



## Clinical trial results: Improving Inhaler Treatment and Small Airways Assessment in Chronic Obstructive Pulmonary Disease

### Summary

EudraCT number	2011-005544-10
Trial protocol	GB
Global end of trial date	27 November 2017

### Results information

Result version number	v1 (current)
This version publication date	19 October 2019
First version publication date	19 October 2019

### Trial information

#### Trial identification

Sponsor protocol code	NIHRCDF
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01721291
WHO universal trial number (UTN)	-

Notes:

### Sponsors

Sponsor organisation name	Imperial College London
Sponsor organisation address	South Kensington Campus, London, United Kingdom, SW7 2AZ
Public contact	Dr Omar Usmani, National Heart & Lung Institute, +44 20 7351 8051, o.usmani@imperial.ac.uk
Scientific contact	Dr Omar Usmani, National Heart & Lung Institute, +44 20 7351 8051, o.usmani@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:

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**Results analysis stage**

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Analysis stage	Final
Date of interim/final analysis	27 November 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 November 2017
Global end of trial reached?	Yes
Global end of trial date	27 November 2017
Was the trial ended prematurely?	No

Notes:

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**General information about the trial**

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Main objective of the trial:

What is the lung deposition behaviour of inhaled bronchodilator (salbutamol) aerosols of different particle size within the airways of patients with chronic obstructive pulmonary disease (COPD)? How does this distribution compare to that observed in healthy subjects with no lung disease?

Protection of trial subjects:

no protection

Background therapy:

no background therapy

Evidence for comparator: -

Actual start date of recruitment	01 October 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

Country: Number of subjects enrolled	United Kingdom: 65
Worldwide total number of subjects	65
EEA total number of subjects	65

Notes:

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**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)	34
From 65 to 84 years	31
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Participants were recruited at Royal Brompton Hospital, London between 01.10.2012 and 27.11.2017

### Pre-assignment

Screening details:

A total numbers of 70 participants were screened for eligibility, of whom were 65 randomized, the remaining 5 participant were excluded due to not meeting inclusion criteria. The study had two term, first was the deposition study with healthy and COPD patients, second part was the lung physiology study with COPD and Asthmatic patients.

### Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	COPD 1.

Arm description:

COPD patients

Arm type	Experimental
Investigational medicinal product name	Salbutamol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Visit1 - 1.5um particle 30ug slow, Visit2 - 1.5um particle 30ug fast, Visit3 - 3um particle 30ug slow, Visit4 - 3um particle 30ug fast, Visit5 - 6um particle 30ug slow, Visit6 - 6um particle 30ug fast, Visit7 - pMDI 200ug slow.

<b>Arm title</b>	Healthy
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Arm description:

Healthy participant

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

Dosage and administration details:

Visit1 - 1.5um particle 30ug slow, Visit2 - 1.5um particle 30ug fast, Visit3 - 3um particle 30ug slow, Visit4 - 3um particle 30ug fast, Visit5 - 6um particle 30ug slow, Visit6 - 6um particle 30ug fast, Visit7 - pMDI 200ug slow.

<b>Arm title</b>	COPD 2.
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Arm description:

COPD patients

Arm type	Experimental
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Investigational medicinal product name	Salbutamol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Visit1 - 1.5um particle 15ug, Visit2 - 1.5um particle 30ug, Visit3 - 3um particle 15ug, Visit4 - 3um particle 30ug , Visit5 - 6um particle 15ug, Visit6 - 6um particle 30ug, Visit7 - pMDI 200ug.

<b>Arm title</b>	Asthmatic
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Arm description:

Asthmatic

Arm type	Experimental
Investigational medicinal product name	Salbutamol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation solution
Routes of administration	Inhalation use

Dosage and administration details:

Visit1 - 1.5um particle 15ug, Visit2 - 1.5um particle 30ug, Visit3 - 3um particle 15ug, Visit4 - 3um particle 30ug , Visit5 - 6um particle 15ug, Visit6 - 6um particle 30ug, Visit7 - pMDI 200ug.

