Open Respiratory Archives 8 (2026) 100519

Sociedad Española de Neumología y Cirugía Torácica SEPAR

Open Respiratory Archives

www.elsevier.es/ora

Original Article

Predictors of Progression in Pre-COPD: The 3P Study Rationale and Design

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ARTICLE INFO

Article history:
Received 11 August 2025
Accepted 29 October 2025
Available online 17 November 2025

Keywords:
Pre-COPD
Biomarker
Chronic bronchitis
Emphysema
Smoking
Spirometry

ABSTRACT

Introduction: The diagnosis of chronic obstructive pulmonary disease (COPD) requires the demonstration of poorly reversible airflow obstruction (defined by a forced expiratory volume in 1 s [FEV_1]/forced vital capacity [FVC] ratio <0.7 post-bronchodilation) in the appropriate clinical context (risk factors and exposures). Nevertheless, some individuals, who may be labeled "pre-COPD", can present respiratory symptoms, structural lung abnormalities (e.g., emphysema), or other physiological abnormalities (e.g., low FEV_1 [preserved ratio impaired spirometry, PRISm], gas trapping, hyperinflation, reduced lung diffusing capacity of carbon monoxide [DL_{co}] and/or rapid FEV_1 decline), all in the absence of airflow obstruction. For reasons that are still unclear, some – but not all – patients will eventually progress and develop airflow obstruction (i.e., COPD) over time. The aim of this study is to investigate the clinical, physiological, radiological and/or biological factors that are associated with progression from pre-COPD to COPD.

Material and methods: This will be a prospective (5-year follow-up), multicenter (conducted in 12 Spanish centers across eight geographical autonomous communities), observational, comparative study (www.clinicaltrials.gov NCT04409275), that will recruit 285 current or former smokers (≥10 pack-years) with respiratory symptoms (dyspnea, chronic cough, sputum production, wheezing or recurrent lower respiratory tract infections) and spirometry without obstruction (pre-COPD status). Multivariate regression analysis and other tests will be used to analyze results.

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◊ A complete list of the Field Investigators listed in the Appendix 1.

https://doi.org/10.1016/j.opresp.2025.100519

Conclusion: Results are expected to provide novel, useful information for identifying pre-COPD individuals who are likely to develop progressive airflow obstruction and are potential candidates for prompt intervention.

Predictores de progresión en la pre-EPOC: estudio 3P, justificación y diseño

Palabras clave:
Pre-EPOC
Biomarcador
Bronquitis crónica
Enfisema
Tabaquismo
Espirometría

R E S U M E N

Introducción: El diagnóstico de la enfermedad pulmonar obstructiva crónica (EPOC) requiere la demostración de una obstrucción del flujo aéreo escasamente reversible (definida por una relación entre el volumen espiratorio forzado en 1 segundo [FEV1] y la capacidad vital forzada [FVC] <0,7 tras la broncodilatación) en el contexto clínico adecuado (factores de riesgo y exposiciones). Sin embargo, algunas personas (las denominadas «pre-EPOC») pueden presentar síntomas respiratorios y/o anomalías estructurales pulmonares (p. ej., enfisema) y/u otras anomalías fisiológicas (p. ej., FEV1 bajo espirometría con ratio preservada y deterioro [PRISm], atrapamiento aéreo, hiperinsuflación, reducción de la capacidad de difusión pulmonar del monóxido de carbono [DL_{co}] y/o rápido descenso del FEV1) en ausencia de obstrucción del flujo aéreo. Por razones que no están claras, con el tiempo, algunas de ellas (pero no todas) acaban progresando y desarrollando obstrucción del flujo aéreo (y, por lo tanto, EPOC). El objetivo de este estudio es investigar qué factores clínicos, fisiológicos, radiológicos y/o biológicos están asociados con la progresión de la pre-EPOC a la EPOC.
Material y métodos: Se trata de un estudio prospectivo (seguimiento de cinco años), multicéntrico (n = 12 centros españoles en ocho comunidades autónomas), observacional y comparativo (www.clinicaltrials.gov NCT04409275) en 285 fumadores actuales o exfumadores (≥10 paquetes-año) con síntomas respiratorios (disnea, tos crónica, producción de esputo, sibilancias o infecciones recurrentes del tracto respiratorio inferior) y espirometría sin obstrucción (pre-EPOC). Se utilizará un análisis de regresión multivariante (entre otros) para analizar los resultados.
Conclusión: Es probable que los resultados proporcionen información novedosa de posible utilidad para identificar a las personas con pre-EPOC que pueden desarrollar una obstrucción progresiva del flujo aéreo, lo que permitiría una intervención rápida.

Introduction

According to the current recommendations of the Global Initiative for Chronic Obstructive Lung Disease (GOLD), the diagnosis of chronic obstructive pulmonary disease (COPD) requires the presence of poorly reversible airflow obstruction in the appropriate clinical context (risk factors and exposures).[1] However, GOLD recognizes that some individuals can present respiratory symptoms, structural pulmonary lesions (e.g., emphysema, airway remodeling), or other physiological abnormalities (e.g., low forced expiratory volume in 1 s [FEV_1] with preserved ratio impaired spirometry [PRISm], gas trapping, hyperinflation, reduced lung diffusing capacity of carbon monoxide [DL_{co}], or rapid FEV_1 decline) in the absence of airflow obstruction (FEV_1/forced vital capacity [FVC] ≥0.7 post-bronchodilation).[2] These individuals are labeled "pre-COPD".[3] For reasons that are still unclear, some – but not all – will eventually progress and develop airflow obstruction (i.e., COPD) over time. Identifying these progressor patients early during the course of their disease can offer novel opportunities for intervention.[4]

Several potential markers of increased risk of disease progression in pre-COPD subjects are easily identifiable and include, firstly, continued exposure to inhaled pollutants, mostly tobacco smoking, and secondly, presence of emphysema (a marker of structural lung damage) and airway remodeling,[5] despite the absence of airflow obstruction. In this context, DL_{co} is a well-established marker of emphysema and some studies have shown that DL_{co} abnormalities may precede the development of airflow obstruction.[6] Likewise, chest computed tomography (CT) can quantify the extent and distribution of emphysema, air trapping and airway wall thickness, although its sensitivity may be low during the early course of the disease.[7,8] Other lung function abnormalities (e.g., gas trapping, PRISm) may also precede the development of airflow obstruction. Thirdly, given that COPD is characterized by chronic inflammation and oxidative stress, circulating levels of various inflammatory and oxidative biomarkers, including cytokines (TNFα, IL-6 and IL-18), chemokines (MCP-1/CCL2, MIP-1β/CCL4, PARC/CCL18, MDC/CCL22, IL-8/CXCL8, BCA-1/CXCL13), and soluble adhesion molecules (ICAM-1)[9,10] may possibly contribute to predicting which pre-COPD patients will eventually develop full-blown COPD. Identifying these progressor patients early during the course of their disease can provide opportunities for prompt intervention. Finally, the potential role of gender differences and/or early life events has not been explored in this setting to date.

In this study we sought to investigate prospectively factor(s) associated with disease progression (i.e., development of airflow obstruction during a 5-year follow-up) in smokers and former smokers with respiratory symptoms and no evidence of spirometric airflow obstruction at baseline (i.e., pre-COPD). Study markers will include: (1) DL_{co} at COPD screening; (2) lung function markers such as DL_{co}, small airway and lung volume measurements by body plethysmography and PRISm; (3) persistent smoking; (4) CT changes, with a particular focus on emphysema distribution and severity; (5) circulating inflammatory and oxidative stress marker levels; (6) potential gender differences; (7) relevant early life events (such as prematurity, low birth weight, infections, asthma, childhood exposures (smoking parents), COPD or asthma in parents); and (8) associated comorbidities.

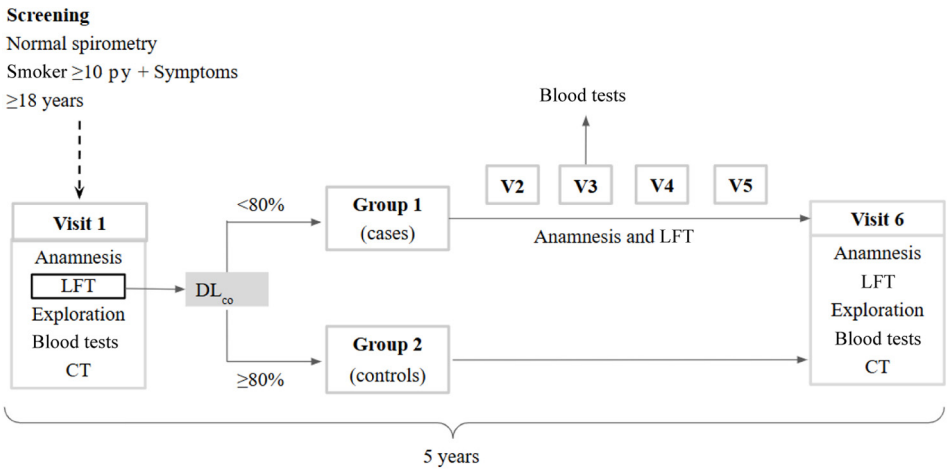

Fig. 1. Study design. Prospective observational case–control study. Patients' pulmonary diffusion measured by carbon monoxide (DL_{co}) during screening will determine the group to which they are assigned. Cases will attend an annual visit over a 5-year period, while controls will attend only the baseline and final visit. Case patients will provide a blood sample in the middle of the follow-up period (V3). py: pack-years (smoking exposure); CT: computed tomography; DL_{co}: lung diffusing capacity of carbon monoxide; LFT: lung function tests; V2: visit 2; V3: visit 3; V4: visit 4; V5: visit 5.

Material and methods

Study design

This will be a prospective, multicenter (12 Spanish centers across 8 geographical autonomous communities), observational, comparative study (www.clinicaltrials.gov NCT04409275) conducted in current or former smokers (≥10 pack-years) with respiratory symptoms (dyspnea, chronic cough, sputum production, wheezing or recurrent lower respiratory tract infections) and normal spirometry (pre-COPD status). After signing the informed consent, participants will be classified into two groups according to their DL_{co} values: <80% or ≥80% predicted. The former group will be followed up annually for 5 years, whereas the latter will be visited only at baseline and after 5 years (Fig. 1). The project is endorsed by the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR).

Participants

The study will include both males and females, older than 18 years of age, current or former smokers (≥10 pack-year), with respiratory symptoms (dyspnea, chronic cough, sputum production, wheezing or recurrent lower respiratory tract infections), who are able to understand the aim of the study and perform its procedures, who agree to be followed up over 5 years, and who have a normal spirometry at screening (in the absence of respiratory infection symptoms in the previous 8 weeks). Exclusion criteria include a life expectancy <2 years due to cancer or other serious systemic diseases, participation in another clinical study, alpha-1-antitrypsin deficiency, presence of an interstitial pattern on CT, or refusal to sign informed consent. Participants will then be stratified by their baseline DL_{co} value (< or ≥80% predicted) to guide their follow-up (Fig. 1).

Ethical considerations

This study (version 3.2; September 24, 2020) has been approved by the local Ethics Research Committee in compliance with the principles of the Declaration of Helsinki for human studies. All subjects will receive information about the study and its objectives in a detailed information sheet and verbal explanation containing information on the risks and benefits of their participation before signing informed consent and before any procedure is performed. A separate signed authorization will be obtained for storing blood samples in a biobank. A pulmonologist will act as a local principal investigator (PI) in each participating center. Prior to data collection, these PIs will be trained in collecting and transferring data to the electronic case report form (eCRF), which will automatically generate an alphanumeric code that identifies each of the participants, ensuring their anonymity. The eCRF incorporates all the variables to be collected, along with their intervals. Data will be monitored remotely on a periodic basis to guarantee data quality and processed according to Regulation (EU) 2016/679 of the European Parliament and the Council of 27 April 2016 on Data Protection.

Measurements

Table 1 shows the specific procedures to be performed at each visit (Fig. 1). Table 2 lists all variables to be collected during the study: demographic, anthropometric and socioeconomic aspects, personal and family history, tobacco exposure, comorbidities, current respiratory symptoms, use of health resources, previous exacerbations, vital signs, and auscultation data. All patients will also be characterized using the following validated tests: COPD Assessment Test[11]; Hospital Anxiety-Depression Scale[12]; St. George's Quality of Life Questionnaire[13]; and the London Chest Activity of Daily Living Scale.[14]

Lung function tests will be forced spirometry before and after bronchodilation, lung volumes and airway resistance by plethysmography, DL_{co} by single breath technique, exhaled cotinine concentration, and the 6-minute walk test. All procedures will be performed according to international recommendations.[15–20] The BODE index (Body mass index, airflow Obstruction, Dyspnea, and Exercise) and BODEx index (Body mass index, airflow Obstruction, Dyspnea, and Exacerbations) will be calculated accordingly.[21,22]

Two blood samples will be obtained by peripheral venipuncture from fasting participants at visit 1 (V1) and visit 6 (V6) in both groups. A third sample mid-study (V3) will also be obtained from participants with low DL_{co} at recruitment. Seven aliquots will be drawn from each patient, 3 of which will be processed in the local laboratory for biochemistry, blood count and coagulation. For the study of soluble inflammatory mediators, a heparinized blood sample will be obtained to obtain plasma levels of 100 U/ml to promote the release of erythrocyte-bound chemokines. Plasma samples will be stored at −80 °C until ELISA determinations are performed.

Metabolites present will be studied by high-field nuclear magnetic resonance spectroscopy (NMR) (500 and 600 MHz)

Table 1
Procedures associated with each follow-up annual visit in both groups.

Visit					
Visit 1 Groups 1 and 2	Visit 2 Group 1	Visit 3 Group 1	Visit 4 Group 1	Visit 5 Group 1	Visit 6 Groups 1 and 2
Clinical assessment Lung function test Blood sample Chest CT	Clinical assessment Lung function test	Clinical assessment Lung function test Blood sample	Clinical assessment Lung function test	Clinical assessment Lung function test	Clinical assessment Lung function test Blood sample Chest CT

Group 1: low lung diffusing capacity of carbon monoxide (DL_{co}); group 2: normal DL_{co} at recruitment (both with normal spirometry at visit 1).
CT: computed tomography.

Table 2
Variables determined in the study.

General clinical data	
Demographics	Sex, age and date of birth
Anthropometry	Weight (kg), height (cm), body mass index (BMI; kg/m^2)
Socioeconomic data	Occupation, employment and social situation, education level, population type
Physical activity	Number of minutes walked per day (<30; 30–120; >120)
Comorbidities	Arterial hypertension, dyslipidemia, diabetes, cardiovascular, peripheral arterial disease, obstructive sleep apnea syndrome, digestive disease
Family, childhood history and exposures	
Family history	Respiratory diseases and smoking in parents
Childhood history	Birth term and weight, smoking parents, respiratory diseases, infections in childhood
Smoking	Age at onset, cigarettes/day, cumulative exposure, current status, time ex-smoker
Cotinine	Cotinine value and units
Current clinical condition	
Respiratory symptoms	mMRC dyspnea scale, expectoration and cough, nocturnal symptoms or symptoms suggestive of asthma, allergy, heart failure, or reflux
Questionnaires	COPD Assessment Test[10]; Hospital Anxiety-Depression Scale[11]; St. George's Quality of Life Questionnaire[12]; London Chest Activity of Daily Living Scale[13]
Current treatment	Inhalers, roflumilast, theophyllines, mucolytics, influenza, and pneumococcal vaccine
Health care resources used for respiratory cause (12 m)	Number of visits to primary care, emergency department, hospital admissions, and antibiotic and/or corticosteroid courses
Prognostic indexes	BODE score, BODEx score
Lung function test	
Spirometry	Forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1). FEV_1/FVC. Results of pre- and post-bronchodilator test, absolute and percentage
DL_{co}	DL_{co} single breath (absolute and percentage)
Plethysmography	Total lung capacity (TLC), residual volume (RV), functional residual capacity (FRC), inspiratory capacity (IC), RV/TLC, IC/TLC; specific airway resistance (SRaw), specific airway conductance (SGaw)
6-Minute walk test	Borg scale, saturation, heart rate (initial-final), distance
Systemic measures	
General biochemistry	Complete blood count, chemistry and coagulation, determination of alpha-1-antitrypsin, and immunoglobulins (A-E-G-M), vitamin D, CRP, and fibrinogen
Inflammatory biomarkers	Cytokines: TNF-alpha, IL-6, IL-8; chemokines: MCP-1/CCL2, MIP-1B/CCL4, following RANTES/CCL5, PARC/CCL18, MDC/CCL22, PF4/CXCL4, IL-8/CXCL8, BCA-1/CXCL13; soluble adhesion molecules: P-SELECTIN, ICAM-1, and VCAM-1
Analysis of oxidative stress and metabolomics study	Reduced/oxidized glutathione (GSH/GSSG); DNA oxidative damage: 8 OHDG levels; lipid oxidative damage: isoprostanes levels; protein oxidative damage: protein carbonylation; GSH mRNA and enzyme expression levels; GSH metabolism enzymatic activity; reactive oxygen species (ROS) and nitrogen (RNS) generation; metabolites
Imaging	
Chest computed tomography	Emphysema, type, distribution, and quantification

BMI: body mass index; BODE: Body mass index, Obstruction, Dyspnea, Exercise; BODEx: Body mass index, Obstruction, Dyspnea, Exacerbations; DL_{co}: lung diffusing capacity of carbon monoxide; mMRC: modified Medical Research Council.

with 1D and 2D homo- and heteronuclear spectra for their unequivocal identification, and ultra-high performance liquid chromatography–MS/MS (UHPLC–MS/MS). Two EDTA aliquots of serum will be reserved for this purpose, and a third EDTA tube will be obtained for the oxidative stress study.

Finally, CT scans will be performed in all patients at V1 and V6. Images will be acquired in the supine position without contrast and will be evaluated by expert chest radiologists for the detection and description of emphysema. Images will be post-processed using *StratX Pulmonx*, a cloud-based quantitative CT analysis service that provides information on emphysema destruction, destruction score per lobe and lobar volume, fissure completeness, and lobar volume for volumetric quantification of the extent of emphysema. Signs of airway remodeling (airway wall thickening, bronchiectasis, mucus plugs, air trapping) will also be assessed. Prior to this procedure, women of childbearing age will undergo a pregnancy test.

Data analysis

Sample size was estimated using the *ARCSINUS* approximation based on the New York study in which 22% of smokers with respiratory symptoms, normal spirometry, and DL_{co} <80%, developed COPD.[23] Accepting an alpha risk of 0.05 and a beta risk of 0.1 in a 2-tailed test, 116 subjects will be needed in first group and 116 in the second to find a statistically significant proportional difference,

expected to be 0.2 in group 1 and 0.05 in group 2. A drop-out rate of 20% is anticipated.

Normality will be determined using the Shapiro–Wilks test. In case of normality, mean values of quantitative variables will be compared using the Student's *t*-test; otherwise, the Mann–Whitney test will be performed. For qualitative variables, the comparison of percentages between groups will be performed with Fisher's exact test for dichotomous variables or the chi-squared test for contingency tables with more than two categories.

A 2-sample proportions test based on the *z*-statistic and logistic regression analysis will be used appropriately to investigate the different objectives of the study. The main confounding factors to be taken into account will be age, gender, smoking history, and the presence of comorbidities. R software (version 3.6.1; R Core Team, 2019) will be used for the primary outcome. Factors associated with disease progression will be studied using survival analysis methods.

Conclusions

COPD is often diagnosed late, when the disease is fairly advanced in terms of the severity of airflow limitation that characterizes the disease. The term pre-COPD refers to individuals with respiratory symptoms, and/or structural and/or physiological lung abnormalities in the absence of airflow obstruction. Pre-COPD patients are at risk of developing airflow obstruction over time, but not all of them do. This study will be the first to systematically and comprehensively investigate the clinical (including early life events), functional (including lung volumes by plethysmography and DL_{CO}), imaging (CT scan), and/or biological factors (circulating inflammatory and oxidative stress markers) associated with disease progression from pre-COPD to full-blown COPD. Results are expected to provide novel, useful information for identifying pre-COPD individuals who are likely to develop progressive airflow obstruction and are potential candidates for prompt intervention.

Participating centers have been selected throughout Spain to generate a representative national sample. All have previous experience in this type of clinical research and sample sizes have been calculated to allow some losses during follow-up, so we do not expect any major limitations in this regard. However, the inherent limitations of observational design mean that direct causal relationships cannot be established, so further studies will be necessary.

Declaration of generative AI and AI-assisted technologies in the writing process

No artificial intelligence has been used to perform any of the procedures.

Ethical approval

This study (version 3.2; September 24, 2020) has been approved by the Ethics Research Committee from Hospital Clínico, INCLIVA (Valencia, Spain) (2019/036), and by local committees when necessary. All subjects will sign the informed consent form prior to undergoing any procedure.

Funding

Supported in part by an unrestricted grant from GSK, SEPAR and Fundación de Neumología de la Comunidad Valenciana. None of the funding bodies were involved in the study design.

Authors' contributions

The study was led by CG-V, who contributed to the study design, collected patient data, literature search, drafting of the manuscript and critical revision of the work. JT contributed to collecting patient data, drafting the manuscript and preparation of tables and figures. DM-P, JARM, EG-C, CGR, LCH, PSE, JS, ENS, FJCG, AYL, LVG, MNF, and MPC collected patient data. JAC is the independent statistician and contributed to the study design. AA contributed to the literature search, drafting the manuscript and critical revision of the work.

Conflicts of interest

- Dr. C. González-Villaescusa has received honoraria for lecturing, scientific advice, participation in clinical studies or writing for publications from: *AstraZeneca*, *BIAL*, *Boehringer Ingelheim*, *Chiesi*, *Gebro*, *GlaxoSmithKline*, *Grifols*, *CLS Behring*, and *Menarini* outside the submitted work.
- Dr. J. Tarrasó Castillo has received honoraria for lecturing from *AstraZeneca* and *Chiesi* and funding for conferences from *Zambón*.
- Dr. D. Martínez-Pitarch has received fees for giving conferences and attending congresses from (in alphabetical order): *AstraZeneca*, *Bial*, *Boehringer Ingelheim*, *Chiesi*, *Gebro*, *GSK*, *Sanofi*, and *Zambon*.
- Dr. J.A. Riesco reports grants and personal fees from *Aflofarm*, *GSK*, grants, personal fees and non-financial support from *Pfizer*, *Novartis AG*, *Menarini*, personal fees and non-financial support from *Boehringer Ingelheim*, personal fees and non-financial from *AstraZeneca*, grants and personal fees from *Gebro*, and personal fees from *Laboratorios Rovi*, outside the submitted work.
- Dr. E. García-Castillo has received honoraria for giving lectures from (in alphabetical order): *AstraZeneca*, *Bial*, *Chiesi*, *Faes* and *GSK*.
- Dr. C. Gotera has received honoraria for giving lectures at scientific conferences and congresses from (in alphabetical order): *AstraZeneca*, *Chiesi*, *GSK*, *Insmed*, and *Menarini*.
- Dr. L. Carraso Hernández has received fees for participation in clinical studies, scientific advice and writing publications from (in alphabetical order): *AstraZeneca*, *Behring*, *Bial*, *Chiesi*, *CSL Gebro*, and *Vertex*.
- Dr. P. Sobradillo Ecenarro has received honoraria during the last 3 years for lecturing, scientific advice, participation in clinical studies or writing for publications from (in alphabetical order): *AstraZeneca*, *Boehringer Ingelheim*, *Chiesi*, *Gebro*, *GlaxoSmithKline*, *Menarini*, and *Teva*.
- Dr. J. Signes-Costa has received honoraria for lectures, sponsored courses and participation in expert committees from *Aflofarm*, *Adamed*, *Boehringer Ingelheim*, *Faes*, *GSK*, *Menarini*, and *Teva*.
- Dr. E. Naval Sendra has received honoraria for lecturing for (in alphabetical order): *Astra Zeneca*, *Boehringer Ingelheim*, *GSK*, and *Menarini*.
- Dr. F.J. Callejas González has received speaking or advisory fees, or economic aid to attend congresses from *AstraZeneca*, *Bial*, *GSK*, *FAES*, *Chiesi*, *Mundipharma*, *TEVA*, *Sanofi*, *Grifols*, *GSL Behring*, *Boehringer Ingelheim*, and *Gebro*.
- Dr. L. Vigil Gimenez has received lecture fees from (in alphabetical order): *MSD*, *TUV-Nord*; and has received support for attendance at scientific congresses from (in alphabetical order): *AstraZeneca*, *Chiesi*, *Gebro-Pharma*, *Menarini*, and *Philips*.
- Dr. M. Núñez Fernández has received honoraria for giving lectures and support for attending scientific congresses from (in alphabetical order): *GSK*, *Menarini*, and *Zambon*.
- Dr. A. Yordi León and Dr. M. Palop Cervera declare that they have no conflicts of interest.

- Dr. A. Agusti has received honoraria for lectures and participation in advisory boards from *AZ*, *GSK*, *Chiesi*, *Menarini*, *Sanofi*, *Roche*, *Zambon*, and *Gebro*. His institution has also received research funds from *AZ*, *GSK*, and *Menarini*, SEPAR, EU, and ISCiii. He is the current Chair of the Board of Directors of GOLD (unpaid).

Acknowledgments

The authors gratefully thank the supporting institutions. We would like to acknowledge that the study 217161 is being financially supported by GSK.

GSK had the opportunity to review a preliminary version of the manuscript; only the authors are responsible for the content of the manuscript and the interpretation of the results.

Appendix A. Appendix 1. Field Investigators (authors and co-workers)

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- Servicio de Neumología. Hospital Lluís Alcanyís (Xátiva): Dolores Martínez-Pitarch
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