Clinical trial results:
Reversal of steroid insensitivity in COPD by theophylline

Summary

EudraCT number	2006-003561-13
Trial protocol	GB
Global end of trial date	29 August 2007

Results information

Result version number	v1 (current)
This version publication date	02 December 2019
First version publication date	02 December 2019

Trial information

Trial identification

Sponsor protocol code	cro488

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00241631
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Imperial College London
Sponsor organisation address	South Kensington, London, United Kingdom, SW7 2AZ
Public contact	Ian Adcock, Imperial College London, ian.adcock@imperial.ac.uk
Scientific contact	Ian Adcock, Imperial College London, ian.adcock@imperial.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 August 2008
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 August 2007
Global end of trial reached?	Yes
Global end of trial date	29 August 2007
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Does the addition of low dose theophylline restore the anti-inflammatory effects of steroids?

Protection of trial subjects:

None

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 April 2006
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: 49
Worldwide total number of subjects	49
EEA total number of subjects	49

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)	24
From 65 to 84 years	25
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Forty-nine theophylline-naive (Global Initiative for Chronic Obstructive Lung Disease stage 2 or 3) patients with COPD were recruited, between April 2006 and August 2007.

Pre-assignment

Screening details:

Forty-nine theophylline-naive (Global Initiative for Chronic Obstructive Lung Disease stage 2 or 3) patients with COPD were recruited. Thirty completed the trial and were suitable for analysis.

Period 1

Period 1 title	Run in (2 Weeks)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	All participants

Arm description:

Run in period, no intervention

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	All participants
Started	49
Completed	43
Not completed	6
Physician decision	6

Period 2

Period 2 title	Phase 1 (4 Weeks)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes

Arm title	Placebo
Arm description: participants received placebo	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Inhalation use
Dosage and administration details: Single dose for four weeks	
Investigational medicinal product name	Theophylline Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: Single dose for four weeks	
Arm title	Steroid
Arm description: placebo theophylline capsules and inhaled fluticasone propionate (FP) (500 mg bid)	
Arm type	Experimental
Investigational medicinal product name	Fluticasone propionate (FP) (500 mg bid)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Inhalation use
Dosage and administration details: 500 mg bid for four weeks	
Investigational medicinal product name	Theophylline Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: Single dose for four weeks	

Number of subjects in period 2	Placebo	Steroid
Started	22	21
Completed	14	16
Not completed	8	5
Consent withdrawn by subject	4	4
Sore throat	1	-
Lost to follow-up	3	-
Lack of efficacy	-	1

Period 3	
Period 3 title	Wash Out (2 Weeks)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms	
Arm title	All participants
Arm description: wash out period, no intervention	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 3	All participants
Started	30
Completed	30

Period 4	
Period 4 title	Phase 2 (4 Weeks)
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms	
Are arms mutually exclusive?	Yes
Arm title	Placebo
Arm description: Participants received placebo	
Arm type	Placebo
Investigational medicinal product name	Theophylline Active
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: Single dose for four weeks	

Arm title	Steroid
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Theophylline Active
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Single dose for four weeks

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: The baseline characteristics are only for the participants who completed the study.

Number of subjects in period 4[2]	Placebo	Steroid
Started	14	16
Completed	14	16

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: The baseline characteristics are only for the participants who completed the study.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description: Participants received placebo	
Reporting group title	Steroid
Reporting group description: -	

Reporting group values	Placebo	Steroid	Total
Number of subjects	14	16	30
Age categorical Units: Subjects			
Adults (18-64 years)	14	0	14
From 65-84 years	0	16	16
Age continuous Units: years			
geometric mean	61	69	
standard deviation	± 2.2	± 1.9	-
Gender categorical Units: Subjects			
Female	3	2	5
Male	11	14	25

End points

End points reporting groups

Reporting group title	All participants
Reporting group description: Run in period, no intervention	
Reporting group title	Placebo
Reporting group description: participants received placebo	
Reporting group title	Steroid
Reporting group description: placebo theophylline capsules and inhaled fluticasone propionate (FP) (500 mg bid)	
Reporting group title	All participants
Reporting group description: wash out period, no intervention	
Reporting group title	Placebo
Reporting group description: Participants received placebo	
Reporting group title	Steroid
Reporting group description: -	

Primary: Sputum Inflammatory Cell Counts

End point title	Sputum Inflammatory Cell Counts
End point description:	
End point type	Primary
End point timeframe: 10 weeks	

End point values	Placebo	Steroid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	16		
Units: millions cells/ ml				
geometric mean (confidence interval 95%)	5.42 (3.56 to 8.2)	3.89 (2.6 to 5.76)		

Statistical analyses

Statistical analysis title	Sputum Inflammatory Cell Counts
Comparison groups	Placebo v Steroid

Number of subjects included in analysis	30
Analysis specification	Post-hoc
Analysis type	superiority
P-value	= 0.012
Method	Mixed models analysis

Secondary: Interleukin 8 (IL8)

End point title	Interleukin 8 (IL8)

End point description:

End point type	Secondary

End point timeframe:

10 weeks

End point values	Placebo	Steroid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	16		
Units: ng/mL				
geometric mean (confidence interval 95%)	33.3 (20 to 56)	28.3 (19 to 42)		

Statistical analyses

Statistical analysis title	Interleukin 8 (IL8)
Comparison groups	Placebo v Steroid
Number of subjects included in analysis	30
Analysis specification	Post-hoc
Analysis type	superiority
P-value	< 0.05
Method	Mixed models analysis

Secondary: Total Sputum Eosinophils

End point title	Total Sputum Eosinophils

End point description:

End point type	Secondary

End point timeframe:

10 weeks

End point values	Placebo	Steroid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	14	16		
Units: millions cells/ml				
geometric mean (confidence interval 95%)	0.132 (0.09 to 0.2)	0.053 (0.03 to 0.1)		

Statistical analyses

Statistical analysis title	Total Sputum Eosinophils
Comparison groups	Placebo v Steroid
Number of subjects included in analysis	30
Analysis specification	Post-hoc
Analysis type	superiority
P-value	< 0.05
Method	Mixed models analysis

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 10 weeks	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	10.0
Reporting groups	
Reporting group title	Placebo
Reporting group description: Participants received placebo	
Reporting group title	Steroid
Reporting group description: -	

Serious adverse events	Placebo	Steroid	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 14 (0.00%)	0 / 16 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

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

Non-serious adverse events	Placebo	Steroid	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 14 (0.00%)	4 / 16 (25.00%)	
Gastrointestinal disorders			
Nausea and upset stomach			
subjects affected / exposed	0 / 14 (0.00%)	4 / 16 (25.00%)	
occurrences (all)	0	4	

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

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/20299628

http://www.ncbi.nlm.nih.gov/pubmed/15888697