Clinical trial results:
An open label, randomised, three arm, single dose, multicentre, parallel group study in healthy subjects to compare the pharmacokinetics of subcutaneous mepolizumab when delivered as a liquid drug product in a safety syringe or an auto injector with a reconstituted lyophilised drug product from a vial

Summary

EudraCT number	2016-002405-19
Trial protocol	DE GB
Global end of trial date	11 August 2017

Results information

Result version number	v1 (current)
This version publication date	02 August 2018
First version publication date	02 August 2018

Trial information

Trial identification

Sponsor protocol code	204958

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)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 November 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 August 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the pharmacokinetics of subcutaneous mepolizumab following a single dose of the liquid drug product in safety syringe with the lyophilized drug product. To compare the pharmacokinetics of subcutaneous mepolizumab following a single dose of the liquid drug product in autoinjector with the lyophilized drug product.

Protection of trial subjects:

Not Applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 January 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 136
Country: Number of subjects enrolled	United Kingdom: 45
Country: Number of subjects enrolled	United States: 63
Worldwide total number of subjects	244
EEA total number of subjects	181

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	209
From 65 to 84 years	35

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a randomized, multi-center, open-label, parallel-group, single-dose study in healthy participants. The participants were administered one of 3 different mepolizumab treatments (a liquid drug product in a safety syringe; a liquid drug product in an autoinjector; a reconstituted lyophilized drug product from a vial).

Pre-assignment

Screening details:

A total of 246 participants were randomized and 244 participants received study treatment. Two participants were randomized in error.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Lyophilized vial

Arm description:

Participants were administered 100 milligram per milliliter (mg/mL) subcutaneous (SC) dose of mepolizumab as lyophilized powder reconstituted with sterile water for injection from vial. Participants were administered a single SC dose in upper arm, abdomen or thigh.

Arm type	Active comparator
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:

Participants were administered 100 milligram per milliliter (mg/mL) subcutaneous (SC) dose of mepolizumab as lyophilized powder reconstituted with sterile water for injection from vial. Participants were administered SC dose in upper arm, abdomen or thigh.

Arm title	Liquid autoinjector

Arm description:

Participants were administered 100 mg/mL SC dose of mepolizumab liquid formulation via disposable pre-filled autoinjector. Participants were administered a single SC dose in upper arm, abdomen or thigh.

Arm type	Experimental
Investigational medicinal product name	Mepolizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants were administered 100 mg/mL SC dose of mepolizumab liquid formulation via disposable pre-filled autoinjector. Participants were administered SC dose in upper arm, abdomen or thigh.

Arm title	Liquid safety syringe

Arm description:

Participants were administered 100 mg/mL SC dose of mepolizumab liquid formulation via disposable pre-filled safety syringe. Participants were administered a single SC dose in upper arm, abdomen or thigh.

Arm type	Experimental
Investigational medicinal product name	Mepolizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants were administered 100 mg/mL SC dose of mepolizumab liquid formulation via disposable pre-filled safety syringe. Participants were administered SC dose in upper arm, abdomen or thigh.

Number of subjects in period 1	Lyophilized vial	Liquid autoinjector	Liquid safety syringe
Started	85	79	80
Completed	84	79	80
Not completed	1	0	0
Consent withdrawn by subject	1	-	-

Baseline characteristics

Reporting groups	
Reporting group title	Lyophilized vial
Reporting group description:	
Participants were administered 100 milligram per milliliter (mg/mL) subcutaneous (SC) dose of mepolizumab as lyophilized powder reconstituted with sterile water for injection from vial. Participants were administered a single SC dose in upper arm, abdomen or thigh.	
Reporting group title	Liquid autoinjector
Reporting group description:	
Participants were administered 100 mg/mL SC dose of mepolizumab liquid formulation via disposable pre-filled autoinjector. Participants were administered a single SC dose in upper arm, abdomen or thigh.	
Reporting group title	Liquid safety syringe
Reporting group description:	
Participants were administered 100 mg/mL SC dose of mepolizumab liquid formulation via disposable pre-filled safety syringe. Participants were administered a single SC dose in upper arm, abdomen or thigh.	

Reporting group values	Lyophilized vial	Liquid autoinjector	Liquid safety syringe
Number of subjects	85	79	80
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	46.1	46.5	47.5
standard deviation	± 15.06	± 15.00	± 14.94
Gender categorical Units: Subjects			
Female	40	36	38
Male	45	43	42
Race/Ethnicity, Customized Units: Subjects			
Black or African American	18	15	18
American Indian or Alaska native	1	0	0
Central/South Asian heritage	1	0	0
East Asian heritage	0	1	0
Native Hawaiian or other pacific islander	0	1	0
Arabic/ North African heritage	0	0	1
White/Caucasian/European heritage	64	61	61
Asian and White	0	1	0
Black or African American and White	1	0	0

Reporting group values	Total		
Number of subjects	244		
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	- 		
Gender categorical Units: Subjects			
Female	114		
Male	130		
Race/Ethnicity, Customized Units: Subjects			
Black or African American	51		
American Indian or Alaska native	1		
Central/South Asian heritage	1		
East Asian heritage	1		
Native Hawaiian or other pacific islander	1		
Arabic/ North African heritage	1		
White/Caucasian/European heritage	186		
Asian and White	1		
Black or African American and White	1		

End points

End points reporting groups

Reporting group title	Lyophilized vial
Reporting group description:	
Participants were administered 100 milligram per milliliter (mg/mL) subcutaneous (SC) dose of mepolizumab as lyophilized powder reconstituted with sterile water for injection from vial. Participants were administered a single SC dose in upper arm, abdomen or thigh.	
Reporting group title	Liquid autoinjector
Reporting group description:	
Participants were administered 100 mg/mL SC dose of mepolizumab liquid formulation via disposable pre-filled autoinjector. Participants were administered a single SC dose in upper arm, abdomen or thigh.	
Reporting group title	Liquid safety syringe
Reporting group description:	
Participants were administered 100 mg/mL SC dose of mepolizumab liquid formulation via disposable pre-filled safety syringe. Participants were administered a single SC dose in upper arm, abdomen or thigh.	

Primary: Maximum observed plasma concentration (Cmax) of mepolizumab

End point title	Maximum observed plasma concentration (Cmax) of mepolizumab
End point description:	
Blood samples were collected at indicated time points. Cmax following a single dose administration of liquid mepolizumab using a safety syringe and an autoinjector were compared with reconstituted lyophilized drug product from the vial. Pharmacokinetic (PK) Population comprised of all participants receiving study drug for whom a pharmacokinetic sample was obtained and analyzed.	
End point type	Primary
End point timeframe:	
Day 1 (pre-dose, 2 hours, and 8 hours post-dose), Days 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 22, 29, 43, 57 and 85 post-dose	

End point values	Lyophilized vial	Liquid autoinjector	Liquid safety syringe	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	85[1]	79[2]	80[3]	
Units: micrograms per milliliter (µg/mL)				
geometric mean (geometric coefficient of variation)				
micrograms per milliliter (µg/mL)	11.57 (± 27.43)	11.98 (± 24.96)	12.07 (± 27.29)	

Notes:

[1] - PK Population

[2] - PK Population

[3] - PK Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Liquid autoinjector v Lyophilized vial

Number of subjects included in analysis	164
Analysis specification	Pre-specified
Analysis type	equivalence[4]
Parameter estimate	Ratio
Point estimate	1.04
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.98
upper limit	1.11

Notes:

[4] - Interpretation of the comparability of the autoinjector and safety syringe with the reconstituted lyophilized drug product was guided by a two-sided 90% confidence interval (CI) for the ratio of the geometric mean of test treatment to reference treatment in the range (0.80, 1.25) for Cmax.

Statistical analysis title	Statistical analysis 2
Comparison groups	Liquid safety syringe v Lyophilized vial
Number of subjects included in analysis	165
Analysis specification	Pre-specified
Analysis type	equivalence[5]
Parameter estimate	Ratio
Point estimate	1.06
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.99
upper limit	1.12

Notes:

[5] - Interpretation of the comparability of the autoinjector and safety syringe with the reconstituted lyophilized drug product was guided by a two-sided 90% CI for the ratio of the geometric mean of test treatment to reference treatment in the range (0.80, 1.25) for Cmax.

Primary: Area under the plasma concentration time curve (AUC) from time zero to the time of last quantifiable concentration (AUC[0-t]), AUC from time zero extrapolated to infinite time (AUC[0-inf]) of mepolizumab

End point title	Area under the plasma concentration time curve (AUC) from time zero to the time of last quantifiable concentration (AUC[0-t]), AUC from time zero extrapolated to infinite time (AUC[0-inf]) of mepolizumab

End point description:

Blood samples were collected at indicated time points. AUC(0-t) and AUC(0-inf) following a single dose administration of liquid mepolizumab using a safety syringe and an autoinjector were compared with lyophilized drug product. Fixed effects analysis of covariance model was used for analysis. Only those participants with data available at the specified data points were analyzed (represented by n=X in category titles).

End point type	Primary

End point timeframe:

Day 1 (pre-dose, 2 hours, and 8 hours post-dose), Days 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 22, 29, 43, 57 and 85 post-dose

End point values	Lyophilized vial	Liquid autoinjector	Liquid safety syringe	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	85[6]	79[7]	80[8]	
Units: Days*µg/mL				
geometric mean (geometric coefficient of variation)				
AUC(0-t), n=85, 79, 80	403.84 (± 25.84)	434.49 (± 22.62)	415.15 (± 27.25)	
AUC(0-inf), n=84, 79, 80	450.83 (± 25.65)	478.06 (± 24.76)	454.11 (± 28.88)	

Notes:

[6] - PK Population

[7] - PK Population

[8] - PK Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Lyophilized vial v Liquid autoinjector
Number of subjects included in analysis	164
Analysis specification	Pre-specified
Analysis type	equivalence[9]
Parameter estimate	Ratio
Point estimate	1.08
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.01
upper limit	1.15

Notes:

[9] - Interpretation of the comparability of the autoinjector and safety syringe with the reconstituted lyophilized drug product was guided by a two-sided 90% CI for the ratio of the geometric mean of test treatment to reference treatment in the range (0.80, 1.25) for AUC (0-t)

Statistical analysis title	Statistical analysis 2
Comparison groups	Liquid safety syringe v Lyophilized vial
Number of subjects included in analysis	165
Analysis specification	Pre-specified
Analysis type	equivalence[10]
Parameter estimate	Ratio
Point estimate	1.04
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.97
upper limit	1.12

Notes:

[10] - Interpretation of the comparability of the autoinjector and safety syringe with the reconstituted lyophilized drug product was guided by a two-sided 90% CI for the ratio of the geometric mean of test treatment to reference treatment in the range (0.80, 1.25) for AUC (0-t).

Statistical analysis title	Statistical analysis 3
Comparison groups	Lyophilized vial v Liquid autoinjector

Number of subjects included in analysis	164
Analysis specification	Pre-specified
Analysis type	equivalence[11]
Parameter estimate	Ratio
Point estimate	1.07
Confidence interval	
level	90 %
sides	2-sided
lower limit	1
upper limit	1.13

Notes:

[11] - Interpretation of the comparability of the autoinjector and safety syringe with the reconstituted lyophilized drug product was guided by a two-sided 90% CI for the ratio of the geometric mean of test treatment to reference treatment in the range (0.80, 1.25) for AUC (0-inf).

Statistical analysis title	Statistical analysis 4
Comparison groups	Liquid safety syringe v Lyophilized vial
Number of subjects included in analysis	165
Analysis specification	Pre-specified
Analysis type	equivalence[12]
Parameter estimate	Ratio
Point estimate	1.02
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.95
upper limit	1.09

Notes:

[12] - Interpretation of the comparability of the autoinjector and safety syringe with the reconstituted lyophilized drug product was guided by a two-sided 90% CI for the ratio of the geometric mean of test treatment to reference treatment in the range (0.80, 1.25) for AUC (0-inf).

Secondary: Time to Cmax (tmax) and last time point where the concentration is above the limit of quantification (tlast) of mepolizumab

End point title	Time to Cmax (tmax) and last time point where the concentration is above the limit of quantification (tlast) of mepolizumab

End point description:

Blood samples were collected at indicated time points. Tmax and tlast following a single dose administration of liquid mepolizumab using a safety syringe and an autoinjector were compared with lyophilized drug product.

End point type	Secondary

End point timeframe:

Day 1 (pre-dose, 2 hours, and 8 hours post-dose), Days 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 22, 29, 43, 57 and 85 post-dose

End point values	Lyophilized vial	Liquid autoinjector	Liquid safety syringe	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	85[13]	79[14]	80[15]	
Units: Days				
median (full range (min-max))				
tmax	7.04 (0.9 to 14.1)	7.05 (2.9 to 21.0)	7.06 (1.9 to 14.0)	
tlast	83.97 (14.0 to 87.0)	83.98 (81.1 to 87.1)	83.99 (55.9 to 87.9)	

Notes:

[13] - PK Population

[14] - PK Population

[15] - PK Population

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent clearance (CL/F) of mepolizumab

End point title	Apparent clearance (CL/F) of mepolizumab

End point description:

Blood samples were collected at indicated time points . CL/F following a single dose administration of liquid mepolizumab using a safety syringe and an autoinjector were compared with lyophilized drug product. Only those participants with data available were analyzed.

End point type	Secondary

End point timeframe:

Day 1 (pre-dose, 2 hours, and 8 hours post-dose), Days 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 22, 29, 43, 57 and 85 post-dose

End point values	Lyophilized vial	Liquid autoinjector	Liquid safety syringe	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	84[16]	79[17]	80[18]	
Units: Liters per hour (L/h)				
geometric mean (geometric coefficient of variation)				
Liters per hour (L/h)	0.009242 (± 27.91)	0.008716 (± 28.74)	0.009175 (± 39.30)	

Notes:

[16] - PK Population

[17] - PK Population

[18] - PK Population

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent volume of distribution (Vd/F) of mepolizumab

End point title	Apparent volume of distribution (Vd/F) of mepolizumab

End point description:

Blood samples were collected at indicated time points. Vd/F following a single dose administration of

liquid mepolizumab using a safety syringe and an autoinjector were compared with lyophilized drug product. Only those participants with data available were analyzed.

End point type	Secondary

End point timeframe:

Day 1 (pre-dose, 2 hours, and 8 hours post-dose), Days 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 22, 29, 43, 57 and 85 post-dose

End point values	Lyophilized vial	Liquid autoinjector	Liquid safety syringe	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	84[19]	79[20]	80[21]	
Units: Liters (L)				
geometric mean (geometric coefficient of variation)				
Liters (L)	7.02 (± 22.49)	6.74 (± 26.34)	6.94 (± 31.84)	

Notes:

[19] - PK Population

[20] - PK Population

[21] - PK Population

Statistical analyses

No statistical analyses for this end point

Secondary: Terminal phase elimination rate constant (lambda z) of mepolizumab

End point title	Terminal phase elimination rate constant (lambda z) of mepolizumab

End point description:

Blood samples were collected at indicated time points. Lambda z following a single dose administration of liquid mepolizumab using a safety syringe and an autoinjector were compared with lyophilized drug product. Only those participants with data available were analyzed.

End point type	Secondary

End point timeframe:

Day 1 (pre-dose, 2 hours, and 8 hours post-dose), Days 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 22, 29, 43, 57 and 85 post-dose

End point values	Lyophilized vial	Liquid autoinjector	Liquid safety syringe	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	84[22]	79[23]	80[24]	
Units: Per hours				
geometric mean (geometric coefficient of variation)				
Per hours	0.0013157 (± 21.51)	0.0012930 (± 26.20)	0.0013228 (± 26.71)	

Notes:

[22] - PK Population

[23] - PK Population

[24] - PK Population

Statistical analyses

No statistical analyses for this end point

Secondary: Terminal phase half-life (t½) of mepolizumab

End point title	Terminal phase half-life (t½) of mepolizumab

End point description:

Blood samples were collected at indicated time points for calculating t½. t½ following a single dose administration of liquid mepolizumab using a safety syringe and an autoinjector were compared with lyophilized drug product. Only those participants with data available were analyzed.

End point type	Secondary

End point timeframe:

Day 1 (pre-dose, 2 hours, and 8 hours post-dose), Days 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 22, 29, 43, 57 and 85 post-dose

End point values	Lyophilized vial	Liquid autoinjector	Liquid safety syringe	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	84[25]	79[26]	80[27]	
Units: Days				
geometric mean (geometric coefficient of variation)				
Days	21.95 (± 18.66)	22.34 (± 21.38)	21.83 (± 21.62)	

Notes:

[25] - PK Population

[26] - PK Population

[27] - PK Population

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of AUC(0-inf) obtained by extrapolation (% AUCex) of mepolizumab

End point title	Percentage of AUC(0-inf) obtained by extrapolation (% AUCex) of mepolizumab

End point description:

Blood samples were collected at indicated time points. Percentage AUCex following a single dose administration of liquid mepolizumab using a safety syringe and an autoinjector were compared with lyophilized drug product. Only those participants with data available were analyzed.

End point type	Secondary

End point timeframe:

Day 1 (pre-dose, 2 hours, and 8 hours post-dose), Days 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 22, 29, 43, 57 and 85 post-dose

End point values	Lyophilized vial	Liquid autoinjector	Liquid safety syringe	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	84[28]	79[29]	80[30]	
Units: Percentage				
geometric mean (geometric coefficient of variation)				
Percentage	7.67 (± 42.06)	7.64 (± 47.30)	7.20 (± 48.24)	

Notes:

[28] - PK Population

[29] - PK Population

[30] - PK Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with on-treatment non-serious adverse events (AEs) and serious AEs (SAEs)

End point title	Number of participants with on-treatment non-serious adverse events (AEs) and serious AEs (SAEs)

End point description:

An AE is any untoward medical occurrence in a 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 events associated with liver injury and impaired liver function were categorized as SAE. All Treated Subjects (Safety) comprised of all participants who received mepolizumab. Participants with non-serious AEs (3 percentage threshold) and SAEs has been reported.

End point type	Secondary

End point timeframe:

Up to 28 days post-dose

End point values	Lyophilized vial	Liquid autoinjector	Liquid safety syringe	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	85[31]	79[32]	80[33]	
Units: Participants				
Non-serious AEs	11	13	14	
SAEs	0	0	0	

Notes:

[31] - All Treated Subjects (Safety) Population

[32] - All Treated Subjects (Safety) Population

[33] - All Treated Subjects (Safety) Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with on-treatment systemic reactions and injection site reactions

End point title	Number of participants with on-treatment systemic reactions

	and injection site reactions

End point description:

Adverse events of special interest like local injection site reactions and systemic reactions like allergic Type I hypersensitivity were reported along with AEs and SAEs. Participants with local injection site reaction and Allergic Type I hypersensitivity systemic reactions are reported here.

End point type	Secondary

End point timeframe:

Up to 28 days post-dose

End point values	Lyophilized vial	Liquid autoinjector	Liquid safety syringe	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	85[34]	79[35]	80[36]	
Units: Participants				
Systemic reactions	0	0	0	
Injection site reactions	1	1	2	

Notes:

[34] - All Treated Subjects (Safety) Population

[35] - All Treated Subjects (Safety) Population

[36] - All Treated Subjects (Safety) Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with hematology parameters shifts from Baseline relative to normal range

End point title	Number of participants with hematology parameters shifts from Baseline relative to normal range

End point description:

Hematology parameters included assessment of platelet count, erythrocytes, leukocytes, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), neutrophils, lymphocytes, monocytes, eosinophils, basophils, hemoglobin and hematocrit. Participants were counted in the worst case category that their value changes to Low, Normal or High. Participants whose value category was unchanged or whose value became normal, were recorded in the "To Normal or No Change" category. The worst case post-Baseline values has been reported. For basophils the “to low” category is not applicable (99999) as the lower limit of normal is zero for this parameter.

End point type	Secondary

End point timeframe:

Up to Day 85

End point values	Lyophilized vial	Liquid autoinjector	Liquid safety syringe	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	85[37]	79[38]	80[39]	
Units: Participants				
Basophils, To low	99999	99999	99999	
Basophils, To normal or no change	85	79	80	
Basophils, To high	0	0	0	
Eosinophils, To low	58	46	55	

Eosinophils, To normal or no change	27	33	24	
Eosinophils, To high	0	0	1	
Hematocrit, To low	8	6	4	
Hematocrit, To normal or no change	76	72	75	
Hematocrit, To high	1	1	1	
Hemoglobin, To low	12	8	13	
Hemoglobin, To normal or no change	73	70	67	
Hemoglobin, To high	0	1	0	
Lymphocytes, To low	2	0	1	
Lymphocytes, To normal or no change	83	79	79	
Lymphocytes, To high	0	0	0	
MCH, To low	0	5	2	
MCH, To normal or no change	84	74	78	
MCH, To high	1	0	0	
MCV, To low	1	0	1	
MCV, To normal or no change	83	79	79	
MCV, To high	1	0	0	
Monocytes, To low	11	8	12	
Monocytes, To normal or no change	74	71	68	
Monocytes, To high	0	0	0	
Neutrophils, To low	7	11	9	
Neutrophils, To normal or no change	77	68	71	
Neutrophils, To high	1	0	0	
Platelets, To low	0	0	1	
Platelets, To normal or no change	85	78	79	
Platelets, To high	0	1	0	
Erythrocytes, To low	4	0	3	
Erythrocytes, To normal or no change	81	78	77	
Erythrocytes, To high	0	1	0	
Leukocytes, To low	11	9	8	
Leukocytes, To normal or no change	73	70	72	
Leukocytes, To high	1	0	0	

Notes:

[37] - All Treated Subjects (Safety) Population

[38] - All Treated Subjects (Safety) Population

[39] - All Treated Subjects (Safety) Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with clinical chemistry parameters shifts from Baseline relative to normal range

End point title	Number of participants with clinical chemistry parameters shifts from Baseline relative to normal range

End point description:

Blood samples were collected to evaluate clinical chemistry parameters, which included assessment of creatinine, creatine kinase, glucose, protein, potassium, urea, sodium, calcium, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), direct bilirubin (D.bili) and bilirubin, and albumin. Participants were counted in the worst case category that their value changes to Low, Normal or High. Participants whose value category was unchanged or whose value became normal, were recorded in the "To Normal or No Change" category. The worst case post-Baseline values has been reported. Only those participants with data available at the specified data points were analyzed. For the category “to low ” 99999 indicates data was not available as the lower limit of normal is zero for this parameter.

End point type	Secondary
End point timeframe: Up to Day 85	

End point values	Lyophilized vial	Liquid autoinjector	Liquid safety syringe	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	84[40]	79[41]	80[42]	
Units: Participants				
Glucose, To low	1	0	0	
Glucose, To normal or no change	83	79	80	
Glucose, To high	0	0	0	
Albumin, To low	0	0	0	
Albumin, To normal or no change	83	79	80	
Albumin, To high	1	0	0	
ALP, To low	0	0	0	
ALP, To normal or no change	84	79	80	
ALP, To high	0	0	0	
ALT, To low	99999	99999	99999	
ALT, To normal or no change	84	78	80	
ALT, To high	0	1	0	
AST, To low	99999	99999	99999	
AST, To normal or no change	84	78	80	
AST, To high	0	1	0	
D.bilirubin, To low	99999	99999	99999	
D.bilirubin, To normal or no change	83	79	80	
D.bilirubin, To high	1	0	0	
Bilirubin, To low	99999	99999	99999	
Bilirubin, To normal or no change	82	79	78	
Bilirubin, To high	2	0	2	
Calcium, To low	0	0	0	
Calcium, To normal or no change	83	79	79	
Calcium, To high	1	0	1	
Creatine kinase, To low	99999	99999	99999	
Creatine kinase,To normal or no change	76	68	70	
Creatine kinase, To high	8	11	10	
Creatinine, To low	4	4	1	
Creatinine, To normal or no change	79	75	79	
Creatinine, To high	1	0	0	
Potassium, To low	0	0	0	
Potassium, To normal or no change	84	79	80	
Potassium, To high	0	0	0	
Protein, To low	1	1	0	
Protein, To normal or no change	83	78	80	
Protein, To high	0	0	0	
Sodium, To low	1	0	0	
Sodium, To normal or no change	83	79	80	
Sodium, To high	0	0	0	
Urea, To low	1	2	1	

Urea, To normal or no change	83	75	79	
Urea, To high	0	2	0	

Notes:

[40] - All Treated Subjects (Safety) Population

[41] - All Treated Subjects (Safety) Population

[42] - All Treated Subjects (Safety) Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Diastolic blood pressure (DBP) and systolic blood pressure (SBP)

End point title	Change from Baseline in Diastolic blood pressure (DBP) and systolic blood pressure (SBP)

End point description:

SBP and DBP were measured in supine position after 5 minutes rest. Baseline values for each assessment was the latest available assessment prior to receiving the single dose of mepolizumab. Change from Baseline was defined as difference between the post-Baseline visit value and the Baseline value. Only those participants available at the specified time points (represented by n=X in the category titles) were analyzed.

End point type	Secondary

End point timeframe:

Baseline and up to Day 85

End point values	Lyophilized vial	Liquid autoinjector	Liquid safety syringe	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	85[43]	79[44]	80[45]	
Units: Millimeter of mercury (mmHg)				
arithmetic mean (standard deviation)				
DBP, Day 2, n=85, 79, 80	1.9 (± 7.36)	3.1 (± 6.90)	3.0 (± 6.47)	
DBP, Day 3, n=85, 79, 79	0.2 (± 7.06)	1.7 (± 6.60)	0.8 (± 7.90)	
DBP, Day 4, n=85, 78, 80	0.7 (± 6.44)	1.6 (± 7.55)	0.8 (± 6.33)	
DBP, Day 5, n=85, 79, 80	1.2 (± 7.04)	2.4 (± 7.48)	1.8 (± 6.40)	
DBP, Day 6, n=85, 78, 80	0.8 (± 6.80)	0.9 (± 7.11)	0.2 (± 7.96)	
DBP, Day 7, n=85, 78, 80	0.4 (± 7.44)	0.3 (± 6.70)	1.2 (± 7.50)	
DBP, Day 43, n=84, 79, 80	0.9 (± 8.04)	2.2 (± 6.70)	1.3 (± 7.22)	
DBP, Follow up, n=84, 79, 80	3.3 (± 8.26)	3.5 (± 6.69)	2.3 (± 6.70)	
SBP, Day 2, n=85, 79, 80	3.1 (± 10.61)	2.0 (± 11.15)	3.5 (± 11.25)	
SBP, Day 3, n=85, 79, 79	2.4 (± 10.45)	0.7 (± 10.28)	1.3 (± 11.12)	
SBP, Day 4, n=85, 78, 80	1.7 (± 9.51)	1.7 (± 9.95)	0.7 (± 10.07)	
SBP, Day 5, n=85, 79, 80	2.1 (± 11.03)	2.5 (± 10.39)	1.3 (± 9.67)	
SBP, Day 6, n=85, 78, 80	1.1 (± 9.38)	-0.6 (± 9.72)	-0.2 (± 10.81)	
SBP, Day 7, n=85, 78, 80	1.1 (± 10.95)	0.1 (± 10.37)	1.4 (± 11.30)	
SBP, Day 43, n=84, 79, 80	2.5 (± 11.21)	2.2 (± 10.70)	0.3 (± 11.93)	
SBP, Follow up, n=84, 79, 80	5.7 (± 10.21)	3.8 (± 11.93)	2.9 (± 11.67)	

Notes:

[43] - All Treated Subjects (Safety) Population

[44] - All Treated Subjects (Safety) Population

[45] - All Treated Subjects (Safety) Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in pulse rate

End point title	Change from Baseline in pulse rate

End point description:

Pulse rate was measured in supine position after 5 minutes rest. Baseline values for each assessment was the latest available assessment prior to receiving the single dose of mepolizumab. Change from Baseline was defined as difference between the post-Baseline visit value and the Baseline value. Only those participants available at the specified time points (represented by n=X in the category titles) were analyzed.

End point type	Secondary

End point timeframe:

Baseline and up to Day 85

End point values	Lyophilized vial	Liquid autoinjector	Liquid safety syringe	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	85[46]	79[47]	80[48]	
Units: Beats per minute				
arithmetic mean (standard deviation)				
Day 2, n=85, 79, 80	5.3 (± 9.19)	5.6 (± 7.03)	6.1 (± 9.78)	
Day 3, n= 85, 79, 79	4.5 (± 8.01)	5.0 (± 8.85)	5.0 (± 9.37)	
Day 4, n= 85, 78, 80	3.7 (± 8.57)	3.9 (± 7.93)	3.2 (± 8.06)	
Day 5, n= 85, 79, 80	1.0 (± 9.02)	1.0 (± 7.58)	1.0 (± 8.73)	
Day 6, n= 85, 78, 80	2.4 (± 8.81)	3.4 (± 8.46)	4.3 (± 9.53)	
Day 7, n= 85, 78, 80	3.6 (± 9.05)	2.5 (± 8.15)	3.6 (± 10.33)	
Day 43, n= 84, 79, 80	3.6 (± 10.29)	3.7 (± 7.83)	3.7 (± 10.77)	
Follow up, n= 84, 79, 80	0.8 (± 10.56)	1.0 (± 8.47)	0.8 (± 8.91)	

Notes:

[46] - All Treated Subjects (Safety) Population

[47] - All Treated Subjects (Safety) Population

[48] - All Treated Subjects (Safety) Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in temperature

End point title	Change from Baseline in temperature

End point description:

Temperature was measured in supine position after 5 minutes rest. Baseline values for each assessment was the latest available assessment prior to receiving the single dose of mepolizumab. Change from

Baseline was defined as difference between the post-Baseline visit value and the Baseline value. Only those participants available at the specified time points (represented by n=X in the category titles) were analyzed.

End point type	Secondary

End point timeframe:

Baseline and up to Day 85

End point values	Lyophilized vial	Liquid autoinjector	Liquid safety syringe	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	85[49]	79[50]	80[51]	
Units: degree Celsius				
arithmetic mean (standard deviation)				
Day 2, n=85, 79, 80	0.08 (± 0.362)	0.08 (± 0.389)	0.01 (± 0.273)	
Day 3, n=85, 79, 79	0.09 (± 0.392)	0.07 (± 0.310)	-0.02 (± 0.272)	
Day 4, n=85, 78, 80	0.04 (± 0.289)	0.05 (± 0.329)	-0.01 (± 0.293)	
Day 5, n=85, 79, 80	-0.02 (± 0.264)	-0.02 (± 0.335)	-0.04 (± 0.317)	
Day 6, n= 85, 78, 80	0.01 (± 0.347)	0.05 (± 0.350)	0.00 (± 0.332)	
Day 7, n= 85, 78, 80	0.02 (± 0.281)	0.10 (± 0.348)	0.07 (± 0.280)	
Day 43, n= 84, 79, 80	0.04 (± 0.300)	0.06 (± 0.340)	-0.01 (± 0.293)	
Follow up, n= 84, 79, 80	0.02 (± 0.296)	0.02 (± 0.364)	0.02 (± 0.280)	

Notes:

[49] - All Treated Subjects (Safety) Population

[50] - All Treated Subjects (Safety) Population

[51] - All Treated Subjects (Safety) Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in respiratory rate

End point title	Change from Baseline in respiratory rate

End point description:

Respiratory rate was measured in supine position after 5 minutes rest. Baseline values for each assessment was the latest available assessment prior to receiving the single dose of mepolizumab. Change from Baseline was defined as difference between the post-Baseline visit value and the Baseline value. Only those participants available at the specified time points (represented by n=X in the category titles) were analyzed.

End point type	Secondary

End point timeframe:

Baseline and up to Day 85

End point values	Lyophilized vial	Liquid autoinjector	Liquid safety syringe	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	85[52]	79[53]	80[54]	
Units: breaths per minute				
arithmetic mean (standard deviation)				
Day 2, n= 85, 79, 80	0.0 (± 1.90)	0.3 (± 2.30)	0.5 (± 2.15)	
Day 3, n= 85, 79, 79	-0.2 (± 2.44)	0.3 (± 2.60)	0.1 (± 2.36)	
Day 4, n= 85, 78, 80	-0.5 (± 2.09)	0.4 (± 2.35)	0.1 (± 2.10)	
Day 5, n= 85, 79, 80	-0.2 (± 2.16)	0.0 (± 2.80)	0.2 (± 2.42)	
Day 6, n= 85, 78, 80	-0.1 (± 2.03)	0.2 (± 2.20)	0.5 (± 2.45)	
Day 7, n= 85, 78, 80	-0.2 (± 2.02)	0.1 (± 2.23)	0.2 (± 2.06)	
Day 43, n= 84, 79, 80	0.3 (± 2.03)	0.4 (± 2.14)	0.3 (± 2.07)	
Follow up, n= 84, 79, 80	-0.1 (± 2.17)	0.6 (± 2.11)	0.5 (± 2.07)	

Notes:

[52] - All Treated Subjects (Safety) Population

[53] - All Treated Subjects (Safety) Population

[54] - All Treated Subjects (Safety) Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with change from Baseline in electrocardiogram (ECG) findings

End point title	Number of participants with change from Baseline in electrocardiogram (ECG) findings

End point description:

Single measurements of 12-lead ECGs were obtained after 5 minutes of rest in a supine position for the participant. ECG was performed on Day 1 and Day 85 using an automated ECG machine. Baseline values for each assessment was the latest available assessment prior to receiving the single dose of mepolizumab. Change from Baseline was defined as difference between the post-Baseline visit value and the Baseline value. Participants with abnormal ECG findings that are clinically not significant and clinically significant data has been presented here. The data of worst case post-Baseline is presented here. Only those participants available at the specified time points were analyzed.

End point type	Secondary

End point timeframe:

Baseline and Day 85

End point values	Lyophilized vial	Liquid autoinjector	Liquid safety syringe	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	84[55]	79[56]	80[57]	
Units: Participants				
Abnormal not clinically significant	15	16	19	
Abnormal clinically significant	1	0	1	

Notes:

[55] - All Treated Subjects (Safety) Population

[56] - All Treated Subjects (Safety) Population

[57] - All Treated Subjects (Safety) Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with positive anti-mepolizumab binding antibodies

End point title	Number of participants with positive anti-mepolizumab binding antibodies

End point description:

Blood samples were collected for the determination of anti-mepolizumab antibodies. A binding anti-drug antibody (ADA) assay was performed. There were three tiered analysis: screening, confirmation and titration. The results of binding ADA were categorized as negative, transient positive (defined as a single confirmatory positive immunogenic response that does not occur at the final study assessment) or persistent positive (defined as a confirmatory positive immunogenic response for at least 2 consecutive assessments excluding the Screening visit, or a single result at the final study assessment). A participant was considered positive if they had at least one positive post-Baseline ADA result. Number of participants with positive anti-mepolizumab antibodies at any time post-Baseline are presented here. Only those participants available at the specified time points were analyzed.

End point type	Secondary

End point timeframe:

Up to Day 85

End point values	Lyophilized vial	Liquid autoinjector	Liquid safety syringe	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	84[58]	79[59]	80[60]	
Units: Participants				
Transient positive	1	1	0	
Persistent positive	2	4	3	

Notes:

[58] - All Treated Subjects (Safety) Population

[59] - All Treated Subjects (Safety) Population

[60] - All Treated Subjects (Safety) Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with positive neutralizing antibodies

End point title	Number of participants with positive neutralizing antibodies

End point description:

Blood samples were collected for the determination of positive neutralizing antibodies. A neutralizing antibody assay was performed. Neutralizing antibody test was only carried out for participants who have had a positive confirmatory binding antibody test result at visit. A participant was considered positive if they had at least one positive post-Baseline neutralizing antibody result. Number of participants with positive neutralizing antibodies at any time post-Baseline are presented here. Only those participants available at the specified time points were analyzed.

End point type	Secondary

End point timeframe:

Up to Day 85

End point values	Lyophilized vial	Liquid autoinjector	Liquid safety syringe	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	3[61]	5[62]	3[63]	
Units: Participants				
Participants	0	0	0	

Notes:

[61] - All Treated Subjects (Safety) Population

[62] - All Treated Subjects (Safety) Population

[63] - All Treated Subjects (Safety) Population

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 adverse events (AEs) were collected from the start of study treatment and up to 28 days post-dose.	
Adverse event reporting additional description:	
All Treated Subjects (Safety) comprised of all participants who received mepolizumab.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups	
Reporting group title	Lyophilized vial
Reporting group description:	
Participants were administered 100 milligram per milliliter (mg/mL) subcutaneous (SC) dose of mepolizumab as lyophilized powder reconstituted with sterile water for injection from vial. Participants were administered a single SC dose in upper arm, abdomen or thigh.	
Reporting group title	Liquid autoinjector
Reporting group description:	
Participants were administered 100 mg/mL SC dose of mepolizumab liquid formulation via disposable pre-filled autoinjector. Participants were administered a single SC dose in upper arm, abdomen or thigh.	
Reporting group title	Liquid safety syringe
Reporting group description:	
Participants were administered 100 mg/mL SC dose of mepolizumab liquid formulation via disposable pre-filled safety syringe. Participants were administered a single SC dose in upper arm, abdomen or thigh.	

Serious adverse events	Lyophilized vial	Liquid autoinjector	Liquid safety syringe
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 85 (0.00%)	0 / 79 (0.00%)	0 / 80 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

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

Non-serious adverse events	Lyophilized vial	Liquid autoinjector	Liquid safety syringe
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 85 (12.94%)	13 / 79 (16.46%)	14 / 80 (17.50%)
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 85 (7.06%)	9 / 79 (11.39%)	8 / 80 (10.00%)
occurrences (all)	6	9	9

General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	5 / 85 (5.88%)	2 / 79 (2.53%)	1 / 80 (1.25%)
occurrences (all)	5	2	1
Infections and infestations			
Viral upper respiratory tract infection			
subjects affected / exposed	2 / 85 (2.35%)	3 / 79 (3.80%)	6 / 80 (7.50%)
occurrences (all)	2	3	6

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 November 2016	Amendment No. 1: Update to the content of the Device error forms to reflect consistency with other data captured in similar studies. Updated withdrawal wording in Section 5.4.1. Removal of Cardiovascular and deaths events in Section 7.3.1.4.
17 November 2016	Amendment No. 2: Minor changes incorporated throughout the document as part of the QC step
10 July 2017	Amendment No. 3: In Section 7.3.1.4 Cardiovascular and Death Events section has been removed. In subsequent Section 7.3.1.5 "Regulatory reporting requirements for SAE's" is assigned and section number 7.3.1.4 to maintain numerical sequence.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported