

Long-term Triple Therapy De-escalation to Indacaterol/Glycopyrronium in COPD Patients (SUNSET): a Randomized, Double-Blind, Triple-Dummy Clinical Trial

Kenneth R. Chapman^{1*}, John R. Hurst^{2*}, Stefan-Marian Frent^{3†}, Michael Larbig⁴, Robert Fogel⁵, Tadhg Guerin⁶, Donald Banerji⁵, Francesco Patalano⁴, Pankaj Goyal⁴, Pascal Pfister⁴, Konstantinos Kostikas⁴, Jadwiga A. Wedzicha⁷

¹Asthma and Airway Centre, University Health Network, University of Toronto, Toronto, ON, Canada; ²UCL Respiratory, University College London, London, United Kingdom; ³Department of Pulmonology, University of Medicine and Pharmacy, Timisoara, Romania; ⁴Novartis Pharma AG, Basel, Switzerland; ⁵Novartis Pharmaceuticals Corporation, East Hanover, NJ, United States; ⁶Novartis Ireland Limited, Dublin, Ireland; ⁷Respiratory Clinical Science Section National Heart and Lung Institute, Imperial College London, London, United Kingdom; *These authors have contributed equally to this manuscript. [†]Dr. Frent was a European Respiratory Society Fellow at Novartis Pharma AG, Basel, Switzerland during his engagement in the study.

Corresponding author:

Prof. Jadwiga A. Wedzicha

National Heart and Lung Institute, Imperial College London,

Guy Scadding Building, Dovehouse Street, London SW3 6LY, UK

e-mail: j.wedzicha@imperial.ac.uk

Tel.: +44 (0) 207 594 7947

Author contributions:

JAW contributed to the conception and design of the study, the analysis and interpretation of data and the writing of the manuscript. RF, ML and PP contributed to the conception, design and conduct of the study. KRC, JH and KK contributed to the analysis and interpretation of data and participated in the writing of the manuscript. TG provided statistical advice and oversaw the statistical analysis. SF, DB, FP and PG contributed to the interpretation of data, and on the writing of the manuscript. All authors revised the manuscript critically for intellectual content and provided approval of the version to be published.

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At a Glance Commentary**Scientific Knowledge on the Subject:**

- Add-on Inhaled corticosteroids (ICS) are currently recommended for COPD patients with frequent exacerbations that occur despite effective long-acting bronchodilator treatment.

- Many patients receiving triple therapy, i.e. a long-acting β_2 agonist (LABA) plus a long-acting muscarinic antagonist (LAMA) plus an ICS are not frequent exacerbators.
- The WISDOM study evaluated the stepwise withdrawal of ICS from triple therapy in COPD patients with a history of exacerbations, but only a proportion of these patients were on triple therapy prior to study inclusion.
- There are no randomized controlled trials investigating ICS withdrawal in patients on long-term triple therapy without frequent exacerbations.

What This Study Adds to the Field

- This is the first study to evaluate the efficacy and safety of the direct de-escalation from long-term triple therapy (tiotropium plus salmeterol/fluticasone) to the once-daily LABA/LAMA combination of indacaterol/glycopyrronium on lung function and exacerbations in patients with moderate-to-severe COPD who do not experience frequent exacerbations.
- In COPD patients without frequent exacerbations while receiving long-term triple therapy, the direct change to the dual bronchodilator indacaterol/glycopyrronium led to a small decrease in lung function, with no difference in COPD exacerbations.
- In patients with ≥ 300 blood eosinophils/ μL there was a greater decline in lung function and increased exacerbation risk, and these patients are more likely to benefit from continuing triple therapy.
- However, for the majority of patients the switch did not have any impact on lung function or exacerbations. The results of the SUNSET study provide evidence for the personalized management of COPD patients.

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ABSTRACT (Word Count: 250)

Rationale: There are no studies on ICS withdrawal in patients on long-term triple therapy in the absence of frequent exacerbations.

Objective: To evaluate the efficacy and safety of the direct de-escalation from long-term triple therapy to indacaterol/glycopyrronium in non-frequently exacerbating COPD patients.

Methods: This 26-week, randomized, double-blind, triple-dummy study assessed the direct change from long-term triple therapy to indacaterol/glycopyrronium (110/50 µg once daily) or continuation of triple therapy (tiotropium 18 µg once daily plus combination of salmeterol/fluticasone propionate [50/500 µg] twice daily) in non-frequently exacerbating patients with moderate-to-severe COPD. Primary endpoint was non-inferiority on change from baseline in trough forced expiratory volume in 1 second (FEV₁). Moderate or severe exacerbations were predefined secondary endpoints.

Measurements and Main Results: 527 patients were randomized to indacaterol/glycopyrronium and 526 to triple therapy. ICS withdrawal led to a reduction in trough FEV₁ of -26mL (95% confidence interval [CI], -53 to 1 mL) with confidence limits exceeding the non-inferiority margin of -50 mL. The annualized rate of moderate or severe COPD exacerbations did not differ between treatments (rate ratio 1.08; 95%CI, 0.83 to 1.40). Patients with ≥300 blood eosinophils/µL at baseline presented greater lung function loss and higher exacerbation risk. Adverse events were similar in the two groups.

Conclusions: In COPD patients without frequent exacerbations on long-term triple therapy, the direct de-escalation to indacaterol/glycopyrronium led to a small decrease in lung function, with

no difference in exacerbations. The higher exacerbation risk in patients with ≥ 300 blood eosinophils/ μL suggests that these patients are likely to benefit from triple therapy.

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterized by persistent respiratory symptoms and airflow limitation for which recommended treatments include long-acting bronchodilators (long-acting β_2 agonists, LABA; and long-acting muscarinic antagonists, LAMA) alone or in combination (LABA/LAMA) (1). The current GOLD strategy document suggests that the addition of inhaled corticosteroids (ICS) to LABA and LAMA in the form of “triple therapy” (LABA plus LAMA plus ICS) is to be reserved for high-risk patients still experiencing exacerbations on LABA/LAMA therapy (1). However, the majority of patients with COPD are not frequent exacerbators (2, 3), and despite current recommendations, many of these patients receive triple therapy (4). In part, this reflects the historic introduction of ICS plus LABA then LAMA therapy in COPD, and previous guideline recommendations (5, 6). This approach is not without risk; the long-term use of ICS is associated with an increased risk of adverse events, including pneumonia (7), mycobacterial infections (8), diabetes onset and progression (9), or fractures (10).

It is therefore important to personalize COPD management by identifying patients who may be more likely to benefit from continued long-term triple therapy and those who would be optimally managed by LABA/LAMA after ICS withdrawal. The WISDOM trial showed that in severe-to-very severe COPD patients susceptible to exacerbations, the risk of moderate or severe exacerbations was similar in patients who followed a stepwise ICS withdrawal compared to those who continued with ICS (11). However, there are no data on direct ICS withdrawal in patients on long-term triple therapy without a history of frequent exacerbations.

In the **Study to UnderstaNd the Safety and Efficacy of ICS Withdrawal from Triple therapy in COPD (SUNSET)** trial we evaluated the efficacy and safety of the direct cessation of ICS from

long-term triple therapy to the second-generation LABA/LAMA combination of indacaterol/glycopyrronium, in non-frequently exacerbating COPD patients. Uniquely, we answer the clinically relevant question of which patients on historic triple therapy who do not experience frequent exacerbations can be maintained on effective dual bronchodilator therapy alone.

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METHODS

Study Design

From November 2015 through July 2017 we performed this 26-week, randomized, double-blind, triple-dummy, parallel-group multicenter study. After a 4-week run-in period on standard triple therapy (tiotropium 18 µg once daily plus combination of salmeterol/fluticasone propionate 50/500 µg twice daily), patients were randomized (1:1) to indacaterol/glycopyrronium (110/50 µg) once daily or triple therapy (tiotropium plus salmeterol/fluticasone; Figure 1). The study protocol and all amendments were reviewed by the Independent Ethics Committee or Institutional Review Board for each center and the trial was registered at clinicaltrials.gov (NCT02603393). All patients provided written informed consent.

Patients

We enrolled patients 40 years of age or older who had stable COPD, a post-bronchodilator forced expiratory volume in 1 second (FEV₁) of at least 40% to less than 80% predicted, a post-bronchodilator ratio of FEV₁ to forced vital capacity (FVC) of less than 0.70, and a smoking history of at least 10 pack-years. Patients were not frequent exacerbators, i.e. they had a history of no more than one moderate or severe exacerbation in the previous year. Patients must have received long-term triple therapy (for *at least* 6 months) before enrolment into the study. Patients with a history of asthma and those with a blood eosinophil count >600 cells/µL during screening were excluded from the study. Additional details are provided in the Supplementary Appendix.

Procedures

Patients received either (1) indacaterol/glycopyrronium 110/50 µg once daily via Breezhaler® (Novartis Pharma AG, Basel, Switzerland) *or* tiotropium matching placebo once daily via HandiHaler® (Boehringer Ingelheim, Ingelheim, Germany) *plus* salmeterol/fluticasone matching placebo via Accuhaler® [GlaxoSmithKline, United Kingdom) *or* Indacaterol–glycopyrronium matching placebo once daily via Breezhaler®; *or* (2) tiotropium 18 µg once daily via HandiHaler® *plus* salmeterol/fluticasone propionate 50/500 µg twice daily via Accuhaler®. Salbutamol was provided for use as needed during the study. The study included a 30-day follow-up period to collect patient safety data, during which the study investigator decided on the treatment of the patients.

Outcomes

The primary objective of this study was to demonstrate non-inferiority of indacaterol/glycopyrronium versus tiotropium plus salmeterol/fluticasone on change from baseline in post-dose trough FEV₁ (a mean of the two FEV₁ values measured at 23 h 15 min and 23 h 45 min after the morning dose on Day 181) after 26 weeks of treatment. A secondary objective was to evaluate moderate or severe COPD exacerbations over 26 weeks. Other secondary objectives included comparisons in trough FEV₁ and FVC over 26 weeks, TDI and SGRQ-C scores after 12 and 26 weeks, mean rescue medication use, safety and tolerability over 26 weeks of treatment. Effect of baseline blood eosinophil levels (based on percentage, <2% versus ≥2%; and absolute blood eosinophil counts, <150, 150 to <300, ≥300 cells/µL) on trough FEV₁ and exacerbation rate were also evaluated as pre-specified analyses.

Exacerbations, defined according to Anthonisen criteria (12), were categorized as mild (worsening of symptoms for ≥ 2 consecutive days and not treated with systemic corticosteroids and/or antibiotics), moderate (treated with systemic corticosteroids and/or antibiotics) or severe (requiring hospitalization [or an emergency room visit of >24 hours] in addition to treatment with systemic corticosteroids and/or antibiotics). Worsening of symptoms was captured in an electronic diary that alerted patients and physicians to the presence of an exacerbation.

Statistical Analysis

Sample size for non-inferiority testing on post-dose trough FEV₁ at day 182 for patients in the indacaterol/glycopyrronium group compared to the tiotropium plus salmeterol/fluticasone group assumed a non-inferiority margin of -50 mL (13-15), a standard deviation of 200 mL and a one-sided alpha level of 0.025. To ensure that the study was sufficiently powered (92%), 375 evaluable patients in each treatment arm were required, and taking into account an expected drop-out rate of at least 15%, we estimated that approximately 1000 patients should be enrolled. The primary endpoint was evaluated in the Full Analysis Set (FAS) and confirmed in the Per-Protocol set (PPS) populations. The FAS consisted of all patients in the randomized set who received at least one dose of study medication. Following the intent-to-treat principle, patients in the FAS were analyzed according to the treatment they were assigned to at randomization. The PPS included all patients in the FAS without any major protocol deviations. The primary analysis of the change from baseline in post-dose trough FEV₁ used a mixed-effect model for repeated measures (MMRM). The model included fixed, categorical effects of treatment and visit, region and treatment-by-visit interaction as well as continuous, fixed covariates of baseline and baseline-by-visit interaction. Subgroup analyses of the primary endpoint were performed to

investigate the relationship between treatment and disease-relevant baseline characteristics (i.e. blood eosinophils, smoking status, FEV₁ reversibility, and exacerbation history). The same MMRM model as the primary endpoint was performed with the inclusion of a treatment by subgroup interaction effect. The mixed model repeated measures is based on the assumption of missing at random (MAR) and the assumption that dropouts behave similarly to other patients in the same treatment group and similar covariate values, had they not dropped out.

The rate of moderate or severe COPD exacerbations during the treatment period was analyzed using a generalized linear model assuming a negative binomial distribution. The time at risk for a patient was the length of time exposed to study treatment and the model included terms for treatment, region and COPD exacerbation history. A Cox proportional-hazards regression model was performed to analyze the time to first moderate or severe exacerbation and the model included the same terms as for analysis of the rate of moderate or severe exacerbations. Additional details are provided in the Supplementary Appendix.

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RESULTS

Patients

A total of 1684 patients were screened, 1053 were randomized to the two treatment groups (FAS: 527 in the indacaterol/glycopyrronium and 526 in the tiotropium plus salmeterol/fluticasone group) and 928 patients completed the study (456 in the indacaterol/glycopyrronium and 472 in the tiotropium plus salmeterol/fluticasone group) (Figure 2). Most of the patients discontinued during screening and run-in were screen failures, with the most common reason being related to spirometric inclusion and exclusion criteria. The PPS included 928 patients (462 in the indacaterol/glycopyrronium and 466 in the tiotropium plus salmeterol/fluticasone group). Baseline demographic and clinical characteristics of the patients are presented in Table 1; a total of 70.6% of the randomized patients were male, with a mean post-bronchodilator FEV₁ of 1.6 L (56.6% predicted) and 34.1% had one exacerbation in the previous year. There were no differences in the distribution of patients according to their exacerbation history and the baseline blood eosinophil counts (Supplementary Table S5). Compliance was high in both treatment groups, with 98.7% of the patients in the indacaterol/glycopyrronium and 97.9% in the triple therapy groups achieving ≥80% compliant days during the double-blind treatment period.

PRIMARY ENDPOINT

We could not confirm non-inferiority of indacaterol/glycopyrronium to tiotropium plus salmeterol/fluticasone in terms of post-dose trough FEV₁. In the FAS, ICS withdrawal led to a difference in mean change from baseline in post-dose trough FEV₁ between

indacaterol/glycopyrronium and tiotropium plus salmeterol/fluticasone group of -26 mL (95% confidence interval [CI], -53 to 1 mL) at Week 26, with the lower limit of the 95% CI exceeding the non-inferiority margin (-50 mL). In the PPS population, the withdrawal of ICS led to a mean difference of -29 mL (95% CI, -58 to 0 mL) in trough FEV₁ at Week 26 (Figure 3A). Over the 26-week treatment period, the withdrawal of ICS resulted in differences in trough FEV₁ between the two treatments of -26 mL to -33 mL (Figure 3B). The difference was evident from Day 29 and did not change throughout the 26-week treatment period.

Subgroup analysis of trough FEV₁ by baseline blood eosinophils

There was no significant difference between treatments in post-dose trough FEV₁ at week 26 in patients with baseline blood eosinophil levels of <2%, and eosinophil count of <300 cells/ μ L; differences in post-dose trough FEV₁ between treatments were higher in patients with high blood eosinophil counts at baseline (\geq 2% or \geq 300 cells/ μ L) (Figure 3C).

SECONDARY ENDPOINTS

COPD exacerbations

Patients in the two groups experienced similar annualized rates of moderate or severe COPD exacerbations (indacaterol/glycopyrronium vs. tiotropium plus salmeterol/fluticasone 0.52 versus 0.48, rate ratio 1.08; 95%CI, 0.83 to 1.40; Figure 4A) and all (mild, moderate, and severe) exacerbations (4.11 versus 3.86, rate ratio 1.07; 95% CI, 0.93 to 1.22). There was no difference between treatments in the time to first moderate or severe COPD exacerbation (hazard ratio 1.11; 95% CI 0.85 to 1.46; Figure 4B).

Subgroup analysis of moderate or severe exacerbations by baseline blood eosinophils

The rate of moderate or severe exacerbations according to baseline blood eosinophils subgroups did not differ between the two treatment arms, with the exception of patients with baseline blood eosinophil counts ≥ 300 cells/ μL who were at increased risk of exacerbations (rate ratio 1.86; 95% CI, 1.06 to 3.29; Figure 4C). There was no difference in the time to first exacerbation between the two arms in patients with < 300 cells/ μL (hazard ratio 0.95; 95% CI, 0.70 to 1.29; Figure 4D), whereas a difference in favor of tiotropium plus salmeterol/fluticasone was observed in patients with ≥ 300 cells/ μL (hazard ratio 1.80; 95% CI, 0.98 to 3.28; Figure 4E). In a post-hoc analysis, we observed that the patients at increased risk of exacerbations were only those who demonstrated blood eosinophils consistently ≥ 300 cells/ μL at both the screening and baseline measurements (Figure E1 and Figure E2 in the Supplementary Appendix).

Other secondary endpoints

In subgroup analyses of post-dose trough FEV₁, according to baseline characteristics other than eosinophils, there were no differences between treatments, except for patients who were ex-smokers and those with moderate airflow limitation whose FEV₁ changes favored triple therapy (Figure E3 in the Supplementary Appendix).

There were no differences in trough FVC between indacaterol/glycopyrronium and tiotropium plus salmeterol/fluticasone at all the time points of the study (−6 mL on Day 29, −5 mL on Day 85, 0 mL on Day 181 and +18 mL on Day 182) (Figure E4 in the Supplementary Appendix).

The change from baseline in SGRQ-C score at Week 12 was −0.7 and −2.5 units for indacaterol/glycopyrronium and tiotropium plus salmeterol/fluticasone respectively ($\Delta=1.8$ units; 95%CI, 0.7 to 3.0); similar changes were observed at Week 26 (−1.0 and −2.5 units with

indacaterol/glycopyrronium and tiotropium plus salmeterol/fluticasone, respectively; $\Delta=1.4$ units; 95% CI, 0.2 to 2.6 units). The changes from baseline in TDI score were similar for the two treatments at Week 12 ($\Delta=-0.24$; 95% CI, -0.58 to 0.10 units) or Week 26 ($\Delta=-0.28$; 95% CI, -0.63 to 0.06 units). During the 26-week treatment period, use of rescue medication ($\Delta=0.177$ puffs/day; 95% CI, -0.01 to 0.36) or the days without rescue medication use ($\Delta=0.103$ days; 95% CI, -3.25 to 3.25) were similar for both treatment groups.

SAFETY

The incidence of adverse events and serious adverse events were similar across both treatment arms (Table 2). Adverse events leading to permanent discontinuation of study drug were similar (indacaterol/glycopyrronium 3.6% and tiotropium plus salmeterol/fluticasone 3.4%). There were numerical differences in ICS-related adverse events (oropharyngeal candidiasis and pneumonias) between the two treatment groups. Seven deaths were reported during the 26-week treatment period (three in indacaterol/glycopyrronium and four in tiotropium plus salmeterol/fluticasone group).

DISCUSSION

This is the first study to evaluate the direct de-escalation of ICS from long-term triple therapy to the second-generation LABA/LAMA combination of indacaterol/glycopyrronium in a population of low-risk COPD patients with no more than one exacerbation in the previous year. We have shown that the treatment de-escalation led to a small but significant decrease in lung function of 26 mL in trough FEV₁ with no difference in the rates or risk of COPD exacerbations between treatments. Patients with high blood eosinophils (≥ 300 cells/ μ L) at baseline showed greater differences in lung function and were at increased risk of exacerbations after ICS withdrawal. Our study answers the clinically relevant question of how to manage patients who are on triple therapy started under previous recommendations (e.g. FEV₁ <50% predicted and/or ≥ 2 exacerbations in the previous year according to GOLD 2011) (6), or those who have been inappropriately escalated.

Although the study did not meet the primary endpoint of non-inferiority in trough FEV₁, the observed reduction of 26 mL in the indacaterol/glycopyrronium versus triple therapy group is consistent with the long-acknowledged small benefit in lung function seen with the use of ICS (16). This change is of uncertain clinical significance and is too small to be measured reliably in individual patients. Our results show a marginal difference between the two treatments, since the 95% CI (-53 to 1 mL) includes the non-inferiority margin (-50 mL) and does not exclude the margin of 0 mL (17). This difference was evident 4 weeks after ICS withdrawal and did not change further throughout the treatment period, a finding consistent with the results of the WISDOM study (11). Importantly, in the current study we were also able to identify that the patients at higher risk for more prominent loss of lung function were those with higher blood eosinophils

(i.e. the ones with ≥ 300 cells/ μL presented a mean decrease of -69 mL). Older studies that explored the abrupt withdrawal of ICS in COPD patients showed increase in exacerbations and decline in lung function (18-21); however, these studies used short-acting bronchodilators or twice-daily LABA as maintenance treatment. More recent studies showed that ICS discontinuation from LABA/ICS is safe in the presence of effective long-acting bronchodilation in appropriate patients (22, 23). The differences in lung function after the abrupt withdrawal of ICS observed in our study are smaller than those observed after the stepwise withdrawal in the WISDOM study (11). In the SUNSET study we chose the simplified approach of abrupt ICS withdrawal as is often employed in clinical practice. This approach is bolstered by the observation from WISDOM that the FEV₁ decrease in the ICS withdrawal group occurred only after the complete withdrawal of ICS (11, 24). The difference in trough FEV₁ may reflect differences in study populations and potentially the greater efficacy of the dual bronchodilator regimen of the present study (indacaterol/glycopyrronium vs. salmeterol + tiotropium), incorporating a second-generation once-daily LABA of greater potency (25). An interesting observation in the subgroup analyses is the difference in lung function favoring triple therapy in ex-smokers (Supplementary Figure E3) that may be related to corticosteroid resistance associated with current smoking (26). However, such subgroup analyses are exploratory and need to be evaluated in specifically designed studies, as the smaller group sizes do not allow for definite conclusions.

In our study, the ICS withdrawal did not have an impact on moderate or severe exacerbations, with the exception of patients with high blood eosinophil counts (≥ 300 cells/ μL), confirming a post-hoc observation in the WISDOM study (27). Importantly, all patients included in SUNSET were on prior long-term triple therapy, in contrast to only 39% of patients in WISDOM (11). High

blood eosinophil levels may predict the beneficial effects of ICS on exacerbation reduction on top of a LABA (28, 29). Dual bronchodilation with indacaterol/glycopyrronium was superior to LABA/ICS on exacerbation prevention (30), and the two treatments had similar efficacy in patients with high blood eosinophils in secondary analyses of the FLAME study (31). Triple therapy is beneficial for exacerbation prevention compared with LAMA (32) or LABA/ICS (33, 34). Recently, the TRIBUTE study showed that the fixed triple combination of beclometasone/formoterol/glycopyrronium only reduced the rate of moderate-to-severe COPD exacerbations but no other exacerbation endpoints in exacerbating COPD patients (35). However, it still remains unclear which patients will benefit from ICS on top of LABA/LAMA. Our study adds evidence for the clinically relevant question as to which COPD patients can have ICS safely withdrawn from long-term triple therapy, suggesting that these are the non-frequently exacerbating patients with blood eosinophil counts <300 cells/ μL . These patients were at low risk of future exacerbations during the 6-month follow-up and presented minimal, if any, loss in lung function. The patients with ≥ 300 cells/ μL in our study may have been frequent exacerbators or had high blood eosinophil counts in the past and, therefore, were appropriately controlled by triple therapy. Although patients remember accurately the number of exacerbations they experienced in the previous year (36), no data were available in this study regarding the exacerbation history prior to the onset of triple therapy. An interesting observation is that in this group, the majority of the patients exacerbated in the first weeks after ICS withdrawal (Figure 4E), suggesting that patients need to be followed closely during this period. An additional important observation, given the variability of blood eosinophils over time (37), was that the patients at increased risk for exacerbations were those with consistently ≥ 300 cells/ μL on two

separate occasions (screening and baseline), while all patients were on triple therapy. These data suggest that any therapeutic decisions based on blood eosinophilia might best be based on multiple measurements over time. Such a treatment strategy however, requires prospective validation.

We observed small differences in total SGRQ-C score in favor of triple therapy that were comparable with those observed in the WISDOM study upon ICS withdrawal (11). The clinical importance of these differences is unknown, as they did not reach the minimal clinically important difference of -4 units and were not associated overall with increased exacerbation risk. The comparable changes from baseline in TDI score and use of rescue medication between the two arms further support the similar symptomatic response between dual bronchodilation and triple therapy.

The recent evidence of increased efficacy of dual bronchodilators compared to LAMA monotherapy and LABA/ICS combinations (30, 38), combined with the increased risk of potentially serious adverse effects of long-term ICS therapy (39), suggest that there is a need for precision medicine in COPD (40), where ICS use is limited to patients in whom the expected treatment effects outweigh risks. Strategies have been proposed for ICS withdrawal in appropriate patients (41). However, evidence from appropriately designed prospective trials in patients who are stable on long-term triple therapy is missing. In the SUNSET study, we showed that ICS can be effectively and safely withdrawn by switching to the once daily LABA/LAMA combination of indacaterol/glycopyrronium in not frequently exacerbating COPD patients with low blood eosinophil counts.

The study has some strengths and limitations. An important strength is that we have studied for the first time the withdrawal of ICS from patients who were stable and non-frequently exacerbating on long-term triple therapy, providing information that is relevant to clinical practice. An additional strength is the fact that we have carefully excluded patients with a history of asthma, in order to avoid ICS withdrawal in patients who would benefit from this treatment. The six months duration may not be ideal for the evaluation of treatment effects on exacerbations due to seasonal variations. However, there were similar numbers of exacerbations in the two groups in winter-fall and summer-spring, with lower numbers of exacerbation events during summer-spring, as expected (data not shown). Moreover, patients were recruited across seasons and exacerbations were meticulously collected as per previous methodology (30), ensuring appropriate reporting of events. Importantly, the increased risk for exacerbations with ≥ 300 eosinophils/ μL was observed in the first weeks after ICS withdrawal, providing guidance for the close follow-up of such patients during this period for symptoms deterioration. This duration also may not allow the identification of differences in adverse events related to long-term ICS use between treatment arms; the numerical differences in oral candidiasis and pneumonia, however, may be suggestive of an increased risk of ICS-related adverse events in the triple therapy arm. Importantly, all patients included in the study had previously been on long-term ICS regimens and most likely had not experienced serious ICS-related side effects. Finally, we evaluated ICS withdrawal from triple therapy to a specific second-generation LABA/LAMA combination (indacaterol/glycopyrronium); it is likely that the results are influenced also by the different bronchodilators and, therefore, may not be applicable to other drug combinations. Therefore, this study cannot be considered as a “pure” ICS withdrawal study, as the LABA and LAMA

components differ; however, our results address the clinically relevant question whether the switch from prescribed triple therapy to a modern LABA/LAMA fixed dose combination is appropriate.

In conclusion, in patients on long-term triple therapy and no more than one exacerbation in the previous year, the direct change to indacaterol/glycopyrronium led to a small decrease in lung function, but with no significant difference in the rates of COPD exacerbations between treatments. For the majority of the patients, the switch to indacaterol/glycopyrronium did not have any impact on lung function or exacerbations, while avoiding the long-term exposure to ICS and related adverse effects. A difference in exacerbations in patients with consistently high blood eosinophils (≥ 300 cells/ μL), measured whilst on triple therapy, suggests that it is these patients who will most likely benefit from continuation of triple therapy. These results are clinically relevant and may support the personalized management of COPD patients.

Declaration of interests

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REFERENCES

1. Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD). *Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease* 2018.
2. Han MK, Quibrera PM, Carretta EE, Barr RG, Bleecker ER, Bowler RP, Cooper CB, Comellas A, Couper DJ, Curtis JL, Criner G, Dransfield MT, Hansel NN, Hoffman EA, Kanner RE, Krishnan JA, Martinez CH, Pirozzi CB, O'Neal WK, Rennard S, Tashkin DP, Wedzicha JA, Woodruff P, Paine R, 3rd, Martinez FJ, investigators S. Frequency of exacerbations in patients with chronic obstructive pulmonary disease: an analysis of the SPIROMICS cohort. *Lancet Respir Med* 2017; 5: 619-626.
3. Hurst JR, Vestbo J, Anzueto A, Locantore N, Mullerova H, Tal-Singer R, Miller B, Lomas DA, Agusti A, Macnee W, Calverley P, Rennard S, Wouters EF, Wedzicha JA, Evaluation of CLIPSEI. Susceptibility to exacerbation in chronic obstructive pulmonary disease. *N Engl J Med* 2010; 363: 1128-1138.
4. Simeone JC, Luthra R, Kaila S, Pan X, Bhagnani TD, Liu J, Wilcox TK. Initiation of triple therapy maintenance treatment among patients with COPD in the US. *Int J Chron Obstruct Pulmon Dis* 2017; 12: 73-83.
5. Chronic obstructive pulmonary disease in over 16s: diagnosis and management. Clinical guideline [CG101]. Published date: June 2010. Available at: <https://www.nice.org.uk/guidance/cg101/>. Accessed 16 January 2018. 2010.
6. Vestbo J, Hurd SS, Agusti AG, Jones PW, Vogelmeier C, Anzueto A, Barnes PJ, Fabbri LM, Martinez FJ, Nishimura M, Stockley RA, Sin DD, Rodriguez-Roisin R. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med* 2013; 187: 347-365.
7. Kew KM, A S. Inhaled steroids and risk of pneumonia for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2014; 10.
8. Brode SK, Campitelli MA, Kwong JC, Lu H, Marchand-Austin A, Gershon AS, Jamieson FB, Marras TK. The risk of mycobacterial infections associated with inhaled corticosteroid use. *Eur Respir J* 2017; 50.
9. Suissa S, Kezouh A, Ernst P. Inhaled corticosteroids and the risks of diabetes onset and progression. *Am J Med* 2010; 123: 1001-1006.
10. Gonzalez AV, Coulombe J, Ernst P, Suissa S. Long-term Use of Inhaled Corticosteroids in COPD and the Risk of Fracture. *Chest* 2017.
11. Magnussen H, Disse B, Rodriguez-Roisin R, Kirsten A, Watz H, Tetzlaff K, Towse L, Finnigan H, Dahl R, Decramer M, Chanez P, Wouters EF, Calverley PM, Investigators W. Withdrawal of inhaled glucocorticoids and exacerbations of COPD. *N Engl J Med* 2014; 371: 1285-1294.
12. Anthonisen NR, Manfreda J, Warren CP, Hershfield ES, Harding GK, Nelson NA. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Annals of internal medicine* 1987; 106: 196-204.
13. Nannini LJ, Cates CJ, Lasserson TJ, Poole P. Combined corticosteroid and long-acting beta-agonist in one inhaler versus long-acting beta-agonists for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2007: CD006829.
14. Wise RA, Anzueto A, Cotton D, Dahl R, Devins T, Disse B, Dusser D, Joseph E, Kattenbeck S, Koenen-Bergmann M, Pledger G, Calverley P, Investigators T. Tiotropium Respimat inhaler and the risk of death in COPD. *N Engl J Med* 2013; 369: 1491-1501.
15. Yang IA, Clarke MS, Sim EH, Fong KM. Inhaled corticosteroids for stable chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2012: CD002991.
16. Burge PS, Calverley PM, Jones PW, Spencer S, Anderson JA, Maslen TK. Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. *BMJ* 2000; 320: 1297-1303.
17. Mauri L, D'Agostino RB, Sr. Challenges in the Design and Interpretation of Noninferiority Trials. *N Engl J Med* 2017; 377: 1357-1367.
18. Choudhury AB, Dawson CM, Kilvington HE, Eldridge S, James WY, Wedzicha JA, Feder GS, Griffiths CJ. Withdrawal of inhaled corticosteroids in people with COPD in primary care: a randomised controlled trial. *Respir Res* 2007; 8: 93.

19. Jarad NA, Wedzicha JA, Burge PS, Calverley PM. An observational study of inhaled corticosteroid withdrawal in stable chronic obstructive pulmonary disease. ISOLDE Study Group. *Respir Med* 1999; 93: 161-166.
20. van der Valk , Monnikhof E, van der Palen J, Zielhuis G, C vH. Effect of discontinuation of inhaled corticosteroids in patients with chronic obstructive pulmonary disease: the COPE study. *Am J Respir Crit Care Med* 2002; 166: 1358-1363.
21. Wouters EF, Postma DS, Fokkens B, Hop WC, Prins J, Kuipers AF, Pasma HR, Hensing CA, Creutzberg EC, Group CS. Withdrawal of fluticasone propionate from combined salmeterol/fluticasone treatment in patients with COPD causes immediate and sustained disease deterioration: a randomised controlled trial. *Thorax* 2005; 60: 480-487.
22. Rossi A, van der Molen T, del Olmo R, Papi A, Wehbe L, Quinn M, Lu C, Young D, Cameron R, Bucchioni E, Altman P. INSTEAD: a randomised switch trial of indacaterol versus salmeterol/fluticasone in moderate COPD. *Eur Respir J* 2014; 44: 1548-1556.
23. Vogelmeier CF, Gaga M, Aalamian-Mattheis M, Greulich T, Marin JM, Castellani W, Ninane V, Lane S, Nunez X, Patalano F, Clemens A, Kostikas K, investigators Cs. Efficacy and safety of direct switch to indacaterol/glycopyrronium in patients with moderate COPD: the CRYSTAL open-label randomised trial. *Respir Res* 2017; 18: 140.
24. Magnussen H, Tetzlaff K, Bateman ED, Watz H, Kirsten AM, Wouters EF, Disse B, Finnigan H, Rodriguez-Roisin R, Calverley PM. Lung function changes over time following withdrawal of inhaled corticosteroids in patients with severe COPD. *Eur Respir J* 2016; 47: 651-654.
25. Donohue JF, Betts KA, Du EX, Altman P, Goyal P, Keininger DL, Gruenberger JB, Signorovitch JE. Comparative efficacy of long-acting beta2-agonists as monotherapy for chronic obstructive pulmonary disease: a network meta-analysis. *Int J Chron Obstruct Pulmon Dis* 2017; 12: 367-381.
26. Barnes PJ. Corticosteroid resistance in patients with asthma and chronic obstructive pulmonary disease. *J Allergy Clin Immunol* 2013; 131: 636-645.
27. Watz H, Tetzlaff K, Wouters EF, Kirsten A, Magnussen H, Rodriguez-Roisin R, Vogelmeier C, Fabbri LM, Chanez P, Dahl R, Disse B, Finnigan H, Calverley PM. Blood eosinophil count and exacerbations in severe chronic obstructive pulmonary disease after withdrawal of inhaled corticosteroids: a post-hoc analysis of the WISDOM trial. *Lancet Respir Med* 2016; 4: 390-398.
28. Pascoe S, Locantore N, Dransfield MT, Barnes NC, Pavord ID. Blood eosinophil counts, exacerbations, and response to the addition of inhaled fluticasone furoate to vilanterol in patients with chronic obstructive pulmonary disease: a secondary analysis of data from two parallel randomised controlled trials. *Lancet Respir Med* 2015; 3: 435-442.
29. Siddiqui SH, Guasconi A, Vestbo J, Jones P, Agusti A, Paggiaro P, Wedzicha JA, Singh D. Blood Eosinophils: A Biomarker of Response to Extrafine Beclomethasone/Formoterol in Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2015; 192: 523-525.
30. Wedzicha JA, Banerji D, Chapman KR, Vestbo J, Roche N, Ayers RT, Thach C, Fogel R, Patalano F, Vogelmeier CF, Investigators F. Indacaterol-Glycopyrronium versus Salmeterol-Fluticasone for COPD. *N Engl J Med* 2016; 374: 2222-2234.
31. Papi A, Kostikas K, Wedzicha JA, Vogelmeier CF, Roche N, Shen S, Banerji D, Fogel R, Patalano F, Chapman KR. Dual Bronchodilation Response by Exacerbation History and Eosinophilia in the FLAME Study. *Am J Respir Crit Care Med* 2017.
32. Vestbo J, Papi A, Corradi M, Blazhko V, Montagna I, Francisco C, Cohuet G, Vezzoli S, Scuri M, Singh D. Single inhaler extrafine triple therapy versus long-acting muscarinic antagonist therapy for chronic obstructive pulmonary disease (TRINITY): a double-blind, parallel group, randomised controlled trial. *Lancet* 2017; 389: 1919-1929.
33. Singh D, Papi A, Corradi M, Pavlisova I, Montagna I, Francisco C, Cohuet G, Vezzoli S, Scuri M, Vestbo J. Single inhaler triple therapy versus inhaled corticosteroid plus long-acting beta2-agonist therapy for chronic obstructive pulmonary disease (TRILOGY): a double-blind, parallel group, randomised controlled trial. *Lancet* 2016; 388: 963-973.
34. Lipson DA, Barnacle H, Birk R, Brealey N, Locantore N, Lomas DA, Ludwig-Sengpiel A, Mohindra R, Tabberer M, Zhu CQ, Pascoe SJ. FULFIL Trial: Once-Daily Triple Therapy for Patients with Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2017; 196: 438-446.
35. Papi A, Vestbo J, Fabbri L, Corradi M, Prunier H, Cohuet G, Guasconi A, Montagna I, Vezzoli S, Petruzzelli S, Scuri M, Roche N, Singh D. Extrafine inhaled triple therapy versus dual

- bronchodilator therapy in chronic obstructive pulmonary disease (TRIBUTE): a double-blind, parallel group, randomised controlled trial. *Lancet* 2018; 391: 1076-1084.
36. Quint JK, Donaldson GC, Hurst JR, Goldring JJ, Seemungal TR, Wedzicha JA. Predictive accuracy of patient-reported exacerbation frequency in COPD. *Eur Respir J* 2011; 37: 501-507.
 37. Oshagbemi OA, Burden AM, Braeken DCW, Henskens Y, Wouters EFM, Driessen JHM, Maitland-van der Zee AH, de Vries F, Franssen FME. Stability of Blood Eosinophils in Patients with Chronic Obstructive Pulmonary Disease and in Control Subjects, and the Impact of Sex, Age, Smoking, and Baseline Counts. *Am J Respir Crit Care Med* 2017; 195: 1402-1404.
 38. Rodrigo GJ, Price D, Anzueto A, Singh D, Altman P, Bader G, Patalano F, Fogel R, Kostikas K. LABA/LAMA combinations versus LAMA monotherapy or LABA/ICS in COPD: a systematic review and meta-analysis. *Int J Chron Obstruct Pulmon Dis* 2017; 12: 907-922.
 39. Price D, Yawn B, Brusselle G, Rossi A. Risk-to-benefit ratio of inhaled corticosteroids in patients with COPD. *Prim Care Respir J* 2013; 22: 92-100.
 40. Suissa S, Ernst P. Precision Medicine Urgency: The Case of Inhaled Corticosteroids in COPD. *Chest* 2017; 152: 227-231.
 41. Miravittles M, Cosio BG, Arnedillo A, Calle M, Alcazar-Navarrete B, Gonzalez C, Esteban C, Trigueros JA, Rodriguez Gonzalez-Moro JM, Quintano Jimenez JA, Balotra A. A proposal for the withdrawal of inhaled corticosteroids in the clinical practice of chronic obstructive pulmonary disease. *Respir Res* 2017; 18: 198.

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TABLES

Table 1: Baseline Characteristics of the Patients.*

Characteristic	Indacaterol/ glycopyrronium (N = 527)	Tiotropium plus salmeterol/fluticasone (N = 526)	All patients (N= 1053)
Age (years), Mean \pm SD	65.4 \pm 7.99	65.2 \pm 7.62	65.3 \pm 7.80
BMI (kg/m ²), Mean \pm SD	27.8 \pm 5.35	28.2 \pm 5.38	27.98 \pm 5.37
Sex: Male, n (%)	378 (71.7)	365 (69.4)	743 (70.6)
Race: Caucasian, n (%)	526 (99.8)	523 (99.4)	1049 (99.6)
Duration of COPD (years), Mean \pm SD	8.2 \pm 5.60	7.8 \pm 5.17	8.0 \pm 5.39
Airflow limitation (GOLD), n (%) [†]			
Moderate	363 (68.9)	372 (70.7)	735 (69.8)
Severe	161 (30.6)	154 (29.3)	315 (29.9)
Post-bronchodilator FEV ₁ (L), Mean \pm SD	1.6 \pm 0.44	1.6 \pm 0.46	1.6 \pm 0.45
Post-bronchodilator FEV ₁ (% predicted), Mean \pm SD	56.2 \pm 9.66	57.0 \pm 10.30	56.6 \pm 9.97
Post-bronchodilator FEV ₁ /FVC (%), Mean \pm SD	49.1 \pm 9.27	50.1 \pm 9.31	49.6 \pm 9.29
FEV ₁ bronchodilator reversibility (%), Mean \pm SD	11.0 \pm 10.53	10.4 \pm 9.41	10.74 \pm 9.98
mMRC dyspnea scale, n (%)			

0-1	134 (25.4)	170 (32.3)	304 (28.9)
≥2	393 (74.6)	354 (67.3)	747 (70.9)
Number of COPD exacerbations in the previous year, n (%)			
0 exacerbation	334 (63.4)	360 (68.4)	694 (65.9)
1 exacerbation	193 (36.6)	166 (31.6)	359 (34.1)
Patients with baseline blood eosinophil counts, n (%)#			
<300 cells/μL	401 (76.2)	406 (77.3)	807 (76.8)
≥300 cells/μL	125 (23.8)	119 (22.7)	244 (23.2)
Patients with consistent and inconsistent blood eosinophil counts at screening and baseline, n(%)#			
Consistently <300 cells/μL	359 (68.2)	357 (68.0)	716 (68.1)
Inconsistent: both above and below 300 cells/μL	86 (16.4)	83 (15.8)	169 (16.1)
Consistently ≥300 cells/μL	81 (15.4)	85 (16.2)	166 (15.8)
* Data are presented as means ±SD or n (%), as indicated. BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV ₁ , forced expiratory volume in 1 second; FVC, forced vital capacity; mMRC, modified Medical Research Council; SD, standard deviation.			

[†]The airflow limitation was determined on the basis of Global Initiative for Chronic Obstructive Lung Disease (GOLD) staging system, in which moderate is $50\% \leq FEV_1 < 80\%$ predicted and severe is $30\% \leq FEV_1 < 50\%$ predicted.

[#]Numbers of eligible patients in the corresponding exacerbation analyses

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Table 2. Adverse Events and Serious Adverse Events.

	Indacaterol/glycopyrronium	Tiotropium plus salmeterol/fluticasone
	N = 527 n (%)	N = 526 n (%)
Patients with at least one adverse event	426 (80.8)	434 (82.5)
Patients with at least one serious adverse event	32 (6.1)	34 (6.5)
Deaths	4 (0.8)	5 (1.0)
Adverse events that occurred in ≥1% of either treatment group		
Chronic obstructive pulmonary disease	372 (70.6)	358 (68.1)
Viral upper respiratory tract infection	57 (10.8)	59 (11.2)
Blood creatinine increased*	26 (4.9)	24 (4.6)
Cough	24 (4.6)	15 (2.9)
Oral candidiasis	12 (2.3)	18 (3.4)
Bronchitis	13 (2.5)	5 (1.0)
Oropharyngeal candidiasis	6 (1.1)	7 (1.3)

Influenza	6 (1.1)	6 (1.1)
Back pain	8 (1.5)	9 (1.7)
Headache	7 (1.3)	13 (2.5)
Oropharyngeal pain	7 (1.3)	7 (1.3)
Hypertension	7 (1.3)	10 (1.9)
Pneumonia	6 (1.1)	9 (1.7)

*The blood creatinine events were recorded via the renal monitoring process that was applied in the study.

Two patients, one on tiotropium plus salmeterol/fluticasone and one on indacaterol/glycopyrronium, died after completion of the treatment phase.

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FIGURE LEGENDS

Figure 1. SUNSET Study design

There were 7 follow up visits at clinic after Randomization Visit (on Days 15, 29, 57, 85, 141, 181 and 182; spirometry measurements were performed on Days 29, 85, 181 and 182). Safety follow up was performed by phone 30 days after last clinic visit.

Figure 2. Screening, Run-in, Randomization and Study Completion.

*Eight patients who were screen failures in screening phase returned for run-in period in error and were once again discontinued. † These patients were also screening failures (reports were received after initiation of run-in period).

Figure 3. Lung function.

Figure 3A. Difference (indacaterol/glycopyrronium – tiotropium plus salmeterol/fluticasone) in change from baseline in post-dose trough FEV₁ after 26 weeks of treatment in the FAS and PPS patient populations.

FAS, full analysis set; FEV₁; forced expiratory volume in 1 second; PPS, per protocol set

Figure 3B. Change from baseline in trough FEV₁ over the 26-week treatment period (Full Analysis Set).

Data are presented as least squares mean \pm standard error.

Δ , Least squares mean treatment difference; N, number of patients in full analysis set; FEV₁, forced expiratory volume in 1 second

Figure 3C. Difference (indacaterol/glycopyrronium versus tiotropium plus salmeterol/fluticasone) in mean change from baseline in post-dose trough FEV₁ (L) at week 26 by baseline blood eosinophil levels (Full Analysis Set).

FEV₁, forced expiratory volume in 1 second.

*Post-hoc analysis not pre-specified in the statistical analysis plan. The dotted line is the non-inferiority line (of -50 mL).

Figure 4. Moderate or Severe COPD Exacerbations.

Figure 4A. Annualized rate of moderate or severe COPD exacerbations during the 26-week treatment period (Full Analysis Set).

N, number of patients in full analysis set

Figure 4B. Kaplan-Meier plot of the time to first moderate or severe COPD exacerbation, all patients (n=1053).

n, number of patients in the analysis set

Figure 4C. Rate ratios of moderate or severe COPD exacerbations during the 26-week treatment period by baseline blood eosinophil levels (Full Analysis Set).

*Post-hoc analysis not pre-specified in the statistical analysis plan.

Figure 4D. Kaplan-Meier plot of the time to first moderate or severe COPD exacerbation in patients with baseline blood eosinophil level of <300 cells/ μ L (n=807)*.

*Post-hoc analysis not pre-specified in the statistical analysis plan. n, number of patients in the analysis set

Figure 4E. Kaplan-Meier plot of the time to first moderate or severe COPD exacerbation in patients with baseline blood eosinophil level of ≥ 300 cells/ μL (n=244)*.

*Post-hoc analysis not pre-specified in the statistical analysis plan. n, number of patients in the analysis set

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