



## Clinical trial results:

### Prospective randomised controlled trial to investigate the effectiveness of inhalers for the relief of breathlessness in patients with lung cancer and COPD

#### Summary

EudraCT number	2010-021412-42
Trial protocol	GB
Global end of trial date	14 July 2016

#### Results information

Result version number	v1 (current)
This version publication date	11 July 2019
First version publication date	11 July 2019

#### Trial information

##### Trial identification

Sponsor protocol code	ADOPT Version 4
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##### Additional study identifiers

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

Notes:

#### Sponsors

Sponsor organisation name	The Royal Marsden NHS Foundation Trust
Sponsor organisation address	Fulham Road, London, United Kingdom, SW3 6JJ
Public contact	The Royal Marsden NHS Foundation Trust, The Royal Marsden NHS Foundation Trust, +44 02086426011,
Scientific contact	The Royal Marsden NHS Foundation Trust, The Royal Marsden NHS Foundation Trust, +44 02086426011,

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	10 April 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 July 2016
Global end of trial reached?	Yes
Global end of trial date	14 July 2016
Was the trial ended prematurely?	Yes

Notes:

## General information about the trial

Main objective of the trial:

To investigate whether optimisation of inhaler therapy in patients with lung cancer and co-existing COPD improves breathlessness (an increase in the proportion of patients with COPD and Lung cancer who have an improvement in their visual analogue scale for breathlessness) at 4 weeks compared to best supportive care.

Protection of trial subjects:

The study design took into account the possible poor prognosis of patients with lung cancer. The aim was to attain the maximum possible benefit with inhaler therapy in the shortest period of time with minimal disturbance to the patients. Therefore it was decided a priori that the intervention group would be treated with maximum inhaled therapy rather than the stepwise approach suggested by the British Thoracic Society and similar organisations.

There were regular meetings to review adverse events and progress of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 April 2011
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: 65
Worldwide total number of subjects	65
EEA total number of subjects	65

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)	23

From 65 to 84 years	42
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

First patient was recruited to the study on 08/04/2011. Recruitment of subjects continued until the last patient recruited to the study on 16/06/2016.

### Pre-assignment

Screening details:

65 patients were screened but 1 patient was a screening failure.

Out of the 64 patients consenting to study, 1 patient failed inclusion criteria with only 63 patients being eligible for study.

### Pre-assignment period milestones

Number of subjects started	65
Number of subjects completed	63

### Pre-assignment subject non-completion reasons

Reason: Number of subjects	failed inclusion criteria of VAS dyspnoea $\geq 4$ : 1
Reason: Number of subjects	ineligible as no spirometry evidence of COPD: 1

### Period 1

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

### Arms

Are arms mutually exclusive?	Yes
Arm title	Inhalers + BSC

Arm description:

Best supportive care and optimisation of inhalers

Arm type	Experimental
Investigational medicinal product name	Ventolin <sup>TM</sup> Evohaler <sup>TM</sup>
Investigational medicinal product code	R03AK04
Other name	
Pharmaceutical forms	Inhalation vapour
Routes of administration	Inhalation use

Dosage and administration details:

All patients will be commenced on -

Evohaler<sup>TM</sup> 100 microgram Evohaler 2 puffs inhaled 4 times a day (Maximum dose of 200 micrograms)

Maximum duration of treatment of a subject according to the protocol - 4 weeks during the study period but patients may continue after the study

Investigational medicinal product name	Spiriva <sup>®</sup>
Investigational medicinal product code	R03BB04
Other name	
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use

Dosage and administration details:

All patients will be commenced on -

Spiriva<sup>®</sup> 18 micrograms inhaled once daily via Handihaler<sup>®</sup> (1 capsule)

Maximum dose of 18 micrograms)

Maximum duration of treatment of a subject according to the protocol - 4 weeks during the study period but patients may continue after the study

Investigational medicinal product name	Seretide® Accuhaler® 50 micrograms (salmeterol)/500 micrograms (fluticasone)
Investigational medicinal product code	R03BA04
Other name	Fluticasone propionate
Pharmaceutical forms	Inhalation powder, pre-dispensed
Routes of administration	Inhalation use

Dosage and administration details:

Participants with an FEV1 of < 50% predicted normal and a history suggestive of repeated exacerbations despite bronchodilator use will also be commenced on -

Fluticasone propionate 500 micrograms twice a day (total dose of 14 mg)

Maximum duration of treatment of a subject according to the protocol - 4 weeks during the study period but patients may continue after the study

<b>Arm title</b>	BSC (control)
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Arm description:

Best supportive care alone

Arm type	Active comparator
Investigational medicinal product name	Oramorph
Investigational medicinal product code	
Other name	oral morphine solution
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Patients will have no alterations to their current COPD management or no intervention if previously not diagnosed with COPD. Breathlessness will be managed according to local practice guidelines for managing breathlessness. The clinician managing the patient, in consultation with the patient, will decide the most appropriate intervention. This may include non-pharmacological as well as pharmacological measures.

Current guidelines at the Royal Marsden recommend that oramorph (oral morphine solution) is used if pharmacological measures are required. Opiate naïve patients are prescribed oramorph 10mg/5ml solution and are instructed to take 2.5mg as required at 4 hourly intervals. Patients on regular opioids for pain relief are prescribed 10mg/5ml and are prescribed 5mg at 4 hourly intervals.

<b>Number of subjects in period 1<sup>[1]</sup></b>	Inhalers + BSC	BSC (control)
Started	32	31
Completed	32	31

Notes:

[1] - 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: 65 patients were screened but 1 patient was a screening failure. Out of the 64 patients consenting to the study, 1 patient failed inclusion criteria with only 63 patients being eligible for study.

## Period 2

Period 2 title	4 week assessment
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

## Arms

Are arms mutually exclusive?	Yes
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<b>Arm title</b>	Inhalers + BSC
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Arm description:

Best supportive care and optimisation of inhalers

Arm type	Experimental
Investigational medicinal product name	Ventolin <sup>TM</sup> Evohaler <sup>TM</sup>
Investigational medicinal product code	R03AK04
Other name	
Pharmaceutical forms	Inhalation vapour
Routes of administration	Inhalation use

Dosage and administration details:

All patients will be commenced on -

Evohaler<sup>TM</sup> 100 microgram Evohaler 2 puffs inhaled 4 times a day (Maximum dose of 200 micrograms)

Maximum duration of treatment of a subject according to the protocol - 4 weeks during the study period but patients may continue after the study

Investigational medicinal product name	Spiriva <sup>®</sup>
Investigational medicinal product code	R03BB04
Other name	
Pharmaceutical forms	Inhalation powder, hard capsule
Routes of administration	Inhalation use

Dosage and administration details:

All patients will be commenced on -

Spiriva<sup>®</sup> 18 micrograms inhaled once daily via Handihaler<sup>®</sup> (1 capsule)

Maximum dose of 18 micrograms)

Maximum duration of treatment of a subject according to the protocol - 4 weeks during the study period but patients may continue after the study

Investigational medicinal product name	Seretide <sup>®</sup> Accuhaler <sup>®</sup> 50 micrograms (salmeterol)/500 micrograms (fluticasone)
Investigational medicinal product code	R03BA04
Other name	Fluticasone propionate
Pharmaceutical forms	Inhalation powder, pre-dispensed
Routes of administration	Inhalation use

Dosage and administration details:

Participants with an FEV1 of < 50% predicted normal and a history suggestive of repeated exacerbations despite bronchodilator use will also be commenced on -

Fluticasone propionate 500 micrograms twice a day (total dose of 14 mg)

Maximum duration of treatment of a subject according to the protocol - 4 weeks during the study period but patients may continue after the study

<b>Arm title</b>	BSC (control)
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Arm description:

Best supportive care alone

Arm type	Active comparator
Investigational medicinal product name	Oramorph
Investigational medicinal product code	
Other name	oral morphine solution
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Patients will have no alterations to their current COPD management or no intervention if previously not diagnosed with COPD. Breathlessness will be managed according to local practice guidelines for managing breathlessness. The clinician managing the patient, in consultation with the patient, will decide the most appropriate intervention. This may include non-pharmacological as well as pharmacological measures.

Current guidelines at the Royal Marsden recommend that oramorph (oral morphine solution) is used if pharmacological measures are required. Opiate naïve patients are prescribed oramorph 10mg/5ml solution and are instructed to take 2.5mg as required at 4 hourly intervals. Patients on regular opioids for pain relief are prescribed 10mg/5ml and are prescribed 5mg at 4 hourly intervals.

<b>Number of subjects in period 2</b>	Inhalers + BSC	BSC (control)
Started	32	31
Completed	30	28
Not completed	2	3
Adverse event, non-fatal	2	3

## Baseline characteristics

### Reporting groups

Reporting group title	Inhalers + BSC
Reporting group description:	
Best supportive care and optimisation of inhalers	
Reporting group title	BSC (control)
Reporting group description:	
Best supportive care alone	

Reporting group values	Inhalers + BSC	BSC (control)	Total
Number of subjects	32	31	63
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 Diagnosis)			
Units: years			
median	68	67	
inter-quartile range (Q1-Q3)	59 to 75	61 to 71	-
Gender categorical			
Units: Subjects			
Female	21	19	40
Male	11	12	23
Smoking History			
Units: Subjects			
Current Smoker	4	8	12
Ex-Smoker	28	23	51
Histology/Cytology			
Units: Subjects			
NSCLC	28	25	53
SCLC	4	6	10
Staging - NSCLC			
NSCLC categories are 1, 2, 3, 4			
Units: Subjects			
1/2	7	12	19
03	11	5	16
04	10	8	18
Missing	4	6	10



Staging - SCLC			
Units: Subjects			
Limited	3	4	7
Extensive	1	2	3
Missing	28	25	53
ECOG Performance Status			
Units: Subjects			
ECOG-0	1	0	1
ECOG-1	25	25	50
ECOG-2	6	6	12
Treatment Paradigm			
Units: Subjects			
Radical	16	13	29
Palliative	16	18	34
Prior Thoracic Surgery			
Units: Subjects			
Yes	9	13	22
No	23	18	41
Prior Thoracic Radiotherapy			
Units: Subjects			
Yes	15	16	31
No	17	15	32
Tumour position			
Units: Subjects			
Large airway	14	10	24
Peripheral	17	20	37
Not Applicable	1	1	2
VAS dyspnoea			
Units: 0 to 10cm scale			
median	7.1	7.1	
inter-quartile range (Q1-Q3)	5.4 to 7.7	4.9 to 7.7	-
Six-minute walk distance (6MWD)			
Units: Meters			
median	375	396.5	
inter-quartile range (Q1-Q3)	325 to 450	333 to 450	-
MRC Dyspnoea			
MRC Dyspnoea scale ranges from score 1 (Breathless only with strenuous exercise) up to score 5 (Too breathless to leave the house) ; taking integer values			
Units: integer score (1 to 5)			
median	3	3	
inter-quartile range (Q1-Q3)	2 to 4	2 to 3	-
BODE index			
Units: integer score 0 to 10			
median	3	3.5	
inter-quartile range (Q1-Q3)	2 to 4	2.5 to 4.5	-
FEV1			
Forced Expiratory Volume which calculates the amount of air that a person can force out of their lungs in 1 second			
Units: Litres			
median	1.5	1.5	
inter-quartile range (Q1-Q3)	1.2 to 1.9	1.2 to 2.1	-
FEV1 (% predicted normal)			

Units: % predicted normal			
median	64	63	
inter-quartile range (Q1-Q3)	53 to 74.5	53 to 73	-
PEFR			
Peak Expiratory Flow Rate			
Units: Liters per minute (L/min)			
median	198.5	204	
inter-quartile range (Q1-Q3)	154 to 283	172 to 292	-
QOL Global Health			
Health-related Quality of Life Assessed by the EORTC QLQ-C30 Questionnaire - scores are for global health-status scale			
Units: score from 0 to 100			
median	66.7	66.7	
inter-quartile range (Q1-Q3)	50 to 75	50 to 83.3	-
QOL Dyspnoea			
Health-related Quality of Life Assessed by the EORTC QLQ-C30 Questionnaire - scores are for dyspnoea scale			
Units: score from 0 to 100			
median	38.9	33.3	
inter-quartile range (Q1-Q3)	33.3 to 44.4	22.2 to 55.6	-
SGRQ physical activity scale			
St George's Respiratory Questionnaire (SGRQ) Activity scale. The Activity score measures disturbances to patients daily physical activity that cause or are limited by breathlessness. Scores are expressed as a percentage of overall impairment where 100 represents worst possible health status and 0 indicates best possible health status.			
Units: score from 0 to 100			
median	66.3	66.2	
inter-quartile range (Q1-Q3)	53.5 to 79.1	47.7 to 73.2	-

## End points

### End points reporting groups

Reporting group title	Inhalers + BSC
Reporting group description:	
Best supportive care and optimisation of inhalers	
Reporting group title	BSC (control)
Reporting group description:	
Best supportive care alone	
Reporting group title	Inhalers + BSC
Reporting group description:	
Best supportive care and optimisation of inhalers	
Reporting group title	BSC (control)
Reporting group description:	
Best supportive care alone	
Subject analysis set title	VAS Dyspnoea response at 4 weeks (Inhalers + BSC)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Patients are classed as responders if their VAS dyspnoea measurement at 4 weeks is recorded as a $\geq$ 2 point reduction compared to baseline.	
Patients whose score is not recorded or withdrawn before the 4 week assessment for any reason are considered to be non-responders.	
Subject analysis set title	VAS Dyspnoea response at 4 weeks (BSC control)
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Patients are classed as responders if their VAS dyspnoea measurement at 4 weeks is recorded as a $\geq$ 2 point reduction compared to baseline.	
Patients whose score is not recorded or withdrawn before the 4 week assessment for any reason are considered to be non-responders.	
Subject analysis set title	VAS Dyspnoea response at 4 weeks - All eligible subjects
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Patients are classed as responders if their VAS dyspnoea measurement at 4 weeks is recorded as a $\geq$ 2 point reduction compared to baseline.	
Patients whose score is not recorded or withdrawn before the 4 week assessment for any reason are considered to be non-responders.	
<b>Primary: To investigate whether optimisation of inhaler therapy increases the proportion of patients who have a <math>\geq</math> 2 point change in their visual analogue scale (VAS) for dyspnoea (breathlessness) at 4 weeks compared to best supportive care</b>	
End point title	To investigate whether optimisation of inhaler therapy increases the proportion of patients who have a $\geq$ 2 point change in their visual analogue scale (VAS) for dyspnoea (breathlessness) at 4 weeks compared to best supportive care
End point description:	
Patients are classed as responders if their VAS dyspnoea measurement at 4 weeks is recorded as a $\geq$ 2 point reduction compared to baseline.	
Patients whose score is not recorded or withdrawn before the 4 week assessment for any reason are considered to be non-responders.	
Analysed as per ITT population i.e. all randomised patients fulfilling the eligibility criteria (63 patients).	
End point type	Primary
End point timeframe:	
VAS Dyspnoea measure at baseline and 4 weeks	

<b>End point values</b>	VAS Dyspnoea response at 4 weeks (Inhalers + BSC)	VAS Dyspnoea response at 4 weeks (BSC control)	VAS Dyspnoea response at 4 weeks - All eligible subjects	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	32	31	63	
Units: proportion				
number (confidence interval 95%)				
Response rate	53 (35 to 71)	26 (12 to 45)	40 (28 to 53)	
Non-response rate	47 (29 to 65)	74 (55 to 88)	60 (47 to 72)	

<b>Attachments (see zip file)</b>	Response rate/ADOPT Primary endpoint.pdf
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### Statistical analyses

<b>Statistical analysis title</b>	VAS response at 4 weeks from baseline between arms
Statistical analysis description: Difference between responders and non-responders of 2-points (or more) reduction in VAS dyspnoea at 4 weeks compared to baseline, when compared between the two treatment groups	
Comparison groups	VAS Dyspnoea response at 4 weeks (Inhalers + BSC) v VAS Dyspnoea response at 4 weeks (BSC control)
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.027
Method	Chi-squared

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse event that develops or worsens in severity during the course of the study, as well as worsening of a pre-existing medical condition from the time that a patient has signed informed consent to the time of initiation of study treatment.

Assessment type	Systematic
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### Dictionary used

Dictionary name	CTCAE
Dictionary version	3.0

### Reporting groups

Reporting group title	Inhalers + BSC
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Reporting group description:

Best supportive care and optimisation of inhalers

Reporting group title	BSC (control)
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Reporting group description:

Best supportive care alone

Serious adverse events	Inhalers + BSC	BSC (control)	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 32 (3.13%)	1 / 31 (3.23%)	
number of deaths (all causes)	2	5	
number of deaths resulting from adverse events	0	0	
General disorders and administration site conditions			
Fatigue	Additional description: Grade 3		
subjects affected / exposed	0 / 32 (0.00%)	1 / 31 (3.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchial infection	Additional description: Grade 3		
subjects affected / exposed	1 / 32 (3.13%)	0 / 31 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	Inhalers + BSC	BSC (control)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 32 (3.13%)	0 / 31 (0.00%)	
Psychiatric disorders			
Insomnia	Additional description: Grade 2		
subjects affected / exposed	1 / 32 (3.13%)	0 / 31 (0.00%)	
occurrences (all)	1	0	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 July 2014	Protocol updated to version 4.0 dated 01-May-2014, revised to add new secondary end points. More information provided about assessment schedule and process of blood samples.

Notes:

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### 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 study did not meet its recruitment target but due to changes in the treatment landscapes, it was not beneficial to continue. The trial was slow to recruit reflecting a trend towards wider prescribing of long-acting bronchodilators by physicians.

Notes: