Study Protocol Version 6 (01/09/16)

TARGETING OF THE SMALL AIRWAYS IN PATIENTS WITH COPD: AIRWAY EFFECTS OF TIOTROPIUM – Respimat vs. Handihaler

NCT02683668

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EudraCT No: 2015-001615-13

REC/IRAS number: 15/LO/0982

OUTLINE OF PROTOCOL FOR PROPOSED TRIAL

For official use:
Date received _____
Date approved _____
CTA no. _____

1. ADMINISTRATIVE INFORMATION	
Name of sponsor	Imperial College London
Name of funder	Boehringer Ingelheim
Name of the investigational medicinal product	Tiotropium bromide
Eudract number for proposed trial	2015-001615-13
Chief Investigator responsible for conducting the trial	**Title**: Dr **Forename/Initials:** Omar S **Surname:** Usmani **Post:** Clinical Senior Lecturer and Honorary Consultant in Respiratory Medicine **Qualifications:** MBBS, MRCP, PhD **Organisation:** Imperial College London, National Heart & Lung Institute and RBH **Work Address:** Guy Scadding Building (c/o Asthma Lab) Dovehouse Street, London SW3 6LY **E−mail:** o.usmani@imperial.ac.uk **Telephone:** 0207 351 8051 **Fax:** 0207 351 8937
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2. CLINICAL USE	
Medical condition or disease under investigation	Inhaled Drug Delivery in COPD
Any other medical condition or disease under investigation with this product	No
3. DATE OF PROTOCOL OVERVIEW SUBMISSION	30.03.3015
4. TITLE OF CLINICAL TRIAL	Targeting of the Small Airways in Patients with COPD: Airway Effects of Tiotropium – Respimat vs. Handihaler.

5. PURPOSE OF CLINICAL TRIAL	Bronchodilator targeting throughout the whole airway tree is important in respiratory disease and more so in COPD where the disease pathology and airflow physiological limitation arises from the small airways. However many drugs do not reach the small airways. Respimat is a novel inhaler platform that has small particles and a slow inhalation allowing deeper lung drug delivery. Small particle ICS and LABA combinations have been shown to improve markers of large and small airways that are also now being translated into meaningful improvements in patients with asthma and COPD [10c]. We aim to investigate the effect of tiotropium from different devices on a panel of small (IOS, MBNW, DLCO, FVC) and large airway (FEV1, PEF) responses in patients with mild-moderate COPD. We will compare Tiotropium Handihaler 18 micrograms once daily with Tiotropium Respimat 5 micrograms once daily
6. DESIGN OF CLINICALTRIAL	Open label. Sequential
7. PATIENT POPULATION IN CLINICAL TRIAL	Mild-Moderate COPD
8. MAXIMUM NUMBER OF PATIENTS TO BE INCLUDED IN CLINICAL TRIAL	N= 44
9. MAIN INCLUSION CRITERIA IN CLINICAL TRIAL	**COPD** 1) COPD patients with FEV1/FVC <70% predicted. 2) Mild (GOLD stage I: FEV1 >80% pred.) to moderate (GOLD stage II: FEV1 50-80% pred.) 3) Aged 30 years onwards – there is no upper age limit as we do not want to exclude elderly patients as COPD is primarily a disease in the elderly population. 4) Have ongoing symptoms or exercise limitation (determined by CAT score) 5) Stable COPD (no chest infection requiring antibiotics and/or oral steroids in the past 2 months). 6) Capable of giving informed consent, which includes compliance with the requirements and restrictions listed in the consent form.

10. MAIN EXCLUSION CRITERIA IN CLINICAL TRIAL	**COPD** 1) We will not recruit subjects who lack the capacity to consent. 2) Current or past diagnosis of asthma. 3) Patients on concurrent oral bronchodilators (theophylline, PDE4 inhibitors) will not be included. 4) Patients on other LAMAs will not be included 5) History of any chronic respiratory diseases other than COPD. 6) History of another medical condition, which in the opinion of the Unit Physician, contraindicates his/her participation in the study. 7) Clinical evidence of heart failure (NYHA class III-IV). 8) Unstable respiratory disease in the last four weeks prior to the screening visit (indicated by any change in their maintenance inhaled therapy or who have had a lower respiratory tract infection in the previous four weeks). 9) Evidence of a respiratory exacerbation requiring emergency room treatment and/or hospitalisation within four weeks before screening. 10) Use of systemic (oral or intravenous) steroids 4 weeks prior to inclusion (injectable depot steroids 6 weeks) or more than 3 periods during the last 12 months. 11) Participants with a known or suspected allergy, sensitivity or intolerance to the study drugs (this will be asked directly at the screening visit) or patients with a history of another drug allergy which, in the opinion of the Unit Physician, contraindicates his/her participation in the study. 12 Patients with known or suspected cardiac rhythm disorders 13) Patients treated with beta-blockers in the week preceding the screening visit and during the study period. 14) Females who are pregnant or lactating or are likely to become pregnant during the trial (a urine pregnancy test will be performed. Women of childbearing potential may be included in the study if, in the opinion of the investigator, they are taking adequate contraceptive precautions. 15) Patients who have evidence of alcohol or substance abuse. 16) Participation in another clinical trial with an investigational drug in the four weeks preceding the screening visit.

11. PROCEDURES FOR SAFETY MONITORING DURING TRIAL	Direct questioning about medical symptoms at the beginning of each study visit (see also 'Safety' section and 'Adverse Events' section below).
12. CRITERIA FOR WITHDRAWAL OF PATIENTS ON SAFETY GROUNDS	Suspected Unexpected Serious Adverse Reaction (SUSAR) The data to be collected on withdrawn subjects and their follow-up is listed under the 'Adverse Events' section (see later).
13. ROUTE(S) OF ADMINISTRATION (use standard terms)	Inhalation
14. MAXIMUM DOSAGE ALLOWED (specify daily or total)	14 days of handihaler tiotropium 18 micrograms once daily (14 x 18 micrograms = 252 micrograms total dose tiotropium via handihaler device) And 14 days of respimat tiotropium 5 micrograms once daily (14 x 5 micrograms = 70 micrograms total dose tiotropium via respimat device) 252 + 70 micrograms = 322 maximum dose tiotropium in study
15. MAXIMUM DURATION OF TREATMENT OF A SUBJECT	28 days
16. ACTIVE COMPARATOR PRODUCT(S)	No
17. ON-GOING TRIALS IN OTHER EU MEMBER STATES	No
18. REGULATORY SUBMISSIONS ON SAFETY GROUNDS	No

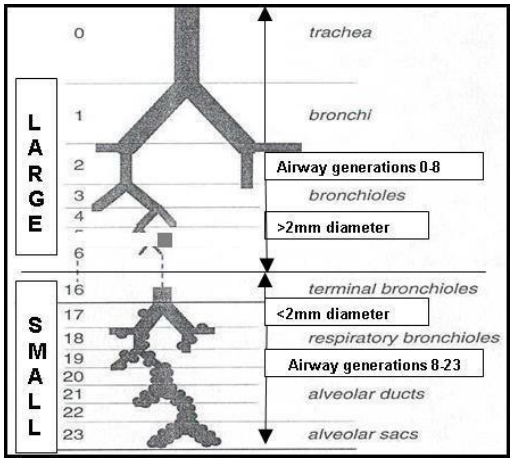
1. <u>BACKGROUND AND RATIONALE</u> (references at end of document)

Small airways

Patients with asthma and chronic obstructive airways disease (COPD) undergo routine testing of their lung function in the diagnosis, progression, management and, response to treatment of their disease [1]. Standard lung function obtains measurements based on the forced flow of air moving within the airways. Such measurements give a reasonable assessment of disease affecting the large airways, but not an accurate estimate of small airways disease [2]. Small airways are less than 2mm in diameter [Fig. 1]. However, both asthma and COPD have disease that involves not only the large but also the small airways that has important clinical consequences. Indeed, COPD predominantly affects the small airways [3, 3b].

Silent zone

Figure 1. Small vs. large airways of the lungs**.** For this reason, the small airways of the lungs are often referred to as the 'silent zone'. This is because airways disease in this zone may not be detected by standard clinical lung function measures, such as spirometry. For example, a recent study showed that small airway function became abnormal after only 10 pack-yrs of smoking, whereas spirometry became abnormal after 20 pack-yrs [4]. Also, lung pathology such as airways inflammation & narrowing and lung tissue destruction may be well-established before patients present with symptoms. This is of particular concern in lung transplant recipients where lung rejection often



starts with small airways disease, which is difficult to monitor [5].

Clinical healthcare needs

Better clinical assessments of small airways function and physiology are required. Clinicians need information in order to manage small airways disease of the lungs with clinical tests that are non-invasive, specific and do not expose patients to repeat X-Rays (such as CT scans) or are unpleasant and invasive (such as bronchoscopy). Non-invasive lung imaging such as positron emission tomography (PET) and magnetic resonance imaging (MRI) have been used, but give poor image resolution of the small airways compared to larger airways [Fig. 1].

Sensitive physiological technologies: IOS and MBNW

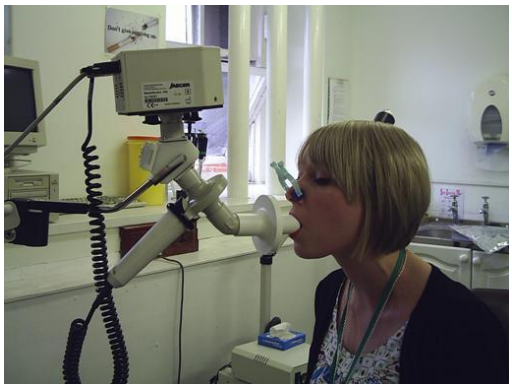


Figure 2. Patient set-up for IOS. We have set-up and validated [6, 7] the impulse oscillometry (IOS) and multi-breath nitrogen washout (MBNW) techniques in our lab. These are non-invasive physiological instruments that give a sensitive assessment of small airways function. They are practical methods of measurement that could be used in everyday clinical practice to routinely measure small airway function because of ease of administration and potentially, production of relatively cheap portable devices [8]. IOS [Fig. 2] uses oscillating pressure-flow signals of moving air within the lungs to determine peripheral lung mechanical parameters [9] which include small airway resistance and an estimate of lung compliance and air-trapping [Fig. 3], whereas MBNW utilizes the exhalation of nitrogen gas from the airways to determine changes in lung ventilation and derive small airways indices [10]. Patients are seated and gently breathe for a couple of minutes through the machines. Importantly, IOS & MBNW can be comfortably used in children and elderly populations.

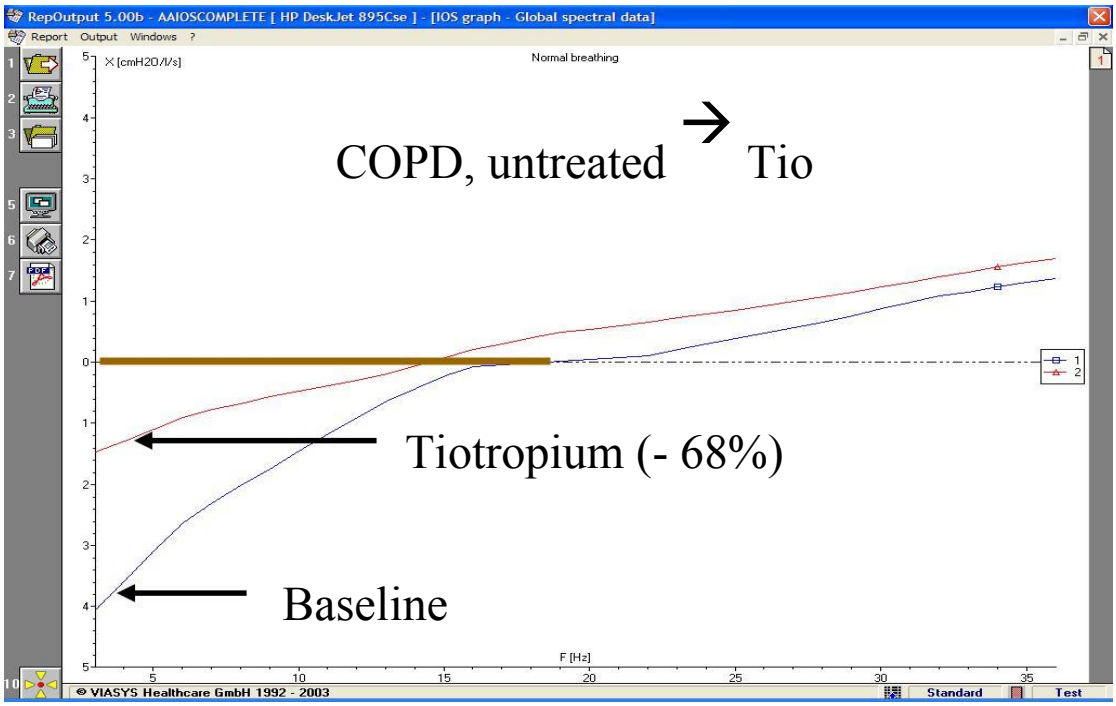


Figure 3. effect of tiotropim (18µg) on small airway reactance as assessed by IOS. Most recently, we have developed specific technique with IOS to distinguish patients with COPD from asthma [10b].

Therapeutic target

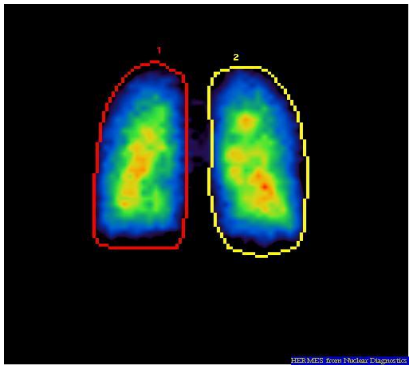
It is clear that the small airways are an important target in the treatment of asthma, COPD and other respiratory diseases [10c]. Recent clinical trials have used physiologic measures of small airways such as MBNW to assess the intervention of pharmacological treatments such as montelukast [11], inhaled tiotropium [12], inhaled corticosteroid formulated with specific ability to penetrate into the distal lung [13] and also, non–drug interventions such as smoking cessation [14], in the management of patients with asthma and COPD.

FEV_1 is the standard measurement used to measure drug effects in COPD clinical studies, however it does not reflect small airway resistance and may not provide information about lung compliance. IOS and plethysmography have been shown to have a higher sensitivity than FEV_1 for assessing short acting bronchodilator [14b] effects in COPD, and recently these techniques have been shown to sensitively differentiate the effect of tiotropium over salmeterol when FEV_1 measurements are similar [14c].

FEV_1 is insensitive to small airway changes and to alterations of the lung mechanics. On the contrary, the combined use of IOS, MBNW, and plethysmography besides providing information on the "silent zone" may also reflect changes of lung mechanics. The use of these methods in the same patients is unprecedented and we are confident it will provide valuable physiological and pharmacological data.

Inhaled drug delivery technologies: drug particle size

Figure 4. Drug particles of 1.5µm in lungs Usmani et al AJRCCM 2005. Aerosol drug particle size is the most important determinant of where inhaled drug deposits within the lungs. We have developed and validated an aerosol particle generator system able to produce therapeutic drug aerosols, all of one particle size, for controlled delivery to patients [15]. We have shown that by altering inhaled drug particle size, we can direct inhaled drug to different airway regions in the lungs [16, Fig. 4]. Determining the optimal particle size of inhaled drug therapy may contribute knowledge towards the development of new inhalers and drugs that require greater selectivity for treating the small airways.



Small airway function in vitro

We have developed a way to study the pharmacology of small human airways in vitro using precision-cut lung slices and videomicroscopy [16b]. Using this technique we have demonstrated the pharmacological characterization of indacaterol, a novel once daily inhaled 2 adrenoceptor agonist, on small airways in human and rat precision-cut lung slices.

LAMA'S (tiotropium) in COPD and the Respimat Inhaler

Monotherapy with bronchodilators (LABA or LAMA) are first line therapy in the GOLD guidelines [GOLD]. According to the current GOLD guidelines [GOLD, bronchodilators should be used in preference to LABA and ICS combinations.

Tiotropium (Spiriva, Boehringer Ingelheim), a long-acting inhaled anticholinergic bronchodilator, improves lung function, quality of life, and exercise endurance and reduces exacerbations in patients with chronic obstructive pulmonary disease (COPD) [Vogelmeier, C , NEJM 2011; Bateman, Respir Med 2010; Cooper, CB, Chest 2013; Tashkin, DP, N Engl J Med 2008] Tiotropium is approved and marketed as

a dry-powder formulation delivered by means of the HandiHaler inhalation device (at a dose of 18 µg) [Boehringer Ingelheim. Summary of Product Characteristics (SPC): Spiriva 18 microgram inhalation powder, hard capsule. eMC, 2012] and as an aqueous solution delivered by means of the Respimat inhaler (at a dose of 5 µg) in many countries [Summary of Product Characteristics (SPC): Spiriva Respimat 2.5 microgram solution for inhalation. eMC, 2013]Crossover trials of tiotropium Respimat at a dose of 5 µg and HandiHaler at a dose of 18 µg for up to 4 weeks have shown similar efficacy, safety, and pharmacokinetic profiles. [van Noord, JA, Respir Med 2009; Ichinose, M, Respir Med 2010]. Cross-study comparisons have suggested the potential superiority of tiotropium Respimat in terms of COPD exacerbations, as compared with HandiHaler [Bateman, Respir Med 2010; Tashkin, DP, N Engl J Med 2008]. Recently, Tiotropium Respimat at a dose of 5 µg or 2.5 µg had a safety profile and exacerbation efficacy similar to those of Tiotropium HandiHaler at a dose of 18 µg in patients with COPD *Wise, NEJM 2013].

Respimat Soft MistTM Inhaler (SMI) is a novel inhaler delivering a unique slow-moving Soft MistTM that allows gentle inhalation – making it easy to inhale. Importantly it has drug particles that are ~ 2microns [16c] that allow an increase in the total lung deposition of drug (~52%) [16d] and also the potential for penetration to treat the small and large airways in patients with COPD; that is targeting the whole airway tree.

2. QUESTIONS THIS STUDY WILL ANSWER

PHASE 1: Effect of Inhaler Training with Handihaler on airway function and symptoms
If we train patients with the Handihaler properly can we

- improve (i) lung function (large and small airway)?
- improve(ii) clinical symptoms (determined by CAT score)?

Mild-moderate COPD [GOLD], established (>1 month) already on HandiHaler- Tiotropium 18 mcg once daily but have ongoing symptoms or exercise limitation (determined by CAT score) to be eligible to enter. So their clinical state may be due to 'real-life' poor inhaler technique (which will be assessed by the research observer). Patients receiving Handihaler who have not been trained for over 3 months on its use will be recruited.

We will train patients in the optimal use of the Handihaler.

So if we train patients with the Handihaler properly can we improve (i) lung function (large and small airway) and (ii) clinical symptoms (determined by CAT score).

Data comparison: Data from Visit 1 will be compared to the Screening Visit data.

PHASE 2: Is the device important in treating the small airways

- Does changing the device from a DPI-Handihaler (in a trained patient) to a SMI-Respimat give an added advantage to the patient? (keeping the dose of the drug equivalent from each device – that is Tio 18mcg HH = Tio 5mcg Resp).
- That is – is there an added advantage with the device that is observed with a change (improvement) in (i) lung function (large and small airway) and (ii) clinical symptoms (determined by CAT score).

• Do the properties of the Respimat device with deeper lung deposition (slow velocity and small particles) can improve small airway measures (and indeed large airway measures) that might also be related to an improvement in symptoms.

Data comparison: Data from Visit 2 will be compared to the Visit 1 data.

3 . RESEARCH AIM & HYPOTHESIS

We aim to investigate the effect of tiotropium from different devices on a panel of small (IOS, MBNW, DLCO, FVC) and large airway (FEV1, PEF) responses in patients with mild-moderate COPD. We will compare Tiotropium Handihaler 18 micrograms once daily with Tiotropium Respimat 5 micrograms once daily.

We will identify a COPD cohort with ongoing symptoms or exercise limitation on HandiHaler, as proposed. The science behind this is why are people still limited (even if partially as determined using the CAT score) and could it be that relatively we need more distal airway targeting (this doesn't necessarily mean acinar/alveolar beyond the terminal bronchioles, but just a little bit more going deeper into the distal conducting airway) that can be achieved with Respimat.

4. STUDY DESIGN: (also see **study treatment dosing flowchart below)**
Target population: N=44 mild COPD patients.
Open (as patients can identify inhaler device), Sequential, 3 visits (including screening visit).

Patients on concurrent oral bronchodilators (theophylline, PDE4 inhibitors) will not be included. Patents on concurrent LABAs will be allowed.

N=44 Patients: Mild-moderate COPD [GOLD], established (>1 month) already on HandiHaler- Tiotropium 18 mcg once daily **but have ongoing symptoms or exercise limitation (determined by CAT score)**

There will be three phases.

- **Phase 0** (Screening visit)
  Patients receiving Handihaler who have not been trained (real-life use) for over 3 months on its use
- **Phase 1**
  Patients will be trained in their use of Handihaler-Tiotropium and asked to take 18 mcg once daily for 14 days to see if their (i) airway lung function and or (ii) clinical symptoms improve AND THEN
- **Phase 2**
  Patients will be switched to trained Respimat Tiotropium 5 mcg once daily for 14 days to see if their (i) airway lung function and or (ii) clinical symptoms improve.

  WHAT HAPPENS AT EACH VISIT?
  (i) Phase 0 - SCREENING VISIT: (DAY 0)
  - IDENTIFY : Mild-moderate COPD [G.O.L.D], established (>1 month) already on HandiHaler-Tiotropium 18 mcg once daily but have ongoing symptoms or exercise limitation (determined by CAT score) to be eligible to enter

  - Patient to avoid short acting SABA and SAMA and LABA on day of visit

- 9am Baseline: Lung physiology measurements undertaken in this order; IOS, MBNW, Spirometry (FVC) /Body plethysmography (DLCO).

- Patient asked to demonstrate how they use Handihaler with a demonstration device. Research observer notes how patient takes Handihaler-Tiotropium to assess good or poor inhalation technique /errors.

- Patient receives training in how to use Handihaler correctly until observer satisfied.

- 10am Patient takes Handihaler-Tiotropium 18 mcg od in Lab. Research observer notes how patient takes Handihaler-Tiotropium.

- 3hours post dosing: Lung physiology measurements undertaken in this order; IOS, MBNW, Spirometry (FVC) /Body plethysmography (DLCO).

Tests:

- Small (IOS, MBNW, DLCO, FVC) airways (these will be done on physiology machines of Dr Usmani)
- Large (FEV1, PEF) airways (these will be done on physiology machines of Dr Usmani)
- CAT score

AIM OF THIS PHASE (0) OF STUDY: Here we want to see that if patients have ongoing symptoms but are on Handihaler-Tiotropium what is happening PRIOR to proper inhaler technique training – that is their 'real-life' use of the inhaler - to their lung function (large and small airways) and also symptoms or exercise limitation (determined by CAT score) will already be recorded as entry criteria

- Patient will be asked to take Handihaler-Tiotropium 18 mcg od at 10am every day for 14 days

(ii) Phase 1 - VISIT 1 (Day 14) (After 14 days OF HANDIHALER TREATMENT)

The patient attends the department.

- Patient to avoid short acting SABA and SAMA and LABA on day of visit

- 9am Baseline: Lung physiology measurements undertaken in this order; IOS, MBNW, Spirometry (FVC) /Body plethysmography (DLCO).

- Patient is trained for Respimat using Respimat demonstration device until observer satisfied.

- Patients switched to Respimat-Tiotropium 5 mcg od and instructed to take it at 10am every day. Patient takes first dose of Respimat-Tiotropium 5 mcg in the department during visit 1 at 10 am.

- 3 hours post dosing: Measurements IOS, MBNW, Spirometry/Body plethysmography undertaken 3 hours post-dosing

Tests:

- Small (IOS, MBNW, DLCO, FVC) airways (these will be done on physiology machines of Dr Usmani)
- Large (FEV1, PEF) airways (these will be done on physiology machines of Dr Usmani)
- CAT score

AIM OF THIS PHASE (1) OF STUDY: *So here we want to see what is happening AFTER proper inhaler technique training on large and small airways lung function and also symptoms or exercise limitation (determined by CAT score)

(iii) Phase 2 - VISIT 2 (DAY 28 OF TIOTROPIUM TREATMENT)

- Patient to avoid short acting SABA and SAMA and LABA on day of visit

- On Day 28 of -Tiotropium treatment patient attends lab and performs the following tests at 9am: IOS, MBNW, Spirometry/Body plethysmography.

- Measurements IOS, MBNW, Spirometry/Body plethysmography undertaken at 10 am.

AIM OF THIS PHASE (2) OF STUDY: *So here we want to see what is happening AFTER this efficient device Respimat (trained) compared to PREVIOUS device Handihaler (trained) on large and small airways lung function and also symptoms or exercise limitation (determined by CAT score). Here we want to see if the properties of the Respimat device with deeper lung deposition (slow velocity and small particles) can improve small airway measures (and indeed large airway measures) that might also be related to an improvement in symptoms.

5. PATIENT ELIGIBILITY

Patients will be eligible for the study if they have COPD and satisfy the following criteria:

Inclusion Criteria

1) Patients with FEV1/FVC <70% predicted.

2) Mild (GOLD stage I: FEV1 >80% pred.) to moderate (GOLD stage II: FEV1 50-80% pred.)

3) Aged 30 years onwards – there is no upper age limit as we do not want to exclude elderly patients as COPD is primarily a disease in the elderly population.

4) Have ongoing symptoms or exercise limitation (determined by CAT score)

5) Stable COPD (no chest infection requiring antibiotics and/or oral steroids in the past 2 months).

6) Capable of giving informed consent, which includes compliance with the requirements and restrictions listed in the consent form.

Exclusion Criteria

1) We will not recruit subjects who lack the capacity to consent.

2) Current or past diagnosis of asthma.

3) Patients on concurrent oral bronchodilators (theophylline, PDE4 inhibitors) will not be included.

4) Patients on other LAMAs will not be included

5) History of any chronic respiratory diseases other than COPD.

6) History of another medical condition, which in the opinion of the Unit Physician, contraindicates his/her participation in the study.

7) Clinical evidence of heart failure (NYHA class III-IV).

8) Unstable respiratory disease in the last four weeks prior to the screening visit (indicated by any change in their maintenance inhaled therapy or who have had a lower respiratory tract infection in the previous four weeks).

9) Evidence of a respiratory exacerbation requiring emergency room treatment and/or hospitalisation within four weeks before screening.

10) Use of systemic (oral or intravenous) steroids 4 weeks prior to inclusion (injectable depot steroids 6 weeks) or more than 3 periods during the last 12 months.

11) Participants with a known or suspected allergy, sensitivity or intolerance to the study drugs (this will be asked directly at the screening visit) or patients with a history of another drug allergy which, in the opinion of the Unit Physician, contraindicates his/her participation in the study.

12 Patients with known or suspected cardiac rhythm disorders

13) Patients treated with beta-blockers in the week preceding the screening visit and during the study period.

14) Females who are pregnant or lactating or are likely to become pregnant during the trial. Women of childbearing potential may be included in the study if, in the opinion of the investigator, they are taking adequate contraceptive precautions.

15) Patients who have evidence of alcohol or substance abuse.

16) Participation in another clinical trial with an investigational drug in the four weeks preceding the screening visit.

17) Contraindication to taking Tiotropium bromide

6. CONCOMITANT THERAPIES

Patients on other LAMAs including oral bronchodilators (theophylline, PDE4 inhibitors) are excluded from the trial. Patents on concurrent LABAs will be allowed.

7. STUDY TESTS

- Small (IOS, MBNW, DLCO, FVC) airways (these will be done on the physiology machines of Dr Usmani)
- Large (FEV1, PEF) airways (these will be done on the physiology machines of Dr Usmani)
- CAT score

8. DRUG DOSING

The study drugs, Handihaler tiotropium 18 micrograms and Respimat tiotropium 5 micrograms and the placebo, for training purposes, will be supplied by Boehringer Ingelheim (Germany) to the Pharmacy of the Royal Brompton Hospital where it will be stored until required. Labels will be assigned to study medication and placebo in accordance to the protocol and ICH GCP by the Pharmacy of the Royal Brompton Hospital – as final packaged medication for each patient. The labels on the packages and unit medication will specify all necessary information for a correct identification of the medication boxes and individual medication units. The Pharmacy of the Royal Brompton Hospital will dispense the study drugs to the patients. All study medication accountability will be performed at the Royal Brompton Hospital by members of the study team and returned/unused medication will be destroyed by the Royal Brompton Hospital Pharmacy at study closure.

We will give 14 days duration of treatment in order to achieve steady state dosing of Tiotropium drug.

- The first dose will be given in the Hospital but subsequent doses will be taken at home.
- Dosing of the drug will be undertaken at the same time each day (ideally 9am)
- We will undertake measurements 3 hours post dosing (applies only to the dose given in the department). The reason we have used 3 hours is to achieve the maximal response pharmacologically with Tiotropium in order to elicit differences within Phase 1 of the study (device training) and Phase 2 (device effects) in Study Group 1.

- We will use Handihaler tiotropium 18 micrograms daily which is licensed for use in COPD.
- We will use Respimat tiotropium 5 micrograms daily which is licensed for use in COPD.

9. DRUG SUPPLY AND MANAGEMENT

- Drugs will be bought from the Royal Brompton Hospital Pharmacy (Where it has been delivered to by Boehringer Ingelheim).
- Placebos for training will be supplied by Boehringer Ingelheim.

10 . SAMPLE SIZE CALCULATION: PRIMARY ENDPOINT / SECONDARY ENDPOINTS

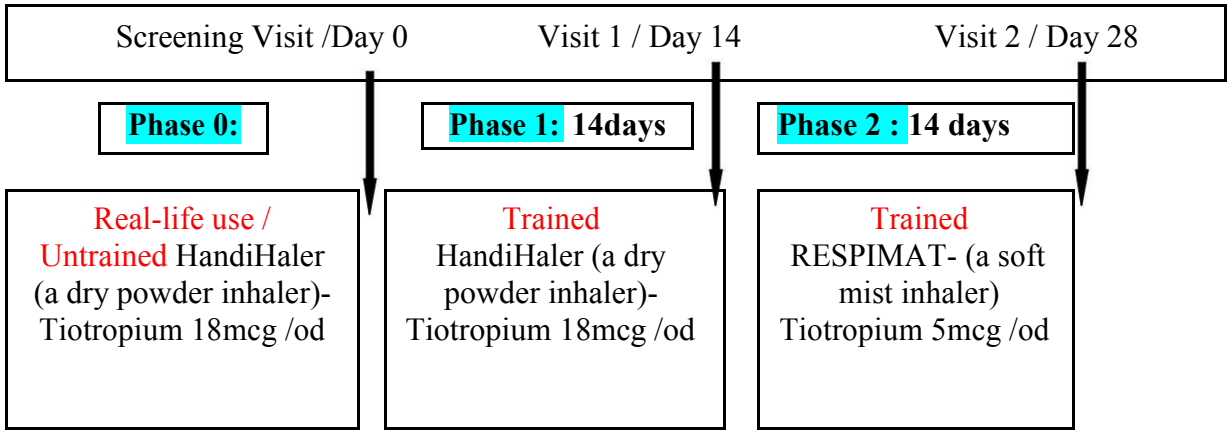
The primary endpoint is the Impulse oscillometry measure of IOS R5-R20.

Each subject will act as their own control and assuming the treatment effect (ie the difference R5-R20 between baseline and 14 days) to be 0.03kPa(L/s) with an SD of 0.05, then 44 subjects will be required to achieve the treatment effect at 1% significance and 90% power.

ANALYSIS:

The secondary endpoints are small airways (MBNW, DLCO, FVC) and large airways (FEV1, PEF) airways physiology and also the CAT score.

11. STUDY TREATMENT DOSING FLOW-CHART



12. INFORMED CONSENT

Patients will be recruited by a member of Dr Usmani's team at the Royal Brompton. At this point they will receive an information sheet and an appointment will be made for them with the research nurse to discuss enrolment into the study. All participants will provide written informed consent. The Informed Consent Form will be signed and dated by the participant before entering the study. The Investigator will explain the details of the study and again provide a Participant Information Sheet, ensuring that the participant has sufficient time to consider participating or not. The Investigator will answer any questions that the participant has concerning study participation.

Each participant has the right to withdraw from the trial at any time. In addition, the investigator may discontinue a participant from the trial at any time if the investigator considers it necessary for any reason e.g. pregnancy, ineligibility

13. TREATMENT DISCONTINUATION CRITERIA

A patient that experiences any serious adverse event *(*SAE), intolerable adverse event (AE), or becomes pregnant must have treatment withdrawn. Patients who fail eligibility criteria must be withdrawn from the trial

14. DEFINITION OF END OF TRIAL

The last visit of the last subject

15. SAFETY AND ETHICAL CONSIDERATIONS:

Safety of Procedures & Intervention:

i) ***Lung Function*** is performed in a safe environment in the RBH Respiratory BRU CRF. Some participants may experience transient coughing after performing a forced blowing manoeuvre into the machine, but this is often short lived and self-rectifying.

ii) ***Impulse Oscillometry (IOS)***is performed in a safe environment in the RBH Respiratory BRU CRF. There are no potential adverse effects associated with IOS.

iii) ***Multi–Breath Washout Test (MBW)*** is performed in a safe environment in the RBH Respiratory BRU CRF. Participants may experience a slight dryness in their mouth from the breathing test which takes approximately 5 minutes. Water will be provided for patients and they will be seated on a comfortable chair.

iv) ***Tiotropium Bromide***

Any patient with a contraindication to taking Tiotropium bromide, listed in the British National Formularly (BNF) will not be entered into this study. This will form part of the exclusion criteria.

v) Foreseeable A serious adverse event (SAE) for Tiotropium as listed in BNF.

Taste disturbance, stomatitis, gastro-oesophageal reflux, epistaxis, oropharyngeal candididiasis, intestinal obstruction (including paralytic ileus) laryngitis, insomnia, urinary-tract infection, skin infection, sinusitis, dental caries, gingivitis, glossaitis, skin ulcer, joint swelling, dry skin. These will not be reported as SAE but will be logged appropriately.

Adverse events

An **adverse event** (AE) is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not

considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or wash-out periods, even if no study treatment has been administered.

A **serious adverse event (SAE)** is an AE occurring during any study period (i.e., run-in, treatment, wash-out, follow-up), and at any dose of the investigational product, comparator or placebo, that fulfils one or more of the following criteria:

- results in death
- is immediately life-threatening
- requires in-patient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect
- is an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above

A distinction should be drawn between serious and severe events. A severe event is a major event of its type. The term “severe” is used to indicate the intensity of a specific event, while the term “serious” is based on patient/event outcome or action criteria.

A **suspected unexpected serious adverse reaction (SUSAR)** is any adverse event with a reasonable possibility of a link to the study drug that is both serious and unexpected (i.e. not consistent with the information about the study drug in either the SPC or IB).

Procedures for Serious Adverse Event Reporting

An SAE form should be completed and faxed to the Trial Manager/Chief Investigator for all SAEs (or AESIs) within 24 hours. The Trial Manager/Chief Investigator should inform the sponsor of all SAEs within 24 hours of receiving notice. All SAEs should be recorded on the annual safety reports that are sent to the MHRA and REC on the anniversary of the date a favourable opinion for the study was given.
Contact details for reporting SAEs and SUSARs Fax: 0044 207 351 8937, attention Dr Omar Usmani Please send SAE forms to: Dr Omar Usmani Tel: 0044 207 351 8051 (Mon to Fri 09.00 – 17.00)
Contact details for reporting SAEs and SUSARs to the Sponsor Fax: 0203 311 0203

SUSAR reporting

Expedite Reporting will be performed by the Principal Investigator in case of any suspected, unexpected, serious adverse reaction (SUSAR) or in case of other safety issues that qualify for expedite reporting, in accordance with the European Directive 2001/20/EC. In the case of suspected unexpected serious adverse reactions, the staff at the site should:
Complete the SAE case report form & send it immediately (within 24 hours, preferably by fax), signed and dated to the study coordination centre together with relevant treatment forms and anonymised copies of all relevant investigations.
Or
Contact the study coordination centre and/or the CI as above by phone and then send the completed SAE form to the study coordination centre within the following 24 hours as above.

The study coordination centre will notify the MHRA, REC and the Sponsor of all SUSARs occurring during the study according to the following timelines; fatal and life-threatening within 7 days of notification and non-life threatening within 15 days. All investigators will be informed of all SUSARs occurring throughout the study.

The expedite reporting to the Competent Authority and Ethics Committee will be performed as follows:

- fatal or life-threatening SUSAR, will be reported as soon as possible but no later than 7 calendar days after first knowledge of the minimum criteria for expediting reporting. Relevant follow-up information will be completed as soon as possible and sent within an additional 8 calendar days.
- non fatal or life-threatening SUSAR, will be reported as soon as possible but no later than 15 calendar days after first knowledge of the minimum criteria for expediting reporting.

SUSAR and SAE reporting

Copy of SAE/SUSAR reporting will be notified by the Principal Investigator to the Sponsor's Representative at Imperial College Joint Research Compliance Office (JRCO) within 24 hrs of becoming aware of the event.

Data Handling and Record Keeping

Hard copies of participant's trial research files will kept under lock and key in the RBH Respiratory BRU CRF. Access to these will be limited to the Respiratory Physician conducting the study (Dr Omar Usmani), the Co-Investigator (Dr Martyn Biddiscombe) and the Clinical Research Nurse (Ms Sally Meah). All files will have non identifiable information, that is, each participant will only be identified by a study code and the study codes for each participant will be kept in a separate locked cabinet.

The Investigators will permit trial-related monitoring, audits, IRB/IEC reviews and internal and external regulatory inspection with provision and direct access to source documents and data. The following has been included in the Patient Information Sheet to patients;

It will be the responsibility of the Chief Investigator and Consultant Respiratory Physician conducting the study − Dr Omar Usmani, to ensure the well−being of all participants and that they are able to contact him for any queries regarding the study. Dr Usmani & Ms Sally Meah will also be responsible for the daily management and monitoring of the research data and management of the staff involved with the research.

Dr Usmani & Ms Sally Meah will liaise with the clinical research governance office at Imperial College with respect to auditing the research study.

Overall responsibility for the study lies with the Chief Investigator, Dr Omar Usmani, Clinical Senior Lecturer and Honorary Consultant in Respiratory Medicine, National Heart and Lung Institute, Imperial College. The project will be registered with the Clinical Research Office of Imperial College London and on **ClinicalTrials.gov**.

Indemnity

Indemnity will be provided by Imperial College Indemnity Scheme which has been arranged through the Clinical Research Office at Imperial College. Public Liability cover is also provided for Imperial College under this policy reference number.

Publication

It is hoped that the results and data from the research will be available publicly in peer-reviewed publications. Although no specific publications will be produced for the research participants, should a participant request feedback on the outcome of research towards which they have contributed, this will be provided to them. Information about publication arrangements will be included in the participant information sheet, as well as a statement regarding information on individual requests for feedback on the study results.

16. STUDY COSTS

PERSONNEL (ICL)	
STUDY	
PHARMACY (RBH)	
	-set-up
	-IMP management fee/month
	-dispensation inc. reconciliation
	-DRUG COSTS
RBH CRF COSTS	**- room use**
R&D (RBH)	
	-set-up
	-per patient RBH Trust
INFORM DATA MANAGEMENT	
	Design, development and documentation of e-CRF with monitor/audit in place
PATIENTS (ICL)	
	patient inc travel, food and inconvenience
EQUIPMENT SMALL AIRWAYS & SERVICE (ICL)	
	IOS and MBNW / annum
CONFERENCE	
	Support to either ERS or ATS inclusive of economy travel, registration, hotel

- ***Statistical support will be given by Boehringer Ingelheim***
- ***Placebo inhalers Handihaler and Respimat will be supplied by Boehringer Ingelheim***

Study Budget	**GBP**
STAFF COSTS (salary & on-costs)	

PI	£39,658.11
Researcher (adjust start date June 1st 2015)	£179,526.97
DIRECT STUDY CONSUMABLES	
Patient volunteer payments	£12,740.69
Consumables	£2,919.15
Pharmacy costs	£6,024.36
Drug costs	XXXX
R&D costs	£6,625.16
BRU(Biomedical Research Unit) costs (room hire)	XXXX
Travel costs	£2,038.51
InForm costs	£21,842.80
FACILITIES & EQUIPMENT	
Access charges	£34,503.47
Infrastructure costs	£8,972.65
TOTAL	**£314,851.87**

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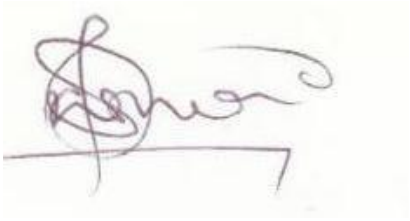
SIGNED:
DR OMAR S USMANI



PRINCIPAL INVESTIGATOR
01.09.2016