<b>Number of subjects in period 1</b>	COPD 1.	Healthy	COPD 2.
Started	14	12	26
Completed	12	12	26
Not completed	2	0	0
Consent withdrawn by subject	1	-	-
did not like the treatment	1	-	-

<b>Number of subjects in period 1</b>	Asthmatic
Started	13
Completed	12
Not completed	1
Consent withdrawn by subject	1
did not like the treatment	-

## Baseline characteristics

### Reporting groups

Reporting group title	COPD 1.
Reporting group description:	
COPD patients	
Reporting group title	Healthy
Reporting group description:	
Healthy participant	
Reporting group title	COPD 2.
Reporting group description:	
COPD patients	
Reporting group title	Asthmatic
Reporting group description:	
Asthmatic	

Reporting group values	COPD 1.	Healthy	COPD 2.
Number of subjects	14	12	26
Age categorical			
Units: Subjects			
Adults (18-64 years)	5	5	12
From 65-84 years	9	7	14
Age continuous			
Units: years			
arithmetic mean	66.08	64.08	64.5
full range (min-max)	56 to 77	50 to 76	58 to 79
Gender categorical			
Units: Subjects			
Female	8	5	17
Male	6	7	9
Force experation in 1s (FEV1 )			
Units: litre(s)			
arithmetic mean	1.63	2.55	1.46
full range (min-max)	0.97 to 2.24	1.55 to 3.76	0.71 to 2.13

Reporting group values	Asthmatic	Total	
Number of subjects	13	65	
Age categorical			
Units: Subjects			
Adults (18-64 years)	12	34	
From 65-84 years	1	31	
Age continuous			
Units: years			
arithmetic mean	40.4		
full range (min-max)	19 to 66	-	
Gender categorical			
Units: Subjects			
Female	8	38	
Male	5	27	

Force experation in 1s (FEV1 )			
Units: litre(s)			
arithmetic mean	2.85		
full range (min-max)	2.03 to 3.9	-	

## End points

### End points reporting groups

Reporting group title	COPD 1.
Reporting group description: COPD patients	
Reporting group title	Healthy
Reporting group description: Healthy participant	
Reporting group title	COPD 2.
Reporting group description: COPD patients	
Reporting group title	Asthmatic
Reporting group description: Asthmatic	
Subject analysis set title	Healthy_1.5 um slow
Subject analysis set type	Sub-group analysis
Subject analysis set description: Healthy participants with treatment of 1.5 um Salbutamol	
Subject analysis set title	Healthy_1.5 um fast
Subject analysis set type	Sub-group analysis
Subject analysis set description: Healthy participants with treatment of 1.5 um Salbutamol fast	
Subject analysis set title	COPD_1.5 um slow
Subject analysis set type	Sub-group analysis
Subject analysis set description: COPD participants with treatment of 1.5 um Salbutamol	
Subject analysis set title	COPD_1.5 um fast
Subject analysis set type	Sub-group analysis
Subject analysis set description: COPD participants with treatment of 1.5 um Salbutamol fast	
Subject analysis set title	Healthy_3 um slow
Subject analysis set type	Sub-group analysis
Subject analysis set description: Healthy participants with treatment of 3 um Salbutamol slow	
Subject analysis set title	Healthy_3 um fast
Subject analysis set type	Sub-group analysis
Subject analysis set description: Healthy participants with treatment of 3 um Salbutamol fast	
Subject analysis set title	COPD_3 um slow
Subject analysis set type	Sub-group analysis
Subject analysis set description: COPD with treatment of 3 um Salbutamol slow	
Subject analysis set title	COPD_3 um fast
Subject analysis set type	Sub-group analysis
Subject analysis set description: COPD participants with treatment of 3 um Salbutamol fast	
Subject analysis set title	Healthy_6 um slow
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Healthy participants with treatment of 6 µm Salbutamol slow

Subject analysis set title	COPD_6 µm fast
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Healthy participants with treatment of 6 µm Salbutamol fast

Subject analysis set title	COPD_6 µm slow
Subject analysis set type	Sub-group analysis

Subject analysis set description:

COPD participants with treatment of 6 µm Salbutamol slow

Subject analysis set title	Healthy_6 µm fast
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Healthy participants with treatment of 6 µm Salbutamol fast

Subject analysis set title	COPD_1.5µm, 15ug
Subject analysis set type	Sub-group analysis

Subject analysis set description:

COPD participants with treatment of 15 ug Salbutamol

Subject analysis set title	COPD_1.5µm, 30ug
Subject analysis set type	Sub-group analysis

Subject analysis set description:

COPD participants with treatment of 1.5µm, 30 ug Salbutamol

Subject analysis set title	COPD_3µm, 15 ug
Subject analysis set type	Sub-group analysis

Subject analysis set description:

COPD participants with treatment of 3µm, 15 ug Salbutamol

Subject analysis set title	COPD_3µm, 30 ug
Subject analysis set type	Sub-group analysis

Subject analysis set description:

COPD participants with treatment of 3µm, 30 ug Salbutamol

Subject analysis set title	COPD_6µm, 15 ug
Subject analysis set type	Sub-group analysis

Subject analysis set description:

COPD participants with treatment of 6µm, 15 ug Salbutamol

Subject analysis set title	COPD_6µm,30 ug
Subject analysis set type	Sub-group analysis

Subject analysis set description:

COPD participants with treatment of 6µm, 30 ug Salbutamol

Subject analysis set title	COPD_pMDI
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participant treatment with pMDI and Salbutamol

Subject analysis set title	Asthmatics_1.5µm, 15ug
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Asthmatics participants with treatment of 1.5µm, 15 ug Salbutamol

Subject analysis set title	Asthmatics_1.5µm, 30ug
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Asthmatics participants with treatment of 1.5µm, 30 ug Salbutamol

Subject analysis set title	Asthmatics_3µm, 15ug
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Asthmatics participants with treatment of 3um, 15 ug Salbutamol

Subject analysis set title	Asthmatics_3um, 30ug
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Asthmatics participants with treatment of 3um, 30 ug Salbutamol

Subject analysis set title	Asthmatics_6um, 15ug
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Asthmatics participants with treatment of 6um, 15 ug Salbutamol

Subject analysis set title	Asthmatics_6um, 30ug
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Asthmatics participants with treatment of 6um, 15 ug Salbutamol

Subject analysis set title	Asthmatics_pMDI
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Asthmatics participants with treatment of pMDI and Salbutamol

### Primary: Penetration index

End point title	Penetration index
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End point description:

End point type	Primary
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End point timeframe:

5min

End point values	Healthy_1.5 um slow	Healthy_1.5 um fast	COPD_1.5 um slow	COPD_1.5 um fast
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	12	12	12	12
Units: ratio				
arithmetic mean (standard deviation)	0.8 (± 0.08)	0.72 (± 0.12)	0.69 (± 0.13)	0.58 (± 0.14)

End point values	Healthy_3 um slow	Healthy_3 um fast	COPD_3 um slow	COPD_3 um fast
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	12	12	12	12
Units: ratio				
arithmetic mean (standard deviation)	0.75 (± 0.11)	0.63 (± 0.15)	0.65 (± 0.18)	0.48 (± 0.16)

End point values	Healthy_6 um slow	COPD_6 um fast	COPD_6 um slow	Healthy_6 um fast
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Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	12	12	12	12
Units: ratio				
arithmetic mean (standard deviation)	0.51 ( $\pm$ 0.1)	0.46 ( $\pm$ 0.04)	0.37 ( $\pm$ 0.12)	0.32 ( $\pm$ 0.08)

## Statistical analyses

<b>Statistical analysis title</b>	Comparisons of Penetration Index for COPD
Comparison groups	COPD_1.5 um slow v COPD_1.5 um fast v COPD_3 um slow v COPD_3 um fast v COPD_6 um fast v COPD_6 um slow
Number of subjects included in analysis	72
Analysis specification	Post-hoc
Analysis type	superiority
P-value	< 0.05
Method	ANOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	1-sided
lower limit	-0.0489
upper limit	0.2739
Variability estimate	Standard deviation

## Primary: Multi-breath nitrogen washout (MBNW) indices of conducting airways (Scnd)

End point title	Multi-breath nitrogen washout (MBNW) indices of conducting airways (Scnd) <sup>[1]</sup>
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End point description:

End point type	Primary
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End point timeframe:

120min

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis has been performed on this endpoint.

<b>End point values</b>	COPD_1.5 um slow	COPD_1.5 um fast	COPD_3 um slow	COPD_3 um fast
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	12	12	12	12
Units: litre(s) -1				
arithmetic mean (full range (min-max))	0.047 (0 to 0.089)	0.04 (0.011 to 0.089)	0.047 (0.022 to 0.069)	0.044 (0.011 to 0.078)

<b>End point values</b>	COPD_6 um	COPD_6 um		
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	fast	slow		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	12		
Units: litre(s) -1				
arithmetic mean (full range (min-max))	0.047 (0.011 to 0.089)	0.045 (0.022 to 0.078)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Multi-breath nitrogen washout (MBNW) indices of acinar airways (Sacin)

End point title	Multi-breath nitrogen washout (MBNW) indices of acinar airways (Sacin)
End point description:	
End point type	Secondary
End point timeframe:	
120min	

End point values	COPD_1.5 um slow	COPD_1.5 um fast	COPD_3 um slow	COPD_3 um fast
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	12	12	12	12
Units: litre(s) -1				
arithmetic mean (full range (min-max))	0.462 (0.229 to 1.27)	0.508 (0.179 to 0.734)	0.471 (0.158 to 1.534)	0.437 (0.198 to 1.090)

End point values	COPD_6 um fast	COPD_6 um slow	Healthy_6 um fast	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	12	12	12	
Units: litre(s) -1				
arithmetic mean (full range (min-max))	0.487 (0.163 to 1.365)	0.426 (0.170 to 0.949)	0 (0 to 0)	

## Statistical analyses

Statistical analysis title	Multi-breath nitrogen washout indices (Sacin)
Comparison groups	COPD_1.5 um slow v COPD_1.5 um fast v COPD_3 um slow v COPD_3 um fast v COPD_6 um fast v COPD_6 um slow v Healthy_6 um fast

Number of subjects included in analysis	84
Analysis specification	Post-hoc
Analysis type	superiority <sup>[2]</sup>
P-value	< 0.05 <sup>[3]</sup>
Method	ANOVA
Parameter estimate	Mean difference (final values)
Confidence interval	
sides	1-sided
Variability estimate	Standard deviation

Notes:

[2] - 2-way ANOVA

[3] - No significance was found between any of the parameters

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

6 months

Assessment type	Non-systematic
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### Dictionary used

Dictionary name	SNOMED CT
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Dictionary version	10
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### Reporting groups

Reporting group title	COPD 1.
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Reporting group description:

COPD patients

Reporting group title	Healthy
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Reporting group description:

Healthy participant

Reporting group title	COPD 2.
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Reporting group description:

COPD patients

Reporting group title	Asthmatic
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Reporting group description:

Asthmatic

Serious adverse events	COPD 1.	Healthy	COPD 2.
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 26 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Asthmatic		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 13 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

<b>Non-serious adverse events</b>	COPD 1.	Healthy	COPD 2.
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 12 (50.00%)	0 / 12 (0.00%)	2 / 26 (7.69%)
Surgical and medical procedures			
Hernia operation			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Cataract operation			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Hypertension			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	1 / 26 (3.85%)
occurrences (all)	1	0	1
Musculoskeletal and connective tissue disorders			
Pulled muscle			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Chest infection			
subjects affected / exposed	1 / 12 (8.33%)	0 / 12 (0.00%)	0 / 26 (0.00%)
occurrences (all)	1	0	0
Sore throat			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	1 / 26 (3.85%)
occurrences (all)	0	0	1

<b>Non-serious adverse events</b>	Asthmatic		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 13 (0.00%)		
Surgical and medical procedures			
Hernia operation			
subjects affected / exposed	0 / 13 (0.00%)		
occurrences (all)	0		
Cataract operation			

subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0		
Cardiac disorders Hypertension subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0		
Musculoskeletal and connective tissue disorders Pulled muscle subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0		
Infections and infestations Chest infection subjects affected / exposed occurrences (all)  Sore throat subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0  0 / 13 (0.00%) 0		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 May 2013	AMENDMENTS made to Protocol (Flow chart), PIS and Consent form
07 August 2015	Amendments to GP letter, Protocol Flow chart) PIS and Consent form
11 April 2016	The request relates to an extension to the current ethics approval to be extended to 31st March 2017.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported