Full Clinical Study Protocol

Validation of the Concept of COPD Control In Clinical Practice

Protocol Version 1.0

Study number: REG-RES1503

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This clinical study will be conducted in accordance with current Good Clinical Practice (GCP) as directed by the provisions of the International Conference on Harmonization (ICH); European Union (EU) Directives; Directive 2001/20/EC ('The Clinical Trials Directive') and local country regulations

INVESTIGATOR AGREEMENT

Clinical Study Protocol:

Validation of the concept of COPD control in Clinical Practice **v.1**

Investigator:

Title:

Address of Investigational Center

Tel:

I have read the protocol and agree that it contains all necessary details for carrying out this study. I am qualified by education, experience and training to conduct this clinical research study. I will conduct the study as outlined therein.
I will provide copies of the protocol and all information on the drug relating to the nonclinical and prior clinical experience, which were furnished to me by the sponsor, to all physicians and other study personnel responsible to me who participate in this study, and will discuss this material with them to ensure that they are fully informed regarding the drug and the conduct of the study.
I agree to keep records on all patient information (i.e. case report forms and informed consent statements, in accordance with local and national Good Clinical Practice (GCP) regulations.

Investigator's Signature **Date**

Marc Miravitlles

Sponsor's Authorised Representative **Date**

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CLINICAL STUDY PERSONNEL CONTACT INFORMATION

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CLINICAL STUDY PROTOCOL SUMMARY

Title of Study: Validation of the Concept of COPD Control In Clinical Practice
Protocol version: 1.0
Study Number: REG-RES1503
Chief Investigator: Dr Marc Miravitlles
Clinical Research Organisation: Respiratory Effectiveness Group
Part study funder: REG and Novartis
Name of Active Ingredients: NA
Name of Investigational Product: NA
Phase of Clinical Development: 4
Number of Investigational Centres Planned: approximately 10 Centres
Country of the study: International – Spain, France, UK, Ireland, Canada
General Design and Methodology:
This is a 21-month pragmatic non-interventional trial comprising one baseline assessment and 4 follow-up visits.
Objectives: The primary aims of the study will be to evaluate the:

- Levels of COPD control (vs poor COPD control) in an international cohort of routine care COPD patients, and
- The clinical implications of control status.

Secondary objectives of the study are to:

- Compare the utility of the COPD Control (as defined) as a tool to identify COPD impact and stability with the CAT and CCQ;
- Evaluate the role of “adequate” (i.e. guideline-recommended) treatment prescribing on COPD control.
- Identify demographic and clinical characteristics associated with COPD control
- Evaluate the cost-utility of patients with controlled (as compared to poorly controlled) COPD.

Number of Patients Planned: 328
Study Population: It is planned to enrol approximately 328 patients older than 40 years with a diagnosis of COPD The diagnosis of COPD will be based on a post-bronchodilator FEV1/FVC<0.7 in patients smokers or smokers of at least 10 pack-years, in accordance with the Global Initiative for Obstructive Lung Disease (GOLD).
Length of the Study: Length of the study will be approximately 21 months from baseline screening to final patient follow-up.
End of the Study: Last patient’s last visit.
Inclusion Criteria: Patients may be included in the study if they meet all of the following criteria:

- Spirometry-defined COPD (i.e. post-bronchodilator FEV1/FVC<0.7)
- Age ≥40 years
- Smokers or ex-smokers of at least 10 pack-years
- In stable state (as judged by the investigator) at point of recruitment

Exclusion Criteria: Patients will be excluded from participating in this study if they meet any of the following criteria:

- Have any concomitant chronic respiratory condition other than asthma or bronchiectasis (e.g. cystic fibrosis, lung fibrosis)
- Have severe comorbidity with a life expectancy shorter than 2 years
- Are unable to understand the instructions of the study or to fill the questionnaires
- Are unwilling to sign the informed consent
- Are participating in another clinical study or clinical trial

Investigational Product: NA (non-interventional study)
Placebo: NA (non-interventional study)

Blinding: NA (non-interventional study)
Method of Randomisation: NA (non-interventional study)

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table of abbreviations

Abbreviation	Definition
BMI	Body Mass Index
BODE	Composite COPD severity index: BMI, Obstruction, Dysnea, Exacerbations
CAT	COPD Assessment Test
CCQ	Clinical COPD Questionnaire
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case report form
eCRF	electronic case report form
FEV1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
ICS	inhaled corticosteroid
LABA	long-acting beta-agonist
SAB	Short-acting bronchodilator
SABA	short-acting beta-agonist
SAMA	short acting muscarinic antagonist
Mild to moderate disease severity	BODE/Ex ≤4 points
mMRC	modified medical research council dyspnea scale
Severe / very Severe disease severity	BODE/Ex ≥5 points

Definitions

Impact

Clinical impact refers to the current repercussion the disease has on the patient. According to the ECLIPSE study, patients with the same level of prognostic severity (FEV_1 and/or BODE index) can have a wider distribution of across a range of clinical characteristics, such as dyspnea, HRQoL and 6-minute walking test (1). Within a given severity category of COPD, COPD is defined using a number of clinical variables: degree of dyspnea, the use of rescue medication, the limitations in daily physical activity and the usual sputum color, OR using validated questionnaires (the CAT and CCQ) (2, 3).

Table 1. Definition of COPD summary by COPD Severity Category

	Mild to moderate severity (BODE/Ex ≤ 4 points)		Severe/very severe COPD (BODE/Ex > 5 points)	
Impact	**Low***	**High**	**Low**	**High**
Dyspnea (mMRC)	0 – 1	≥ 2	0 - 2	≥ 3
Rescue medication	≤ 3 times in the last week	> 3 times in the last week	≤ 2 times a day	> 2 times a day
Daily physical activity (time walked/day)	≥ 60 min	< 60 min	≥ 30 min	< 30 min
Sputum color^	Absent or White	Dark	Absent or white	Dark
OR (if using validated COPD questionnaires to assess impact), **either of the following:**				
- CAT	≤ 10	>10	≤ 20	>20
- CCQ	≤ 1	>1	≤ 2	>2

Stability

Clinical stability over time is defined as a composite of the following over a 3-month evaluation period:

1. Absence of exacerbation (including the inherent phase of recovery from the exacerbation), AND
2. Absence of significant clinical worsening* during a period of time, that is, that stability includes the absence of significant clinical changes and/or the presence of improvement (positive changes).

*The CAT and CCQ have demonstrated potential utility in evaluate clinical changes over time (4,5). Clinically significant deterioration has been described as being associated with a change of ≥2 CAT points (6) and/or a change of ≥0.4 CCQ points (6).

Table 2. Definition of COPD stability by COPD Severity Category

Clinical stability over time (3-month evaluation period)		**Mild to moderate severity (BODE/Ex ≤ 4 points)**		**Severe/very severe COPD (BODE/Ex > 5 points)**	
		Stable	**Unstable**	**Stable**	**Unstable**
No Exacerbations	Exacerbations	None	≥1	None	≥1
AND					
No Clinical Worsening	Changes in the CAT	<2	≥2	<2	≥2
	AND/OR				
	Changes in the CCQ	< 0.4	≥ 0.4	≤ 20	>20

Definition of COPD Control

Control of COPD is defined as a composite of low disease impact, adapted to the patients' level of COPD severity, and clinical stability over time.

Mild to moderate disease severity (BODE/Ex ≤4 points)

Controlled: Patients are controlled if, at the time of evaluation, their COPD:

- Impact is low, i.e. all of the following criteria are satisfied:
  - *Limited signs of dyspnea*: mMRC 0–1
  - *Minimal recent rescue medication (short-acting bronchodilator) usage*: ≤3 times in the last week
  - *Limited impact on daily physical activity:* ≥60 minutes walked per day
  - *Absence of sputum,* or (if present) white sputum

  OR
  - CAT: ≤10,

  AND
  - CCQ: ≤1

  AND
- Clinically Stable in the last 3 months:
  - Absence of COPD exacerbations, AND
  - Any changes in CAT have been less than <2 points in magnitude, OR,
  - Any changes in CCQ <0.4

Uncontrolled: all others

Severe / Very Severe Disease (BODE/Ex ≥5 points)

Controlled: Patients are controlled if, at the time of evaluation, their COPD:

- Impact is low, i.e. all of the following criteria are satisfied:
  - *Limited signs of dyspnea*: mMRC 0–2
  - *Minimal recent rescue medication (short-acting bronchodilator) usage*: ≤2 times a day
  - *Limited impact on daily physical activity:* ≥60 minutes walked per day
  - *Absence of sputum*, or (if present) white sputum

  OR
  - *CAT ≤20*

  AND
  - *CCQ ≤2*

  AND
- Clinically Stable in the last 3 months:
  - Absence of COPD exacerbations, AND
  - Any changes in CAT have been less than <2 points in magnitude, OR,
  - Any changes in CCQ <0.4

Uncontrolled: all others

Table 3. COPD Control definition represented in tabular form, by COPD severity

Patients with COPD will be defined as having controlled disease if they satisfy all of of the following criteria		**Mild to moderate severity (BODE/Ex ≤ 4 points)**	**Severe/very severe COPD (BODE/Ex > 5 points)**
IMPACT (cross-sectional evaluation)	Dyspnea (mMRC)	0 – 1	0 - 2
	Rescue medication	≤ 3 times in the last week	≤ 2 times a day
	Daily physical activity (time walked/day)	≥ 60 min	≥ 30 min
	Sputum color^	Absent or White	Absent or white
	OR (if using validated COPD questionnaires to assess impact), **either of the following:**		
	CAT	≤ 10	≤ 20
	CCQ	≤ 1	≤ 2
AND			
CLINCIAL STABILITY (longitudinal evaluation)	Exacerbations	None	None
	AND		
	Changes in the CAT	<2	<2
	AND		
	Changes in the CCQ	<0.4	<0.4

1. BACKGROUND

1.1. Introduction

Chronic obstructive pulmonary disease (COPD) is a broadly heterogeneous condition. Optimum therapeutic outcomes require treatment to be tailored to the different clinical characteristics and severity of each patient (7-9). To a certain extent, the Spanish Guidelines for COPD (GesEPOC) represent a model of transition towards personalized medicine (10). In these guidelines pharmacological treatment is established with a combination of two essential elements: (i) the determination of the clinical phenotype and (ii) evaluation of the level of severity with the use of a multidimensional index. Multiple therapeutic alternatives emerge from the interaction between these two axes (clinical phenotype and the level of severity), constituting the first step towards individualization of treatment, which has been followed by other national clinical guidelines (11).

However, this approach can overlook changes in the day-to-day activities or symptoms of the patient, changes that may warrant modifications to their existing treatment. Within each clinical phenotype and each level of severity of COPD there are patients with a range of different “expressions” (i.e. symptoms, activity limitations, short-term changes) of their disease. Thus, the concept of disease control may help to better assess the state of the patients and their likely response to treatment. A third axis (control of the disease) should help in therapeutic decision making and has been recently proposed (12,13).

The concept of control has been extensively developed in asthma but little-explored in COPD. Recently, however, Soler-Cataluña et al proposed a new definition/concept of control for COPD. The concept aims to help describe the current clinical “situation” of the patient and to provide a tool that will help guide optimum treatment approaches for patients with COPD(14).

The definition has two components: (i) COPD impact and (ii) COPD stability. “Impact” is a cross-sectional concept that evaluates the clinical status of a patient. It is static assessment corresponding to a specific moment and can be assessed by questionnaires (i.e. the COPD Assessment Test [CAT] or the Clinical COPD Questionnaire [CCQ]) or evaluated based on a patient’s degree of dyspnea, use of rescue medication, level of physical activity and sputum colour. The temporal evolution of this impact (i.e. COPD stability) is a dynamic term. “Stability” is a

longitudinal concept that requires the absence of exacerbations and deterioration in the aforementioned variables or in CAT or CCQ scores. Hence, control is defined as a condition that has both low impact (adjusted for severity) and stability (14).

Having proposed the concept of control in COPD, it is now important to establish whether the it has clinical validity and utility, specifically in terms of predicting outcomes and guiding on-going COPD management (and/or whether the measure may benefit from further refinement).

1.2. Compliance statement

This study will be conducted in full accordance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Consolidated Guideline (E6) and any applicable national and local laws and regulations (e.g. European Union [EU] Directive 2001/20/EC and 2005/28/EC). Any episodes of noncompliance will be documented.

The investigators are responsible for performing the study in accordance with this protocol and the applicable GCP guidelines for collecting, recording, and reporting the data accurately and properly. Investigator Agreements to conduct and administer this study in accordance with the protocol will be documented in separate study agreements with the sponsor.

Each investigator is responsible for ensuring the privacy, health, and welfare of the patients during and after the study and must ensure that trained personnel are immediately available in the event of a medical emergency. Each investigator and the applicable study staff must be familiar with the background and requirements of the study.

The Chief Investigator has overall responsibility for the conduct and administration of the study at different study centres and the Principal Investigators in each local study centre have the overall responsibility for the conduct and administration in each individual local study centre.

1.3. Population to be studied

It is planned that this study will enroll no fewer than 328 patients with a range of COPD severities, Eligible patients will have spirometry-defined COPD (i.e. post-bronchodilator FEV1/FVC<0.7), be over 40 years' of age, be current smokers or ex-smokers with at least 10 pack-years of smoking exposure and be in a stable clinical state (as judged by the investigator) at point of recruitment.

2. STUDY OBJECTIVES AND RATIONALE

2.1. Hypothesis

Control in COPD is a new conceptual dimension requiring demonstration of both low impact and clinical stability. The developers of the concept hypothesize that a status of control in COPD will be associated with better clinical outcomes (reduced frequency of exacerbations and mortality and improved health-related quality of life); reduced rate of decline in lung function and/or BODE/BODEx and reduced direct COPD-related healthcare costs.

2.2. Primary objectives

Following the publication of the Concept of COPD Control (6) and building on a retrospective pilot study designed to characterize evaluate the clinical implications of COPD control status within a UK primary care COPD population, the aim of this study is to validate the concept of control utilizing an international, multi-centre prospectively trial design.

The primary aims of the study will be to evaluate, in an international cohort of routine care / unselected COPD patients, the:

1) Levels of COPD control (vs poor COPD control), and
2) Clinical implications of control status.

2.3. Secondary objectives

With a view to identifying opportunities to refine the tool to optimize its clinical utility and ability to guide treatment decisions to improve COPD outcomes (reduce disease burden and improve stability) and to identify patients in whom it may be best targeted (in terms of beneficially modifying outcomes and achieving cost efficiencies, a number of secondary objectives will also be evaluated. The secondary objectives of the study will aim to:

1) Compare the utility of the COPD Control (as defined) as a tool to identify COPD impact and stability with the CAT and CCQ;
2) Evaluate the role of “adequate” (i.e. guideline-recommended) treatment prescribing on COPD control.
3) Identify demographic and clinical characteristics associated with COPD control status

3. PARTICIPATING / RECRUITING CENTRES

Patients will be recruited to the study from centres across 5 participating countries[1]. Where there are multiple participating centres in one country, one centre has been selected to be the lead, coordinating centre for that country.

The coordinating centres for the study will be:

Country	Centre	Clinical Lead
Canada	Montreal Chest Institute	Jean Bourbeau
Ireland	R□□□□□□□□□□□□□□□□□ □□□□□□□, Dublin	R□□□□□□□□□□□□ □□□
Spain	Hospital Universitari Vall d'Hebron, Barcelona	M□□□□□□□□□□□□ □□□
France	Initiatives BPCO	N□□□□□□□□□□□e
Singapore	Singapore General Hospital (SingHealth)	Therese Lapperre

4. STUDY DESIGN

4.1. General design and study scheme

This will be a 21 months prospective pragmatic trial, comprising 5 evaluation points: one screening evaluation and 4 follow-up evaluations (see Figure 1). At screening visit, eligible patients will have a full clinical assessment, including evaluation of: current smoking status, presence of comorbidities; spirometry and baseline questionnaires (including CAT and CCQ). Control will be evaluated at each follow-up visit. Throughout the trial, patients will be managed according to the criteria of the investigators. Clinical assessments will be carried out either by the participating clinicians/investigators or nominated colleagues.

Figure 1. Schematic overview of the study

[1] A sixth country—the United Kingdom—will collect the data outlined in this study protocol through a best practice COPD service that will run in parallel to the trial and be implemented by the not-for-profit social enterprise, Optimum Patient Care Ltd: http://optimumpatientcare.org

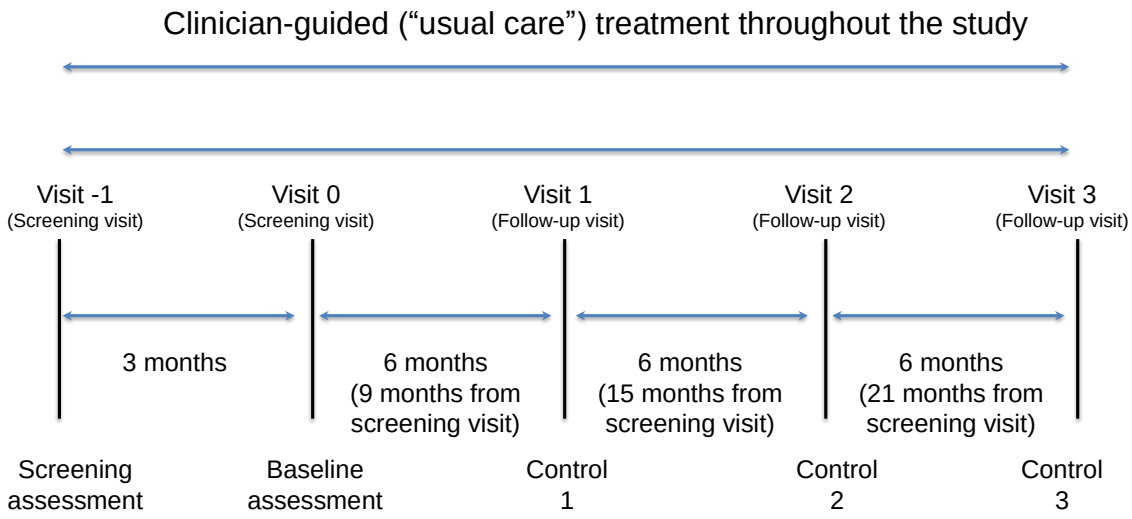

Table 4. Visit summary

Visit number	-1	0	1, 2 and 3
Time of Visit	Inclusion	Baseline 3 months	9, 15 and 21 months or discontinuation
Inclusion/Exclusion criteria	✔		
Information & Informed consent	✔		
Clinical assessment	✔	✔	✔
Assessment of exacerbations since last visit*	✔	✔	✔
Assessment of clinical status since last visit	✔	✔	✔
CAT/CCQ	✔		
Adverse events		✔	✔

4.2. Eligibility Criteria

4.2.1. Inclusion criteria

Eligible patients must meet the following inclusion criteria, be/have:

1) Spirometry-defined COPD (i.e. post-bronchodilator FEV1/FVC<0.7)
2) Age ≥40 years
3) Smokers or ex-smokers of at least 10 pack-years
4) In stable state (as judged by the investigator) at point of recruitment

4.2.2. Exclusion criteria

Patients will be excluded from the trial if any of the following are true, they:

1) Have any chronic concomitant respiratory condition other than asthma or bronchiectasis (e.g. cystic fibrosis, lung fibrosis)
2) Have severe comorbidity with a life expectancy shorter than 2 years

3) Are unable to understand the instructions of the study or to fill the questionnaires
4) Are unwilling to sign the informed consent
5) Are participating in another clinical study or clinical trial.

4.3. Outcomes

4.3.1. Primary outcomes

The primary study outcome will be measured over the 21-month follow-up period.

The primary outcome of interest will be the difference in (annualized) rates of a composite endpoint ("Mortality, hospitalisations and serious COPD morbidity") for patients controlled vs uncontrolled at baseline. The composite endpoint is defined as occurrence of any of the following:

- For COPD: unscheduled visits to the physician; emergency room attendance
- An exacerbation of COPD
- All-cause: hospitalization or mortality

4.3.2. Secondary outcomes

The secondary outcome for the study will be:

1) The (annualized) rate of exacerbations in patients controlled and uncontrolled at baseline
2) Time to the first composite event in patients controlled and uncontrolled at baseline
3) Time to the first exacerbations in patients controlled and uncontrolled at baseline
4) Comparison of CAT and CCQ as tools to identify impact and stability in COPD (i.e. a comparison of their scores' alignment with other relevant scores over the 24-month follow up period).
5) Distribution of control level across in those receiving guideline vs non-guideline recommended therapy (i.e. stratification of control across different treatment groups)
6) Demographic and clinical characteristics associated with poor control of COPD (i.e. comparison of control status across different demographic groups).

4.4 Clinical Visits

4.4.1. Visit -1 (inclusion visit)

4.4.1.1. Visit -1: Inclusion Procedures

Visit -1 will consist of one consultation, split into two components – a pre-screening phase and (in eligible patients) a post screening further assessment component. A

signed and dated informed consent will be obtained during visit -1, before any screening procedures commence. After giving informed consent, patients will proceed through the study visit as depicted in Figure 1.

4.4.1.2. Visit -1: Inclusion Assessment

Patients eligibility will be assessed at the screening visit before any further information / data is / are collected.

Table 5. Inclusion data collection

Visit number: -1
Inclusion/Exclusion criteria: • Age • Smoking: – Current status – History (pack years) • Spirometry: – FEV1 – FEV1/FVC
Information & Informed consent
Clinical assessment (additional to inclusion/exclusion criteria): • Comorbidities (physician-diagnosed) • Post-bronchodilator spirometry • History of previous exacerbations/hospitalisations • Respiratory symptoms • Respiratory medications • Medications for comorbidities • COPD clinical phenotype • Mood (PhQ-4)

Visit number: -1
Demographic assessment (additional to inclusion/exclusion criteria): • Sex • Height • Weight • Lifestyle factors: occupation; alcohol use
Assessment of COPD Impact • Sputum – Absent – Present: colour = white – Present: colour = dark • Daily physical activity (time walked/day) – <30 minutes – ≥30 minutes but <60 minutes – ≥60 minutes • Dyspnea (mMRC score) – 0–1 – 0–2 – ≥2 – ≥3 • Resucue medication use (SAB) – Number of times in the last week (0-3; >3) – Number of times a day (0-2; >2) – ≥3
COPD Severity: BODE/BODEx Index (calculated; components captured as part of other assessments outlined)
CAT **CCQ**

4.1.3. Informed Consent

All patients will be asked to give written informed consent having had sufficient time to review and consider the patient information sheet. A signed and dated informed consent form will be obtained before screening procedures commence.

After informed consent is obtained, patients who are screened will be assigned a permanent identification number such that all patients from each investigational centre are given consecutive identification numbers following their inclusion.

A patient who is screened but not enrolled, e.g. because entry criteria were not met or enrolment did not occur within the specified time, may not be considered for screening again.

4.4.1.3. COPD review

Demographics and life-style

Demographic information including age, height, weight, date of diagnosis of COPD and occupation, and life-style information including current and past smoking history

and alcohol consumption will be recorded.

Lung Function

Post-bronchodilator forced expiratory volume in one second (FEV1), percentage of predicted forced expiratory volume in one second (FEV1 % predicted), forced vital capacity (FVC) and percentage of predicted forced vital capacity (FVC % predicted) will be measured.

COPD history in the last 12 months (routine data and patient reported)

A review of the routine data will also be performed to establish the number of COPD exacerbations (defined as acute course of antibiotics or oral steroids course for COPD or an emergency room attendance or hospitalisation for COPD) recorded in the 12-month period prior to screening visit.

Patients will also be asked the number of times they have had a COPD exacerbation in the12 months prior to screening visit to confirm events recorded in the routine data.

CAT (total score and individual component responses), EQ5-D and CCQ will be evaluated to enable change in these measures/scores to be evaluated at follow-up visits.

COPD Severity

In order to assess patients COPD severity at baseline, their BODEx Index Score will be evaluated: BMI, obstruction, dyspnea (breathlessness); exacerbations.

COPD Impact Assessment

In order to assess patients' degree of COPD impact at baseline, information on sputum (presence and colour), breathlessness (mMRC), daily physical activity (minutes walked/day) and (patient reported) rescue medication use will be recorded.

Co-morbidities

Current co-morbidities will be identified by diagnostic codes (and or therapy) and will be confirmed by the patient.

COPD and other medications

A review of COPD and concomitant therapies currently prescribed and used by the patient will be performed to support evaluation of the secondary objective (role of guideline-recommended therapy on COPD control).

4.4.2. Visits 0–3: Baseline and follow-up assessment

In baseline visit (3 months after screening visit) patients will be included in one of the study groups (controlled patients or uncontrolled patients) according definitions. The following data will be collected at the time of each follow-up visit in order to assess disease stability between follow-up visits and disease control at time of each visit.

Table 7. Follow up visit date capture

Visit numbers: 0-3 (inclusive)
Time of Visit: Follow-up (3 months; 9 months; 15 months; 21 months)
Information & Informed consent
Clinical assessment (additional to inclusion/exclusion criteria): • History of previous exacerbations/hospitalisations • Respiratory symptoms • Respiratory medications • Mood (PhQ-4)[2]
Assessment of COPD Impact • Sputum – Absent – Present: colour = white – Present: colour = dark • Daily physical activity (time walked/day) – <30 minutes – ≥30 minutes but <60 minutes – ≥60 minutes • Dyspnea (mMRC score) – 0–1 – 0–2 – ≥2 – ≥3 • Resucue medication use (SAB) – Number of times in the last week (0-3; >3) – Number of times a day (0-2; >2) – ≥3
COPD Severity: BODE/BODEx Index (calculated; components captured as part of other assessments outlined)
CAT **CCQ**

[2] Visit 0 and 3 only

4.5. SAMPLE SIZE CALCULATION

Based on a previous pilot study in Spain, approximately 55% of patients with COPD are controlled based on the proposed criteria. The sample size has to be calculated in order to have enough sample of both subgroups (controlled/non controlled) in both levels of severity (mild to moderate and severe to very severe) that will allow to identify differences in outcomes (main outcome: difference in annualised rate of composite outcome). Since there is not previous information about the frequency of the composite outcome, we have performed a conservative approach using the expected frequency of exacerbations in the sample calculation. According to results from ECLIPSE Study, annualised rate of exacerbations in COPD patients in entire sample was 1.2 per person (15). We hypothesize that, in controlled COPD patients, this annual rate can be 40% lower (0.72 per person). Accepting an alpha risk of 5% and a beta risk of 10% in a two-sided test, a total of 285 COPD patients will be necessary to find this annualised incidence ratio difference as statistically significant. It is expected that two thirds of controlled patients have mild to moderate COPD and one third of these have severe to very severe COPD. With an expected drop-out rate of 15%, a total of 328 patients will be enrolled in the study. Sample size has been calculated with !NI2IS macro (SPSS V20).

5. PATIENT MANAGEMENT DURING THE CONDUCT OF THE STUDY

In accordance with a pragmatic study design, patients will receive usual care by their own physician during the conduct of the study. The time between visits, 3-6 months, is in accordance with usual clinical practice and the recommendations of guidelines for regular follow-up of moderate to severe COPD patients.

Other than attending the required number of clinical visits (baseline, and 4 follow-up visits) patients will not be contacted by the research team in relation to this study.

6. STUDY TERMINATION AND PATIENT WITHDRAWAL

6.1. Study termination

There are no formal rules for early termination of this study. During the conduct of the study, serious adverse events will be reviewed as they are reported from the investigational centre to identify safety concerns. The study may be terminated by the sponsor at any time.

6.2. Patient withdrawal

In accordance with the Declaration of Helsinki, each patient is free to withdraw from the study at any time for any reason. The investigator also has the right to withdraw a patient from the study in the event of intercurrent illness, adverse events, or other reasons concerning the health or well-being of the patient, or in case of a protocol deviations.

Should a patient decide to withdraw, all efforts will be made to complete and report all observations up to the time of withdrawal. A complete final evaluation at the time of the patient's withdrawal should be made, and any explanation given by the patient as to why they are withdrawing from the study should be recorded.

The reason for and date of withdrawal from the study must be recorded in the eCRF. If a patient withdraws consent, every attempt will be made to determine the reason. If the reason for withdrawal is an adverse event, monitoring will be continued at the discretion of the investigator (e.g. until the event has resolved or stabilised, until the patient is referred to the care of a health care professional, or until a determination of a cause unrelated to the study drug or study procedure is made). The specific event must be recorded in the eCRF.

7. PAYMENTS TO PARTICIPATING CENTRES

Participating centres will be reimbursed in lieu of incremental cost associated with administration of the study, up to a maximum of ~€100 per patient for the first 50 patients. Payment for additional patients will not be guaranteed, but can be discussed with the Authorised Sponsor Representative on a centre-by-centre basis.

8. ADVERSE EVENT REPORTING

No solicited safety data capture is required as this is a prospective study using primary data collection without a drug of interest. However, if during the course of the study participation an adverse event suspected to be associated with the use of a medicinal product is identified in a patient it will be reported to the local Health Authority in accordance with national regulatory requirements or the Marketing Authorization Holder.

The occurrence of adverse events will be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments.

8.1. Definition of Adverse Events

All types of Adverse Events are defined in Table 8, below.
Worsening of the disease during the study will be recorded as an Adverse Event only if the presentation and/or outcome is more severe than would normally be expected from the normal course of the disease in a particular patient.

An exacerbation of COPD is defined as worsening COPD requiring the use of systemic corticosteroids, antibiotics and/or emergency room visit or hospitalisation.

An COPD exacerbation will not be considered an Adverse Event unless it meets the criteria for a serious adverse event. COPD exacerbations that do not meet the criteria for reporting as a serious adverse event will be documented separately from Adverse Events.

Patients with a COPD exacerbation will not be discontinued from the study unless hospitalisation is required, the patient meets any of the stopping criteria in Section 8, or the Principal Investigator believes it is in the patient's best interest to be withdrawn from the study.

Table 8. Definition of adverse events

Adverse Event (AE)	An untoward medical occurrence which does not necessarily have a causal relationship to the IMP or comparator, such as: □ intercurrent illnesses □ physical injuries □ events possibly related to concomitant medication □ significant worsening (change in nature, severity, or frequency) of the disease under study or other pre-existing conditions. (Note: A condition recorded as pre-existing that is intermittently symptomatic [eg, headache] and which occurs during the study should be recorded as an adverse event.)
Adverse Drug Reaction (ADR)	An untoward and unintended response to an IMP which has a reasonable causal relationship to the IMP
Unexpected ADR	An ADR whose nature, severity, specificity, or outcome is not consistent with the term or description used in the local/regional product labeling (e.g. Package Insert or Summary of Product Characteristics) should be considered unexpected.
Serious Adverse Event (SAE)	An untoward medical occurrence which does not necessarily have a causal relationship to the IMP or comparator but which: □ results in death □ is life threatening □ results in persistent or significant disability or incapacity □ is a congenital anomaly or birth defect. □ is a medically important event or reaction
Serious Adverse Reaction (SAR)	An SAE that has a causal relationship to the IMP
Suspected Serious Adverse Reaction (SSAR)	A SAR is consistent with the information about the IMP listed in the Summary of Product Characteristics (SPC).
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A SAR that is suspected to be caused by the IMP but which is not consistent with the information about the IMP in the SPC.

8.2. Recording and reporting adverse events

The study period is defined for each patient as the time period from signature of the informed consent form through to the final follow up visit (visit 3). All adverse events (as defined in Table 8) that occur during the defined study period will be identified, recorded in the eCRF, including the following information:

1. The severity grade (mild, moderate, severe) or (grade 1-4)
2. Its relationship to the drug(s) of interest (suspected/not suspected)
3. Its duration (start and end dates or if continuing at final exam)
4. Whether it constitutes a serious adverse event (SAE)

In addition, all reports of the following special scenarios will be considered an adverse event irrespective of whether a clinical event has occurred:

- Drug-drug or drug-food interaction
- Drug exposure during pregnancy
- Drug use during lactation or breast-feeding,
- Lack of effectiveness
- Overdose
- Drug abuse and misuse
- Drug maladministration or accidental exposure
- Dispensing errors / Medication errors
- Off-label use
- Withdrawal or rebound symptoms

This includes any SAEs likely to arise from the trial indication or progression of underlying/concomitant illness(es) (e.g. progression of cancer in oncology trials), unless specified in the protocol as study specific exemptions.

All serious adverse events (SAEs) will be reported by the Investigator to the Sponsor within 24 hours of the investigator learning that an SAE occurred.

All non-serious AEs will be reported by the Investigator to the Sponsor within 7 days of awareness that the non-serious AE occurred.

Any occurrences of a pregnancy in a patient (or a patients partner) during study participation will be collected. All pregnancies will be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications

8.2.1. Follow-up reports

AEs will be followed until resolution or until it is judged to be permanent, and an assessment will be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the drug of interest, the interventions required to treat it, and the outcome.

9. STATISTICAL ANALYSIS

9.1. General

Intention-to-treat and per-protocol analyses will be undertaken. For the Intention-to-treat analysis, all patients entered into the study will be included in the analysis. For the per-protocol analysis, all patients entered who complete the study as per protocol (defined as attending baseline and all follow-up visits irrespective) will be included.

9.2. Summary statistics

Summary statistics will be produced for both Phase 1 and Phase 2 of the study and for all baseline and outcome variables as a complete dataset and by treatment groups.

For variables measured on the interval or ratio scale, these will include:

- Sample size (n)
- Percentage non-missing
- Mean
- Variance / Standard Deviation
- Range (Minimum / Maximum)
- Median
- Inter-quartile Range (25th and 75th percentiles)

For categorical variables, the summary statistics will include:

- Sample size (n)
- Range (if applicable)
- Count and Percentage by category (distribution).

9.3. Statistical analysis

Baseline and outcome variables will be analysed as a complete dataset and by treatment groups (split by baseline COPD severity).

9.3.1. Baseline variables

Baseline variables will include:

- Demographics and lifestyle:
  - Sex
  - Age

  - Height, weight, BMI
  - Occupation
- Impact:
  - Dysnea (mMRC score)
  - Sputum presence; sputum colour
  - Daily physical activity (minutes walked / day)
  - CAT
  - CCQ
  - Impact at time of assessment (High vs Low)
- Stability
  - Exacerbations in the last 3 months (patient-reported and based on clinical records)
  - Change in CAT and CCQ in the last 3 months (where available)
  - Stable (vs unstable) disease at time of assessment (Y/N)
- COPD Control Status:
  - Controlled
  - Poorly controlled
- Comorbidities
- COPD medications (and cost)
- Other concomitant medications (and cost)
- Lung function (FEV1, FVC, FEV_1/FVC)
- BODE Index
- Smoking Status
  - History (pack years)
  - Current status

9.3.2. Outcome variables

Outcome variables, captured at each follow-up visit will include:

- Impact:
  - Dysnea (mMRC score)
  - Sputum presence; sputum colour
  - Daily physical activity (minutes walked / day)
  - CAT (total score)
  - CCQ (total score)
  - Impact at time of assessment (High vs Low)
  - Change in impact since prior visit (Y/N)

  - Change in impact from baseline (Y/N)
- Stability
  - Exacerbations in the last 3 months (patient-reported and based on clinical records)
  - Change in CAT and CCQ in the last 3 months (where available)
  - Stable (vs unstable) disease at time of assessment (Y/N)
  - Change in stability since prior visit (Y/N)
  - Change in stability from baseline (for visits 2-4; Y/N)
- COPD Control Status:
  - Controlled vs Poorly controlled
  - Change in control since prior visit
  - Change in control since baseline (for visits 2-4; Y/N)
- COPD medications (and cost)
- Mood (PhQ-4)
- Other concomitant medications (and cost)
- Lung function (FEV1, FVC, FEV_1/FVC)
- Adverse events:
  - SAEs
  - AEs

9.3.3. Analysis of primary and secondary outcomes

Descriptive data are reported as means (standard deviations (SD)) or percentages, as appropriate. Comparisons between groups for descriptive summaries will be performed with the use of analysis of variance. The incidence of the composite endpoint (Mortality, hospitalisations and serious COPD morbidity) will be summarized as a per-person per-year rate.

Differences in the composite endpoint between groups (controlled and uncontrolled COPD patients) will be analyzed with the use of a nonparametric U-Mann Whitney test. In the initial exploration of data, composite endpoint will be analyzed as an qualitative variable (presence or not presence of death, hospitalisations or serious COPD morbidity) during year 1, with the use of logistic regression.

Multinomial logistic regression will be performed with the frequency of exacerbations during year 1 classified as none, one, or two or more to more fully characterize the associations between selected baseline factors and composite endpoind frequency.

Frequent exacerbations as two or more exacerbations in a year will be defined for the analysis.

A final multivariate logistic regression analysis will be used to calculate Odds ratios (OR) and their 95% confidence intervals (95%CI) for frequent exacerbations that will be included in the model as dependent variable. A previous analysis of potential confounding factors will be carried. The interaction was analyzed using the likelihood ratio test. Receiver operating characteristic (ROC) curves will be constructed derived from the final model to determine its capacity to predict endpoint.The Hosmer-Lemeshow goodness-of-fit test will be performed to assess the overall fit of the model (*Hosmer DW, Lemeshow S: Applied Logistic Regression, ed 1. New York, John Wiley and Sons Inc., 1989)*.

9.3.4. Analysis of secondary outcomes

Secondary outcomes (EQ5, CCQ, changes in lung function, BODE index) will be analyzed using analysis of covariance (ANCOVA), once assumptions for the convenience of this analysis are confirmed, with baseline values and potential confounding factors as covariates and study group as independent variable (Miller, G. A., & Chapman, J. P. 2001). After, Least square (LS) mean ± standard error (SE) will be calculated for variables involving each outcome.

Baseline differences between study groups (controlled and uncontrolled COPD patients) will be performed using the Chi-square test (exact Fisher test with observed frequencies < 5) for categorical variables whereas continuous variables were tested using *t* test (U-Mann Whitney test if the variables were not normally distributed). A stepwise multivariate logistic regression model to predict control in COPD patients will be performed. All variables explored in the univariate analyses will be considered in the multivariate model as covariates. A conservative significance threshold of 0.01 was used to determine the qualification of data for entry into or deletion from the model.

Finally, an analysis will be performed to evaluate the cost-utility of patients with controlled (as compared to poorly controlled) COPD using analysis of covariance. Data will be collected from the economic department of each collaborating center.

All tests were two-tailed, and significance was set at 5%. All analyses will be carried out using SPSS version 20, SAS version 9.3 and Microsoft Office EXCEL 2007.

9.4. Missing data

The per-protocol will not account for missing data as missing data will be seen as a protocol violation and therefore a patient with missing data will be excluded from this population.

The Intent-to-Treat population (ITT) will have missing values imputed as follows:
Any missing data will be assessed and attempts made to ensure that there are no underlying reasons for the data not being collected. i.e. that the data are missing at random.

10. ELECTRONIC CASE REPORT FORM & STUDY DATASET

10.1. Data collection

A clinical data management system (CDMS) will be used to hold data collected during the study. Data will be incorporated into the system from the eCRF. The CDMS will be fully validated to ensure that it meets the scientific, regulatory, and logistical requirements of the study before it is used to capture study data. Before using the CDMS, all users will receive training on the system and any study-specific training. After they are trained, users will be provided with individual system access rights.

Data will be collected at the investigational centres by appropriately designated and trained personnel and CRFs must be completed for each patient screened who provided informed consent/assent according to the data source. Patient identity should not be discernible from the data provided on the CRF. Data will be reviewed for consistency by Data Management using both automated logical checks and manual review. All data collected will be approved by each investigator at each investigational centre. This approval acknowledges the investigator's review and acceptance of the data as being complete and accurate.

10.1. Electronic case report form (eCRF)

An eCRF will be designed for the purposes of recording study information provided by the patient during study visits. Features of the eCRF will include:

- Password protected, with access limited to staff essential for entering or verifying data.
- Identification of patients by unique patient and practice identifiers to maintain patient confidentiality.
- Ensure that each time the patient record is accessed by a Researcher, Investigator or Monitor, the access will be logged.
- Data management strategies to minimise missing data and incorrect data entry.

Data captured into the eCRF will be directly incorporated into the database system.

10.2. Data quality control

Data Management is responsible for the accuracy, quality, completeness, and internal consistency of the data from this study. Data handling, including data quality assurance, will comply with international regulatory guidelines, including ICH GCP

guidelines. Data management and control processes specific to this study, along with all steps and actions taken regarding data management and data quality assurance, will be described in a Data Management plan.

Data captured will be processed and reviewed for completeness, consistency, and the presence of mandatory values. Applicable terms will be coded according to the coding conventions for this study. Logical checks will be implemented to ensure data quality and accuracy. Any necessary changes will be made in the clinical database, and data review and validation procedures will be repeated as needed.

10.3. Data queries

Data queries will be raised by the data management team and the trial monitor to be resolved by the Investigator team.

11. QUALITY CONTROL AND QUALITY ASSURANCE

11.1. Protocol amendments and protocol deviations

11.1.1. Protocol amendments

No changes from the final protocol will be initiated without prior written approval and favourable opinion of a written amendment by the Research Ethics Committee (REC), except when necessary to address immediate safety concerns to the patients or when the change involves only logistics or administration.

Each Principal Investigator and the sponsor will sign the protocol amendment.

11.1.2. Protocol deviations

Any significant deviation from the protocol will be considered a protocol violation. Protocol violations include non-adherence on the part of the patient, the investigator, or the sponsor to protocol-specific inclusion/exclusion criteria, primary objective variable criteria, or GCP guidelines; noncompliance to study drug administration; use of prohibited medications; or any other deviations that may have an impact on the processes put in place for the care and safety of the patients.

When a protocol violation is reported, the sponsor will determine whether to discontinue the patient(s) affected by the violation from the study or permit the patient(s) to continue in the study, with documented approval from the medical representative. The decision will be based on ensuring patient safety and preserving the integrity of the study.

Deviations from the inclusion/exclusion criteria of the protocol are not prospectively granted by the sponsor. If investigational centre personnel learn that a patient who did not meet protocol eligibility criteria was entered into the study, they must immediately inform the sponsor of the protocol violation. If such a patient has already completed the study or has withdrawn early, no action will be taken but the violation will be recorded.

11.2. Information to study personnel

The investigator is responsible for giving information about the study to all staff members involved in the study or in any element of patient management, both before starting the study and during the course of the study (e.g. when new staff become involved). The investigator must assure that all study staff members are qualified by

education, experience, and training to perform their specific responsibilities. These study staff members must be listed on the investigational centre authorisation form, which includes a clear description of each staff member's responsibilities. This list must be updated throughout the study, as necessary.

The study monitor is responsible for explaining the protocol to participating investigators to ensure its accurate implementation. Additional information will be made available during the study when new staff become involved in the study and as otherwise agreed upon with either the investigator or the study monitor.

11.3. Study monitoring

To ensure compliance with GCP guidelines, the local lead investigator is responsible for ensuring that patients have signed the informed consent form and that the study is conducted according to applicable SOPs, the study protocol, and other written instructions and regulatory guidelines.

It is the responsibility of the local lead investigator to ensure that all data are correctly and completely recorded and reported, and that informed consent is obtained and recorded for all patients before they participate in the study and whenever changes to the consent form are warranted.

The study monitor will monitor the various records relating to the study remotely to assess adherence to the protocol and the completeness, consistency, and accuracy of the data being recorded.

11.4. Audit and inspection

The sponsor may audit the investigational centre to evaluate study conduct and compliance with protocols, SOPs, GCPs, and applicable regulatory requirements. Each investigator must accept that regulatory authorities and sponsor representatives may conduct inspections to verify compliance with GCP guidelines.

12. ETHICS

12.1. Compliance with laws and regulations

This study will be conducted in full conformance with the ICH E6 guideline for GCP and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2D guideline (Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting), as well as with the EU Clinical Trials Directive (2001/20/EC). The investigator is responsible for conducting the study in accordance with the procedures described in this protocol. All the personnel involved in the study will be fully informed about the nature of the study and will be subject to protocol procedures concerning their duties in the study. The investigator and the sponsor should ensure that all work and services described herein, or incidental to those described herein, shall be conducted in accordance to the highest standards of ICH E6 GCP guidelines and other relevant UK regulations.

12.2. Registration of the Clinical Study

This clinical study will be registered on clinical trials registry websites.

12.3. Research Ethics Committees

The study protocol and related forms will be submitted to independent Research Ethics Committee (REC) in each country where ethics are required. Notification of approval must be obtained from the REC in writing by the investigator before study initiation. The investigator is required to maintain accurate and complete records of all written correspondence sent to and received from the REC.

The study will be conducted on behalf of Dr Marc Miravitlles who will be responsible for conducting the study including submissions to the REC.

12.4. Informed consent

The investigator, or a qualified person designated by the investigator, should fully inform the patient of all pertinent aspects of the study. Written informed consent will be obtained from each patient before any study-specific procedures or assessments are done and after the aims, methods, anticipated benefits, and potential hazards are explained. The patient's willingness to participate in the study will be documented in

writing in a consent form, which will be signed and dated by the patient. The investigator will keep the original consent form and provide a copy to the patient. It will also be explained to the patients that they are free to refuse entry into the study and are free to withdraw from the study at any time without prejudice to future treatment. Written and/or oral information about the study given to patients will be in simple terms, however, as specified in the study inclusion criteria, only patients who are able and willing to read and comprehend written and verbal instructions will be enrolled into the study.

12.5. Confidentiality regarding study patients

The investigator will assure that the privacy of the patients, including their identity and all personal medical information, is maintained at all times. In this study, patients will be identified not by their names or initials, but only by an identification code. Personal medical information may be reviewed for the purpose of patient safety and/or verifying data in the eCRF. This review may be conducted by the study monitor, properly authorised persons on behalf of the sponsor, the quality assurance unit, and/or regulatory authorities. Personal medical information will always be treated as confidential.

13. TIME SCHEDULE AND DELIVERY

The total length of the study will be approximately 24 months from screening the first patient to completion of the last patient visit. The patient will be in the study for 24 months, attending 5 visits at 6-monthly visits.

The approximate timelines for the different phases of the study – data collection through to publicaito are detailed in Table 9, below.

Table 9. Anticipated study timelines

Study Element		Milestone / Delivery Date
Data collection	Commence (recruitment & baseline data collection)	Q4 2015–Q3 2016 October 2015–July 2016
	Complete data collection	Q3 2018; July 2018
Reporting	Baseline cross-sectional impact measurements	Q4 2016; November 2016
	Final report, including longitudinal study and control measurements	Q4 2018; December 2018
Publication	Baseline characteristics	Q1 2017: January 2017
	Final manuscript	Q2 2019; April 2019

14. FINANCING

This study is sponsored by the Respiratory Effectiveness Group (REG; registered as Respiratory Effectiveness Ltd) with partial funding from Novartis according to an ITT study agreement signed by both parties on [enter date].

15. REPORTING AND PUBLICATION OF RESULTS

The clinical study report and a final review of the safety data should be completed no later than 5 months after study database lock. Submission of a paper for publication in the scientific literature should be completed within 12 months of study database lock.

16. STEERING COMMITTEE

The study will be overseen and implemented by an independent, international steering committee. The steering committee will review the final study report and interpret the findings in terms of their clinical importance. The committee will also oversee and co-author the final study manuscript(s).

The members of the committee include:

Marc Miravitlles, Pneumology Department, Vall d' Hebron University Hospital, Barcelona, Spain

Juan José Soler-Cataluña: Pneumology Department, Hospital Arnau de Vilanova, Valencia, Spain

Bernardino Alcazar Navarrete: Respiratory Department, Hospital de Alta Resolucion, Granada, UK

David Price: University of Aberdeen, Aberdeen, UK

Jennifer Quint: Imperial College, London, UK

David Halpin: Department of Respiratory Medicine, Royal Devon & Exeter Hospital, Exeter, UK

Dermot Ryan: Honorary Fellow at the University of Edinburgh, UK

Nicolas Roche: University of Paris Descartes, Paris, France

Alberto Papi: S. Anna University Hospital, Ferrara, Italy

Richard Costello: Royal College of Surgeons, Dublin, Ireland

Faisal Yunus: Department of Pulmonology and Respiratory Medicine, Universitas Indonesia (FMUI), Jakarta

Helgo Magnussen: Pulmonary Research Institute at Lung Clinic Grosshansdorf, Germany

Akio Niimi: Department of Respiratory Medicine, Kyoto University Graduate School of Medicine, Japan

Jean Bourbeau: Montreal Chest Institute, Montreal, Quebec, Canada

Don Sin: University of British Columbia, Canada

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