Journal of Asthma and Allergy

Dovepress
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REVIEW

Mometasone/Indacaterol/Glycopyrronium (MF/IND/GLY) and MF/IND at Different MF Strengths versus Fluticasone Propionate/Salmeterol Xinafoate (FLU/SAL) and FLU/SAL+ Tiotropium in Patients with Asthma

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Background: Once-daily, single-inhaler mometasone furoate/indacaterol acetate/glycopyrronium bromide (MF/IND/GLY, an ICS/LABA/LAMA) and MF/IND (an ICS/LABA) via Breezhaler® have been approved for the maintenance treatment of patients with asthma inadequately controlled with medium-or high-dose ICS or medium-or high-dose ICS/LABA treatment.

Objective: Once-daily (o.d.) formulations of MF/IND/GLY and MF/IND at different MF dose strengths have been compared with twice-daily (b.i.d.) fluticasone propionate/salmeterol xinafoate (FLU/SAL), and b.i.d. FLU/SAL+ o.d. tiotropium (TIO) in the PALLADIUM, IRIDIUM and ARGON studies.

Methods: The similarity in study design and consistent outcomes in these studies prompted the pooling of data in this review to better characterise these novel once-daily controller formulations.

Results: Pooled data from PALLADIUM and IRIDIUM studies showed comparable or greater efficacy with o.d. MF/IND formulations versus b.i.d. FLU/SAL. The o.d. MF/IND/GLY was superior to b.i.d. FLU/SAL in the IRIDIUM study, and similar to, if not more efficacious than b.i.d. FLU/SAL + o.d. TIO in the ARGON study.

Conclusion: These formulations therefore provide novel once-daily treatment options for patients across asthma severity and flexibility for clinicians to step-up or step-down the treatment using the same device and formulations.

Keywords: mometasone/indacaterol/glycopyrronium, mometasone/indacaterol, fluticasone/salmeterol, tiotropium, bronchodilator, lung function, asthma control, exacerbation

Introduction

The Global Initiative for Asthma (GINA) 2021 strategy recommends the combination of medium- or high-dose inhaled corticosteroids (ICS) with a long-acting β_2-agonist (LABA) as a preferred regular controller treatment in patients with asthma who are uncontrolled on low-dose ICS/LABA.[1] Treatment with medium- or high-dose ICS/LABA is the preferred controller for patients with asthma at GINA step 4, and high-dose ICS/LABA can be considered for GINA

Received: 11 October 2022
Accepted: 10 January 2023
Published: 20 January 2023

step 5.[1] This approach forms the basis for a control-based, stepwise treatment for asthma management, using various safe and effective once-daily and twice-daily fixed dose combinations (FDC) of ICS/LABA.[2–4]

Various ICS with different chemical, pharmacological and metabolic characteristics are available for asthma treatment.[5] Mometasone furoate (MF), a hydrocortisone derivative, administered as a dry powder has a long half-life, which makes it suitable for daily dosing.[6] MF when combined with a LABA exhibits more effectiveness compared with the same dose of MF alone.[7] The LABA, once daily Indacaterol (IND) has shown sustained 24-hour bronchodilation, fast onset and good safety and tolerability profiles.[8] The combination of MF and IND has shown improvements in lung function, symptom control and use of rescue medication, and reduction in the annual rate of exacerbations in asthmatics.[9,10] Additionally, the combination inhaler reduces the possibility of standalone SABA usage for symptom relief while also eliminating the possibility of ICS discontinuation with reduction in the overall expenses.[11] While both once-daily and twice-daily combinations have comparable efficacy, the once-daily dosing regimens are described to be associated with better adherence and a reduced risk of treatment discontinuation.[12,13]

However, despite these advantages of receiving ICS/LABA, it is estimated globally that about 30–50% patients with moderate/severe asthma remain symptomatic.[2] In addition, many patients receiving the therapy report poor disease control and a lower quality of life.[14] Patients with uncontrolled asthma stand out due to the extent of their disease-related physical, social, and economic burdens.[15,16] Therefore, in patients whose asthma is uncontrolled on medium- or high-dose ICS/LABA, the addition of a long-acting muscarinic receptor antagonist (LAMA) can provide further benefit.[16–20]

GINA 2021 recommends add-on treatment with LAMA for patients at GINA 5 and suggests the addition of a LAMA as another controller option for step 4. The addition of LAMA to ICS/LABA in patients with inadequately controlled asthma is known to improve lung function and delay the time to exacerbation; however, the use of two separate inhalers to deliver these medications may increase the likelihood of suboptimal treatment adherence.[19–21]

Once-daily (o.d.), single-inhaler mometasone furoate/indacaterol acetate/glycopyrronium bromide (MF/IND/GLY, an ICS/LABA/LAMA FDC), and MF/IND (an ICS/LABA FDC) via Breezhaler® have been approved for maintenance treatment of patients with inadequately controlled asthma. MF/IND/GLY combinations have been formulated and developed with medium- and high-dose of MF, whereas MF/IND have been formulated and developed with low-, medium- and high-dose of MF. The development process for MF doses in MF/IND/GLY and MF/IND has been reviewed in detail elsewhere.[22] MF/IND and MF/IND/GLY, at different MF doses, improved lung function, asthma control, and reduced exacerbations in studies of the PLATINUM programme (PALLADIUM,[23] IRIDIUM[17] and ARGON[21]) in patients with inadequately controlled asthma.[17,21,23,24] The pharmacokinetic profiles showed a similar systemic exposure for triple combination versus all 3 mono components, indicating a lack of pharmacokinetic interaction.[22,25,26] These formulations could therefore provide a novel once-daily treatment option for patients across asthma severity and flexibility for clinicians to step-up or step-down the treatment using the same device and molecules.

The PALLADIUM study (NCT02554786) assessed the efficacy and safety of medium-dose MF/IND (160/150 µg) and high-dose MF/IND (320/150 µg) o.d. versus corresponding doses of MF monotherapy; furthermore, high-dose MF/IND o.d. was compared with the well-established ICS/LABA combination of FLU/SAL high-dose (500/50 µg) twice-daily (b.i.d.) over 52 weeks.[23]

IRIDIUM, a 52-week treatment study (NCT02571777) evaluated the efficacy and safety of medium-dose MF/IND/GLY (150/50/80 µg) o.d. and high-dose MF/IND/GLY (150/50/160 µg) o.d. with medium- and high-dose MF/IND o.d. and high-dose FLU/SAL (500/50 µg) b.i.d. in adult patients whose asthma was inadequately controlled with medium- or high-dose ICS/LABA.[17]

The ARGON study (NCT03158311) compared medium- and high-dose MF/IND/GLY o.d. in a single inhaler to a loose triple combination of high-dose FLU/SAL b.i.d. + tiotropium (TIO) o.d. (ICS plus LABA, and LAMA delivered separately via different inhalers) over 24 weeks of treatment, in patients who were uncontrolled on medium- and high-dose ICS/LABA.[21]

These three studies in the PLATINUM program (PALLADIUM, IRIDIUM, and ARGON) used similar interventions (drugs and their doses) with consistent outcome measurements and study design elements. All studies used well-studied and widely used external comparators. These commonalities prompted the pooling of data in this review to better characterise these novel once-daily controller formulations (MF/IND and MF/IND/GLY) for severe asthma.

Methods

Study Details and Patient Criteria

This review presents the efficacy of MF/IND versus FLU/SAL using pooled data from the PALLADIUM[23] and IRIDIUM[17] studies, and the efficacy and safety of MF/IND/GLY versus FLU/SAL and FLU/SAL + TIO using data from IRIDIUM and ARGON studies, respectively.[21] The results from individual studies are published elsewhere.[17,21,23,27] A brief description of all Phase III studies including PALLADIUM, IRIDIUM, and ARGON is provided in Table 1. Details of the individual study descriptions, methods, and patient inclusion criteria are published.[17,21,23]

Table 1 An Overview of Included Studies (PALLADIUM, IRIDIUM, and ARGON)

(A) Study Design and Patient Inclusion Criteria		
PALLADIUM[23]	**IRIDIUM[17]**	**ARGON[21]**
52-week, multicentre, randomised, double-blind, triple-dummy, parallel-group study	52-week, multicentre, randomised, double-blind, double-dummy, parallel-group, controlled study	24-week, multicentre, randomised, partially blinded, open-label, active-controlled parallel-group, study
Aged ≥12 to ≤75 years	Aged ≥18 to ≤75 years	Aged ≥18 years
Prior medium- or high-dose ICS or low-dose ICS/LABA for ≥3 months and at stable doses for ≥1 month	Prior medium- or high-dose ICS/LABA for ≥3 months and at a stable dose for ≥1 month	Prior medium or high-dose ICS/LABA for ≥3 months and at a stable dose for ≥1 month
Exacerbation history not required	≥1 severe asthma exacerbation in last 12 months	≥1 severe asthma exacerbation in last 12 months
ACQ-7 score: ≥1.5	ACQ-7 score: ≥1.5	ACQ-7 score: ≥1.5
Pre-bronchodilator FEV_1% predicted: ≥50% and <85%	Pre-bronchodilator FEV_1% predicted: <80%	Pre-bronchodilator FEV_1% predicted: <85%
FEV_1, reversibility*: Increase in FEV_1 of ≥12% and 200 mL	FEV_1, reversibility*: Increase in FEV_1 of ≥12% and 200 mL	FEV_1, reversibility*: Increase in FEV_1 of ≥12% and 200 mL

(B) Treatment Arms				
	Pooled Analysis of PALLADIUM and IRIDIUM[27] (N = 3154)	**IRIDIUM[17] (N = 1857)†**	**ARGON[21] (N = 1426)**	**Total (N = 6437)**
Medium-dose MF/IND	1044	–	–	1044
High-dose MF/IND	1054	–	–	1054
Medium-dose MF/IND/GLY	–	620	474	1094
High-dose MF/IND/GLY	–	619	476	1095
High-dose FLU/SAL	1056	618	–	1674
High-dose FLU/SAL + TIO	–	–	476	476

Notes: *After administration of 400 µg salbutamol/360 µg albuterol (or equivalent dose). †Patients in the MF/IND arm from the PALLADIUM and IRIDIUM studies are included in the pooled analysis of PALLADIUM and IRIDIUM who had received the same dose of high-dose MF/IND, medium-dose MF/IND, and high-dose FLU/SAL in similar proportion. Medium-dose MF/IND/GLY, MF/IND/GLY 80/150/50 µg o.d.; High-dose MF/IND/GLY, MF/IND/GLY 160/150/50 µg o.d.; Medium-dose MF/IND, MF/IND 160/150 µg o.d.; High-dose MF/IND, MF/IND 320/150 µg o.d.; High-dose FLU/SAL, FLU/SAL 500/50 µg b.i.d; TIO, 5 µg.

Abbreviations: ACQ, Asthma Control Questionnaire; FEV_1, forced expiratory volume in 1 second; MF/IND/GLY, mometasone furoate/indacaterol acetate/glycopyrronium bromide; MF/IND, mometasone furoate/ indacaterol acetate; ICS/LABA, inhaled corticosteroid/long-acting β_2-agonist; o.d., once-daily; FLU/SAL, fluticasone propionate/ salmeterol xinafoate; TIO, tiotropium.

Assessments

Efficacy of MF/IND versus FLU/SAL, and MF/IND/GLY versus FLU/SAL and FLU/SAL + TIO was evaluated in terms of lung function, asthma control, and exacerbations. Lung function was assessed using trough forced expiratory volume in 1 second (FEV_1) and morning (12 hours post-dose) and evening (23 hours post-dose; 12 hours post-dose for FLU/SAL) peak expiratory flow (PEF); asthma control was assessed using the asthma control questionnaire (ACQ-7) and responder analysis (Minimal Clinically Important Difference [MCID], patients showing an improvement from baseline in ACQ-7 score of ≥0.5 units). Annualised rates of moderate or severe, severe, and all (mild, moderate, or severe) exacerbations were analysed. The detailed descriptions of the assessments are described in the respective manuscripts.[17,21,23] For all these parameters, comparisons were made:

(i) Medium- and high-dose MF/IND versus high-dose FLU/SAL (pooled data from PALLADIUM[23] and IRIDIUM[17] studies).[27]
(ii) Medium- and high-dose MF/IND/GLY versus high-dose FLU/SAL (data from the IRIDIUM study).[17]
(iii) Medium- and high-dose MF/IND/GLY versus high-dose FLU/SAL + TIO (data from the ARGON study).[21]

When comparing both doses of MF/IND and MF/IND/GLY versus high-dose FLU/SAL, the improvement in trough FEV_1 and ACQ-7 score was assessed at Week 26 and Week 52, and PEF (morning and evening) and exacerbations over 52 weeks. When comparing both doses of MF/IND/GLY with high-dose FLU/SAL + TIO, the lung function endpoints were evaluated at Week 24 (end of study). Trough FEV_1 and ACQ-7 scores were analysed using the mixed model for repeated measures model (MMRM). Responder analysis was performed using a logistic regression model via generalised estimating equations. PEF was analysed using analysis of covariance (ANCOVA) and similar MMRM was used for trough FEV_1, with the baseline FEV_1 values replaced with the baseline PEF. Asthma exacerbations were analysed using a generalised linear model assuming a negative binomial distribution. All p values reported from the pooled analysis should be considered as nominal, with all treatment comparisons being descriptive. Detailed descriptions of the methods and statistical analysis have been published in the respective manuscripts.[17,21,23]

Results

Baseline Demographics and Clinical Characteristics

Baseline demographics and clinical characteristics for the individual studies included in this review are provided in Table 2. A detailed description of baseline demographics and clinical characteristics is provided in the respective manuscripts.[17,21,23,27]

Table 2 Baseline Demographics and Clinical Characteristics in the Randomised Set

	PALLADIUM[23] (N = 2216)	**IRIDIUM[17] (N = 3092)**	**ARGON[21] (N = 1426)**
Age, years Female, n (%)	47.9 ± 14.78 1293 (58)	52.2 ± 12.70 1918 (62)	52.5 ± 13.33 902 (63.3)
Never-smoker, n (%)	1812 (82)	2480 (80)	1086 (76.2)
Duration of asthma, years	14.6 ± 12.75	18.1 ± 15.29	20.7 ± 15.33
Baseline ACQ-7 score	2.3 ± 0.48	2.5 ± 0.57	2.6 ± 0.54
Number of asthma exacerbations in the 12 months prior to screening, n (%)			
0	1539 (69)	2 (<1)	0
1	534 (24.1)*	2483 (80.0)	1137 (79.7)
2	–	484 (16)	221 (15.5)

(*Continued*)

Table 2 (Continued).

	PALLADIUM[23] (N = 2216)	IRIDIUM[17] (N = 3092)	ARGON[21] (N = 1426)
3	–	79 (3)	52 (3.6)
≥4	–	44 (1)	16 (1.1)
Prior asthma treatment; n (%)			
Low-dose ICS	16 (1)	–	–
Medium-dose ICS	442 (20)	–	–
High-dose ICS	154 (7)	–	–
Low-dose ICS/LABA	1524 (69)	13 (<1)[†]	–
Medium-dose ICS/LABA	65 (3)[‡]	1928 (62)	700 (49.1)
High-dose ICS/LABA	–	1143 (37)	713 (50.0)
Missing	15 (1%)	8 (<1)	8 (0.6)
Pre-bronchodilator FEV_1, % predicted	67.3 ± 8.64	54.8 ± 13.65	62.9 ± 13.89
FEV_1 reversibility, % increase	22.8 ± 13.09	27.7 ± 20.15	28.1 ± 17.39

Notes: *>1, 143 (7%), [†]Low-dose ICS/LABA or no dose of ICS/LABA, [‡]Medium- or high-dose ICS/LABA. Data are presented as mean ± SD unless otherwise specified.

Abbreviations: ACQ-7, Asthma Control Questionnaire; FEV_1, forced expiratory volume in 1 second; ICS/LABA, inhaled corticosteroid/long-acting β_2-agonist; N, number of patients.

Trough FEV_1

Pooled data from PALLADIUM and IRIDIUM studies showed comparable improvements in trough FEV_1 between medium-dose MF/IND and high-dose FLU/SAL at Weeks 26 and 52 in patients with asthma inadequately controlled on ICS monotherapy or low- to high-dose ICS/LABA (Table 3). Greater improvements in trough FEV_1 were observed with high-dose MF/IND versus high-dose FLU/SAL at Weeks 26 and 52. In patients who were inadequately controlled with medium- or high-dose ICS/LABA, medium- and high-dose MF/IND/GLY demonstrated a greater improvement in trough FEV_1 compared with high-dose FLU/SAL at Weeks 26 and 52 (Table 3). Medium-dose MF/IND/GLY showed comparable improvements versus high-dose FLU/SAL + TIO in patients uncontrolled on medium- or high-dose ICS/LABA. Greater improvements were observed with high-dose MF/IND/GLY versus FLU/SAL + TIO at Week 24 (Table 3).

Peak Expiratory Flow

Over 52 weeks, both doses of MF/IND demonstrated greater improvement in morning and evening PEF versus high-dose FLU/SAL in patients inadequately controlled on ICS monotherapy or low- to high-dose ICS/LABA (Table 4). Greater improvements were obtained with both doses of MF/IND/GLY compared with high-dose FLU/SAL in patients inadequately controlled on medium-to high-dose ICS/LABA over 52 weeks. Over 24 weeks, the improvements in PEF were comparable between medium-dose MF/IND/GLY and high-dose FLU/SAL + TIO, and greater with high-dose MF/IND/GLY versus high-dose FLU/SAL + TIO in patients who were uncontrolled on medium-or high-dose ICS/LABA (Table 4).

Asthma Control

All treatment arms showed improvement of asthma control in ACQ-7 score from baseline (≥0.5-point reduction from baseline, MCID) at respective study time points.[17,21,27] Medium-dose MF/IND showed comparable, and high-dose MF/IND showed a greater reduction in ACQ-7 score versus high-dose FLU/SAL at Week 26 (Table 5). These ACQ-7 score improvements were comparable between treatments at Week 52. Comparable improvement in ACQ-7 score was

Table 3 Improvement in Trough FEV_1 with Medium- and High-Dose MF/IND and MF/IND/GLY versus High-Dose FLU/SAL, and Medium- and High-Dose MF/IND/GLY versus High-Dose FLU/SAL + TIO

Treatments	Δ, mL (95% CI); p-value	
	Week 26/24*	Week 52
MF/IND versus FLU/SAL		
Medium-dose MF/IND versus High-dose FLU/SAL	28 (2 to 55); 0.034	19 (−7 to 45); 0.154
High-dose MF/IND versus High-dose FLU/SAL	43 (17 to 69); 0.001	51 (25 to 77); <0.001
MF/IND/GLY versus FLU/SAL		
Medium-dose MF/IND/GLY versus High-dose FLU/SAL	99 (64 to 133); <0.001	87 (52 to 122); 0.001
High-dose MF/IND/GLY versus High-dose FLU/SAL	119 (85 to 154); <0.001	145 (111 to 180); <0.001
MF/IND/GLY versus FLU/SAL+ TIO*		
Medium-dose MF/IND/GLY versus High-dose FLU/SAL + TIO	9 (−41 to 60); 0.713	-
High-dose MF/IND/GLY versus High-dose FLU/SAL + TIO	96 (46 to 146); <0.001	-

Notes: All comparisons presented are not adjusted for multiplicity, and therefore, p-values are nominal. *MF/IND/GLY versus FLU/SAL + TIO comparison was evaluated at Week 24. Medium-dose MF/IND/GLY, MF/IND/GLY 80/150/50 µg o.d.; high-dose MF/IND/GLY, MF/IND/GLY 160/150/50 µg o.d.; medium-dose MF/IND, MF/IND 160/150 µg o.d.; high-dose MF/IND, MF/IND 320/150 µg o.d.; high-dose FLU/SAL, FLU/SAL 500/50 µg b.i.d.; TIO, 5 µg o.d.

Abbreviations: Δ, LS mean treatment difference; b.i.d., twice-daily; FEV_1, forced expiratory volume in 1 second; LS, least square; MF/IND, mometasone furoate/indacaterol acetate; MF/IND/GLY, mometasone furoate/indacaterol acetate/glycopyrronium bromide; o.d., once-daily; FLU/SAL, fluticasone propionate/salmeterol xinafoate; TIO, tiotropium.

observed with medium-dose MF/IND/GLY versus high-dose FLU/SAL at Weeks 26 and 52, with greater improvement observed with high-dose MF/IND/GLY over high-dose FLU/SAL at Weeks 26 and 52 (Table 5). High-dose and medium-dose MF/IND/GLY showed greater and comparable improvement versus high-dose FLU/SAL+ TIO at Week 24, respectively, in patients with asthma uncontrolled on medium- to high-dose ICS/LABA. All treatment groups

Table 4 Improvement in Peak Expiratory Flow (PEF) with High-Dose MF/IND and Medium- and High-Dose MF/IND/GLY versus High-Dose FLU/SAL Over 52 Weeks and Medium- and High-Dose MF/IND/GLY versus FLU/SAL + TIO Over 24 Weeks

Treatment	Morning PEF	Evening PEF
	Δ, L/min (95% CI); p-value	
MF/IND versus FLU/SAL		
High-dose MF/IND versus High-dose FLU/SAL	14.5 (9.7 to 19.3); <0.001	11 (6.2 to 15.7); <0.001
MF/IND/GLY versus FLU/SAL		
Medium-dose MF/IND/GLY versus High-dose FLU/SAL	28.5 (23.2 to 33.8); <0.001	25.8 (20.5 to 31.0); <0.001
High-dose MF/IND/GLY versus High-dose FLU/SAL	34.8 (29.5 to 40.1); <0.001	29.5 (24.2 to 34.7); <0.001
MF/IND/GLY versus FLU/SAL+ TIO*		
Medium-dose MF/IND/GLY versus High-dose FLU/SAL + TIO	5.9 (0.3 to 11.6); 0.038	2.7 (−2.8 to 8.2); 0.335
High-dose MF/IND/GLY versus High-dose FLU/SAL + TIO	11.8 (6.1 to 17.4); <0.001	9.8 (4.3 to 15.3); <0.001

Notes: All comparisons presented are not adjusted for multiplicity, and therefore, p-values are nominal. *Data analysed over 17 to 24 weeks. Medium-dose MF/IND/GLY, MF/IND/GLY 80/150/50 µg o.d.; High-dose MF/IND/GLY, MF/IND/GLY 160/150/50 µg o.d.; High-dose MF/IND, MF/IND 320/150 µg o.d.; High-dose FLU/SAL, FLU/SAL 500/50 µg b.i.d.; TIO, TIO 5 µg o.d.

Abbreviations: Δ, LS mean treatment difference; b.i.d., twice-daily; MF/IND, mometasone furoate/indacaterol acetate; MF/IND/GLY, mometasone furoate/indacaterol acetate/glycopyrronium bromide; LS, least square; PEF, peak expiratory flow, TIO, tiotropium; o.d., once-daily; FLU/SAL, fluticasone propionate/salmeterol xinafoate.

Table 5 Improvement in ACQ-7 Scores and Proportion of Patients Achieving MCID Improvement in ACQ-7 Scores (ACQ Responders) with MF/IND and Medium- and High-Dose MF/IND/GLY versus High-Dose FLU/SAL and Medium- and High-Dose MF/IND/GLY versus High-Dose FLU/SAL + TIO at Different Time Points

Treatment	Week 26/24*	Week 52
ACQ-7 Score	**Δ (95% CI); p-value**	
MF/IND versus FLU/SAL		
Medium-dose MF/IND versus High-dose FLU/SAL	−0.043 (−0.105 to 0.018); 0.169	−0.015 (−0.077 to 0.048); 0.646
High-dose MF/IND versus High-dose FLU/SAL	−0.091 (−0.153 to −0.030); 0.004	−0.041 (−0.104 to 0.021); 0.197
MF/IND/GLY versus FLU/SAL		
Medium-dose MF/IND/GLY versus High-dose FLU/SAL	–0.084 (–0.164 to –0.005); 0.038	0.008 (−0.073 to 0.090); 0.845
High-dose MF/IND/GLY versus High-dose FLU/SAL	–0.086 (–0.165 to –0·006); 0.034	−0.121 (−0.202 to −0.040); 0.003
MF/IND/GLY versus FLU/SAL+ TIO*		
Medium-dose MF/IND/GLY versus High-dose FLU/SAL + TIO	−0.032 (−0.125 to 0.060); 0.245	-
High-dose MF/IND/GLY versus High-dose FLU/SAL + TIO	−0.124 (−0.216 to −0.032); 0.004	-
ACQ-7 responder (≥0.5-point reduction from baseline)	**Odds ratio (95% CI); p-value**	
MF/IND versus FLU/SAL		
Medium-dose MF/IND versus High-dose FLU/SAL	1.05 (0.86 to 1.28); 0.648	1.07 (0.86 to 1.32); 0.564
High-dose MF/IND versus High-dose FLU/SAL	1.20 (0.98 to 1.47); 0.083	1.17 (0.94 to 1.45); 0.154
MF/IND/GLY versus FLU/SAL		
Medium-dose MF/IND/GLY versus High-dose FLU/SAL	1.20 (0.92 to 1.57); 0.17	0.99 (0.75 to 1.29); 0.922
High-dose MF/IND/GLY versus High-dose FLU/SAL	1.21 (0.93 to 1.57); 0.15	1.41 (1.06 to 1.86); 0.017
MF/IND/GLY versus FLU/SAL+ TIO*		
Medium-dose MF/IND/GLY versus High-dose FLU/SAL + TIO	1.23 (0.94 to 1.61); 0.061	-
High-dose MF/IND/GLY versus High-dose FLU/SAL + TIO	1.11 (0.85 to 1.46); 0.227	-

Notes: *Data analysed at Week 24. All comparisons presented are not adjusted for multiplicity, and therefore, p-values are nominal. Medium-dose MF/IND/GLY, MF/IND/GLY 80/150/50 µg o.d.; high-dose MF/IND/GLY, MF/IND/GLY 160/150/50 µg o.d.; medium-dose MF/IND, MF/IND 160/150 µg o.d.; high-dose MF/IND, MF/IND 320/150 µg o.d.; high-dose FLU/SAL, FLU/SAL 500/50 µg b.i.d.; TIO, TIO 5 µg o.d.

Abbreviations: Δ, LS mean treatment difference; ACQ, Asthma Control Questionnaire; b.i.d., twice-daily; LS, least square; MF/IND, mometasone furoate/indacaterol acetate; MF/IND/GLY, mometasone furoate/indacaterol acetate/glycopyrronium bromide; TIO, tiotropium; o.d., once-daily; FLU/SAL, fluticasone propionate/salmeterol xinafoate.

(high-dose and medium-dose MF/IND and MF/IND/GLY) showed meaningful change in ACQ-7 score from baseline in terms of MCID improvements (≥0.5). The proportion of patients achieving MCID in ACQ-7 score was comparable across treatment arms in all reviewed studies, except for the higher proportion of patients achieving the MCID with high-dose MF/IND/GLY compared with high-dose FLU/SAL at Week 52, and high-dose FLU/SAL + TIO at Week 24, respectively (Table 5).

Asthma Exacerbations

In patients with asthma inadequately controlled on ICS monotherapy or low- to high-dose ICS/LABA, medium-dose MF/IND demonstrated a reduction of 6% in moderate or severe, 9% in severe and 16% in all exacerbations compared to high-dose FLU/SAL (Table 6). However, high-dose MF/IND demonstrated reductions of 22% in moderate or severe, 26% in severe, and 19% in all exacerbations compared with high-dose FLU/SAL over 52 weeks. In patients with asthma inadequately controlled on medium- to high-dose ICS/LABA, medium-dose MF/IND/GLY demonstrated a comparable

Table 6 Reduction in Annualised Rate of Moderate or Severe, Severe, and All (Mild. Moderate, Severe) Exacerbations with Medium- and High-Dose of MF/IND and MF/IND/GLY versus High-Dose FLU/SAL and with MF/IND/GLY versus High-Dose FLU/SAL + TIO

Treatment	Moderate or Severe Exacerbations	Severe Exacerbations	All (mild. Moderate, severe) exacerbations
	Rate Ratio (95% CI); p-value		
MF/IND versus FLU/SAL			
Medium-dose MF/IND versus High-dose FLU/SAL	0.94 (0.79 to 1.12); 0.479	0.91 (0.75 to 1.11); 0.359	0.84 (0.72 to 0.98); 0.024
High-dose MF/IND versus High-dose FLU/SAL	0.78 (0.66 to 0.93); 0.006	0.74 (0.61 to 0.91); 0.004	0.81 (0.70 to 0.94); 0.006
MF/IND/GLY versus FLU/SAL			
Medium-dose MF/IND/GLY versus High-dose FLU/SAL	0.81 (0.66 to 0.99); 0.041	0.84 (0.67 to 1.05); 0.117	0.70 (0.58 to 0.84); <0.001
High-dose MF/IND/GLY versus High-dose FLU/SAL	0.64 (0.52 to 0.78); <0.001	0.58 (0.45 to 0.73); <0.001	0.60 (0.50 to 0.72); <0.001
MF/IND/GLY versus FLU/SAL+ TIO*			
Medium-dose MF/IND/GLY versus High-dose FLU/SAL + TIO	1.04 (0.77 to 1.39); 0.798	1.22 (0.85 to 1.75); 0.282	1.01 (0.79 to 1.31); 0.915
High-dose MF/IND/GLY versus High-dose FLU/SAL + TIO	0.88 (0.65 to 1.19); 0.414	1.14 (0.79 to 1.64); 0.494	0.81 (0.62 to 1.06); 0.123

Notes: Data are presented as annualised rate (95% CI); error bars represent CI values. All comparisons presented are not adjusted for multiplicity, and therefore, p-values are nominal. *Comparisons were analysed over 24 weeks. Medium-dose MF/IND/GLY, MF/IND/GLY 80/150/50 µg o.d.; high-dose MF/IND/GLY, MF/IND/GLY 160/150/50 µg o.d.; medium-dose MF/IND, MF/IND 160/150 µg o.d.; High-dose MF/IND, MF/IND 320/150 µg o.d.; high-dose FLU/SAL, FLU/SAL 500/50 µg b.i.d.; TIO, 5 µg o.d.
Abbreviations: b.i.d., twice-daily; MF/IND, indacaterol acetate/mometasone furoate; MF/IND/GLY, mometasone furoate/indacaterol acetate/glycopyrronium bromide; TIO, tiotropium; o.d., once-daily; FLU/SAL, fluticasone propionate/salmeterol xinafoate.

reduction in the annualised rate of exacerbations (except for all exacerbations) versus high-dose FLU/SAL (moderate or severe, 19%; severe, 16% and all exacerbations, 30%). There was a greater reduction in the annualised rate of exacerbations with high-dose MF/IND/GLY versus high-dose FLU/SAL (moderate or severe, 36%; severe, 42% and all exacerbations, 40%). Medium- and high-dose MF/IND/GLY showed a comparable rate of exacerbations versus FLU/SAL + TIO over 24 weeks in patients uncontrolled on medium- to high-dose ICS/LABA (Table 6).

Safety

The detailed safety results for MF/IND and MF/IND/GLY versus FLU/SAL and FLU/SAL + TIO are available in the published papers of the individual studies.[17,21,23,27] Safety was assessed over 52 weeks in the PALLADIUM and IRDIUM studies and over 24 weeks in the ARGON study. Overall, the safety profile was comparable across the treatment arms; MF/IND and MF/IND/GLY were well tolerated. Either dose of MF/IND/GLY and FLU/SAL did not report any new safety signals that indicated no further risks with the addition of LAMA. Moreover, high-dose MF/IND/GLY was not associated with an increased risk of adverse events (frequency of pneumonia, candidiasis, or adrenal ground suppression), compared with the medium-dose MF/IND/GLY via the Breezhaler®.

Discussion

Pooled data from PALLADIUM and IRIDIUM studies showed comparable or greater efficacy with MF/IND o.d. formulations than FLU/SAL b.i.d. in patients with inadequately controlled asthma. Single-inhaler FDCs of MF/IND/GLY o.d. were superior to FLU/SAL b.i.d. and similar to those if not more efficacious than FLU/SAL b.i.d. with TIO o.d. added. Our study design did not allow us to determine with certainty which elements of the once-daily formulations produce these differences. However, we should emphasise that all study designs except the ARGON study were double-blind and used double- or triple-dummies to maintain blinding. Although we believe that once-daily formulations are associated with significant adherence advantages in clinical practice, such an advantage could not be evaluated in these blinded, double- or triple-dummy trials.

The clinical improvements with MF/IND/GLY and MF/IND may be attributed to the individual components (MF, IND, and GLY), and their relative contributions towards the clinical efficacy of these FDCs were explored in the

additional analysis of the IRIDIUM study.[28] MF has stronger glucocorticoid receptor binding than FLU and has been used from its introduction as a once-daily controller. IND is a second-generation LABA or an "ultra LABA" with a much longer duration of action than SAL. Both TIO and GLY are once-daily LAMAs, and both seem to produce a comparable and maximum achievable impact on cholinergic airway tone. If we assume at least a comparable lower airway deposition between delivery devices, the superiority of MF/IND to FLU/SAL would suggest that the difference is attributable to either ICS or LABA differences or both. The most striking and demonstrated difference would seem to be the IND's potency and duration of effect versus SAL. Finally, it has been suggested that the synergy of the molecular elements plays some role in the superiority of ICS/LABA to ICS monotherapy.[29] To our knowledge, such synergy has not been studied for the combination of MF and IND. Comparison of MF/IND/GLY and FLU/SAL was also supported using data from a Phase II lung function profiling study.[30]

MF/IND demonstrated comparable or greater improvements in lung function than FLU/SAL at weeks 26 and 52; whereas the improvement in FEV_1 with MF/IND/GLY versus FLU/SAL was greater, thus showing the benefits in addition to LAMA in patients who needed them. Lung functions were further complemented by improvements in morning and evening PEF with MF/IND and MF/IND/GLY versus FLU/SAL, high-dose MF/IND/GLY versus high-dose FLU/SAL + TIO, with greater treatment differences for all comparisons of MF/IND/GLY versus FLU/SAL. The improvement in PEF with medium-dose MF/IND/GLY versus high-dose FLU/SAL + TIO was comparable.

All treatments improved asthma control, with improvements in ACQ-7 score exceeding MCID values for all treatments. Comparable improvements (greater with high-dose MF/IND) in ACQ-7 scores from baseline were seen with MF/IND and with MF/IND/GLY (substantial improvement) versus FLU/SAL. However, medium-dose MF/IND/GLY showed comparable and high-dose MF/IND/GLY showed greater improvement versus high-dose FLU/SAL+ TIO. In general, the proportions of patients achieving MCID in ACQ-7 were comparable across treatment arms in all the reviewed studies.[17,21,23,27]

Both IRIDIUM and ARGON studies recruited patients with asthma who had suffered ≥1 exacerbation in the year prior to the study, thereby increasing the likelihood of detecting significant differences in exacerbation reduction amongst controller formulations. Medium-dose MF/IND showed comparable (greater for all exacerbations with medium-dose) or greater reduction for moderate or severe, severe, and all exacerbations compared to high-dose FLU/SAL over 52 weeks. MF/IND/GLY demonstrated comparable (30% greater reduction in "all" exacerbations with medium-dose) or greater reductions in moderate or severe, severe, and all exacerbations versus high-dose FLU/SAL. These reductions in exacerbations were achieved with a lower dose of ICS with medium-dose MF/IND/GLY versus high-dose FLU/SAL. A comparable reduction in exacerbations was observed with both doses of MF/IND/GLY versus high-dose FLU/SAL + TIO.

Both doses of MF/IND demonstrated benefits compared with high-dose FLU/SAL across a range of endpoints apart from a few parameters where a comparable improvement was obtained. This was achieved at a reduced steroid dose with medium-dose MF/IND versus high-dose FLU/SAL and with once-daily dosing regimen as opposed to the twice-daily dose regimen in high-dose FLU/SAL. The availability of an ICS/LABA/LAMA FDC in a single device combined with once-daily dosing may offer the advantages of improved patient adherence and convenience.[31,32] The medium-dose MF/IND/GLY combination offers a potential alternative over high-dose ICS/LABA, providing maximum disease control with a reduced steroid burden in line with the GINA approach. High-dose MF/IND/GLY may be helpful in patients who are inadequately controlled on high-dose ICS/LABA or medium-dose MF/IND/GLY and require dose escalation. It may provide a viable option to gain asthma control before escalating to biological therapies. Both the doses of MF/IND and MF/IND/GLY combinations were well tolerated and demonstrated an acceptable safety profile.

Conclusion

In patients with inadequately controlled asthma on ICS monotherapy or low-to-high dose ICS/LABA combination, single-inhaler MF/IND o.d. provided a reduction in asthma exacerbations and improvement in lung function with better asthma control than FLU/SAL b.i.d. (GINA Step 4). Similarly, single-inhaler MF/IND/GLY o.d. improved lung function and reduced exacerbations in patients with asthma inadequately controlled on medium- or high-dose ICS/LABA (GINA Step 4–5). In addition, MF/IND/GLY o.d. via Breezhaler® showed greater improvement in lung function and asthma

control with a comparable annualised rate of exacerbations versus high-dose FLU/SAL b.i.d. + TIO o.d. delivered via two different inhalers in patients with uncontrolled asthma on medium- or high-dose ICS/LABA (GINA Step 5). Safety was similar in all treatment arms. The newly approved combinations (MF/IND and MF/IND/GLY) offer a novel once-daily regimen through a single inhaler to potentially provide clinical benefits versus the current standards of care. They are beneficial in patients across asthma severity with the flexibility to step-up and step-down treatment as needed, based on patient's disease control with the advantage of the same inhaler platform.

Abbreviations

Δ, least square mean treatment difference; ACQ, asthma control questionnaire; AE, adverse event; b.i.d., twice-daily; FDC, fixed dose combination; FEV_1, forced expiratory volume in 1 second; FLU, fluticasone propionate; GINA, Global Initiative for Asthma; GLY, glycopyrronium bromide; ICS, inhaled corticosteroid; IND, indacaterol acetate; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; MCID, minimal clinically important difference; MF, mometasone furoate; MMRM, mixed model for repeated measures; o.d., once-daily; OR, odd's ratio; PEF, peak expiratory flow; RR, rate ratio; SAE, serious adverse event; SAL, salmeterol xinafoate.

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 anonymised to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations.

Acknowledgment

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship of this manuscript. The authors contributed to the preparation of the manuscript draft, along with critical review and approval of the manuscript for submission to the journal. All authors contributed to the intellectual content of the manuscript and approved for publication. Under the direction of the authors, Rabi Panigrahy, Aakash Katdare, and Phani Dantu (professional medical writers; Novartis) assisted in the preparation of this article in accordance with the third edition of Good Publication Practice (GPP3) guidelines (http://www.ismpp.org/gpp3).

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

The studies included in this review were funded by Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA.

Disclosure

Authors received no compensation related to the development of the manuscript. RNvZ-S reports receiving personal fees for consultancy or advisory board participation from Aspen–GlaxoSmithKline, Pfizer, Roche, AstraZeneca, Novartis, Glennmark, Merck Sharp & Dohme, Johnson & Johnson, Boehringer Ingelheim and Cipla, outside of the submitted work. KRC reports grant and personal fees from AstraZeneca, grants, and personal fees from Boehringer Ingelheim, personal fees from CSL, Behring, grant and personal fees from GlaxoSmithKline, personal fees from Inhibrx, personal fees from Merck, grants and personal fees from Grifols, personal fees from Kamada, grants and personal fees from Sanofi, grants and personal fees from Regeneron, grants and personal fees from Novartis, grants and personal fees from Takeda, grants from Vertex, grants from Bellus, outside the submitted work. HAMK reports grants and fees for consultancy or advisory board participation from Novartis, during the conduct of the study; and grants and fees for

consultancy or advisory board participation from AstraZeneca, GlaxoSmithKline and Boehringer Ingelheim, and a grant from Chiesi, outside of the submitted work. All were paid to his institution. CG reports receiving personal fees for advisory board and honoraria for academic talks from GSK, Pfizer, AstraZeneca, Teva, Roche, Novartis, BMS, MSD, Berlin-Chemie, Chiesi, Boehringer Ingelheim, and Sanofi, outside of the submitted work. HS received lecture fees from Astellas Pharma, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Kyorin Pharma, and Novartis Pharma. A-MT, MH and DL are employees of Novartis Pharma AG. AP and PD'A are employees of Novartis Pharmaceutical Corporation. HCT is an employee of Novartis Institutes for BioMedical Research. The authors report no other conflicts of interest in this work.

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