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

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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.

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- 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 (FEV_1). 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 FEV_1 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 **S**tudy to **U**nderstaN**d** the **S**afety a**n**d **E**fficacy of ICS Withdrawal from **T**riple 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 (FEV_1) of at least 40% to less than 80% predicted, a post-bronchodilator ratio of FEV_1 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 FEV_1 (a mean of the two FEV_1 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 FEV_1 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 FEV_1 and exacerbation rate were also evaluated as pre-specified analyses.

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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 FEV_1 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 FEV_1 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, FEV_1 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 FEV_1 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 FEV_1. In the FAS, ICS withdrawal led to a difference in mean change from baseline in post-dose trough FEV_1 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 FEV_1 at Week 26 (Figure 3A). Over the 26-week treatment period, the withdrawal of ICS resulted in differences in trough FEV_1 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 FEV_1 by baseline blood eosinophils

There was no significant difference between treatments in post-dose trough FEV_1 at week 26 in patients with baseline blood eosinophil levels of <2%, and eosinophil count of <300 cells/μL; differences in post-dose trough FEV_1 between treatments were higher in patients with high blood eosinophil counts at baseline (≥2% or ≥300 cells/μL) (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

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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 FEV_1, 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 FEV_1 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 (Δ=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; Δ=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 (Δ=−0.24; 95% CI, −0.58 to 0.10 units) or Week 26 (Δ=−0.28; 95% CI, −0.63 to 0.06 units). During the 26-week treatment period, use of rescue medication (Δ=0.177 puffs/day; 95% CI, −0.01 to 0.36) or the days without rescue medication use (Δ=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).

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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 FEV_1 with no difference in the rates or risk of COPD exacerbations between treatments. Patients with high blood eosinophils (≥300 cells/μL) 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. FEV_1 <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 FEV_1, 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 FEV_1 decrease in the ICS withdrawal group occurred only after the complete withdrawal of ICS (11, 24). The difference in trough FEV_1 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

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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.

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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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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 ± SD	65.4 ± 7.99	65.2 ± 7.62	65.3 ± 7.80
BMI (kg/m^2), Mean ± SD	27.8 ± 5.35	28.2 ± 5.38	27.98 ± 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 ± SD	8.2 ± 5.60	7.8 ± 5.17	8.0 ± 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 ± SD	1.6 ± 0.44	1.6 ± 0.46	1.6 ± 0.45
Post-bronchodilator FEV_1 (% predicted), Mean ± SD	56.2 ± 9.66	57.0 ± 10.30	56.6 ± 9.97
Post-bronchodilator FEV_1/FVC (%), Mean ± SD	49.1 ± 9.27	50.1 ± 9.31	49.6 ± 9.29
FEV_1 bronchodilator reversibility (%), Mean ± SD	11.0 ± 10.53	10.4 ± 9.41	10.74 ± 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

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(GOLD) staging system, in which moderate is 50%≤ FEV_1<80% predicted and severe is 30% ≤ FEV_1<50% predicted.

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

Table 2. Adverse Events and Serious Adverse Events.

	Indacaterol/glycopyrronium N = 527 n (%)	**Tiotropium plus salmeterol/fluticasone** 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)

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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.

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 FEV_1 after 26 weeks of treatment in the FAS and PPS patient populations.

FAS, full analysis set; FEV_1; forced expiratory volume in 1 second; PPS, per protocol set

Figure 3B. Change from baseline in trough FEV_1 over the 26-week treatment period (Full Analysis Set).

Data are presented as least squares mean ± standard error.

Δ, Least squares mean treatment difference; N, number of patients in full analysis set; FEV_1, forced expiratory volume in 1 second

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Figure 3C. Difference (indacaterol/glycopyrronium versus tiotropium plus salmeterol/fluticasone) in mean change from baseline in post-dose trough FEV_1 (L) at week 26 by baseline blood eosinophil levels (Full Analysis Set).

FEV_1, 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/µL (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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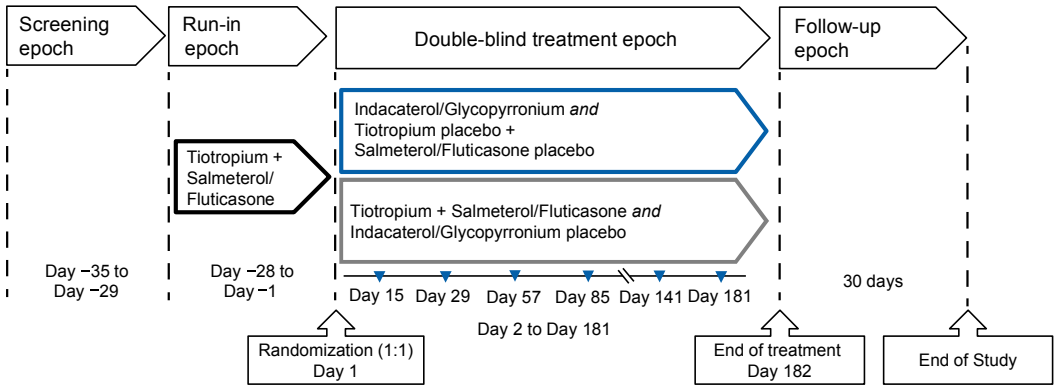

Figure 1

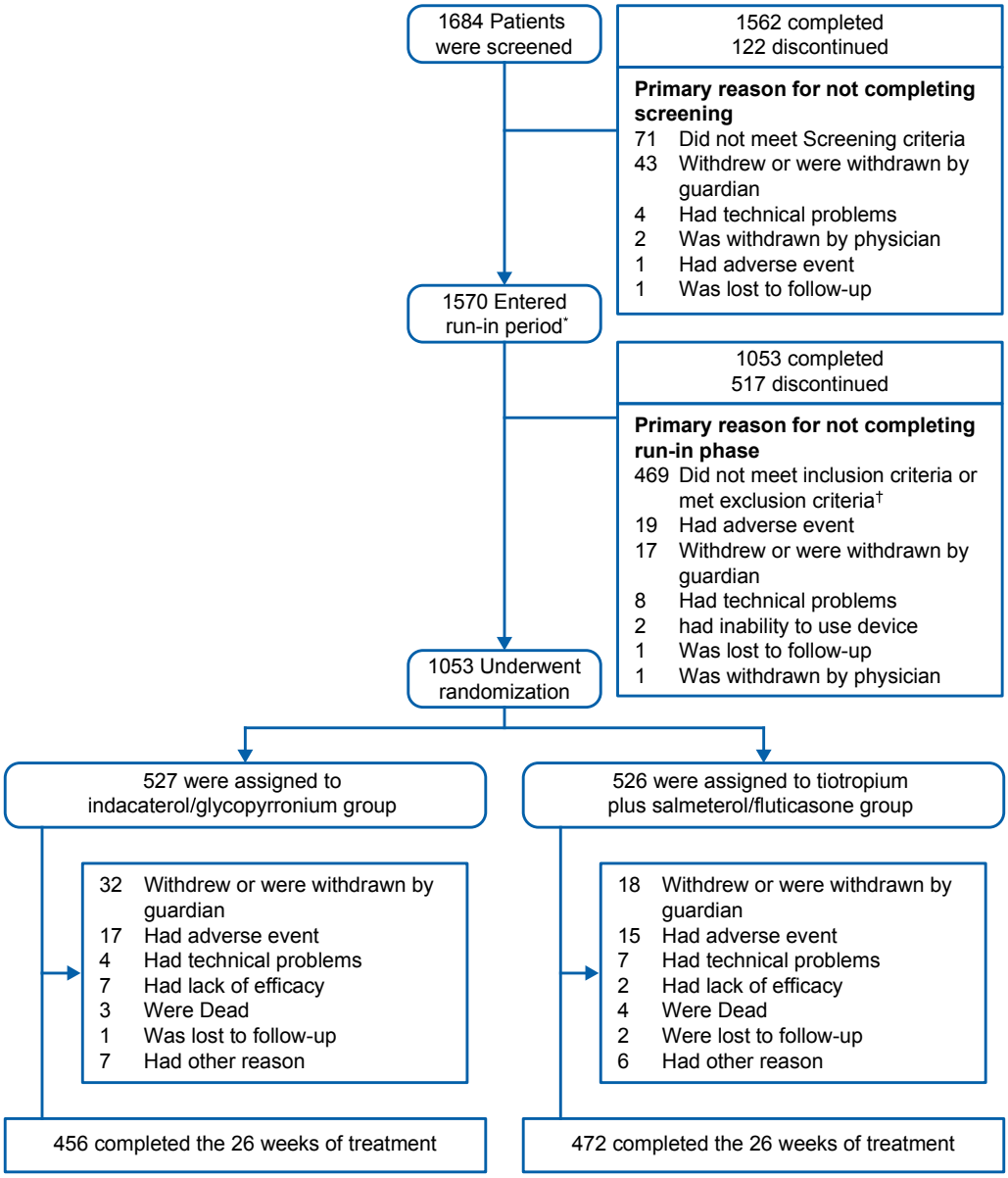

Figure 2

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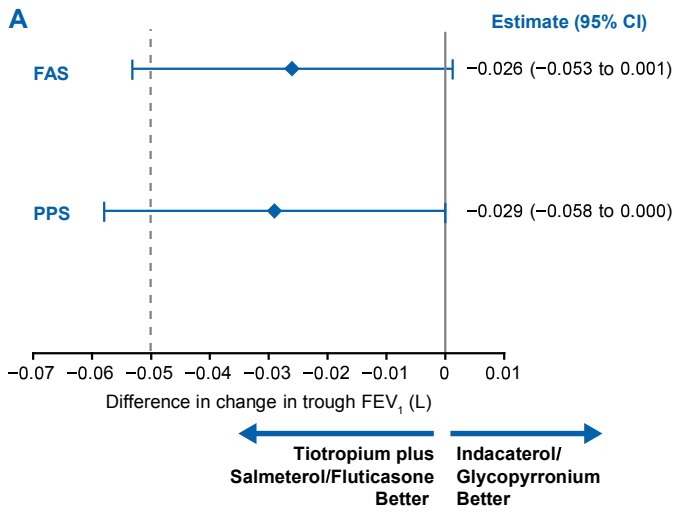

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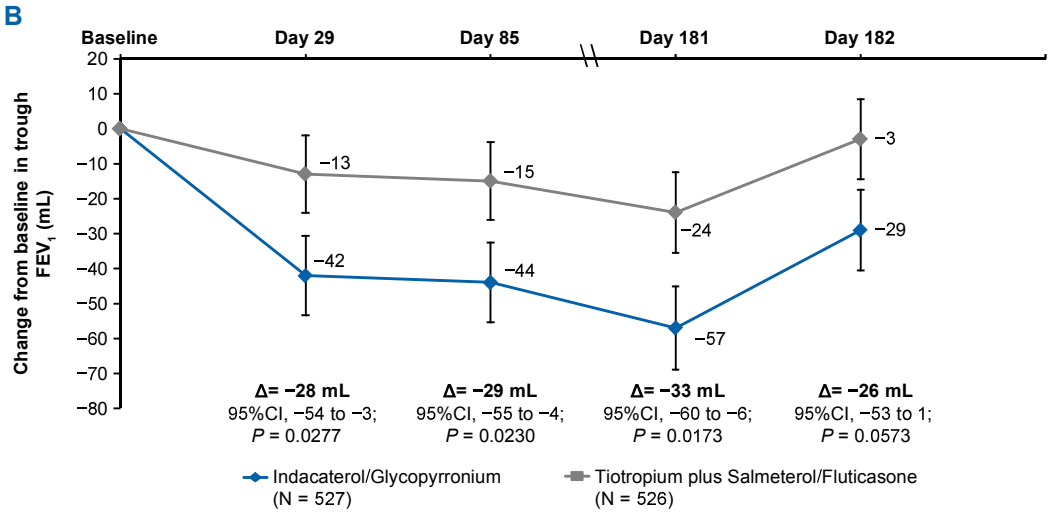

Figure 3B

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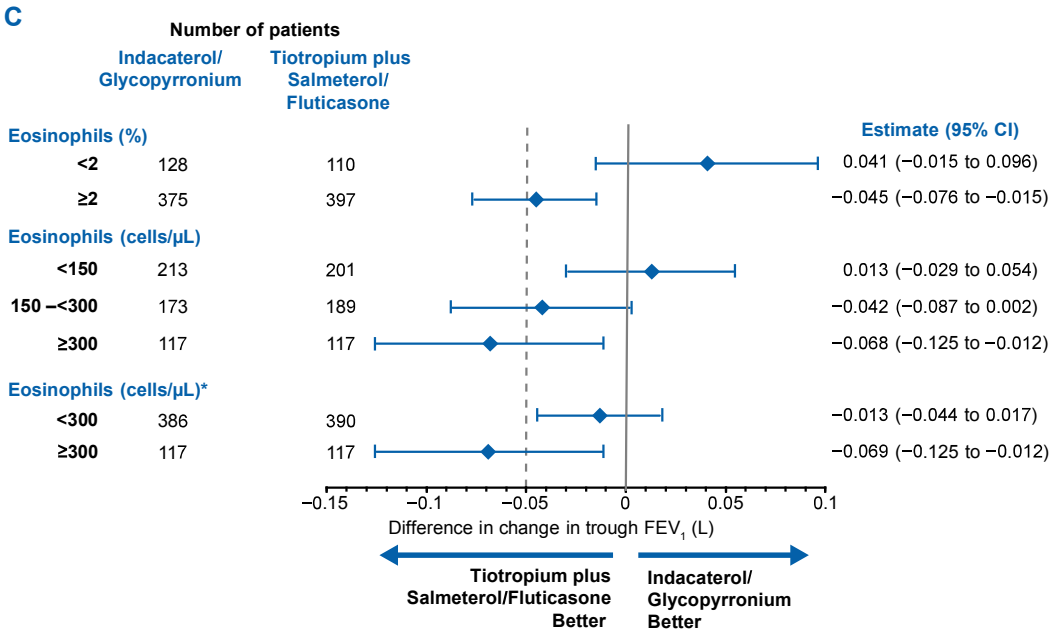

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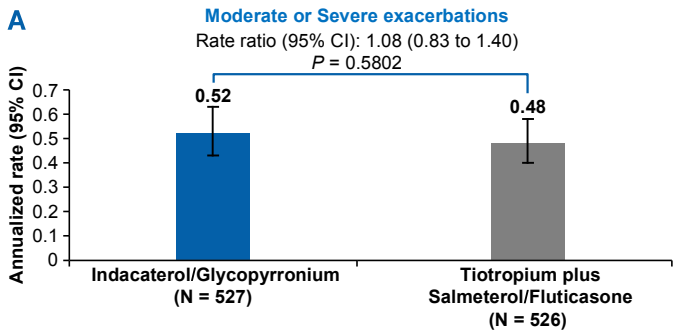

Figure 4A

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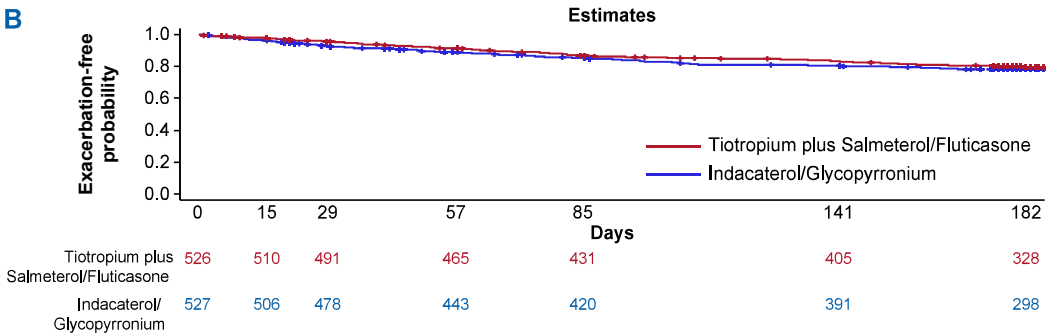

Figure 4B

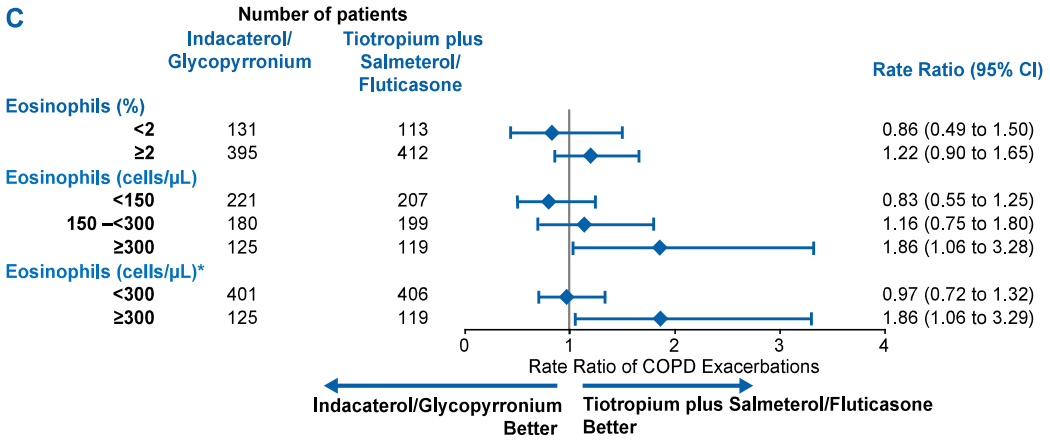

Figure 4C

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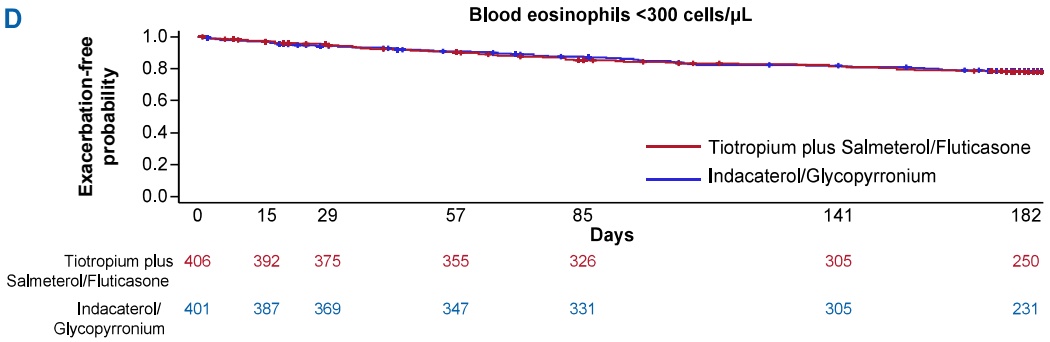

Figure 4D

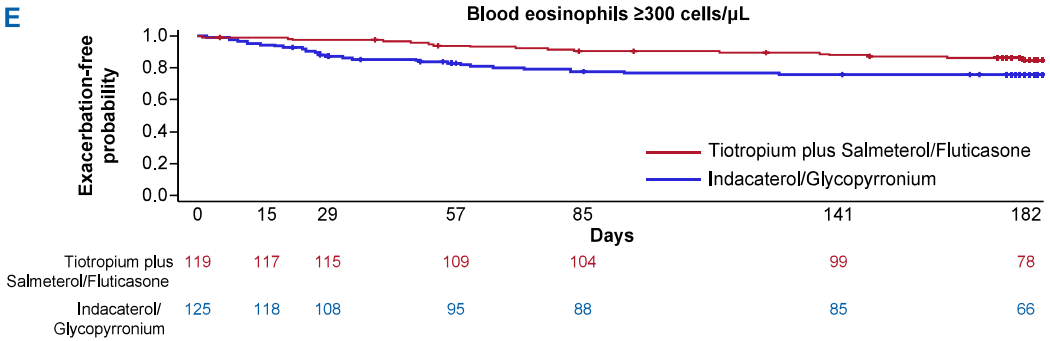

Figure 4E

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SUPPLEMENTARY APPENDIX

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

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	Dr. Andreas Fritzsche, Dr. Karin Foerster, Dr. Christian Gessner, Dr. Christine Elisabeth Grigat, Dr. Gabriele Illies, Dr. Heike Schlichthaar, Dr. Peter Heymer, Dr. Margret Jandl, Dr. Claus Keller, Dr. Oliver Kornmann, Dr. Olaf Schmidt, Dr. Matthias Kruell, Dr. Frank Kaessner, Dr. Thomas Lienert, Dr. Anneliesse Linnhoff, Dr. Andrea Ludwig-Sengpiel, Dr. Irmgard Marten, Dr. Hilger Mueller, Dr. Ruth Nischik, Dr. Axel Overlack, Dr. Guenther Preiss, Dr. Ronald Redlich, Dr. Lennart Schaper, Dr. Isabelle Schenkenberger, Dr. Christian Schlenska, Dr. Anne-Kathrin Schmidt, Dr. Wolfgang Schuermann, Dr. Michael Sebert, Dr. Ulrike Westerhausen, Dr. Silke Wiemer, Dr. Joerg Winkler
Greece	Dr. Evangelos Balis, Prof. Nikolaos Tzanakis, Prof. Konstantinos Zarogoulidis
Hungary	Dr. Eva Radeczky, Dr. Katalin Gomori, Dr Gergely Lupkovics, Dr Maria Hejja
Latvia	Dr. Iveta Kroica, Dr. Sarmite Puzule, Dr. Inga Vikmane, Dr. Aurika Babjoniseva, Dr. Natalija Visocka, Dr. Lilita Mitrofanova, Dr. Sandra Audere, Dr. Zinaida Lapkovska
Lithuania	Dr. Violeta Griskeviciene, Dr. Violeta Matukiene, Dr. Dalius Vaicius, Dr. Teresa Volosevic, Dr. Vitalija Nausediene
Netherlands	Dr. Wim Boersma, Dr. Pascal Wielders, Dr. Martijn Goosens, Dr. Remco Djamin
Poland	Dr. Beata Asankowicz-Bargiel, Prof. Piotr Kuna, Prof. Robert Mroz, Dr. Grazyna Pulka, Dr. Joanna Waszkuc-Golonko, Dr Andrzej Obojski, Dr. Teresa Hofman,

	Dr. Ewa Pisarczyk-Bogacka, Mrs. Iwona Karpiuk, Dr. Wojciech Naumnik, Dr. Anna Olech-Cudzik, Dr. Danuta Madra-Rogacka, Dr. Irena Ratjar, Dr Justyna Jeridi-Kolodynska, Dr. Zenon Bukowczan
Romania	Dr. Ana Maria Trailescu, Dr. Stefan Mihaicuta, Dr. Cristina Gica, Dr. Milena Adina Man, Dr. Ioan Dorin Petrui, Dr. Claudia Toma, Dr. Dana Olar, Dr. Dana Sorina Alexandrescu, Dr. Ruxandra Rajnoveanu, Prof. Florin Dumitru Mihaltan, Dr. Dana Matei, Dr. Mirela Tudorache
Serbia	Ass.prof. Aleksandra Ilic, Prof. Ivan Cekerevac, Dr. Milan Grujic, Dr. Dejan Sofronic, Dr. Dejan Zujovic, Dr. Vesna Dopudja Pantic
Slovakia	Dr. Luboslava Frajtova, Dr. Alexander Golubov, Dr. Slavomir Hrebenar, Dr. Denisa Kavkova
Spain	Dr. Mar Rodriguez Alvarez, Dr. Jose Luis Velasco, Dr. Elia Gomez Merino, Dr. Salud Santos Perez, Dr. Elsa Naval Sendra
United Kingdom	Dr Paul Ainsworth, Dr. Dinesh Saralaya, Dr. Patrick Eavis, Dr. Lee Dowson, Dr. Timothy Hall, Dr. Neil Jackson, Dr. Elizabeth Sapey, Dr. Alice Turner

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SECTION 2. FULL INCLUSION AND EXCLUSION CRITERIA (ADDITIONAL DETAILS)

INCLUSION

Patients eligible for inclusion in this study had to fulfill all of the following criteria:

1. Written informed consent was obtained before any assessment was performed.
2. Male and female adults aged ≥ 40 years.
3. Patients with moderate to severe airflow obstruction with stable COPD (Stage 2 or Stage 3) according to the GOLD classification of airflow limitation.
4. Patients with a post-bronchodilator FEV_1 ≥40 and < 80% of the predicted normal value, and post-bronchodilator FEV_1/FVC < 0.70 at Run-in Visit. (Post refers to 15 min after inhalation of 400 µg of salbutamol)
5. Current or ex-smokers who had a smoking history of at least 10 pack years (e.g. 10 pack years = 1 pack /day x 10 years, or ½ pack/day x 20 years). An ex-smoker was defined as a patient who had not smoked for ≥ 6 months at screening.
6. Patients who were on triple treatment at least for the last 6 months (LAMA +LABA/ICS).

EXCLUSION

Patients fulfilling any of the following criteria were not eligible for inclusion in the study. No additional exclusions were applied by the investigator, in order to ensure that the study population was representative of all eligible patients.

1. Used other investigational drugs/devices (approved or unapproved) at the time of enrollment, or within 30 days or 5 half-lives of Screening, whichever was longer.

2. Patients contraindicated for treatment with, or having a history of reactions/ hypersensitivity to any of the following inhaled drugs, drugs of a similar class or any component thereof:
    - long acting anticholinergic agents and short acting anticholinergic agents
    - long acting β_2-agonists and short acting β_2-agonists
    - sympathomimetic amines
    - lactose or any of the other excipients of trial medication
3. History or current diagnosis of ECG abnormalities which indicated significant risk of safety for patients participating in the study such as:
    - Concomitant clinically significant cardiac arrhythmias, e.g., sustained ventricular tachycardia, and clinically significant second or third degree AV block without a pacemaker
    - History of familial long QT syndrome or known family history of Torsades de Pointes
4. Resting QTc (Fridericia method) ≥450 msec for males and females at Run-In.
5. Concomitant use of agents known to significantly prolong the QT interval unless it was permanently discontinued for the duration of study.
6. Patients who had a clinically significant laboratory abnormality at Run-in and would be at potential risk if enrolled into the study.
7. Patients who had clinically significant renal, cardiovascular (such as but not limited to unstable ischemic heart disease, NYHA Class III/IV left ventricular failure, myocardial infarction), arrhythmia (see below for patients with atrial fibrillation), neurological,

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endocrine, immunological, psychiatric, gastrointestinal, hepatic, or hematological abnormalities which could interfere with the assessment of the efficacy and safety of the study treatment.

8. Patients with paroxysmal (e.g. intermittent) atrial fibrillation were excluded. Patients with persistent atrial fibrillation as defined by continuous atrial fibrillation for at least 6 months and controlled with a rate control strategy (i.e., beta blocker, calcium channel blocker, pacemaker placement, digoxin or ablation therapy) for at least 6 months could have been considered for inclusion. In such patients, atrial fibrillation had to be present at Run-in and Randomization Visits, with a resting ventricular rate < 100/min. At Run-in Visit, atrial fibrillation was confirmed by central reading.
9. Patients with narrow-angle glaucoma, symptomatic benign prostatic hyperplasia or bladder-neck obstruction or moderate to severe renal impairment or urinary retention (BPH patients who were stable on treatment were considered).
10. Patients who had not achieved acceptable spirometry results at Run-in Visit in accordance with ATS (American Thoracic Society)/ERS (European Respiratory Society) criteria for acceptability (one retest could be performed for patients who did not meet the acceptability criteria).
11. Patients who had more than one COPD exacerbation that required treatment with antibiotics and/or oral corticosteroids and/or hospitalization in the last year prior to screening.
12. Patients who developed a COPD exacerbation of any severity either 6 weeks before the Screening Visit or between Screening Visit and Randomization Visit were not eligible but

were permitted to be re-screened after a minimum of 6 weeks after the resolution of the COPD exacerbation.

13. Patients who had a respiratory tract infection within 4 weeks prior to Screening Visit.
14. Patients who developed a respiratory tract infection between screening and treatment were not eligible, but were permitted to be re-screened 4 weeks after the resolution of the respiratory tract infection.
15. Patients requiring long term oxygen therapy prescribed for >12 hours per day.
16. Patients with any history of asthma.
17. Patients with a blood eosinophil count > 600/mm^3 during Screening Visit.
18. Patients with allergic rhinitis who used a H1 antagonist or intra-nasal corticosteroids intermittently (treatment with a stable dose or regimen was permitted).
19. Patients with concomitant pulmonary disease (e.g. lung fibrosis, sarcoidosis, interstitial lung disease, pulmonary hypertension, clinically significant bronchiectasis).
20. Patients with a diagnosis of α-1 anti-trypsin deficiency.
21. Patients with active pulmonary tuberculosis.
22. Patients with pulmonary lobectomy or lung volume reduction surgery or lung transplantation.
23. Patients participating in or planning to participate in the active phase of a supervised pulmonary rehabilitation program during the study (maintenance program was permitted).
24. Patients receiving any medications in the classes listed in Table S1.

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25. Patients receiving any COPD related medications in the classes specified in Table S2 had to undergo the required washout period prior to Run-in Visit and follow the adjustment to treatment program.
26. Patients receiving medications in the classes listed in Table S3 was excluded unless the medication had been stable for the specified period and the stated conditions were met.
27. Patients unable to use an electronic patient diary.
28. Patients unable to use a dry powder inhaler device or a pressurized MDI (rescue medication) or unable to comply with the study regimen. Spacer devices were not permitted.
29. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there was evidence of local recurrence or metastases.
30. Pregnant or nursing (lactating) women, where pregnancy was defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human Chorionic Gonadotropin laboratory test.
31. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they were using effective methods of contraception during dosing of study treatment. Effective contraception methods included:
    - Total abstinence (when this was in line with the preferred and usual lifestyle of the patient). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal were not acceptable methods of contraception

- Female sterilization (had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman had been confirmed by follow up hormone level assessment
- Male sterilization (at least 6 month prior to screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient
- Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/ vaginal suppository
- Used oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that had comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception
- Placement of an intrauterine device (IUD) or intrauterine system (IUS)

32. In case of use of oral contraception women should had been stable on the same pill for a minimum of 3 months before taking study treatment. Women were considered post-menopausal and not of child bearing potential if they had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman had been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

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SECTION 3: METHODS (ADDITIONAL DETAILS)

STUDY DESIGN

During the Run-in Epoch, all patients were given tiotropium (18 µg o.d.) + salmeterol-fluticasone (50/500 µg b.i.d.) regardless of their triple combination before study entry. If they were already taking this triple combination they were to continue to take the same treatment during the Run-in Epoch.

During the Treatment Epoch, patients were assigned to one of the following 2 treatment groups in a 1:1 ratio:

- Indacaterol–glycopyrronium 110/50 µg o.d., delivered via Novartis single-dose dry-powder inhaler plus tiotropium matching placebo o.d., delivered via the manufacturer's HandiHaler® plus salmeterol-fluticasone matching placebo b.i.d., delivered via the manufacturer's Accuhaler®
- Indacaterol–glycopyrronium matching placebo o.d, delivered via Novartis single-dose dry-powder inhaler, plus tiotropium 18 µg o.d., delivered via the manufacturer's HandiHaler®, plus salmeterol-fluticasone 500/50 µg b.i.d. dry inhalation powder delivered via the manufacturer's Accuhaler®

The study protocol and all amendments were reviewed by the Independent Ethics Committee or Institutional Review Board for each center and the study was registered at clinicaltrials.gov (NCT02603393). The study was conducted according to the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from all patients.

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Randomization and Masking

At Randomization Visit (Day 1), all eligible patients were randomised to one of the two treatment groups via interactive response technology (IRT). The Investigator or delegate accessed the IRT after having confirmed that the patient fulfilled all the inclusion/exclusion criteria. The IRT assigned a randomization number to the patient, which was used to link the patient to a treatment group and specified a unique medication number for the first package of study treatment to be dispensed. The randomization number was not communicated to the caller. The randomization numbers were generated by the IRT provider using a validated system that automated the random assignment of patient numbers to randomization numbers. These randomization numbers were linked to the different treatment groups, which in turn were linked to medication numbers. A separate medication list was produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automated the random assignment of medication numbers to packs containing the study treatments.

Patients, investigator staff, persons performing the assessments, and data analysts remained blinded to the identity of the treatment from the time of randomization until database lock. Randomization data were kept strictly confidential until the time of unblinding, and were not accessible by anyone involved in the study. The identity of the treatments was concealed by identical packaging, labelling and schedule of administration. A triple-dummy design was used because the different forms of the study treatments did not allow disguising their identity.

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Procedures

Patients received indacaterol–glycopyrronium (indacaterol 110 µg and glycopyrronium 50 µg) once daily delivered via a single-dose dry-powder inhaler (Breezhaler® device [Novartis Pharma AG, Basel, Switzerland] or tiotropium matching placebo once daily delivered via the manufacturer's dry-powder inhaler (HandiHaler® [Boehringer Ingelheim, Ingelheim, Germany]) plus salmeterol-fluticasone matching placebo twice daily delivered via the manufacturer's dry-powder inhaler (Accuhaler® [GlaxoSmithKline, United kingdom]) or Indacaterol–glycopyrronium matching placebo once daily delivered via a single-dose dry-powder inhaler (Breezhaler® device [Novartis Pharma AG, Basel, Switzerland]), or tiotropium 18 µg once daily, delivered via the manufacturer's dry-powder inhaler (HandiHaler® [Boehringer Ingelheim, Ingelheim, Germany]), plus salmeterol-fluticasone (salmeterol [50 µg] and fluticasone propionate [500 µg]) twice daily via the manufacturer's dry-powder inhaler (Accuhaler® [GlaxoSmithKline, United kingdom]). Salbutamol was provided for use as needed during the study. The study included a 30 day follow-up period to collect patient safety data. At each visit the following assessments were performed: St. George's Respiratory Questionnaire for COPD (SGRQ-C), modified Medical Research Council dyspnea scale (mMRC), COPD Assessment Test (CAT), Baseline Dyspnea Index/Transition Dyspnea Index (BDI/TDI), ECG, vital signs (pulse rate, blood pressure), blood sample/urine samples and spirometry measurement at scheduled time points. Treatment compliance and rescue medication use were monitored using an electronic diary; these data were reviewed by the investigator regularly and at least at each visit.

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SAFETY

Safety was assessed through recording adverse events (AEs) and serious adverse events (SAEs), including regular monitoring of hematology, blood chemistry, and urine, and regular assessments of vital signs, physical condition, and body weight.

An SAE was defined as any adverse event (appearance of [or worsening of] any pre-existing undesirable sign[s], symptom[s] or medical conditions[s]) which meets any one of the following criteria:

- was fatal or life-threatening
- resulted in persistent or significant disability/incapacity
- constituted a congenital anomaly/birth defect
- required inpatient hospitalization or prolongation of existing hospitalization, unless
- hospitalization was for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - elective or pre-planned treatment for a pre-existing condition that was unrelated to the indication under study and has not worsened since signing the informed consent
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
    - social reasons and respite care in the absence of any deterioration in the patient's general condition

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- was medically significant, i.e. defined as an event that jeopardizes the patient or may require medical or surgical intervention.

All malignant neoplasms were assessed as serious under “medically significant” if other seriousness criteria were not met.

Pneumonia was defined as an event characterized by increased respiratory symptoms (e.g. increased cough, dyspnea, wheezing, purulent sputum and fever) (i.e. body temperature greater than 38°C) or pleuritic chest pain or leukocytosis or other clinical signs consistent with pneumonia considered relevant in the opinion of the investigator. Radiographic imaging (chest X-ray or CT scan), was required to confirm the diagnosis. The diagnosis of COPD exacerbation will not preclude a diagnosis of pneumonia. The investigator used clinical judgment to determine if the events were occurring simultaneously.

An independent adjudication committee assessed all deaths, serious cardio- and cerebrovascular (CCV) events that occurred during the study.

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STATISTICAL ANALYSIS

Efficacy analyses were performed on the Full Analysis Set (FAS) which consisted of all the patients who were assigned a randomization number and who received at least one dose of study treatment. Following the intent-to-treat principle, patients in the FAS were analyzed according to the treatment they were randomized to. The Per-Protocol Set (PPS) was used for supportive analysis to assess robustness of the primary analysis and included all the patients in the FAS without any major protocol deviations, which were defined prior to database lock.

The primary variable was the mean change from baseline in post-dose trough FEV_1 after 26 weeks of treatment. Post-dose trough FEV_1 was defined as the mean of the two FEV_1 values measured at 23 hours 15 minutes and 23 hours 45 minutes after the morning dose taken at the study site on Day 181. Baseline FEV_1 was defined as the average of the pre-dose FEV_1 measured at −45 minutes and −15 minutes at Day 1.

If FEV_1 measurements were taken within 6 hours of rescue medication use or within 7 days of systemic corticosteroid use, or the actual measurement times were outside of the 22 to 25-hour post-morning dose time window, then the individual FEV_1 value was considered missing. Post dose FEV_1 where no morning dose was taken at the corresponding visit were set to missing. If pre-dose measurements were performed one day after treatment end date (Day 182), or if the last dose was not an evening dose (Day 181), they were set to missing. Scheduled pre-dose values which were performed post-dose and scheduled post-dose values which were performed prior to morning dose or after evening dose (serial spirometry set only) were set to missing. The pre-dose trough value is defined as the average of values measured 45 and 15

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minutes prior to the morning dose. If one of the two values were missing (or is not confirmed to be pre- dose) then the remaining non-missing value will be used as average pre-dose value.

The primary efficacy endpoint was analyzed using a mixed-effect model for repeated measures (MMRM), which included fixed, categorical effects of treatment and visit, region, and treatment-by-visit interaction as well as the continuous, fixed covariates of baseline and baseline-by-visit interaction. The within patient correlation was modeled using an unstructured covariance matrix. Restricted maximum likelihood methods were used and the Kenward-Roger approximation was used to estimate denominator degrees of freedom. The between-treatment comparison was carried out using the adjusted mean difference between treatments at Day 182.

Non-inferiority of IND/GLY with respect to tiotropium o.d + salmeterol/fluticasone propionate FDC b.i.d. was to be demonstrated if the confidence interval (CI) for the mean FEV_1 difference of IND/GLY minus tiotropium o.d + salmeterol/fluticasone propionate FDC b.i.d. lied entirely to the right of (higher than) −50 mL.

The following supportive analyses for trough FEV_1 were also performed:

- The same MMRM analysis used for the primary variable was performed for the PPS
- The robustness of the primary results in the presence of missing data was assessed by
    - An analysis of covariance (ANCOVA) model (including treatment, country/region, and baseline FEV_1)
    - The ANCOVA model to analyze trough FEV_1 at Week 26 with missing data imputed with last observation carried forward (LOCF) from Day 29

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Exploratory subgroup analyses were performed for trough FEV_1 using the same MMRM as for the primary analysis but with the inclusion of a treatment by subgroup interaction. Each subgroup analysis was run separately for the following subgroups:

- Blood eosinophils (< 2% vs ≥ 2% , < 150, 150 - < 300, ≥ 300 cells/µL and < 300 versus ≥ 300 cells/µL)
- COPD exacerbation in the previous year (0 vs 1)

The number of moderate or severe COPD exacerbations during the treatment Epoch was summarized by treatment group, as continuous variables and as categorical variables classified into 0, 1, 2, 3, ≥ 4 events. The rate of moderate or severe COPD exacerbations during the treatment Epoch was analyzed using a generalized linear model that assumed a negative binomial distribution. The time at risk for a patient was the time from the start of treatment until the first exacerbation or censoring. In patients with multiple exacerbations, if the start date of an exacerbation was less than 7 days after the end date of a previous episode, then this was assumed to be one continuous exacerbation with the start date taken from the first episode and the end date from the second or last episode. The worst severity of these episodes was taken as the severity of the collapsed exacerbation. Time to first exacerbation was also analyzed using a Cox regression model. The model included the same terms in the rate of protocol-defined exacerbations analysis above.

The change from baseline in trough FEV_1, FVC, SGRQ-C total score, and TDI total score during the Treatment Epoch were analyzed using the same MMRM described for the primary endpoint. The mean daily number of puffs and percentage of days without rescue medication

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usage was calculated for each patient over the 26 weeks of the Treatment Epoch. The use of rescue medication during the Run-in Epoch served as baseline. The mean daily number of puffs was analyzed using a linear mixed model (LMM) with fixed categorical effects of treatment and region, a random effect of study site nested within region and a fixed continuous covariate of baseline. The percentage of days without rescue medication was analyzed with a similar model. All subgroup analyses of secondary endpoints were performed through inclusion of treatment by subgroup interaction terms into the respective models.

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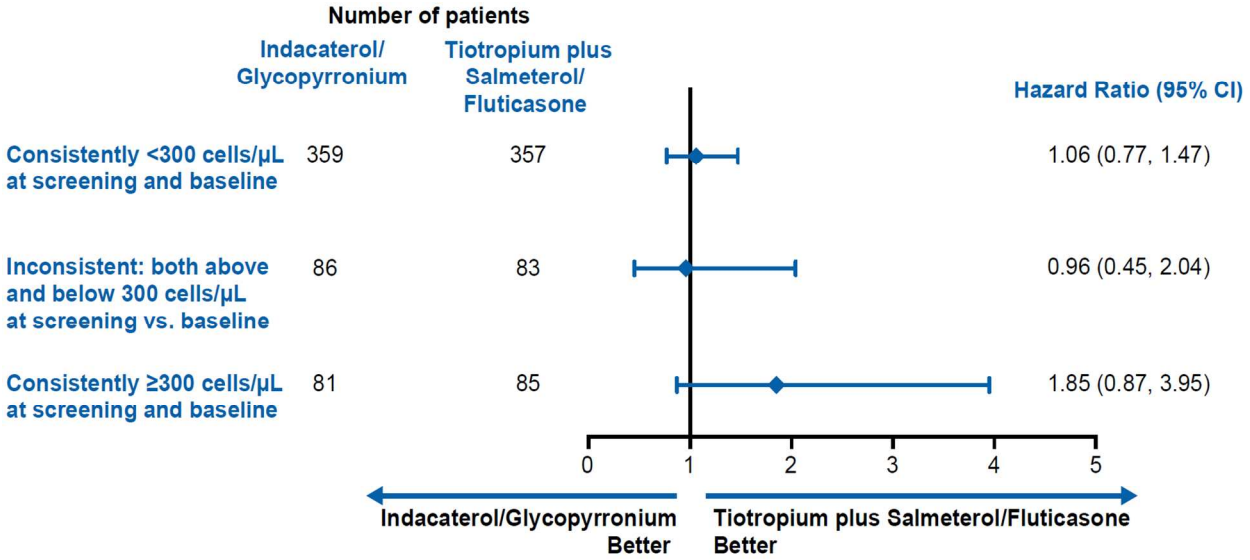
SUPPLEMENTARY FIGURES AND TABLES

Figure Legends

Supplementary Figure E1. Rate of moderate/severe COPD exacerbations by blood eosinophils category at screening and baseline



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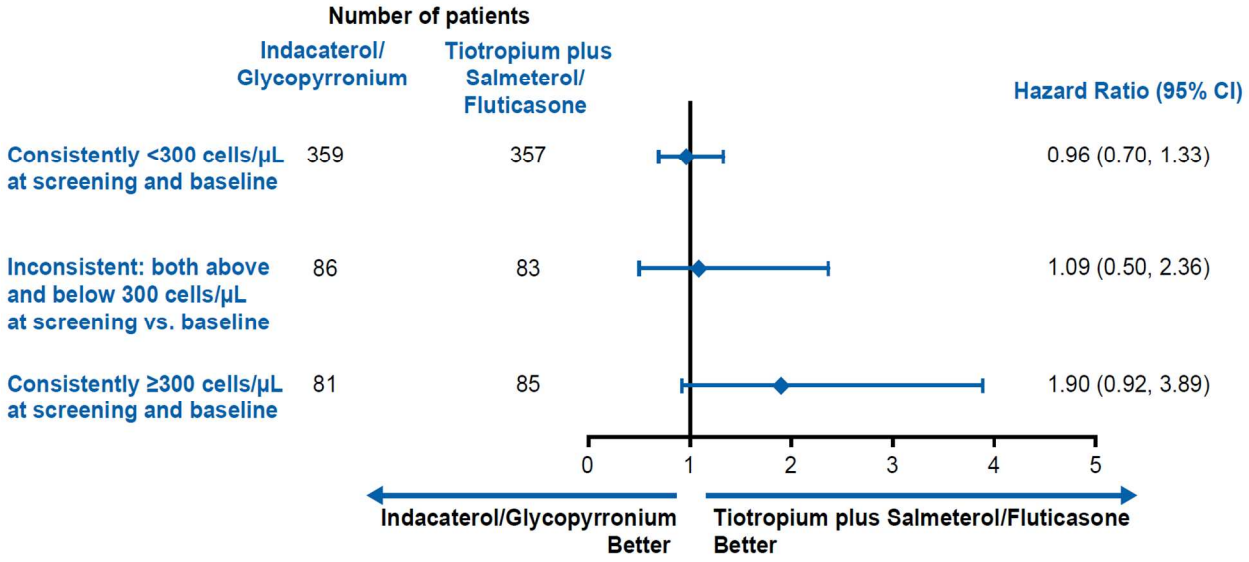
Supplementary Figure E2. Time to first moderate/severe COPD exacerbation by blood eosinophils category at screening and baseline



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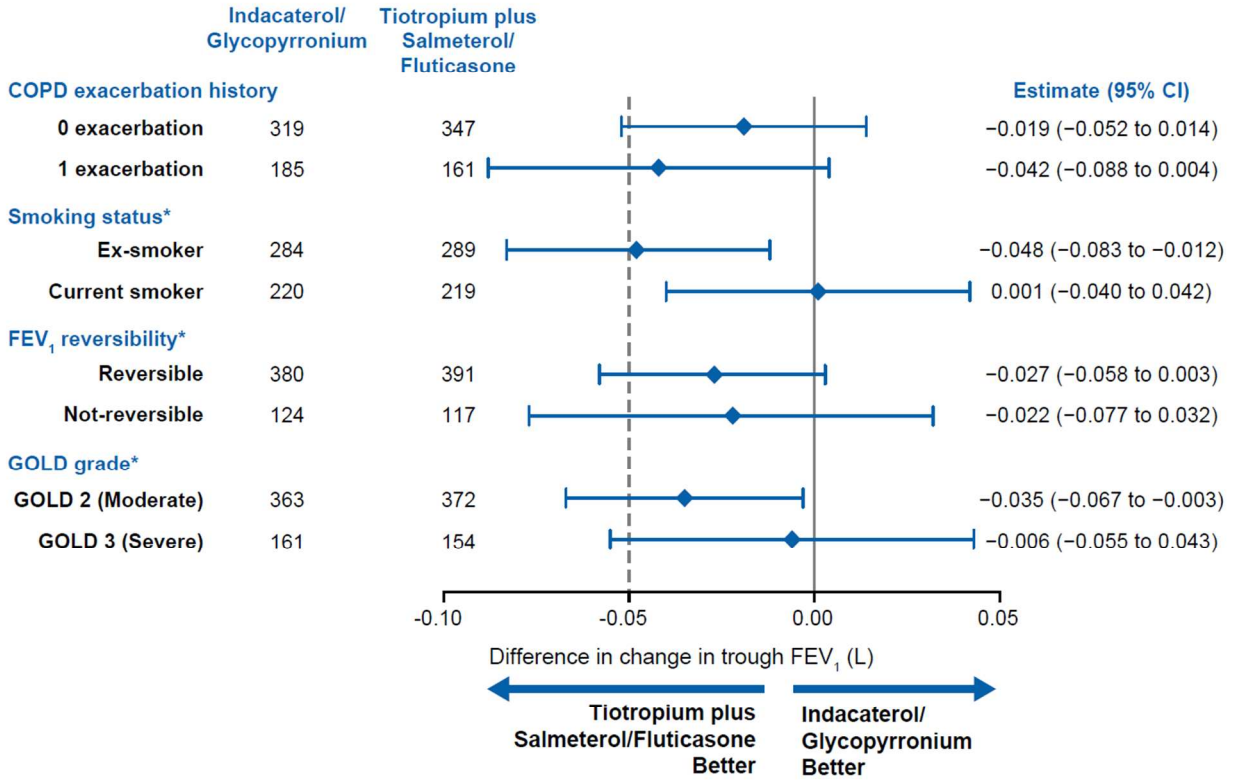
Supplementary Figure E3. Difference (Indacaterol–glycopyrronium versus Tiotropium plus salmeterol–fluticasone) in mean change from baseline in post-dose trough FEV_1 (L) by baseline characteristics



FEV_1, 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).

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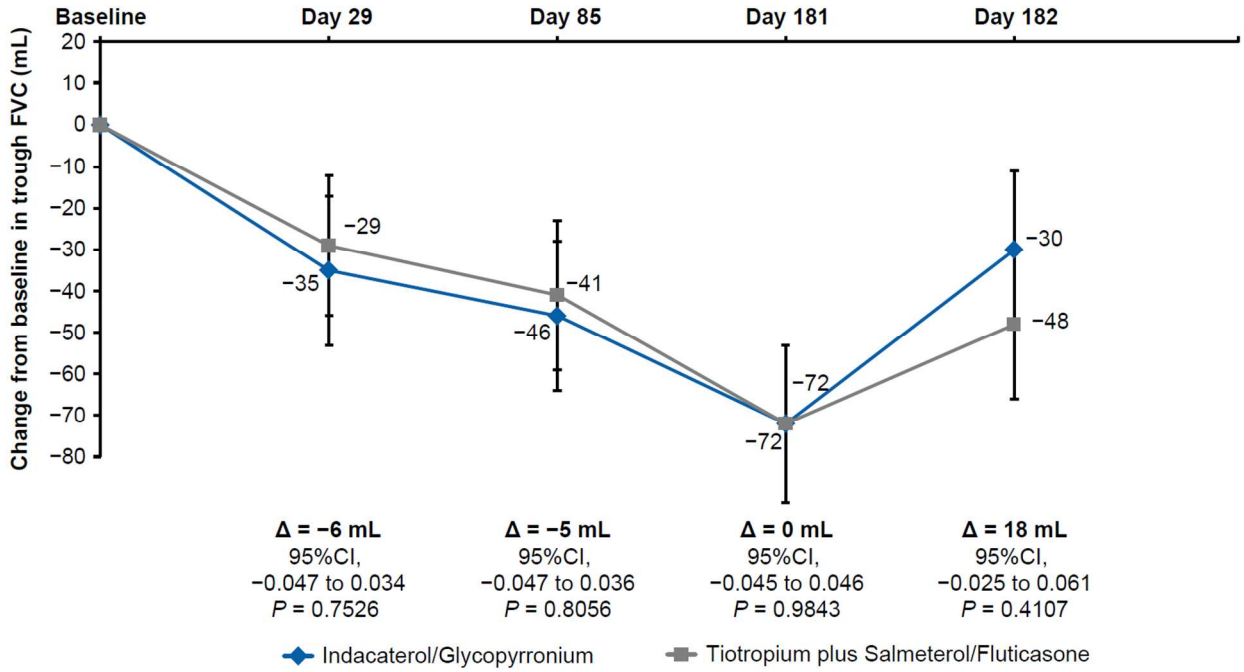
Supplementary Figure E4. Change from baseline in trough FVC over the 26-week treatment period (Full Analysis Set)



Data are presented as least squares mean ± SE.

Δ, least squares mean treatment difference; FVC, forced vital capacity; SE, standard error

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Supplementary Table S1. Prohibited COPD-related Medications During the Trial.

Class of medication *
Non-potassium-sparing diuretics (unless administered as a fixed dose combination with a potassium-conserving drug
Non-selective systemic β-blocking agents [1]
Cardiac anti-arrhythmics Class Ia
Cardiac anti-arrhythmics Class III
Other drugs with potential to significantly prolong the QT-interval
Tricyclic antidepressants (tetracyclics, which are similar in class with regards to drug interaction were also to be excluded)
All antipsychotic agents (first-, second- and third-generation, inclusive of atypical antipsychotics). Combinations of antipsychotic agents with antidepressants were prohibited
Serotonin noradrenaline reuptake inhibitors
Other noradrenaline reuptake inhibitors
Monoamine oxidase inhibitors
Live attenuated vaccines
Antibiotics (long-term maintenance) [2]
Systemic mast cell stabilizers (e.g., cromoglycate, nedocromil, ketotifen)

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Systemic anticholinergics
IgE inhibitors
Leukotriene antagonists and leukotriene synthesis inhibitors
* This table was not considered all-inclusive. Medications were to be assessed for adherence to the indication and other inclusion/exclusion criteria. [1] Selective β1-blocking agents were permitted. [2] Short courses of antibiotics were permitted during the study. Washout of these prohibited medications was not encouraged.

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Supplementary Table S2. Prohibited COPD-related medications during the study

Class of medication [1, 2]
Short-acting muscarinic antagonist [2]
Fixed combinations of short-acting β_2 agonists and short-acting muscarinic antagonists
Short-acting β_2 agonists [3]
Oral phosphodiesterase-IV inhibitors
Xanthines (any formulation)
Parenteral or oral corticosteroids
Intra-muscular depot corticosteroids
[1] This table was not considered all-inclusive. Medications were to be assessed for adherence to the indication and other inclusion/exclusion criteria. These medications were also prohibited if administered for other indications. [2] All of these medications, except depot corticosteroids, were permitted for the treatment of COPD exacerbations during the study. If depot corticosteroids were required, the patient was to be withdrawn from the study treatment. [3] Prohibited with the exception of rescue medication.

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Supplementary Table S3. Medication allowed under certain conditions

Class of medication [1]
Selective serotonin reuptake inhibitors
Intra-nasal corticosteroids
H_1-antagonists
Inactivated influenza, pneumococcal or any other inactivated vaccines
[1] This table was not considered all-inclusive. Medications were to be assessed for adherence to the indication and other inclusion/exclusion criteria.

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Supplementary Table S4. Number and Percentage of Adjudicated MACE and/or CV Deaths.

Adjudicated outcome, n (%)	Indacaterol–glycopyrronium N = 527	Tiotropium plus salmeterol–fluticasone N = 526	All Patients N = 1053
Number of MACE and/or CV Death	4 (0·8)	5 (1·0)	9 (0·9)
Cancer	0	1 (0·2)	1 (0·1)
Lung	0	1 (0·2)	1 (0·1)
Cardiovascular	3 (0·6)	4 (0·8)	7 (0·7)
Sudden death	1 (0·2)	2 (0·4)	3 (0·3)
Fatal Stroke - Hemorrhagic	1 (0·2)	0	1 (0·1)
Other CV - Aortic aneursym rupture	0	1 (0·2)	1 (0·1)
Other CV - Presumed sudden death	0	1 (0·2)	1 (0·1)
Presumed CV Death	1 (0·2)	0	1 (0·1)

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MACE	1 (0·2)	0	1 (0·1)
Non-Fatal Stroke	1 (0·2)	0	1 (0·1)
Other	1 (0·2)	0	1 (0·1)
Accidental	1 (0·2)	0	1 (0·1)

Analysis of the Safety set. Classification was determined by an independent adjudication committee. All deaths were adjudicated. All MACE events and deaths on or after the time of first administration of double-blind drug but not later than 30 days after the last administration are included.

CV, cardiovascular; MACE, Major Adverse Cardiovascular Event; N, number of patients in each treatment group

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Supplementary Table S5. Number and percentage of patients with 0 and 1 exacerbation (baseline exacerbation history) in the <300 and ≥300 blood eosinophils/µL subgroup.

		<300 cells/µL	**≥300 cells/µL**	**Missing**
Indacaterol–glycopyrronium	0 exacerbations	256 (48.7)	77 (14.6)	1
	1 exacerbations	145 (27.6)	48 (9.1)	0
Tiotropium plus salmeterol–fluticasone	0 exacerbations	278 (53.0)	81 (15.4)	1
	1 exacerbations	128 (24.4)	38 (7.2)	0