Clinical trial results:
An open-label study to characterize the pharmacokinetics and pharmacodynamics of mepolizumab administered subcutaneously in children from 6 to 11 years of age with severe eosinophilic asthma

Summary

EudraCT number	2014-002666-76
Trial protocol	GB Outside EU/EEA
Global end of trial date	

Results information

Result version number	v2
This version publication date	15 December 2017
First version publication date	23 June 2017
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	200363

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, 1 866-435-7343,
Scientific contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000069-PIP02-10
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	Interim
Date of interim/final analysis	31 March 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 December 2016
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

Pharmacokinetic/Pharmacodynamic Phase (Part A):
- To characterize the pharmacokinetics of mepolizumab administered subcutaneously to subjects aged 6 to 11 years old with severe eosinophilic asthma
- To characterize the pharmacodynamics of mepolizumab administered subcutaneously to subjects aged 6 to 11 years old with severe eosinophilic asthma
Long-Term Safety / Long-Term Pharmacodynamic Phase (Part B):
- To assess the long-term (52 weeks) safety and tolerability of mepolizumab when administered subcutaneously to subjects aged 6 to 11 years old with severe eosinophilic asthma

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 August 2015
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	Japan: 7
Country: Number of subjects enrolled	Poland: 11
Country: Number of subjects enrolled	United Kingdom: 17
Country: Number of subjects enrolled	United States: 9
Worldwide total number of subjects	44
EEA total number of subjects	28

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)	43
Adolescents (12-17 years)	1
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a multi-centre, open-label study to assess the pharmacokinetics (PK) and pharmacodynamics (PD) of three (4-weekly) doses of mepolizumab 40 or 100 milligrams (mg) subcutaneously (SC), administered to participants with severe eosinophilic asthma aged 6-11 years. The results presented are based on the interim analysis, following Part A.

Pre-assignment

Screening details:

This study consisted of two phases: Part A consist of pre-screening/ screening/ run-in, treatment, and Follow-up. Part B consisted of long-term treatment and Follow-up. A total of 44 participants were screened and 36 were enrolled to treatment in Part A. Study was conducted at 13 sites in 4 countries (Japan, Poland, United Kingdom and United States

Period 1

Period 1 title	Part A (20 weeks) (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Mepolizumab 40 mg SC

Arm description:

Participants with bodyweight < 40 kilogram (kg) received 0.4 milliliter (mL) of reconstituted mepolizumab subcutaneously every four weeks, in upper arm or thigh directly from the investigator or designee, under medical supervision. Participant's weight at Week 0 (Visit 2) was considered to select dosage in Part A. Prior to administration, each vial of mepolizumab were reconstituted and swirled gently to enable complete dissolution of the product.

Arm type	Experimental
Investigational medicinal product name	Mepolizumab 40 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants with bodyweight < 40 kg received 0.4 mL of reconstituted mepolizumab subcutaneously every four weeks, in upper arm or thigh. Investigational product was administered subcutaneously by the investigator or designee, under medical supervision. Prior to administration, each vial of mepolizumab were reconstituted and swirled gently to enable complete dissolution of the product.

Arm title	Mepolizumab 100 mg SC

Arm description:

Participants with bodyweight >= 40 kg received 1.0 mL of reconstituted mepolizumab subcutaneously every four weeks, in upper arm or thigh directly from the investigator or designee, under medical supervision. Prior to administration, each vial of mepolizumab were reconstituted and swirled gently to enable complete dissolution of the product. On investigator discretion, injected volume was split between two injection sites and was given as 2 injections of 0.5 mL each if required.

Arm type	Experimental
Investigational medicinal product name	Mepolizumab 100 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants with bodyweight >= 40 kg received 1.0 mL of reconstituted mepolizumab subcutaneously every four weeks, in upper arm or thigh. Investigational product was administered subcutaneously by the investigator or designee, under medical supervision. Prior to administration, each vial of mepolizumab were reconstituted and swirled gently to enable complete dissolution of the product.

Number of subjects in period 1[1]	Mepolizumab 40 mg SC	Mepolizumab 100 mg SC
Started	26	10
Completed	22	10
Not completed	4	0
Physician decision	1	-
AE of Asthma Exacerbation	1	-
Consent withdrawn by subject	2	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: A total of 44 participants were screened and 36 were enrolled to treatment in Part A.

Baseline characteristics

Reporting groups	
Reporting group title	Mepolizumab 40 mg SC
Reporting group description:	
Participants with bodyweight < 40 kilogram (kg) received 0.4 milliliter (mL) of reconstituted mepolizumab subcutaneously every four weeks, in upper arm or thigh directly from the investigator or designee, under medical supervision. Participant's weight at Week 0 (Visit 2) was considered to select dosage in Part A. Prior to administration, each vial of mepolizumab were reconstituted and swirled gently to enable complete dissolution of the product.	
Reporting group title	Mepolizumab 100 mg SC
Reporting group description:	
Participants with bodyweight >= 40 kg received 1.0 mL of reconstituted mepolizumab subcutaneously every four weeks, in upper arm or thigh directly from the investigator or designee, under medical supervision. Prior to administration, each vial of mepolizumab were reconstituted and swirled gently to enable complete dissolution of the product. On investigator discretion, injected volume was split between two injection sites and was given as 2 injections of 0.5 mL each if required.	

Reporting group values	Mepolizumab 40 mg SC	Mepolizumab 100 mg SC	Total
Number of subjects	26	10	36
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	8.0	10.0	
standard deviation	± 1.79	± 1.33	-
Gender categorical Units: Subjects			
Female	6	5	11
Male	20	5	25
Race/Ethnicity, Customized Units: Subjects			
Central/South Asian Heritage (Her.)	1	0	1
Japanese Her.	6	1	7
Black or African American (B or Af Am)	4	3	7
White/Caucasian/European Her.	14	6	20
B or Af Am and White-White/Caucasian/European Her.	1	0	1

End points

End points reporting groups

Reporting group title	Mepolizumab 40 mg SC

Reporting group description:

Participants with bodyweight < 40 kilogram (kg) received 0.4 milliliter (mL) of reconstituted mepolizumab subcutaneously every four weeks, in upper arm or thigh directly from the investigator or designee, under medical supervision. Participant's weight at Week 0 (Visit 2) was considered to select dosage in Part A. Prior to administration, each vial of mepolizumab were reconstituted and swirled gently to enable complete dissolution of the product.

Reporting group title	Mepolizumab 100 mg SC

Reporting group description:

Participants with bodyweight >= 40 kg received 1.0 mL of reconstituted mepolizumab subcutaneously every four weeks, in upper arm or thigh directly from the investigator or designee, under medical supervision. Prior to administration, each vial of mepolizumab were reconstituted and swirled gently to enable complete dissolution of the product. On investigator discretion, injected volume was split between two injection sites and was given as 2 injections of 0.5 mL each if required.

Subject analysis set title	mepolizumab sc
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Participants received mepolizumab 40 or 100 mg SC, depending on participant’s bodyweight (40 mg for <40 kg and 100 mg for >=40 kg). Participants received 0.4 mL of reconstituted mepolizumab subcutaneously (for 40 mg dose) or 1.0 mL of reconstituted mepolizumab subcutaneously (for 100 mg dose) every four weeks, in upper arm or thigh directly from the investigator or designee, under medical supervision. Prior to administration, each vial of mepolizumab were reconstituted and swirled gently to enable complete dissolution of the product.

Primary: Maximum plasma concentration (Cmax) of mepolizumab for Part A

End point title	Maximum plasma concentration (Cmax) of mepolizumab for Part A[1]

End point description:

PK of mepolizumab was evaluated in participants using Cmax. PK samples were collected at pre-dose on Week 4 and 8; and at Week 9, 12, 16 and 20. Cmax was evaluated by population PK methods and mean and standard error from the final model has been tabulated. Estimates have been presented from the final model centred to mean bodyweights of 27kg, 50kg and 70kg. Note the average bodyweight of 70kg (mean body weight observed in adults) was not investigated in the study. PK Population included all participants receiving at least one dose of mepolizumab beginning at Visit 2 (Week 0) and having at least one blood sample taken at Visit 3 (Week 4) or thereafter with measurable mepolizumab plasma concentration.

End point type	Primary

End point timeframe:

Week 4, 8, 9, 12, 16 and 20

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report.

End point values	mepolizumab sc			
Subject group type	Subject analysis set			
Number of subjects analysed	36[2]			
Units: Microgram (ug)/mL				
arithmetic mean (standard error)				
70 kg	12.8188 (± 0.7843)			
50 kg	16.3412 (± 0.6364)			

27 kg	10.1960 (± 0.3345)			

Notes:

[2] - PK Population

Statistical analyses

No statistical analyses for this end point

Primary: Area under concentration time curve to infinity (AUC [0-inf]) of mepolizumab for Part A

End point title	Area under concentration time curve to infinity (AUC [0-inf]) of mepolizumab for Part A[3]

End point description:

PK of mepolizumab was evaluated in participants using AUC (0-inf). PK samples were collected pre-dose on Week 4 and 8; and at Week 9, 12, 16 and 20. AUC (0-inf) was evaluated by population PK methods and mean and standard error from the final model has been tabulated. Estimates have been presented from the final model centred to mean bodyweights of 27kg, 50kg and 70kg. Note the average bodyweight of 70kg (mean body weight observed in adults) was not investigated in the study.

End point type	Primary

End point timeframe:

Week 4, 8, 9, 12, 16 and 20

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report.

End point values	mepolizumab sc			
Subject group type	Subject analysis set			
Number of subjects analysed	36[4]			
Units: Day*ug/mL				
arithmetic mean (standard error)				
70 kg	508.23 (± 41.8036)			
50 kg	675.20 (± 35.8980)			
27 kg	454.39 (± 15.8876)			

Notes:

[4] - PK Population

Statistical analyses

No statistical analyses for this end point

Primary: Terminal phase elimination half-life (t1/2) of mepolizumab during treatment period for Part A

End point title	Terminal phase elimination half-life (t1/2) of mepolizumab during treatment period for Part A[5]

End point description:

PK of mepolizumab was evaluated in participants using t1/2. PK samples were collected at pre-dose on Week 4 and 8; and at Week 9, 12, 16 and 20. T1/2 was evaluated by population PK methods and mean and standard error from the final model has been tabulated. Estimates have been presented from the

final model centred to mean bodyweights of 27kg, 50kg and 70kg. Note the average bodyweight of 70kg (mean body weight observed in adults) was not investigated in the study.

End point type	Primary

End point timeframe:

Week 4, 8, 9, 12, 16 and 20

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report.

End point values	mepolizumab sc			
Subject group type	Subject analysis set			
Number of subjects analysed	36[6]			
Units: Days				
arithmetic mean (standard error)				
70 kg	20.9583 (± 1.6520)			
50 kg	21.8420 (± 1.0999)			
27 kg	23.5582 (± 0.8406)			

Notes:

[6] - PK Population

Statistical analyses

No statistical analyses for this end point

Primary: Plasma Apparent Clearance (CL/F) of mepolizumab in Part A

End point title	Plasma Apparent Clearance (CL/F) of mepolizumab in Part A[7]

End point description:

PK of mepolizumab was evaluated in participants using CL/F. PK samples were collected at pre-dose on Week 4 and 8; and at Week 9, 12, 16 and 20. CL was evaluated by population PK methods and mean and standard error from the final model has been tabulated. Estimates have been presented from the final model centred to mean bodyweights of 27kg, 50kg and 70kg. Note the average bodyweight of 70kg (mean body weight observed in adults) was not investigated in the study.

End point type	Primary

End point timeframe:

Week 4, 8, 9, 12, 16 and 20

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report.

End point values	mepolizumab sc			
Subject group type	Subject analysis set			
Number of subjects analysed	36[8]			
Units: Liter (L)/ day				
arithmetic mean (standard error)				
70 kg	0.1968 (± 0.01618)			
50 kg	0.1481 (± 0.007874)			

27 kg	0.08803 (± 0.003078)			

Notes:

[8] - PK Population

Statistical analyses

No statistical analyses for this end point

Primary: Ratio to Baseline in absolute blood eosinophil count at Week 12 for Part A

End point title	Ratio to Baseline in absolute blood eosinophil count at Week 12 for Part A[9]

End point description:

PD of mepolizumab was evaluated in participants using ratio to Baseline in absolute blood eosinophil count. Blood samples were collected at Screening and at Week 0, 4, 8, 9, 12, 16 and 20. Baseline was defined as the latest value recorded prior to the first dose of mepolizumab. Ratio to Baseline was calculated as post-dose visit value/Baseline value. It was evaluated by Pharmacodynamic Eosinophils (PDe) Population which included all participants receiving at least one dose of mepolizumab beginning at Visit 2 (Week 0) and having at least one Part A blood sample evaluable for blood eosinophil count.

End point type	Primary

End point timeframe:

Baseline and Week 12

Notes:

[9] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report.

End point values	Mepolizumab 40 mg SC	Mepolizumab 100 mg SC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26[10]	10		
Units: Ratio				
geometric mean (confidence interval 95%)				
Ratio	0.115 (0.067 to 0.196)	0.166 (0.087 to 0.318)		

Notes:

[10] - PDe Population

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with any adverse event (AE) and any serious adverse events (SAE) in Part B

End point title	Number of participants with any adverse event (AE) and any serious adverse events (SAE) in Part B[11]

End point description:

An AE is any untoward medical occurrence in a participant or clinical investigation participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Any untoward event resulting in death, life threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, congenital anomaly/birth defect, any other situation according to medical or scientific judgment or all events of possible drug-induced liver injury with hyperbilirubinaemia are to be categorized as SAE. Safety Population includes all participants who received at least one dose of mepolizumab beginning at Visit 9. Participants who enter

into Part B of the study and receive any of the study treatment and have any on-treatment AE or SAE (defined as events occurring from the first dose until 28 days after the last dose of mepolizumab) is planned to be considered for analysis.

End point type	Primary

End point timeframe:

From Week 20 up to Week 80

Notes:

[11] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report.

End point values	Mepolizumab 40 mg SC	Mepolizumab 100 mg SC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[12]	0[13]		
Units: Participants				

Notes:

[12] - Part B data is not available and so will not be posted until August 2018.

[13] - Part B data is not available and so will not be posted until August 2018.

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with positive anti-mepolizumab binding antibodies and neutralizing antibodies response in Part B

End point title	Number of participants with positive anti-mepolizumab binding antibodies and neutralizing antibodies response in Part B[14]

End point description:

Blood samples for immunogenicity are to be collected for anti-mepolizumab binding antibodies and neutralizing antibodies response in Part B at Week 44, 68 and 80. Number of participants with positive anti-mepolizumab binding antibodies and neutralizing antibodies response is planned to be summarized.

End point type	Primary

End point timeframe:

From Week 20 up to Week 80

Notes:

[14] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report.

End point values	Mepolizumab 40 mg SC	Mepolizumab 100 mg SC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[15]	0[16]		
Units: Participants				

Notes:

[15] - Part B data is not available and so will not be posted until August 2018.

[16] - Part B data is not available and so will not be posted until August 2018.

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with clinically significant changes in vital sign measurements in Part B

End point title	Number of participants with clinically significant changes in vital sign measurements in Part B[17]

End point description:

Sitting pulse rate and blood pressure measurements are to be performed in Part B at Week 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72 and 80. Mean change from baseline and standard deviation in vital sign measurements are planned to be summarized.

End point type	Primary

End point timeframe:

From Week 20 up to Week 80

Notes:

[17] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report.

End point values	Mepolizumab 40 mg SC	Mepolizumab 100 mg SC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[18]	0[19]		
Units: Participants				
arithmetic mean (standard deviation)	()	()		

Notes:

[18] - Part B is not available and so will not be posted until August 2018.

[19] - Part B data is not available and so will not be posted until August 2018.

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with clinically significant changes in clinical laboratory parameters in Part B

End point title	Number of participants with clinically significant changes in clinical laboratory parameters in Part B[20]

End point description:

Blood samples are to be collected at Week 32, 44, 56, 68, 72 and 80 in Part B to perform hematology and clinical chemistry. Number of participants with clinically significant changes in clinical laboratory parameters are planned to be summarized.

End point type	Primary

End point timeframe:

From Week 20 up to Week 80

Notes:

[20] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There are no statistical data to report.

End point values	Mepolizumab 40 mg SC	Mepolizumab 100 mg SC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[21]	0[22]		
Units: Participants				

Notes:

[21] - Part B is not available and so will not be posted until August 2018.

[22] - Part B data is not available and so will not be posted until August 2018.

Statistical analyses

No statistical analyses for this end point

Secondary: Body weight-adjusted apparent clearance of Mepolizumab for Part A

End point title	Body weight-adjusted apparent clearance of Mepolizumab for Part A

End point description:

PK samples were collected at pre-dose on Week 4 and 8; and at Week 9, 12, 16 and 20. The body weight-adjusted apparent clearance was compared between adults and participants aged 6 to 11 years old with severe eosinophilic asthma when mepolizumab was administered subcutaneously. Point estimate and 90% CI for participants aged 6 to 11 years (centred to a mean bodyweight of 70kg) was compared with the historic adult estimated body-weight adjusted clearance of 0.22 Liter (L)/day, around which a proposed 80-125% interval was applied i.e. 0.18-0.28 L/day. Assuming an absolute bioavailability of 75% this corresponds to an apparent clearance of 0.29 L/day with the proposed 80% to 125% interval of 0.23 to 0.36 L/day. Note the average bodyweight of 70kg (mean body weight observed in adults) was not observed in the study.

End point type	Secondary

End point timeframe:

Week 4, 8, 9, 12, 16 and 20

End point values	mepolizumab sc			
Subject group type	Subject analysis set			
Number of subjects analysed	36[23]			
Units: L/day				
arithmetic mean (confidence interval 90%)				
Weight 70kg	0.1968 (0.1694 to 0.2241)			
Weight 50kg	0.1481 (0.1348 to 0.1614)			
Weight 27kg	0.0880 (0.0828 to 0.0932)			

Notes:

[23] - PK Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Asthma Control Questionnaire-7 (ACQ-7) at Week 12 in Part A

End point title	Change from Baseline in Asthma Control Questionnaire-7 (ACQ-7) at Week 12 in Part A

End point description:

ACQ-7 is a simple questionnaire to measure the adequacy of asthma control and change in asthma control which occurs either spontaneously or a result of treatment. The ACQ-7 uses a 7-point scale (0=no impairment, 6= maximum impairment for symptoms and rescue use; and 7 categories for forced expiratory volume in 1 second [FEV1]%). The instrument has a reported high test-retest reproducibility with an intraclass correlation coefficient =0.90. The minimally important change in score is 0.5. Baseline was defined as the latest value recorded prior to the first dose of mepolizumab. Change from Baseline was calculated as score obtained at Week 12 minus Baseline Score. Pharmacodynamic Outcome (PDo) Population included all participants who received at least one dose of mepolizumab beginning at Visit 2

and having at least one Part A assessment of pharmacodynamic outcomes.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Mepolizumab 40 mg SC	Mepolizumab 100 mg SC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23[24]	10		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Score on a scale	-0.414 (± 1.1354)	0.082 (± 1.3432)		

Notes:

[24] - PDo Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Asthma Control Questionnaire-7 (ACQ-7) at Week 4,8,16 and 20 in Part A

End point title	Change from Baseline in Asthma Control Questionnaire-7 (ACQ-7) at Week 4,8,16 and 20 in Part A

End point description:

ACQ-7 is a simple questionnaire to measure the adequacy of asthma control and change in asthma control which occurs either spontaneously or a result of treatment. The ACQ-7 uses a 7-point scale (0=no impairment, 6= maximum impairment for symptoms and rescue use; and 7 categories for FEV1%). The instrument has a reported high test-retest reproducibility with an intraclass correlation coefficient =0.90. The minimally important change in score is 0.5. Baseline was defined as the latest value recorded prior to the first dose of mepolizumab. Change from Baseline was calculated as score obtained at the indicated time point minus Baseline Score. Only those participants with data available at the specified time points were analyzed (represented by n=X in the category titles).

End point type	Secondary

End point timeframe:

Baseline and up to Week 20

End point values	Mepolizumab 40 mg SC	Mepolizumab 100 mg SC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26[25]	10		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Week 4, n=26, 10	-0.548 (± 1.1351)	-0.473 (± 0.9607)		
Week 8, n=26, 10	-0.652 (± 1.2270)	-0.302 (± 1.2445)		
Week 16, n=23, 10	-0.154 (± 1.2336)	-0.087 (± 1.2541)		

Week 20, n=24, 10	-0.261 (± 1.2303)	-0.088 (± 1.0632)		

Notes:

[25] - PDo Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Childhood Asthma Control Test (C-ACT) at Week 12 for Part A

End point title	Change from Baseline in Childhood Asthma Control Test (C-ACT) at Week 12 for Part A

End point description:

The C-ACT assesses asthma control in children 4-11 years of age. The C-ACT is a 7-question, 2-part questionnaire, with items one through 4 were completed by the child (with assistance from a caregiver, as needed) and items 5 to 7 were completed by the caregiver. A total sum score based upon responses to all items was calculated to provide an overall measure of asthma control. The derived C-ACT score ranges from 0 (maximum impairment) to 27 (no impairment), where higher scores represent a better outcome. Baseline was defined as the latest value recorded prior to the first dose of mepolizumab. Change from Baseline was calculated as score obtained at Week 12 minus Baseline Score.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Mepolizumab 40 mg SC	Mepolizumab 100 mg SC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22[26]	10		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Score on a scale	2.1 (± 4.45)	-0.3 (± 5.19)		

Notes:

[26] - PDo Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in C-ACT at Week 4,8,16 and 20 in Part A

End point title	Change from Baseline in C-ACT at Week 4,8,16 and 20 in Part A

End point description:

The C-ACT assesses asthma control in children 4-11 years of age. The C-ACT is a 7-question, 2-part questionnaire, with items one through 4 were completed by the child (with assistance from a caregiver, as needed) and items 5 to 7 were completed by the caregiver. A total sum score based upon responses to all items was calculated to provide an overall measure of asthma control. The derived C-ACT score ranges from 0 (maximum impairment) to 27 (no impairment), where higher scores represent a better outcome. Baseline was defined as the latest value recorded prior to the first dose of mepolizumab. Change from Baseline was calculated as score obtained at the indicated time point minus Baseline Score. Only those participants with data available at the specified time points were analyzed (represented by n=X in the category titles).

End point type	Secondary

End point timeframe:

Baseline and Weeks 4, 8, 16, and 20

End point values	Mepolizumab 40 mg SC	Mepolizumab 100 mg SC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26[27]	10		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Week 4, n=26, 10	1.8 (± 4.19)	2.4 (± 4.55)		
Week 8, n=26, 10	3.0 (± 5.77)	1.5 (± 4.28)		
Week 16, n=23, 10	1.5 (± 4.62)	-0.7 (± 5.19)		
Week 20, n=24, 10	1.0 (± 4.23)	0.9 (± 4.28)		

Notes:

[27] - PDo Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with any AE and any SAE in Part A

End point title	Number of participants with any AE and any SAE in Part A

End point description:

An AE is any untoward medical occurrence in a participant or clinical investigation participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Any untoward event resulting in death, life threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, congenital anomaly/birth defect, any other situation according to medical or scientific judgment or all events of possible drug-induced liver injury with hyperbilirubinaemia were categorized as SAE. Participants who received any of the study treatment and had any on-treatment AE or SAE (defined as events occurring from the first dose until 28 days after the last dose of mepolizumab) were considered for analysis.

End point type	Secondary

End point timeframe:

Up to Week 20

End point values	Mepolizumab 40 mg SC	Mepolizumab 100 mg SC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26[28]	10		
Units: Participants				
Any AE	18	6		
Any SAE	5	1		

Notes:

[28] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with any time change from Baseline relative to normal range in hematology parameters in Part A

End point title	Number of participants with any time change from Baseline relative to normal range in hematology parameters in Part A

End point description:

Blood samples were collected at Screening and at Week 0, 4, 8, 9, 12, 16 and 20 in Part A to perform basophils, eosinophils, leukocyte (also called as white blood cells), monocyte, neutrophils, lymphocyte, platelet count, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), hemoglobin (Hgb), mean corpuscular volume (MCV), erythrocytes, hematocrit, reticulocytes/erythrocytes. The Baseline was the latest value recorded prior to the first dose of mepolizumab. Any time post Baseline = all visits (scheduled and unscheduled) post Baseline was considered for this visit derivation. If participant had at least one value for categories "To Low" and/or "To High" along with "To Normal or No Change" then participant was counted under "To Low" and/or "To High". If participant had values which belong only to "To Normal or No Change" then participant was counted under "To Normal or No Change" only. n=X:Number of participants with data analyzed at specified time points.

End point type	Secondary

End point timeframe:

Baseline and Weeks 4, 8, 9, 12, 16 and 20

End point values	Mepolizumab 40 mg SC	Mepolizumab 100 mg SC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26[29]	10		
Units: Participants				
Basophils, To low, n=26, 10	0	0		
Basophils, To Normal or No Change n=26, 10	25	10		
Basophils, To high n=26, 10	1	0		
Eosinophils, To low n=26, 10	15	6		
Eosinophils, To Normal or No Change n=26, 10	10	4		
Eosinophils, To high n=26, 10	1	0		
Leukocyte, To low n=26, 10	8	2		
Leukocyte, To Normal or No Change n=26, 10	17	8		
Leukocyte, To high n=26, 10	1	0		
Monocyte, To low n=26, 10	6	3		
Monocyte, To Normal or No Change n=26, 10	19	7		
Monocyte, To high n=26, 10	1	0		
Neutrophils, To low n=26, 10	8	3		
Neutrophils, To Normal or No Change n=26, 10	16	7		
Neutrophils, To high n=26, 10	2	0		
Lymphocyte, To low n=26, 10	4	1		
Lymphocyte, To Normal or No Change n=26, 10	20	8		
Lymphocyte, To high n=26, 10	2	1		
Platelet count, To low n=25, 10	0	1		
Platelet count, To Normal or No change n=25,10	22	9		

Platelet count, To high n=25, 10	3	0		
MCH, To low n=26, 10	2	0		
MCH, To Normal or No Change n=26, 10	24	10		
MCH, To high n=26, 10	0	0		
MCHC, To low n=26, 10	1	1		
MCHC, To Normal or No Change n=26, 10	25	9		
MCHC, To high n=26, 10	0	0		
Hgb, To low n=26, 10	0	1		
Hgb, To Normal or No Change n=26, 10	26	9		
Hgb, To high n=26, 10	0	0		
MCV, To low n=26, 10	2	0		
MCV, To Normal or No Change n=26, 10	24	10		
MCV, To high n=26, 10	0	0		
Erythrocytes, To low n=26, 10	0	0		
Erythrocytes, To Normal or No Change n=26, 10	21	8		
Erythrocytes, To high n=26, 10	5	2		
Hematocrit, To low n=26, 10	0	2		
Hematocrit, To Normal or No Change n=26, 10	26	8		
Hematocrit, To high n=26, 10	0	0		
Reticulocytes(Ret)/erythrocytes(Ery),To lown=26,10	8	1		
Ret/Ery, To Normal or No change n=26,10	15	9		
Ret/Ery, To high n=26,10	3	0		

Notes:

[29] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with any time change from Baseline relative to normal range in clinical chemistry parameters in Part A

End point title	Number of participants with any time change from Baseline relative to normal range in clinical chemistry parameters in Part A

End point description:

Blood samples were collected at Screening and at Week 4, 8, 12 and 20 in Part A to perform alanine aminotransferase (ALT), alkaline phosphatase (ALP), aspartate aminotransferase (AST), gamma glutamyl transferase (GGT), albumin, protein, total billirubin, creatinine, direct billirubin, urate, calcium, carbon dioxide (CO2), chloride, glucose, potassium, sodium and urea. The Baseline was defined as the latest value recorded prior to the first dose of mepolizumab. Any time post Baseline = all visits (including scheduled and unscheduled) post Baseline was considered for this visit derivation. If participant had at least one value for categories "To Low" and/or "To High" along with "To Normal or No Change" then participant was counted under "To Low" and/or "To High". If participant had values which belong only to "To Normal or No Change" then participant was counted under "To Normal or No Change" only.

End point type	Secondary

End point timeframe:

Baseline and Weeks 4, 8, 12, and 20

End point values	Mepolizumab 40 mg SC	Mepolizumab 100 mg SC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26[30]	10		
Units: Participants				
ALT, To low	0	0		
ALT, To Normal or No Change	26	10		
ALT, To high	0	0		
AST, To low	0	0		
AST, To Normal or No Change	26	10		
AST, To high	0	0		
ALP, To low	0	0		
ALP, To Normal or No Change	26	10		
ALP, To high	0	0		
GGT, To low	0	0		
GGT, To Normal or No Change	26	10		
GGT, To high	0	0		
Albumin, To low	0	0		
Albumin, To Normal or No Change	22	10		
Albumin, To high	4	0		
Protein, To low	0	0		
Protein, To Normal or No Change	23	10		
Protein, To high	3	0		
Total billirubin, To low	0	0		
Total billirubin, To Normal or No Change	26	10		
Total billirubin, To high	0	0		
Creatinine, To low	4	1		
Creatinine, To Normal or No Change	22	9		
Creatinine, To high	0	0		
Direct billirubin, To low	0	0		
Direct billirubin, To Normal or No Change	26	10		
Direct billirubin, To high	0	0		
Urate, To low	1	0		
Urate, To Normal or No Change	25	10		
Urate, To high	0	0		
Calcium, To low	0	0		
Calcium, To Normal or No Change	22	8		
Calcium, To high	4	2		
CO2, To low	12	3		
CO2, To Normal or No Change	14	7		
CO2, To high	0	0		
Chloride, To low	0	0		
Chloride, To Normal or No Change	23	9		
Chloride, To high	3	1		
Glucose, To low	2	0		
Glucose, To Normal or No Change	17	8		
Glucose, To high	7	2		
Potassium, To low	0	0		

Potassium, To Normal or No Change	26	10		
Potassium, To high	0	0		
Sodium, To low	0	0		
Sodium, To Normal or No Change	26	10		
Sodium, To high	0	0		
Urea, To low	1	3		
Urea, To Normal or No Change	25	7		
Urea, To high	0	0		

Notes:

[30] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with positive anti-mepolizumab binding antibodies and neutralizing antibodies response in Part A

End point title	Number of participants with positive anti-mepolizumab binding antibodies and neutralizing antibodies response in Part A

End point description:

Blood sample for immunogenicity was collected for anti-mepolizumab binding antibodies and neutralizing antibodies response in Part A at Week 0, 16 and 20 prior to study treatment administration. Number of participants with positive anti-mepolizumab binding antibodies and neutralizing antibodies response was summarized. Participant was considered 'Positive' if they had at least one positive post-baseline assay result. Any Time Post Baseline has been presented, which included all visits (including scheduled and unscheduled) post-baseline was considered for this visit derivation. Only those participants with data available at the specified time points were analyzed (represented by n=X, X in the category titles).

End point type	Secondary

End point timeframe:

Baseline and Weeks 16 and 20

End point values	Mepolizumab 40 mg SC	Mepolizumab 100 mg SC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26[31]	10		
Units: Participants				
number (not applicable)				
Anti-drug antibody,Any time post-baseline,n=25,10	1	1		
Neutralizing antibody,Any time post-baseline,n=1,1	0	0		

Notes:

[31] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in sitting systolic blood pressure (SBP) and diastolic blood pressure (DBP) in Part A

End point title	Change from Baseline in sitting systolic blood pressure (SBP)

	and diastolic blood pressure (DBP) in Part A

End point description:

Sitting blood pressure measurements were performed in Part A at Screening and at Week 0, 4, 8, 9, 12, 16 and 20. Measurements were done pre-infusion/injection with the participant sitting, having rested in this position for at least 5 minutes before each reading. The Baseline was defined as the latest value recorded prior to the first dose of mepolizumab. Change from Baseline was defined as value at indicated time point minus Baseline value. Only those participants with data available at the specified time points were analyzed (represented by n=X, X in the category titles).

End point type	Secondary

End point timeframe:

Baseline and Weeks 4, 8, 9, 12, 16 and 20

End point values	Mepolizumab 40 mg SC	Mepolizumab 100 mg SC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26[32]	10		
Units: mmHg				
arithmetic mean (standard deviation)				
Sitting DBP, Week 4, n=26, 10	0.4 (± 5.72)	2.1 (± 3.87)		
Sitting DBP, Week 8, , n=26, 10	-0.4 (± 5.45)	3.4 (± 7.59)		
Sitting DBP, Week 9, , n=22, 10	1.8 (± 9.82)	4.9 (± 9.13)		
Sitting DBP, Week 12, , n=23, 10	1.5 (± 8.88)	0.3 (± 9.98)		
Sitting DBP, Week 20, , n=24, 10	0.7 (± 6.94)	5.1 (± 7.03)		
Sitting DBP, Week 16, , n=23, 10	0.6 (± 6.99)	3.9 (± 7.06)		
Sitting SBP, Week 4, n=26, 10	3.6 (± 9.92)	-1.9 (± 8.81)		
Sitting SBP, Week 8, , n=26, 10	1.8 (± 8.65)	-0.2 (± 6.23)		
Sitting SBP, Week 9, , n=22, 10	2.8 (± 10.39)	-0.2 (± 12.04)		
Sitting SBP, Week 12, , n=23, 10	4.3 (± 9.89)	-2.9 (± 11.10)		
Sitting SBP, Week 16, , n=23, 10	4.3 (± 11.53)	-4.6 (± 9.94)		
Sitting SBP, Week 20, , n=24, 10	5.0 (± 9.21)	1.4 (± 9.91)		

Notes:

[32] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in sitting pulse rate in Part A

End point title	Change from Baseline in sitting pulse rate in Part A

End point description:

Sitting pulse rate measurements was performed in Part A at Screening and at Week 0, 4, 8, 9, 12, 16 and 20. Measurements were done pre-infusion/injection with the participant sitting, having rested in this position for at least 5 minutes before each reading. The Baseline was defined as the latest value recorded prior to the first dose of mepolizumab. Change from Baseline was defined as value at indicated time point minus Baseline value. Only those participants with data available at the specified time points were analyzed (represented by n=X, X in the category titles).

End point type	Secondary

End point timeframe:

Baseline and Weeks 4, 8, 9, 12, 16 and 20

End point values	Mepolizumab 40 mg SC	Mepolizumab 100 mg SC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26[33]	10		
Units: Beats per minute				
arithmetic mean (standard deviation)				
Sitting pulse rate, Week 4, n=26, 10	-4.0 (± 10.91)	-1.1 (± 10.56)		
Sitting pulse rate, Week 8, , n=26, 10	-3.2 (± 9.11)	1.8 (± 7.42)		
Sitting pulse rate, Week 9, , n=22, 10	-2.9 (± 8.31)	2.3 (± 9.33)		
Sitting pulse rate, Week 12, , n=23, 10	-0.8 (± 8.31)	-0.5 (± 10.73)		
Sitting pulse rate, Week 16, , n=23, 10	-0.6 (± 7.65)	3.5 (± 10.20)		
Sitting pulse rate, Week 20, , n=24, 10	-3.9 (± 13.13)	1.8 (± 8.22)		

Notes:

[33] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Week 0 (Visit 2) in absolute blood eosinophil count at Weeks 32, 44, 56, 68, 72 and 80

End point title	Change from Week 0 (Visit 2) in absolute blood eosinophil count at Weeks 32, 44, 56, 68, 72 and 80

End point description:

Long term durability of PD of mepolizumab is to be evaluated in participants using change from Week 0 in absolute blood eosinophil count. Change from Week 0 (Visit 2) is to be calculated as post-dose visit value minus Week 0 value in PDe Population.

End point type	Secondary

End point timeframe:

Weeks 0, 32, 44, 56, 68, 72 and 80

End point values	Mepolizumab 40 mg SC	Mepolizumab 100 mg SC		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[34]	0[35]		
Units: 10^9/ L				
geometric mean (confidence interval 95%)	(to)	(to)		

Notes:

[34] - Part B is not available and so will not be posted until August 2018.

[35] - Part B data is not available and so will not be posted until August 2018.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

On-treatment serious adverse events (SAEs) and non-serious AEs were defined as events occurring from the first dose until 28 days after the last dose of mepolizumab.

Adverse event reporting additional description:

Serious adverse events (SAEs) and Non-serious AEs were collected in members of Safety Population, comprised of all participants who received at least one dose of open label mepolizumab medication.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Mepolizumab 40 mg SC

Reporting group description:

Participants with bodyweight < 40 kilogram (kg) received 0.4 milliliter (mL) of reconstituted mepolizumab subcutaneously every four weeks, in upper arm or thigh directly from the investigator or designee, under medical supervision. Participant's weight at Week 0 (Visit 2) was considered to select dosage in Part A. Prior to administration, each vial of mepolizumab were reconstituted and swirled gently to enable complete dissolution of the product.

Reporting group title	Mepolizumab 100 mg SC

Reporting group description:

Participants with bodyweight >= 40 kg received 1.0 mL of reconstituted mepolizumab subcutaneously every four weeks, in upper arm or thigh directly from the investigator or designee, under medical supervision. Prior to administration, each vial of mepolizumab were reconstituted and swirled gently to enable complete dissolution of the product. On investigator discretion, injected volume was split between two injection sites and was given as 2 injections of 0.5 mL each if required.

Serious adverse events	Mepolizumab 40 mg SC	Mepolizumab 100 mg SC	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 26 (19.23%)	1 / 10 (10.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 26 (3.85%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 26 (3.85%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration			

site conditions			
Chest pain			
subjects affected / exposed	1 / 26 (3.85%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 26 (3.85%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 26 (3.85%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	3 / 26 (11.54%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 26 (3.85%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 26 (3.85%)	0 / 10 (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	1 / 26 (3.85%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Mepolizumab 40 mg SC	Mepolizumab 100 mg SC	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 26 (69.23%)	6 / 10 (60.00%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 26 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Body temperature increased			
subjects affected / exposed	1 / 26 (3.85%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Neutrophil count decreased			
subjects affected / exposed	1 / 26 (3.85%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	1 / 26 (3.85%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 26 (3.85%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Dizziness postural			
subjects affected / exposed	0 / 26 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Headache			
subjects affected / exposed	3 / 26 (11.54%)	2 / 10 (20.00%)	
occurrences (all)	3	3	
Lethargy			
subjects affected / exposed	1 / 26 (3.85%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Injection site reaction			

subjects affected / exposed	5 / 26 (19.23%)	0 / 10 (0.00%)	
occurrences (all)	7	0	
Pain			
subjects affected / exposed	1 / 26 (3.85%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
subjects affected / exposed	1 / 26 (3.85%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 26 (3.85%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 26 (3.85%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Abdominal pain upper			
subjects affected / exposed	1 / 26 (3.85%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Constipation			
subjects affected / exposed	2 / 26 (7.69%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Gastritis			
subjects affected / exposed	1 / 26 (3.85%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	3 / 26 (11.54%)	0 / 10 (0.00%)	
occurrences (all)	3	0	
Vomiting			
subjects affected / exposed	1 / 26 (3.85%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 26 (3.85%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Cough			

subjects affected / exposed	1 / 26 (3.85%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Dysphonia			
subjects affected / exposed	0 / 26 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Epistaxis			
subjects affected / exposed	1 / 26 (3.85%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Fibrinous bronchitis			
subjects affected / exposed	1 / 26 (3.85%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Nasal congestion			
subjects affected / exposed	0 / 26 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Oropharyngeal pain			
subjects affected / exposed	2 / 26 (7.69%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Pharyngeal erythema			
subjects affected / exposed	1 / 26 (3.85%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Productive cough			
subjects affected / exposed	0 / 26 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	2	
Upper respiratory tract inflammation			
subjects affected / exposed	1 / 26 (3.85%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Wheezing			
subjects affected / exposed	2 / 26 (7.69%)	1 / 10 (10.00%)	
occurrences (all)	3	1	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 26 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Dermatitis allergic			
subjects affected / exposed	0 / 26 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	

Dry skin			
subjects affected / exposed	0 / 26 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Rash			
subjects affected / exposed	2 / 26 (7.69%)	0 / 10 (0.00%)	
occurrences (all)	4	0	
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	1 / 26 (3.85%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain			
subjects affected / exposed	1 / 26 (3.85%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	1 / 26 (3.85%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Bronchitis			
subjects affected / exposed	1 / 26 (3.85%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Croup infectious			
subjects affected / exposed	1 / 26 (3.85%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Eczema infected			
subjects affected / exposed	1 / 26 (3.85%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Gastroenteritis			
subjects affected / exposed	1 / 26 (3.85%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Nasopharyngitis			
subjects affected / exposed	3 / 26 (11.54%)	1 / 10 (10.00%)	
occurrences (all)	3	1	
Oral herpes			
subjects affected / exposed	0 / 26 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	

Otitis media acute			
subjects affected / exposed	1 / 26 (3.85%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Pharyngitis			
subjects affected / exposed	1 / 26 (3.85%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Pneumonia			
subjects affected / exposed	1 / 26 (3.85%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Respiratory tract infection viral			
subjects affected / exposed	1 / 26 (3.85%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Rhinitis			
subjects affected / exposed	0 / 26 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	2	
Sinusitis			
subjects affected / exposed	1 / 26 (3.85%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Tinea infection			
subjects affected / exposed	1 / 26 (3.85%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
subjects affected / exposed	2 / 26 (7.69%)	1 / 10 (10.00%)	
occurrences (all)	2	1	
Viral upper respiratory tract infection			
subjects affected / exposed	2 / 26 (7.69%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Wound infection			
subjects affected / exposed	0 / 26 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	0 / 26 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Hyperglycaemia			

subjects affected / exposed	0 / 26 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Hypertriglyceridaemia			
subjects affected / exposed	0 / 26 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 June 2015	- Addition of the C-ACT questionnaire to assess asthma control - To allow of the use of the ACQ tool to be administered in each country for which there is a validated translation available - Use of the Global Lung Function Initiative 2012 equations by Quanjer (2012) to estimate FEV1 predicted values - To add a copy of the ACQ-7, ACQ-IA and C-ACT questionnaire - To clarify that blood samples will be stored for up to 15 years after the end of the study. - To correct few typographical errors and few minor changes
30 September 2015	- To change the details of the Primary and Secondary Medical Monitors for the study. - To permit extended mepolizumab treatment for a minimum of 52 weeks upon completion of the pharmacokinetic/pharmacodynamic phase (Part A) of the protocol. - To add long-term safety (52 weeks) as the primary objective for the extended treatment phase (Part B). - To add long-term pharmacodynamic response as a secondary objective for the extended treatment phase. - To amend Section 9.3.2 to specify a pre-planned interim analyses to report results of the initial pharmacokinetic/pharmacodynamic phase upon completion of all required assessment for all subjects. - To add Section 9.5 to define the primary and secondary analysis plans for the extended treatment phase
30 March 2016	- Protocol Synopsis, Treatment Arms and Duration, Part B Treatment were updated to clarify the design and procedure - Section 4 Part A Follow-up: To change "positive neutralizing antibody" to "positive anti-mepolizumab antibody" and to clarify the timeline for obtaining a repeat sample - To clarify that subjects should be monitored for 1 hour post-dose during Part A only and thereafter monitoring in Part B will be according to standard practice at the site and to give guidance regarding the capability requirements at site during this monitoring. - To clarify that sample size is not determined for Part B and that all subjects completing Part A are eligible for Part B. - Changes in inclusion and exclusion criteria - Withdrawal/Stopping Criteria: To clarify that the Early Withdrawal Visit should be completed for subjects withdrawing from the study. - Permitted Medications and Non-Drug Therapies: To clarify that time of administration of concomitant medications is not required in the electronic case report form. To clarify that rescue medication will be provided for the study. To clarify that oral corticosteroids are permitted during this study and to clarify that baseline inhaled corticosteroids (ICS) and Baseline controller levels should not be changed between screening and Visit 2. - Few typographical corrections - To correct sample size assumptions, Secondary and Exploratory Analyses assumptions for Part B.
05 May 2016	- Inclusion Criteria for Part A: To correct an error in Protocol Amendment 03 when text was deleted from Inclusion Criterion 4 in error.

18 January 2017	- Protocol Synopsis, Rationale: To clarify that Part B follow-up is not required for subjects transitioning to the long-term access program. - Secondary and Exploratory Endpoints will be measured from Week 0 in Part A instead of Week 20 in Part B: - "Change from Week 20 (Visit 9)" is amended to "Change from Week 0 (Visit 2)" and that Secondary and Exploratory Endpoints will be measured at Week 80 only for subjects that will not transition to the long-term access program. To clarify that Part B follow-up is not required for subjects transitioning to the long term access program. - To clarify the definition of "completed subject" for subjects transitioning to the long-term access program and for those that do not transition. - Treatment After the Completion of Part A and Part B: Updated to include the long-term access program as an option for treatment of subjects after the end of Part B. - To clarify that immunoglobulin E (IgE) total only will be measured for this study. - Sample Size Considerations updated to clarify that the clearance mentioned in the section refers to apparent clearance. To quote the body-weight adjusted clearance value in adults (instead of the bodyweight-adjusted apparent clearance) and the 80-125% interval around this value, and to provide as additional information the value of the corresponding apparent clearance. - Abbreviations and Trademarks: Apparent clearance after extravascular (e.g., subcutaneous) administration added. - Reporting of SAEs to GlaxoSmithKline: clarification made to the point regarding reporting SAEs when the electronic system is down.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported