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ORIGINAL ARTICLE

Indacaterol/glycopyrronium versus tiotropium or glycopyrronium in long-acting bronchodilator-naïve COPD patients: A pooled analysis

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ABSTRACT

Background and objective: **Indacaterol/glycopyrronium (IND/GLY) 110/50 µg once daily (q.d.) has demonstrated greater improvements in lung function, patient-reported outcomes and lower exacerbation rates versus mono long-acting muscarinic antagonists (LAMA) in chronic obstructive pulmonary disease (COPD) patients. However, data are limited on initial treatment with IND/GLY 110/50 µg q.d. versus mono LAMA in COPD patients, not previously on maintenance treatment with long-acting bronchodilators (LABD).**

Methods: **A pooled analysis of ARISE, SHINE and SPARK trials was conducted to evaluate the efficacy of IND/GLY 110/50 µg q.d. versus open-label (OL) tiotropium (TIO) 18 µg q.d. and GLY 50 µg q.d. in COPD patients, not on maintenance treatment with LABD at study entry (LABD-naïve). Efficacy was assessed after 24/26 weeks of treatment.**

Results: **In total, 998 LABD-naïve patients were included (IND/GLY: 353; OL TIO: 328; GLY: 317). Patients treated with IND/GLY 110/50 µg q.d. experienced greater improvements in trough forced expiratory volume in 1 s (FEV_1) versus OL TIO 18 µg q.d. (least squares mean treatment difference (Δ): 0.086 L) and GLY 50 µg q.d. (Δ: 0.080 L) after 24/26 weeks. Improvements in electronic diary (eDiary) symptom scores, transition dyspnoea index (TDI) focal score, St George's Respiratory Questionnaire (SGRQ) total score and rescue medication use were also greater with IND/GLY versus OL TIO and GLY. Greater proportion of patients achieved minimal clinically important difference in trough FEV_1, TDI and SGRQ with IND/GLY versus OL TIO and GLY.**

Conclusion: **LABD-naïve patients treated with IND/GLY 110/50 µg q.d. achieved improvements in lung function, daily symptoms, dyspnoea, health-related quality of life and rescue medication use versus those who received single LAMA.**

SUMMARY AT A GLANCE

Data are limited on initial treatment with indacaterol/glycopyrronium (IND/GLY) versus mono long-acting muscarinic antagonist (LAMA) in long-acting bronchodilator (LABD)-naïve chronic obstructive pulmonary disease (COPD) patients. This pooled analysis of ARISE, SHINE and SPARK trials demonstrated improvements with IND/GLY in lung function, daily symptoms, dyspnoea, health-related quality of life and rescue medication use versus tiotropium or GLY in LABD-naïve COPD patients.

Key words: bronchodilator-naïve, chronic obstructive pulmonary disease, glycopyrronium, indacaterol–glycopyrronium combination, tiotropium.

INTRODUCTION

Inhaled bronchodilators provide improvements in lung function, reduce symptoms and exacerbations and are therefore the mainstay of pharmacological management of chronic obstructive pulmonary disease (COPD).[1,2] The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2019 recommends initial treatment with a single bronchodilator—long-acting β_2-agonist (LABA) or long-acting muscarinic antagonist (LAMA) for GOLD group B and LAMA for group C patients.[2] However, many COPD patients receiving long-acting bronchodilator (LABD) monotherapy continue to experience significant symptoms and poor quality of life, and therefore a dual bronchodilator therapy (LABA/LAMA) is recommended for follow-up treatment in these patients.[2]

Treatment with LABA/LAMA is recommended based on its superior results versus standard of care therapy

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with LAMA monotherapy or LABA/inhaled corticosteroid (ICS), and lower risk of development of pneumonia versus ICS-containing treatment.[3–5] Dual bronchodilator therapy with fixed-dose LABA/LAMA has demonstrated improvements in lung function and health-related quality of life, and has reduced the usage of rescue medication in patients with prior maintenance therapy with a single bronchodilator.[6,7]

Once-daily (q.d.) indacaterol/glycopyrronium (IND/GLY) is a fixed-dose combination (FDC) of a LABA, IND 110 μg and a LAMA, GLY 50 μg, approved in over 90 countries (excluding the United States) for the maintenance treatment of patients with COPD.[8] IND/GLY 110/50 μg q.d. has demonstrated greater improvements in lung function, exacerbations and patient-reported outcomes (PRO) versus tiotropium (TIO) 18 μg q.d. (open-labelled in many trials) and GLY 50 μg q.d. in the Indacaterol and GlycopyrroNium bromide clInical sTudiEs (IGNITE) trial programme.[9] TIO 18 μg q.d. and GLY 50 μg q.d. are well-established LAMA in the management of COPD[10] and have demonstrated improvements in lung function, exacerbations, breathlessness, exercise capacity and PRO versus placebo, LABA and LAMA in clinical trials.[11–19]

Limited data are available on initial treatment with LABA/LAMA versus single LAMA in COPD patients, who were not previously on maintenance treatment with a LABD. The objective of this post hoc pooled analysis of the ARISE, SHINE and SPARK trials is to evaluate the efficacy of IND/GLY 110/50 μg q.d. versus open-label (OL) TIO 18 μg q.d. and GLY 50 μg q.d. in COPD patients who were not on maintenance treatment with a LABD at study entry (LABD-naïve).

METHODS

Study design

This is a pooled post hoc analysis of data from the ARISE (NCT01285492), SHINE (NCT01202188) and SPARK (NCT01120691) studies. ARISE[20] was a 52-week, multicentre, OL, parallel-group, active-controlled study that randomized (3:1) Japanese patients to either IND/GLY 110/50 μg q.d. or OL TIO 18 μg q.d. SHINE[3] was a 26-week, multicentre, double-blind, parallel-group, placebo- and active-controlled study that randomized (2:2:2:2:1) patients to either IND/GLY 110/50 μg q.d., IND 150 μg q.d., GLY 50 μg q.d., OL TIO 18 μg q.d. or placebo. SPARK[4] was a 64-week, multicentre, double-blind, parallel-group study that randomized (1:1:1) patients to either IND/GLY 110/50 μg q.d., GLY 50 μg q.d. or OL TIO 18 μg q.d. IND/GLY 110/50 μg q.d., IND 150 μg q.d. and GLY 50 μg q.d. were delivered via the Breezhaler device (Novartis, Basel, Switzerland) and OL TIO 18 μg q.d. was delivered via the HandiHaler device in the above-mentioned studies.

Patients with moderate-to-severe COPD were enrolled in SHINE and ARISE studies, and severe-to-very severe COPD patients were enrolled in the SPARK study. Patients treated with ICS at baseline continued its use when LABA/LAMA or LAMA treatment was started. Considering the different durations of these studies, this pooled analysis was performed after 24/26 weeks of treatment.

All the 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 inclusion in the studies.

Patients

The analysis included LABD-naïve patients, that is those patients who were not on maintenance treatment with a LABD (LABA, LAMA, LABA/ICS or LABA/ICS + LAMA) at baseline/study entry. Key eligibility criteria are tabulated in Table 1A,B. Detailed study methodology and patient criteria were reported previously.[3,4,20]

Assessments

This pooled analysis compared the efficacy of IND/GLY 110/50 μg q.d. versus OL TIO 18 μg q.d. and GLY 50 μg q.d. in LABD-naïve patients using the efficacy endpoints that were common to all the studies except for electronic diary (eDiary) total symptom score, which was not evaluated in the ARISE study.

Improvement in trough forced expiratory volume in 1 s (FEV_1) and proportion of patients achieving clinically meaningful improvement of ≥100-mL[22] increase in trough FEV_1 were evaluated after 24–26 weeks of treatment. Change in daily total symptom scores were collected through eDiary[23] at Week 24/26. Treatment effect on breathlessness was evaluated by change from baseline at Week 24/26 in transition dyspnoea index (TDI) focal score[24] and proportion of patients achieving minimal clinically important difference (MCID) of ≥1-point improvement in the score. Improvement in health status was assessed by change from baseline in St George's Respiratory Questionnaire (SGRQ) total score and proportion of patients achieving MCID of ≥4-unit reduction in the score[25] at Week 24/26. Change from baseline in rescue medication use (number of puffs per day) was evaluated during 24/26 week of treatment. Exacerbations were evaluated only in the SPARK study, and were not assessed in this pooled analysis. Assessments were performed at Week 26 in ARISE and SHINE studies, and at Week 24 in the SPARK study.[3,4,20]

Statistical analysis

All analyses were performed in the full analysis set, which consisted of all randomized patients who received at least one dose of medication. Patients included in this analysis were not on maintenance treatment with a LABD (LABA, LAMA, LABA/ICS or LABA/ICS + LAMA) at baseline/study entry. Responder analyses were performed using the logistic regression models, and treatment differences were evaluated using appropriate analysis of covariance (ANCOVA) model. Both the logistic regression and ANCOVA model included fixed effects of treatment, baseline covariates as appropriate (FEV_1, FEV_1 reversibility components for analyses related to FEV_1; SGRQ total score for SGRQ; TDI focal score for TDI; daily total symptom

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Table 1 (A) Key inclusion criteria. (B) Key exclusion criteria

(A)	
ARISE and SHINE studies	SPARK study
Men and women aged ≥40 years with moderate-to-severe COPD according to the GOLD 2008[21] criteria	Men and women aged ≥40 years with severe-to-very severe COPD according to the GOLD 2008[21] criteria
Post-bronchodilator FEV_1 with ≥30% and <80% of predicted normal	Post-bronchodilator FEV_1 with <50% of predicted normal
Post-bronchodilator FEV_1/FVC < 0.70	Post-bronchodilator FEV_1/FVC < 0.70
Smoking history of ≥10 pack-years	Smoking history of ≥10 pack-years
	History of ≥1 COPD exacerbation in the previous year that required treatment with systemic corticosteroids and/or antibiotics
(B)	
ARISE, SHINE and SPARK studies	
COPD exacerbation that required treatment with antibiotics and/or systemic corticosteroids and/or hospitalization in the 6 weeks prior to screening	
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 s; forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

score for symptoms and average number of puffs for rescue medication), baseline ICS use, baseline smoking status, country and the study. The centre was considered as a random effect nested within country.

RESULTS

Study population

In total, 998 LABD-naïve patients (IND/GLY: 353; OL TIO: 328; GLY: 317) were included in this pooled analysis. Baseline demographics and clinical characteristics were comparable between the treatment groups (Table 2). Most patients were men and more than half of the patients experienced severe airflow limitation.

Lung function

IND/GLY 110/50 μg q.d., OL TIO 18 μg q.d. and GLY 50 μg q.d. showed clinically relevant improvement in trough FEV_1 of >100 mL from baseline (0.194, 0.108 and 0.114 L, respectively). Greater improvements in

Table 2 Baseline demographics and clinical characteristics (full analysis set)

Characteristic	IND/GLY 110/50 μg q.d. (*n* = 353)	OL TIO 18 μg q.d. (*n* = 328)	GLY 50 μg q.d. (*n* = 317)
Age (years)	63.4 ± 9.33	63.0 ± 8.95	62.1 ± 9.42
Men, *n* (%)	283 (80.2)	263 (80.2)	239 (75.4)
BMI (kg/m^2)	24.6 ± 5.19	25.0 ± 5.72	25.3 ± 5.95
Current smoker, *n* (%)	145 (41.1)	135 (41.2)	139 (43.8)
Estimated number of pack-years	43.9 ± 25.99	43.5 ± 26.10	42.7 ± 23.66
Duration of COPD (years)	5.8 ± 5.97	6.4 ± 5.56	6.0 ± 5.29
Severity of airflow limitation[†], *n* (%)			
Mild (GOLD 1)	0	0	2 (0.6)
Moderate (GOLD 2)	132 (37.4)	116 (35.4)	121 (38.2)
Severe (GOLD 3)	196 (55.5)	175 (53.4)	162 (51.1)
Very severe (GOLD 4)	25 (7.1)	37 (11.3)	32 (10.1)
ICS users at baseline, *n* (%)	135 (38.2)	132 (40.2)	141 (44.5)
COPD exacerbation(s) in the previous year, *n* (%)			
0	168 (47.6)	152 (46.3)	152 (47.9)
1	151 (42.8)	142 (43.3)	138 (43.5)
≥2	34 (9.6)	34 (10.4)	27 (8.5)

Data are presented as mean ± SD unless otherwise specified.

[†]Defined according to GOLD 2008.

BMI, body mass index; COPD, chronic obstructive pulmonary disease; GLY, glycopyrronium; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroid; IND, indacaterol; OL, open-label; q.d., once daily; TIO, tiotropium.

trough FEV_1 were seen with IND/GLY 110/50 μg q.d. versus OL TIO 18 μg q.d. and GLY 50 μg q.d. after 24/26 weeks of treatment (Fig. 1).

Daily total symptom score and dyspnoea

Improvements in daily total symptom score after 24/26 weeks of treatment were greater with IND/GLY 110/50 μg q.d. compared with OL TIO 18 μg q.d. and GLY 50 μg q.d. (Fig. 2A).

All the evaluated treatments improved dyspnoea, as is evident from clinically relevant improvement in TDI focal score from baseline. Improvements in TDI focal score after 24/26 weeks of treatment were numerically greater with IND/GLY 110/50 μg q.d. compared with TIO 18 μg q.d. and GLY 50 μg q.d. (Fig. 2B).

Health status and rescue medication use

After 24/26 weeks of treatment, clinically relevant improvements from baseline in health status (reduction in the SGRQ total score) were observed with IND/GLY 110/50 μg q.d., OL TIO 18 μg q.d. and GLY 50 μg q.d. Improvement in health status was found to be numerically greater with IND/GLY 110/50 μg q.d. compared with OL TIO 18 μg q.d. and GLY 50 μg q.d. (Fig. 3A).

IND/GLY 110/50 μg q.d. reduced daily rescue medication use during 24/26 weeks of treatment versus OL TIO 18 μg q.d. and GLY 50 μg q.d. (Fig. 3B).

Responder analysis

The proportion of patients achieving MCID of ≥100 mL improvement in trough FEV_1 was greater with IND/GLY 110/50 μg q.d. than OL TIO 18 μg q.d. and GLY 50 μg q.d. after 24/26 weeks of treatment. At Week 24/26, there was a numerical difference between proportion of patients achieving a ≥4-unit reduction in the SGRQ total score (MCID) IND/GLY 110/50 μg q.d. versus OL TIO 18 μg q.d. and GLY 50 μg q.d. Furthermore, a numerical difference was also observed in the proportion of patients who achieved clinically meaningful improvement in TDI focal score with IND/GLY 110/50 μg q.d. compared with OL TIO 18 μg q.d. and GLY 50 μg q.d. (Fig. 4).

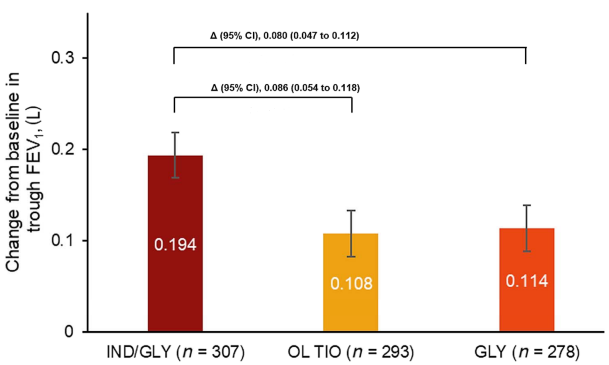

Figure 1 Treatment difference with IND/GLY versus OL TIO and GLY for trough FEV_1 after 24/26 weeks of treatment (full analysis set). Data are presented as LSM ± SE. Error bars represent SE values. Δ, LSM treatment difference; FEV_1, forced expiratory volume in 1 s; GLY, glycopyrronium 50 μg q.d.; IND, indacaterol 110 μg q.d.; LSM, least squares mean; OL, open-label; q.d., once daily; TIO, tiotropium 18 μg q.d.

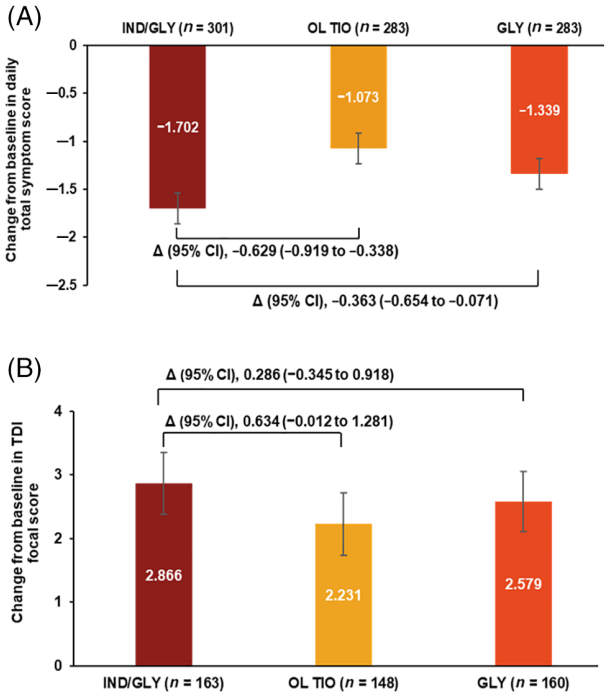

Figure 2 Treatment difference with IND/GLY versus OL TIO and GLY for (A) daily total symptom score and (B) TDI focal score after 24/26 weeks of treatment (full analysis set). Daily total symptom scores were not assessed in the ARISE study. Data are presented as LSM ± SE. Error bars represent SE values. Δ, LSM treatment difference; GLY, glycopyrronium 50 μg q.d.; IND, indacaterol 110 μg q.d.; LSM, least squares mean; OL, open-label; q.d., once daily; TDI, transition dyspnoea index; TIO, tiotropium 18 μg q.d.

DISCUSSION

This post hoc analysis of pooled data from ARISE, SHINE and SPARK studies compared the efficacy of LABA/LAMA (IND/GLY) versus LAMA (TIO and GLY) in LABD-naïve COPD patients. The results of this analysis showed that dual bronchodilation with IND/GLY improved trough FEV_1 compared with LAMA monotherapies (TIO and GLY) in LABD-naïve patients. Improvement in lung function with IND/GLY was complemented by improvements in daily symptoms, dyspnoea, health-related quality of life and rescue medication use compared with TIO and GLY. Furthermore, a higher proportion of patients on IND/GLY achieved a clinically meaningful improvement in trough FEV_1 (≥100 mL), SGRQ total score (≥4 units) and TDI focal score (≥1 unit) versus TIO and GLY.

Disease severity and study duration are important considerations while interpreting results of a clinical trial in COPD patients.[26,27] Unlike exacerbations (that were not evaluated in this pooled analysis), efficacy outcomes evaluated in this pooled analysis respond

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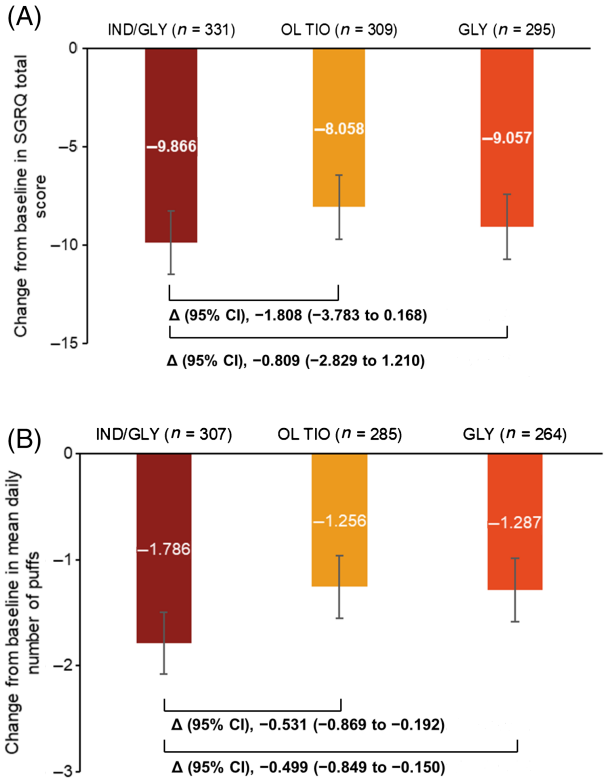

Figure 3 Treatment difference with IND/GLY versus OL TIO and GLY for (A) SGRQ total score after 24/26 weeks of treatment and (B) in rescue medication use (full analysis set). Data are presented as LSM ± SE. Error bars represent SE values. Δ, LSM treatment difference; GLY, glycopyrronium 50 μg q.d.; IND, indacaterol 110 μg q.d.; LSM, least squares mean; OL, open-label; q.d., once daily; SGRQ, St George's Respiratory Questionnaire; TIO, tiotropium 18 μg q.d.

quickly to treatment[28] and 24/26 weeks present an ideal time period for their assessment. Patients with moderate-to-severe COPD were enrolled in SHINE and ARISE trials, while patients with severe-to-very severe COPD were included in the SPARK trial. This pooled analysis included patients across the range of COPD severities who can benefit from dual LABD. It should also be noted that SPARK study enrolled patients with history of ≥1 exacerbation in the previous year.[4] The improvement in efficacy outcomes with IND/GLY versus OL TIO and GLY in LABD-naïve patients is in line with the results observed in overall population in the above-mentioned studies, and also with data from the IGNITE trial programme.[9]

Results from this pooled analysis are consistent with a post hoc analysis of two 12-week OTEMTO studies, where TIO/olodaterol (TIO/OLO) 5/5 μg q.d. demonstrated improvements in trough FEV_1, SGRQ total score and TDI versus TIO 5 μg q.d. (all treatments via the Respimat device; Boehringer Ingelheim, Ingelheim, Germany) in treatment-naïve patients. However, it should be noted that these studies were of a 12-week duration in patients with moderate-to-severe COPD,[29] while our post hoc analysis included studies of at least 26 weeks' duration, and COPD severity ranged from moderate-to-very severe. Similarly, in a post hoc analysis from TONADO studies, TIO/OLO 5/5 μg q.d. and 2.5/5 μg q.d. improved trough FEV_1 versus TIO 5 μg q.d. (all treatments via the Respimat device) in treatment-naïve patients with moderate-to-very severe COPD.[7] Other PRO, however, were not assessed in the post hoc analysis of TONADO studies. In another pooled analysis of three 24-week randomized trials, umeclidinium/vilanterol (UMEC/VI) 62.5/25 μg q.d. (via Ellipta device; GlaxoSmithKline, Middlesex, UK) provided improvement in trough FEV_1, SGRQ for

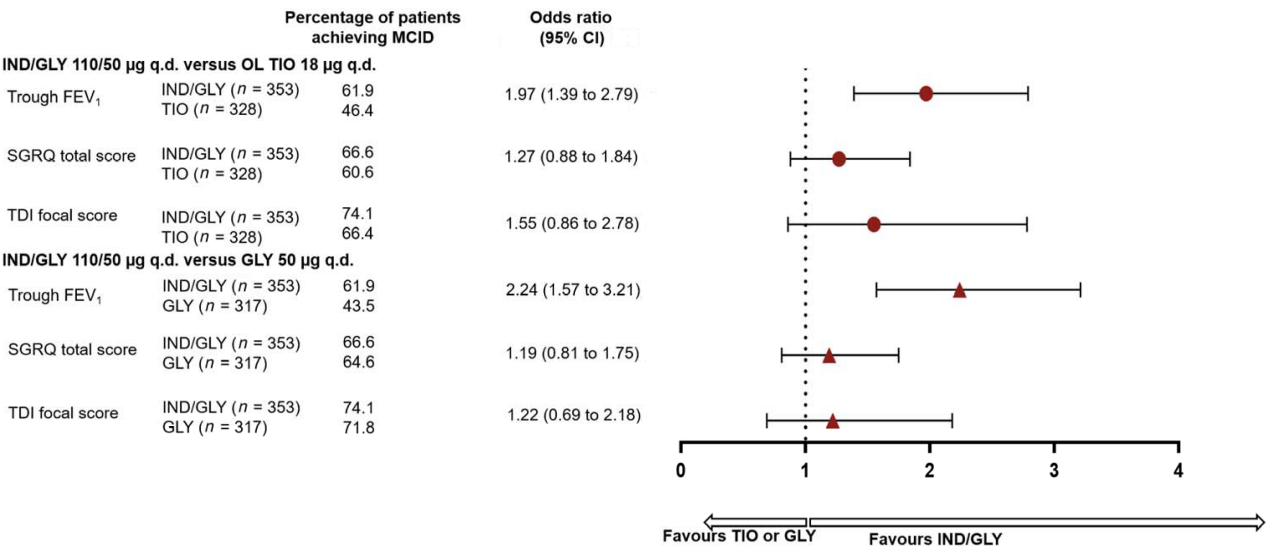

Figure 4 Proportion of patients achieving MCID for trough FEV_1, SGRQ total score and TDI focal score with IND/GLY, OL TIO and GLY at Week 24/26 (full analysis set). FEV_1, forced expiratory volume in 1 s; GLY, glycopyrronium 50 μg q.d.; IND, indacaterol 110 μg q.d.; MCID, minimal clinically important difference; OL, open-label; q.d., once daily; SGRQ, St George's Respiratory Questionnaire; TDI, transition dyspnoea index; TIO, tiotropium 18 μg q.d.

COPD (SGRQ-C) total score and rescue medication use versus TIO 18 μg q.d. (via HandiHaler device; Boehringer Ingelheim, Ingelheim, Germany) in maintenance-naïve COPD patients. TDI and symptom scores were not evaluated in this pooled analysis.[6]

A large proportion of COPD patients receive suboptimum treatment.[30,31] Previous studies have suggested that early initiation of maintenance therapy may provide long-term benefits.[32,33] An OL study in Japanese COPD patients demonstrated improvements in lung function and quality of life with guideline-based pharmacotherapy in treatment-naïve patients versus those who received prior COPD treatment.[34] This further highlights the importance of selection of initial therapy in COPD patients.

LAMA, LABA/LAMA and LABA/ICS are widely used maintenance therapies in COPD. GOLD 2019 recommends LAMA monotherapy as initial treatment in the majority of COPD patients; however, many patients remain symptomatic on monotherapy, and LABA/LAMA is recommended in these patients.[2,35,36] On the other hand, use of ICS in COPD is associated with side effects—pneumonia, diabetes, osteoporosis and mycobacterial infections.[37–40] Furthermore, as per GOLD 2019 update, initial treatment with LABA/ICS may be the first choice only for COPD patients with history of asthma or with blood eosinophil counts ≥300 cells/μL.[2] LABA/LAMA combinations, particularly IND/GLY, have shown improvements in lung function, PRO, rescue medication use and exacerbations versus monocomponents, placebo and well-established COPD treatments including LABA/ICS.[9,26] Considering the above-mentioned aspects, a rationale for dual bronchodilators as first-line maintenance therapy in COPD patients is emerging. Data from this post hoc analysis and other pooled analyses[6,7,29] further support this rationale.

Safety evaluations were not performed in this pooled analysis; however, the safety profile of all treatments is well established.[10,41] A systematic review and meta-analysis by Rodrigo *et al.* showed comparable safety profile between LABA/LAMA and LAMA.[42] In particular, IND/GLY has demonstrated comparable safety profile as its monocomponents and TIO.[41] A real-world study using the UK Clinical Practice Research Datalink database showed that adding a second LABD does not increase the risk of most cardiovascular events.[43] To the best of our knowledge, no clinical trials have evaluated safety of adding a second LABD to existing one in patients with COPD.

The current analysis has certain strengths and limitations. The most important strength is that we compared the efficacy of dual bronchodilation with IND/GLY 110/50 μg q.d. versus mono LAMA in a relatively large population, with a wide range of COPD severity, to answer a clinically relevant question. Also, the post hoc analysis demonstrated greater improvements with IND/GLY 110/50 μg q.d. versus OL TIO 18 μg q.d. and GLY 50 μg q.d., whereas previous similar analyses have considered only TIO as comparator.

The limitation of this evaluation was that this was a post hoc analysis and was not powered for comparison between the treatment groups. Due to its post hoc nature, the authors do not claim statistical significance between treatments groups for any of the parameters described in this analysis. Prospective studies in LABD-naïve patients are required to validate these outcomes. Exacerbations were evaluated only in the SPARK study, and therefore these were not assessed in this pooled analysis. Comparison with TIO was open-labelled in all the studies included in this pooled analysis. Lastly, this analysis was done by pooling data from three studies and then selecting those patients who were not on maintenance treatment with a LABD at baseline/study entry. This led to an unbalanced distribution of LABD-naïve patients across studies, which can be expected from such post hoc analyses.

In conclusion, this post hoc analysis has shown that in COPD patients who were not receiving LABD at study entry, the introduction of IND/GLY 110/50 μg q.d. provided improvements in lung function, daily symptoms, dyspnoea, health-related quality of life and rescue medication use compared with LAMA monotherapy. Given the safety of LABA/LAMA combinations such as IND/GLY, the results of the current analysis suggest that initial therapy with two bronchodilators may be considered in LABD-naïve symptomatic COPD patients.

Data availability statement: Novartis as the study sponsor is committed to sharing with qualified external researchers, access to patient-level data and supporting clinical documents from eligible studies. 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 the applicable laws and regulations.

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P.G., S.M., J.A.W. Writing—review and editing: S.M., H.Y., K.K., P.O., P.G., J.A.W.

Abbreviations: Δ, LSM treatment difference; ANCOVA, analysis of covariance; eDiary, electronic diary; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; GLY, glycopyrronium; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroid; IGNITE, Indacaterol and GlycopyrroNium bromide clInical sTudiEs; IND, indacaterol; LABA, long-acting β_2-agonist; LABD, long-acting bronchodilator; LAMA, long-acting muscarinic antagonist; LSM, least squares mean; MCID, minimal clinically important difference; OL, open-label; OLO, olodaterol; PRO, patient-reported outcome; q.d., once daily; SGRQ, St George's Respiratory Questionnaire; TDI, transition dyspnoea index; TIO, tiotropium.

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Supplementary Information

Additional supplementary information can be accessed via the *html* version of this article at the publisher's website.

Visual Abstract 'IND/GLY' versus 'TIO' or 'GLY' in long-acting bronchodilator-naïve COPD patients: A pooled analysis.