Clinical trial results:
A Pragmatic Proof of Concept Study to Evaluate the Effect of Benralizumab on Mannitol Challenge in Severe Eosinophilic Asthma

Summary

EudraCT number	2019-003763-22
Trial protocol	GB
Global end of trial date	01 July 2022

Results information

Result version number	v1 (current)
This version publication date	15 December 2022
First version publication date	15 December 2022

Trial information

Trial identification

Sponsor protocol code	1.027.19

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	University of Dundee - NHS Tayside
Sponsor organisation address	Residency block, level 3, Ninewells Hospital, George Pirie Way, Dundee, United Kingdom, DD1 9SY
Public contact	Anna Forber, General enquiries Scottish Centre for Respiratory Research 01382 383 902 scrr@dundee.ac.uk, 01382 383902, scrr@dundee.ac.uk
Scientific contact	Anna Forber, General enquiries Scottish Centre for Respiratory Research 01382 383 902 scrr@dundee.ac.uk, 01382 383902, scrr@dundee.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	01 July 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 July 2022
Global end of trial reached?	Yes
Global end of trial date	01 July 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the effect of benralizumab on airway hyper-responsiveness (AHR), after 3 months of treatment, measured by mannitol challenge as the provocative dose causing a 10% fall in forced expratory volume in 1 second (FEV1) (PD10 Mannitol), from post-run-in baseline in severe eosinophilic asthma.

Protection of trial subjects:

The provocative dose of mannitol required to drop a subject's FEV1 by 10% (PD10) was chosen as this was a cohort of severe asthma patients and therefore we opted for a safer cut point than other studies that have traditionally used PD15. We monitored patients 1 on 1 for the entirety of the mannitol challenges to minimise distress.

Background therapy:

Subjects were maintained on their usual inhaler and oral therapy for asthma control to ensure safety. This meant that benralizumab was used as an additional medication on top of their usual standard of care.

Evidence for comparator:

There was no comparison in this trial as large Phase III trials have shown good efficacy for benralizumab in the treatment of severe eosinophilic asthma. Our study was a single arm open label trial as we felt it was unethical to give patients placebo when there is established evidence that benralizumab improves clinical outcomes.

Actual start date of recruitment	16 December 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 21
Worldwide total number of subjects	21
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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	13
From 65 to 84 years	8
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

21 severe eosinophilic asthma patients were recruited between 16/12/20 and 15/12/21 from Dundee, Scotland, UK.

Pre-assignment

Screening details:

Key inclusion criteria included patients aged 18 - 75 with severe GINA defined asthma taking a medium to high dose of ICS/LABA. Patients also had to have uncontrolled asthma (ACQ≥1.5), mannitol PD10 ≤635mg at visit 1 and eosinophilic asthma. There was a 4 week run-in period between screen and visit 1. In total 34 patients were screened.

Period 1

Period 1 title	overall trial
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Baseline
Arm description: -	
Arm type	Single arm open label
Investigational medicinal product name	Benralizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

30mg every 4 weeks for 3 doses

Number of subjects in period 1	Baseline
Started	21
Completed	21

Period 2

Period 2 title	none
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	none
Arm description: -	
Arm type	none
No investigational medicinal product assigned in this arm	

Number of subjects in period 2[1]	none
Started	1
Completed	1

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Our study was a single arm open label study. However the system does not allow submission of the form unless there are two arms so we have created one with zero values to facilitate form submission.

Baseline characteristics

Reporting groups	
Reporting group title	overall trial

Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	21	21	
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	53		
standard deviation	± 16	-	
Gender categorical Units: Subjects			
Female	9	9	
Male	12	12	
Body mass index Units: kg/m2			
arithmetic mean	30		
standard deviation	± 5.5	-	
Inhaled corticosteroid beclomethasone diproprionate equivalent dose Units: mcg			
arithmetic mean	1895		
standard deviation	± 273	-	
Peripheral blood eosinophils Units: cells/microlitre			
arithmetic mean	439		
standard deviation	± 316	-	
Asthma control questionnaire (6 point) Units: points			
arithmetic mean	2.6		
standard deviation	± 0.9	-	
mini Asthma Quality of Life Questionnaire Units: points			
arithmetic mean	3.6		

standard deviation	± 1.3	-	
Forced expiratory volume in 1 second Units: litre(s)			
arithmetic mean	2.37		
standard deviation	± 1.00	-	
Forced expiratory flow rate between 25 and 75% of forced vital capacity Units: L/s			
arithmetic mean	1.48		
standard deviation	± 0.90	-	
Fractional exhaled nitric oxide Units: ppb			
arithmetic mean	51		
standard deviation	± 42	-	
Forced vital capacity Units: litre(s)			
arithmetic mean	3.62		
standard deviation	± 1.42	-	
FEV1/FVC ratio Units: unit(s)			
arithmetic mean	65.5		
standard deviation	± 9.4	-	
R5-R20 Units: kPa/L/s			
arithmetic mean	0.14		
standard deviation	± 0.12	-	
X5 Units: kPa/L/s			
arithmetic mean	-0.28		
standard deviation	± 0.22	-	
AX Units: kPa/L			
arithmetic mean	2.77		
standard deviation	± 2.83	-	
Mannitol PD10 Units: mg			
log mean	1.8278		
standard deviation	± 0.66186	-	
R5 Units: kPa/L/s			
arithmetic mean	0.53		
standard deviation	± 0.18	-	
R20 Units: kPa/L/s			
arithmetic mean	0.39		
standard deviation	± 0.10	-	
Fres Units: Hz			
arithmetic mean	22.32		
standard deviation	± 6.57	-	
Eosinophil derived neurotoxin Units: ng/ml			

arithmetic mean	65.6		
standard deviation	± 26.6	-	
Diary card peak flow			
Units: litre(s)			
arithmetic mean	357		
standard deviation	± 130	-	
Diary card symptoms			
Units: units			
arithmetic mean	1.7		
standard deviation	± 0.6	-	
Diary card reliever use			
Units: number of puffs used			
arithmetic mean	3.4		
standard deviation	± 3.1	-	

End points

End points reporting groups

Reporting group title	Baseline
Reporting group description: -	
Reporting group title	none
Reporting group description: -	

Primary: Mannitol PD10

End point title	Mannitol PD10
End point description:	
End point type	Primary
End point timeframe:	
12 weeks	

End point values	Baseline	none		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	1		
Units: milligram(s)				
geometric mean (confidence interval 95%)	67 (34 to 135)	0 (0 to 0)		

Statistical analyses

Statistical analysis title	Geometric mean fold difference at 12 weeks
Comparison groups	Baseline v none
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	< 0.01 [2]
Method	ANOVA

Notes:

[1] - Single arm open label

[2] - Bonferroni corrected

Secondary: Mannitol RDR

End point title	Mannitol RDR
End point description:	
End point type	Secondary
End point timeframe:	
12 weeks	

End point values	Baseline	none		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	1		
Units: geometric mean fold difference				
geometric mean (confidence interval 95%)	0.2 (0.1 to 0.5)	0 (0 to 0)		

Statistical analyses

Statistical analysis title	Geometric mean fold difference in RDR at 12 weeks
Comparison groups	Baseline v none
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	< 0.01 [4]
Method	ANOVA

Notes:

[3] - Single arm open label

[4] - Bonferroni corrected

Secondary: FEV1

End point title	FEV1

End point description:

End point type	Secondary

End point timeframe:

12 weeks

End point values	Baseline	none		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	1		
Units: litre(s)				
arithmetic mean (confidence interval 95%)	0.12 (-0.15 to 0.39)	0 (0 to 0)		

Statistical analyses

Statistical analysis title	Change in FEV1 at 12 weeks
Comparison groups	Baseline v none

Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	> 0.05 [6]
Method	ANOVA

Notes:

[5] - Single arm open label

[6] - Bonferroni corrected

Secondary: FEF25-75

End point title	FEF25-75

End point description:

End point type	Secondary

End point timeframe:

12 weeks

End point values	Baseline	none		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	1		
Units: litres/second				
arithmetic mean (confidence interval 95%)	0.05 (-0.27 to 0.37)	0 (0 to 0)		

Statistical analyses

Statistical analysis title	Change in FEF25-75 at 12 weeks
Comparison groups	Baseline v none
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	> 0.05 [8]
Method	ANOVA

Notes:

[7] - Single arm open label

[8] - Bonferroni corrected

Secondary: FVC

End point title	FVC

End point description:

End point type	Secondary

End point timeframe:

12 weeks

End point values	Baseline	none		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	1		
Units: litres				
arithmetic mean (confidence interval 95%)	0.16 (-0.05 to 0.37)	0 (0 to 0)		

Statistical analyses

Statistical analysis title	Change in FVC at 12 weeks
Comparison groups	Baseline v none
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	> 0.05 [10]
Method	ANOVA

Notes:

[9] - Single arm open label

[10] - Bonferroni corrected

Secondary: FEV1/FVC

End point title	FEV1/FVC

End point description:

End point type	Secondary

End point timeframe:

12 weeks

End point values	Baseline	none		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	1		
Units: ratio				
arithmetic mean (confidence interval 95%)	1.0 (-1.9 to 3.9)	0 (0 to 0)		

Statistical analyses

Statistical analysis title	Change in FEV1/FVC at 12 weeks
Comparison groups	Baseline v none

Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	
P-value	> 0.05 [11]
Method	ANOVA

Notes:

[11] - Bonferroni corrected

Secondary: R5-R20

End point title	R5-R20

End point description:

End point type	Secondary

End point timeframe:

12 weeks

End point values	Baseline	none		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	1		
Units: kPa/L/s				
arithmetic mean (confidence interval 95%)	0.00 (-0.04 to 0.04)	0 (0 to 0)		

Statistical analyses

Statistical analysis title	Change in R5-R20 at 12 weeks
Comparison groups	none v Baseline
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	other[12]
P-value	> 0.05 [13]
Method	ANOVA

Notes:

[12] - Single arm open label

[13] - Bonferroni corrected

Secondary: X5

End point title	X5

End point description:

End point type	Secondary

End point timeframe:

12 weeks

End point values	Baseline	none		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	1		
Units: kPa/L/s				
arithmetic mean (confidence interval 95%)	0.04 (-0.04 to 0.12)	0 (0 to 0)		

Statistical analyses

Statistical analysis title	Change in X5 at 12 weeks
Comparison groups	Baseline v none
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	other[14]
P-value	> 0.05 [15]
Method	ANOVA

Notes:

[14] - Single arm open label

[15] - Bonferroni corrected

Secondary: AX

End point title	AX

End point description:

End point type	Secondary

End point timeframe:

12 weeks

End point values	Baseline	none		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	1		
Units: kPa/L				
arithmetic mean (confidence interval 95%)	-0.46 (-1.43 to 0.50)	0 (0 to 0)		

Statistical analyses

Statistical analysis title	Change in AX at 12 weeks
Comparison groups	Baseline v none

Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	other[16]
P-value	> 0.05 [17]
Method	ANOVA

Notes:

[16] - Single arm open label

[17] - Bonferroni corrected

Secondary: Peripheral blood eosinophils

End point title	Peripheral blood eosinophils

End point description:

End point type	Secondary

End point timeframe:

12 weeks

End point values	Baseline	none		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	1		
Units: cells/microlitre				
arithmetic mean (confidence interval 95%)	-426 (-574 to -277)	0 (0 to 0)		

Statistical analyses

Statistical analysis title	Change in PBE at 12 weeks
Comparison groups	Baseline v none
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	other[18]
P-value	< 0.0001 [19]
Method	ANOVA

Notes:

[18] - Single arm open label

[19] - Bonferroni corrected

Secondary: Eosinophil derived neurotoxin

End point title	Eosinophil derived neurotoxin

End point description:

End point type	Secondary

End point timeframe:

12 weeks

End point values	Baseline	none		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	1		
Units: ng/ml				
arithmetic mean (confidence interval 95%)	-50.3 (-62.2 to -38.5)	0 (0 to 0)		

Statistical analyses

Statistical analysis title	Change in EDN at 12 weeks
Comparison groups	none v Baseline
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	other[20]
P-value	< 0.0001 [21]
Method	ANOVA

Notes:

[20] - Single arm open label

[21] - Bonferroni corrected

Secondary: Fractional exhaled nitric oxide

End point title	Fractional exhaled nitric oxide

End point description:

End point type	Secondary

End point timeframe:

12 weeks

End point values	Baseline	none		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	1		
Units: Parts per billion				
arithmetic mean (confidence interval 95%)	8 (-11 to 28)	0 (0 to 0)		

Statistical analyses

Statistical analysis title	Change in FeNO at 12 weeks
Comparison groups	Baseline v none

Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	other[22]
P-value	> 0.05 [23]
Method	ANOVA

Notes:

[22] - Single arm open label

[23] - Bonferroni corrected

Secondary: Asthma Control Questionnaire 6

End point title	Asthma Control Questionnaire 6

End point description:

End point type	Secondary

End point timeframe:

12 weeks

End point values	Baseline	none		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	1		
Units: units				
arithmetic mean (confidence interval 95%)	-1.5 (-2.0 to -1.1)	0 (0 to 0)		

Statistical analyses

Statistical analysis title	Change in ACQ6 at 12 weeks
Comparison groups	Baseline v none
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	other[24]
P-value	< 0.0001 [25]
Method	ANOVA

Notes:

[24] - Single arm open label

[25] - Bonferroni corrected

Secondary: Mini Asthma Quality of Life Questionnaire

End point title	Mini Asthma Quality of Life Questionnaire

End point description:

End point type	Secondary

End point timeframe:

12 weeks

End point values	Baseline	none		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	1		
Units: units				
arithmetic mean (confidence interval 95%)	1.7 (1.1 to 2.3)	0 (0 to 0)		

Statistical analyses

Statistical analysis title	Change in mii-AQLQ at 12 weeks
Comparison groups	Baseline v none
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	other[26]
P-value	< 0.0001 [27]
Method	ANOVA

Notes:

[26] - Single arm open label

[27] - Bonferroni corrected

Secondary: Diary card peak expiratory flow

End point title	Diary card peak expiratory flow

End point description:

End point type	Secondary

End point timeframe:

12 weeks

End point values	Baseline	none		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	1		
Units: litres/minute				
arithmetic mean (confidence interval 95%)	48 (21 to 74)	0 (0 to 0)		

Statistical analyses

Statistical analysis title	Change in PEF at 12 weeks
Comparison groups	Baseline v none

Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	other[28]
P-value	< 0.01 [29]
Method	ANOVA

Notes:

[28] - Single arm open label

[29] - Bonferroni corrected

Secondary: Diary card symptoms

End point title	Diary card symptoms

End point description:

End point type	Secondary

End point timeframe:

12 weeks

End point values	Baseline	none		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	1		
Units: units				
arithmetic mean (confidence interval 95%)	-0.7 (-0.9 to -0.5)	0 (0 to 0)		

Statistical analyses

Statistical analysis title	Change in diary card symptoms at 12 weeks
Comparison groups	Baseline v none
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	other[30]
P-value	< 0.0001 [31]
Method	ANOVA

Notes:

[30] - Single arm open label

[31] - Bonferroni corrected

Secondary: Diary card reliever use

End point title	Diary card reliever use

End point description:

End point type	Secondary

End point timeframe:

12 weeks

End point values	Baseline	none		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	1		
Units: units				
arithmetic mean (confidence interval 95%)	-2 (-3 to 0)	0 (0 to 0)		

Statistical analyses

Statistical analysis title	Change in diary card reliever use at 12 weeks
Comparison groups	Baseline v none
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	other[32]
P-value	< 0.05 [33]
Method	ANOVA

Notes:

[32] - Single arm open label

[33] - Bonferroni corrected

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From study enrolment to last patient last visit	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups	
Reporting group title	BISA

Reporting group description: -

Serious adverse events	BISA		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 21 (4.76%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Respiratory, thoracic and mediastinal disorders			
Hospitalisation	Additional description: Coronavirus disease 2019		
subjects affected / exposed	1 / 21 (4.76%)		
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	BISA		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 21 (85.71%)		
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 21 (19.05%)		
occurrences (all)	20		
General disorders and administration site conditions			
Sinusitis			
subjects affected / exposed	4 / 21 (19.05%)		
occurrences (all)	7		

Fatigue subjects affected / exposed occurrences (all) Mechanical fall subjects affected / exposed occurrences (all)	3 / 21 (14.29%) 3 2 / 21 (9.52%) 2		
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 2		
Gastrointestinal disorders Heartburn subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	1 / 21 (4.76%) 2 2 / 21 (9.52%) 2 2 / 21 (9.52%) 3		
Respiratory, thoracic and mediastinal disorders Breathlessness subjects affected / exposed occurrences (all) Lower respiratory tract infection subjects affected / exposed occurrences (all) Exacerbation of asthma subjects affected / exposed occurrences (all)	3 / 21 (14.29%) 12 4 / 21 (19.05%) 5 5 / 21 (23.81%) 5		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	2 / 21 (9.52%) 2		
Musculoskeletal and connective tissue disorders			

Musculoskeletal chest pain subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Allergic rhinitis subjects affected / exposed occurrences (all)	3 / 21 (14.29%) 4 4 / 21 (19.05%) 5 2 / 21 (9.52%) 4		
Infections and infestations Coronavirus disease 2019 subjects affected / exposed occurrences (all) Flu-like illness subjects affected / exposed occurrences (all)	7 / 21 (33.33%) 7 2 / 21 (9.52%) 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? Yes

Date	Interruption	Restart date
01 January 2021	Government mandated lockdown in response to coronavirus disease 2019 pandemic	13 April 2021

Notes:

Limitations and caveats

None reported