SC every 4 weeks for the remainder of the treatment period (up to 52 weeks after randomization).

Reporting group title	Part C: Mepolizumab 100mg

Reporting group description:

Upon completion of the fixed run-in period, participants entered a double-blind study treatment and received continued mepolizumab 100 mg SC every 4 weeks up to 52 weeks. Participants who experienced a clinically significant asthma exacerbation were assessed by the investigator to determine if they could continue double-blind treatment or should instead enter OL mepolizumab 100 mg SC every 4 weeks for the remainder of the treatment period (up to 52 weeks after randomization).

Reporting group title	Part D: Mepolizumab 100mg SC (Previous Placebo)

Reporting group description:

Participants who experienced a clinically significant asthma exacerbation were assessed by the investigator to determine if they could continue double-blind treatment or should instead enter OL mepolizumab 100 mg SC every 4 weeks for the remainder of the treatment period (up to 52 weeks after randomization).

Reporting group title	Part D: Mepolizumab 100mg SC (Previous Mepolizumab)

Reporting group description:

Participants who experienced a clinically significant asthma exacerbation were assessed by the investigator to determine if they could continue double-blind treatment or should instead enter OL mepolizumab 100 mg SC every 4 weeks for the remainder of the treatment period (up to 52 weeks after randomization).

Serious adverse events	Part A/B: Mepolizumab 100mg SC	Part C: Placebo	Part C: Mepolizumab 100mg
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 306 (2.29%)	10 / 151 (6.62%)	9 / 144 (6.25%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Hip fracture			
subjects affected / exposed	0 / 306 (0.00%)	1 / 151 (0.66%)	0 / 144 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal fracture			
subjects affected / exposed	0 / 306 (0.00%)	0 / 151 (0.00%)	1 / 144 (0.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meniscus injury			
subjects affected / exposed	0 / 306 (0.00%)	0 / 151 (0.00%)	0 / 144 (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
Rib fracture			
subjects affected / exposed	0 / 306 (0.00%)	0 / 151 (0.00%)	0 / 144 (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
Traumatic haemothorax			
subjects affected / exposed	0 / 306 (0.00%)	0 / 151 (0.00%)	0 / 144 (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
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant polyp			
subjects affected / exposed	1 / 306 (0.33%)	0 / 151 (0.00%)	0 / 144 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Benign ovarian tumour			
subjects affected / exposed	0 / 306 (0.00%)	1 / 151 (0.66%)	0 / 144 (0.00%)
occurrences causally related to	0 / 0	0 / 1	0 / 0

treatment / all			
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer stage 0			
subjects affected / exposed	0 / 306 (0.00%)	0 / 151 (0.00%)	1 / 144 (0.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intraductal papillary mucinous neoplasm			
subjects affected / exposed	0 / 306 (0.00%)	0 / 151 (0.00%)	1 / 144 (0.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	0 / 306 (0.00%)	0 / 151 (0.00%)	1 / 144 (0.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma			
subjects affected / exposed	0 / 306 (0.00%)	1 / 151 (0.66%)	0 / 144 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	3 / 306 (0.98%)	6 / 151 (3.97%)	2 / 144 (1.39%)
occurrences causally related to treatment / all	0 / 4	0 / 6	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory failure			
subjects affected / exposed	0 / 306 (0.00%)	0 / 151 (0.00%)	0 / 144 (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
Paranasal cyst			
subjects affected / exposed	0 / 306 (0.00%)	0 / 151 (0.00%)	0 / 144 (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 aspiration			
subjects affected / exposed	0 / 306 (0.00%)	0 / 151 (0.00%)	0 / 144 (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			
Myasthenia gravis			
subjects affected / exposed	0 / 306 (0.00%)	0 / 151 (0.00%)	1 / 144 (0.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Device related thrombosis			
subjects affected / exposed	0 / 306 (0.00%)	1 / 151 (0.66%)	0 / 144 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	0 / 306 (0.00%)	0 / 151 (0.00%)	1 / 144 (0.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	1 / 306 (0.33%)	0 / 151 (0.00%)	0 / 144 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 306 (0.00%)	0 / 151 (0.00%)	1 / 144 (0.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 306 (0.00%)	0 / 151 (0.00%)	0 / 144 (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
Salivary gland calculus			
subjects affected / exposed	0 / 306 (0.00%)	0 / 151 (0.00%)	0 / 144 (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	0 / 306 (0.00%)	1 / 151 (0.66%)	0 / 144 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 306 (0.33%)	0 / 151 (0.00%)	0 / 144 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	0 / 306 (0.00%)	0 / 151 (0.00%)	0 / 144 (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			
Cytomegalovirus infection			
subjects affected / exposed	1 / 306 (0.33%)	0 / 151 (0.00%)	0 / 144 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	1 / 306 (0.33%)	0 / 151 (0.00%)	0 / 144 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngeal abscess			
subjects affected / exposed	1 / 306 (0.33%)	0 / 151 (0.00%)	0 / 144 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 306 (0.33%)	0 / 151 (0.00%)	0 / 144 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	0 / 306 (0.00%)	0 / 151 (0.00%)	1 / 144 (0.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Bronchitis			
subjects affected / exposed	0 / 306 (0.00%)	1 / 151 (0.66%)	0 / 144 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 306 (0.00%)	0 / 151 (0.00%)	1 / 144 (0.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia pyelonephritis			
subjects affected / exposed	0 / 306 (0.00%)	1 / 151 (0.66%)	0 / 144 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atypical pneumonia			
subjects affected / exposed	0 / 306 (0.00%)	0 / 151 (0.00%)	0 / 144 (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
Sinusitis fungal			
subjects affected / exposed	0 / 306 (0.00%)	0 / 151 (0.00%)	0 / 144 (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	Part D: Mepolizumab 100mg SC (Previous Placebo)	Part D: Mepolizumab 100mg SC (Previous Mepolizumab)	
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 84 (11.90%)	4 / 45 (8.89%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Hip fracture			
subjects affected / exposed	0 / 84 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	0 / 84 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	

deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus injury			
subjects affected / exposed	1 / 84 (1.19%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	1 / 84 (1.19%)	0 / 45 (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	1 / 84 (1.19%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant polyp			
subjects affected / exposed	0 / 84 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign ovarian tumour			
subjects affected / exposed	0 / 84 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer stage 0			
subjects affected / exposed	0 / 84 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intraductal papillary mucinous neoplasm			
subjects affected / exposed	0 / 84 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	0 / 84 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	

deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyoma			
subjects affected / exposed	0 / 84 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	4 / 84 (4.76%)	4 / 45 (8.89%)	
occurrences causally related to treatment / all	0 / 4	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	1 / 84 (1.19%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paranasal cyst			
subjects affected / exposed	1 / 84 (1.19%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 84 (1.19%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Myasthenia gravis			
subjects affected / exposed	0 / 84 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Device related thrombosis			
subjects affected / exposed	0 / 84 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			

subjects affected / exposed	0 / 84 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	0 / 84 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 84 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	1 / 84 (1.19%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salivary gland calculus			
subjects affected / exposed	0 / 84 (0.00%)	1 / 45 (2.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 84 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 84 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 84 (1.19%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Cytomegalovirus infection			
subjects affected / exposed	0 / 84 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 84 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngeal abscess			
subjects affected / exposed	0 / 84 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 84 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 84 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 84 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 84 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia pyelonephritis			
subjects affected / exposed	0 / 84 (0.00%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia			

subjects affected / exposed	1 / 84 (1.19%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis fungal			
subjects affected / exposed	1 / 84 (1.19%)	0 / 45 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Part A/B: Mepolizumab 100mg SC	Part C: Placebo	Part C: Mepolizumab 100mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 306 (4.58%)	69 / 151 (45.70%)	82 / 144 (56.94%)
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 306 (0.00%)	1 / 151 (0.66%)	5 / 144 (3.47%)
occurrences (all)	0	1	6
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 306 (0.00%)	14 / 151 (9.27%)	10 / 144 (6.94%)
occurrences (all)	0	16	14
Cough			
subjects affected / exposed	0 / 306 (0.00%)	6 / 151 (3.97%)	1 / 144 (0.69%)
occurrences (all)	0	7	1
Oropharyngeal pain			
subjects affected / exposed	0 / 306 (0.00%)	0 / 151 (0.00%)	0 / 144 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 306 (0.00%)	9 / 151 (5.96%)	9 / 144 (6.25%)
occurrences (all)	0	11	12
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 306 (0.00%)	0 / 151 (0.00%)	0 / 144 (0.00%)
occurrences (all)	0	0	0

