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ORIGINAL RESEARCH

Triple Therapy with Mometasone/Indacaterol/Glycopyrronium or Doubling the ICS/LABA Dose in GINA Step 4: IRIDIUM Analyses

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ABSTRACT

Introduction: GINA guidelines recommend increasing the dose of inhaled corticosteroids (ICS) as a step-up option for patients with inadequately controlled asthma at GINA step 4 [inadequately controlled asthma on medium-dose ICS/long-acting beta-2 agonist (LABA)]. The aim of this study was to compare the efficacy and safety of long-acting muscarinic antagonists (LAMA) add-on to medium-dose ICS/LABA in patients at GINA 2022 step 4.

Methods: This post hoc analysis of the IRIDIUM study evaluated the change from baseline in trough forced expiratory volume (FEV_1) in patients receiving medium-dose MF/IND/GLY versus high-dose MF/IND and high-dose FLU/SAL at Week 26. Other outcomes included improvement in lung functions [peak expiratory flow (PEF), forced vital capacity (FVC), forced expiratory flow between 25% and 75% of the FVC $(FEF)_{25–75\%}$)], asthma control [Asthma Control Questionnaire (ACQ-7)], responder analysis (≥ 0.5 unit improvement in ACQ-7), and reduction in asthma exacerbations at Weeks 26 and 52.

Results: A total of 1930 patients were included in this analysis. Medium-dose MF/IND/GLY improved trough FEV_1 versus high-dose MF/IND (Δ 41 mL; 95% CI – 7–90) and high-dose FLU/SAL (Δ 88 mL; 95% CI 39–137) at Week 26 which were sustained until Week 52. Exacerbation rates were 16% lower with medium-dose

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MF/IND/GLY versus high-dose MF/IND for all (mild, moderate, and severe) exacerbations and 21–30% lower versus high-dose FLU/SAL for all (mild, moderate, and severe), moderate or severe, and severe exacerbations over 52 weeks. Further improvements in other lung functions were observed with medium-dose MF/IND/GLY. No new safety signals were identified.
Conclusion: Medium-dose MF/IND/GLY improved lung function and reduced asthma exacerbations compared to high-dose ICS/LABA and may be an undervalued option in patients at GINA 2022 step 4.
Trial Registration: ClinicalTrials.gov Identifier: NCT02571777.

Keywords: Asthma exacerbations; Glycopyrronium; GINA step 4; IRIDIUM; Inadequately controlled asthma; ICS/LABA; LAMA add-on; Lung function

Key Summary Points

Why carry out the study?

GINA guidelines recommend increasing the dose of inhaled corticosteroids (ICS) as a step-up option for patients with inadequately controlled asthma on medium-dose ICS/long-acting beta-2 agonist (LABA) (GINA 2022 step 4). However, this may increase the risk of side effects.

Add-on long-acting muscarinic antagonists (LAMA) as a controller medication for patients with inadequately controlled asthma receiving medium-dose ICS/LABA (GINA 2022 step 4) was associated with improved lung function parameters and reduced exacerbation rates, with no new safety signals.

What was learned from the study?

Our findings support that LAMA add-on to medium-dose ICS/LABA is more beneficial than increasing the dose of ICS, and can be an important option for patients inadequately controlled at medium-dose ICS/LABA (GINA 2022 step 4).

INTRODUCTION

Increasing the dose of inhaled corticosteroids (ICS) is recommended as a step-up option for patients who continue to have inadequately controlled asthma with frequent symptoms and exacerbations while on medium-dose ICS/long-acting beta-2 agonist (LABA), i.e., at GINA 2022 step 4 [1]. Although, high-dose ICS/LABA is effective in reducing the frequency of asthma exacerbations [2], increasing the dose of ICS may increase the risk of side effects due to cumulative exposure [3]. Therefore, the GINA guidelines also suggest the addition of a long-acting muscarinic antagonist (LAMA) to ICS/LABA as add-on rather than ICS step-up therapy as an alternative approach [4]. Indeed, add-on LAMA to ICS/LABA has been shown to improve lung function and reduce exacerbations in patients with asthma who were inadequately controlled on ICS/LABA [5–7].

The combination of ICS/LABA/LAMA in asthma has mainly been investigated in patients at GINA 2022 step 5 [5, 8], but limited data exist around its efficacy and safety, especially when delivered in a single device, in patients at GINA 2022 step 4. The phase 3 IRIDIUM study [6] assessed the efficacy and safety of glycopyrronium bromide (GLY) as an add-on to medium- (160/150 µg) or high-dose (320/150 µg) mometasone furoate (MF)/indacaterol acetate (IND) combination in patients receiving moderate- to high-dose ICS at entry (GINA step 4–5). Add-on GLY was shown to provide significant improvements in trough forced expiratory volume in 1 s (FEV_1) over 26 weeks versus corresponding doses of MF/IND and high dose of twice-daily (b.i.d.) fluticasone (FLU)/salmeterol (SAL). The annualized rates of exacerbations were reduced with MF/IND/GLY versus high-dose FLU/SAL. This once-daily (o.d.) fixed-dose combination of MF/IND/GLY administered via Breezhaler® has been approved for the maintenance treatment of asthma for adults inadequately controlled on high-dose ICS/LABA combination [9, 10].

Given the drawbacks of higher doses of ICS [3], we sought to investigate the option of adding a LAMA, specifically for patients at GINA

2022 step 4, instead of increasing the dose of ICS. In the current post hoc analysis of the IRIDIUM study, we focus on the efficacy and safety of o.d. medium-dose MF/IND/GLY versus o.d. high-dose MF/IND and b.i.d. high-dose FLU/SAL in patients at GINA 2022 step 4.

METHODS

Study Design

The IRIDIUM (NCT02571777) was a multicenter, Phase 3 study. Patients in this active-controlled, double-blind, double-dummy, parallel-group study were randomized in a 1:1:1:1:1 manner to receive either medium-dose MF/IND/GLY (80/150/50 μg) o.d. or high-dose MF/IND/GLY (160/150/50 μg) o.d. or medium-dose MF/IND (160/150 μg) o.d. or high-dose MF/IND (320/150 μg) o.d. via Breezhaler® or high-dose FLU/SAL (500/50 μg) b.i.d. via Diskus® over 52 weeks of treatment. The detailed study design has been published elsewhere [6]. The approved MF doses of 200 μg o.d., 400 μg o.d., and 400 μg b.i.d. delivered by Twisthaler® are comparable with MF doses of 80 μg o.d., 160 μg o.d., and 320 μg o.d., respectively, in MF/IND/GLY delivered by Breezhaler® [11].

The current analysis was prespecified in the main IRIDIUM study and conducted in patients who were on medium-dose ICS/LABA (GINA 2022 step 4 [4]) prior to study enrolment. The IRIDIUM study was approved by the independent ethics committee or institutional review boards of each participating center and was conducted in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki. All participants provided written informed consent for participation in the IRIDIUM study. Here, we report the efficacy and safety findings of medium-dose MF/IND/GLY versus high-dose MF/IND and high-dose FLU/SAL. Considering the complete original trial design, the comparisons of high-dose MF/IND/GLY versus high-dose MF/IND and high-dose FLU/SAL are also presented.

Participants

Patients with asthma for a period of at least 1 year before screening were included. They were aged between 18 to 75 years. Patients were included if they had a predicted FEV_1 of $< 80\%$, an increase in FEV_1 of at least 12% and 200 mL after administration of salbutamol (albuterol), an Asthma Control Questionnaire 7 (ACQ-7) score of ≥ 1.5, and a documented history of ≥ 1 asthma exacerbation in the 12 months before screening.

Excluded patients were those who smoked tobacco products within 6 months before screening or had a history of smoking of ≥ 10 pack-years, or had a chronic lung disease other than asthma, or within 4 weeks before screening had respiratory tract infection or worsening asthma, or within 6 weeks of screening had an asthma exacerbation requiring systemic corticosteroids, hospitalization, or emergency room visit. Patients with clinically significant comorbidities during the run-in period were also excluded. Please refer to the IRIDIUM primary study for additional details on inclusion and exclusion criteria [6].

Outcomes

The change from baseline in trough FEV_1 with medium- or high-dose MF/IND/GLY versus high-dose MF/IND and high-dose FLU/SAL at Week 26 was evaluated. In addition, the change from baseline in ACQ-7 score at 26 weeks and minimal clinically important difference (MCID) improvement from baseline ACQ-7 score of ≥ 0.5 units (responder analysis) were assessed.

Other outcomes of interest included rate of asthma exacerbations and time to first asthma exacerbation [moderate or severe, severe, and all (mild, moderate, and severe) exacerbations] over 52 weeks, change from baseline in blood eosinophil count at Week 52, improvement in other lung functions [FEV_1, forced vital capacity (FVC), and forced expiratory flow at 25–75% ($FEF_{25–75\%}$) over 52 weeks, post-dose FEV_1 (1 h post-dose) at various time points (5, 15, 30, and 60 min) on Day 1 and at Weeks 26 and 52,

morning and evening peak expiratory flow (PEF) over 26 and 52 weeks of treatment], ACQ-7 score over 52 weeks as change from baseline, total daily symptom score, percentage of days with no symptoms, and percentage of nights with no night-time awakenings over 52 weeks, and rescue medication use (reduction in the number of puffs and percentage of days without use) over 52 weeks.

Statistical Analysis

In all cases, a subgroup refers to whether the patient was receiving a medium-dose ICS/LABA treatment or a high-dose ICS/LABA treatment prior to the study. Only results from the medium-dose ICS/LABA treatment (GINA 2022 step 4 [4]) subgroup are reported here.

The analysis of efficacy data was performed on the full analysis set that included all patients who were randomized and received at least one dose of the study medication. Patients were analyzed according to the treatment they were assigned to at randomization. The changes from baseline in trough FEV_1 and ACQ-7 were reported as least-square (LS) mean and 95% confidence intervals (CI), analyzed by means of a mixed model for repeated measures (MMRM). The model contained treatment, baseline FEV_1 or ACQ-7 measurement, region, visit, treatment-by-visit interaction, baseline FEV_1/ACQ-7-by-visit interaction, subgroup-by-treatment interaction, subgroup-by-treatment-by-visit interaction, and FEV_1 prior to and within 15–30 min after inhalation of salbutamol or albuterol as covariates. The annual rate of asthma exacerbations was analyzed using a generalized linear model assuming a negative binomial distribution with fixed effects of treatment, region, number of asthma exacerbations in the 12 months prior to screening, subgroup-by-treatment interaction, subgroup-by-treatment-by-visit interaction, and FEV_1 prior to and 15–30 min after inhalation of salbutamol/albuterol. The estimated rate ratio, two-sided 95% CI, and corresponding *p* values are provided.

Other continuous variables (trough FVC, trough $FEF_{25–75\%}$, pre-dose trough FEV_1, post-dose FEV_1) were reported as LS means using the MMRM model. The detailed statistical methods are described in the supplementary materials. All safety evaluations were based on the safety set and included all patients who received at least one dose of the study medication. Patients were analyzed according to the treatment they received. All analyses were performed using SAS v.9.4.

RESULTS

Of the 4851 patients screened during the IRIDIUM study, 1930 were on medium-dose ICS/LABA background therapy. Of these, 1928 patients were randomized to different treatment arms and 1801 (93.4%) completed the 52-week treatment. The disposition of patients is shown in Fig. 1. The baseline demographics and clinical characteristics were balanced across the treatment groups (Table 1).

Lung Function Parameters

The improvements from baseline to Week 26 in trough FEV_1 were greater in patients treated with medium-dose MF/IND/GLY versus high-dose MF/IND o.d. [mean treatment difference (Δ): 41 mL; 95% CI − 7 to 90] and high-dose FLU/SAL b.i.d. (Δ: 88 mL; 95% CI 39–137) (Fig. 2; Supplementary Fig. S1A). The improvements were slightly higher with high-dose MF/IND/GLY versus high-dose MF/IND o.d. (Δ: 48 mL; 95% CI 1–96) and high-dose FLU/SAL b.i.d (Δ: 94 mL; 95% CI 46–143) at Week 26 (Supplementary Fig. S2; Supplementary Fig. S1A). The changes in trough FEV_1 up to 52 weeks followed the same pattern as for 26 weeks (Supplementary Fig. S1B).

The change from baseline in evening and morning PEF with medium-dose MF/IND/GLY during Weeks 1–52 was greater than high-dose MF/IND (Δ: 9.95 L/min 95% CI 3.26–16.65; and Δ: 8.43 L/min 95% CI 1.62–15.24, respectively) and high-dose FLU/SAL (Δ: 22.93 L/min 95% CI 16.18–29.68; and Δ: 24.99 L/min 95% CI 18.14–31.83, respectively). Similarly, high-dose MF/IND/GLY also showed greater evening and morning PEF compared with high-dose MF/IND

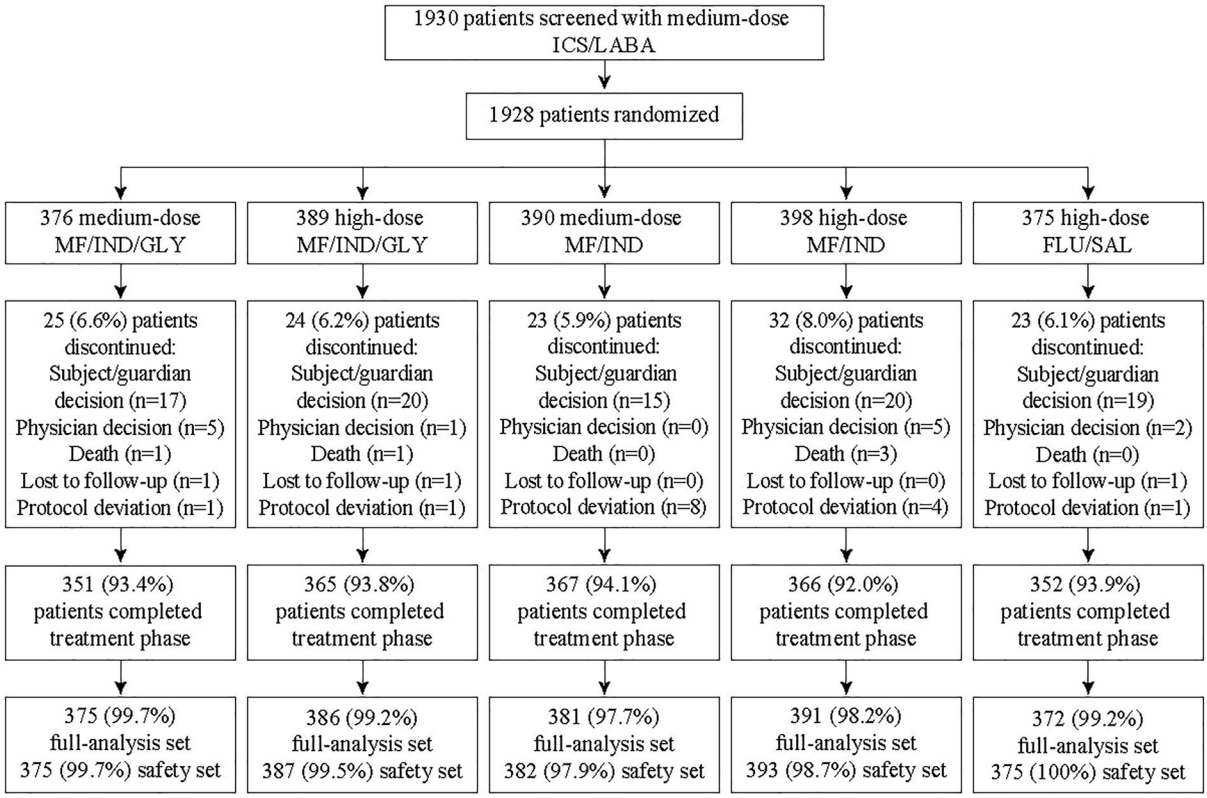

Fig. 1 Disposition of patients who were on medium-dose ICS/LABA. Participants were randomly assigned to receive medium-dose MF/IND/GLY (80/150/50 µg) o.d.; or high-dose MF/IND/GLY (160/150/50 µg) o.d.; or medium-dose MF/IND (160/150 µg) o.d.; or high-dose MF/IND (320/150 µg) o.d.; or high-dose FLU/SAL (500/50 µg) b.i.d. *FLU/SAL* fluticasone/salmeterol, *ICS/LABA* inhaled corticosteroids/long-acting beta 2 agonists, *MF/IND* mometasone/indacaterol, *MF/IND/GLY* mometasone/indacaterol/glycopyrronium

(15.11 and 17.42 L/min, respectively) and high-dose FLU/SAL (28.09 and 33.98 L/min, respectively) during Weeks 1–52 (Fig. 3).

Improvements were seen in FVC and post-dose FEV_1 (1-h post-dose) with medium-dose MF/IND/GLY versus higher doses of MF/IND (Δ: 77; 95% CI 18–136; and Δ: 102; 95% CI 53–152, respectively) and FLU/SAL (Δ: 119; 95% CI 58–179; and Δ: 119; 95% CI 69–168) at 26 weeks which were maintained until Week 52. Similar trends of improvement in FVC and post-dose FEV_1 were also observed with high-dose MF/IND/GLY when compared with high-dose MF/IND and high-dose FLU/SAL at Weeks 26 and 52. Improvement in $FEF_{25–75\%}$ was comparable between medium-dose MF/IND/GLY versus high-dose MF/IND at both 26 and 52 weeks (Supplementary Table S1). Improvements in post-dose FEV_1 were seen with both medium- and high-dose MF/IND/GLY as early as 5 min after the first study drug administration on Day 1 (Supplementary Fig. S3).

Asthma Control and Responder Analysis

The improvements in ACQ-7 scores from baseline were observed in all treatment arms (almost double the MCID) at Week 26 and sustained up to 52 weeks (Supplementary Figs. S4, S5A). When compared with high-dose MF/IND, the treatment differences for ACQ-7 scores did not favor either medium-dose MF/IND/GLY or high-dose MF/IND/GLY at Week 26. However, both medium- and high-dose MF/IND/GLY improved ACQ-7 scores versus high-dose FLU/

Table 1 Baseline demographics and clinical characteristics of patients with inadequately controlled asthma on prior medium-dose ICS/LABA (GINA 2022 step 4) prior to study enrolment (randomized set)

Variable	Medium-dose MF/IND/GLY (80/150/50 µg o.d.) *n* = 376	High-dose MF/IND/GLY (160/150/50 µg o.d.) *n* = 389	High-dose MF/IND (320/150 µg o.d.) *n* = 398	High-dose FLU/SAL (500/50 µg b.i.d.) *n* = 375
Age (years)	52.9 ± 12.89	52.4 ± 12.89	51.6 ± 12.75	52.0 ± 12.22
Sex, *n* (%)				
Male	150 (39.9)	147 (37.8)	161 (40.5)	114 (30.4)
Female	226 (60.1)	242 (62.2)	237 (59.5)	261 (69.6)
Body mass index (kg/m^2)	28.0 ± 5.62	28.2 ± 5.63	28.3 ± 5.45	27.9 ± 5.90
Duration of asthma (years)	17.3 ± 14.75	17.4 ± 14.95	15.7 ± 14.09	17.5 ± 15.63
Number of asthma exacerbations that required treatment in the 12 months before the study, *n* (%)				
0	1 (0.3)	0	1 (0.3)	0
1	317 (84.3)	332 (85.3)	326 (81.9)	306 (81.6)
2	47 (12.5)	43 (11.1)	62 (15.6)	54 (14.4)
3	9 (2.4)	9 (2.3)	6 (1.5)	10 (2.7)
≥ 4	2 (0.5)	5 (1.3)	3 (0.8)	5 (1.3)
Smoking status, *n* (%)				
Never smoker	296 (78.7)	313 (80.5)	325 (81.7)	308 (82.1)
Former smoker	80 (21.3)	76 (19.5)	73 (18.3)	67 (17.9)
ACQ-7 score	2.5 ± 0.57	2.5 ± 0.62	2.5 ± 0.57	2.4 ± 0.55
Eosinophils (10E^9/L)	0.3 ± 0.60	0.3 ± 0.64	0.3 ± 0.21	0.3 ± 0.26
< 150 cells/µL, *n* (%)	95 (25.3)	87 (22.4)	84 (21.1)	69 (18.4)
≥ 150 cells/µL, *n* (%)	280 (74.5)	300 (77.1)	307 (77.1)	302 (80.5)
Pre-bronchodilator (% predicted FEV_1)	53.3 ± 14.56	54.6 ± 13.46	54.2 ± 13.83	55.5 ± 13.38
FEV_1 post-bronchodilator (% predicted FEV_1)	67.0 ± 17.04	68.0 ± 15.34	68.0 ± 15.65	70.7 ± 16.06
FEV_1 reversibility (%) after salbutamol inhalation	27.6 ± 18.77	27.0 ± 21.07	27.8 ± 19.24	29.8 ± 23.40
FEV_1/FVC (%) post-bronchodilator	63.0 ± 13.07	64.3 ± 12.18	64.2 ± 12.35	66.1 ± 12.13

Table 1 continued

Variable	Medium-dose MF/IND/GLY (80/150/50 µg o.d.)*n* = 376	High-dose MF/IND/GLY (160/150/50 µg o.d.)*n* = 389	High-dose MF/IND (320/150 µg o.d.)*n* = 398	High-dose FLU/SAL (500/50 µg b.i.d.)*n* = 375
$FEF_{25–75\%}$ (L/s) pre-bronchodilator	0.8 ± 0.51	0.9 ± 0.52	0.9 ± 0.53	0.9 ± 0.57
$FEF_{25–75\%}$ (L/s) post-bronchodilator	1.2 ± 0.76	1.2 ± 0.76	1.2 ± 0.78	1.3 ± 0.84

Data represented as mean ± SD, unless otherwise specified. Duration of asthma was calculated from the start date of asthma recorded on the eCRF until the date of screening. Baseline ACQ-7 score was reported at screening or, if missing, at the last visit from run-in. FEV_1 reversibility is calculated as an increase in FEV_1 value after inhalation of bronchodilator (400-µg salbutamol or 360-µg albuterol, or equivalent doses) relative to FEV_1 before inhalation of bronchodilator. Trough FEV_1 was defined as the average of the two FEV_1 measurements taken 23 h 15 min and 23 h 45 min post-evening dose. All spirometry measurements were collected at run-in visit 101; % predicted FEV_1 was collected at both run-in visit 101 and 102 [6]
ACQ-7 Asthma Control Questionnaire 7, *eCRF* electronic case report form, *FEV_1* forced expiratory volume in 1 s, *FVC* forced vital capacity, *FEF* forced expiratory flow, *FLU/SAL* fluticasone/salmeterol, *ICS/LABA* inhaled corticosteroid/long-acting β_2-adrenoceptor agonist, *MF/IND* mometasone/indacaterol, *MF/IND/GLY* mometasone/indacaterol/glycopyrronium

SAL at Week 26 (Δ: − 0.097; 95% CI − 0.205 to 0.011; Δ: − 0.114; 95% CI − 0.221 to − 0.008, respectively) (Fig. 4; Supplementary Fig. S6).

At Week 26, a greater proportion of patients achieved the MCID (≥ 0.5 units from baseline) with medium-dose MF/IND/GLY compared with high-dose FLU/SAL [odds ratio (OR): 1.42; 95% CI 1.02–1.98] (Fig. 5). Similar results were observed with high-dose MF/IND/GLY versus high-dose FLU/SAL (OR: 1.46; 95% CI 1.05–2.04) (Supplementary Fig. S7). However, the improvements were higher with high-dose MF/IND, compared to either medium- or high-dose MF/IND/GLY (Fig. 5; Supplementary Fig. S6). The Week 52 data showed higher proportion of patients achieving MCID with only high-dose MF/IND/GLY (Supplementary Fig. S5B). The proportion of patients achieving MCID were numerically higher with high-dose MF/IND, compared with medium-dose MF/IND/GLY at Week 52 (77.6% vs. 74.8%) (Supplementary Table S2).

Asthma Exacerbations

The annualized rate of all (mild, moderate, and severe) asthma exacerbations favored medium-dose MF/IND/GLY versus high-dose MF/IND over 52 weeks (16%, Fig. 6). Medium-dose MF/IND/GLY reduced all (mild, moderate, and severe), moderate or severe, and severe asthma exacerbations by 21–30%, compared with high-dose FLU/SAL. High-dose MF/IND/GLY treatment resulted in 19%, 20%, and 27% reductions of all (mild, moderate, and severe), moderate or severe, and severe asthma exacerbations, respectively, as compared with high-dose MF/IND. Similar results were observed with high-dose MF/IND/GLY versus high-dose FLU/SAL (Supplementary Figs. S8, S9). The results on mean absolute eosinophil count and reduction in the absolute count of eosinophils are shown in Supplementary Fig. S10.

Asthma Symptoms and Rescue Medications

The reductions in the mean night-time number of puffs of rescue medication, mean daily number of puffs of rescue medication, and percentage of rescue medication free days were higher with high-dose MF/IND/GLY than with high-dose FLU/SAL ($p = 0.022$, $p = 0.040$, and $p = 0.028$, respectively) over 52 weeks. The reductions in daytime asthma symptom score, total daily asthma symptom scores, percentage

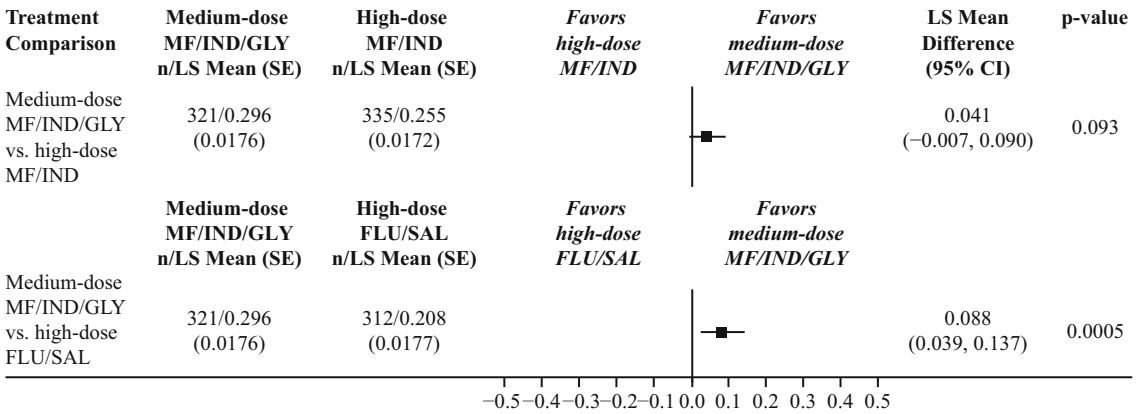

Fig. 2 Treatment differences in change from baseline in trough FEV_1 with medium-dose MF/IND/GLY versus high-dose MF/IND and high-dose FLU/SAL at Week 26 in GINA 4 subgroup (full analysis set). Values for change from baseline in trough FEV_1 are in liters (L). *CI* confidence interval, *FEV_1* forced expiratory volume in 1 s, *FLU/SAL* fluticasone/salmeterol, *GINA* global initiative for asthma, *LS* least square, *MF/IND* mometasone/indacaterol, *MF/IND/GLY* mometasone/indacaterol/glycopyrronium, *SE* standard error

of asthma symptom-free days, percentage of mornings with no symptoms on awakening, percentage of nights with no night-time awakenings, and percentage of days with no daytime symptoms were similar across all treatment groups over 52 weeks. These outcomes were comparable across the other treatments (Supplementary Table S3).

Safety

The overall incidence of adverse events (AEs) was similar across the treatment groups. The most frequently observed AEs are shown by preferred term in Table 2. Asthma, nasopharyngitis, and upper respiratory tract infection were the most commonly reported AEs, as expected for an asthma population. The proportion of patients reporting at least 1 AE and serious AE (SAE) was comparable across all treatment arms. Numerically higher number of patients in high-dose MF/IND group had at least 1 SAE, which was suspected to be study drug-related. The incidence rates of AEs suspected to be treatment-related were generally low and similar across treatment groups. Seven deaths were reported in the main IRIDIUM population, of which five were reported in this subgroup of patients. None was attributed to the study drugs. Out of four deaths with high-dose MF/IND (as seen in the overall IRIDIUM patients), three (one accident, one lymphoma, and one sudden death in a patient with multiple, severe cardiovascular comorbidities) were reported among patients at GINA step 4. Likewise, one sudden death and one aortic dissection were reported with high-dose MF/IND/GLY and medium-dose MF/IND/GLY, respectively, in patients included in this subgroup. In the overall population, one additional death due to aortic dissection was seen in patients receiving high-dose MF/IND/GLY. See Supplementary Table S4 for AEs shown by system organ class.

DISCUSSION

Current asthma treatment guidelines recommend the use of high-dose ICS with LABA in patients with severe persistent asthma inadequately controlled by the combination of medium-dose ICS/LABA, i.e., GINA step 4 [4]. While the use of high-dose ICS is effective in controlling asthma, owing to the inherent safety concerns following their long-term use, the guidelines also recommend lowering ICS doses once asthma control is achieved and sustained [4, 12]. Previous studies have demonstrated an improvement of lung function and

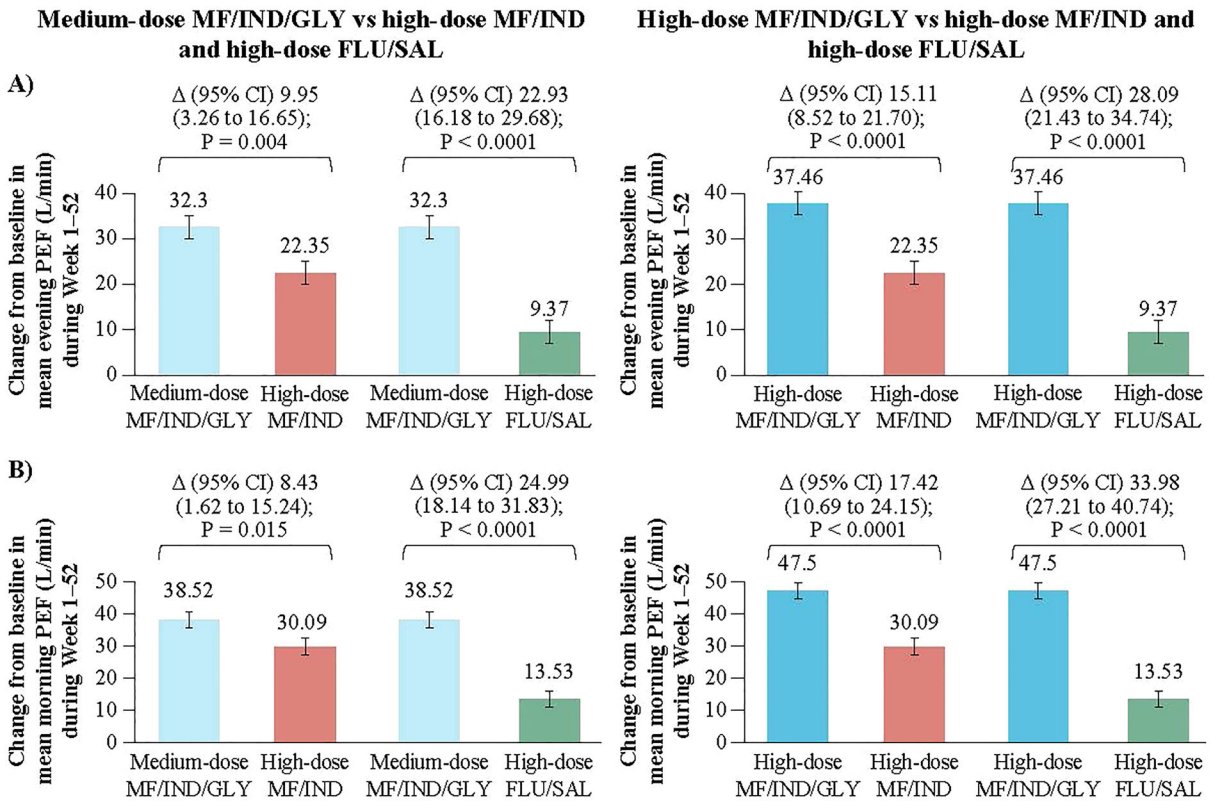

Fig. 3 Treatment differences in change from baseline in **A** mean evening and **B** morning PEF with medium-and high-dose MF/IND/GLY versus high-dose MF/IND and high-dose FLU/SAL during Weeks 1–52 in GINA 4 subgroup (full analysis set). Δ, treatment difference, *CI* confidence interval, *FLU/SAL* fluticasone/salmeterol, *GINA* global initiative for asthma, *MF/IND* mometasone/indacaterol, *MF/IND/GLY* mometasone/indacaterol/glycopyrronium, *PEF* peak expiratory flow

reduction in exacerbation rates with LAMA add-on to ICS/LABA in patients with inadequately controlled asthma [7, 13], indicating that the addition of LAMA can be a potential alternative to the increasing ICS dose. This analysis of the IRIDIUM study was aimed to understand if add-on LAMA was more beneficial than increasing ICS dose in patients with inadequately controlled asthma, despite medium-dose ICS/LABA (GINA 2022 step 4 therapy [4]) prior to study enrolment.

The results from these analyses are in line with the primary IRIDIUM findings [6], where medium-dose MF/IND/GLY showed a better improvement in trough FEV_1 when compared with high-dose MF/IND and high-dose FLU/SAL at Week 26. Similar results on FEV_1 improvements were also seen with high-dose MF/IND/GLY versus high-dose MF/IND and high-dose FLU/SAL. The effects of both treatments were continued long-term until Week 52. The post-dose FEV_1 improved as early as 5 min after the first study drug administration on Day 1 with both doses of MF/IND/GLY, and was maintained through Week 52. This shows that the improvements were both rapid and sustained for the long-term in lung function. Similar results were also observed for other lung function parameters, such as trough FVC, $FEF_{25\%-75\%}$, and evening and morning PEF at Week 26, and which were maintained until Week 52.

Previous placebo-controlled trials with LAMA add-on, tiotropium, have shown an improved lung function in patients who had poor lung function, with FEV_1 of ~ 55% of their predicted value and taking ICS/LABA

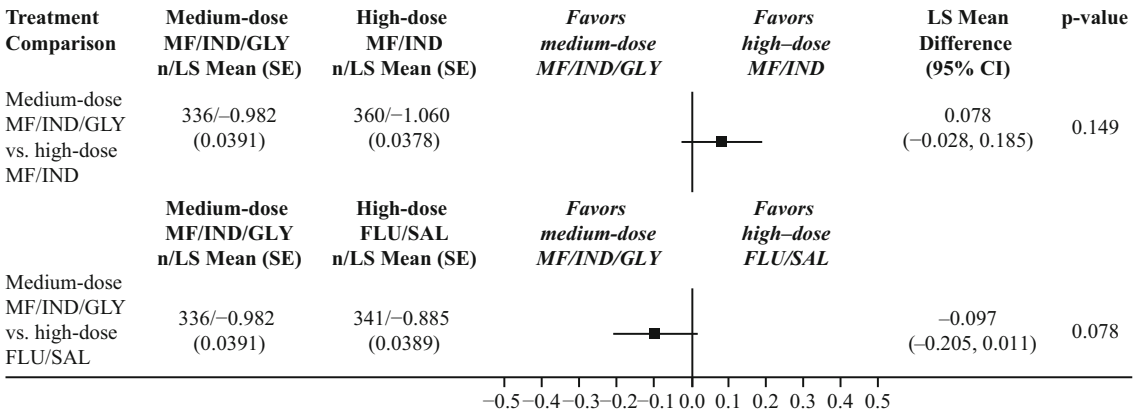

Fig. 4 Treatment differences in change from baseline in ACQ–7 score with medium-dose MF/IND/GLY versus high-dose MF/IND and high-dose FLU/SAL at Week 26 in GINA 4 subgroup (full analysis set). *ACQ* asthma control questionnaire, *CI* confidence interval, *FLU/SAL* fluticasone/salmeterol, *GINA* global initiative for asthma, *LS* least square, *MF/IND* mometasone/indacaterol, *MF/IND/GLY* mometasone/indacaterol/glycopyrronium, *SE* standard error

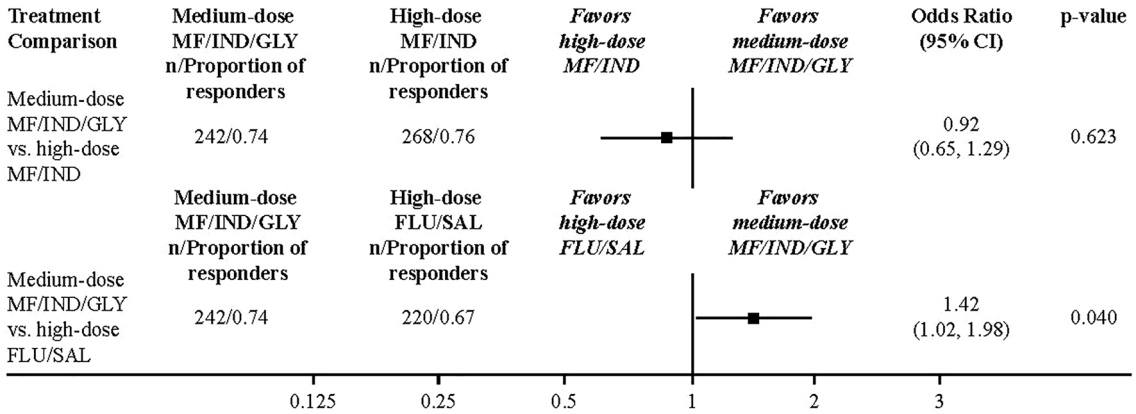

Fig. 5 Improvement in the ACQ-7 scores [≥ 0.5 units from baseline (MCID)] at Week 26 in GINA 4 subgroup with medium-dose MF/IND/GLY versus high-dose MF/IND and high-dose FLU/SAL (full analysis set). *ACQ* asthma control questionnaire, *CI* confidence interval, *FLU/SAL* fluticasone/salmeterol, *GINA* global initiative for asthma, *MCID* minimal clinically important differences, *MF/IND* mometasone/indacaterol, *MF/IND/GLY* mometasone/indacaterol/glycopyrronium

combinations over 48–52 weeks [7, 14, 15] In a trial with two replicate designs, Kerstjens et al. reported 42–92 mL improvement in trough FEV_1 with add-on tiotropium in patients receiving ICS (≥ 800 µg of budesonide or the equivalent) and LABAs at 48 weeks and had poor asthma control and persistent airflow limitation [7]. An improvement of 139–170 mL in peak FEV_1 was shown with add-on tiotropium in patients at GINA steps 4 and 5 and receiving maintenance treatment of high-dose ICS/LABA [14]. Ohta and coworkers demonstrated an improvement in trough FEV_1 and peak expiratory flow rate, with treatment differences of 112 mL and 34.2 L/min, respectively, at Week 52 [15].

Asthma control, measured by ACQ-7 score, as well as responders (MCID ≥ 0.5 units decrease in the ACQ-7 score from baseline) did not improve in the current analyses with medium-dose MF/IND/GLY at Week 26 compared to high-dose MF/IND; however, there were higher

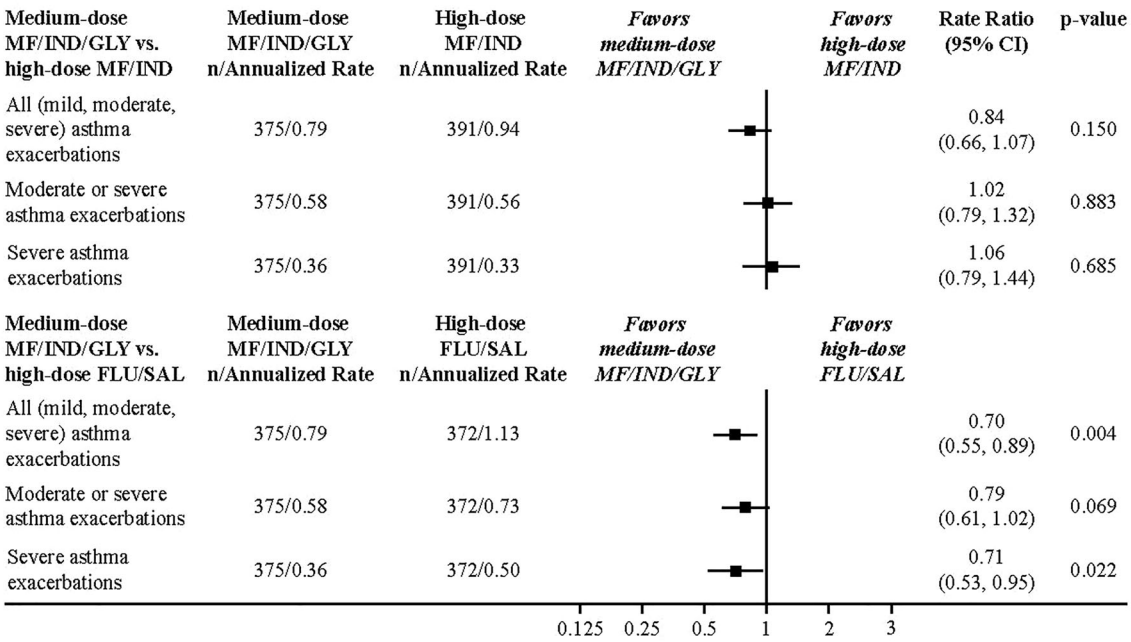

Fig. 6 Rate of asthma exacerbations with medium-dose MF/IND/GLY versus high-dose MF/IND and high-dose FLU/SAL in GINA 4 subgroup (full analysis set). *CI* confidence interval, *FLU/SAL* fluticasone/salmeterol, *GINA* global initiative for asthma, *MF/IND* mometasone/indacaterol, *MF/IND/GLY* mometasone/indacaterol/glycopyrronium

number of responders in the medium-dose MF/IND/GLY versus high-dose FLU/SAL group at Week 26. Similar results were seen in the primary IRIDIUM study, where a superiority in ACQ-7 score at Week 26 for either dose of MF/IND/GLY versus the respective dose of MF/IND was not established [6]. Two replicate trials by Kerstjens et al. also demonstrated a smaller improvement in ACQ-7 score with tiotropium add-on where the MCID was not achieved [7]. These results seem to indicate little added benefit of LAMA on asthma control over high-dose ICS/LABA alone. It is, however, important to acknowledge that large improvements (almost twice the MCID on average) were achieved with all treatments in the current study, limiting the ability for analyzing differential improvements.

The current study demonstrated that the use of medium-dose MF/IND/GLY was associated with a 16–30% reduction of annualized exacerbation rate over 52 weeks than patients receiving high-dose ICS/LABA. An earlier trial on patients randomly assigned to either of tiotropium (a total dose of 5 μg) or placebo as add-on therapy to high-dose ICS/LABA showed evidence of benefits on severe asthma exacerbations with the addition of tiotropium compared to those on ICS/LABA only, with a significant increase in time to first severe exacerbation and an overall risk reduction of 21% [7]. Additionally, there have been reports of severe exacerbations in approximately one-third of patients despite an increase in ICS dose [1], and a similar proportion of patients failing to achieve disease control [16]. Studies have suggested that ICS treatment is characterized by a relatively flat dose–response curve with 80–90% of the maximum achievable therapeutic effect in adult asthma obtained at 200 μg of fluticasone propionate or equivalent, with little clinical benefit from increasing the ICS dose although the risk of adverse effects is increased [17]. Therefore, addition of a bronchodilator controller therapy such as a LAMA could be the preferred treatment strategy over increasing the ICS dose [18].

Safety findings from the current study are in line with main IRIDIUM findings [6] and further supported by multiple studies [15, 19, 20]. Five

Table 2 Adverse events, serious adverse events, and deaths (safety set)

	Medium-dose MF/IND/GLY (*n* = 375) exp = 345.4 years	**High-dose MF/IND/GLY (*n* = 387) exp = 366.3**	**High-dose MF/IND (*n* = 393) exp = 367.7 years**	**High-dose FLU/SAL (*n* = 375) exp = 349.0 years**
Patients with ≥ 1 AE	283 (176.8)	286 (170.7)	288 (169.7)	300 (203.8)
Asthma	143 (54.2)	145 (52.2)	160 (59.3)	183 (76.2)
Nasopharyngitis	44 (13.8)	41 (12.0)	49 (14.4)	55 (17.2)
Upper respiratory tract infection	32 (9.8)	24 (6.8)	37 (10.7)	33 (10.0)
Bronchitis	25 (7.5)	30 (8.5)	23 (6.5)	31 (9.3)
Viral upper respiratory tract infection	22 (6.6)	10 (2.8)	28 (7.9)	32 (9.7)
Cough	11 (3.2)	18 (5.0)	5 (1.4)	7 (2.0)
Hypertension	12 (3.5)	11 (3.1)	12 (3.3)	16 (4.7)
Influenza	14 (4.1)	11 (3.1)	10 (2.8)	11 (3.2)
Pharyngitis	14 (4.1)	13 (3.6)	12 (3.3)	15 (4.4)
Upper respiratory tract infection bacterial	12 (3.5)	12 (3.3)	14 (3.9)	16 (4.7)
Lower respiratory tract infection	5 (1.5)	8 (2.2)	10 (2.7)	18 (5.3)
Number of patients with at least 1 AE suspected by the investigator to be study drug related	28 (8.5)	32 (9.3)	24 (6.8)	29 (8.7)
Number of patients with at least 1 AE leading to permanent discontinuation of study drugs	18 (5.2)	8 (2.2)	14 (3.8)	15 (4.3)
Patients with ≥ 1 SAE	32 (9.6)	30 (8.5)	37 (10.4)	24 (7.1)
Asthma	9 (2.6)	5 (1.4)	7 (1.9)	7 (2.0)
Pneumonia	2 (0.6)	3 (0.8)	0	2 (0.6)
Lower respiratory tract infection	0	1 (0.3)	3 (0.8)	2 (0.6)
Hypertension	2 (0.6)	0	0	0
Cholelithiasis	0	3 (0.8)	0	1 (0.3)
Urinary tract infection	0	2 (0.5)	0	1 (0.3)
Number of patients with at least 1 SAE suspected by the investigator to be study drug-related	1 (0.3)	0	4 (1.1)	1 (0.3)

Table 2 continued

	Medium-dose MF/IND/GLY (n = 375) exp = 345.4 years	High-dose MF/IND/GLY (n = 387) exp = 366.3	High-dose MF/IND (n = 393) exp = 367.7 years	High-dose FLU/SAL (n = 375) exp = 349.0 years
Death	1 (0.3)	1 (0.3)	3 (0.8)	0
Cancer	0	0	1 (0.3)	0
Cardiovascular	1 (0.3)	1 (0.3)	1 (0.3)	0
Accidental	0	0	1 (0.3)	0

Data are presented as n (IR). IR is reported per 100 patient-years (100 × number of patients with at least one event/time at risk for given adverse event in patient-years). Patients received medium-dose MF/IND/GLY (80/150/50 μg) o.d., or high-dose MF/IND/GLY (160/150/50 μg) o.d., or medium-dose MF/IND (160/150 μg) o.d., or high-dose MF/IND (320/150 μg) o.d., or high-dose FLU/SAL (500/50 μg) b.i.d.

AE adverse event, *exp* exposure in total number of patient-years, *FLU/SAL* fluticasone/salmeterol, *IR* incidence rate, *MF/IND* mometasone/indacaterol, *MF/IND/GLY* mometasone/indacaterol/glycopyrronium, *SAE* serious AE

deaths were reported in the current analyses; none were attributed to the study drugs. A review of four randomized controlled trials ($n = 1197$) has shown that patients with LAMA add-on were less likely to have AEs than those on ICS/LABA alone [21], reiterating the safety benefit observed in this study due to lowering the ICS dose and LAMA add-on.

Through the evaluation of a range of assessments, this analysis provides the first evidence on the benefits of add-on GLY to medium- or high-dose ICS/LABA versus high-dose ICS/LABA in patients who were at GINA 2022 step 4 prior to study enrolment. The current study has some limitations. This is an analysis with no adjustment for multiple testing; furthermore, it may not be adequately powered to ascertain the differences between the treatment groups. Nevertheless, this study has demonstrated evidence of improved lung function, reductions in exacerbations, and better asthma control with add-on GLY. Moreover, patients receiving GLY add-on were less likely to experience any additional AEs than those receiving increased ICS dose in the ICS/LABA combination. Our findings suggest that, in patients with inadequately controlled asthma, the addition of a LAMA as an additional controller has greater overall benefit in the long term compared to increasing the ICS dose. This can have clinical implications for the treatment of asthma and can be considered clinically directive; however, further adequately powered studies aimed specifically to patients at GINA step 4 as the primary target are warranted to fully establish the clinical efficacy and safety of add-on GLY in these patients.

CONCLUSION

Taken together, these observations have demonstrated that add-on LAMA for patients at medium-dose ICS/LABA (GINA 2022 step 4) compared to increasing the dose of ICS may result in improved outcomes of lung function measures and reduction in asthma exacerbations with no new safety signals. Owing to the beneficial effect of LAMA add-on to medium-dose ICS/LABA, this could be an important option and perhaps an undervalued choice in patients at GINA 2022 step 4.

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Compliance with Ethics Guidelines. The IRIDIUM study was approved by the independent ethics committee or institutional review boards of each participating centre and was conducted in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki. All participants provided written informed consent for participation in the IRIDIUM study.

Data Availability. 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.

REFERENCES

1. Aalbers R, Vogelmeier C, Kuna P. Achieving asthma control with ICS/LABA: a review of strategies for asthma management and prevention. Respir Med. 2016;111:1–7.

2. Pauwels RA, Löfdahl CG, Postma DS, et al. Effect of inhaled formoterol and budesonide on exacerbations of asthma. Formoterol and Corticosteroids Establishing Therapy (FACET) International Study Group. N Engl J Med. 1997;337:1405–11.

3. Dahl R. Systemic side effects of inhaled corticosteroids in patients with asthma. Respir Med. 2006;100(8):1307–17.

4. Global Initiative for Asthma. Global strategy for asthma management and prevention, 2022. Available from: http://www.ginasthma.org/. Accessed 07 Oct 2022.

5. Virchow JC, Kuna P, Paggiaro P, et al. Single inhaler extrafine triple therapy in uncontrolled asthma (TRIMARAN and TRIGGER): two double-blind, parallel-group, randomised, controlled phase 3 trials. Lancet. 2019;394(10210):1737–49.

6. Kerstjens HAM, Maspero J, Chapman KR, et al. Once-daily, single-inhaler mometasone-indacaterol-glycopyrronium vs. mometasone-indacaterol or twice-daily fluticasone-salmeterol in patients with inadequately controlled asthma (IRIDIUM): a randomised, double-blind, controlled phase 3 study. Lancet Respir Med. 2020;8(10): 1000–12.

7. Kerstjens HAM, Engel M, Dahl R, et al. Tiotropium in asthma poorly controlled with standard combination therapy. N Engl J Med. 2012;367:1198–207.

8. Lee LA, Bailes Z, Barnes N, et al. Efficacy and safety of once-daily single-inhaler triple therapy (FF/UMEC/VI) versus FF/VI in patients with inadequately controlled asthma (CAPTAIN): a double-blind, randomised, phase 3A trial. Lancet Respir Med. 2021;9:69–84.

9. Enerzair® Breezhaler®. Summary of product characteristics (SmPC), 2022. Available from: https://www.medicines.org.uk/emc/product/11886/smpc#gref. Accessed 07 Oct 2022.

10. Atectura® Breezhaler®. Summary of product characteristics (SmPC), 2022. Available from: https://www.medicines.org.uk/emc/product/11885/smpc#gref. Accessed 07 Oct 2022.

11. Buhl R, Tanase AM, Hosoe M, et al. A randomized, double-blind study to compare the efficacy and safety of two doses of mometasone furoate delivered via Breezhaler® or Twisthaler® in patients with asthma. Pulm Pharmacol Ther. 2020;62: 101919.

12. Rogers L, Reibman J. Stepping down asthma treatment: how and when. Curr Opin Pulm Med. 2012;18:70–5.

13. Hoshino M, Ohtawa J, Akitsu K. Effects of the addition of tiotropium on airway dimensions in symptomatic asthma. Allergy Asthma Proc. 2016;37:147–53.

14. Kerstjens HA, Disse B, Schröder-Babo W, et al. Tiotropium improves lung function in patients with severe uncontrolled asthma: a randomized controlled trial. J Allergy Clin Immunol. 2011;128: 308–14.

15. Ohta K, Ichinose M, Tohda Y, et al. Long-term once-daily tiotropium Respimat® is well tolerated and maintains efficacy over 52 weeks in patients with symptomatic asthma in Japan: a randomised, placebo-controlled study. PLoS ONE. 2015;10: e0124109.

16. Cao H, Wilson A, Loefroth E, Keininger D, Fogel R. Significant percentage of asthma patients failed to achieve control in the first year after initiating medium or high dose ICS/LABA. Eur Respir J. 2017;50(Suppl 61):PA3866.

17. Beasley R, Harper J, Bird G, Maijers I, Weatherall M, Pavord ID. Inhaled corticosteroid therapy in adult asthma. Time for a new therapeutic dose terminology. Am J Respir Crit Care Med. 2019;199: 1471–7.

18. Powell H, Gibson PG. High dose vs. low dose inhaled corticosteroid as initial starting dose for asthma in adults and children. Cochrane Database Syst Rev. 2004;2004:CD004109.

19. Gessner C, Kornmann O, Maspero J, et al. Fixed-dose combination of indacaterol/glycopyrronium/mometasone furoate once-daily vs. salmeterol/fluticasone twice-daily plus tiotropium once-daily in patients with uncontrolled asthma: a randomised, Phase IIIb, non-inferiority study (ARGON). Respir Med. 2020;170: 106021.

20. Dahl R, Engel M, Dusser D, et al. Safety and tolerability of once daily tiotropium Respimat(®) as add-on to at least inhaled corticosteroids in adult patients with symptomatic asthma: a pooled safety analysis. Respir Med. 2016;118:102–11.

21. Kew KM, Dahri K. Long-acting muscarinic antagonists (LAMA) added to combination long-acting beta2-agonists and inhaled corticosteroids (LABA/ICS) versus LABA/ICS for adults with asthma. Cochrane Database Syst Rev. 2016;2016(1):CD011721. https://doi.org/10.1002/14651858.CD011721.pub2