Clinical trial results:
Does a low exhaled Nitric Oxide level exclude a clinical benefit from inhaled corticosteroids in suspected asthma; a double-blind, randomised, placebo controlled trial.

Summary

EudraCT number	2016-000338-23
Trial protocol	GB
Global end of trial date	22 June 2018

Results information

Result version number	v1 (current)
This version publication date	17 November 2019
First version publication date	17 November 2019

Trial information

Trial identification

Sponsor protocol code	16013

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02771717
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Nottingham
Sponsor organisation address	Jubilee Campus, Triumph Road, Nottingham, United Kingdom, NG8 1DH
Public contact	Angela Shone, University of Nottingham, +44 1158467906, sponsor@nottingham.ac.uk
Scientific contact	Angela Shone, University of Nottingham, +44 1158467906, sponsor@nottingham.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	25 October 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 June 2018
Global end of trial reached?	Yes
Global end of trial date	22 June 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of the study is to determine if a low exhaled nitric oxide level (<27ppb) is a good predictor of a negative clinical benefit from inhaled corticosteroids in patients with suspected asthma?

The primary objective is to determine if asthma symptoms, using the 7 point ACQ (Asthma Control Questionnaire), differ between the low dose inhaled steroid and placebo groups.

Protection of trial subjects:

None applicable

Background therapy:

None

Evidence for comparator:

Not applicable

Actual start date of recruitment	22 February 2016
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: 180
Worldwide total number of subjects	180
EEA total number of subjects	180

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)	156

From 65 to 84 years	24
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited from 47 primary care practices across Nottinghamshire, Leicestershire and Derbyshire as well as from the Nottingham Respiratory Research database and from advertisements in the University of Nottingham and Nottingham University Hospitals between May 2016 and March 2018.

Pre-assignment

Screening details:

236 patients were screened for entry, 180 were randomised. 56 participants failed screening; 45 patients were denied entry into the study due to FeNO levels greater than 27, 4 due to FEV1 less than 70%, 1 due to insufficient short-acting bronchodilator use,2 due to spirometry contraindications and 4 who withdrew consent prior to randomisation.

Period 1

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

Blinding implementation details:

Patients were randomized to treatment groups in blocks of eight with stratification according to their smoking status; current (or smoked within 12 months) or never/ex (never or quit more than one year ago). Allocation sequences were generated using a pseudo-random number generator (sealedenvelop.com). This sequence was linked to an electronic case report form (eCRF) where the participants' study data was recorded. If the participants' study data was recorded.

Arms

Are arms mutually exclusive?	Yes
Arm title	Budesonide

Arm description:

Participants received200 mcg Budesonide (Pulmicort) via a Turbuhaler or placebo one puff twice daily. The total daily dose of budesonide was therefore 400 mcg per day.

Arm type	Active comparator
Investigational medicinal product name	Budesonide (Pulmicort)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Pressurised inhalation
Routes of administration	Inhalation use

Dosage and administration details:

200 micrograms per inhalation

Arm title	Placebo

Arm description:

Placebo 200 mcg via a Turbuhaler or placebo one puff twice daily.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	na
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

200mcg per inhalation one puff twice daily

Number of subjects in period 1	Budesonide	Placebo
Started	91	89
Completed	68	66
Not completed	23	23
Consent withdrawn by subject	9	11
unknown reason	3	4
Lost to follow-up	10	7
Protocol deviation	1	1

Period 2

Period 2 title	End of Trial (12 weeks)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Data analyst

Blinding implementation details:

Patients were randomized to treatment groups in blocks of eight with stratification according to their smoking status; current (or smoked within 12 months) or never/ex (never or quit more than one year ago). Allocation sequences were generated by the Respiratory Research Unit's database manager using a pseudo-random number generator (sealedenvelop.com). This sequence was linked to an electronic case report form (eCRF) where the participants' study data was recorded.

Arms

Are arms mutually exclusive?	Yes
Arm title	Budesonide

Arm description:

Participants received200 mcg Budesonide (Pulmicort) via a Turbuhaler or placebo one puff twice daily. The total daily dose of budesonide was therefore 400 mcg per day.

Arm type	Active comparator
Investigational medicinal product name	Budesonide (Pulmicort)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Pressurised inhalation
Routes of administration	Inhalation use

Dosage and administration details:

200 micrograms per inhalation

Arm title	Placebo

Arm description:

Placebo 200 mcg via a Turbuhaler or placebo one puff twice daily.

Arm type	Placebo

Investigational medicinal product name	Budesonide (Pulmicort)
Investigational medicinal product code	19162
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

200 mcg per inhalation one puff twice daily

Number of subjects in period 2	Budesonide	Placebo
Started	68	66
Completed	68	66

Baseline characteristics

Reporting groups	
Reporting group title	Budesonide
Reporting group description:	
Participants received200 mcg Budesonide (Pulmicort) via a Turbuhaler or placebo one puff twice daily. The total daily dose of budesonide was therefore 400 mcg per day.	
Reporting group title	Placebo
Reporting group description:	
Placebo 200 mcg via a Turbuhaler or placebo one puff twice daily.	

Reporting group values	Budesonide	Placebo	Total
Number of subjects	91	89	180
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 at Baseline			
Units: years			
arithmetic mean	42.49	45.38	
standard deviation	± 18.76	± 18.31	-
Gender categorical			
Units: Subjects			
Female	64	66	130
Male	27	23	50
Cough			
Cough			
Units: Subjects			
Yes	74	69	143
No	17	20	37
Wheeze			
Wheeze			
Units: Subjects			
Yes	58	62	120
No	33	27	60
SOB			
Shortness of Breath			
Units: Subjects			
Yes	65	69	134
No	26	20	46

Smoking status			
Cigarette smoking status			
Units: Subjects			
Never	71	72	143
Current	20	17	37
Ethnicity			
Ethnicity			
Units: Subjects			
Caucasian	80	78	158
Asian	2	3	5
Black	2	5	7
Other	7	3	10
ACQ7			
Asthma Control Questionnaire			
Units: points			
median	1.28	1.28	
inter-quartile range (Q1-Q3)	0.85 to 2.00	0.57 to 1.86	-
FEV1			
Forced Expiratory Volume Over One Second			
Units: Liters			
arithmetic mean	3.02	2.73	
standard deviation	± 0.78	± 0.72	-
LCQ			
Leicester Cough Questionnaire			
Units: points			
median	17.46	17.36	
inter-quartile range (Q1-Q3)	12.93 to 20.07	13.43 to 19.96	-
MRC			
Medical Research Council Dyspnea Questionnaire			
Units: points			
median	2.00	2.00	
inter-quartile range (Q1-Q3)	1.00 to 2.00	1.00 to 2.00	-
FEV1 percent predicted			
Forced Expiratory Volume Over One Second percent predicted			
Units: Liters			
arithmetic mean	95.00	93.11	
standard deviation	± 13.79	± 14.74	-
FVC			
Full Vital Capacity			
Units: Liters			
arithmetic mean	3.81	3.52	
standard deviation	± 20.91	± 0.87	-
FEV1/FVC			
ratio of forced expiratory volume over one second to the full vital capacity			
Units: ratio			
arithmetic mean	79.24	77.41	
standard deviation	± 8.20	± 8.50	-
FeNO			
Fractional Exhaled Nitric Oxide			
Units: Parts per billion			
arithmetic mean	16.31	16.46	
standard deviation	± 6.24	± 6.75	-

Blood Eosinophils			
Blood Eosinophils			
Units: cells x10^9			
median	0.16	0.20	
inter-quartile range (Q1-Q3)	0.10 to 0.24	0.10 to 0.30	-
ACQ6			
Asthma Control Questionnaire 6			
Units: points			
median	1.33	1.17	
inter-quartile range (Q1-Q3)	0.83 to 2.17	0.67 to 1.83	-
Duration of Asthma			
Length of diagnosis			
Units: Months			
median	1.30	2.00	
inter-quartile range (Q1-Q3)	0.20 to 84.00	0.20 to 89.00	-
BMI			
Body Mass Index			
Units: Kg/m^2			
median	28.20	26.67	
inter-quartile range (Q1-Q3)	23.53 to 33.80	23.32 to 31.60	-

End points

End points reporting groups

Reporting group title	Budesonide
Reporting group description:	
Participants received200 mcg Budesonide (Pulmicort) via a Turbuhaler or placebo one puff twice daily. The total daily dose of budesonide was therefore 400 mcg per day.	
Reporting group title	Placebo
Reporting group description:	
Placebo 200 mcg via a Turbuhaler or placebo one puff twice daily.	
Reporting group title	Budesonide
Reporting group description:	
Participants received200 mcg Budesonide (Pulmicort) via a Turbuhaler or placebo one puff twice daily. The total daily dose of budesonide was therefore 400 mcg per day.	
Reporting group title	Placebo
Reporting group description:	
Placebo 200 mcg via a Turbuhaler or placebo one puff twice daily.	

Primary: ACQ7

End point title	ACQ7
End point description:	
Statistical analysis of the primary outcome was assessed using a two one-sided equivalence test (TOST) conducted with a delta of 0.5, the widely validated minimal clinical difference in ACQ score, and a type 1 error rate of 0.05 (5 %).	
End point type	Primary
End point timeframe:	
Baseline to end of study (12 weeks)	

End point values	Budesonide	Placebo	Budesonide	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	91	89	68	66
Units: Points				
median (inter-quartile range (Q1-Q3))	1.28 (0.85 to 2.00)	1.28 (0.57 to 1.86)	0.85 (0.28 to 1.42)	0.71 (0.42 to 1.71)

Statistical analyses

Statistical analysis title	Equivalence
Statistical analysis description:	
Two One Sided Equivalence Test (TOST)	
Comparison groups	Budesonide v Placebo v Budesonide v Placebo

Number of subjects included in analysis	314
Analysis specification	Pre-specified
Analysis type	equivalence[1]
P-value	< 0.0001 [2]
Method	TOST
Parameter estimate	TOST
Confidence interval	

Notes:

[1] - Difference baseline to 12 weeks between active and placebo

[2] - P values : <0.001, 0.0462

CI: -0.004 to 0.49 around the equivalence margin of -0.5 to 0.5

Secondary: FEV1

End point title	FEV1

End point description:

Lung function as assessed by forced expiratory volume over one second where the minimum clinically significant improvement was 02 L from baseline to 12 weeks.

End point type	Secondary

End point timeframe:

Baseline to end of study (12 weeks)

End point values	Budesonide	Placebo	Budesonide	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	91	89	68	66
Units: Liters				
arithmetic mean (standard deviation)	3.02 (± 0.78)	2.73 (± 0.72)	2.92 (± 0.77)	2.69 (± 0.66)

Statistical analyses

Statistical analysis title	TOST

Statistical analysis description:

Two One-Sided T-Test (TOST)

Comparison groups	Budesonide v Budesonide v Placebo v Placebo
Number of subjects included in analysis	314
Analysis specification	Pre-specified
Analysis type	equivalence[3]
P-value	< 0.001 [4]
Method	TOST
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.06
upper limit	0.06

Notes:

[3] - TOST for equivalence -0.2 to 0.2

[4] - P values: <0.0001, <0.0001

CI: -.0.6 to 0.06

Secondary: LCQ

End point title	LCQ

End point description:

LCQ possible scores ranged from 3-21 where 3 represented the worst cough and 21 was no cough. An increase of ≥ 1.3 was required for the difference to be considered clinically significant

End point type	Secondary

End point timeframe:

Baseline to end of study (12 weeks)

End point values	Budesonide	Placebo	Budesonide	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	91	89	68	66
Units: points				
median (inter-quartile range (Q1-Q3))	17.46 (12.93 to 20.07)	17.36 (13.43 to 19.96)	19.65 (18.03 to 20.69)	19.04 (15.95 to 20.5)

Statistical analyses

Statistical analysis title	TOST

Statistical analysis description:

two one-sides t-test (TOST)

Comparison groups	Budesonide v Placebo v Budesonide v Placebo
Number of subjects included in analysis	314
Analysis specification	Pre-specified
Analysis type	equivalence[5]
P-value	= 0.0501 [6]
Method	TOST
Confidence interval	
level	90 %
sides	2-sided
lower limit	-1.06
upper limit	1.31

Notes:

[5] - equivalnce with delta -1.3 to 1.3

[6] - P values: =0.0235, =0.0501

CI: -1.06 to 1.31

Secondary: MRC

End point title	MRC

End point description:

MRC assessed the level of perceived breathlessness on a 1-5 stage scale where any decrease in points was considered a clinically significant improvement.

End point type	Secondary

End point timeframe:
Baseline to end of study (12 weeks)

End point values	Budesonide	Placebo	Budesonide	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	91	89	68	66
Units: points				
median (inter-quartile range (Q1-Q3))	2.00 (1.00 to 2.00)	2.00 (1.00 to 2.00)	1.00 (1.00 to 2.00)	2.00 (1.00 to 2.00)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Regular monitoring took place throughout the trial by the CI.

Adverse event reporting additional description:

The stopping rules and discontinuation from the study were an increase in ACQ7 of > 0.5 points or a fall in FEV1 of 20% from baseline. Discontinuation was assessed on an individual basis by the CI

Assessment type	Systematic

Dictionary used

Dictionary name	no dictionary used
Dictionary version	0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Control treatment with placebo

Reporting group title	Budesonide

Reporting group description:

Active treatment with budesonide

Serious adverse events	Placebo	Budesonide	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 89 (0.00%)	0 / 91 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Placebo	Budesonide	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 89 (0.00%)	0 / 91 (0.00%)	

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: Budesonide is routinely prescribed with a high safety profile and within the short time frame of the study, no new unexpected adverse events were expected.

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.

none

Notes: