Clinical trial results:
The utility of feNO in the differential diagnosis of chronic cough: The response to anti-inflammatory therapy with prednisolone and montelukast

Summary

EudraCT number	2015-001736-38
Trial protocol	GB
Global end of trial date	09 March 2017
Results information	
Result version number	v1 (current)
This version publication date	21 September 2019
First version publication date	21 September 2019
Summary attachment (see zip file)	Trial Summery (Trial summary TUF, 29.06.16.doc) Article 1 (Article3.L_Author.pdf) Abstract (A23.full.bts A1.pdf) Abstract (A140.1.full,bts A2.pdf)

Trial information

Trial identification	
Sponsor protocol code	Academed100215
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02479074
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	Hull and East Yorkshire Hospitals NHS trust
Sponsor organisation address	Casle Road, Cottingham , United Kingdom,
Public contact	Mahboobeh Haji Sadeghi, Hull and East Yorkshire Hospitals NHS trust, 0044 1482 624009, Mahboobeh.HajiSadeghi@hyms.ac.uk
Scientific contact	Mahboobeh Haji Sadeghi, Hull and East Yorkshire Hospitals NHS trust, 0044 1482 624009, Mahboobeh.HajiSadeghi@hyms.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	17 April 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 March 2017
Global end of trial reached?	Yes
Global end of trial date	09 March 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to determine the difference in 24 hr cough counts measured using the Hull Automated Cough Counter (HACC), from baseline and after two weeks and four weeks treatment with either montelukast or prednisolone followed by montelukast in patients with FeNO≥30 ppb at screening or montelukast in patients with normal NO measurement of ≤20 ppb.

Protection of trial subjects:

All the measurements has been followed according the approved SOP and a study doctor was available during the visits if it was needed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 June 2015
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: 50
Worldwide total number of subjects	50
EEA total number of subjects	50

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)	38
From 65 to 84 years	12
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

50 non-asthmatic patients with chronic cough were recruited sequentially from a specialist cough clinic. 30 patients with FeNO ≥30ppb were randomised to either two weeks prednisolone 20mg or two weeks montelukast 10mg followed by montelukast 10mg for the subsequent two weeks. 20 patients with low FeNO ≤20 received four weeks montelukast.

Pre-assignment

Screening details:

Patients with a history of chronic cough at least 8 weeks duration were included.
Subjects with the following criteria were excluded ; current diagnosis of classic asthma, any significant concomitant disease, a lower respiratory tract infection in the last 4 weeks, subjects who were taking ACE and current smokers.

Period 1

Period 1 title	V1
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Blinding was not applicable to the period.

Arms

Are arms mutually exclusive?	Yes
Arm title	First Arm, High FeNO

Arm description:

Following baseline assessments 30 eligible subjects with FeNO≥30 were randomized in a 1:1 ratio to receive either two weeks montelukast 10mg film-coated tablets or prednisolone 20mg tablets followed by montelukast 10 mg film-coated tablets for the subsequent two weeks in both arms. Allocation was performed by Research & Development Department based on a balanced block randomisation scheme, which was prepared using computerised system – sealed envelope, which was prepared using computerised system – sealed envelope.
Subject in the first Arm High FeNO were received 4 weeks Montelukast.

Arm type	Active comparator
Investigational medicinal product name	Montelukast
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Four weeks montelukast 10mg once daily.

Arm title	Second Arm High FeNO

Arm description:

Following baseline assessments 30 eligible subjects with FeNO≥30 were randomized in a 1:1 ratio to receive either two weeks montelukast 10mg film-coated tablets or prednisolone 20mg tablets followed by montelukast 10 mg film-coated tablets for the subsequent two weeks in both arms. Allocation was performed by Research & Development Department based on a balanced block randomisation scheme, which was prepared using computerised system – sealed envelope, which was prepared using computerised system – sealed envelope.
Subject in the second Arm High FeNO were received two weeks prednisolone 20mg tablets followed by two weeks montelukast 10 mg film-coated tablets.

Arm type	Active comparator

Investigational medicinal product name	Prednisolone & Montelukast
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Two weeks prednisolone 20mg once a day followed by two weeks Montelukast 10mg per day.

Arm title	Low FeNO

Arm description:

A control group of 20 patients with low FeNO (≤20 ppb) were enrolled who received four weeks Montelukast 10 mg.

Arm type	Active comparator
Investigational medicinal product name	Montelukast
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Four weeks montelukast 10mg once daily.

Number of subjects in period 1[1]	First Arm, High FeNO	Second Arm High FeNO	Low FeNO
Started	15	15	20
Baseline	15	15	20
Completed	15	14	20
Not completed	0	1	0
Transferred to other arm/group	-	1	-

Notes:

[1] - The number of subjects transferring in and out of the arms in the period are not the same. It is expected the net number of transfers in and out of the arms in a period, will be zero.
Justification: In the Second arm high FeNO one of the subjects was wrongly randomized to the High FeNO group while the subject had a Low FeNO. Therefore transferred to the low FeNO group. 15 subject randomized to the second arm hifg FeNO group but only 14 subjects completed the baseline visit.

Period 2

Period 2 title	V3
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

The blinding was not applicable to the period.

Arms

Are arms mutually exclusive?	Yes

Arm title	First Arm, High FeNO

Arm description:

Following baseline assessments 30 eligible subjects with FeNO≥30 were randomized in a 1:1 ratio to receive either two weeks montelukast 10mg film-coated tablets or prednisolone 20mg tablets followed by montelukast 10 mg film-coated tablets for the subsequent two weeks in both arms. Allocation was performed by Research & Development Department based on a balanced block randomisation scheme, which was prepared using computerised system – sealed envelope, which was prepared using computerised system – sealed envelope.
Subject in the first Arm High FeNO were received 4 weeks Montelukast.

Arm type	Active comparator
Investigational medicinal product name	Montelukast
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Four weeks montelukast 10mg once daily.

Arm title	Second Arm High FeNO

Arm description:

Following baseline assessments 30 eligible subjects with FeNO≥30 were randomized in a 1:1 ratio to receive either two weeks montelukast 10mg film-coated tablets or prednisolone 20mg tablets followed by montelukast 10 mg film-coated tablets for the subsequent two weeks in both arms. Allocation was performed by Research & Development Department based on a balanced block randomisation scheme, which was prepared using computerised system – sealed envelope, which was prepared using computerised system – sealed envelope.
Subject in the second Arm High FeNO were received two weeks prednisolone 20mg tablets followed by two weeks montelukast 10 mg film-coated tablets.

Arm type	Active comparator
Investigational medicinal product name	Prednisolone & Montelukast
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Two weeks prednisolone 20mg once a day followed by two weeks Montelukast 10mg per day.

Arm title	Low FeNO

Arm description:

A control group of 20 patients with low FeNO (≤20 ppb) were enrolled who received four weeks Montelukast 10 mg.

Arm type	Active comparator
Investigational medicinal product name	Montelukast
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Four weeks montelukast 10mg once daily.

Number of subjects in period 2[2]	First Arm, High FeNO	Second Arm High FeNO	Low FeNO
Started	14	14	20
Two weeks therapy	14	14	20
Completed	14	14	20

Notes:

[2] - 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: In the second period after two weeks therapy in first arm 14, second arm 14 and third arm 20 patients completed the visit. One subject from third arm was withdraw from the study.

Period 3

Period 3 title	V5
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

The blinding was not applicable to the period.

Arms

Are arms mutually exclusive?	Yes
Arm title	First Arm, High FeNO

Arm description:

Following baseline assessments 30 eligible subjects with FeNO≥30 were randomized in a 1:1 ratio to receive either two weeks montelukast 10mg film-coated tablets or prednisolone 20mg tablets followed by montelukast 10 mg film-coated tablets for the subsequent two weeks in both arms. Allocation was performed by Research & Development Department based on a balanced block randomisation scheme, which was prepared using computerised system – sealed envelope, which was prepared using computerised system – sealed envelope.
Subject in the first Arm High FeNO were received 4 weeks Montelukast.

Arm type	Active comparator
Investigational medicinal product name	Montelukast
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Four weeks montelukast 10mg once daily.

Arm title	Second Arm High FeNO

Arm description:

Following baseline assessments 30 eligible subjects with FeNO≥30 were randomized in a 1:1 ratio to receive either two weeks montelukast 10mg film-coated tablets or prednisolone 20mg tablets followed by montelukast 10 mg film-coated tablets for the subsequent two weeks in both arms. Allocation was performed by Research & Development Department based on a balanced block randomisation scheme, which was prepared using computerised system – sealed envelope, which was prepared using computerised system – sealed envelope.
Subject in the second Arm High FeNO were received two weeks prednisolone 20mg tablets followed by two weeks montelukast 10 mg film-coated tablets.

Arm type	Active comparator

Investigational medicinal product name	Prednisolone & Montelukast
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Two weeks prednisolone 20mg once a day followed by two weeks Montelukast 10mg per day.

Arm title	Low FeNO

Arm description:

A control group of 20 patients with low FeNO (≤20 ppb) were enrolled who received four weeks Montelukast 10 mg.

Arm type	Active comparator
Investigational medicinal product name	Montelukast
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Four weeks montelukast 10mg once daily.

Number of subjects in period 3[3]	First Arm, High FeNO	Second Arm High FeNO	Low FeNO
Started	14	14	19
Four weeks therapy	14	14	19
Completed	14	14	19

Notes:

[3] - 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: In the end of the study after four weeks therapy in first arm 14, second arm 14 and third arm 19 patients completed the study.

Baseline characteristics

Reporting groups	
Reporting group title	V1

Reporting group description: -

Reporting group values	V1	Total	
Number of subjects	50	50	
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			
Average (± SD) age of the subjects studied was 62 ± 9.5 (range, 45-82 years).			
Units: years			
arithmetic mean	62		
standard deviation	± 9.5	-	
Gender categorical			
33 patients (65%) of the subjects were female while only 17 patients (35%) of the subjects were male.			
Units: Subjects			
Female	33	33	
Male	17	17	

End points

End points reporting groups

Reporting group title	First Arm, High FeNO

Reporting group description:

Following baseline assessments 30 eligible subjects with FeNO≥30 were randomized in a 1:1 ratio to receive either two weeks montelukast 10mg film-coated tablets or prednisolone 20mg tablets followed by montelukast 10 mg film-coated tablets for the subsequent two weeks in both arms. Allocation was performed by Research & Development Department based on a balanced block randomisation scheme, which was prepared using computerised system – sealed envelope, which was prepared using computerised system – sealed envelope.
Subject in the first Arm High FeNO were received 4 weeks Montelukast.

Reporting group title	Second Arm High FeNO

Reporting group description:

Following baseline assessments 30 eligible subjects with FeNO≥30 were randomized in a 1:1 ratio to receive either two weeks montelukast 10mg film-coated tablets or prednisolone 20mg tablets followed by montelukast 10 mg film-coated tablets for the subsequent two weeks in both arms. Allocation was performed by Research & Development Department based on a balanced block randomisation scheme, which was prepared using computerised system – sealed envelope, which was prepared using computerised system – sealed envelope.
Subject in the second Arm High FeNO were received two weeks prednisolone 20mg tablets followed by two weeks montelukast 10 mg film-coated tablets.

Reporting group title	Low FeNO

Reporting group description:

A control group of 20 patients with low FeNO (≤20 ppb) were enrolled who received four weeks Montelukast 10 mg.

Reporting group title	First Arm, High FeNO

Reporting group description:

Following baseline assessments 30 eligible subjects with FeNO≥30 were randomized in a 1:1 ratio to receive either two weeks montelukast 10mg film-coated tablets or prednisolone 20mg tablets followed by montelukast 10 mg film-coated tablets for the subsequent two weeks in both arms. Allocation was performed by Research & Development Department based on a balanced block randomisation scheme, which was prepared using computerised system – sealed envelope, which was prepared using computerised system – sealed envelope.
Subject in the first Arm High FeNO were received 4 weeks Montelukast.

Reporting group title	Second Arm High FeNO

Reporting group description:

Following baseline assessments 30 eligible subjects with FeNO≥30 were randomized in a 1:1 ratio to receive either two weeks montelukast 10mg film-coated tablets or prednisolone 20mg tablets followed by montelukast 10 mg film-coated tablets for the subsequent two weeks in both arms. Allocation was performed by Research & Development Department based on a balanced block randomisation scheme, which was prepared using computerised system – sealed envelope, which was prepared using computerised system – sealed envelope.
Subject in the second Arm High FeNO were received two weeks prednisolone 20mg tablets followed by two weeks montelukast 10 mg film-coated tablets.

Reporting group title	Low FeNO

Reporting group description:

A control group of 20 patients with low FeNO (≤20 ppb) were enrolled who received four weeks Montelukast 10 mg.

Reporting group title	First Arm, High FeNO

Reporting group description:

Following baseline assessments 30 eligible subjects with FeNO≥30 were randomized in a 1:1 ratio to receive either two weeks montelukast 10mg film-coated tablets or prednisolone 20mg tablets followed by montelukast 10 mg film-coated tablets for the subsequent two weeks in both arms. Allocation was performed by Research & Development Department based on a balanced block randomisation scheme, which was prepared using computerised system – sealed envelope, which was prepared using computerised system – sealed envelope.
Subject in the first Arm High FeNO were received 4 weeks Montelukast.

Reporting group title	Second Arm High FeNO

Reporting group description:

Following baseline assessments 30 eligible subjects with FeNO≥30 were randomized in a 1:1 ratio to receive either two weeks montelukast 10mg film-coated tablets or prednisolone 20mg tablets followed by montelukast 10 mg film-coated tablets for the subsequent two weeks in both arms. Allocation was performed by Research & Development Department based on a balanced block randomisation scheme, which was prepared using computerised system – sealed envelope, which was prepared using computerised system – sealed envelope.
Subject in the second Arm High FeNO were received two weeks prednisolone 20mg tablets followed by two weeks montelukast 10 mg film-coated tablets.

Reporting group title	Low FeNO

Reporting group description:

A control group of 20 patients with low FeNO (≤20 ppb) were enrolled who received four weeks Montelukast 10 mg.

Primary: Number of coughs in 24 hours

End point title	Number of coughs in 24 hours

End point description:

Compared changes in 24 hours cough counting (using the Hull Automated Cough Counter (HACC)) at baseline after 2 and 4 weeks treatment between three treatment groups with an associated elevated FeNO was the primary endpoint.

End point type	Primary

End point timeframe:

In the baseline after 2 and 4 weeks treatment

End point values	First Arm, High FeNO	Second Arm High FeNO	Low FeNO	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	14	17	
Units: Numbers				
V1	292	237	566	
V3	173	89	449	
V5	150	114	265	

Statistical analyses

Statistical analysis title	Number of cough in 24 hours

Statistical analysis description:

Repeated measures ANCOVA was used to compare changes in the number of coughs in 24 hr at baseline, after 2 and 4 weeks treatment between high FeNO treatment groups and low FeNO treatment group.

Comparison groups	First Arm, High FeNO v Second Arm High FeNO v Low FeNO
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.005 [1]
Method	ANCOVA

Notes:
[1] - P<0.005

Secondary: Hull Airways Reflux Questionnaire (HARQ) score

End point title	Hull Airways Reflux Questionnaire (HARQ) score

End point description:

Subjective measures of cough were compared using the Hull Airways Reflux Questionnaire (HARQ) and Leicester Cough Questionnaire (LCQ) between the treatment groups at the baseline and after 2 week and 4 weeks treatment.

End point type	Secondary

End point timeframe:

At the baseline and after 2 week and 4 weeks treatment.

End point values	First Arm, High FeNO	Second Arm High FeNO	Low FeNO	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	14	17	
Units: Numbers				
V1	33	27	40	
V3	23	14	37	
V5	20	15	31	

Statistical analyses

Statistical analysis title	HARQ score

Statistical analysis description:

Repeated measures ANCOVA was used to compare changes in HARQ score at baseline, after 2 and 4 weeks treatment between high FeNO treatment groups and low FeNO treatment group.

Comparison groups	First Arm, High FeNO v Second Arm High FeNO v Low FeNO
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.005
Method	ANCOVA

Secondary: Leicester Cough Questionnaire (LCQ)

End point title	Leicester Cough Questionnaire (LCQ)

End point description:

Subjective measures of cough were compared using the Hull Airways Reflux Questionnaire (HARQ) and Leicester Cough Questionnaire (LCQ) between the treatment groups at the baseline and after 2 week and 4 weeks treatment.

End point type	Secondary

End point timeframe:

At the baseline and after 2 week and 4 weeks treatment.

End point values	First Arm, High FeNO	Second Arm High FeNO	Low FeNO	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	14	17	
Units: Number				
V1	14	15	12	
V3	15	18	14	
V5	16	17	15	

Statistical analyses

Statistical analysis title	LCQ

Statistical analysis description:

Repeated measures ANCOVA was used to compare changes in the number of coughs in 24 hr, sputum eosinophil cell count, spirometry measurements, HARQ and LCQ score at baseline, after 2 and 4 weeks treatment between high FeNO treatment groups and low FeNO treatment group.

Comparison groups	First Arm, High FeNO v Second Arm High FeNO v Low FeNO
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.005
Method	ANCOVA

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The AE reporting period for this trial begins as soon as patients have consented to the trial and ends 30 days after the patients final study medication visit.
The health status of subjects were checked at each study visit.

Adverse event reporting additional description:

The investigator recorded all directly observed AEs and all AEs spontaneously reported by the trial subject.
All adverse events were recorded by the investigator in patients data collection forms (CRFs) using R&D's adverse event report form. All adverse events were recorded by the investigator in patients' medical notes.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10

Reporting groups

Reporting group title	First arm High FeNO

Reporting group description:

This group of subjects received four weeks Montelukast 10mg daily.

Reporting group title	Second arm High FeNO

Reporting group description:

Subjects in this group received two weeks prednisolone 20mg followed by two weeks montelukast 10mg.

Reporting group title	Low FeNO Group

Reporting group description:

Subjects in this group received four weeks montelukast 10mg.

Serious adverse events	First arm High FeNO	Second arm High FeNO	Low FeNO Group
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 15 (0.00%)	0 / 14 (0.00%)	0 / 20 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

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

Non-serious adverse events	First arm High FeNO	Second arm High FeNO	Low FeNO Group
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 15 (53.33%)	1 / 14 (7.14%)	8 / 20 (40.00%)
General disorders and administration site conditions			

Headache			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	2 / 20 (10.00%)
occurrences (all)	1	0	2
Dizziness			
subjects affected / exposed	0 / 15 (0.00%)	1 / 14 (7.14%)	1 / 20 (5.00%)
occurrences (all)	0	1	1
Respiratory, thoracic and mediastinal disorders			
Respiratory tract infection			
subjects affected / exposed	4 / 15 (26.67%)	0 / 14 (0.00%)	1 / 20 (5.00%)
occurrences (all)	4	0	1
Cough			
subjects affected / exposed	1 / 15 (6.67%)	0 / 14 (0.00%)	1 / 20 (5.00%)
occurrences (all)	1	0	1

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.

The results shown a significant reduction in cough frequency in the low FeNO group. To confirm effectiveness of montelukast in cough patients without presence of eosinophilic biomarkers there is a need for a large placebo controlled study.

Notes: