Clinical trial results:
OPTIMAL - Titration of treatment with biologics in severe asthma

Summary

EudraCT number	2020-003358-63
Trial protocol	DK
Global end of trial date	28 September 2023

Results information

Result version number	v1 (current)
This version publication date	28 January 2024
First version publication date	28 January 2024

Trial information

Trial identification

Sponsor protocol code	2020033183.

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04648761
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bispebjerg Hospital
Sponsor organisation address	Ebba Lunds Vej 48, Copenhagen NV, Denmark, 2400
Public contact	Lungemedicinsk Forskningsenhed, Bispebjerg Hospital, +45 38635122,
Scientific contact	Lungemedicinsk Forskningsenhed, Bispebjerg Hospital, +45 38635122,

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	27 September 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 September 2023
Global end of trial reached?	Yes
Global end of trial date	28 September 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of the OPTIMAL study is to is to examine the OPTIMAL algorithm as a clinical tool for safe dose titration of biologics in patients with severe asthma. We will investigate if treatment with biologics can be stepped down or even terminated in some patients without loss of disease control. We will investigate possible predictors of successful dose tapering in order to identify patients who are can have their dosage tapered and those who cannot. The OPTIMAL study will also describe potential adverse effects of stepping down or discontinuing treatment. The OPTIMAL study will focus on biologics with an anti-IL5/IL5r effect. We will also describe immunological changes during dosetitration.

Protection of trial subjects:

All patients were on high dose ICS during the trial

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 January 2021
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	Denmark: 73
Worldwide total number of subjects	73
EEA total number of subjects	73

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)	46
From 65 to 84 years	27

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruited from respiratory outpatient clinical at the five participating centers in Denmark

Pre-assignment

Screening details:

Patient eligable for the trial were on an anti-IL5 biologic (mepolizumab, benralizumab or reslizumab) and had been free from exacerbations of oral corticosteroid use in the 12 moths before inclusion.

Period 1

Period 1 title	January 13th 2021 - September 27th 2023 (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

The study was open-label

Arms

Are arms mutually exclusive?	Yes
Arm title	Control arm

Arm description:

Patients randomised to continue biological treatment withput intervention

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Active arm

Arm description:

Randomised to have intervals between biological treatment adjusted by the OPTIMAL titration algorithm

Arm type	Experimental
Investigational medicinal product name	Mepolizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for dispersion for injection
Routes of administration	Injection

Dosage and administration details:

To be adjusted via the OPTIMAL titration algorithm

Investigational medicinal product name	Benralizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for dispersion for injection
Routes of administration	Injection

Dosage and administration details:

Ti be adjusted via the OPTIMAL titration algorithm

Number of subjects in period 1	Control arm	Active arm
Started	36	37
Completed	35	37
Not completed	1	0
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Control arm
Reporting group description:	
Patients randomised to continue biological treatment withput intervention	
Reporting group title	Active arm
Reporting group description:	
Randomised to have intervals between biological treatment adjusted by the OPTIMAL titration algorithm	

Reporting group values	Control arm	Active arm	Total
Number of subjects	36	37	73
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Age			
Units: years			
arithmetic mean	59	61	
standard deviation	± 13	± 10	-
Gender categorical Units: Subjects			
Female	15	13	28
Male	21	24	45

Subject analysis sets	
Subject analysis set title	Control arm
Subject analysis set type	Per protocol
Subject analysis set description:	
Patient who completed the study	

Reporting group values	Control arm		
Number of subjects	35		
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			

Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
Age			
Units: years arithmetic mean standard deviation	 59 ± 13		
Gender categorical Units: Subjects			
Female Male	15 20		

End points

End points reporting groups

Reporting group title	Control arm
Reporting group description:	
Patients randomised to continue biological treatment withput intervention	
Reporting group title	Active arm
Reporting group description:	
Randomised to have intervals between biological treatment adjusted by the OPTIMAL titration algorithm	
Subject analysis set title	Control arm
Subject analysis set type	Per protocol
Subject analysis set description:	
Patient who completed the study	

Primary: Proportion of patients with an exacerbation

End point title	Proportion of patients with an exacerbation[1]
End point description:	
End point type	Primary
End point timeframe:	
During the one year follow-up	

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: I have only reported for the patients who hjave completed the study i.e. the all patient in the active arm and the sub group (35 of 36) in the control arm.

End point values	Active arm	Control arm		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	37	35		
Units: Percent	32	17		

Statistical analyses

Statistical analysis title	Chi squared test
Comparison groups	Active arm v Control arm
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.13
Method	Chi-squared
Parameter estimate	Proportion

Secondary: Ability to titrate in active arm

End point title	Ability to titrate in active arm[2]

End point description:

End point type	Secondary

End point timeframe:

At the end of the trial

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only relevant in the active arm.

End point values	Active arm			
Subject group type	Reporting group			
Number of subjects analysed	37			
Units: Percent				
Uanble to titrate	22			
Interval increase of 50 %	18			
Interval increase of 125 %	38			
Cessation of treatment	22			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

January 13th 2021 to September 27th 2023

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	1

Reporting groups

Reporting group title	All patients

Reporting group description: -

Serious adverse events	All patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 72 (8.33%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Mesothelioma malignant			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Aortic valve stenosis			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Cervical spinal stenosis			

subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Borrelia infection			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	All patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 72 (22.22%)		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
General disorders and administration site conditions			
Nephrolithiasis			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
International normalised ratio increased			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
Epistaxis			
subjects affected / exposed	1 / 72 (1.39%)		
occurrences (all)	1		
Endocrine disorders			

Hypokalaemia subjects affected / exposed occurrences (all)	2 / 72 (2.78%) 2		
Musculoskeletal and connective tissue disorders Trigger finger subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all) Cramp-fasciculation syndrome subjects affected / exposed occurrences (all) Fracture subjects affected / exposed occurrences (all)	 1 / 72 (1.39%) 1 2 / 72 (2.78%) 2 1 / 72 (1.39%) 1 1 / 72 (1.39%) 1		
Infections and infestations COVID-19 subjects affected / exposed occurrences (all) Oral candidiasis subjects affected / exposed occurrences (all) Pneumonia subjects affected / exposed occurrences (all) Rhinitis subjects affected / exposed occurrences (all) Malaise subjects affected / exposed occurrences (all)	 1 / 72 (1.39%) 1 1 / 72 (1.39%) 1 1 / 72 (1.39%) 1 1 / 72 (1.39%) 1 1 / 72 (1.39%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 November 2022	Reduction of requried participant from 150 to 74

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported