Clinical trial results:
A Randomised Controlled Trial of Mepolizumab Initiated During Admission to Hospital for a Severe Exacerbation of Eosinophilic COPD

Summary

EudraCT number	2018-003924-35
Trial protocol	GB
Global end of trial date	14 March 2025

Results information

Result version number	v1 (current)
This version publication date	30 January 2026
First version publication date	30 January 2026

Trial information

Trial identification

Sponsor protocol code	0690

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04075331
WHO universal trial number (UTN)	-
Other trial identifiers	IRAS Number: 255237, REC Reference Number: 19/EE/0286

Notes:

Sponsors

Sponsor organisation name	University of Leicester
Sponsor organisation address	Research Governance Office, Research & Enterprise Office, University of Leicester, Leicester, United Kingdom,
Public contact	COPD-HELP Trial Manager, Leicester Clinical trials Unit, University of Leicester, 0044 01162297247, mepo@leicester.ac.uk
Scientific contact	Prof Christopher Brightling, Chief Investigator, Department of Respiratory Sciences, University of Leicester, 0044 0116 250 2704, ceb17@leicester.ac.uk

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	09 August 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 June 2024
Global end of trial reached?	Yes
Global end of trial date	14 March 2025
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective: To evaluate the efficacy of mepolizumab initiated during hospitalisation on future hospital readmission or death (all cause) compared with placebo in severe exacerbations of eosinophilic COPD.
The secondary objective: To assess the effects of mepolizumab on health status, well-being, exercise capacity, frailty, moderate exacerbations, healthcare usage, and death, compared with placebo in patients admitted to hospital with an eosinophilic exacerbation of COPD.

Protection of trial subjects:

Eligibility criteria for this trial were carefully considered to ensure the safety of the participants. Patients with respiratory conditions including active lung cancer, interstitial lung disease, primary pulmonary hypertension or any other conditions that in the view of the investigator will affect the trial were excluded from the trial. Cardiac safety was evaluated with monitoring of clinical assessments and investigations (heart rate, blood pressure, temperature), the collection of relevant AEs, and other assessments described in the protocol.
Serious Adverse Events (SAEs), Suspected Unexpected Serious Adverse Reaction (SUSARs) and deaths were subject to expedited reporting by the site to the Sponsor. Leicester CTU and the Sponsor provided safety updates to the Data Safety Monitoring Committee (DSMC) and Trial Steering Committee (TSC), who reviewed the trial data periodically, and GlaxoSmithKline (funder and supplier of the trial drug and placebo).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 September 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 238
Worldwide total number of subjects	238
EEA total number of subjects	0

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)	71
From 65 to 84 years	160
85 years and over	7

Subject disposition

Recruitment

Recruitment details:

Trial participants were recruited from inpatient admissions to the Clinical Decisions Unit (CDU) at Glenfield Hospital, University Hospitals of Leicester NHS Trust.

Pre-assignment

Screening details:

Potential participants were screened against eligibility criteria. Pseudonymised data were recorded in the screening log. Eligible participants provided informed consent and were randomised. Ineligible or non-consenting participants were recorded as screen failures with reasons.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Blinding implementation details:

Participants, investigators, and all involved in trial conduct, sample analysis, or with any other interest in this trial remained blind to the randomised treatment assignments until after final analysis is complete. Unblinded personnel included the trial statistician, the pharmacy team, trial personnel from the Respiratory BRC responsible for reconstituting the IMP/placebo, where applicable, and dosing the participants, and the DMC in order to periodically review trial data.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants randomised to a matched placebo.

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

Dosage and administration details:

Sterile saline solution was used for the placebo for those dosed before 01 March 2024; from 01 March 2024, a matched placebo in a pre-filled syringe was used.

Arm title	Mepolizumab

Arm description:

Participants randomised to receive monthly subcutaneous injections of 100 mg mepolizumab.

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

Dosage and administration details:

Dosing was undertaken every four weeks (+/- 7 days) over 48 weeks (12 doses in total), each consisting of 100mg of mepolizumab administered subcutaneously or for those dosed from 01 March 2024 to June 2024, solution for injection in pre-filled syringe administered.

Number of subjects in period 1	Placebo	Mepolizumab
Started	119	119
Completed	119	119

Period 2

Period 2 title	Week 4
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Blinding implementation details:

Participants, investigators, and all involved in trial conduct, sample analysis, or with any other interest in this trial remained blind to the randomised treatment assignments until after final analysis is complete. Unblinded personnel included the trial statistician, the pharmacy team, trial personnel from the Respiratory BRC responsible for reconstituting the IMP/placebo, where applicable, and dosing the participants, and the DMC in order to periodically review trial data.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants randomised to a matched placebo.

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

Dosage and administration details:

Sterile saline solution was used for the placebo for those dosed before 01 March 2024; from 01 March 2024, a matched placebo in a pre-filled syringe was used.

Arm title	Mepolizumab

Arm description:

Participants randomised to receive monthly subcutaneous injections of 100 mg mepolizumab.

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

Dosage and administration details:

Dosing was undertaken every four weeks (+/- 7 days) over 48 weeks (12 doses in total), each consisting of 100mg of mepolizumab administered subcutaneously or for those dosed from 01 March 2024 to June 2024, solution for injection in pre-filled syringe administered.

Number of subjects in period 2	Placebo	Mepolizumab
Started	119	119
Completed	114	113
Not completed	5	6
Death	-	1
Lost to follow-up	5	5

Period 3

Period 3 title	Week 8
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Blinding implementation details:

Participants, investigators, and all involved in trial conduct, sample analysis, or with any other interest in this trial remained blind to the randomised treatment assignments until after final analysis is complete. Unblinded personnel included the trial statistician, the pharmacy team, trial personnel from the Respiratory BRC responsible for reconstituting the IMP/placebo, where applicable, and dosing the participants, and the DMC in order to periodically review trial data.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants randomised to a matched placebo.

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

Dosage and administration details:

Sterile saline solution was used for the placebo for those dosed before 01 March 2024; from 01 March 2024, a matched placebo in a pre-filled syringe was used.

Arm title	Mepolizumab

Arm description:

Participants randomised to receive monthly subcutaneous injections of 100 mg mepolizumab.

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

Dosage and administration details:

Dosing was undertaken every four weeks (+/- 7 days) over 48 weeks (12 doses in total), each consisting of 100mg of mepolizumab administered subcutaneously or for those dosed from 01 March 2024 to June 2024, solution for injection in pre-filled syringe administered.

Number of subjects in period 3	Placebo	Mepolizumab
Started	114	113
Completed	110	109
Not completed	4	4
Death	2	1
Lost to follow-up	2	3

Period 4

Period 4 title	Week 12
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Blinding implementation details:

Participants, investigators, and all involved in trial conduct, sample analysis, or with any other interest in this trial remained blind to the randomised treatment assignments until after final analysis is complete. Unblinded personnel included the trial statistician, the pharmacy team, trial personnel from the Respiratory BRC responsible for reconstituting the IMP/placebo, where applicable, and dosing the participants, and the DMC in order to periodically review trial data.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants randomised to a matched placebo.

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

Dosage and administration details:

Sterile saline solution was used for the placebo for those dosed before 01 March 2024; from 01 March 2024, a matched placebo in a pre-filled syringe was used.

Arm title	Mepolizumab

Arm description:

Participants randomised to receive monthly subcutaneous injections of 100 mg mepolizumab.

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

Dosage and administration details:

The Investigational Medicinal Product (IMP) for this trial was mepolizumab 100mg powder for solution for injection, or for those dosed from 01 March 2024 to June 2024, solution for injection in pre-filled syringe. Dosing was undertaken every four weeks (+/- 7 days) over 48 weeks (12 doses in total), each consisting of 100mg of mepolizumab administered subcutaneously.

Number of subjects in period 4	Placebo	Mepolizumab
Started	110	109
Completed	109	106
Not completed	1	3
Death	-	2
Lost to follow-up	1	1

Period 5

Period 5 title	Week 16
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Blinding implementation details:

Participants, investigators, and all involved in trial conduct, sample analysis, or with any other interest in this trial remained blind to the randomised treatment assignments until after final analysis is complete. Unblinded personnel included the trial statistician, the pharmacy team, trial personnel from the Respiratory BRC responsible for reconstituting the IMP/placebo, where applicable, and dosing the participants, and the DMC in order to periodically review trial data.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants randomised to a matched placebo.

Arm type	Placebo

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

Dosage and administration details:

Sterile saline solution was used for the placebo for those dosed before 01 March 2024; from 01 March 2024, a matched placebo in a pre-filled syringe was used.

Arm title	Mepolizumab

Arm description:

Participants randomised to receive monthly subcutaneous injections of 100 mg mepolizumab.

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

Dosage and administration details:

The Investigational Medicinal Product (IMP) for this trial was mepolizumab 100mg powder for solution for injection, or for those dosed from 01 March 2024 to June 2024, solution for injection in pre-filled syringe. Dosing was undertaken every four weeks (+/- 7 days) over 48 weeks (12 doses in total), each consisting of 100mg of mepolizumab administered subcutaneously.

Number of subjects in period 5	Placebo	Mepolizumab
Started	109	106
Completed	106	103
Not completed	3	3
Death	3	2
Lost to follow-up	-	1

Period 6

Period 6 title	Week 20
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Blinding implementation details:

Participants, investigators, and all involved in trial conduct, sample analysis, or with any other interest in this trial remained blind to the randomised treatment assignments until after final analysis is complete. Unblinded personnel included the trial statistician, the pharmacy team, trial personnel from the Respiratory BRC responsible for reconstituting the IMP/placebo, where applicable, and dosing the participants, and the DMC in order to periodically review trial data.

Arms

Are arms mutually exclusive?	Yes

Arm title	Placebo

Arm description:

Participants randomised to a matched placebo.

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

Dosage and administration details:

Sterile saline solution was used for the placebo for those dosed before 01 March 2024; from 01 March 2024, a matched placebo in a pre-filled syringe was used.

Arm title	Mepolizumab

Arm description:

Participants randomised to receive monthly subcutaneous injections of 100 mg mepolizumab.

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

Dosage and administration details:

The Investigational Medicinal Product (IMP) for this trial was mepolizumab 100mg powder for solution for injection, or for those dosed from 01 March 2024 to June 2024, solution for injection in pre-filled syringe. Dosing was undertaken every four weeks (+/- 7 days) over 48 weeks (12 doses in total), each consisting of 100mg of mepolizumab administered subcutaneously.

Number of subjects in period 6	Placebo	Mepolizumab
Started	106	103
Completed	105	102
Not completed	1	1
Lost to follow-up	1	1

Period 7

Period 7 title	Week 24
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Blinding implementation details:

Participants, investigators, and all involved in trial conduct, sample analysis, or with any other interest in this trial remained blind to the randomised treatment assignments until after final analysis is complete. Unblinded personnel included the trial statistician, the pharmacy team, trial personnel from the Respiratory BRC responsible for reconstituting the IMP/placebo, where applicable, and dosing the participants, and the DMC in order to periodically review trial data.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants randomised to a matched placebo.

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

Dosage and administration details:

Sterile saline solution was used for the placebo for those dosed before 01 March 2024; from 01 March 2024, a matched placebo in a pre-filled syringe was used.

Arm title	Mepolizumab

Arm description:

Participants randomised to receive monthly subcutaneous injections of 100 mg mepolizumab.

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

Dosage and administration details:

The Investigational Medicinal Product (IMP) for this trial was mepolizumab 100mg powder for solution for injection, or for those dosed from 01 March 2024 to June 2024, solution for injection in pre-filled syringe. Dosing was undertaken every four weeks (+/- 7 days) over 48 weeks (12 doses in total), each consisting of 100mg of mepolizumab administered subcutaneously.

Number of subjects in period 7	Placebo	Mepolizumab
Started	105	102
Completed	103	98
Not completed	2	4
Consent withdrawn by subject	1	-
Death	1	1
Lost to follow-up	-	3

Period 8

Period 8 title	Week 28
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Blinding implementation details:

Participants, investigators, and all involved in trial conduct, sample analysis, or with any other interest in this trial remained blind to the randomised treatment assignments until after final analysis is complete. Unblinded personnel included the trial statistician, the pharmacy team, trial personnel from the Respiratory BRC responsible for reconstituting the IMP/placebo, where applicable, and dosing the participants, and the DMC in order to periodically review trial data.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants randomised to a matched placebo.

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

Dosage and administration details:

Sterile saline solution was used for the placebo for those dosed before 01 March 2024; from 01 March 2024, a matched placebo in a pre-filled syringe was used.

Arm title	Mepolizumab

Arm description:

Participants randomised to receive monthly subcutaneous injections of 100 mg mepolizumab.

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

Dosage and administration details:

The Investigational Medicinal Product (IMP) for this trial was mepolizumab 100mg powder for solution for injection, or for those dosed from 01 March 2024 to June 2024, solution for injection in pre-filled syringe. Dosing was undertaken every four weeks (+/- 7 days) over 48 weeks (12 doses in total), each consisting of 100mg of mepolizumab administered subcutaneously.

Number of subjects in period 8	Placebo	Mepolizumab
Started	103	98
Completed	101	97
Not completed	2	1
Lost to follow-up	2	1

Period 9

Period 9 title	Week 32
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Blinding implementation details:

Participants, investigators, and all involved in trial conduct, sample analysis, or with any other interest in this trial remained blind to the randomised treatment assignments until after final analysis is complete. Unblinded personnel included the trial statistician, the pharmacy team, trial personnel from the Respiratory BRC responsible for reconstituting the IMP/placebo, where applicable, and dosing the participants, and the DMC in order to periodically review trial data.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants randomised to a matched placebo.

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

Dosage and administration details:

Sterile saline solution was used for the placebo for those dosed before 01 March 2024; from 01 March 2024, a matched placebo in a pre-filled syringe was used.

Arm title	Mepolizumab

Arm description:

Participants randomised to receive monthly subcutaneous injections of 100 mg mepolizumab.

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

Dosage and administration details:

The Investigational Medicinal Product (IMP) for this trial was mepolizumab 100mg powder for solution for injection, or for those dosed from 01 March 2024 to June 2024, solution for injection in pre-filled syringe. Dosing was undertaken every four weeks (+/- 7 days) over 48 weeks (12 doses in total), each consisting of 100mg of mepolizumab administered subcutaneously.

Number of subjects in period 9	Placebo	Mepolizumab
Started	101	97
Completed	100	94
Not completed	1	3
Death	1	1
Lost to follow-up	-	2

Period 10

Period 10 title	Week 36
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Blinding implementation details:

Participants, investigators, and all involved in trial conduct, sample analysis, or with any other interest in this trial remained blind to the randomised treatment assignments until after final analysis is complete. Unblinded personnel included the trial statistician, the pharmacy team, trial personnel from the Respiratory BRC responsible for reconstituting the IMP/placebo, where applicable, and dosing the participants, and the DMC in order to periodically review trial data.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants randomised to a matched placebo.

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

Dosage and administration details:

Sterile saline solution was used for the placebo for those dosed before 01 March 2024; from 01 March 2024, a matched placebo in a pre-filled syringe was used.

Arm title	Mepolizumab

Arm description:

Participants randomised to receive monthly subcutaneous injections of 100 mg mepolizumab.

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

Dosage and administration details:

The Investigational Medicinal Product (IMP) for this trial was mepolizumab 100mg powder for solution for injection, or for those dosed from 01 March 2024 to June 2024, solution for injection in pre-filled syringe. Dosing was undertaken every four weeks (+/- 7 days) over 48 weeks (12 doses in total), each consisting of 100mg of mepolizumab administered subcutaneously.

Number of subjects in period 10	Placebo	Mepolizumab
Started	100	94
Completed	97	92
Not completed	3	2
Death	1	1
Lost to follow-up	2	1

Period 11

Period 11 title	Week 40
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Blinding implementation details:

Participants, investigators, and all involved in trial conduct, sample analysis, or with any other interest in this trial remained blind to the randomised treatment assignments until after final analysis is complete. Unblinded personnel included the trial statistician, the pharmacy team, trial personnel from the Respiratory BRC responsible for reconstituting the IMP/placebo, where applicable, and dosing the participants, and the DMC in order to periodically review trial data.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants randomised to a matched placebo.

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

Dosage and administration details:

Sterile saline solution was used for the placebo for those dosed before 01 March 2024; from 01 March 2024, a matched placebo in a pre-filled syringe was used.

Arm title	Mepolizumab

Arm description:

Participants randomised to receive monthly subcutaneous injections of 100 mg mepolizumab.

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

Dosage and administration details:

The Investigational Medicinal Product (IMP) for this trial was mepolizumab 100mg powder for solution for injection, or for those dosed from 01 March 2024 to June 2024, solution for injection in pre-filled syringe. Dosing was undertaken every four weeks (+/- 7 days) over 48 weeks (12 doses in total), each

consisting of 100mg of mepolizumab administered subcutaneously.

Number of subjects in period 11	Placebo	Mepolizumab
Started	97	92
Completed	95	91
Not completed	2	1
Lost to follow-up	2	1

Period 12

Period 12 title	Week 44
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Blinding implementation details:

Participants, investigators, and all involved in trial conduct, sample analysis, or with any other interest in this trial remained blind to the randomised treatment assignments until after final analysis is complete. Unblinded personnel included the trial statistician, the pharmacy team, trial personnel from the Respiratory BRC responsible for reconstituting the IMP/placebo, where applicable, and dosing the participants, and the DMC in order to periodically review trial data.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants randomised to a matched placebo.

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

Dosage and administration details:

Sterile saline solution was used for the placebo for those dosed before 01 March 2024; from 01 March 2024, a matched placebo in a pre-filled syringe was used.

Arm title	Mepolizumab

Arm description:

Participants randomised to receive monthly subcutaneous injections of 100 mg mepolizumab.

Arm type	Experimental

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

Dosage and administration details:

The Investigational Medicinal Product (IMP) for this trial was mepolizumab 100mg powder for solution for injection, or for those dosed from 01 March 2024 to June 2024, solution for injection in pre-filled syringe. Dosing was undertaken every four weeks (+/- 7 days) over 48 weeks (12 doses in total), each consisting of 100mg of mepolizumab administered subcutaneously.

Number of subjects in period 12	Placebo	Mepolizumab
Started	95	91
Completed	92	91
Not completed	3	0
Death	1	-
Lost to follow-up	2	-

Period 13

Period 13 title	Week 48
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Blinding implementation details:

Participants, investigators, and all involved in trial conduct, sample analysis, or with any other interest in this trial remained blind to the randomised treatment assignments until after final analysis is complete. Unblinded personnel included the trial statistician, the pharmacy team, trial personnel from the Respiratory BRC responsible for reconstituting the IMP/placebo, where applicable, and dosing the participants, and the DMC in order to periodically review trial data.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants randomised to a matched placebo.

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

Dosage and administration details:

Sterile saline solution was used for the placebo for those dosed before 01 March 2024; from 01 March 2024, a matched placebo in a pre-filled syringe was used.

Arm title	Mepolizumab

Arm description:

Participants randomised to receive monthly subcutaneous injections of 100 mg mepolizumab.

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

Dosage and administration details:

The Investigational Medicinal Product (IMP) for this trial was mepolizumab 100mg powder for solution for injection, or for those dosed from 01 March 2024 to June 2024, solution for injection in pre-filled syringe. Dosing was undertaken every four weeks (+/- 7 days) over 48 weeks (12 doses in total), each consisting of 100mg of mepolizumab administered subcutaneously.

Number of subjects in period 13	Placebo	Mepolizumab
Started	92	91
Completed	88	87
Not completed	4	4
Death	2	-
Lost to follow-up	2	4

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants randomised to a matched placebo.	
Reporting group title	Mepolizumab
Reporting group description:	
Participants randomised to receive monthly subcutaneous injections of 100 mg mepolizumab.	

Reporting group values	Placebo	Mepolizumab	Total
Number of subjects	119	119	238
Age categorical Units: Subjects			
Adults (18-64 years)	38	33	71
From 65-84 years	78	82	160
85 years and over	3	4	7
Gender categorical Units: Subjects			
Female	60	61	121
Male	59	58	117
eMRC score			
eMRC Dyspnea Scale scores category			
Units: Subjects			
≤3	39	39	78
>3	80	80	160
Past hospitalisation in previous 12 months Units: Subjects			
No hospitalisation	39	40	79
≥1 hospitalised	80	79	159
Ethnicity Units: Subjects			
White	117	119	236
Asian or Asian British	2	0	2
Smoking status Units: Subjects			
Current Smoker	28	24	52
Ex-Smoker	91	95	186
eMRC dyspnoea current score Units: Subjects			
Grade 2	12	8	20
Grade 3	27	31	58
Grade 4	55	50	105
Grade 5A	19	23	42
Grade 5B	6	6	12
Missing	0	1	1
eMRC dyspnoea baseline score (stable state)			

Units: Subjects			
Grade 2	12	8	20
Grade 3	27	31	58
Grade 4	55	50	105
Grade 5A	19	23	42
Grade 5B	6	6	12
Missing	0	1	1
WHO Highest level of intervention during baseline admission Units: Subjects			
No oxygen therapy	51	47	98
Oxygen by mask or nasal prongs	57	62	119
Oxygen by NIV or high flow	11	10	21
Background inhaled medication Units: Subjects			
Triple therapy	110	113	223
LABA+ICS	9	6	15
Cardiovascular disease			
Defined as the presence of any of atrial fibrillation, previous myocardial infarction, ischemic heart disease, heart failure, or valvular heart disease.			
Units: Subjects			
Yes	37	48	85
No	82	71	153
Diabetes Units: Subjects			
Yes	33	28	61
No	86	91	177
Anxiety or depression Units: Subjects			
Yes	49	41	90
No	70	78	148
Gastroesophageal reflux disease Units: Subjects			
Yes	33	39	72
No	86	80	166
BMI Units: kg/m2			
arithmetic mean	27.7	27.4	
standard deviation	± 7.6	± 7.2	-
Number of cigarettes per day Units: Cigarettes			
arithmetic mean	21.4	21.0	
standard deviation	± 10.0	± 9.5	-
Number of years smoked Units: Years			
arithmetic mean	41.6	40.5	
standard deviation	± 11.5	± 13.0	-
Number of emergency admissions			
Number of emergency admissions (all cause) in previous 12 months			
Units: Admissions			
median	1.0	1.0	
inter-quartile range (Q1-Q3)	0.0 to 3.0	0.0 to 3.0	-

Number of courses of steroids without antibiotics			
Number of courses of steroids without antibiotics for your chest (COPD exacerbations) in previous 12 months			
Units: Courses			
arithmetic mean	1.0	0.8	
standard deviation	± 2.1	± 2.3	-
Number of courses of antibiotics without steroids			
Number of courses of antibiotics without steroids for your chest (COPD exacerbations) in previous 12 months			
Units: Courses			
arithmetic mean	1.1	0.8	
standard deviation	± 1.9	± 1.7	-
Number of courses of both antibiotics and steroids			
Number of courses of both antibiotics and steroids for your chest (COPD exacerbations) in previous 12 months			
Units: Courses			
arithmetic mean	3.8	3.3	
standard deviation	± 2.9	± 2.7	-
Number of courses of either glucocorticoid, antibiotic, or both			
Number of courses of either glucocorticoid, antibiotic, or both (COPD exacerbations) in previous 12 months			
Units: Courses			
arithmetic mean	5.7	4.9	
standard deviation	± 4.8	± 4.3	-
Systolic Blood Pressure Pre Dose			
Systolic (mmHg) Pre-Dose			
Units: mmHg			
arithmetic mean	128.8	127.2	
standard deviation	± 18.5	± 17.2	-
Diastolic Blood Pressure Pre Dose			
Diastolic (mmHg) Pre-Dose			
Units: mmHg			
arithmetic mean	72.0	72.1	
standard deviation	± 12.5	± 10.6	-
Heart rate Pre Dose			
Heart rate (bpm) Pre-Dose			
Units: bpm			
arithmetic mean	83.9	85.9	
standard deviation	± 15.8	± 13.4	-
Temperature Pre Dose			
Temperature (oC) Pre-Dose			
Units: oC			
arithmetic mean	36.6	36.6	
standard deviation	± 0.4	± 0.3	-
SpO2 Pre Dose			
SpO2 (%) Pre-Dose			

Units: Percent %			
arithmetic mean	93.5	93.6	
standard deviation	± 3.2	± 3.0	-
Respiratory rate Pre Dose			
Respiratory rate (per min) Pre-Dose			
Units: per min			
arithmetic mean	18.8	18.9	
standard deviation	± 2.6	± 3.2	-
Systolic Blood pressure Post-Dose			
Systolic (mmHg) Post-Dose			
Units: mmHg			
arithmetic mean	130.2	129.3	
standard deviation	± 17.6	± 17.3	-
Diastolic Blood Pressure Post-Dose			
Diastolic (mmHg) Post-Dose			
Units: mmHg			
arithmetic mean	74.7	75.0	
standard deviation	± 13.9	± 11.8	-
Heart rate Post-Dose			
Heart rate (bpm) Post-Dose			
Units: bpm			
arithmetic mean	85.8	86.7	
standard deviation	± 16.5	± 15.5	-
Temperature Post-Dose			
Units: oC			
arithmetic mean	36.6	36.6	
standard deviation	± 0.4	± 0.4	-
SpO2 Post-Dose			
Units: Percent %			
arithmetic mean	18.6	19.0	
standard deviation	± 2.3	± 3.0	-
Respiratory rate Post-Dose			
Units: per min			
arithmetic mean	18.6	19.0	
standard deviation	± 2.3	± 3.0	-
Length of hospital stay for index admission (days)			
Time to discharge from index admission (days)			
Units: Days			
median	4	4	
inter-quartile range (Q1-Q3)	2 to 7	3 to 7	-
FEV1, litre			
Units: litre			
arithmetic mean	1.3	1.3	
standard deviation	± 0.5	± 0.5	-
FEV1, %			
Units: percent			
arithmetic mean	50.8	51.0	
standard deviation	± 21.3	± 18.2	-

FVC, litre			
Units: litre			
arithmetic mean	2.6	2.6	
standard deviation	± 0.9	± 0.8	-
FVC, %			
Units: percent			
arithmetic mean	81.8	82.6	
standard deviation	± 22.1	± 20.1	-
FEV1/FVC ratio, %			
Units: percent			
arithmetic mean	48.4	48.9	
standard deviation	± 13.3	± 13.4	-
Highest eosinophil count			
Highest eosinophil count in previous 12 months			
Units: cells/µl			
arithmetic mean	570	570	
standard deviation	± 410	± 340	-
Length of hospital stay for index admission			
Units: Days			
median	4	4	
inter-quartile range (Q1-Q3)	2 to 7	3 to 7	-
CAT total score			
Units: Score			
arithmetic mean	26.1	25.2	
standard deviation	± 6.1	± 6.2	-
SGRQ-C total score			
Units: Score			
arithmetic mean	72.0	69.9	
standard deviation	± 13.8	± 15.7	-
SGRQ-C domains: Symptoms Score			
Units: Score			
arithmetic mean	75.6	78.5	
standard deviation	± 16.1	± 14.3	-
SGRQ-C domains: Activity Score			
Units: Score			
arithmetic mean	85.2	82.9	
standard deviation	± 15.5	± 17.9	-
SGRQ-C domains: Impact Score			
Units: Score			
arithmetic mean	62.8	58.6	
standard deviation	± 18.2	± 20.2	-

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: Participants randomised to a matched placebo.	
Reporting group title	Mepolizumab
Reporting group description: Participants randomised to receive monthly subcutaneous injections of 100 mg mepolizumab.	
Reporting group title	Placebo
Reporting group description: Participants randomised to a matched placebo.	
Reporting group title	Mepolizumab
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Reporting group title	Mepolizumab
Reporting group description: Participants randomised to receive monthly subcutaneous injections of 100 mg mepolizumab.	
Reporting group title	Placebo
Reporting group description: Participants randomised to a matched placebo.	
Reporting group title	Mepolizumab

Reporting group description:

Participants randomised to receive monthly subcutaneous injections of 100 mg mepolizumab.

Reporting group title	Placebo

Reporting group description:

Participants randomised to a matched placebo.

Reporting group title	Mepolizumab

Reporting group description:

Participants randomised to receive monthly subcutaneous injections of 100 mg mepolizumab.

Reporting group title	Placebo

Reporting group description:

Participants randomised to a matched placebo.

Reporting group title	Mepolizumab

Reporting group description:

Participants randomised to receive monthly subcutaneous injections of 100 mg mepolizumab.

Reporting group title	Placebo

Reporting group description:

Participants randomised to a matched placebo.

Reporting group title	Mepolizumab

Reporting group description:

Participants randomised to receive monthly subcutaneous injections of 100 mg mepolizumab.

Reporting group title	Placebo

Reporting group description:

Participants randomised to a matched placebo.

Reporting group title	Mepolizumab

Reporting group description:

Participants randomised to receive monthly subcutaneous injections of 100 mg mepolizumab.

Reporting group title	Placebo

Reporting group description:

Participants randomised to a matched placebo.

Reporting group title	Mepolizumab

Reporting group description:

Participants randomised to receive monthly subcutaneous injections of 100 mg mepolizumab.

Primary: Time from randomisation to next hospital readmission or death (all cause)

End point title	Time from randomisation to next hospital readmission or death (all cause)

End point description:

The primary outcome of the trial was defined as the time from randomisation to next hospital readmission or death (all cause).

End point type	Primary

End point timeframe:

Patients were followed up for up to 48 weeks (an absolute maximum of 49 weeks as the 48 week visit had a visit window of +- 1 week).

End point values	Placebo	Mepolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	119		
Units: Weeks				
median (confidence interval 95%)	25.7 (20.1 to 39.0)	24.4 (17.9 to 33.0)		

Statistical analyses

Statistical analysis title	Time to readmission or death Log Rank Test

Statistical analysis description:

The analysis took place on the intention to treat population. The Cox proportional hazard model was used for the primary outcome of the time to re-hospitalisation or death (any cause) as the dependent variable. The treatment group served as an explanatory factor, while baseline MRC dyspnoea score (≤3, >3) and past hospitalisation in the previous 12 months (0, ≥1) were included as stratification factors.

Comparison groups	Placebo v Mepolizumab
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.811
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1.32

Secondary: St George’s Respiratory Questionnaire for COPD Patients (SGRQ-C)

End point title	St George’s Respiratory Questionnaire for COPD Patients (SGRQ-C)

End point description:

End point type	Secondary

End point timeframe:

(Week 0 and) Week-4, Week-8, Week-12, Week-24, Week-36 & Week-48

End point values	Placebo	Mepolizumab	Placebo	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	117	111	95	84
Units: SGRQ-c total score				
arithmetic mean (standard deviation)	72 (± 13.8)	69.8 (± 15.7)	66.2 (± 16.4)	64.4 (± 18.1)

End point values	Placebo	Placebo	Placebo	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	85	76	67	77
Units: SGRQ-c total score				
arithmetic mean (standard deviation)	63.3 (± 16.3)	61.7 (± 18.2)	60.4 (± 20.0)	62.4 (± 18.9)

End point values	Mepolizumab	Mepolizumab	Mepolizumab	Mepolizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	102	86	79	73
Units: SGRQ-c total score				
arithmetic mean (standard deviation)	65.5 (± 16.0)	64.3 (± 15.9)	64.3 (± 16.4)	64.3 (± 18.0)

End point values	Mepolizumab	Mepolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	67		
Units: SGRQ-c total score				
arithmetic mean (standard deviation)	61.2 (± 18.1)	60.7 (± 19.1)		

Statistical analyses

Statistical analysis title	SGRQ-c total score - mixed effect linear model

Statistical analysis description:

A mixed effect linear model with dependent variable of the outcome at baseline and follow-up time points; explanatory variables of treatment arm, baseline MRC dyspnoea score (≤3, >3) and past hospitalisation in the previous 12 months (0, ≥1) (Stratification factors), visit time point (as categorical variable), baseline score; an interaction term between treatment and visit; and patient identification as a random effect was fitted for each outcome.

Comparison groups	Mepolizumab v Placebo
Number of subjects included in analysis	228
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.726
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.63
upper limit	3.78

Variability estimate	Standard error of the mean

Secondary: COPD Assessment Tool (CAT)

End point title	COPD Assessment Tool (CAT)

End point description:

End point type	Secondary

End point timeframe:

(Week 0 and) Week-4, Week-8, Week-12, Week-24, Week-36 & Week-48

End point values	Placebo	Mepolizumab	Placebo	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	119	117	99	90
Units: CAT total score				
arithmetic mean (standard deviation)	26.1 (± 6.1)	25.2 (± 6.2)	23.9 (± 6.2)	23.8 (± 7.1)

End point values	Placebo	Placebo	Placebo	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	95	83	77	82
Units: CAT total score				
arithmetic mean (standard deviation)	23.0 (± 7.7)	23.4 (± 7.6)	22.5 (± 8.4)	24.0 (± 7.4)

End point values	Mepolizumab	Mepolizumab	Mepolizumab	Mepolizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	102	95	88	84
Units: CAT total score				
arithmetic mean (standard deviation)	22.3 (± 6.6)	23.6 (± 6.4)	23.6 (± 6.6)	23.5 (± 6.8)

End point values	Mepolizumab	Mepolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72	81		
Units: CAT total score				
arithmetic mean (standard deviation)	22.8 (± 7.3)	22.3 (± 7.3)		

Statistical analyses

Statistical analysis title	CAT score - mixed effect linear model

Statistical analysis description:

A mixed effect linear model with dependent variable of the outcome at baseline and follow-up time points; explanatory variables of treatment arm, baseline MRC dyspnoea score (≤3, >3) and past hospitalisation in the previous 12 months (0, ≥1) (Stratification factors), visit time point (as categorical variable), baseline score; an interaction term between treatment and visit; and patient identification as a random effect was fitted for each outcome.

Comparison groups	Placebo v Mepolizumab
Number of subjects included in analysis	236
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.73
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.88
upper limit	1.25

Secondary: Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS)

End point title	Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS)

End point description:

End point type	Secondary

End point timeframe:

(Week 0 and) Week-4, Week-8, Week-12, Week-24, Week-36 & Week-48

End point values	Placebo	Mepolizumab	Placebo	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	119	116	98	85
Units: WEMWBS total score				
arithmetic mean (standard deviation)	41.2 (± 9.2)	42.9 (± 10.4)	43.3 (± 10.0)	43.2 (± 10.2)

End point values	Placebo	Placebo	Placebo	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	86	77	68	77
Units: WEMWBS total score				
arithmetic mean (standard deviation)	45.2 (± 10.0)	45.0 (± 10.8)	47.0 (± 9.4)	46.6 (± 9.4)

End point values	Mepolizumab	Mepolizumab	Mepolizumab	Mepolizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	103	90	82	75
Units: WEMWBS total score				
arithmetic mean (standard deviation)	44.9 (± 11.7)	44.7 (± 11.6)	45.0 (± 11.9)	44.5 (± 12.3)

End point values	Mepolizumab	Mepolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	69		
Units: WEMWBS total score				
arithmetic mean (standard deviation)	48.4 (± 11.0)	47.6 (± 11.6)		

Statistical analyses

Statistical analysis title	WEMWBS total score - mixed effect linear model

Statistical analysis description:

A mixed effect linear model with dependent variable of the outcome at baseline and follow-up time points; explanatory variables of treatment arm, baseline MRC dyspnoea score (≤3, >3) and past hospitalisation in the previous 12 months (0, ≥1) (Stratification factors), visit time point (as categorical variable), baseline score; an interaction term between treatment and visit; and patient identification as a random effect was fitted for each outcome.

Comparison groups	Placebo v Mepolizumab
Number of subjects included in analysis	235
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.789
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.34
upper limit	1.79

Secondary: London Chest Activities of Daily Living Questionnaire (LCADL)

End point title	London Chest Activities of Daily Living Questionnaire (LCADL)

End point description:

End point type	Secondary

End point timeframe:
(Week 0 and) Week-4, Week-8, Week-12, Week-24, Week-36 & Week-48

End point values	Placebo	Mepolizumab	Placebo	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	119	117	98	86
Units: LCADL total score				
arithmetic mean (standard deviation)	28.9 (± 10.8)	27.6 (± 11.3)	26.5 (± 11.8)	24.8 (± 12.3)

End point values	Placebo	Placebo	Placebo	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	87	79	68	77
Units: LCADL total score				
arithmetic mean (standard deviation)	26.2 (± 12.3)	25.2 (± 12.0)	24.4 (± 12.4)	26.4 (± 12.9)

End point values	Mepolizumab	Mepolizumab	Mepolizumab	Mepolizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	103	90	82	75
Units: LCADL total score				
arithmetic mean (standard deviation)	24.7 (± 11.2)	24.6 (± 10.2)	24.3 (± 10.7)	24.6 (± 12.1)

End point values	Mepolizumab	Mepolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	69		
Units: LCADL total score				
arithmetic mean (standard deviation)	22.8 (± 12.2)	23.6 (± 11.4)		

Statistical analyses

Statistical analysis title	LCADL score-mixed effect linear model

Statistical analysis description:

A mixed effect linear model with dependent variable of the outcome at baseline and follow-up time points; explanatory variables of treatment arm, baseline MRC dyspnoea score (≤3, >3) and past hospitalisation in the previous 12 months (0, ≥1) (Stratification factors), visit time point (as categorical variable), baseline score; an interaction term between treatment and visit; and patient identification as a random effect was fitted for each outcome.

Comparison groups	Placebo v Mepolizumab

Number of subjects included in analysis	236
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.563
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.06
upper limit	1.12

Secondary: Extended MRC Dyspnoea Score (eMRC)

End point title	Extended MRC Dyspnoea Score (eMRC)

End point description:

End point type	Secondary

End point timeframe:

(Week 0 and) Week-4, Week-8, Week-12, Week-24, Week-36 & Week-48

End point values	Placebo	Mepolizumab	Placebo	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	109	106	94	80
Units: eMRC Dyspnoea Score				
median (inter-quartile range (Q1-Q3))	5.0 (4.0 to 5.0)	5.0 (5.0 to 5.0)	4.0 (3.0 to 4.0)	4.0 (3.0 to 4.0)

End point values	Placebo	Placebo	Placebo	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	80	81	70	78
Units: eMRC Dyspnoea Score				
median (inter-quartile range (Q1-Q3))	4.0 (3.0 to 4.5)	4.0 (3.0 to 4.0)	4.0 (3.0 to 4.0)	4.0 (3.0 to 4.0)

End point values	Mepolizumab	Mepolizumab	Mepolizumab	Mepolizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	94	87	77	77
Units: eMRC Dyspnoea Score				
median (inter-quartile range (Q1-Q3))	4.0 (3.0 to 5.0)	4.0 (3.0 to 5.0)	4.0 (3.0 to 4.0)	4.0 (3.0 to 5.0)

End point values	Mepolizumab	Mepolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	79		
Units: eMRC Dyspnoea Score				
median (inter-quartile range (Q1-Q3))	4.0 (3.0 to 4.0)	4.0 (3.0 to 5.0)		

Statistical analyses

Statistical analysis title	eMRC dyspnoea score Wilcoxon rank sum test Week 4
Comparison groups	Placebo v Mepolizumab
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.87
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	eMRC dyspnoea score Wilcoxon rank sum test Week 8
Comparison groups	Placebo v Mepolizumab
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	eMRC dyspnoea score Wilcoxon rank sum test Week 12
Comparison groups	Placebo v Mepolizumab
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.52
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	eMRC dyspnoea score Wilcoxon rank sum test Week 24
Comparison groups	Placebo v Mepolizumab

Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.55
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	eMRC dyspnoea score Wilcoxon rank sum test Week 36
Comparison groups	Placebo v Mepolizumab
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.77
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	eMRC dyspnoea score Wilcoxon rank sum test Week 48
Comparison groups	Placebo v Mepolizumab
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.32
Method	Wilcoxon (Mann-Whitney)

Secondary: SGRQ-c domains- Symptoms

End point title	SGRQ-c domains- Symptoms

End point description:

End point type	Secondary

End point timeframe:

(Week 0 and) Week-4, Week-8, Week-12, Week-24, Week-36 & Week-48

End point values	Placebo	Mepolizumab	Placebo	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	118	116	97	87
Units: Symptoms score				
arithmetic mean (standard deviation)	75.6 (± 16.1)	78.5 (± 14.3)	74.8 (± 15.7)	74.6 (± 17.4)

End point values	Placebo	Placebo	Placebo	Placebo

Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	87	80	68	77
Units: Symptoms score				
arithmetic mean (standard deviation)	74.1 (± 15.8)	72.7 (± 18.2)	71.8 (± 17.8)	71.8 (± 19.2)

End point values	Mepolizumab	Mepolizumab	Mepolizumab	Mepolizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	103	89	82	75
Units: Symptoms score				
arithmetic mean (standard deviation)	73.7 (± 14.7)	74.3 (± 15.5)	73.4 (± 14.7)	73.4 (± 16.6)

End point values	Mepolizumab	Mepolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	68		
Units: Symptoms score				
arithmetic mean (standard deviation)	69.3 (± 16.0)	68.8 (± 18.3)		

Statistical analyses

Statistical analysis title	SGRQ-c symptoms domain- mixed effect linear model

Statistical analysis description:

A mixed effect linear model with dependent variable of the outcome at baseline and follow-up time points; explanatory variables of treatment arm, baseline MRC dyspnoea score (≤3, >3) and past hospitalisation in the previous 12 months (0, ≥1) (Stratification factors), visit time point (as categorical variable), baseline score; an interaction term between treatment and visit; and patient identification as a random effect was fitted for each outcome.

Comparison groups	Placebo v Mepolizumab
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.016
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-3.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.1
upper limit	-0.72

Secondary: SGRQ-c domains- Activity

End point title	SGRQ-c domains- Activity

End point description:

End point type	Secondary

End point timeframe:

(Week 0 and) Week-4, Week-8, Week-12, Week-24, Week-36 & Week-48

End point values	Placebo	Mepolizumab	Placebo	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	117	113	96	84
Units: Activity score				
arithmetic mean (standard deviation)	85.2 (± 15.5)	82.9 (± 17.9)	80.8 (± 19.1)	79.0 (± 22.1)

End point values	Placebo	Placebo	Placebo	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	86	77	68	77
Units: Activity score				
arithmetic mean (standard deviation)	79.0 (± 21.3)	79.8 (± 22.2)	76.8 (± 23.0)	80.3 (± 21.5)

End point values	Mepolizumab	Mepolizumab	Mepolizumab	Mepolizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	102	86	80	74
Units: Activity score				
arithmetic mean (standard deviation)	82.4 (± 19.0)	81.6 (± 20.0)	82.2 (± 18.2)	81.6 (± 20.2)

End point values	Mepolizumab	Mepolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	68		
Units: Activity score				
arithmetic mean (standard deviation)	81.2 (± 20.8)	80.5 (± 20.0)		

Statistical analyses

Statistical analysis title	SGRQ-c activity score- mixed effect linear model

Statistical analysis description:

A mixed effect linear model with dependent variable of the outcome at baseline and follow-up time points; explanatory variables of treatment arm, baseline MRC dyspnoea score (≤3, >3) and past hospitalisation in the previous 12 months (0, ≥1) (Stratification factors), visit time point (as categorical variable), baseline score; an interaction term between treatment and visit; and patient identification as

a random effect was fitted for each outcome.

Comparison groups	Placebo v Mepolizumab
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.157
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	2.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.02
upper limit	6.3

Secondary: SGRQ-c domains- Impacts

End point title	SGRQ-c domains- Impacts
End point description:	
End point type	Secondary
End point timeframe:	
(Week 0 and) Week-4, Week-8, Week-12, Week-24, Week-36 & Week-48	

End point values	Placebo	Mepolizumab	Placebo	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	119	115	95	86
Units: SGRQ-c impact score				
arithmetic mean (standard deviation)	62.8 (± 18.2)	58.6 (± 20.2)	54.4 (± 20.5)	52.4 (± 21.2)

End point values	Placebo	Placebo	Placebo	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	86	76	67	77
Units: SGRQ-c impact score				
arithmetic mean (standard deviation)	50.4 (± 18.3)	47.6 (± 20.4)	46.8 (± 22.5)	48.6 (± 22.0)

End point values	Mepolizumab	Mepolizumab	Mepolizumab	Mepolizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	102	88	79	73
Units: SGRQ-c impact score				
arithmetic mean (standard deviation)	52.6 (± 20.3)	50.5 (± 19.6)	50.6 (± 21.2)	50.7 (± 22.5)

End point values	Mepolizumab	Mepolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	68		
Units: SGRQ-c impact score				
arithmetic mean (standard deviation)	46.6 (± 22.2)	46.2 (± 22.8)		

Statistical analyses

Statistical analysis title	SGRQ-c impact score- - mixed effect linear model

Statistical analysis description:

A mixed effect linear model with dependent variable of the outcome at baseline and follow-up time points; explanatory variables of treatment arm, baseline MRC dyspnoea score (≤3, >3) and past hospitalisation in the previous 12 months (0, ≥1) (Stratification factors), visit time point (as categorical variable), baseline score; an interaction term between treatment and visit; and patient identification as a random effect was fitted for each outcome.

Comparison groups	Placebo v Mepolizumab
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.817
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.5
upper limit	4.43

Secondary: Short Physical Performance Battery (SPPB)

End point title	Short Physical Performance Battery (SPPB)

End point description:

End point type	Secondary

End point timeframe:

(Week 0 and) Week-4, Week-8, Week-12, Week-24, Week-36 & Week-48

End point values	Placebo	Mepolizumab	Placebo	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	118	117	97	86
Units: SPPB total score				
median (inter-quartile range (Q1-Q3))	7.0 (5.0 to 9.0)	7.0 (5.0 to 9.0)	7.0 (6.0 to 9.0)	8.0 (6.0 to 9.0)

End point values	Placebo	Placebo	Placebo	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	86	80	68	76
Units: SPPB total score				
median (inter-quartile range (Q1-Q3))	8.0 (6.0 to 10.0)	7.5 (6.0 to 10.0)	8.0 (6.0 to 10.0)	8.0 (6.0 to 11.0)

End point values	Mepolizumab	Mepolizumab	Mepolizumab	Mepolizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	100	88	81	72
Units: SPPB total score				
median (inter-quartile range (Q1-Q3))	8.5 (6.5 to 10.0)	8.0 (6.0 to 11.0)	9.0 (6.0 to 11.0)	9.0 (6.0 to 10.0)

End point values	Mepolizumab	Mepolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	69		
Units: SPPB total score				
median (inter-quartile range (Q1-Q3))	9.0 (6.0 to 11.0)	9.0 (7.0 to 11.0)		

Statistical analyses

Statistical analysis title	SPPB total score Wilcoxon rank sum test Week 4
Comparison groups	Mepolizumab v Placebo
Number of subjects included in analysis	235
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.03
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	SPPB total score Wilcoxon rank sum test Week 8
Comparison groups	Placebo v Mepolizumab

Number of subjects included in analysis	235
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.19
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	SPPB total score Wilcoxon rank sum test Week 12
Comparison groups	Placebo v Mepolizumab
Number of subjects included in analysis	235
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	SPPB total score Wilcoxon rank sum test Week 24
Comparison groups	Placebo v Mepolizumab
Number of subjects included in analysis	235
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	SPPB total score Wilcoxon rank sum test Week 36
Comparison groups	Placebo v Mepolizumab
Number of subjects included in analysis	235
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.52
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	SPPB total score Wilcoxon rank sum test Week 48
Comparison groups	Placebo v Mepolizumab
Number of subjects included in analysis	235
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2
Method	Wilcoxon (Mann-Whitney)

Secondary: Handgrip Strength	
End point title	Handgrip Strength

End point description:

End point type	Secondary

End point timeframe:

(Week 0 and) Week-4, Week-8, Week-12, Week-24, Week-36 & Week-48

End point values	Placebo	Mepolizumab	Placebo	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	114	115	98	85
Units: Hand grip strength				
arithmetic mean (standard deviation)	24.9 (± 9.3)	27.3 (± 9.0)	25.6 (± 9.1)	25.1 (± 8.9)

End point values	Placebo	Placebo	Placebo	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	84	77	66	74
Units: Hand grip strength				
arithmetic mean (standard deviation)	25.0 (± 9.8)	26.6 (± 9.8)	26.8 (± 10.1)	26.7 (± 10.3)

End point values	Mepolizumab	Mepolizumab	Mepolizumab	Mepolizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	103	90	80	73
Units: Hand grip strength				
arithmetic mean (standard deviation)	27.6 (± 9.6)	27.4 (± 9.6)	27.8 (± 9.6)	28.3 (± 10.0)

End point values	Mepolizumab	Mepolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	69		
Units: Hand grip strength				
arithmetic mean (standard deviation)	28.4 (± 11.0)	28.4 (± 10.7)		

Statistical analyses

Statistical analysis title	Hand grip strength- mixed effect linear model

Statistical analysis description:

A mixed effect linear model with dependent variable of the outcome at baseline and follow-up time

points; explanatory variables of treatment arm, baseline MRC dyspnoea score (≤3, >3) and past hospitalisation in the previous 12 months (0, ≥1) (Stratification factors), visit time point (as categorical variable), baseline score; an interaction term between treatment and visit; and patient identification as a random effect was fitted for each outcome.

Comparison groups	Placebo v Mepolizumab
Number of subjects included in analysis	229
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.913
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.83
upper limit	0.93

Secondary: Sputum Eosinophil Count (percentage)

End point title	Sputum Eosinophil Count (percentage)
End point description:	
End point type	Secondary
End point timeframe:	
(Week 0 and) Week-4, Week-8, Week-12, Week-24, Week-36 & Week-48	

End point values	Placebo	Mepolizumab	Placebo	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	42	38	45	41
Units: Sputum Eosinophil Count (%)				
geometric mean (standard error)	0.68 (± 0.224)	0.75 (± 0.235)	0.84 (± 0.182)	0.90 (± 0.219)

End point values	Placebo	Placebo	Placebo	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	43	38	36	34
Units: Sputum Eosinophil Count (%)				
geometric mean (standard error)	0.70 (± 0.198)	0.91 (± 0.215)	0.56 (± 0.187)	0.69 (± 0.210)

End point values	Mepolizumab	Mepolizumab	Mepolizumab	Mepolizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	32	33	28	27

Units: Sputum Eosinophil Count (%)				
geometric mean (standard error)	0.47 (± 0.216)	0.48 (± 0.244)	0.75 (± 0.245)	0.45 (± 0.256)

End point values	Mepolizumab	Mepolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	28		
Units: Sputum Eosinophil Count (%)				
geometric mean (standard error)	0.43 (± 0.220)	0.51 (± 0.231)		

Statistical analyses

Statistical analysis title	Sputum Eosinophil Count (%) mixed effect model

Statistical analysis description:

A mixed effect linear model with dependent variable of the outcome at baseline and follow-up time points; explanatory variables of treatment arm, baseline MRC dyspnoea score (≤3, >3) and past hospitalisation in the previous 12 months (0, ≥1) (Stratification factors), visit time point (as categorical variable), baseline score; an interaction term between treatment and visit; and patient identification as a random effect was fitted for each outcome.

Comparison groups	Placebo v Mepolizumab
Number of subjects included in analysis	80
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	Mixed models analysis
Parameter estimate	Geometric mean ratio
Point estimate	0.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	0.77

Secondary: Serum Eosinophil Count

End point title	Serum Eosinophil Count

End point description:

End point type	Secondary

End point timeframe:

(Week 0 and) Week-4, Week-8, Week-12, Week-24, Week-36 & Week-48

End point values	Placebo	Mepolizumab	Placebo	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	119	118	100	86
Units: 10^9/L				
geometric mean (standard error)	0.13 (± 0.102)	0.15 (± 0.102)	0.24 (± 0.065)	0.28 (± 0.067)

End point values	Placebo	Placebo	Placebo	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	87	81	69	75
Units: 10^9/L				
geometric mean (standard error)	0.27 (± 0.063)	0.25 (± 0.067)	0.26 (± 0.062)	0.24 (± 0.084)

End point values	Mepolizumab	Mepolizumab	Mepolizumab	Mepolizumab
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	99	87	82	76
Units: 10^9/L				
geometric mean (standard error)	0.08 (± 0.066)	0.07 (± 0.066)	0.07 (± 0.065)	0.08 (± 0.069)

End point values	Mepolizumab	Mepolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	70		
Units: 10^9/L				
geometric mean (standard error)	0.07 (± 0.065)	0.07 (± 0.087)		

Statistical analyses

Statistical analysis title	Serum Eosinophil count mixed effects model

Statistical analysis description:

A mixed effect linear model with dependent variable of the outcome at baseline and follow-up time points; explanatory variables of treatment arm, baseline MRC dyspnoea score (≤3, >3) and past hospitalisation in the previous 12 months (0, ≥1) (Stratification factors), visit time point (as categorical variable), baseline score; an interaction term between treatment and visit; and patient identification as a random effect was fitted for each outcome.

Comparison groups	Placebo v Mepolizumab
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Geometric mean ratio
Point estimate	0.29

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.26
upper limit	0.34

Secondary: Adverse Event Rate in the 48 Weeks of the Trial From First Dose

End point title	Adverse Event Rate in the 48 Weeks of the Trial From First Dose

End point description:

End point type	Secondary

End point timeframe:

Patients were followed up for up to 48 weeks (an absolute maximum of 49 weeks as the 48 week visit had a visit window of +- 1 week) i.e. at any point during trial post randomisation.

End point values	Placebo	Mepolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	118		
Units: Individuals at least 1 (nonserious) AE				
At least one (non-serious) AE	91	91		
No (non-serious) AEs	28	27		

Statistical analyses

Statistical analysis title	Adverse event rate

Statistical analysis description:

Calculated using generalized linear model (assuming negative binomial distribution) adjusting for the baseline MRC dyspnoea score (≤3, >3) and past hospitalisation in the previous 12 months (0, ≥1) (stratification factors) and log-time on treatment (in weeks) as an offset.

Comparison groups	Mepolizumab v Placebo
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.07
Method	t-test, 2-sided
Parameter estimate	Incidence Rate Ratio
Point estimate	1.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.98
upper limit	1.56

Secondary: Serious adverse Event Rate in the 48 Weeks of the Trial From First Dose

End point title	Serious adverse Event Rate in the 48 Weeks of the Trial From First Dose

End point description:

End point type	Secondary

End point timeframe:

Patients were followed up for up to 48 weeks (an absolute maximum of 49 weeks as the 48 week visit had a visit window of +- 1 week) i.e. at any point during trial post randomisation.

End point values	Placebo	Mepolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	118		
Units: Serious adverse event rate				
At least 1 SAE during trial	3	2		
No SAEs during trial	116	116		

Statistical analyses

Statistical analysis title	SAEs rate

Statistical analysis description:

Calculated using generalized linear model (assuming negative binomial distribution) adjusting for the baseline MRC dyspnoea score (≤3, >3) and past hospitalisation in the previous 12 months (0, ≥1) (stratification factors) and log-time on treatment (in weeks) as an offset.

Comparison groups	Placebo v Mepolizumab
Number of subjects included in analysis	237
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.686
Method	t-test, 2-sided
Parameter estimate	Incidence Rate Ratio
Point estimate	0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.12
upper limit	4.14

Secondary: Clinical Assessments- Pre-Dose Systolic BP

End point title	Clinical Assessments- Pre-Dose Systolic BP

End point description:

End point type	Secondary

End point timeframe:

Patients were followed up for up to 48 weeks (an absolute maximum of 49 weeks as the 48 week visit had a visit window of +- 1 week).

End point values	Placebo	Mepolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	118		
Units: mmHg				
arithmetic mean (standard deviation)	130.2 (± 19.4)	129.7 (± 18.5)		

Statistical analyses

Statistical analysis title	Pre-Dose Systolic BP- mixed effect linear model

Statistical analysis description:

A mixed effect linear model with dependent variable of the outcome at baseline and follow-up time points; explanatory variables of treatment arm, baseline MRC dyspnoea score (≤3, >3) and past hospitalisation in the previous 12 months (0, ≥1) (Stratification factors), visit time point (as categorical variable), baseline score; an interaction term between treatment and visit; and patient identification as a random effect was fitted for each outcome.

Comparison groups	Placebo v Mepolizumab
Number of subjects included in analysis	235
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.585
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.02
upper limit	2.27

Secondary: Clinical Assessments- Pre-Dose Diastolic BP

End point title	Clinical Assessments- Pre-Dose Diastolic BP

End point description:

End point type	Secondary

End point timeframe:

Patients were followed up for up to 48 weeks (an absolute maximum of 49 weeks as the 48 week visit had a visit window of +- 1 week).

End point values	Placebo	Mepolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	118		
Units: mmHg				
arithmetic mean (standard deviation)	73.2 (± 13.2)	73.1 (± 11.8)		

Statistical analyses

Statistical analysis title	Pre-Dose Diastolic BP- mixed effect linear model

Statistical analysis description:

A mixed effect linear model with dependent variable of the outcome at baseline and follow-up time points; explanatory variables of treatment arm, baseline MRC dyspnoea score (≤3, >3) and past hospitalisation in the previous 12 months (0, ≥1) (Stratification factors), visit time point (as categorical variable), baseline score; an interaction term between treatment and visit; and patient identification as a random effect was fitted for each outcome.

Comparison groups	Placebo v Mepolizumab
Number of subjects included in analysis	235
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.506
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.61
upper limit	1.29

Secondary: Clinical Assessments- Pre-Dose Heart Rate

End point title	Clinical Assessments- Pre-Dose Heart Rate

End point description:

End point type	Secondary

End point timeframe:

Patients were followed up for up to 48 weeks (an absolute maximum of 49 weeks as the 48 week visit had a visit window of +- 1 week).

End point values	Placebo	Mepolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	118		
Units: bpm				
arithmetic mean (standard deviation)	81.4 (± 14.1)	81.8 (± 13.5)		

Statistical analyses

Statistical analysis title	Pre-Dose Heart Rate- mixed effect linear model

Statistical analysis description:

A mixed effect linear model with dependent variable of the outcome at baseline and follow-up time points; explanatory variables of treatment arm, baseline MRC dyspnoea score (≤3, >3) and past hospitalisation in the previous 12 months (0, ≥1) (Stratification factors), visit time point (as categorical variable), baseline score; an interaction term between treatment and visit; and patient identification as a random effect was fitted for each outcome.

Comparison groups	Placebo v Mepolizumab
Number of subjects included in analysis	235
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.423
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.03
upper limit	1.27

Secondary: Clinical Assessments- Pre-Dose Temperature

End point title	Clinical Assessments- Pre-Dose Temperature

End point description:

End point type	Secondary

End point timeframe:

Patients were followed up for up to 48 weeks (an absolute maximum of 49 weeks as the 48 week visit had a visit window of +- 1 week).

End point values	Placebo	Mepolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	118		
Units: °C				
arithmetic mean (standard deviation)	36.4 (± 0.4)	36.4 (± 0.4)		

Statistical analyses

Statistical analysis title	Pre-Dose Temperature- mixed effect linear model

Statistical analysis description:

A mixed effect linear model with dependent variable of the outcome at baseline and follow-up time points; explanatory variables of treatment arm, baseline MRC dyspnoea score (≤3, >3) and past hospitalisation in the previous 12 months (0, ≥1) (Stratification factors), visit time point (as categorical variable), baseline score; an interaction term between treatment and visit; and patient identification as a random effect was fitted for each outcome.

Comparison groups	Placebo v Mepolizumab
Number of subjects included in analysis	235
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.981
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.07
upper limit	0.07

Secondary: Clinical Assessments- Post-Dose Systolic BP

End point title	Clinical Assessments- Post-Dose Systolic BP

End point description:

End point type	Secondary

End point timeframe:

Patients were followed up for up to 48 weeks (an absolute maximum of 49 weeks as the 48 week visit had a visit window of +- 1 week).

End point values	Placebo	Mepolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	118	117		
Units: mmHg				
arithmetic mean (standard deviation)	128.1 (± 19.6)	127.4 (± 17.6)		

Statistical analyses

Statistical analysis title	Post-Dose Systolic BP- mixed effect linear model

Statistical analysis description:

A mixed effect linear model with dependent variable of the outcome at baseline and follow-up time points; explanatory variables of treatment arm, baseline MRC dyspnoea score (≤3, >3) and past hospitalisation in the previous 12 months (0, ≥1) (Stratification factors), visit time point (as categorical variable), baseline score; an interaction term between treatment and visit; and patient identification as a random effect was fitted for each outcome.

Comparison groups	Placebo v Mepolizumab
Number of subjects included in analysis	235
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.58
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.46
upper limit	1.94

Secondary: Clinical Assessments- Post-Dose Diastolic BP

End point title	Clinical Assessments- Post-Dose Diastolic BP

End point description:

End point type	Secondary

End point timeframe:

Patients were followed up for up to 48 weeks (an absolute maximum of 49 weeks as the 48 week visit had a visit window of +- 1 week).

End point values	Placebo	Mepolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	117		
Units: mmHg				
arithmetic mean (standard deviation)	71.9 (± 13.4)	72.3 (± 11.6)		

Statistical analyses

Statistical analysis title	Post-Dose Diastolic BP- mixed effect linear model

Statistical analysis description:

A mixed effect linear model with dependent variable of the outcome at baseline and follow-up time points; explanatory variables of treatment arm, baseline MRC dyspnoea score (≤3, >3) and past hospitalisation in the previous 12 months (0, ≥1) (Stratification factors), visit time point (as categorical variable), baseline score; an interaction term between treatment and visit; and patient identification as

a random effect was fitted for each outcome.

Comparison groups	Placebo v Mepolizumab
Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.729
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.68
upper limit	2.41

Secondary: Clinical Assessments- Post-Dose Heart Rate

End point title	Clinical Assessments- Post-Dose Heart Rate

End point description:

End point type	Secondary

End point timeframe:

Patients were followed up for up to 48 weeks (an absolute maximum of 49 weeks as the 48 week visit had a visit window of +- 1 week).

End point values	Placebo	Mepolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	117		
Units: bpm				
arithmetic mean (standard deviation)	79.8 (± 14.4)	79.6 (± 14.1)		

Statistical analyses

Statistical analysis title	Post-Dose Heart Rate- mixed effect linear model

Statistical analysis description:

A mixed effect linear model with dependent variable of the outcome at baseline and follow-up time points; explanatory variables of treatment arm, baseline MRC dyspnoea score (≤3, >3) and past hospitalisation in the previous 12 months (0, ≥1) (Stratification factors), visit time point (as categorical variable), baseline score; an interaction term between treatment and visit; and patient identification as a random effect was fitted for each outcome.

Comparison groups	Placebo v Mepolizumab

Number of subjects included in analysis	234
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.24
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-1.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.24
upper limit	0.86

Secondary: Clinical Assessments- Post-Dose Temperature

End point title	Clinical Assessments- Post-Dose Temperature

End point description:

End point type	Secondary

End point timeframe:

Patients were followed up for up to 48 weeks (an absolute maximum of 49 weeks as the 48 week visit had a visit window of +- 1 week).

End point values	Placebo	Mepolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115	117		
Units: °C				
arithmetic mean (standard deviation)	36.5 (± 0.4)	36.5 (± 0.4)		

Statistical analyses

Statistical analysis title	Post-Dose Temperature- mixed effect linear model

Statistical analysis description:

A mixed effect linear model with dependent variable of the outcome at baseline and follow-up time points; explanatory variables of treatment arm, baseline MRC dyspnoea score (≤3, >3) and past hospitalisation in the previous 12 months (0, ≥1) (Stratification factors), visit time point (as categorical variable), baseline score; an interaction term between treatment and visit; and patient identification as a random effect was fitted for each outcome.

Comparison groups	Placebo v Mepolizumab
Number of subjects included in analysis	232
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.946
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.002

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.07
upper limit	0.07

Secondary: Moderate exacerbations per participant in 48-weeks

End point title	Moderate exacerbations per participant in 48-weeks

End point description:

End point type	Secondary

End point timeframe:

The rate of moderate exacerbations each participant had over the course of observed time period for each participant (maximum trial duration for a patient was 49 weeks (48 weeks + 7 days))

End point values	Placebo	Mepolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	119		
Units: Moderate exacerbation rate in 48 weeks				
arithmetic mean (standard deviation)	2.22 (± 2.24)	1.83 (± 1.78)		

Statistical analyses

Statistical analysis title	mITT analysis of moderate exacerbation in 48 week

Statistical analysis description:

Calculated using generalized linear model (assuming negative binomial distribution) adjusting for the baseline MRC dyspnoea score (≤3, >3) and past hospitalisation in the previous 12 months (0, ≥1) (stratification factors) and log-time on treatment (in weeks) as an offset.

Comparison groups	Placebo v Mepolizumab
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.14
Method	t-test, 2-sided
Parameter estimate	Rate Ratio
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	1.06

Secondary: Hospital readmissions per participant in 48 weeks

End point title	Hospital readmissions per participant in 48 weeks

End point description:

End point type	Secondary

End point timeframe:

The rate of hospital readmissions each participant had over the course of observed time period for each participant (maximum trial duration for a patient was 49 weeks (48 weeks + 7 days))

End point values	Placebo	Mepolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	119		
Units: Hospital readmission rate in 48 weeks				
arithmetic mean (standard deviation)	1.77 (± 2.88)	1.54 (± 2.18)		

Statistical analyses

Statistical analysis title	mITT analysis of hospital readmissions in 48 weeks

Statistical analysis description:

Calculated using generalized linear model (assuming negative binomial distribution) adjusting for the baseline MRC dyspnoea score (≤3, >3) and past hospitalisation in the previous 12 months (0, ≥1) (stratification factors) and log-time on treatment (in weeks) as an offset.

Comparison groups	Placebo v Mepolizumab
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.505
Method	t-test, 2-sided
Parameter estimate	Rate ratio
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	1.25

Secondary: Severe exacerbations per participant in the 48 weeks

End point title	Severe exacerbations per participant in the 48 weeks

End point description:

End point type	Secondary

End point timeframe:

The rate of severe exacerbations each participant had over the course of observed time period for each participant (maximum trial duration for a patient was 49 weeks (48 weeks + 7 days))

End point values	Placebo	Mepolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	119		
Units: Severe exacerbation rate in 48 weeks				
arithmetic mean (standard deviation)	1.20 (± 2.36)	0.91 (± 1.76)		

Statistical analyses

Statistical analysis title	mITT analysis of severe exacerbation in 48 week

Statistical analysis description:

Calculated using generalized linear model (assuming negative binomial distribution) adjusting for the baseline MRC dyspnoea score (≤3, >3) and past hospitalisation in the previous 12 months (0, ≥1) (stratification factors) and log-time on treatment (in weeks) as an offset.

Comparison groups	Placebo v Mepolizumab
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.263
Method	t-test, 2-sided
Parameter estimate	Rate ratio
Point estimate	0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	1.2

Secondary: Moderate and/or Severe exacerbations per participant in the 48 weeks

End point title	Moderate and/or Severe exacerbations per participant in the 48 weeks

End point description:

End point type	Secondary

End point timeframe:

The rate of exacerbation each participant had over the course of observed time period for each participant (maximum trial duration for a patient was 49 weeks (48 weeks + 7 days))

End point values	Placebo	Mepolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	119		
Units: Exacerbation rate in 48 weeks				
arithmetic mean (standard deviation)	3.42 (± 3.08)	2.74 (± 2.36)		

Statistical analyses

Statistical analysis title	mITT analysis of exacerbation frequency in 48 week

Statistical analysis description:

Calculated using generalized linear model (assuming negative binomial distribution) adjusting for the baseline MRC dyspnoea score (≤3, >3) and past hospitalisation in the previous 12 months (0, ≥1) (stratification factors) and log-time on treatment (in weeks) as an offset.

Comparison groups	Placebo v Mepolizumab
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.054
Method	t-test, 2-sided
Parameter estimate	Rate ratio
Point estimate	0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	1

Secondary: Death (respiratory cause)

End point title	Death (respiratory cause)

End point description:

Respiratory cause death. Number of individuals that died during follow up is reported. Death due to respiratory cause was analysed as a time to event outcome.

End point type	Secondary

End point timeframe:

Patients were followed up for up to 48 weeks (48 week visit had a window of +- 1 week).

End point values	Placebo	Mepolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	119		
Units: Number				
number (not applicable)	8	5		

Statistical analyses

Statistical analysis title	Time to death (respiratory cause)

Statistical analysis description:

The analysis took place on the intention to treat population. The Cox proportional hazard model was used for the primary outcome of the time to re-hospitalisation or death (any cause) as the dependent variable. The treatment group served as an explanatory factor, while baseline MRC dyspnoea score (≤3, >3) and past hospitalisation in the previous 12 months (0, ≥1) were included as stratification factors.

Comparison groups	Placebo v Mepolizumab
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.432
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.21
upper limit	1.95

Secondary: Death (all cause)

End point title	Death (all cause)

End point description:

All cause death. Number of individuals that died during follow up is reported. Death due to all cause was analysed as a time to event outcome.

End point type	Secondary

End point timeframe:

Patients were followed up for up to 48 weeks (48 week visit had a window of +- 1 week).

End point values	Placebo	Mepolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	119		
Units: Number				
number (not applicable)	11	9		

Statistical analyses

Statistical analysis title	Time from randomisation to death (all cause)

Statistical analysis description:

The analysis took place on the intention to treat population. The Cox proportional hazard model was used for the primary outcome of the time to re-hospitalisation or death (any cause) as the dependent variable. The treatment group served as an explanatory factor, while baseline MRC dyspnoea score (≤3, >3) and past hospitalisation in the previous 12 months (0, ≥1) were included as stratification factors.

Comparison groups	Placebo v Mepolizumab
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.705
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.35
upper limit	2.04

Secondary: Hospital readmission (respiratory cause)

End point title	Hospital readmission (respiratory cause)

End point description:

Hospital readmission (respiratory cause). Number of individuals that hospitalised due to respiratory cause during follow up is reported. Hospital readmission due to respiratory cause was analysed as a time to event outcome.

End point type	Secondary

End point timeframe:

Patients were followed up for up to 48 weeks (48 week visit had a window of +- 1 week).

End point values	Placebo	Mepolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	119		
Units: Number				
number (not applicable)	55	52		

Statistical analyses

Statistical analysis title	Time to next hospital readmission (respiratory)

Statistical analysis description:

The analysis took place on the intention to treat population. The Cox proportional hazard model was used for the primary outcome of the time to re-hospitalisation or death (any cause) as the dependent variable. The treatment group served as an explanatory factor, while baseline MRC dyspnoea score (≤3, >3) and past hospitalisation in the previous 12 months (0, ≥1) were included as stratification factors.

Comparison groups	Placebo v Mepolizumab

Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.759
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	1.38

Secondary: Time from randomisation to next hospital readmission or death due to a respiratory cause

End point title	Time from randomisation to next hospital readmission or death due to a respiratory cause

End point description:

End point type	Secondary

End point timeframe:

Patients were followed up for up to 48 weeks (an absolute maximum of 49 weeks as the 48 week visit had a visit window of +- 1 week).

End point values	Placebo	Mepolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	119		
Units: Weeks				
median (confidence interval 95%)	25.7 (20.1 to 39.0)	24.4 (17.9 to 33.0)		

Statistical analyses

Statistical analysis title	Time to next hospital readmission or death (resp)

Statistical analysis description:

The analysis is the same as for the primary outcome because where the first event is death, this was always due to respiratory causes.

Comparison groups	Placebo v Mepolizumab
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.811
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.96

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	1.32

Secondary: Time from randomisation to next hospital readmission (all cause)

End point title	Time from randomisation to next hospital readmission (all cause)

End point description:

End point type	Secondary

End point timeframe:

Patients were followed up for up to 48 weeks (an absolute maximum of 49 weeks as the 48 week visit had a visit window of +- 1 week).

End point values	Placebo	Mepolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	119		
Units: Weeks				
median (confidence interval 95%)	27.9 (20.4 to 40.9)	24.4 (17.9 to 33.0)		

Statistical analyses

Statistical analysis title	Time to next hospital readmission (all cause)

Statistical analysis description:

The analysis took place on the intention to treat population. The Cox proportional hazard model was used for the primary outcome of the time to re-hospitalisation or death (any cause) as the dependent variable. The treatment group served as an explanatory factor, while baseline MRC dyspnoea score (≤3, >3) and past hospitalisation in the previous 12 months (0, ≥1) were included as stratification factors.

Comparison groups	Placebo v Mepolizumab
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.938
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	1.36

Secondary: Time from randomisation to treatment failure

End point title	Time from randomisation to treatment failure

End point description:

Treatment failure is defined as the composite of three endpoints: 1. treatment intensification with systemic corticosteroids and/or antibiotics for respiratory reasons; 2. step-up in hospital care for respiratory reasons including transfer to the intensive care unit or readmission; or 3. all-cause mortality)

End point type	Secondary

End point timeframe:

Patients were followed up for up to 48 weeks (an absolute maximum of 49 weeks as the 48 week visit had a visit window of +- 1 week).

End point values	Placebo	Mepolizumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	119		
Units: Weeks				
median (confidence interval 95%)	10.0 (7.71 to 12.6)	12.9 (10.1 to 15.7)		

Statistical analyses

Statistical analysis title	Time from randomisation to treatment failure

Statistical analysis description:

The analysis took place on the intention to treat population. The Cox proportional hazard model was used for the primary outcome of the time to re-hospitalisation or death (any cause) as the dependent variable. The treatment group served as an explanatory factor, while baseline MRC dyspnoea score (≤3, >3) and past hospitalisation in the previous 12 months (0, ≥1) were included as stratification factors.

Comparison groups	Placebo v Mepolizumab
Number of subjects included in analysis	238
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.849
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.74
upper limit	1.28

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected for the duration of the study until the final trial visit (week 48/Final Follow-up) or 28 days post cessation of trial treatment where this occurs earlier than protocolised.

Adverse event reporting additional description:

Participants were asked about AEs at each study visits and they were recorded on a participant specific AE log.
SAEs/SUSARs: reported to Sponsor and Leicester CTU within 24 hours of research staff learning of the event.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Participants randomised to a matched placebo.

Reporting group title	Mepolizumab

Reporting group description:

Participants randomised to receive monthly subcutaneous injections of 100 mg mepolizumab.

Serious adverse events	Placebo	Mepolizumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 119 (2.52%)	2 / 118 (1.69%)	
number of deaths (all causes)	11	9	
number of deaths resulting from adverse events	3	2	
Vascular disorders			
Aortic aneurysm rupture			
subjects affected / exposed	0 / 119 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac disorders			
Congestive heart failure			
subjects affected / exposed	0 / 119 (0.00%)	1 / 118 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
General disorders and administration site conditions			
Multiple organ dysfunction syndrome			

subjects affected / exposed	1 / 119 (0.84%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Death due to COPD			
subjects affected / exposed	2 / 119 (1.68%)	0 / 118 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	

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

Non-serious adverse events	Placebo	Mepolizumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 119 (22.69%)	34 / 118 (28.81%)	
Investigations			
Liver function test abnormal			
subjects affected / exposed	2 / 119 (1.68%)	6 / 118 (5.08%)	
occurrences (all)	3	6	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	9 / 119 (7.56%)	8 / 118 (6.78%)	
occurrences (all)	11	10	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	5 / 119 (4.20%)	6 / 118 (5.08%)	
occurrences (all)	5	6	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	9 / 119 (7.56%)	12 / 118 (10.17%)	
occurrences (all)	11	20	
Infections and infestations			
COVID-19			
subjects affected / exposed	7 / 119 (5.88%)	8 / 118 (6.78%)	
occurrences (all)	7	8	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 January 2020	SA01: • Section viii Key Words – correction of Phase III to Phase IIb. • Section 7.7.4 Visit 13 – Reinstated urine pregnancy test that was removed in version 3.0. This is required at end of IMP exposure. • Section 8.11 – Addition to final sentence of 3rd paragraph to clarify requirement for urine pregnancy test at Visit 13. • Appendix 1 – add urine pregnancy test to Visit 13 in schedule procedures. • Appendix 1 – correction to safety & tolerability measures. AE/SAEs were removed in error in previous version with the removal of safety blood samples from visits 5&6, 8&9, 11&12. These have now been reinstated.
06 March 2020	SA02: • Section 7.2 Informed Consent – Amendment made to first sentence of second paragraph to include participants that may be admitted and discharged within one week. Wording changed from 'Due to the nature of the study (acute illness resulting in hospitalisation), the participant can be consented at any point within their inpatient stay, or within one week of their index hospital admission' to 'Due to the nature of the study (acute illness resulting in hospitalisation), the participant can be consented at any point within their inpatient stay, or within one week of discharge'. • Section 7.2.1 – Title amended from 'Additional consent for biological specimens' to 'Additional consent for biological specimens and future research'. 'Anonymised' changed to 'pseudonymised'. Additional paragraph included to describe the linking of outcomes of this trial with environmental exposure listed in the optional section of the Informed Consent Form. The PIS has also been amended to reflect this as it was removed in error during the response to the Provisional Opinion. • Appendix 1 Schedule of procedures – reinstatement of safety blood samples from visits 5&6, 8&9, 11&12 that were removed in error in Protocol version 3.0 (17/10/2019) as part of the response to Provisional Opinion. These have been reinstated to correct the inconsistency with the body text (Section 7.7.3).

21 June 2021	SA03: • Section 9.2 - SAEs will be reported following first administration of IMP/placebo rather than following consent. Section 9.1 – clarification provided on events that are clinical outcomes. Section 9.3 – the causality and relatedness assessment may be performed by the PI or a suitably trained delegate (does not require an unblinded doctor). Section 9.4 - clarification provided on notification of deaths. • Section 6.1 and trial summary table: > has been changed to ≥ for the following inclusion criterion: '4. Smoking pack years ≥ 10 years'. • Section 7.7.1 & Appendix 1 - the current (exacerbated state) eMRC score is to be collected at visit 1 in addition to their baseline eMRC score (stable state). • Sections 7.7, 7.8 & Appendix 1 – Clarification that trial assessments (e.g. Quality of Life/Symptoms Assessments) may be completed remotely by telephone consultation, where possible, and when necessary. • Section 7.10 – Pandemic guidance section added. • Sections 3.4.3 and 7.9 – corrections confirming DNA for analysis will only be taken from blood samples at week 0; RNA analysis will occur on blood samples taken at weeks 0, 4, 8, 12, 24, 36, 48. • Section 7.9 - correction to confirm blood tests for Trop I and BNP blood are not stored for the purposes of the study and are either used or destroyed during the testing process. • Section 13.5 - protocol deviations are not required for instances where a participant is unable to produce a sample or for assessments omitted due to a pandemic. • Section 7.7.4 - participants that have discontinued treatment early (prior to visit 12) will be invited back to hospital for visit 13 assessments.
04 July 2022	SA04: There have been several occasions where participants have missed trial visits without contacting the research team, and the research team has been unable to contact the participant by telephone within the window for their visit, if at all. A number of participants have been discontinued because of this, and the research team suggested if they tried writing to the participant for a response, they could demonstrate that every effort had been made to retain them. Therefore a participant contact letter has been devised for this purpose. It has been made clear within the letter that participants are free to discontinue without giving a reason, and that their decision to discontinue will not affect the standard of medical care they receive.
26 October 2022	SA05: • Removal of COVID-19 omitted procedures: o Faecal sample o Post-BD (FEV1/FVC) Spirometry o Oscillometry o Breath volatile organic compounds o Induced sputum samples o Throat swab (viral PCR) o Nasal epithelial sampling • Clarification that only spontaneous sputum samples are collected as part of standard care • Update to study timelines (recruitment, total study duration) in line with funding extension • Update to wording around indemnity (section 13.10) per Sponsor’s request • Update to statistician information

06 February 2023	SA06: • Truncated follow-up for participant recruitment from April 2023 added to protocol and all applicable sections (schedule of events, etc.) amended to reflect new follow-up schedule • Visit 13 also named Final Follow-up for those in the truncated follow-up phase of the trial; patients recruited from April 2023 to September 2023 will be consented to a truncated follow-up model, whereby last patient last visit will remain the same. This will result in participants consented in April to have up to the 44-week follow-up, those in May will have up to the 40-week follow-up, and so on. Patients will be dosed for a minimum of 24 weeks, with secondary outcomes measured as per original timelines (baseline, 4 weeks, 8 weeks, etc.) however final outcome measures normally measured at 48 weeks will occur 4 weeks ± 7 days of final dosing visit.
12 September 2023	SA07: Change to IMP constitution for participants dosed from 01 March 2024 due to funder stock supplies; IMP changed from mepolizumab powder reconstituted to mepolizumab in a pre-filled syringe. Dosing and regime to remain the same - updated details in protocol and new SmPC for drug constitution.
22 January 2024	SA08: Submission for the approval of the new IMP constitution and matched placebo following GNA for SA07 from the MHRA. The change of IMP from a powder reconstituted to a pre-filled syringe, with the placebo changed from saline to a pre-filled syringe matched placebo, was previously submitted and approved by REC via SA07. This SA08 is to re-submit for approval protocol v9.0 12-09-2023, PIS v2.0 12-09-2023 and Nucala 100mg SMPC (23/05/2023), all of which are unchanged from SA07. The newly included documents address the GNA of the MHRA and include the cross-referral letter for placebo IMPD, and labels for new IMP and placebo syringes.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported