Clinical trial results:
SIGNATURE - the 6-gene signature as a predictor of response to treatment in severe asthma and ACOS

Summary

EudraCT number	2017-000495-28
Trial protocol	DK
Global end of trial date	30 June 2019

Results information

Result version number	v1 (current)
This version publication date	06 January 2021
First version publication date	06 January 2021

Trial information

Trial identification

Sponsor protocol code	132

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Respiratory Research Unit
Sponsor organisation address	Ebba Lunds Vej 48, Copenhagen NV, Denmark, 2400
Public contact	Celeste Porsbjerg, Respiratory Research Unit, Bispebjerg University Hospital, laurits.froessing@regionh.dk
Scientific contact	Celeste Porsbjerg, Respiratory Research Unit, Bispebjerg University Hospital, laurits.froessing@regionh.dk

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	30 November 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 June 2019
Global end of trial reached?	Yes
Global end of trial date	30 June 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial is to develop a tool able to predict response to oral corticosteroids in patients with severe asthma or ACOS using the 6-gene signature.

Protection of trial subjects:

Patients were thoroughly informed of the side effects of the intervention (oral corticosteroids) and were encouraged to contact the study team if any symptoms arose.

Background therapy:

All patients received maintenance therapy for asthma included but not limited to inhaled corticosteroids and long acting beta2 agonists.

Evidence for comparator: -

Actual start date of recruitment	01 March 2017
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: 81
Worldwide total number of subjects	81
EEA total number of subjects	81

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)	60
From 65 to 84 years	21
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited from the outpatient clinic at Bispebjerg University Hospital, Denmark.

Pre-assignment

Screening details:

This study had no run-in og screening period. Patients attending the respiratory outpatient clinic at Bispebjerg University Hospital were screened for eligibility by asking them about
* their maintenance asthma treatment
* recent exacerbations or airway infections

Pre-assignment period milestones

Number of subjects started	81
Number of subjects completed	81

Period 1

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

Arms

Arm title	Follow-up

Arm description:

Single-arm Prednisolone 37.5 mg once daily for 14 days

Arm type	Experimental
Investigational medicinal product name	Prednisolon DAK
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

37.5 mg once daily for 14 days
Administered as 1.5 tbl of 25mg.

Number of subjects in period 1	Follow-up
Started	81
Completed	75
Not completed	6
Consent withdrawn by subject	5
Adverse event, non-fatal	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall

Reporting group description: -

Reporting group values	Overall	Total	
Number of subjects	81	81	
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 Units: years			
arithmetic mean	55.6		
standard deviation	± 11.0	-	
Gender categorical Units: Subjects			
Female	38	38	
Male	43	43	

End points

End points reporting groups

Reporting group title	Follow-up
Reporting group description: Single-arm Prednisolone 37.5 mg once daily for 14 days	
Subject analysis set title	Severe asthma only
Subject analysis set type	Per protocol
Subject analysis set description: Analysis of patients with severe asthma only	
Subject analysis set title	Baseline population
Subject analysis set type	Full analysis
Subject analysis set description: Work-around as one-arm study	

Primary: Clinical improvement. Composite end point

End point title	Clinical improvement. Composite end point
End point description: Clinical response to OCS was defined using current ATS/ERS criteria(9–12): a significant change in lung function (increase in FEV1 by ≥12% and ≥200 mL (10); and/or a decrease in FeNO of 20% if baseline FeNO ≥50 ppb or a decrease of ≥10 ppb if FeNO < 50 ppb at baseline(11); and/or a change in asthma control (decrease in ACQ5 of ≥0.5) (12).	
End point type	Primary
End point timeframe: from baseline to end of study	

End point values	Follow-up	Severe asthma only	Baseline population	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	25	25	25	
Units: number				
number (not applicable)				
Improvement	4	4	4	
No improvement	21	21	21	

Attachments (see zip file)	Flow chart of included patients in composite EP/eudract flow

Statistical analyses

Statistical analysis title	Logistic regression, gene expression

Statistical analysis description:

A clinical response to OCS was observed in 68% of patients(n=25): 4% had a significant increase in FEV1, 36% had a significant decrease in FeNO, and 44% had a significant improvement in ACQ5.

Response to OCS was significantly predicted using both a combination of T2 biomarkers (FeNO, B-EOS and sputum eosinophil count; AUC 0.82, p=0.03) and expression of all T2 genes combined (AUC 0.95, p=0.002). Further, OCS response was significantly predicted by the IL-5-related genes a

Comparison groups	Follow-up v Baseline population v Severe asthma only
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.002
Method	Regression, Logistic
Parameter estimate	AUC

Notes:

[1] - Prediction of a favourable composite outcome was predicted using gene expression using the 6-gene signature which is a composite biomarker, consisting of 3 eosinophilic- (CLC, CPA3, DNASE1L3) and 3 neutrophilic genes (IL1B, ALPL and CXCR2) and the genes constituting the signature were chosen based on their ability to predict sputum eosinophilia and sputum neutrophilia, respectively.

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From inrollment in the study to end of study. No extended observation period.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	10.0

Reporting groups	
Reporting group title	Intervention
Reporting group description: Prednisolone 37.5 mg once daily for 14 days	

Serious adverse events	Intervention		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 81 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Intervention		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 81 (17.28%)		
Gastrointestinal disorders			
Increased reflux			
subjects affected / exposed	3 / 81 (3.70%)		
occurrences (all)	3		
Psychiatric disorders			
Sleep disorder			
subjects affected / exposed	10 / 81 (12.35%)		
occurrences (all)	10		
Infections and infestations			
Oral candidiasis			
subjects affected / exposed	2 / 81 (2.47%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

This study has only been analysed for the prespecified severe-asthma only sub-population.

Notes: