


The Impact of Fixed Triple Therapy with Beclometasone/Formoterol/Glycopyrronium on Health Status and Adherence in Chronic Obstructive Pulmonary Disease (COPD) in an Italian Context of Real Life: The TRITRIAL Study Protocol

This article was published in the following Dove Press journal:
International Journal of Chronic Obstructive Pulmonary Disease

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Background: The fixed triple combination Beclometasone dipropionate/Formoterol fumarate/Glycopyrronium (BDP/FF/G, Trimbow[®]), an extrafine formulation in a unique pressurized metered dose inhaler, is indicated for the maintenance treatment in adult patients with moderate to severe COPD, not adequately treated by ICS/LABA or LABA/LAMA. Besides the evidence from three randomized controlled trials, the impact of fixed triple therapy has not been extensively evaluated in a real-world population of COPD patients. TRITRIAL (TRiple Therapy in Real life: Impact on Adherence and HeaLth status) is a non-interventional study to assess the effect of BDP/FF/G in a real world setting in Italy.

Design: TRITRIAL is a 12-month, multicenter, cohort, prospective, longitudinal observational study. Two follow-up visits will be performed at 6 and 12 months, respectively. The study includes the collection of anamnestic clinical and functional data before the start of BDP/FF/G. The study is built for digital conduction, from signature of the informed consent on a dedicated web platform, to the collection of questionnaires and clinical data on the eCRF.

Population: A total of 800 patients with COPD ranging from Global Initiative for Obstructive Lung Disease (GOLD) stages 2 to 4, receiving therapy with BDP/FF/G according to the Summary of Product Characteristics and local clinical practice, will be recruited. All concomitant therapies will be permitted for the duration of the study.

Evaluations: The primary endpoint is the change of CAT score at 12 months versus baseline. Secondary endpoints are adherence, health-related quality of life, sleep quality, disease-related outcomes (lung function and COPD exacerbations), device usability, economic resources consumption, and safety.

Conclusion: TRITRIAL study is expected to give relevant information about effectiveness of BDP/FF/G fixed triple therapy in a real-life setting of patients with COPD, where adherence, usability of inhalers and patient's preference of the device are crucial factors for the success of the therapy.

Keywords: COPD, symptoms, health status, adherence, LAMA, LABA, ICS

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Introduction

Triple therapy is widely prescribed to COPD patients in clinical practice, as a step-up treatment for patients who remain symptomatic and/or continue to experience exacerbations despite maintenance therapy, commonly using two separate inhalers.

A recent review from the United Kingdom showed that, from 2004 to 2009, the use of triple therapy in general practice increased from 25% to 59% for patients with very severe COPD, from 17% to 45% for severe COPD and from 7% to 21% for mild COPD patients, based on lung function assessment.¹ Furthermore, in a study conducted on an Italian database of General Practitioners, 21% of patients with COPD were prescribed a triple therapy over a period of 4.5 years.² Nonetheless, while its use has increased, relatively few studies have been correctly conducted to test the efficacy of triple therapy, administered by separate inhalers, compared to ICS/LABA, LABA/LAMA or LAMA in terms of preventing exacerbations. The fixed triple combination Beclometasone dipropionate/Formoterol fumarate/Glycopyrronium (BDP/FF/G, Trimbow[®], Chiesi Farmaceutici) in an extrafine formulation and a unique pressurized metered dose inhaler (pMDI), has been granted market authorization from the European Commission and the Italian Agency (AIFA) for the maintenance treatment in adult patients with moderate to severe COPD, who are not adequately treated by a combination of an ICS and a LABA or by a combination of a LABA and a LAMA (but this latter extension of indication is not yet reimbursed by AIFA). BDP/FF/G was developed through a clinical program consisting of 18 trials with more than 8,000 patients recruited. Three large Phase III studies, ie, the TRILOGY,³ TRINITY,⁴ and TRIBUTE,⁵ showed that BDP/FF/G fixed triple combination is superior to ICS/LABA, to LAMA monotherapy, and to LABA/LAMA in terms of lung function and exacerbation prevention in COPD patients with history of previous exacerbations. In these studies BDP/FF/G also showed relevant and consistent improvement of the quality of life, assessed by the Saint George Respiratory Questionnaire (SGRQ). BDP/FF/G is an extrafine formulation with a mass median aerodynamic diameter (MMAD) <2 μm ,⁶ designed to reach both large and small airways,⁷ defined as peripheral airways having a diameter < 2 mm.⁸ Despite being considered a “silent zone” of the respiratory tract, impairment of small airways, a condition known as small airway dysfunction (SAD), has a key role in the pathogenesis of COPD and it is considered a functional hallmark of the disease. Indeed, in patients with COPD, inflammation is localized predominantly in small airways, and conventional inhaled therapies (bronchodilators and ICS medications) may not reach a good deposition in small airways.⁹ As demonstrated by Hogg et al, progression of airflow obstruction

in COPD is strongly associated with thickening of the small airways’ walls and with the presence of inflammatory cells (mostly polymorphonuclear leukocytes and macrophages) and lymphocytes.¹⁰ Furthermore, the degree of abnormalities in small airways (ie, luminal occlusion with mucus plugs) is associated with early death in patients with COPD and severe emphysema.¹¹ Thus, extrafine formulations such as BDP/FF/G, may have the potential to treat small airways impairment and thus contribute to improve disease outcomes. Unfortunately, the damage in small airways is not detectable with a standard spirometric assessment, unless in late stages of the disease, when the number of airways involved by the pathologic process is high.⁸ In a recent study by Crisafulli et al, a strong relationship between SAD and COPD Assessment Test (CAT) score was demonstrated, reflecting high impact of SAD also on health status in COPD patients.¹² CAT can easily be used in routine daily clinical practice to assess the impact of COPD symptoms on the risk of developing serious exacerbations of the disease, and thus may help in a clinical setting to match the patient’s therapy more closely to individual needs, as it also reflects the contribution of SAD to the disease. As the CAT is an instrument that measures not only the respiratory symptom burden of COPD, but also the general health status of patients in daily practice (ie, lack of energy or sleep disturbances, limitations in doing activities at home or confidence leaving home), it can be considered as a measure of health-related quality of life (HRQoL) in general.¹³ Heterogeneity of airway constriction, particularly the increase in peripheral resistance (measured with impulse oscillometry) contributes to the circadian variability of respiratory symptoms. Higher values of peripheral resistance, which is a key feature of SAD, are significantly associated with worse sleep disorders.¹⁴ The COPD and Asthma Sleep Impact Scale (CASIS) is a validated questionnaire which evaluates sleep impairment associated with obstructive pulmonary diseases. It comprises 5 items related to trouble falling asleep in the night or staying awake during the day, whereas 2 items specifically investigate sleep quality. Higher scores reflect greater sleep deterioration in the previous week.¹⁵ This test could be useful to identify patients with higher risk of worse outcomes, as sleep disturbances, especially nocturnal dyspnea, are associated with an increased risk of exacerbations and mortality.¹⁶ As previously said, BDP/FF/G is an extrafine formulation, administered twice daily to grant sustained bronchodilation throughout the day and

night, and therefore may counteract the impact of morning and nocturnal symptoms and sleep disturbances (which are common in patients with COPD) on HRQoL. Another fundamental requirement to achieve COPD treatment goals is adherence. Non-adherence to medications is very common in COPD patients, especially when multiple inhaled therapies become necessary.¹⁷ This is usually the case for patients more severely affected by COPD, thus forming a vicious cycle of disease worsening and non-adherence to treatment. Adherence is a multifactorial construct, that documents how compliant the patient is to medical instructions (compliance) but also considers social, anamnestic and health economic factors like: physician-patient-interaction, medical care, patient training on correct inhalation, efficacy, satisfaction with therapy and tolerability of the therapy.¹⁸ The Test of Adherence to Inhalers (TAI) is a validated 12-item questionnaire designed to evaluate adherence to inhaled therapy in COPD and asthmatic patients by the recognition of different behavioral patterns of non-adherence. It is a simple and reliable tool that comprises a patient domain (items from 1 to 10) and a physician domain (items 11 and 12).¹⁹ The adherence measurement and documentation of reasons for non-adherence are more reliable in non-interventional studies compared to clinical trials, as they better reflect the patient's daily life. In a recent retrospective study on General Practice in Italy, 85% of enrolled patients with COPD showed poor adherence to free triple inhaled therapy, and poor adherence was associated with the presence of comorbidities (heart failure, depression, peripheral vascular disease) which are common in those with COPD.²⁰ Furthermore, patients with COPD often need to use multiple inhalers as part of their therapy, which require different inhalation techniques. Thus, the use of one single inhaler device that combines all required compounds for bronchodilation and anti-inflammatory effects may greatly facilitate and improve the usability that in turn might result into improved clinical outcomes. Despite the evidence from regulatory trials, the effects of fixed BDP/FF/G combination on patients' HRQoL, adherence and clinical outcomes have not been extensively assessed on a real-world COPD population. The TRiple Therapy in Real life: Impact on Adherence and Health status (TRITRIAL) Study (ClinicalTrials.gov No. NCT03963167) is a non-interventional study with the aim to assess the effect of treatment with BDP/FF/G on health status, HRQoL and adherence in a real-world setting of COPD patients in Italy. A groundbreaking aspect of this study is the use of

