INSTEAD: a randomised switch trial of indacaterol *versus* salmeterol/fluticasone in moderate COPD

Andrea Rossi[1], Thys van der Molen[2], Ricardo del Olmo[3], Alberto Papi[4], Luis Wehbe[5], Matthew Quinn[6], Chengxing Lu[6], David Young[7], Ray Cameron[7], Enrica Bucchioni[8] and Pablo Altman[6]

Affiliations: [1]Pulmonary Unit, University of Verona, Verona, Italy. [2]University Medical Center Groningen, University of Groningen, Groningen, the Netherlands. [3]Fundación CIDEA and Hospital Maria Ferrer, Buenos Aires, Argentina. [4]University of Ferrara, Ferrara, Italy. [5]Fundacion Enfisema, Buenos Aires, Argentina. [6]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA. [7]Novartis Horsham Research Centre, Horsham, UK. [8]Novartis Farma, Origgio, Italy.

Correspondence: Andrea Rossi, University and General Hospital Verona, Pulmonary Unit, Piazzale Stefani 1, Verona, Italy 37126. E-mail: andrea.rossi_03@univr.it

ABSTRACT The Indacaterol: Switching Non-exacerbating Patients with Moderate COPD From Salmeterol/Fluticasone to Indacaterol (INSTEAD) study investigated the effect of switching patients at low risk of chronic obstructive pulmonary disease (COPD) exacerbations from salmeterol/fluticasone (SFC; inhaled corticosteroid (ICS) regimen) to indacaterol monotherapy (non-ICS regimen).

This 26-week, double-blind, double-dummy, parallel-group, phase IV study, randomised 581 patients with moderate COPD to indacaterol 150 µg once daily or SFC 50/500 µg twice daily. Patients had been receiving SFC 50/500 µg for $\geqslant$3 months, with no COPD exacerbations for more than a year before the study (patients for whom ICS is not recommended). The primary objective was to demonstrate non-inferiority of indacaterol to SFC, measured by trough forced expiratory volume in 1 second (FEV_1) after 12 weeks (non-inferiority margin of 0.06 L).

The primary objective was met, with a mean treatment difference of 9 mL (95% CI -45–26 mL). There were no significant differences between treatments in terms of breathlessness (transition dyspnoea index) or health status (Saint George's Respiratory Questionnaire) at weeks 12 or 26, or rescue medication use or COPD exacerbation rates over 26 weeks. Safety profiles of both treatments were as expected.

This study demonstrated that patients with moderate COPD and no exacerbations in the previous year can be switched from SFC to indacaterol 150 µg with no efficacy loss.

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Introduction

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy document recommends the use of inhaled corticosteroids (ICS)/long-acting β_2-agonist (LABA) combinations as initial treatment only in specific subgroups of patients with chronic obstructive pulmonary disease (COPD); particularly in those at increased risk of future exacerbations [1]. GOLD defines these patients as those having severe or very severe airflow limitation (forced expiratory volume in 1 s (FEV_1) $<$50% predicted) and/or two or more exacerbations (or one exacerbation requiring hospitalisation) in the previous year (GOLD groups C and D) [1]. For patients at low risk of COPD exacerbations (defined as patients with $FEV_1 \geqslant$50% predicted and zero or one exacerbation in the previous year; GOLD groups A and B), treatment recommendations centre on the use of bronchodilators.

Despite these recommendations, ICSs are widely used for the management of COPD, with some data suggesting that a large proportion of patients with COPD are initiated on an ICS-containing regimen; even those patients in whom ICS/LABA combinations are not indicated [2]. A real-world prescription database analysis indicated that 38.8% of patients in GOLD group A (low symptoms and low risk) were receiving an ICS-containing regimen [3]. This percentage increased to 51.8% for patients in GOLD group B (more symptoms, low risk) [3]. The use of ICS in patients with COPD increases the risk of side effects such as diabetes [4], tuberculosis [5], pneumonia [6], cataracts [7] and osteoporosis [8]. Patients at low risk of exacerbations should not be initiated with ICS-containing regimens. However, given the large percentage of patients already initiated on such regimens it would be helpful for a physician to understand the consequences of withdrawal of ICS in such populations.

Indacaterol is a once-daily inhaled long-acting β_2-agonist (LABA) approved for the maintenance treatment of COPD [9]. Prior to the current study, there had been no head-to-head comparisons of maintenance treatment with indacaterol to that of salmeterol/fluticasone fixed-dose combinations. Meanwhile indacaterol 150 μg once daily has demonstrated improved efficacy (in terms of lung function, breathlessness and health status) [10, 11] over salmeterol in patients with moderate to severe COPD.

The INSTEAD study was designed to compare the efficacy of indacaterol 150 μg once daily with that of salmeterol/fluticasone (SFC) 50/500 μg twice daily in a population that had been receiving SFC 50/500 μg for at least 3 months prior to the study. All patients were required to have moderate airflow limitation and a history of no exacerbations in the previous year, and were therefore a patient group in which ICS is not recommended [1]. Consequently, INSTEAD provides information on switching patients who are at low risk of COPD exacerbations from the ICS-containing regimen of SFC to a non-ICS regimen of indacaterol monotherapy.

Materials and methods

Study patients

Male and female patients aged $\geqslant$40 years with moderate COPD (stage II as defined in the GOLD 2010 criteria [12]), received SFC 50/500 μg twice a day *via* the manufacturer's multi-dose dry powder inhaler (MDDPI) (the Accuhaler dry powder inhaler, also known as Diskus in some countries; GlaxoSmithKline, Uxbridge, UK) for the treatment of COPD for $\geqslant$3 months before enrolment. All patients were current or ex-smokers with a smoking history of at least 10 pack-years. Patients were excluded from the study if they had experienced a COPD exacerbation that required treatment with antibiotics and/or oral corticosteroids and/or hospitalisation in the year before the screening visit or during the run-in period. Patients were also excluded if they had a history of asthma, or were receiving any other maintenance treatment for COPD on entry to the study (no washout of maintenance COPD medication was permitted). Detailed inclusion and exclusion criteria are provided in the online supplementary material.

Study design and treatment

INSTEAD was a 26-week, multinational, multicentre, randomised, double-blind, double-dummy, parallel-group, phase IV study comparing the efficacy and safety of indacaterol 150 μg once daily with SFC 50/500 μg twice a day in patients with moderate COPD. After the screening visit, all enrolled patients received unblinded SFC 50/500 μg for a 14-day run-in period. Patients were then randomised (1:1) to either continue to receive SFC 50/500 μg twice a day with no washout period (GlaxoSmithKline), or to be switched to indacaterol 150 μg once daily (Novartis Pharma AG, Basel, Switzerland). Patients attended sites at baseline and at weeks 4, 8, 12 and 26 weeks of treatment. Salbutamol was provided as rescue medication. Additional details of the study design, randomisation and blinding procedures are included in the online supplementary material. The study was approved by institutional review boards and ethics committees at participating centres, and was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. All patients provided

written informed consent before participating in the study. This study was registered with ClinicalTrials.gov, NCT01555138.

Objectives and assessments

The primary objective was to demonstrate the non-inferiority of indacaterol 150 μg once daily to SFC 50/500 μg twice a day in terms of trough FEV_1 after 12 weeks of treatment. Trough FEV_1 was defined as the mean of the FEV_1 measurements at 23 h 10 min and 23 h 45 min after the morning dose on day 84. Secondary endpoints included: trough FEV_1 at other visits; transition dyspnoea index (TDI) [13] and St George's Respiratory Questionnaire for COPD (SGRQ-C) total scores [14] assessed at weeks 12 and 26; and rescue medication use and COPD exacerbations assessed over 26 weeks. Exploratory endpoints included trough inspiratory capacity, assessed in a subgroup of patients at weeks 12 and 26.

Spirometry (for FEV_1 and forced vital capacity (FVC)) was assessed using methodology as per the American Thoracic Society (ATS)/European Respiratory Society (ERS) criteria [15]. COPD exacerbations were defined as worsening for at least two consecutive days of two or more of the major symptoms (dyspnoea, sputum volume or sputum purulence) or worsening of any one major symptom together with any one minor symptom (sore throat, colds (nasal discharge or nasal congestion), fever without other cause, cough or wheeze). Moderate exacerbations were those managed with antibiotics and/or oral corticosteroids; severe exacerbations were those that resulted in hospitalisation.

Adverse events were recorded at each visit; electrocardiogram (ECG) and laboratory analyses (haematology, clinical chemistry and urinalysis) were recorded at screening and study completion.

Statistical analysis

The primary variable (imputed with last observation carried forward (LOCF)) was analysed using a mixed model, with treatment as a fixed effect and baseline FEV_1 and components of the FEV_1 screening test as covariates. The model also used smoking status and country as fixed effects, and centre nested within country as a random effect. Similar models, analysed for superiority, were used for the secondary and exploratory variables, with the relevant baseline parameter used in place of baseline FEV_1. The number of COPD exacerbations during the 26-week treatment period was analysed using a generalised linear model assuming a negative binomial distribution, and the proportions of patients achieving clinically relevant improvements in TDI and SGRQ-C were analysed using logistic regression.

The per-protocol set (PPS) was used for the primary efficacy analysis. The full analysis set (FAS) included all randomised patients who received at least one dose of study drug, and was used for all secondary efficacy analyses. The PPS included all patients in the FAS without any major protocol deviations. The safety set, which was used for all analyses of safety data, included all patients who received at least one dose of study drug whether randomly assigned or not. No interim analyses were planned or performed.

The study was powered for the primary objective, trough FEV_1 at week 12 to demonstrate non-inferiority of indacaterol (150 μg once daily) to salmeterol 50 μg/fluticasone propionate 500 μg twice a day For the calculation of the sample size, it was assumed that the difference between treatments was 0 mL, with a non-inferiority margin of -0.06 L and an estimate for standard deviation of 220 mL. Non-inferiority was to be demonstrated if the 95% confidence interval for the difference between indacaterol and SFC was entirely to the right of (*i.e.* above) -0.06 L. Based on these assumptions, a sample size of 284 patients in each group would provide 90% power for the testing of non-inferiority. Assuming a drop-out rate of 5%, 300 patients were to be recruited into each group.

Results

Patients

Of the 1038 patients screened, 581 patients were randomised to receive either indacaterol (n=293) or SFC (n=288); 496 (85.4%) patients completed the study (fig. 1). Study completion rates were similar between the two treatment groups, the main reasons for discontinuation being adverse events and withdrawal of consent (fig. 1). Baseline patient demographics and other clinical characteristics were similar in the two treatment groups (table 1).

Efficacy

Spirometry

The primary objective was met, with the lower margin of the 95% CI (-0.045 L) being higher than the pre-defined non-inferiority margin of -0.06 L in the PPS (fig. 2). The least square mean trough ± standard error FEV_1 values at week 12 were 1.584±0.0294 for indacaterol and 1.593±0.0300 for SFC. Summary statistics are available in table S1 in the online supplementary material. In the subsequent test for superiority in the

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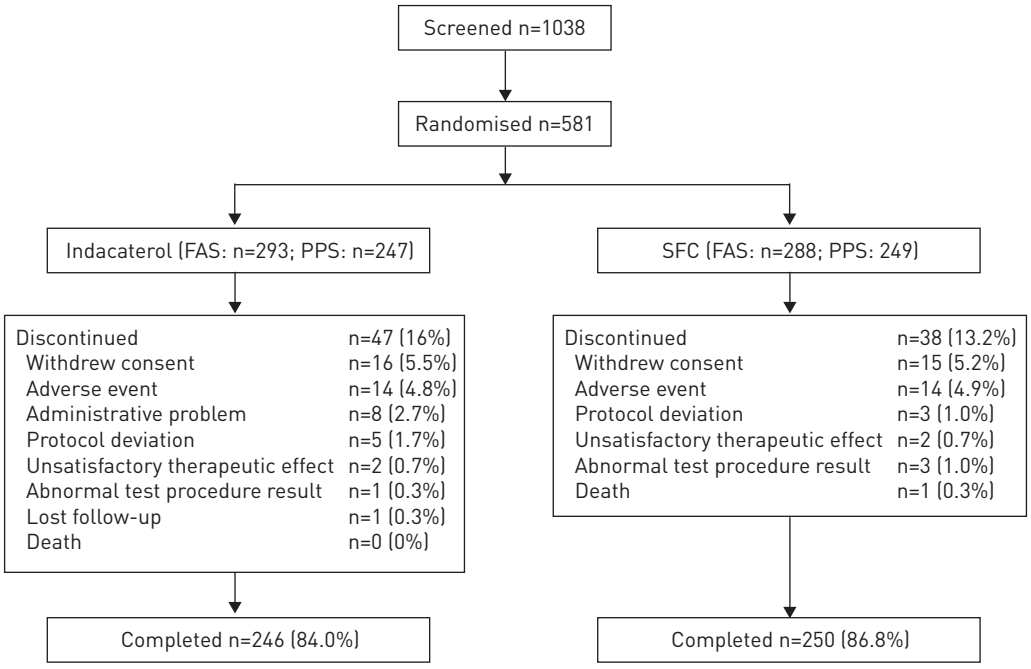

FIGURE 1 Patient disposition. FAS: full analysis set; PPS: per-protocol set; SFC: salmeterol/fluticasone fixed-dose combination.

FAS, there was no statistically significant difference between treatments. There were also no statistically significant differences between treatments in any of the prespecified subgroup analyses of trough FEV_1 at week 12 (table S2 in the online supplementary material).

TABLE 1 Baseline demographics and clinical characteristics

	Indacaterol 150 μg n=293	SFC 50/500 μg n=288	Total n=581
Age years	65.3±8.39	66.8±8.53	66.0±8.49
Male sex	204 (69.6)	197 (68.4)	401 (69.0)
Ethnicity			
Caucasian	252 (86.0)	252 (87.5)	504 (86.7)
Native American	22 (7.5)	21 (7.3)	43 (7.4)
Asian	2 (0.7)	1 (0.3)	3 (0.5)
Other	17 (5.8)	14 (4.9)	31 (5.3)
Duration of COPD years	5.8±5.4	6.7±5.8	6.2±5.6
Severity of COPD#			
Moderate	291 (99.3)	287 (99.7)	578 (99.5)
Missing	2 (0.7)	1 (0.3)	3 (0.5)
Smoking history			
Ex-smokers	214 (73.0)	216 (75.0)	430 (74.0)
Pack-years¶	41.4±26.3	42.0±26.1	41.7±26.2
Pre-bronchodilator FEV_1 L	1.55±0.39	1.53±0.41	1.54±0.40
Post-bronchodilator FEV_1+ L	1.68±0.40	1.67±0.42	1.67±0.41
Post-bronchodilator FEV_1 % predicted+	64.0±8.11	64.2±8.28	64.1±8.18
FEV_1 reversibility %	9.2±7.0	10.2±10.2	9.7±8.7
Post-bronchodilator FEV_1/FVC+ %	53.7±8.9	53.6±9.1	53.7±9.0

Data are presented as mean±SD or n (%). SFC: salmeterol/fluticasone fixed-dose combination; COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity. #: COPD severity is based on the Global Initiative for Chronic Obstructive Lung Disease 2010 criteria; ¶: total years of smoking multiplied by cigarette packs smoked per day; +: assessed after administration of 400 μg salbutamol.

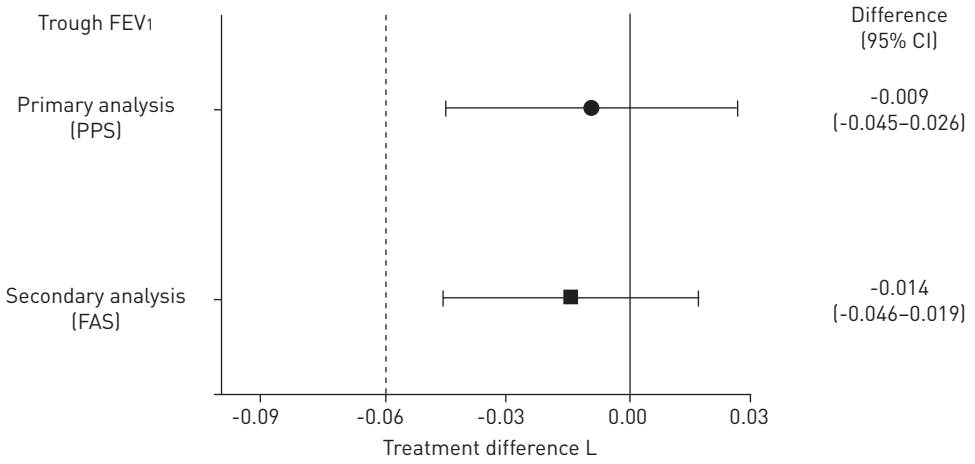

FIGURE 2 Least square mean±95% CI treatment differences for trough forced expiratory volume in 1 s (FEV_1) (primary objective) after 12 weeks (per-protocol set (PPS) and full analysis set (FAS)). The non-inferiority margin was -0.06 L units (shown by the dashed line).

There were no significant differences between treatments in trough FEV_1 at any of the other visits (figure S1 in the online supplementary material), and no significant differences between treatments in individual timepoint FEV_1 at either week 12 or week 26 (table S3 in the online supplementary material). There were also no statistically significant differences between treatments for trough FVC at either week 12 or Week 26 (figure S2 in the online supplementary material).

The inspiratory capacity subgroup included 370 patients (185 in each treatment group). As with the forced spirometry variables, there were no statistically significant differences between treatments, either at week 12 or at week 26 (figure S3 in the online supplementary material).

Dyspnoea, health status and rescue medication use

There were no statistically significant differences between the treatments at weeks 12 or 26 either for TDI total score (fig. 3a) or for the percentages of patients achieving the minimum clinically important difference of 1 unit (fig. 3b). Similarly, there were no statistically significant differences between treatments at weeks 12 or 26 either for SGRQ-C total score (fig. 4a) or for the percentages of patients achieving the minimum clinically important change from baseline of $\geqslant$4 units (fig. 4b). There were also no statistically significant differences between treatments for rescue medication use across the study duration, either for puffs per day or the percentage of days with no rescue use (table S4 in the online supplementary material).

COPD exacerbations

During the 26-week treatment period, 79.5% and 74.7% of patients with indacaterol and SFC, respectively experienced no exacerbations (table 2). There was no statistically significant difference between treatments in the rate of all (*i.e.*, mild, moderate and severe) COPD exacerbations per year, although the rate in the indacaterol group was numerically lower than the rate observed in the SFC group (table 2), with a ratio of rates of 0.86 (95% CI 0.62, 1.20; p=0.367). Table 2 also lists the numbers of patients with mild, moderate or severe exacerbations; all rates were numerically lower in the indacaterol group than the SFC group.

In the time-to-event analysis, the event-free rate at month 6 was 82.3% with indacaterol and 78.7% with SFC, with a hazard ratio for time to first moderate-to-severe exacerbation of 0.80; the difference was not statistically significant (p=0.258). A Kaplan–Meier plot of the time to first moderate or severe COPD exacerbation is provided in figure 5.

Safety

Overall, adverse events were reported in 44.7% of patients in the indacaterol group and 53.5% of patients in the SFC group (table 3). The most common adverse events were COPD exacerbations and nasopharyngitis. Few serious adverse events were reported during the study, and no events were reported by more than one patient (or >0.5%) in the indacaterol group (table 3). Two patients died during the study, both in the SFC group (one patient listed as sudden death and another one due to mesothelioma). Neither of the deaths was suspected to be related to study medication. Overall, ECG data were as expected, and in accordance with approved labels. There

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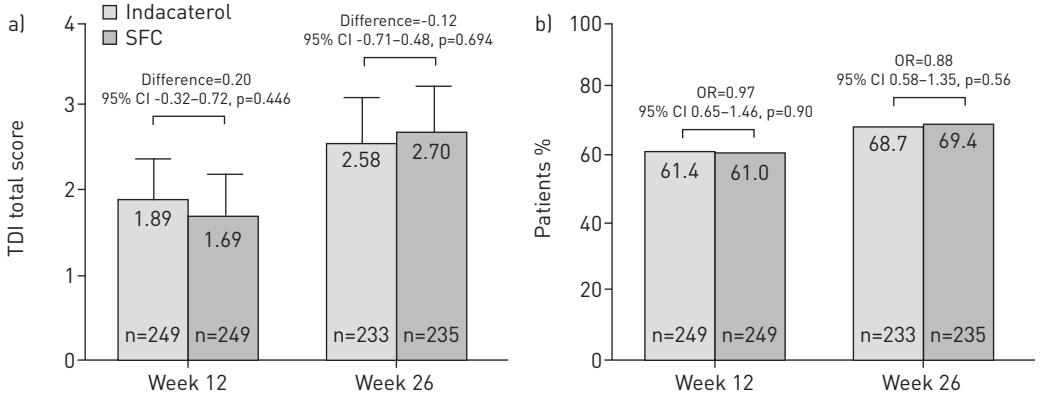

FIGURE 3 Transitional dyspnoea index (TDI) total score after week 12 and week 26. a) TDI total score (least square mean ± SEM) and b) percentage of patients achieving the minimum clinically important difference (⩾1 units) in TDI score (full analysis set). SFC: salmeterol/fluticasone fixed-dose combination; OR: odds ratio.

were no clinically relevant differences between the two treatments in terms of any haematological or biochemical parameter, and no meaningful differences in terms of the vital signs assessments.

Discussion

For the first time, the INSTEAD study, directly compared indacaterol with SFC over 26 weeks. It sought to specifically recruit patients with moderate airflow limitation (FEV_1 50–80% predicted) who were being treated with SFC 50/500 μg *via* MDDPI and who had not exacerbated in the previous 12 months, *i.e.* patients in whom ICS are not recommended [1]. This study aimed to address the question of whether those patients could be switched from the LABA/ICS combination onto indacaterol, with no loss in efficacy. Sufficient patients to enable all study objectives to be assessed participated in and completed the study. There was no difference in discontinuation rate for unsatisfactory therapeutic effect between the groups, suggesting that treatment with indacaterol was adequate even for patients with more severe disease. For lung function, dyspnoea (TDI) and health status (SGRQ), there were no clinically relevant differences between treatments (with the primary endpoint confirming non-inferiority of lung function). There were also no statistically significant differences between the two treatments in terms of rescue medication use. Moreover, there was no statistically significant difference between treatments in terms of COPD exacerbations, with fewer in patients treated with indacaterol. Taken together, these data provide strong and reassuring evidence to physicians that this type of patient can be switched from LABA/ICS to indacaterol.

While almost all patients with persistent asthma require ICS, the efficacy of ICS is less well established in COPD and their role in treatment is limited [16, 17]. As reviewed by PRICE *et al.* [16], the use of ICS

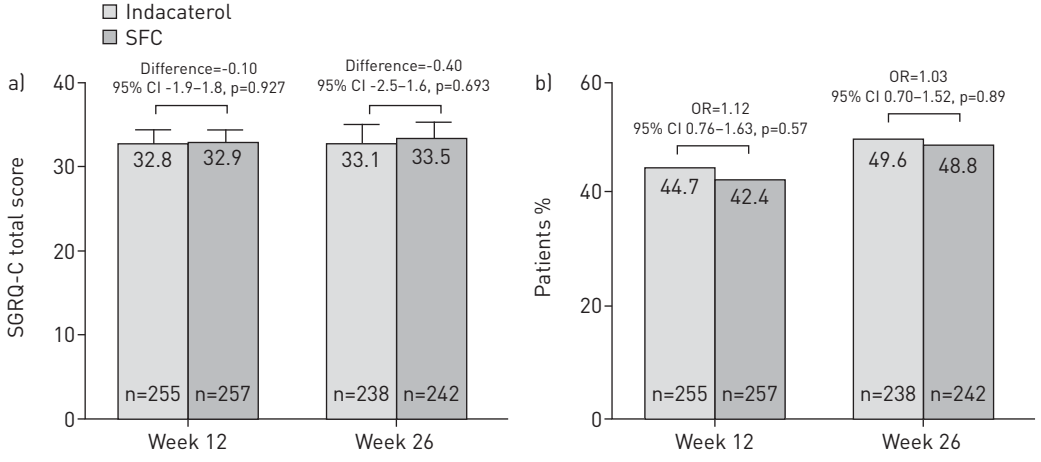

FIGURE 4 St George's Respiratory Questionnaire for chronic obstructive pulmonary disease (SGRQ-C) total score after week 12 and week 26. a) SGRQ-C total score (least squares mean ± SEM) and b) percentage of patients achieving the minimum clinically important change from baseline (⩾4 units) in SGRQ-C score (full analysis set). SFC: salmeterol/fluticasone fixed-dose combination.

TABLE 2 Chronic obstructive pulmonary disease exacerbations over 26 weeks in the full analysis set

	Exacerbations							
	All		Mild		Moderate		Severe	
	Indacaterol[#]	SFC[¶]	Indacaterol[#]	SFC[¶]	Indacaterol[#]	SFC[¶]	Indacaterol[#]	SFC[¶]
Exacerbations per patient								
None	233 (79.5)	215 (74.7)	273 (93.2)	269 (93.4)	246 (84.0)	231 (80.2)	292 (99.7)	286 (99.3)
1	47 (16.0)	57 (19.8)	19 (6.5)	14 (4.9)	40 (13.7)	51 (17.7)	1 (0.3)	2 (0.7)
⩾2	13 (4.5)	16 (5.5)	1 (0.3)	5 (1.7)	7 (2.4)	6 (2.1)	0	0
Total number of exacerbations	75	90	21	25	54	63	1	2
Rate of exacerbations per year	0.57	0.67	0.16	0.19	0.41	0.47	0.01	0.01

Data are presented as n (%), unless otherwise stated. [#]: 150 μg, n=293; [¶]: 50/500 μg, n=288. SFC: salmeterol/fluticasone fixed-dose combination.

indiscriminately in COPD may result in a needless increase in the risk of side-effects including pneumonia, osteoporosis, diabetes and cataracts, using healthcare resource that could possibly be better used on other more appropriate management strategies, such as pulmonary rehabilitation and optimal use of bronchodilators. Treatment recommendations suggest that patients at low risk of COPD exacerbations should be initiated with bronchodilator therapy without ICS [1]. However, physicians considering withdrawal of ICS in patients inappropriately receiving ICS need data to support this prescribing decision. A number of previous studies have examined the implications of withdrawal of ICS in patients with COPD. NADEEM et al. [18] systematically reviewed these studies for a meta-analysis published in 2011. The researchers considered very few of the identified studies to be methodologically acceptable; indeed, only three out of 107 initially identified studies were considered to be acceptable. All three studies recruited patients with a wide spectrum of COPD, from moderate to very severe, and most patients had experienced exacerbations in the year prior to entry (one of the studies required patients to have experienced at least two exacerbations in the year prior to entry). Despite these studies therefore recruiting populations that would be considered by GOLD to be at high risk of future exacerbations [1], the meta-analysis conducted by the researchers suggested that although patients in the ICS withdrawal arms were at an increased risk of exacerbating, this increase in risk was not statistically significant. Furthermore, there were no significant differences between arms in terms of SGRQ total score, and inconsistent differences in terms of lung function. In addition, a recently published, real-life prospective study (On the Appropriateness of Treatment in Moderate COPD Patients; OPTIMO) showed that withdrawal of ICS in patients with moderate airflow limitation (and who had experienced fewer than two exacerbations in the previous year)

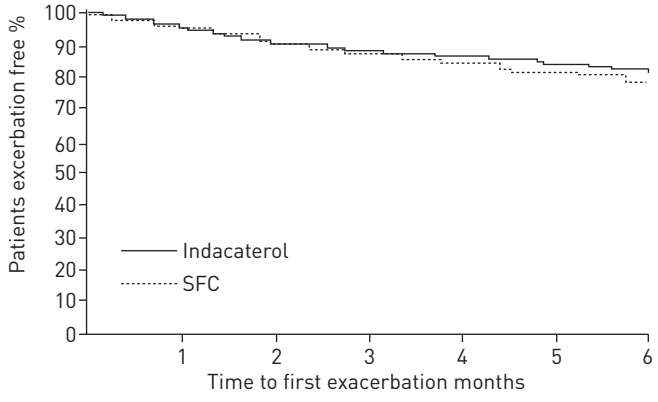

FIGURE 5 Time to first moderate or severe chronic obstructive pulmonary disease exacerbation up to week 26 (full analysis set). SFC: salmeterol/fluticasone fixed-dose combination.

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TABLE 3 Most frequent adverse events (including chronic obstructive pulmonary disease (COPD) exacerbations), serious adverse events (SAEs) and deaths (safety set)

	Indacaterol 150 μg n=293	SFC 50/500 μg n=288
Patients with any AEs	131 (44.7)	154 (53.5)
AEs in ⩾5% of either group		
COPD	60 (20.5)	73 (25.3)
Nasopharyngitis	15 (5.1)	18 (6.3)
Patients with SAEs	5 (1.7)	17 (5.9)
SAEs in ⩾0.5% of either group		
Atrial fibrillation	0	2 (0.7)
Pneumonia[#]	0	2 (0.7)
COPD	1 (0.3)	3 (1.0)
Death	0	2 (0.7)
Discontinuations		
Due to AEs	14 (4.8)	15 (5.2)
Due to SAEs	3 (1.0)	7 (2.4)

Data are presented as n (%). SFC: salmeterol/fluticasone fixed-dose combination; AE: adverse event. [#]: One patient in the indacaterol group experienced pneumonia SAE 5 days after completing the study.

did not affect symptoms, lung function or exacerbation rate over six months [19]. The current study is one of the first (if not the first) randomised, controlled studies to provide evidence of the effect of withdrawal of ICS in a clearly defined population that is at low risk of future exacerbations.

In the TORCH (Towards a Revolution in COPD Health) study, which compared salmeterol/fluticasone 50/500 μg with salmeterol 50 μg, fluticasone 500 μg and placebo in patients with moderate-to-very-severe COPD, the SFC arm provided consistently better efficacy than the salmeterol arm, in terms of lung function and SGRQ total score over 3 years in patients with moderate-to-very-severe COPD [20] In a subsequent analysis of TORCH data by COPD severity, SFC provided better efficacy than salmeterol in terms of SGRQ in the subgroup with FEV_1 ⩾50% predicted, although the separation between treatments for the other endpoints was less marked in this group [21]. Two previous studies have compared indacaterol 150 μg with salmeterol 50 μg in patients with moderate-to-severe COPD. At week 12, indacaterol 150 μg provided better efficacy than salmeterol 50 μg in terms of lung function, and TDI and SGRQ total scores in the INLIGHT (Indacaterol efficacy evaluation using 150 μg doses with COPD patients)-2 study [11], and in terms of lung function and TDI total score in the INSIST (Indacaterol: investigating superiority *versus* salmeterol) study [10]. The hypothesis when designing the INSTEAD study was that the better efficacy of indacaterol compared with salmeterol in these previous studies, and published data showing that ICS treatment is not necessary in non-exacerbating patients with moderate COPD, would confirm that a switch from SFC to indacaterol is possible with no loss in efficacy [1]. This was indeed the case, with the INSTEAD study now providing direct evidence of the comparability of indacaterol 150 μg and salmeterol/fluticasone 50/500 μg in this carefully characterised population.

The exacerbation data, showing no statistical separation between indacaterol and SFC, are important, as ICS are indicated for prevention of exacerbations in COPD [1]. Furthermore, there is a perception amongst some physicians that abrupt withdrawal of ICS can trigger exacerbations in patients with COPD. Although 6 months is a relatively short follow-up period for exacerbations (especially in a study that was powered on lung function and not exacerbations), any numerical increase in the exacerbation rate in the indacaterol group could have been taken as a potential signal that exacerbations were being triggered. Additionally, there should be no concern regarding the effect of seasonality: study recruitment took place from February 2012 to July 2013 in both hemispheres and therefore patients were treated throughout the yearly seasons. Given these points, although there was no statistically significant difference between treatments (and therefore no inferences can be made regarding a reduction in exacerbation rate as a result of treatment with indacaterol), the numerical reduction in exacerbations of all severities (mild, moderate and severe) with indacaterol *versus* SFC will provide reassurance to physicians considering withdrawal of ICS in these low exacerbation-risk patients.

The adverse events, serious adverse events and safety profiles of the two treatments were in line with previous findings. The rates of adverse events, serious adverse events and discontinuation due to adverse events were numerically lower in the indacaterol group than in the SFC group. The most frequent adverse

events were COPD exacerbations and nasopharyngitis in both groups; the rates of both were also numerically lower with indacaterol than with SFC. An event of particular interest in patients receiving ICS is pneumonia. In the 3-year TORCH study there was a statistically greater incidence of pneumonia in patients receiving SFC *versus* salmeterol [20]. In the INSTEAD study, the only two on-treatment pneumonia serious adverse events were both observed in the SFC arm.

In conclusion, the INSTEAD study met its aims, demonstrating that patients with moderate airflow limitation and a history of no exacerbations can be switched from SFC to indacaterol without any loss in efficacy.

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References

1 Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. 2014 Available from: www.goldcopd.org/uploads/users/files/GOLD_Report_2014_Jun11.pdf Date last updated: June 11, 2014. Date last accessed: October 14, 2014.
2 Suissa S, Barnes PJ. Inhaled corticosteroids in COPD: the case against. *Eur Respir J* 2009; 34: 13–16.
3 Vestbo J, Vogelmeier C, Small M, *et al.* Understanding the GOLD 2011 Strategy as applied to a real-world COPD population. *Respir Med* 2014; 108: 729–736.
4 Suissa S, Kezouh A, Ernst P. Inhaled corticosteroids and the risks of diabetes onset and progression. *Am J Med* 2010; 123: 1001–1006.
5 Kim JH, Park JS, Kim KH, *et al.* Inhaled corticosteroid is associated with an increased risk of TB in patients with COPD. *Chest* 2013; 143: 1018–1024.
6 Thornton Snider J, Luna Y, Wong KS, *et al.* Inhaled corticosteroids and the risk of pneumonia in Medicare patients with COPD. *Curr Med Res Opin* 2012; 28: 1959–1967.
7 Cumming RG, Mitchell P, Leeder SR. Use of inhaled corticosteroids and the risk of cataracts. *N Engl J Med* 1997; 337: 8–14.
8 Weatherall M, James K, Clay J, *et al.* Dose-response relationship for risk of non-vertebral fracture with inhaled corticosteroids. *Clin Exp Allergy* 2008; 38: 1451–1458.
9 McKeage K. Indacaterol: a review of its use as maintenance therapy in patients with chronic obstructive pulmonary disease. *Drugs* 2012; 72: 543–563.
10 Korn S, Kerwin E, Atis S, *et al.* Indacaterol once-daily provides superior efficacy to salmeterol twice-daily in COPD: a 12-week study. *Respir Med* 2011; 105: 719–726.
11 Kornmann O, Dahl R, Centanni S, *et al.* Once-daily indacaterol versus twice-daily salmeterol for COPD: a placebo-controlled comparison. *Eur Respir J* 2011; 37: 273–279.
12 Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management and Prevention of COPD. 2010. Available from: www.goldcopd.org/uploads/users/files/GOLDReport_April112011.pdf Date last updated: April 11, 2011. Date last accessed: October 14, 2104.
13 Witek TJ Jr, Mahler DA. Minimal important difference of the transition dyspnoea index in a multinational clinical trial. *Eur Respir J* 2003; 21: 267–272.
14 Jones PW. St. George's Respiratory Questionnaire: MCID. *COPD* 2005; 2: 75–79.
15 Miller MR, Hankinson J, Brusasco V, *et al.* Standardisation of spirometry. *Eur Respir J* 2005; 26: 319–338.
16 Price D, Yawn B, Brusselle G, *et al.* Risk-to-benefit ratio of inhaled corticosteroids in patients with COPD. *Prim Care Respir J* 2013; 22: 92–100.
17 Suissa S. Effectiveness of inhaled corticosteroids in chronic obstructive pulmonary disease: immortal time bias in observational studies. *Am J Respir Crit Care Med* 2003; 168: 49–53.
18 Nadeem NJ, Taylor SJ, Eldridge SM. Withdrawal of inhaled corticosteroids in individuals with COPD–a systematic review and comment on trial methodology. *Respir Res* 2011; 12: 107.
19 Rossi A, Guerriero M, Corrado A, *et al.* Withdrawal of inhaled corticosteroids can be safe in COPD patients at low risk of exacerbation: a real-life study on the appropriateness of treatment in moderate COPD patients (OPTIMO). *Respir Res* 2014; 15: 77.
20 Calverley PM, Anderson JA, Celli B, *et al.* Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *N Engl J Med* 2007; 356: 775–789.
21 Jenkins CR, Jones PW, Calverley PM, *et al.* Efficacy of salmeterol/fluticasone propionate by GOLD stage of chronic obstructive pulmonary disease: analysis from the randomised, placebo-controlled TORCH study. *Respir Res* 2009; 10: 59.

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