Stepwise withdrawal of inhaled corticosteroids in COPD patients receiving dual bronchodilation: WISDOM study design and rationale

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Summary
Long-acting bronchodilators in combination with inhaled corticosteroids (ICS) are recommended to decrease the risk of recurrent exacerbations in patients with Global initiative for chronic Obstructive Lung Disease (GOLD) stage 3–4 chronic obstructive pulmonary disease (COPD). There is increasing concern about the clinical benefit and long-term safety of ICS use in COPD patients. The WISDOM (Withdrawal of Inhaled Steroids During Optimised bronchodilator Management) study (NCT00975195) aims to evaluate the need for ICS use via stepwise withdrawal of ICS in COPD patients (GOLD 3–4 with a history of at least one exacerbation during the 12-month period prior to screening) receiving dual bronchodilation. During the 6-week run-in period, 2456 patients receive tiotropium 18 mg once daily, salmeterol 50 mg twice daily and fluticasone 500 mg twice daily. In a randomized, double-blind, parallel-group, active-
Introduction and rationale

Chronic obstructive pulmonary disease (COPD) continues to be a major cause of chronic morbidity and mortality worldwide [1]. The principal therapeutic options include smoking cessation, pharmacological treatment and pulmonary rehabilitation, which are combined to relieve symptoms and reduce the risk of future events [2]. According to current guidelines, inhaled bronchodilators, as mono-therapy or in combination, remain the mainstay for patients with all categories of disease, with long-acting bronchodilators being preferred over short-acting formulations [2]. Both long-acting beta-2-agonists (LABAs) and long-acting muscarinic antagonists (LAMAs) are effective in improving airflow and decreasing lung hyperinflation, which are important mechanisms involved in preventing exacerbations of COPD [3].

Combined bronchodilator treatment results in improvements in lung function and patient-reported outcomes compared to single bronchodilator therapy and could, therefore, help prevent exacerbations in COPD patients [4]. The combination of twice-daily (BID) LABA and once-daily (QD) LAMA, inhaled through separate devices, is an accepted therapeutic strategy to maximize bronchodilation and is well tolerated by the majority of patients [5]. Recently, QD dual bronchodilation with a fixed dose of the LABA indacaterol and the LAMA glycopyrronium administered via a single inhaler was shown to be superior in preventing moderate to severe exacerbations in COPD patients with severe to very severe airway obstruction compared to glycopyrronium alone [6].

Guidelines for the management of patients with COPD recommend the addition of inhaled corticosteroids (ICS) to long-acting bronchodilator therapy in patients with severe to very severe COPD and a history of frequent exacerbations [2]. The recent update of the Global initiative for chronic Obstructive Lung Disease (GOLD) guidelines recommends that a LAMA or ICS plus LABA should be prescribed for patients at increased risk of exacerbation, though data directly comparing these approaches are limited [7]. According to the assessment scheme suggested by GOLD, patients with an increased risk of exacerbation should be assigned to patient groups C or D, which predominantly include patients with GOLD stage 3 and 4 severity of airflow obstruction [8]. However, in clinical practice, ICS are widely prescribed for the majority of COPD patients, many of whom do not fall into these high-risk groups [9].

ICS are effective anti-inflammatory agents in bronchial asthma but appear much less effective in COPD. Initial clinical trials suggested some benefit from ICS compared to short-acting bronchodilators in preventing exacerbations [10] but in longer-term clinical trials, such as the TORCH (TOwards a Revolution in COPD Health) study, ICS monotherapy was no more effective than a twice-daily LABA and demonstrated a worse adverse-event profile [11,12].

Re-evaluation of several clinical trials assessing the effects of ICS monotherapy in stable COPD by meta-analysis [13], Cochrane review [14] and literature reviews [15] has not confirmed a clinically meaningful benefit of ICS in terms of preventing exacerbations and improving lung function and health-related quality of life in patients with stable COPD.

Currently, ICS are used as an adjunct to LABAs in the prevention of exacerbations [2]. However, combination therapy with ICS/LABA has appeared to be no more effective than monotherapy with tiotropium in preventing exacerbations when compared directly in patients with severe COPD [16], although there were fewer courses of oral corticosteroids prescribed in the ICS/LABA group. This suggests that different therapies may prevent different types of events. Given the potential for more effective sustained bronchodilation with combined LABA/LAMA therapy than with LABA alone, a comparison of this combination, with and without added ICS, should resolve whether a benefit in preventing exacerbations can still occur when lung function is optimized across the full 24-h day. Although the TORCH trial provided reassurance about the anticipated side effects associated with ICS use in general [17], an increased incidence of pneumonia was reported among fluticasone-treated patients [11]. This finding was confirmed in other studies, although whether it applies to all ICS has been disputed [18].

In a pooled analysis of two recent large clinical trials that investigated the fixed-dose combination of vilanterol, a QD LABA, with fluticasone furoate in COPD [19], the observed reduction in rate of exacerbations with combined ICS/LABA therapy compared to vilanterol monotherapy was partly offset by an increased frequency of investigator-reported and radiographically confirmed pneumonias. Given these concerns, it seems reasonable to look for a more targeted use for ICS therapy in patients for whom the benefits outweigh the risks. Indeed, there is accumulating evidence that certain COPD phenotypes, characterized by repeated exacerbations [20], inflammatory patterns [21] and co-morbidities [22], may differ in their response to ICS. Thus, there is a need to assess the benefit-risk profile of ICS when added to optimized maintenance therapy with long-acting bronchodilators in patients with stable COPD. It is also essential to use an appropriate scheme of withdrawing ICS in this patient population, as abrupt withdrawal can be associated with an increased risk of exacerbations, as highlighted by the current guidelines [2].
In this paper, we describe the rationale and trial design for the Withdrawal of Inhaled Steroids During Optimised bronchodilator Management (WISDOM) study (NCT00975195), which aims to clarify the need for continuous ICS use as an addition to dual bronchodilator maintenance therapy and will evaluate the effect of stepwise withdrawal of ICS therapy in patients with severe to very severe COPD (GOLD spirometric grade 3–4). The study also seeks to identify responder patient sub-populations, and markers of steroid need via phenotyping and genotyping.

Methods

Study design

This is a 1-year, multinational, randomized, double-blind, parallel-group, active-controlled study (Fig. 1). Following an initial assessment, patients enter a 6-week run-in period in which they receive tiotropium 18 μg QD via HandiHaler®, salmeterol 50 μg BID (two actuations of 25 μg) and fluticasone 500 μg BID (two actuations of 250 μg), via a metered-dose inhaler. Patients are randomized in blocks for treatment, in a 1:1 allocation ratio, into the double-blind phase of the trial, during which one group of patients continues to receive tiotropium 18 μg QD, salmeterol 50 μg BID and fluticasone 500 μg BID for the duration of the 52-week treatment period. The second group of patients continues to receive tiotropium 18 μg QD and salmeterol 50 μg BID over 52 weeks but initiates a stepwise reduction of fluticasone dose every 6 weeks from a total daily dose of 1000 μg–500 μg, then to 200 μg, and finally to placebo. The stepwise withdrawal period is followed by a stable treatment phase of 40 weeks, with patients receiving tiotropium 18 μg QD, salmeterol 50 μg BID and placebo. Patients in both groups are supplied with new medication packages every 6 weeks to ensure blinding. During the study, patients are permitted to use salbutamol as rescue medication and theophylline preparations, oral corticosteroids or antibiotics to treat exacerbations, as deemed medically necessary. Patients withdrawing prematurely from the study are followed up from time of withdrawal to completion of the trial at 52 weeks.

This study is being carried out according to the Declaration of Helsinki, local regulations and the International Conference on Harmonisation Harmonised Tripartite Guideline for Good Clinical Practice. The protocol has been approved by the local Institutional Review Boards, Independent Ethics Committees and the Competent Authorities (if applicable). All patients provided written, informed consent before the study began.

Patients

Patients enrolled into the study must meet the following inclusion criteria: age ≥40 years; current or ex-smokers with a smoking history of ≥10 pack-years; a diagnosis of severe to very severe COPD (i.e. a post-bronchodilator forced expiratory volume in 1 s [FEV₁] of <50% predicted and FEV₁ <70% of forced vital capacity [FVC]); a history of at least one documented exacerbation during the 12-month period prior to the initial screening visit. Key exclusion criteria include: presence of a disease other than COPD (defined as a disease or condition that, in the opinion of the investigator, may put the patient at risk because of participation in the study or may influence either the results of the study or the patient’s ability to participate in the study); a current clinical diagnosis of asthma; history of thoracotomy with pulmonary resection; unstable or life-threatening cardiac arrhythmia; clinical diagnosis of bronchiectasis; a respiratory tract infection or COPD exacerbation occurring within 6 weeks prior to the initial screening; history of myocardial infarction within 3 months prior to initial screening; or hospitalization for cardiac failure within the past year.

![Figure 1](image_url)  
**Figure 1**  
Study design. BID, twice-daily; ICS, inhaled corticosteroid; QD, once-daily.
Study outcomes and assessments

The primary efficacy end point measured in this study is the time to first moderate or severe on-treatment COPD exacerbation during the 12-month randomized period (Table 1). A COPD exacerbation is defined as an increase or new onset of at least two lower respiratory symptoms related to COPD, with at least one symptom lasting a minimum of 3 days and requiring prescription of antibiotics and/or systemic steroids. The start date of an exacerbation is defined as the onset date of the first recorded COPD symptom.

Key secondary efficacy variables include the number of moderate or severe on-treatment COPD exacerbations, the proportion of patients experiencing at least one moderate or severe on-treatment COPD exacerbation and the number of hospitalizations due to on-treatment COPD exacerbations (i.e. number of severe COPD exacerbations), all assessed over the 12-month randomized period (Table 1). Other secondary efficacy measures include in-clinic FEV₁ at weeks 0, 6, 12, 18 and 52, daily home-based spirometry (FEV₁, FVC and peak expiratory flow rate), body mass index, exercise capacity (6-Minute Walk Test) at weeks 0, 18 and 52, the Body mass index, airflow Obstruction, Dyspnea and Exercise capacity (BODE) index at weeks 0, 18 and 52, Physician’s Global Evaluation at weeks 0, 27 and 52, health-related quality of life (St. George’s Respiratory Questionnaire [SGRQ]) at weeks 0, 27 and 52, and cough and expectoration (Cough and Sputum Assessment Questionnaire [CASA-Q]) at weeks 0, 12, 18 and 52.

Sub-study

A sub-study of approximately 500 patients is being recruited to identify sub-populations and potential markers of steroid need. Patients enrolled into the sub-study undergo high-resolution computed tomography scan prior to randomization for quantification of emphysema and evaluation of bronchiectasis. In addition, body plethysmography and measurement of diffusing capacity for carbon monoxide is performed. Blood samples are taken for pharmacogenetic testing and biomarker determination (adiponectin, leptin, C-reactive protein, interleukin-6, interleukin-8, tumour necrosis factor-α, fibrinogen, soluble interleukin adhesion molecule-1, serum amyloid A, procalcitonin and B-type natriuretic peptide) at visits 3, 6 and 13. The panel of biomarkers may allow further evaluation of the role of systemic inflammation for exacerbations, with fibrinogen being of particular interest [23]. In addition, the cardiac biomarkers procalcitonin and B-type natriuretic peptide may help to understand the impact of concomitant cardiac disease on exacerbations in COPD. Genomic DNA extraction is according to standard molecular genetics methods and analysis by TaqMan® or other standard genotyping technologies. Assessment of airway inflammation through differential cell count is performed at visits 3 and 13 by either induced sputum samples (inhalation of 0.9% saline; total inhalation time of 20 min) in patients with FEV₁ ≥30%, or spontaneous sputum samples in patients with FEV₁ <30% using the method of selected sputum plugs, as described elsewhere [24]. The fraction of exhaled nitric oxide is measured at visits 3, 6 and 13.

Table 1  Key study end points and assessments.

<table>
<thead>
<tr>
<th>End point</th>
<th>Assessment</th>
<th>Time of assessment (weeks)</th>
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<tbody>
<tr>
<td>Primary</td>
<td>Time to first moderate or severe on-treatment COPD exacerbation during the 12-month randomized period</td>
<td>An increase or new onset of ≥2 lower respiratory symptoms related to COPD, with ≥1 symptom lasting ≥3 days requiring a change in treatment&lt;sup&gt;g&lt;/sup&gt;</td>
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<tr>
<td>Secondary</td>
<td>Number of moderate to severe on-treatment COPD exacerbations during the 12-month randomized period</td>
<td>As above, applying a 7-day gap rule, e.g. exacerbations for which onset date of the second exacerbation is ≤7 days after the end of the first exacerbation are combined and considered moderate or severe (if ≥1 of the exacerbation events is moderate or severe)</td>
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Proportion of patients experiencing ≥1 moderate or severe on-treatment COPD exacerbation during the 12-month randomized period

Severity of on-treatment COPD exacerbations during the 12-month randomized period

Number of hospitalizations due to COPD exacerbations over the 12-month randomized period

Number of severe exacerbations after applying a 7-day gap rule

COPD, chronic obstructive pulmonary disease.

<sup>a</sup> Shortness of breath, cough, wheezing, chest tightness, sputum production and purulence.

<sup>b</sup> Hospitalization/treatment in Urgent Care Unit, prescription of antibiotics and/or systemic steroids, or significant change of prescribed respiratory medication (i.e. theophyllines, long-acting beta-2-agonists, inhaled corticosteroids).
Safety

Safety is assessed in all treated patients. All adverse events, irrespective of causality, are monitored, and change from baseline, date of onset, end time, intensity of the event and treatment or action required are recorded at each visit. Vital signs, including blood pressure and pulse rate, are measured and recorded prior to clinic spirometry. Clinical laboratory tests and electrocardiograms are carried out at screening.

Statistical analysis

It is estimated that 2456 patients should be randomized from across 200 centres to ensure that a minimum of 2234 evaluable patients complete the study. Of these 2456 patients, approximately 500 are being recruited to participate in the sub-study. This calculation was conducted considering the primary end point (time to moderate or severe exacerbation over the 12 months of the trial) using a 97.5% one-tail confidence interval and 90% power, based on an expected dropout rate of 15% per year and a standard exponential parameter ($\lambda$) of 0.077 (based on expected median time to first moderate or severe COPD exacerbation of 9 months, from previous studies) and assuming a non-inferiority limit of 1.2.

This study is designed to determine non-inferiority in the hazard of the time to first moderate or severe exacerbation. The primary end point is evaluated using a one-sided confidence interval at the 2.5% level of significance obtained via Cox’s proportional hazard regression adjusting for baseline FEV$_1$. The null hypothesis tested is that the hazard ratio of the mean time to exacerbation for ICS withdrawal versus continued treatment is $\leq$1.2 and the alternative hypothesis states that the ratio is $>1.2$. The number of moderate or severe on-treatment exacerbations is analysed using a negative binomial analysis with log treatment exposure as offset. Changes from baseline in-clinic FEV$_1$, home-based lung function (FEV$_1$, FVC and peak expiratory flow rate), body mass index, exercise capacity, dyspnoea (mMRC scale), BODE index, Physician’s Global Evaluation, health-related quality of life (SGRQ) and cough and expectoration (CASA-Q) are all analysed using a restricted maximum-likelihood model based on a repeated-measures approach. If a patient discontinues the trial due to worsening of disease, his/her missing data will be imputed by the least favourable value observed to that time point. No formal hypothesis is being tested for the sub-study; however, data from all end points will be summarized. Safety is summarized descriptively.

Discussion

The contribution of ICS to the efficacy and long-term safety of concomitant optimized bronchodilator therapy in COPD remains unknown and there is concern over the benefit-risk profile of ICS therapy itself [25]. In particular, abrupt withdrawal of ICS at baseline or during treatment, as used in many studies investigating the contribution of ICS, is considered an artificial condition and may precipitate adverse events, thereby confounding results. Thus, it is necessary to investigate the effects of stepwise ICS withdrawal in patients with severe and very severe COPD receiving otherwise optimized bronchodilator therapy [26,27].

Previous studies investigating the effects of withdrawing ICS therapy have reported acute and persistent deterioration in lung function, dyspnoea, disturbed nights [27,28], and an increased risk of exacerbations and shorter time to exacerbation [29,30]. A systematic review of four trials [26] showed that, while outcomes such as exacerbations, health-related quality of life and lung function were generally worse for patients discontinuing ICS therapy, the differences compared to those who continued were small and not always statistically significant. The contradictory outcomes observed in these ICS-withdrawal trials may be a direct result of some methodological issues [26,31].

In all ICS-withdrawal studies conducted to date, treatment with ICS was stopped abruptly following randomization; this abrupt withdrawal could account for the decreased time to first exacerbation observed in some studies [32]. Patient characteristics, disease severity and concomitant treatments differed across studies, which may contribute to the differences and/or inconsistencies observed in previous ICS-withdrawal studies, especially as the effects of ICS on exacerbations are more likely to be seen in more severe patients. The WISDOM study will add to the limited evidence describing the long-term benefits of dual bronchodilation plus ICS compared to dual bronchodilation alone. Several considerations have been taken into account to enable the most robust and comprehensive evaluation of this important comparison to date.

(1) All patients will receive triple therapy for 6 weeks before randomization, which should avoid any bias similar to that previously reported as a result of withdrawing treatments before randomization [31].

(2) All patients will receive stable dual bronchodilator therapy with tiotropium QD and salmeterol BID in accordance with current guidelines, thus potentially reducing the risk of exacerbations following withdrawal of ICS therapy [16].

(3) The study uses a stepwise withdrawal of ICS therapy from the high dose (fluticasone 500 $\mu$g BID) to zero, a method that has been successfully employed in studies investigating the down-titration of ICS in patients with asthma [33]. Currently, there is no clear evidence that abrupt withdrawal of ICS is safe; stepwise withdrawal should minimize the potential risk of rebound steroid effects, such as relative adrenal insufficiency, associated with abrupt withdrawal of ICS [34]. Thus, only exacerbations attributable to the long-term condition will be captured, rather than those attributable to abrupt withdrawal of high-dose ICS [34]. Blinding to the stepwise ICS withdrawal is ensured by delivery of new medications to all patients every 6 weeks.

(4) The primary end point of time to first exacerbation was chosen as it is sensitive to both the occurrence of an exacerbation and the lag time of that occurrence. Furthermore, it is not affected by the occurrence of multiple exacerbations in some patients and is less
likely to be affected by early discontinuation or changes in concomitant therapies introduced after the first exacerbation.

(5) In the sub-study, we aim to identify potential markers of steroid responsiveness, which could help to identify subgroups of COPD patients who may benefit from long-term steroid treatment. The stepwise withdrawal could offer the chance to identify a minimally effective dose of ICS in COPD.

It should be noted that inclusion criteria for the WISDOM study were established based on spirometry categories from the GOLD 2010 guidelines, i.e., GOLD 3 and 4 [2]. A recent large, observational study has shown that patients who are GOLD 3 and 4 constitute a substantial proportion of the COPD population [20]. Although GOLD assessments have now been updated to include risk of exacerbations and symptoms, the new patient categories C and D are reflected in the included study population of patients with severe and very severe disease. Therefore, the results from this study have the potential to guide treatment in accordance with these latest guidelines [2]. However, the study results will be less suitable for patients with mild to moderate airflow obstruction and a history of frequent exacerbations, as this phenotype was not included in the study [20].

A total of 3425 patients have been screened at 209 investigator sites worldwide, with 2488 patients randomized to treatment. Results of this large, randomized study will help to describe the benefit of ICS therapy to prevent exacerbations and symptoms, the new patient categories C and D are reflected in the included study population of patients with severe and very severe disease. Therefore, the results from this study have the potential to guide treatment in accordance with these latest guidelines [2]. However, the study results will be less suitable for patients with mild to moderate airflow obstruction and a history of frequent exacerbations, as this phenotype was not included in the study [20].

Conflicts of interest

Dr. Magnussen initiated the research proposal and contributed to the study design and conduct. The Pulmonary Research Institute received funding from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Merck, Novartis, Takeda and Roche to conduct clinical studies. He has spoken at meetings and is a member of advisory boards for these and other companies.

Dr. Watz contributed to the study design and conduct. The Pulmonary Research Institute received funding from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Merck, Novartis, Takeda and Roche to conduct clinical studies. He has received payments for lectures, consultancy services and congress travel support from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Chiesi and Merck.

Dr. Kirsten contributed to the study design and conduct. The Pulmonary Research Institute received funding from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Merck, Novartis, Takeda and Roche to conduct clinical studies. She has received payments for lectures and consultancy services from Boehringer Ingelheim, Novartis, Orion Pharma and Intermune.

Dr. Decramer has been part of advisory boards for AstraZeneca, Boehringer Ingelheim/Pfizer, GlaxoSmithKline, Nycomed, Novartis, Altana and Dompe. He has also received lecture fees from these companies and research grants from AstraZeneca and GlaxoSmithKline.

Dr. Dahl has advised on the study design and conduct of trials sponsored by Boehringer Ingelheim, Novartis, ALK-Abello and Vectura. He has spoken at meetings sponsored by these and other companies.

Dr. Calverley has advised on the study design and conduct of several large trials sponsored by GlaxoSmithKline, Boehringer Ingelheim, Takeda and AstraZeneca. He has spoken at meetings sponsored by these and other companies, and his department has received funding from GlaxoSmithKline and Takeda to conduct clinical studies.

Ms Finnigan, and Drs. Towe, Tetzlaff and Disse are employees of Boehringer Ingelheim.

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