patient reported outcomes (PROs) collected through electronically validated questionnaires on a dedicated web platform available for PCs, tablets, and smartphones. Also the informed consent to the study is collected through an electronic procedure, where all the aspects of the study will be ruled out with patients step by step, before signing the document.

Patients and Methods

Study Design and Population

TRITRIAL study is a multicenter, cohort, prospective observational study. COPD patients who have been prescribed BDP/FF/G fixed combination will be recruited and observed for 12 months, as per routine local clinical practice. The study plan includes a brief retrospective phase, consisting of data of assessments performed at time of initiation of BDP/FF/G, which are going to be collected at the baseline visit (Visit 1), and a prospective phase that will include two follow-up visits, after 6±1 months (Visit 2) and 12±1 months (Visit 3) of treatment with BDP/FF/G. In case of premature withdrawal from the study for whatever reason, subjects should undergo an "Early termination Visit". The investigational plan is summarized in [Figure 1](#). The overall study duration from first patient enrolled to the last patient completed is expected to be about 30 months, based on an expected 18-month period for recruitment and a 12-month follow-up. Approximately 720 patients with moderate to very severe COPD (Stage 2–4), according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2019 Update,²¹ will take part in the study. The study has been approved by all local Ethics Committees ([Supplementary Materials](#)). Currently, the enrollment is ongoing and patients will be recruited in 50 Respiratory Medicine Centers (RMC) in Italy. Patients must meet all the following inclusion criteria to be eligible for enrollment into the study: male or female aged ≥ 40 years; COPD assessment test (CAT) score >10 at the start of BDP/FF/G fixed combination; history of at least 1 moderate or severe COPD exacerbation during the previous year; patients having received prescription and having started treatment with BDP/FF/G fixed combination as per local clinical practice and according to Trimbow[®] Summary of Product Characteristics (SmPC) within the previous 14 days. The presence of any of the following criteria will exclude a patient from study enrollment: any condition and/or illness that might interfere with the study purpose

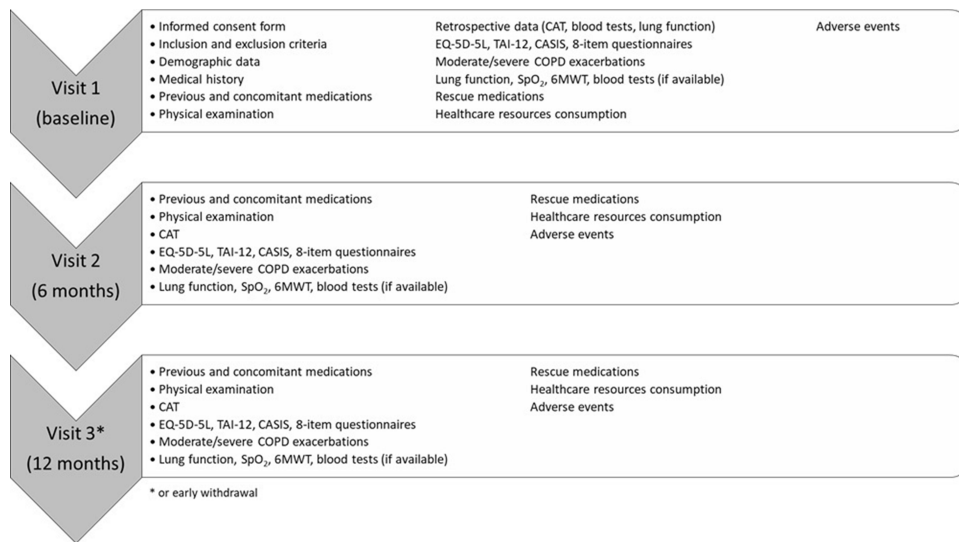


Figure 1 Investigation schedule of assessments. *Or early withdrawal.

(according to Investigator’s judgement); participation in an interventional clinical trial within 30 days prior to enrollment into the present study. Primary objective of the study is to evaluate the impact of BDP/FF/G fixed combination on health status compared to previous therapy. The primary endpoint is the change of CAT score from time of initiation of BDP/FF/G fixed combination to month 12 (or early withdrawal). Secondary objectives are: adherence to BDP/FF/G fixed combination, effect on HRQoL and sleep quality, disease-related outcomes (eg, lung function and COPD exacerbations), economic resources consumption, and safety. Primary and secondary endpoints of the study are summarized in Figure 2. Health status, adherence,

quality of life and sleep impairment will be evaluated by the administration of electronically validated questionnaires (CAT, TAI, EQ-5D-5L, CASIS) which can be easily performed with laptop, tablet or smartphone, reducing waste of time and paper. EQ-5D-5L is a simple validated questionnaire for assessing quality of life on 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and 5 levels of severity, but also gives information about health benefits in terms of quality-adjusted life years (QALY).²² Patients’ satisfaction and usability of the inhaler device will also be assessed by an electronic 8-item questionnaire designed specifically for this study. If patients are not able to use electronic tools,

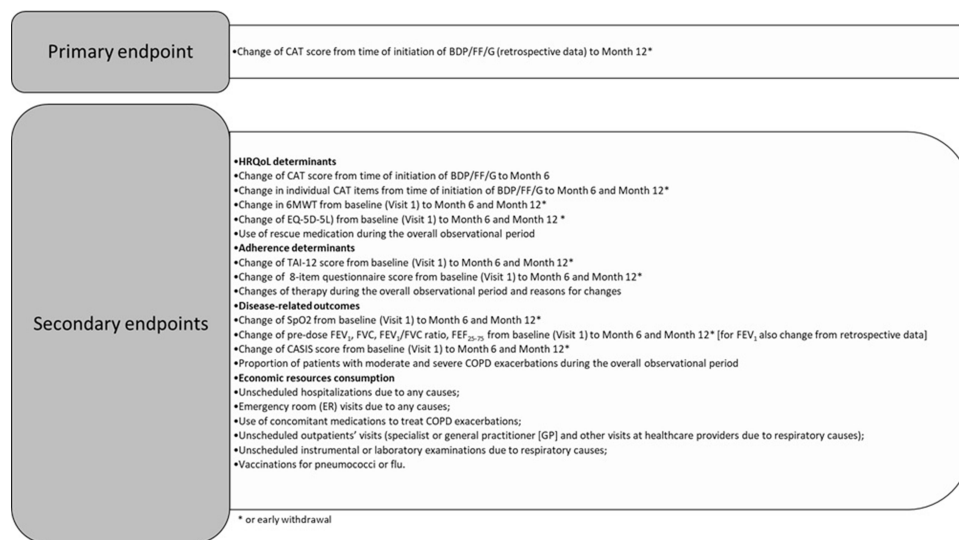


Figure 2 Primary and secondary endpoints of TRITRIAL study. *Or early withdrawal.

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these tests can be administered in paper form. Results of laboratory tests (if required by the physician) will be registered at any time during the study period, or in the 6 months prior to enrollment. Participants will be allowed to use any concomitant medication if necessary for the treatment of pre-existing concomitant diseases or for intercurrent diseases. All concomitant therapies will be permitted after clinical evaluation by the Investigator, and data will be collected for the whole duration of the study. The use of any other therapy for COPD is also allowed, according to clinical judgment and the local standard of care. This study will be conducted in compliance with the Declaration of Helsinki (1964 and amendments), current ICH E6 Good Clinical Practices and all other applicable laws and regulations, as applicable to non-interventional studies.

Statistical Analysis

A sample size of 720 subjects was calculated with a paired distribution, considering an effect size of 0.144, predicted using a minimal clinically important difference of 1²³ in CAT score and a predicted pooled standard deviation of 6.9 – from previous studies,³ an alpha level of 0.01 (two-sided) and a power of 0.90. However, calculating a 10% dropout, a final sample of 800 subjects was established. R statistical analysis (version 3.5.2) with pwr package was used to compute the sample size. The following analysis set will be considered for data analysis: Safety Analysis Set (SAF), consisting of all patients enrolled who signed informed consent and received at least one administration of BDP/FF/G; Full Analysis Set (FAS): consisting of all patients of the SAF who have a valid baseline assessment and at least one post-baseline evaluation of efficacy, according to an intention-to-treat (ITT) principle. The analysis of safety endpoints will be performed in the Safety population (SAF). Analysis of efficacy endpoints will be performed in the FAS population. The following describes the statistical analysis as it was foreseen at the time of planning the investigation. All statistical tests will be performed at 0.05 significance level (two-sided). The results of efficacy and safety results of the study will be presented in the form of descriptive statistics. Continuous variables will be summarized by number of cases, mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized using counts of patients and percentages. Where appropriate, the 95% confidence interval for means and percentages will be presented. In case of study discontinuation between Month 6 (Visit 2) and Month 12 (Visit 3), the last observation carried forward (LOCF) approach will be used to address missing data in efficacy endpoints at Month 12

(Visit 3) or in the Early Termination Visit. No other replacement of missing data will be performed. Demographics and baseline variables will be summarized using descriptive statistics for the SAF population. The following variables will be summarized and listed: age, gender, race, height, weight, BMI, medical history and COPD history (including previous COPD exacerbations and hospitalizations), respiratory medications in the last 6 months (including the reason for starting BDP/FF/G), medications for other non-respiratory diseases in the last month, concomitant diseases and concomitant treatments, physical examination, vital signs. The results of primary efficacy variable will be reported by means of default descriptive statistics. Change of CAT score from the start of treatment with BDP/FF/G (retrospective data) to endpoint (Month 12 or early withdrawal) will be calculated with the two-sided 95% CI. The change of CAT over the study will be analyzed by means of the analysis of variance for repeated measures. The results of secondary efficacy variables will be reported by means of default descriptive statistics. For continuous variables, the two-sided 95% CI for changes from start of treatment with BDP/FF/G (retrospective data) for CAT and pulmonary function tests, and for changes from baseline (Visit 1) for the other secondary efficacy variables, to Month 6 and Month 12 (or early withdrawal) will be calculated. The change in secondary efficacy continuous variables over the study will be analyzed by means of the analysis of variance for repeated measures. Means with their 95% confidence interval will be presented at each study timepoint. Categorical endpoints (ie, proportion of patients with moderate and severe COPD exacerbations during the overall observational period) will be presented using counts of patients, percentages with 95% confidence interval. Analysis by subgroups (eg, gender, age range, COPD severity range or any other subgroup that will be considered of clinical relevance) of primary and secondary efficacy variables will be performed by descriptive statistics provided that the distribution in size of subgroups will be adequately balanced. Comparison between/among subgroups might be investigated using the propensity score methodology, depending on the actual number of patients in the subgroups. Regression analysis may be used to assess the association of any factor/covariate and the primary efficacy endpoint.

Discussion

TRITRIAL study will collect information on the effect of treatment with BDP/FF/G on health status, HRQoL and adherence to therapy, to gather knowledge from routine care on whether a fixed triple therapy with a single inhaler will lead to relevant changes in disease-related outcomes, based on the

available evidence that triple therapy determines an improvement in COPD patients not controlled by maintenance treatment. The primary goals of COPD therapy²¹ are the prevention of future risks (exacerbations or clinical deterioration) and the reduction of symptoms, including improvement of health status. In line with these recommendations, the BDP/FF/G clinical program provided evidence for clinical benefits for a fixed triple therapy using a single pMDI compared to current standard therapies, supporting the rationale for a step-up approach in clinical practice. Despite the fact that improvement in both symptoms and health status is an objective of COPD treatment, the assessment of symptoms is not always adequate to drive the choice of therapy and the measurement of health status may require the use of complex assessment tools. TRITRIAL study will provide a reliable assessment of health status using CAT score as primary objective. CAT score can easily be used in daily clinical practice to quantify the impact of COPD symptoms on the risk of developing serious exacerbations, and thus may help in a clinical setting to match the patient's therapy more closely to individual needs. CAT score is also included in the combined COPD assessment indicated by GOLD recommendations. As the CAT is an instrument that measures not only the respiratory symptom burden of COPD, but also the general health status of patients in daily practice (ie, lack of energy or sleep disturbances, limitations in doing activities at home or confidence leaving home), it can be considered as a measure of HRQoL in general. Furthermore, recent studies have shown that the use of multiple inhalers and mixed inhalation techniques increase the risk of exacerbations compared to COPD patients using single inhalers or multiple inhalers requiring the same inhalation technique.^{24,25} The selection of a single inhaler could be beneficial to adherence and treatment effectiveness, which are also endpoints of the study. There is evidence supporting the association between inhaler satisfaction and patient adherence, as well as improved clinical outcome. Patients who use their preferred inhaler device may obtain a greater degree of satisfaction with therapy, and it is well established that COPD patients are more likely to be compliant and to experience better outcomes when they are satisfied with their inhalers.²⁶ We chose to evaluate patients receiving therapy with the fixed BDP/FF/G combination for several reasons: it was the first fixed triple therapy available for prescription and it has been used in clinical practice for more than a year; it is the only extrafine-particle fixed triple therapy, which is suitable for treating small airway dysfunction in COPD patients,⁷ a respiratory tract that is related to high impact of disease on health status (as measured by CAT)¹² and quality of sleep (as measured by CASIS);¹⁴ it is the only

twice-daily fixed triple and it could also be beneficial in patients with high burden of morning and night-time symptoms.²⁷ In TRITRIAL study, adherence and device usability evaluation, based on validated questionnaires' scores, will be crucial to better understand how fixed triple therapy in a single inhaler could impact on these aspects of the disease. Furthermore, this study will collect data on economic resources consumption over a one-year treatment period with fixed triple therapy, as a secondary variable. In fact, the effectiveness of BDP/FF/G in reducing exacerbations, and in improving HRQoL and disease-related variables may positively impact on healthcare costs, eg, in terms of decrease of hospitalizations, emergency room attendance, further unscheduled healthcare visits and examinations, and prescription of therapy to treat worsening of COPD. Overall, TRITRIAL study is expected to give consistent information about efficacy of fixed triple therapy with BDP/FF/G in a real life setting of patients with COPD, where adherence and other variables associated with the individual subject are crucial factors for the success of the therapy.

Abbreviations

BDP, Beclometasone dipropionate; BMI, body mass index; CASIS, COPD and Asthma Sleep Impact Scale; CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; eCRF, electronic Case Report Form; FAS, Full Analysis Set; FF, Formoterol fumarate; G, Glycopyrronium; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HRQoL, health-related quality of life; ICS, inhaled corticosteroids; ITT, intention-to-treat; LABA, long-acting beta2-agonists; LAMA, Long-acting muscarinic antagonists; LOCF, last observation carried forward; MMAD, mass median aerodynamic diameter; pMDI, pressurized metered dose inhaler; PROs, patient reported outcomes; QALY, quality-adjusted life years; RMC, Respiratory Medicine Centers; SAD, small airway dysfunction; SAF, Safety Analysis Set; SD, standard deviation; SGRQ, Saint George Respiratory Questionnaire; TAI, Test of Adherence to Inhalers.

Acknowledgments

The TRITRIAL Study is sponsored by Chiesi Italia. Editorial support was provided by Ethos srl and was funded by Chiesi Farmaceutici.

Disclosure

LR has received grants/research supports from Roche and Boehringer Ingelheim; he has received honoraria or

consultation fees from Boehringer Ingelheim, Promedior, Biogen, FibroGen, Sanofi-Aventis, Promedior, RespiVant, Roche, Celgene, Nitto, and Veracyte. FM declares no conflict of interests. AP, EI and GM are employees of Chiesi Italia, Parma, Italy. The authors report no other conflicts of interest in this work.

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