Diarrhoea			
subjects affected / exposed	0 / 306 (0.00%)	0 / 151 (0.00%)	0 / 144 (0.00%)
occurrences (all)	0	0	0
Large intestine polyp			
subjects affected / exposed	0 / 306 (0.00%)	0 / 151 (0.00%)	0 / 144 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 306 (0.00%)	6 / 151 (3.97%)	6 / 144 (4.17%)
occurrences (all)	0	12	8
Arthralgia			
subjects affected / exposed	0 / 306 (0.00%)	3 / 151 (1.99%)	6 / 144 (4.17%)
occurrences (all)	0	3	6
Neck pain			
subjects affected / exposed	0 / 306 (0.00%)	0 / 151 (0.00%)	0 / 144 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 306 (0.00%)	0 / 151 (0.00%)	0 / 144 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	14 / 306 (4.58%)	26 / 151 (17.22%)	27 / 144 (18.75%)
occurrences (all)	23	44	36
Upper respiratory tract infection			
subjects affected / exposed	0 / 306 (0.00%)	14 / 151 (9.27%)	12 / 144 (8.33%)
occurrences (all)	0	18	14
Sinusitis			
subjects affected / exposed	0 / 306 (0.00%)	9 / 151 (5.96%)	13 / 144 (9.03%)
occurrences (all)	0	10	14
Bronchitis			
subjects affected / exposed	0 / 306 (0.00%)	5 / 151 (3.31%)	14 / 144 (9.72%)
occurrences (all)	0	5	14
Respiratory tract infection viral			
subjects affected / exposed	0 / 306 (0.00%)	2 / 151 (1.32%)	6 / 144 (4.17%)
occurrences (all)	0	2	11

Viral upper respiratory tract infection			
subjects affected / exposed	0 / 306 (0.00%)	5 / 151 (3.31%)	3 / 144 (2.08%)
occurrences (all)	0	7	3
Influenza			
subjects affected / exposed	0 / 306 (0.00%)	1 / 151 (0.66%)	5 / 144 (3.47%)
occurrences (all)	0	1	5
Urinary tract infection			
subjects affected / exposed	0 / 306 (0.00%)	0 / 151 (0.00%)	0 / 144 (0.00%)
occurrences (all)	0	0	0
Chronic sinusitis			
subjects affected / exposed	0 / 306 (0.00%)	0 / 151 (0.00%)	0 / 144 (0.00%)
occurrences (all)	0	0	0
Pneumonia			
subjects affected / exposed	0 / 306 (0.00%)	0 / 151 (0.00%)	0 / 144 (0.00%)
occurrences (all)	0	0	0
Oral candidiasis			
subjects affected / exposed	0 / 306 (0.00%)	0 / 151 (0.00%)	0 / 144 (0.00%)
occurrences (all)	0	0	0
Tooth infection			
subjects affected / exposed	0 / 306 (0.00%)	0 / 151 (0.00%)	0 / 144 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Part D: Mepolizumab 100mg SC (Previous Placebo)	Part D: Mepolizumab 100mg SC (Previous Mepolizumab)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	44 / 84 (52.38%)	32 / 45 (71.11%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 84 (0.00%)	0 / 45 (0.00%)	
occurrences (all)	0	0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	7 / 84 (8.33%)	4 / 45 (8.89%)	
occurrences (all)	7	12	
Cough			
subjects affected / exposed	0 / 84 (0.00%)	0 / 45 (0.00%)	
occurrences (all)	0	0	

Oropharyngeal pain			
subjects affected / exposed	3 / 84 (3.57%)	1 / 45 (2.22%)	
occurrences (all)	3	1	
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 84 (7.14%)	4 / 45 (8.89%)	
occurrences (all)	7	7	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 84 (1.19%)	2 / 45 (4.44%)	
occurrences (all)	1	2	
Diarrhoea			
subjects affected / exposed	3 / 84 (3.57%)	0 / 45 (0.00%)	
occurrences (all)	3	0	
Large intestine polyp			
subjects affected / exposed	0 / 84 (0.00%)	2 / 45 (4.44%)	
occurrences (all)	0	2	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	3 / 84 (3.57%)	2 / 45 (4.44%)	
occurrences (all)	4	2	
Arthralgia			
subjects affected / exposed	0 / 84 (0.00%)	0 / 45 (0.00%)	
occurrences (all)	0	0	
Neck pain			
subjects affected / exposed	2 / 84 (2.38%)	2 / 45 (4.44%)	
occurrences (all)	2	2	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 84 (1.19%)	2 / 45 (4.44%)	
occurrences (all)	1	2	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	16 / 84 (19.05%)	9 / 45 (20.00%)	
occurrences (all)	22	12	
Upper respiratory tract infection			
subjects affected / exposed	5 / 84 (5.95%)	3 / 45 (6.67%)	

occurrences (all)	5	3	
Sinusitis			
subjects affected / exposed	7 / 84 (8.33%)	5 / 45 (11.11%)	
occurrences (all)	11	8	
Bronchitis			
subjects affected / exposed	7 / 84 (8.33%)	8 / 45 (17.78%)	
occurrences (all)	8	13	
Respiratory tract infection viral			
subjects affected / exposed	0 / 84 (0.00%)	0 / 45 (0.00%)	
occurrences (all)	0	0	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 84 (0.00%)	0 / 45 (0.00%)	
occurrences (all)	0	0	
Influenza			
subjects affected / exposed	1 / 84 (1.19%)	2 / 45 (4.44%)	
occurrences (all)	1	2	
Urinary tract infection			
subjects affected / exposed	4 / 84 (4.76%)	0 / 45 (0.00%)	
occurrences (all)	6	0	
Chronic sinusitis			
subjects affected / exposed	1 / 84 (1.19%)	2 / 45 (4.44%)	
occurrences (all)	1	4	
Pneumonia			
subjects affected / exposed	3 / 84 (3.57%)	0 / 45 (0.00%)	
occurrences (all)	3	0	
Oral candidiasis			
subjects affected / exposed	0 / 84 (0.00%)	2 / 45 (4.44%)	
occurrences (all)	0	2	
Tooth infection			
subjects affected / exposed	0 / 84 (0.00%)	2 / 45 (4.44%)	
occurrences (all)	0	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 November 2015	Amendment 1: Clarified when a participant switches from Part C to Part D; Removed the process of withdrawing a participant due to unblinding; Several minor changes to the Time and Events Table and corresponding text within the protocol to ensure participants entering from MEA115666 and 201312 were consistently and correctly monitored; Removed urinalysis testing; Updated contraception requirements.
07 July 2016	Amendment 2: Amended Section 5.6.1 Risk Assessment; Amended exclusion criterion No. 7-Other Monoclonal Antibodies in Section 6.2: Exclusion Criteria to also include Xolair; Amended Randomization Exclusion criterion No. 7-Current Asthma Exacerbation in Section 6.3.2: Randomization Exclusion Criteria to also include asthma worsening; Added text to Section 7.1 Investigational Product and Other Study Treatment providing details for general safety monitoring and in cases of acute severe reaction; Removed Xolair from Section 7.9.1 Permitted Medications and Non-Drug Therapies; Multiple changes to Section 7.9.2 Prohibited Medications and Non-Drug Therapies; Removed interactive response technology requirements from certain visits of the Time and Events Tables; Added Physical Examination at Visit C1 in Time and Events Table; Updated Participant/Clinician Rating of Global Impression of Disease Severity and Response to Therapy; Clarified unblinding risk when performing local laboratory testing.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Numbing cream or spray was permitted at the site of injection and rescue medications (salbutamol/albuterol) are available to the participant throughout the study.

Notes: