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Original article

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Please cite this article as: Halpin DMG, Vogelmeier CF, Mezzi K, *et al*. Efficacy of indacaterol/glycopyrronium *versus* salmeterol/fluticasone in current and ex-smokers: a pooled analysis of IGNITE trials. *ERJ Open Res* 2020; in press (https://doi.org/10.1183/23120541.00816-2020).

This manuscript has recently been accepted for publication in the *ERJ Open Research*. It is published here in its accepted form prior to copyediting and typesetting by our production team. After these production processes are complete and the authors have approved the resulting proofs, the article will move to the latest issue of the ERJOR online.

Efficacy of indacaterol/glycopyrronium versus salmeterol/fluticasone in current and ex-smokers: a pooled analysis of IGNITE trials

David M.G. Halpin[1], Claus F. Vogelmeier[2], Karen Mezzi[3], Pritam Gupta[4], Konstantinos Kostikas[5], Jadwiga A. Wedzicha[6]

[1]University of Exeter Medical School, College of Medicine and Health, University of Exeter, Exeter, United Kingdom; [2]University Medical Centre Giessen and Marburg, Member of the German Centre for Lung Research (DZL), Marburg, Germany; [3]Novartis Pharma AG, Basel, Switzerland; [4]Novartis Healthcare Pvt. Ltd., Hyderabad, India; [5]Respiratory Medicine Department, University of Ioannina, Greece; [6]National Heart and Lung Institute, Imperial College London, London, United Kingdom

Corresponding author

Prof. David MG Halpin

Consultant Physician & Honorary Professor

University of Exeter Medical School

College of Medicine and Health

University of Exeter

Exeter, UK

Tel +44 (0)1392 402133

Fax +44(0)1392 402828

Take home message

In both current smokers and ex-smokers with COPD, indacaterol/glycopyrronium demonstrated greater efficacy versus salmeterol/fluticasone but the difference was more prominent in current smokers for most of the evaluated parameters.

Abstract

Inhaled corticosteroids have proven to be less effective in smoking asthmatic patients; however, there is limited information on the efficacy of inhaled corticosteroid-containing regimens in COPD patients who continue smoking. We evaluate the differential efficacy of once-daily indacaterol/glycopyrronium 110/50 µg compared with twice-daily salmeterol/fluticasone 50/500 µg in current smokers and ex-smokers, with COPD.

A pooled analysis of data from ILLUMINATE, LANTERN and FLAME studies, was conducted to assess the efficacy of indacaterol/glycopyrronium compared with salmeterol/fluticasone in current smokers and ex-smokers, with COPD. Efficacy was assessed in terms of improvements in trough forced expiratory volume in 1 second (FEV_1), transition dyspnoea index (TDI) focal score, St George's Respiratory Questionnaire (SGRQ) total score, reduced rescue medication use and exacerbation prevention at 26 weeks after the start of the therapy.

In total, 1769 (38%) current smokers and 2848 (62%) ex-smokers were included. Patients treated with indacaterol/glycopyrronium experienced greater improvements in trough FEV_1 versus salmeterol/fluticasone in both current and ex-smokers (least squares mean treatment difference, 105 mL and 78 mL, respectively). Improvements in TDI focal score, SGRQ total score and reduction in rescue medication use were also greater with indacaterol/glycopyrronium versus salmeterol/fluticasone in current and ex-smokers. Further, indacaterol/glycopyrronium reduced all exacerbations (moderate/severe) compared with salmeterol/fluticasone, irrespective of smoking status. The difference in efficacy in favour of indacaterol/glycopyrronium was more prominent in current smokers in most cases.

Indacaterol/glycopyrronium demonstrated greater efficacy versus salmeterol/fluticasone and the differences were generally more prominent in current smokers suggesting smoking may reduce the effects of salmeterol/fluticasone.

Introduction

Smoking is the leading cause of chronic obstructive pulmonary disease (COPD); in 2005, approximately 5.4 million deaths were due to tobacco use. Numbers of tobacco-related deaths are expected to increase to 8.3 million by 2030 [1]. At least 25% of smokers develop COPD, making smoking a major risk factor [2,3]. The prevalence of COPD is considerably higher in smokers and ex-smokers compared with non-smokers [4, 5]. Smoking cessation reduces lung function decline and mortality, and is the most important management strategy for patients with COPD who are smokers [6-8]. Individuals should be encouraged to quit smoking at every available opportunity. Legislative smoking bans are highly effective in promoting quitting and reducing harm from second-hand smoke exposure [9].

However, despite awareness of the benefits of smoking cessation, a high proportion of the COPD population continue to smoke (approximately 20% of the global COPD population) [2, 10-13], which highlights the need for selection of appropriate pharmacological therapy in these patients.

Inhaled long-acting bronchodilators (LABDs) are the mainstay of pharmacological management of COPD [6,14]. LABDs, including long-acting β_2-agonist (LABA) and long-acting muscarinic antagonist (LAMA), improve lung function and health-related quality of life, and reduce rescue medication use and exacerbations in patients with COPD [15]. Use of inhaled corticosteroids (ICS) in combination with LABA, or as triple therapy with LABA and LAMA, is proposed to be guided by exacerbation history and patients' eosinophil counts [6]. ICS have proven to be less effective in patients with asthma who are active smokers, showing fewer short-term lung function improvements and reduced

anti-inflammatory effects, compared with non-smokers [16,17]. Smoking may have similar effects on therapeutic response to ICS in patients with COPD; however, very limited data are available to support this. A *post-hoc* analysis of the SUMMIT trial demonstrated impaired response to ICS-containing therapy for important clinical outcomes in patients with COPD who continued smoking [18].

We conducted a pooled analysis of the ILLUMINATE, LANTERN and FLAME [19-21] trials to evaluate the efficacy of once-daily (o.d.) indacaterol/glycopyrronium 110/50 µg (IND/GLY, a LABA/LAMA) versus twice-daily (b.i.d.) salmeterol/fluticasone 50/500 µg (SFC, a LABA/ICS) in current and ex-smokers with COPD, and to understand if smoking impairs response to ICS in patients with COPD.

Methods

Study design(s)

This is a pooled *post-hoc* analysis of data from the ILLUMINATE (NCT01315249), LANTERN (NCT01709903) and FLAME (NCT01782326) studies. ILLUMINATE and LANTERN were 26-week, multicentre, double-blind, double-dummy, parallel-group studies that randomised (1:1) patients with moderate-to-severe COPD to receive either IND/GLY 110/50 µg o.d. via the Breezhaler® device or SFC 50/500 µg b.i.d. via the Accuhaler® device [19,21]. FLAME was a 52-week, multicentre, double-blind, double-dummy, parallel-group study that randomised (1:1) patients with moderate-to-very-severe COPD with ≥1 exacerbation in the previous year to receive either IND/GLY 110/50 µg o.d. via the Breezhaler® device or SFC 50/500 µg b.i.d. via the Accuhaler® device [20]. Considering the difference in study durations, this pooled analysis included data after 26 weeks of treatment.

All studies were approved by the Independent Ethics Committee or Institutional Review Boards of each participating centre and were conducted in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki. All patients provided their informed consent for being included in the studies.

Patients

This pooled analysis included current and ex-smokers, with a smoking history of at least 10 pack-years (10 pack-years are defined as 20 cigarettes a day for 10 years, or 10 cigarettes a day for 20 years, etc.) from ILLUMINATE, LANTERN and FLAME studies. An ex-smoker was defined as a person who had not smoked for ≥6 months at screening. Smoking status was determined as at baseline.

Key inclusion and exclusion criteria of these studies are presented in **table S1.** Detailed study methodology and patient criteria were reported previously [19-21].

Assessments

This pooled analysis compared the efficacy of IND/GLY 110/50 µg o.d. versus SFC 50/500 µg b.i.d. in current and ex-smokers after Week 26 in terms of efficacy endpoints common to all studies. Lung function as assessed by improvement in pre-dose trough forced expiratory volume in 1 second (FEV_1) and proportion of patients achieving minimal clinically important difference (MCID) of ≥100 mL increase in trough FEV_1 at Week 26 [22]. Dyspnoea, as assessed by improvement in transition dyspnoea index (TDI) focal score and proportion of patients achieving MCID of ≥1-point increase in the score at Week 26 [23]. Health status assessed by improvement in St George's Respiratory Questionnaire (SGRQ) total score and proportion of patients achieving

MCID of ≥4-point reduction in the score at Week 26 [24]. The change from baseline in rescue medication use (number of puffs per day) over 26 weeks, and the annualised rate of all (mild/moderate/severe), moderate/severe and severe exacerbations were also assessed.

Statistical analysis

All analyses were performed in the full analysis set (FAS), which consisted of all patients in the randomised set who received at least one dose of study medication. Patients included in this analysis were smokers or ex-smokers, as assessed at baseline. The changes from baseline in FEV_1, TDI and SGRQ at Week 26 were analysed using a mixed model for repeated measure (MMRM). The response variables considered were the change in pre-dose trough FEV_1, change in TDI score and change in SGRQ score from baseline to Week 26, respectively, for each separate MMRM model. The explanatory variables considered were treatment, baseline value of the parameter of interest (FEV_1, TDI or SGRQ as appropriate), airflow limitation severity, smoking status at baseline, ICS use at screening, region, visit, study and interaction terms between smoking status, treatment, baseline value of the parameter under consideration and visit. The proportion of patients who achieved MCID in terms of FEV_1, TDI and SGRQ were analysed using logistic regression. The model included fixed effects for treatment, baseline FEV_1, baseline ICS, smoking status, COPD exacerbation history, study, region and interaction term for treatment and smoking status, along with a random effect of centre nested within region. A linear mixed model was considered to analyse the change from baseline in mean daily number of puffs of rescue medication over 26 weeks, with fixed effects of treatment, smoking status at baseline, ICS use at

screening, airflow limitation severity, region, study, covariate as baseline mean number of puffs of rescue medication, interaction term between treatment and smoking status at baseline, and random effect of centre nested within region. The rate of annualised COPD exacerbations during 26 weeks of treatment was analysed using a generalised linear model assuming a negative binomial distribution. The time at risk for a patient defined as the exposure time and the log of exposure time in years was used as the offset variable in the model. The explanatory variables considered were: treatment, baseline total symptom score, baseline COPD exacerbation history (i.e. number of COPD exacerbations during the 12 months prior to study), smoking status at baseline, ICS use at screening, region and interaction term between treatment and smoking status.

Results

Patients

In total, 4617 patients (ILLUMINATE, 522; LANTERN, 741; FLAME, 3354) were included in this pooled analysis [19-21]. Of these, 1769 (38%) patients were current smokers and 2848 (62%) were ex-smokers. The majority of patients were men with mean age of ≥60 years in current smokers and ex-smokers. Detailed baseline demographics and clinical characteristics are summarised in **table 1.**

Table 1. Baseline demographics and clinical characteristics (full analysis set)

Characteristic	Current smoker (N = 1769)		Ex-smoker (N = 2848)	
	IND/GLY 110/50 µg o.d. (n = 879)	SFC 50/500 µg b.i.d. (n = 890)	IND/GLY 110/50 µg o.d. (n = 1427)	SFC 50/500 µg b.i.d. (n = 1421)
Age, years	62.1 ± 7.51	62.0 ± 7.07	66.0 ± 7.80	66.0 ± 7.76
Men, n (%)	643 (73.2)	638 (71.7)	1175 (82.3)	1136 (79.9)
BMI, kg/m^2	25.0 ± 5.00	25.1 ± 5.24	26.0 ± 5.07	26.1 ± 4.95
Estimated number of pack-years	43.0 ± 18.51	44.4 ± 21.88	39.6 ± 22.58	39.3 ± 22.00
Duration of COPD, years	6.0 ± 4.75	6.3 ± 5.13	7.2 ± 5.54	7.4 ± 5.60
Blood eosinophil count at baseline (cells/µL)	205.4 ± 141.32	205.9 ± 160.36	209.5 ± 156.47	207.1 ± 166.62
Severity of airflow limitation (GOLD 2019 [25]), n (%)				
Mild (GOLD 1)	2 (0.2)	1 (0.1)	-	-
Moderate (GOLD 2)	386 (43.8)	397 (44.6)	573 (40.2)	573 (40.3)
Severe (GOLD 3)	437 (49.6)	442 (49.6)	761 (53.3)	758 (53.3)
Very severe (GOLD 4)	47 (5.3)	44 (4.9)	85 (6.0)	80 (5.6)
Missing	9 (1.0)	7 (0.8)	8 (0.6)	11 (0.8)
Treatments at baseline*, n (%)				
LABA	430 (48.8)	453 (50.8)	698 (48.9)	674 (47.5)
LAMA	393 (44.6)	415 (46.6)	613 (43.0)	612 (43.0)

ICS	442 (50.2)	448 (50.3)	826 (57.9)	802 (56.4)
LABA/ICS	283 (32.1)	295 (33.1)	501 (35.1)	483 (34.0)
COPD exacerbation history, n (%)				
0	209 (23.7)	200 (22.4)	361 (25.3)	340 (23.9)
1	549 (62.3)	570 (64.0)	863 (60.5)	878 (61.7)
≥2	123 (14.0)	120 (13.5)	203 (14.2)	204 (14.3)

Data are presented as mean ± SD unless otherwise specified.
*Patients might be on more than one COPD therapy at baseline
b.i.d., twice daily; BMI, body mass index; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Obstructive Lung Disease; ICS, inhaled corticosteroid; IND/GLY, indacaterol/glycopyrronium; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; o.d., once daily; SFC, salmeterol/fluticasone

Lung function

At Week 26, IND/GLY 110/50 µg o.d. showed greater improvement in pre-dose trough FEV_1 versus SFC 50/500 µg b.i.d. in both current and ex-smokers (least squares mean treatment difference [Δ], 105 and 78 mL, respectively; figure 1). In current smokers, improvement in trough FEV_1 exceeded the MCID of ≥100 mL with IND/GLY 110/50 µg o.d. versus SFC 50/500 µg b.i.d.

Dyspnoea and health status

Both IND/GLY 110/50 µg o.d. and SFC 50/500 µg b.i.d. demonstrated improvement in TDI focal score from baseline after 26 weeks of treatment. In the current smokers, the improvement in TDI focal score was greater with IND/GLY 110/50 µg o.d. compared with SFC 50/500 µg b.i.d., with a difference of 0.85 points at Week 26, in comparison with the ex-smokers, where the difference was merely 0.29 points (figure 2).

In current smokers and ex-smokers, improvement in health status (as evident from reduction in the SGRQ total score) was found to be greater with IND/GLY 110/50 µg

o.d. compared with SFC 50/500 µg b.i.d. at Week 26, with a more pronounced difference in current smokers (figure 3).

Rescue medication use

In current smokers and ex-smokers, daily rescue medication use over 26 weeks of treatment was reduced with IND/GLY 110/50 µg o.d. compared with SFC 50/500 µg b.i.d.; with greater reduction in use of rescue medication observed in current smokers (figure 4).

Responder analysis

Regardless of smoking status, the proportion of patients achieving MCID of ≥100 mL improvement in trough FEV_1 was higher with IND/GLY 110/50 µg o.d. than SFC 50/500 µg b.i.d. at Week 26 (figure 5). The percentage of patients achieving MCID in trough FEV_1 with IND/GLY 110/50 µg o.d. was slightly higher among smokers than ex-smokers. In current smokers, the proportion of patients achieving clinically meaningful improvement in TDI focal score (MCID of ≥1 point) was numerically greater with IND/GLY 110/50 µg o.d. compared with SFC 50/500 µg b.i.d. at Week 26, while it did not differ between the two treatments in ex-smokers (figure 5). The proportion of patients with a ≥4-unit reduction in the SGRQ total score (MCID) at Week 26, was higher with IND/GLY 110/50 µg o.d. than SFC 50/500 µg b.i.d., regardless of the smoking status (figure 5).

Exacerbations

In both current and ex-smokers, IND/GLY 110/50 µg o.d. reduced all types of exacerbation events (all [mild/moderate/severe], moderate/severe or severe) compared with SFC 50/500 µg b.i.d. at Week 26 (figure 6). In current smokers, exacerbation

prevention was more pronounced for all (mild/moderate/severe) exacerbations and for severe exacerbations.

Discussion

This *post-hoc* analysis of pooled data from ILLUMINATE, LANTERN and FLAME [19-21] studies compared the efficacy of IND/GLY (LABA/LAMA) versus SFC (LABA/ICS) in current and ex-smokers. To the best of our knowledge, this is the first pooled analysis to evaluate efficacy of a LABA/LAMA versus LABA/ICS in patients stratified based on their smoking status.

In both current and ex-smokers, IND/GLY improved lung function, dyspnoea, and health-related quality of life, and reduced rescue medication use and exacerbations versus SFC. However, a more pronounced efficacy was observed in current versus ex-smokers, suggesting a potential reduced efficacy of ICS in COPD patients who continue to smoke. The improvement in efficacy outcomes with IND/GLY versus SFC observed in this analysis are in line with the results observed in the overall population in the above three studies from the IGNITE trial programme [19-21].

Studies in patients with asthma have shown reduced efficacy of ICS in improving lung function and reduced anti-inflammatory effects in smokers [16,17]. However, limited data are available on the efficacy of ICS-containing regimens in patients with COPD who continue smoking compared with ex-smokers, and studies have shown varied results. Results from this *post-hoc* analysis showed that efficacy of SFC was impaired in smokers compared with ex-smokers for lung function, dyspnoea, health-related quality of life, rescue medication use and exacerbations; however, no direct comparison was made between smokers and ex-smokers within the treatment arms. These results show reduced efficacy with ICS in patients with COPD who continue smoking.

A systematic review of studies in patients with COPD revealed reduced efficacy with ICS in terms of lung function and exacerbation rates in current or heavy smokers compared with lighter or ex-smokers [26]. Consistent with our analysis, a *post-hoc* analysis of the SUMMIT trial showed reduced efficacy in current smokers versus former smokers with ICS/LABA (fluticasone furoate/vilanterol [FF/VI]) versus VI in trough FEV_1 [18]. Improvement in SGRQ score was similar with FF/VI versus placebo, irrespective of smoking status.

In the IMPACT study, the percentage reduction in the rate of moderate/severe exacerbation was greater with FF/umeclidinium (UMEC)/VI (an ICS/LABA/LAMA) versus UMEC/VI (a LABA/LAMA) in former smokers (30%), compared with current smokers (14%), suggesting a potentially lower efficacy from the addition of ICS on top of a LABA/LAMA in current smokers [27]. Further, in the SUNSET study, which assessed the direct switch from tiotropium (TIO) plus SFC to IND/GLY, the difference in mean change from baseline in post-dose trough FEV_1 with IND/GLY versus TIO+SFC was −0.048 L in ex-smokers and 0.001 L in current smokers, implying lower efficacy with ICS-containing regimen in current smokers compared with ex-smokers in improving trough FEV_1 [28]. An exception to the described trend is the results from the TRIBUTE study, showing a greater reduction in moderate-to-severe exacerbation with triple therapy versus IND/GLY in current smokers compared with ex-smokers (adjusted rate ratio [RR], 0.778 vs 0.895, respectively) [29]. Lower exacerbation rates in current smokers and ex-smokers and small sample size included in that analysis should be considered while comparing our findings to the results from TRIBUTE study. Except for

the TRIBUTE study, all the above-discussed studies indicate reduced efficacy with ICS in COPD patients who continue smoking, and our data further support this observation. Smoking cessation remains key for management of COPD [6]. Smoking cessation has been shown to reduce lung function decline and mortality in patients with COPD, and must always be encouraged in patients with COPD who continue smoking. However, smoking cessation rates are low and many patients continue to smoke [30,31], and are treated by pharmacotherapy. The current analysis has certain strengths and limitations. It should be noted that this analysis was performed in a large pool of smokers and ex-smokers (N = 4617), with a wide range of COPD severity and a relatively balanced proportion of current and ex-smokers (38% versus 62%, respectively). The *post-hoc* analysis demonstrated efficacy of IND/GLY versus SFC for all the major clinical outcomes of COPD.

A limitation of this evaluation was that this *post-hoc* analysis was not powered for comparison between the treatment groups; prospective studies for efficacy of ICS on top of effective LABDs (preferably LABA/LAMA) in current and ex-smokers are required to validate these outcomes.

Conclusions

In this *post-hoc* pooled analysis, IND/GLY demonstrated greater efficacy versus SFC in terms of lung function, health-related quality of life, dyspnoea, rescue medication use and exacerbation prevention in both current and ex-smokers, with a more pronounced difference in certain parameters in current smokers. This analysis supports the use of LABA/LAMA as a preferred treatment option for the majority of patients with COPD, in both current and ex-smokers, and highlights the importance of selecting appropriate

pharmacotherapy in patients with COPD who continue to smoke. The efficacy of ICS in individuals with COPD who continue to smoke needs to be further elucidated in properly designed prospective trials. Smoking cessation remains fundamentally important in the management of COPD patients.

Acknowledgements

Under the direction of authors, Vatsal Vithlani and Hasitha Shilpa Anantaraju (professional medical writers; Novartis) assisted in the preparation of this article in accordance with the third edition of Good Publication Practice guidelines. Medical writing support was funded by study sponsor. A part of this analysis was presented in the European Respiratory Society annual congress in 2018 (Paris, 15–19 September 2018).

Funding:

The studies were funded by Novartis Pharma AG, Basel, Switzerland

Data Sharing Statement

Novartis is committed to sharing access to patient-level data and supporting documents from eligible studies with qualified external researchers. These requests are reviewed and approved by an independent review panel on the basis of scientific merit. All data provided are anonymized to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations.

Conflict of Interest:

D.M.G. Halpin reports personal fees from AstraZeneca, Chiesi, CSL Behring, GlaxoSmithKline, Pfizer, and Sanofi; personal fees and non-financial support from Boehringer Ingelheim and Novartis outside the submitted work. C. Vogelmeier reports

grants and personal fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Grifols, Mundipharma and Novartis; personal fees from Cipla, Berlin Chemie/Menarini, CSL Behring and Teva; grants from German Federal Ministry of Education and Research (BMBF) Competence Network Asthma and COPD (ASCONET), Bayer Schering Pharma AG, MSD and Pfizer, outside the submitted work. K. Mezzi and P. Gupta are employees of Novartis. K. Kostikas reports grants and personal fees from AstraZeneca, Boehringer Ingelheim, Chiesi, ELPEN, Innovis, Novartis, Menarini and GlaxoSmithKline, outside the submitted work; and was an employee of Novartis Pharma AG, Basel during the conduct of this study. J.A. Wedzicha reports grants from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Johnson and Johnson, and Novartis, other from AstraZeneca, Boehringer Ingelheim and GlaxoSmithKline, outside the submitted work.

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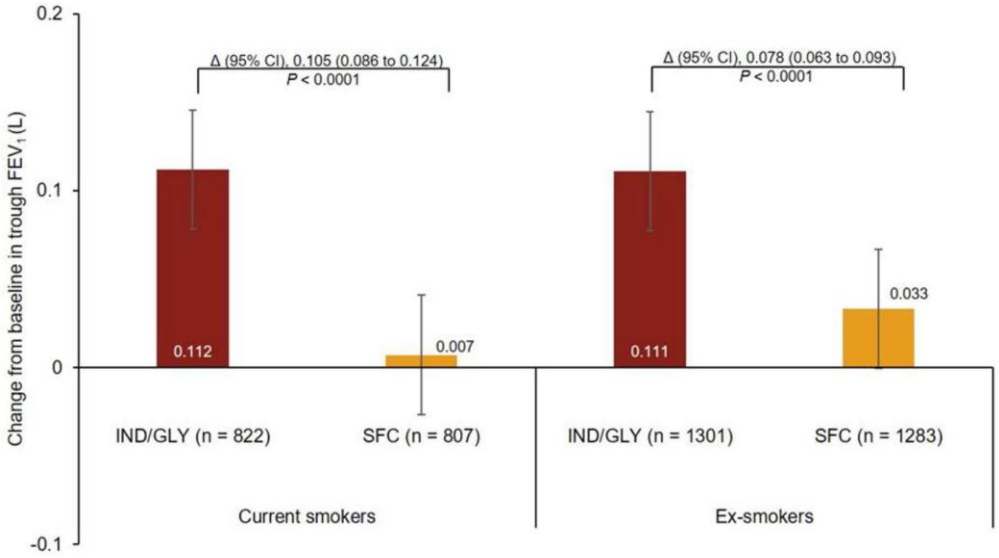

Figure 1. Treatment difference with IND/GLY versus SFC in current and ex-smokers for pre-dose trough FEV1 after 26 weeks of treatment (full analysis set). n, number of patients in each group. Data are presented as LSM ± SE. Error bars represent SE values. Δ, least squares mean treatment difference; b.i.d., twice daily; FEV1, forced expiratory volume in one second; IND/GLY, indacaterol/glycopyrronium 110/50 µg o.d.; o.d., once daily; SFC, salmeterol/fluticasone 50/500 µg b.i.d.

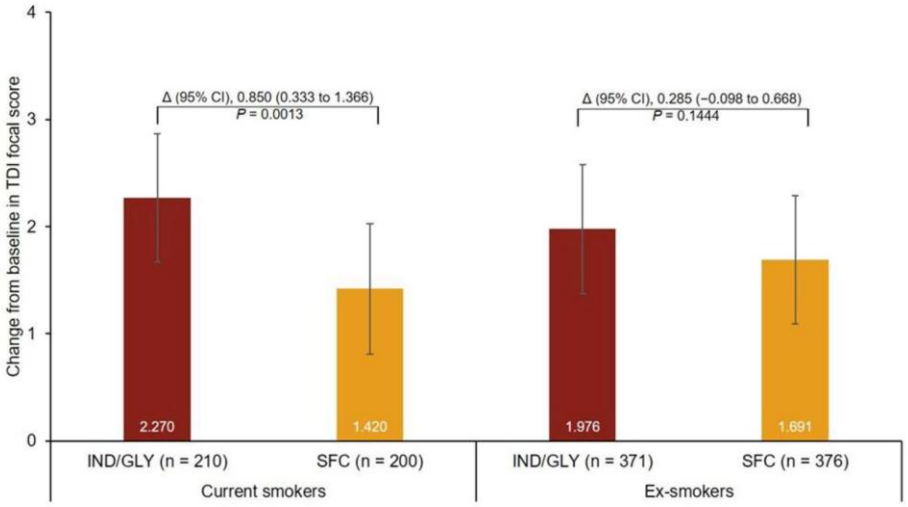

Figure 2. Treatment difference with IND/GLY versus SFC in current and ex-smokers for TDI focal score after 26 weeks of treatment (full analysis set). n, number of patients in each group. Data are presented as LSM ± SE. Error bars represent SE values. Δ, least squares mean treatment difference; b.i.d., twice daily; IND/GLY, indacaterol/glycopyrronium 110/50 µg o.d.; o.d., once daily; SFC, salmeterol/fluticasone 50/500 µg b.i.d.; TDI, transition dyspnoea index.

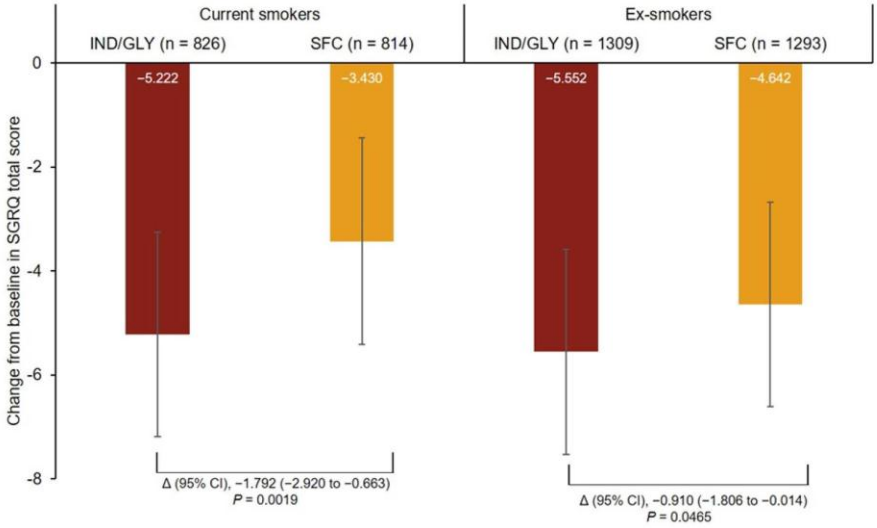

Figure 3. Treatment difference with IND/GLY versus SFC in current and ex-smokers for SGRQ total score after 26 weeks of treatment (full analysis set). n, number of patients in each group. Data are presented as LSM ± SE. Error bars represent SE values. Δ, least squares mean treatment difference; b.i.d., twice daily; IND/GLY, indacaterol/glycopyrronium 110/50 µg o.d.; o.d., once daily; SFC, salmeterol/fluticasone 50/500 µg b.i.d.; SGRQ, St George's Respiratory Questionnaire

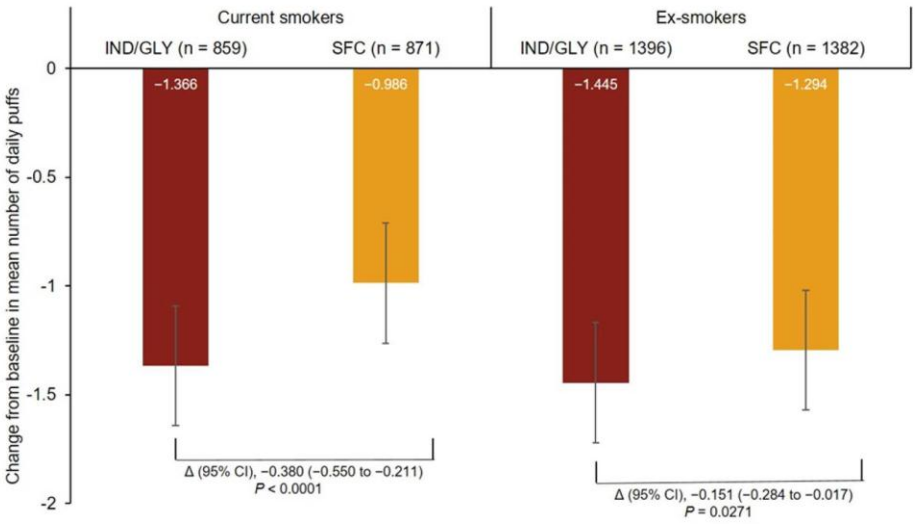

Figure 4. Treatment difference with IND/GLY versus SFC in current and ex-smokers in rescue medication use after 26 weeks of treatment (full analysis set). n, number of patients in each group. Data are presented as LSM ± SE. Error bars represent SE values. Δ, least squares mean treatment difference; b.i.d., twice daily; IND/GLY, indacaterol/glycopyrronium 110/50 µg o.d.; o.d., once daily; SFC, salmeterol/fluticasone 50/500 µg b.i.d.

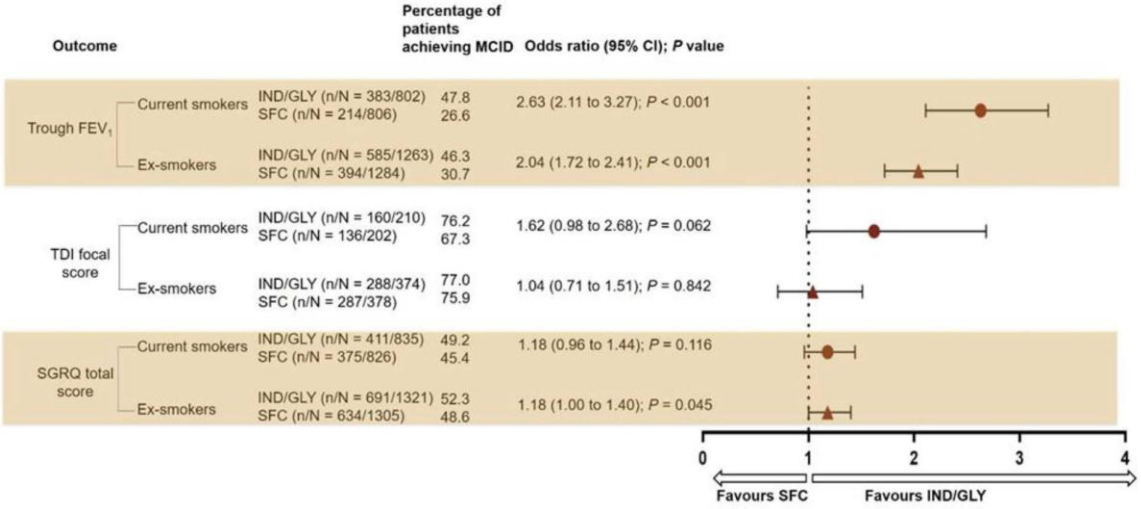

Figure 5. Proportion of patients achieving MCID for trough FEV1, SGRQ total score and TDI focal score with IND/GLY and SFC after 26 weeks (full analysis set). n, number of patients who achieved a clinically important improvement from baseline. N, number of patients included in analysis. b.i.d., twice daily; FEV1, forced expiratory volume in one second; IND/GLY, indacaterol/glycopyrronium 110/50 µg o.d.; MCID, minimal clinically important differences; o.d., once daily; SFC, salmeterol/fluticasone 50/500 µg b.i.d.; SGRQ, St George's Respiratory Questionnaire; TDI, transition dyspnoea index

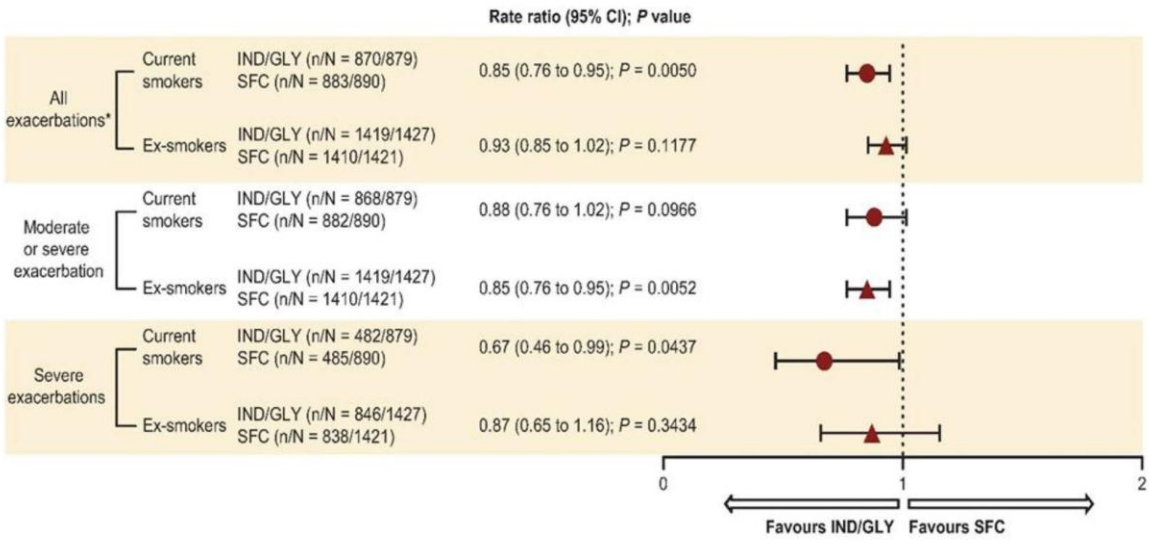

Figure 6. Annualised rate of all (mild/moderate/severe), moderate/severe and severe exacerbations after 26 weeks by baseline smoking status (full analysis set). *All exacerbation include mild/moderate/severe exacerbations. n, number of patients included in the analysis; N, number of patients in the full analysis set. b.i.d., twice daily; IND/GLY, indacaterol/glycopyrronium 110/50 µg o.d.; o.d., once daily; SFC, salmeterol/fluticasone 50/500 µg b.i.d.

Efficacy of indacaterol/glycopyrronium versus salmeterol/fluticasone in current and ex-smokers: a pooled analysis of IGNITE trials

David M.G. Halpin[1], Claus F. Vogelmeier[2], Karen Mezzi[3], Pritam Gupta[4], Konstantinos Kostikas[5], Jadwiga A. Wedzicha[6]

[1]University of Exeter Medical School, College of Medicine and Health, University of Exeter, Exeter, United Kingdom; [2]University Medical Centre Giessen and Marburg, Member of the German Centre for Lung Research (DZL), Marburg, Germany; [3]Novartis Pharma AG, Basel, Switzerland; [4]Novartis Healthcare Pvt. Ltd., Hyderabad, India; [5]Respiratory Medicine Department, University of Ioannina, Greece; [6]National Heart and Lung Institute, Imperial College London, London, United Kingdom

Corresponding author

Prof. David MG Halpin

Consultant Physician & Honorary Professor

University of Exeter Medical School

College of Medicine and Health

University of Exeter

Exeter, UK

Tel +44 (0)1392 402133

Fax +44(0)1392 402828

SUPPLEMENTARY FILE

Table S1. Key inclusion criteria and key exclusion criteria of patients included in the analysis

ILLUMINATE study	LANTERN study	FLAME study
Key inclusion criteria:		
Men and women aged ≥40 years	Men and women aged ≥40 years	Men and women aged ≥40 years
Smoking history of at least 10 pack-years	Smoking history of at least 10 pack-years	Smoking history of at least 10 pack-years
Post-bronchodilator FEV_1 between ≥40% and <80% of predicted normal	Post-bronchodilator FEV_1 between ≥30% and <80% of predicted normal	Post-bronchodilator FEV_1 between ≥25% and <60% of predicted normal
Post-bronchodilator FEV_1/FVC ratio <0.70	Post-bronchodilator FEV_1/FVC ratio <0.70	Post-bronchodilator FEV_1/FVC ratio <0.70
Symptomatic patients, according to daily electronic diary data, with a total score ≥1 on at least 4 of the last 7 days during run-in period	mMRC grade ≥2 at screening	mMRC grade ≥2 at screening
		History of ≥1 COPD exacerbation in the previous year that required treatment with SCS and/or

	antibiotics
Key exclusion criteria:	
ILLUMINATE and LANTERN study	FLAME study
A history of a COPD exacerbation needing treatment with antibiotics, SCS, or hospitalisation in the year prior to screening Any history of asthma Blood eosinophil count >600/mm^3 at the start of run-in period	COPD exacerbation that required treatment with antibiotics and/or SCS and/or hospitalisation in the 6 weeks prior to screening Any history of asthma Blood eosinophil count >600/mm^3 at the start of run-in period
COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global Initiative for Obstructive Lung Disease; mMRC, modified Medical Research Council; SCS, systemic corticosteroid	