Once-daily, single-inhaler mometasone-indacaterol-glycopyrronium versus mometasone-indacaterol or twice-daily fluticasone-salmeterol in patients with inadequately controlled asthma (IRIDIUM)

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Published in:
The Lancet. Respiratory Medicine

DOI:
10.1016/S2213-2600(20)30190-9

Publication date:
2020

Once-daily, single-inhaler mometasone–indacaterol–glycopyrronium versus mometasone–indacaterol or twice-daily fluticasone–salmeterol in patients with inadequately controlled asthma (IRIDIUM): a randomised, double-blind, controlled phase 3 study

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Lancet Respir Med 2020; 8: 1000–12

Published Online July 9, 2020 https://doi.org/10.1016/S2213-2600(20)30190-9

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See Online for appendix 1

Summary

Background Patients with asthma who are inadequately controlled on inhaled corticosteroid–long-acting β_2-adrenoceptor agonist (ICS–LABA) combinations might benefit from the addition of a long-acting muscarinic receptor antagonist. The aim of the IRIDIUM study was to assess the efficacy and safety of a once-daily, single-inhaler combination of mometasone furoate, indacaterol acetate, and glycopyrronium bromide (MF–IND–GLY) versus ICS–LABA in patients with inadequately controlled asthma.

Methods In this 52-week, double-blind, double-dummy, parallel-group, active-controlled phase 3 study, patients were recruited from 415 sites across 41 countries. Patients aged 18 to 75 years with symptomatic asthma despite treatment with medium-dose or high-dose ICS–LABA, at least one exacerbation in the previous year, and a percentage of predicted FEV_1 of less than 80% were included. Enrolled patients were randomly assigned (1:1:1:1:1) via interactive response technology to receive medium-dose or high-dose MF–IND–GLY (80 µg, 150 µg, 50 µg; 160 µg, 150 µg, 50 µg) or MF–IND (160 µg, 150 µg; 320 µg, 150 µg) once daily via Breezhaler, or high-dose fluticasone–salmeterol (FLU–SAL; 500 µg, 50 µg) twice daily via Diskus. The primary outcome was change from baseline in trough FEV_1 with MF–IND–GLY versus MF–IND at week 26 in patients in the full analysis set, analysed by means of a mixed model for repeated measures. Safety was assessed in all patients who received at least one dose of study drug. This study is registered with ClinicalTrials.gov, NCT02571777, and is completed.

Findings Between Dec 8, 2015, and Jun 14, 2019, 3092 of 4851 patients screened were randomly assigned (medium-dose MF–IND–GLY, n=620; high-dose MF–IND–GLY, n=619; medium-dose MF–IND, n=617; high-dose MF–IND, n=618; high-dose FLU–SAL, n=618). 2747 (88·8%) patients completed the 52-week treatment and 321 (10·4%) started but discontinued study treatment prematurely. Medium-dose MF–IND–GLY (treatment difference [Δ] 76 mL [95% CI 41–111]; p<0·001) and high-dose MF–IND–GLY (Δ 65 mL [31–99]; p<0·001) showed superior improvement in trough FEV_1 versus corresponding doses of MF–IND at week 26. Improvements in trough FEV_1 were greater for both medium-dose MF–IND–GLY (99 mL [64–133]; p<0·001) and high-dose MF–IND–GLY (119 mL [85–154]; p<0·001) than for high-dose FLU–SAL at week 26. Overall, the incidence of adverse events was balanced across the treatment groups. Seven deaths were reported (one with medium-dose MF–IND–GLY, two with high-dose MF–IND–GLY, and four with high-dose MF–IND) during the study; none of these deaths was considered by the investigators to be caused by study drugs or other study-related factors.

Interpretation Once-daily, single-inhaler MF–IND–GLY improved lung function versus ICS–LABA combinations (MF–IND and FLU–SAL) in patients with inadequately controlled asthma. The safety profile was similar across treatment groups. MF–IND–GLY therefore constitutes a good treatment option in these patients.

Funding Novartis Pharmaceuticals.

Introduction

The Global Initiative for Asthma (GINA) 2019 report recommends a medium-dose inhaled corticosteroid (ICS) with a long-acting β_2-adrenoceptor agonist (LABA) as the preferred controller treatment for patients with asthma at GINA step 4, and high-dose ICS with LABA for GINA step 5; however, at least 40% of all patients remain symptomatic with reduced quality of life, decreased work productivity, and increased emergency or hospital-based medical care.[1–4] In patients inadequately controlled on

Research in context

Evidence before this study

We did a systematic literature review on PubMed on Nov 19, 2019, using the search terms "triple therapy", "ICS/LABA/LAMA", "asthma", "clinical trial", and "drug therapy combination". This search identified studies that evaluated the combination of inhaled corticosteroid (ICS), long-acting β_2-adrenoceptor agonist (LABA), and long-acting muscarinic receptor antagonist (LAMA) in patients with asthma. Data from two studies evaluated the efficacy and safety of a fixed-dose combination of twice-daily ICS–LABA–LAMA (beclometasone–formoterol–glycopyrronium) from a single inhaler and showed improvement in lung function and reduction in exacerbations in certain patients with uncontrolled asthma over 52 weeks. Other studies evaluated the addition of a LAMA (tiotropium) to an ICS–LABA combination (free combination), and showed improvement in lung function, reduction in the risk of exacerbation, and a safety profile similar to that of an ICS–LABA combination.

Added value of this study

To our knowledge, the IRIDIUM study is the first to evaluate a once-daily, single-inhaler ICS–LABA–LAMA combination—specifically, medium-dose and high-dose mometasone–indacaterol–glycopyrronium (MF–IND–GLY)—in patients with inadequately controlled asthma. We believe that it is also the first study to show the benefit of this new combination versus two different ICS–LABA treatments: the corresponding ICS–LABA (mometasone–indacaterol; MF–IND), showing the additional beneficial effect of glycopyrronium; and high-dose fluticasone–salmeterol (FLU–SAL), showing the combined benefit of MF–IND–GLY versus a well-established ICS–LABA combination. The study data show the potential benefits of a once-daily fixed-dose combination of MF–IND–GLY for patients with asthma that is inadequately controlled with medium-dose and high-dose ICS–LABA. The study also suggests that medium-dose MF–IND–GLY offers an opportunity to prevent escalation to a high-dose ICS treatment, with no loss of efficacy compared with a well established ICS–LABA combination.

Implications of all the available evidence

In patients with inadequately controlled asthma, the combination of MF–IND–GLY improved lung function compared with the respective MF–IND dose and high-dose FLU–SAL, and was well tolerated. Both doses of MF–IND–GLY reduced the rate of moderate-to-severe exacerbations compared with high-dose FLU–SAL. The combination of ICS–LABA–LAMA containing a medium dose of ICS (medium-dose MF–IND–GLY) has the potential to offer similar or better disease control than ICS–LABA combinations containing high ICS doses. A once-daily dosage regimen and administration via a single inhaler might improve treatment adherence and, ultimately, asthma control in a real-world setting.

medium-dose or high-dose ICS–LABA, the addition of a long-acting muscarinic receptor antagonist (LAMA) can provide further benefit.[5,6]

GINA recommends the LAMA tiotropium as an add-on treatment option for patients at GINA steps 4 and 5 with a history of exacerbations.[1] The addition of tiotropium to ICS–LABA in patients with inadequately controlled asthma has been shown to improve lung function and delay time to first exacerbation, but this has traditionally required the use of two inhalers.[7–9] The use of a single inhaler for ICS–LABA can facilitate asthma management by contributing to adherence.[10,11] The use of a once-daily ICS–LABA–LAMA combination in a single inhaler could be an effective treatment option for patients with asthma and potentially simplify asthma management. Earlier studies in patients with chronic disease, including asthma, have highlighted the importance of once-daily treatment regimens in terms of improved adherence and disease control.[12,13]

Mometasone furoate, indacaterol acetate, and glycopyrronium bromide have been formulated as a single, once-daily ICS–LABA–LAMA combination (MF–IND–GLY), delivered via Breezhaler, for maintenance treatment of asthma. In this dry powder formulation, indacaterol–glycopyrronium delivers once-daily bronchodilation,[14,15] and mometasone offers effective once-daily anti-inflammatory therapy with excellent therapeutic index.[16,17] The MF–IND–GLY combination in a single inhaler builds on the PALLADIUM[18] and QUARTZ[19] studies, which showed the efficacy and safety of once-daily mometasone–indacaterol (MF–IND) via Breezhaler in patients with inadequately controlled asthma.

The goal of the phase 3 IRIDIUM study was to assess the efficacy and safety of medium-dose and high-dose MF–IND–GLY once daily versus medium-dose and high-dose MF–IND once daily, to show the beneficial effect of the addition of glycopyrronium, and to compare the benefits of MF–IND–GLY with a well-established ICS–LABA combination, high-dose fluticasone–salmeterol (FLU–SAL) twice daily, in adult patients with inadequately controlled asthma.

Methods

Study design

IRIDIUM was a 52-week, randomised, double-blind, double-dummy, parallel-group, active-controlled study in patients with inadequately controlled asthma despite medium-dose or high-dose ICS–LABA (figure 1). The 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 Harmonisation Guidelines for Good Clinical Practice and the Declaration of Helsinki. All patients provided written informed consent for inclusion in the study. The protocol is included in appendix 2.

See Online for appendix 2

Participants

Patients were recruited from 415 sites across 41 countries, including private clinics, universities, and hospital sites. Eligible patients were men and women aged 18 to 75 years with a diagnosis of asthma for a period of at least 1 year before screening, FEV_1 of less than 80% of the predicted normal, and an increase in FEV_1 of at least 12% and 200 mL after administration of salbutamol or albuterol. Patients were symptomatic at run-in, with an Asthma Control Questionnaire 7 (ACQ-7) score of at least 1·5, a documented history of at least one asthma exacerbation that required medical care from a physician, emergency room visit, hospitalisation, and systemic corticosteroid treatment in the 12 months before screening. All included patients had been receiving medium-dose or high-dose ICS–LABA for at least 3 months and at a stable dose for at least 1 month before screening. Key exclusion criteria were smoking tobacco products within 6 months before screening or a smoking history of greater than 10 pack-years, a chronic lung disease other than asthma, or an asthma exacerbation requiring systemic corticosteroids, hospitalisation, or emergency room visit within 6 weeks of screening. Patients with a respiratory tract infection or asthma worsening within 4 weeks before screening, or during the run-in period, and clinically significant comorbidities were also excluded. Full inclusion and exclusion criteria are shown in appendix 1 (pp 13–15).

Randomisation and masking

Randomisation was done by means of interactive response technology, to ensure that all staff remained masked to allocation assignment, and was stratified by region or country, or both. Details are provided in appendix 1 (p 15). We used an active comparator, FLU–SAL, which was assessed masked with a double-dummy technique. Open-label FLU–SAL (250 µg, 50 µg) twice daily was provided as medium-dose ICS–LABA treatment during the run-in period. Eligible patients were randomly assigned (1:1:1:1:1) to receive MF–IND–GLY with medium-dose ICS (80 µg, 150 µg, 50 µg) once daily; or MF–IND–GLY with high-dose ICS (160 µg, 150 µg, 50 µg) once daily; or medium-dose MF–IND (160 µg, 150 µg) once daily; or high-dose MF–IND (320 µg, 150 µg) once daily; or high-dose FLU–SAL (500 µg, 50 µg) twice daily.

Procedures

The doses of mometasone in the Breezhaler device are based on pharmacokinetic comparisons and in-vitro bridging from corresponding mometasone doses in the approved Twisthaler formulation.[20] The choice of dose was corroborated by pharmacodynamics studies during the development programme, which confirmed mometasone doses in Breezhaler in terms of FEV_1.[21] An in-vitro component interaction study showed an increase in mometasone fine particle mass in MF–IND–GLY,

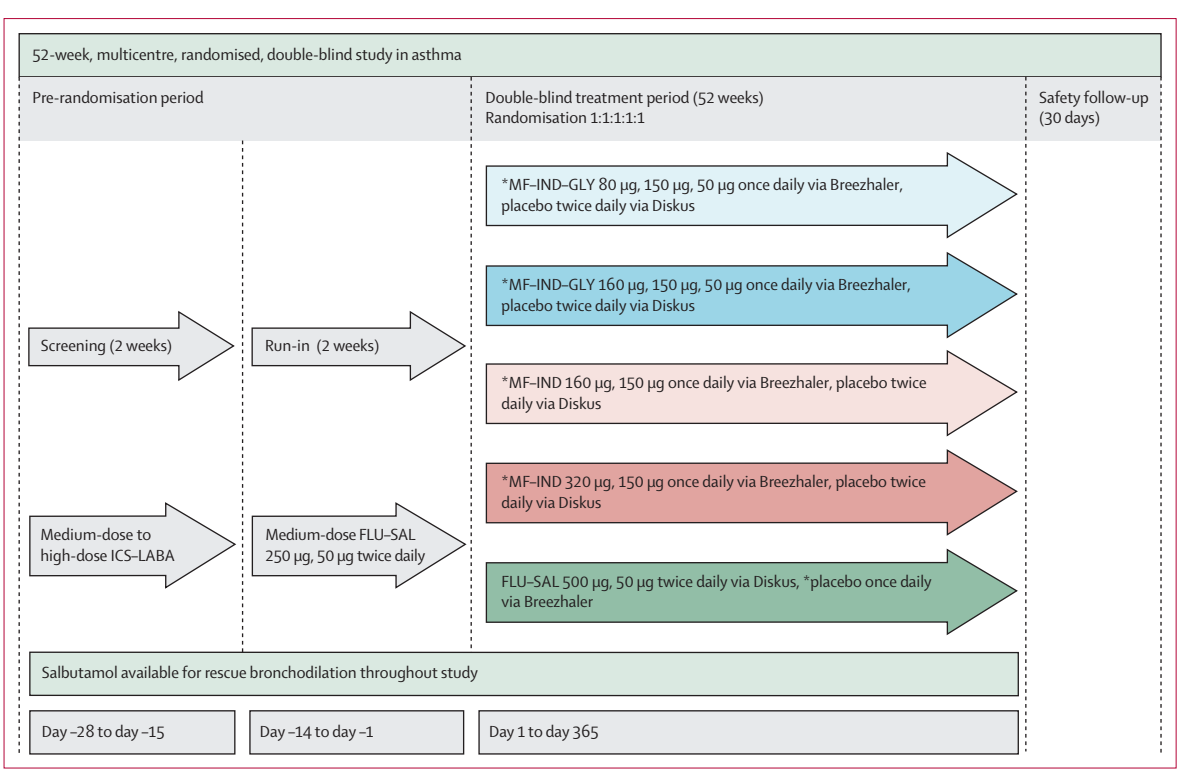

Figure 1: **IRIDIUM study design**

FLU–SAL=fluticasone–salmeterol. ICS–LABA=inhaled corticosteroid–long-acting β_2-adrenoceptor agonist. MF–IND=mometasone–indacaterol. MF–IND–GLY=mometasone–indacaterol–glycopyrronium. *Treatments were administered in the evening.

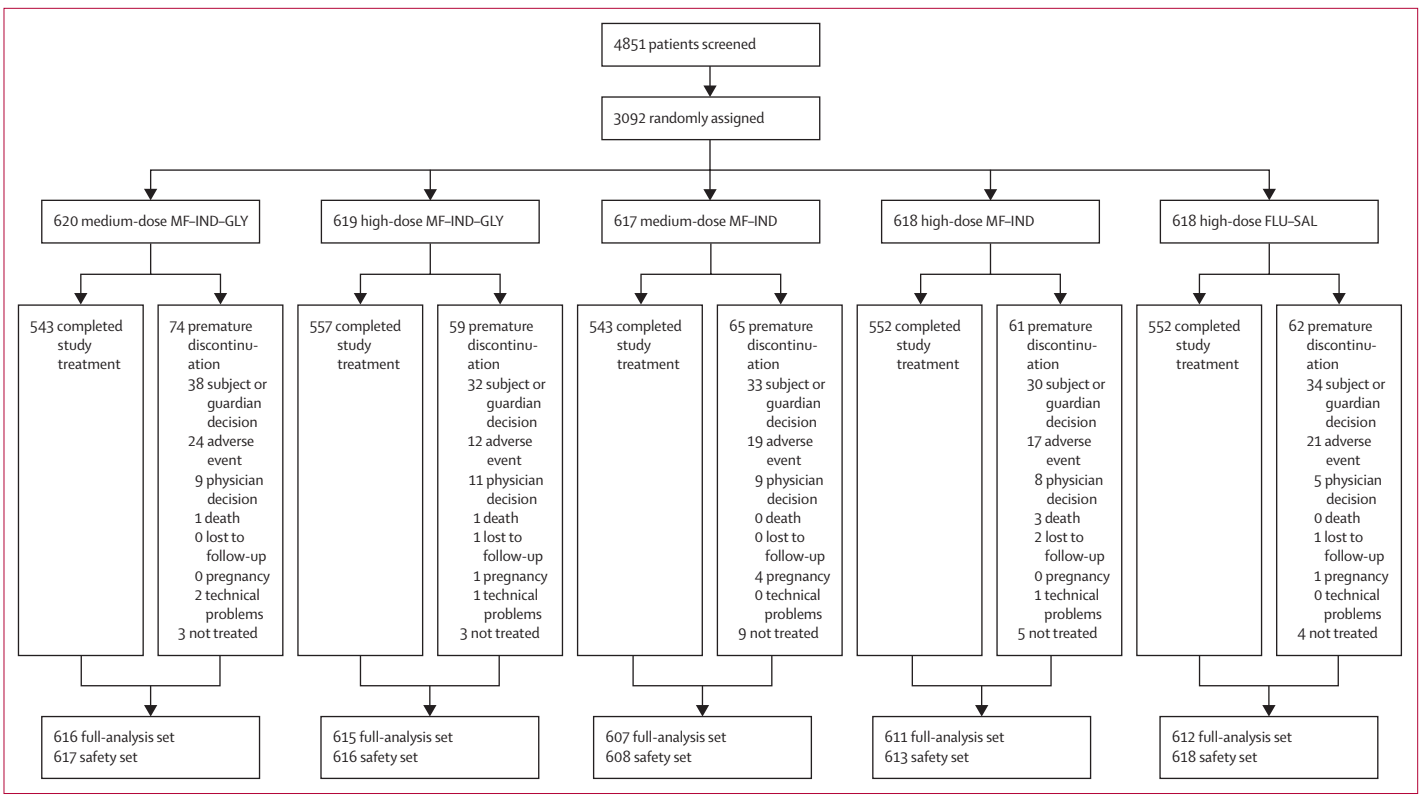

***Figure 2*: Trial profile**

Participants were randomly assigned to receive medium-dose MF–IND–GLY (80 µg, 150 µg, 50 µg) once daily (n=620); or high-dose MF–IND–GLY (160 µg, 150 µg, 50 µg) once daily (n=619); or medium-dose MF–IND (160 µg, 150 µg) once daily (n=617); or high-dose MF–IND (320 µg, 150 µg) once daily (n=618); or high-dose FLU–SAL (500 µg, 50 µg) twice daily (n=618). FLU–SAL=fluticasone–salmeterol. MF–IND=mometasone–indacaterol. MF–IND–GLY=mometasone–indacaterol–glycopyrronium.

compared with the corresponding mometasone dose in MF–IND, delivered via the Breezhaler device. The medium dose of mometasone in the MF–IND–GLY combination was accordingly reduced to 80 µg and the high dose to 160 µg, and they are similar in terms of ICS dose strength to corresponding medium-dose (160 µg) and high-dose (320 µg) mometasone in the MF–IND formulations, which were used as comparators in this study. The efficacy results from a comparison of MF–IND versus mometasone and FLU–SAL have been described in the PALLADIUM study.[18]

MF–IND–GLY and MF–IND were administered once daily in the evening via Breezhaler, and FLU–SAL was administered twice daily, in the morning and evening, via Diskus. A previous study has shown that MF–IND–GLY can be administered effectively and safely either in the morning or in the evening.[22] All patients were trained on all devices and dosing was witnessed at site during visits to ensure correct technique. At screening, all patients were provided with a salbutamol or albuterol metered-dose inhaler as rescue medication. Clinic visits took place at weeks 4, 12, 26, 36, and 52 post-randomisation. Spirometry (FEV_1, forced vital capacity [FVC], forced expiratory flow between 25% and 75% of FVC [$FEF_{25–75\%}$]) was done and ACQ-7 scores were recorded at baseline and at weeks 4, 12, 26, and 52 post-randomisation. Lung function measures were done at the study visits after withholding short-acting β_2-adrenoceptor agonist (SABA) use for 6 h.

Patients were provided with an electronic peak flow meter to record morning and evening peak expiratory flow (PEF), and an e-Diary (Jaeger Asthma Monitor [AM3] combination home spirometer e-Diary, ERT, Germany) to record symptoms and use of rescue medication from the start of the run-in period until the end of the treatment period. Asthma exacerbations were captured throughout the study and reported by investigators on the case report form. Treatment-emergent adverse events were captured along with their severity and association with study treatment throughout the study period. Electrocardiogram, vital signs, and laboratory tests were also measured as part of the safety assessment.

Outcomes

The primary outcome of the study was change from baseline in trough FEV_1 with medium-dose or high-dose MF–IND–GLY versus medium-dose or high-dose MF–IND at week 26. Trough FEV_1 was considered the lung function parameter of choice in line with guidance on the clinical investigation of treatments

	Medium-dose MF–IND–GLY (n=620)	High-dose MF–IND–GLY (n=619)	Medium-dose MF–IND (n=617)	High-dose MF–IND (n=618)	High-dose FLU–SAL (n=618)	Total (n=3092)
Age, years	52·4 (12·71)	52·1 (12·91)	51·8 (12·86)	52·0 (12·81)	52·9 (12·23)	52·2 (12·70)
Sex						
Male	258 (42%)	238 (38%)	239 (39%)	238 (39%)	201 (33%)	1174 (38%)
Female	362 (58%)	381 (62%)	378 (61%)	380 (61%)	417 (68%)	1918 (62%)
Duration of asthma, years	17·6 (14·68)	19·2 (15·58)	18·3 (15·69)	16·8 (14·66)	18·6 (15·75)	18·1 (15·29)
Number of asthma exacerbations that required treatment in the 12 months before the study						
0	1 (<1%)	0	0	1 (<1%)	0	2 (<1%)
1	502 (81%)	515 (83%)	469 (76%)	501 (81%)	496 (80%)	2483 (80%)
2	95 (15%)	78 (13%)	119 (19%)	98 (16%)	94 (15%)	484 (16%)
3	16 (3%)	18 (3%)	18 (3%)	11 (2%)	16 (3%)	79 (3%)
≥4	6 (1%)	8 (1%)	11 (2%)	7 (1%)	12 (2%)	44 (1%)
Smoking status						
Never smokers	489 (79%)	505 (82%)	493 (80%)	501 (81%)	492 (80%)	2480 (80%)
Former smokers	131 (21%)	114 (18%)	124 (20%)	117 (19%)	126 (20%)	612 (20%)
Baseline ACQ-7 score*	2·5 (0·56)	2·5 (0·61)	2·5 (0·54)	2·6 (0·57)	2·5 (0·56)	2·5 (0·57)
Pre-bronchodilator FEV_1, L†	1·6 (0·57)	1·6 (0·59)	1·6 (0·60)	1·6 (0·58)	1·6 (0·58)	1·6 (0·58)
Pre-bronchodilator FEV_1, % predicted†	54·1 (14·22)	55·1 (13·47)	54·9 (13·66)	54·4 (13·50)	55·4 (13·40)	54·8 (13·65)
FEV_1 reversibility after salbutamol inhalation, % increase‡	27·4 (18·63)	26·8 (21·31)	27·8 (19·05)	28·1 (19·65)	28·4 (21·91)	27·7 (20·15)
Previous asthma treatment						
Medium-dose ICS–LABA	376 (61%)	389 (63%)	390 (63%)	398 (64%)	375 (61%)	1928 (62%)
High-dose ICS–LABA	238 (38%)	225 (36%)	223 (36%)	218 (35%)	239 (39%)	1143 (37%)
Low-dose ICS–LABA or no ICS–LABA	4 (1%)	2 (<1%)	3 (1%)	2 (<1%)	2 (<1%)	13 (<1%)
Missing	2 (<1%)	3 (1%)	1 (<1%)	0	2 (<1%)	8 (<1%)

Data are n (%) or mean (SD). 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 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. ACQ-7=Asthma Control Questionnaire 7. eCRF=electronic case report form. FLU–SAL=fluticasone–salmeterol. ICS–LABA=inhaled corticosteroid–long-acting β_2-adrenoceptor agonist. MF–IND=mometasone–indacaterol. MF–IND–GLY=mometasone–indacaterol–glycopyrronium. *High-dose MF–IND–GLY, n=618; total, n=3091. †Medium-dose MF–IND–GLY, n=618; high-dose MF–IND–GLY, n=617; medium-dose MF–IND, n=614; high-dose MF–IND, n=615; high-dose FLU–SAL, n=617; total, n=3081. ‡Medium-dose MF–IND–GLY, n=617; high-dose MF–IND–GLY, n=617; medium-dose MF–IND, n=614; high-dose MF–IND, n=615; high-dose FLU–SAL, n=617; total, n=3080. Patients received medium-dose MF–IND–GLY (80 µg, 150 µg, 50 µg) once daily; or high-dose MF–IND–GLY (160 µg, 150 µg, 50 µg) once daily; or medium-dose MF–IND (160 µg, 150 µg) once daily; or high-dose MF–IND (320 µg, 150 µg) once daily; or high-dose FLU–SAL (500 µg, 50 µg) twice daily. Owing to rounding up, percentages may not add up to 100%.

Table 1: **Baseline characteristics in the randomised set**

for asthma from the European Medicines Agency[23] (CPMP/EWP/2922/01), and 26 weeks was considered to be an appropriate timepoint to assess the trough FEV_1 because the drug effect is expected to reach a steady state in 4 weeks on the basis of the known pharmacokinetic–pharmacodynamic profile of the components. The key secondary outcome was change from baseline in ACQ-7 score with either dose of MF–IND–GLY versus the respective dose of MF–IND at week 26.

Other secondary outcomes were improvement in FEV_1, FVC, and $FEF_{25–75\%}$ over 52 weeks; post-dose FEV_1 (1 h post-dose) at various timepoints (5, 15, 30, and 60 min) on day 1 and at week 26 and week 52; morning and evening PEF over 26 and 52 weeks of treatment; ACQ-7 score over 52 weeks as change from baseline and responder analysis (patients showing improvement from baseline ACQ-7 score of ≥0·5 units); rate of asthma exacerbations and time to first asthma exacerbation (moderate or severe, severe, and all exacerbations), total daily symptom score, percentage of days with no symptoms, and percentage of nights with no night-time awakenings over 52 weeks; reduction in the number of puffs of rescue medication and percentage of days without rescue medication use over 52 weeks; and quality of life as assessed by the Asthma Quality of Life Questionnaire (AQLQ-S) over 52 weeks. For all endpoints, both doses of MF–IND–GLY were compared with the respective doses of MF–IND and with high-dose FLU–SAL. In a post-hoc analysis, we investigated doubling the ICS dose from medium-dose to high-dose MF–IND–GLY. Safety and tolerability were evaluated for all treatments throughout the study and were assessed by an independent, external data safety monitoring board. Serious cardiovascular or cerebrovascular events were evaluated by an independent

adjudication committee and were assigned as major adverse cardiovascular events (MACE) or non-MACE. Cardiovascular deaths were not counted as MACE. Serious asthma outcomes were also adjudicated by an independent committee.

Statistical analysis

To show superiority of MF–IND–GLY versus MF–IND in trough FEV_1 and ACQ-7 score, and assuming a 10% drop-out, a total of 2980 participants (596 patients per treatment group) were needed. Considering a two-sided significance level of 0·05 and after multiplicity adjustment, this number of patients would provide 97% power to detect a treatment difference (Δ) of 90 mL (assuming SD of 380 mL) between MF–IND–GLY and MF–IND at corresponding doses for the primary endpoint of trough FEV_1, and 82% power to detect Δ of 0·15 (assuming SD of 0·80) for the aforementioned treatments in terms of ACQ-7 score.

The primary variable, trough FEV_1, and key secondary variable, ACQ-7, at week 26 were analysed by means of a mixed model for repeated measures on the full analysis set, which included all patients who were assigned a randomisation number and received at least one dose of study medication. The model contained treatment, region, visit, and treatment-by-visit interaction as fixed effects, with baseline FEV_1 or ACQ-7 measurement, baseline-by-visit interaction, FEV_1 before inhalation and FEV_1 within 15–30 min after inhalation of salbutamol or albuterol (components of SABA reversibility) as covariates, and centre nested within region as a random effect. The hypothesis testing on the primary and key secondary endpoints between medium-dose and high-dose MF–IND–GLY versus MF–IND were controlled for multiplicity by means of a graphic testing procedure based on the generalised Simes test in Maurer and colleagues' study.[24] Effects of both doses of MF–IND–GLY versus respective doses of MF–IND were assessed by confirmatory analysis at week 26. No multiplicity adjustments were applied for other secondary endpoints and p values described for these are descriptive.

Asthma exacerbations starting after the first dose and not later than one day after the date of the last dose were included in the analyses of efficacy. A severe exacerbation was defined as an aggravation of asthma symptoms (such as shortness of breath, cough, wheezing, or chest tightness) that requires systemic corticosteroids for at least 3 consecutive days or a need for an emergency room visit, hospitalisation owing to asthma, or death due to asthma. A moderate asthma exacerbation was defined as the occurrence of two or more of the following: progressive increase of at least one asthma symptom; increased use of rescue medication; or deterioration in lung function lasting for 2 days or more that is usually not severe enough to warrant systemic corticosteroids for more than 2 days or hospitalisation. A mild exacerbation was defined as the occurrence of one of the following: deterioration of at least one asthma symptom; increased use of bronchodilator; or deterioration in lung function lasting for 2 days or more that is usually not severe enough to warrant systemic corticosteroids for more than 2 days or hospitalisation. An investigator confirmed that the exacerbation event was clinically significant and went beyond day-to-day variation in asthma control. The annual rates of asthma exacerbations were analysed by means of a generalised linear model assuming the negative binomial distribution. The estimated rate ratio, two-sided 95% CI, and corresponding p values are provided. Time-to-event variables were analysed by means of a Cox regression model. Statistical methods for other secondary variables are detailed in appendix 1 (pp 16–17). All safety evaluations were based on the safety set. All analyses were done by means of SAS version 9.4. The study is registered with ClinicalTrials.gov, NCT02571777.

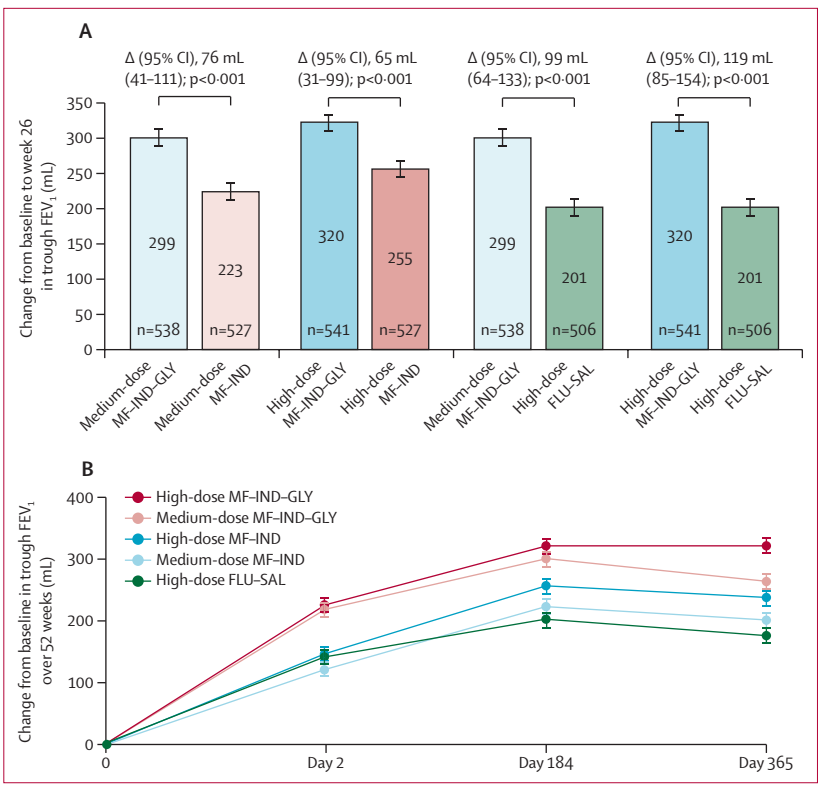

Figure 3: **Change from baseline in trough FEV_1 at week 26 and week 52 in the full analysis set**
Change in trough FEV_1 with MF–IND–GLY versus MF–IND and FLU–SAL at week 26 (A) and over week 52 (B). Data are presented as least squares mean (SE); error bars represent SE values. Patients received medium-dose MF–IND–GLY (80 µg, 150 µg, 50 µg) once daily; or high-dose MF–IND–GLY (160 µg, 150 µg, 50 µg) once daily; or medium-dose MF–IND (160 µg, 150 µg) once daily; or high-dose MF–IND (320 µg, 150 µg) once daily; or high-dose FLU–SAL (500 µg, 50 µg) twice daily. Δ=treatment difference. FLU–SAL=fluticasone–salmeterol. MF–IND=mometasone–indacaterol. MF–IND–GLY=mometasone–indacaterol–glycopyrronium.

Role of the funding source

The funder of the study had a role in the study design, data collection, and data analysis, oversaw study conduct, and was responsible for study report preparation. Medical

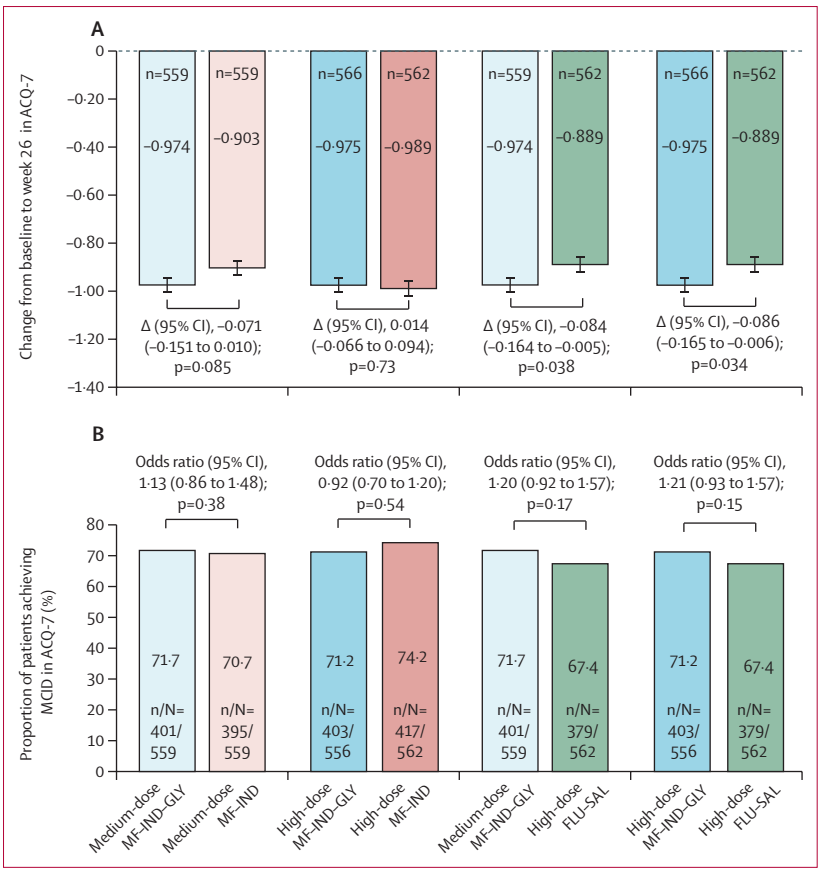

Figure 4: **Change from baseline in ACQ-7 score and proportion of patients achieving MCID in ACQ-7 score at week 26 in the full analysis set**

(A) Treatment difference with MF–IND–GLY versus MF–IND and FLU–SAL in ACQ-7 score; data are presented as least squares mean (SE); error bars represent SE values. (B) Proportion of patients achieving MCID in ACQ-7 score with MF–IND–GLY versus MF–IND and FLU–SAL; number of patients included in analysis (N) and number of patients achieving MCID (n) are given. Patients received medium-dose MF–IND–GLY (80 µg, 150 µg, 50 µg) once daily; or high-dose MF–IND–GLY (160 µg, 150 µg, 50 µg) once daily; or medium-dose MF–IND (160 µg, 150 µg) once daily; or high-dose MF–IND (320 µg, 150 µg) once daily; or high-dose FLU–SAL (500 µg, 50 µg) twice daily. Δ=treatment difference. ACQ-7=Asthma Control Questionnaire 7. FLU–SAL=fluticasone–salmeterol. MCID=minimal clinically important difference. MF–IND=mometasone–indacaterol. MF–IND–GLY=mometasone–indacaterol–glycopyrronium.

writing support was funded by the study sponsor. All authors had full access to all the data in the study and the corresponding author had final responsibility for the decision to submit for publication.

Results

The IRIDIUM study was done between Dec 8, 2015, and Jun 14, 2019, during which time 4851 patients were screened. 3092 were randomly assigned, of whom 2747 (88·8%) completed the 52-week treatment (figures 1, 2), 321 (10·4%) started but discontinued study treatment prematurely, and 24 were not treated. The proportion of patients who prematurely discontinued the treatment phase was balanced across treatment groups; the primary reason for premature discontinuation of the treatment phase was patient or guardian decision.

Patient demographics and clinical characteristics are shown in table 1. The mean (SD) age was 52·2 (12·7) years, with 18·4% of patients aged 65 years and above. Approximately 80% of patients had a history of one asthma exacerbation in the previous 12 months.

The study met its primary endpoint, with medium-dose and high-dose MF–IND–GLY showing superior improvement in trough FEV_1 at week 26 versus the corresponding medium-dose MF–IND once daily (Δ 76 mL [95% CI 41–111]; p<0·001) or high-dose MF–IND once daily (65 mL [31–99]; p<0·001; figure 3A). Compared with high-dose FLU–SAL twice daily, the improvements in trough FEV_1 at week 26 were greater for both medium-dose MF–IND–GLY once daily (99 mL [64–133]; p<0·001) and high-dose MF–IND–GLY once daily (119 mL [85–154]; p<0·001). Improvements in trough FEV_1 with medium-dose and high-dose MF–IND–GLY versus both doses of MF–IND and FLU–SAL observed at week 26 were maintained at week 52 (figure 3B; appendix 1 p 18).

Improvements in post-dose FEV_1 were seen with both doses of MF–IND–GLY versus MF–IND and FLU–SAL (all p<0·001) as early as 5 min after the first study drug administration on day 1. The maximum effect on post-dose FEV_1, observed 1 h after dosing, of 277 mL with medium-dose and 283 mL with high-dose MF–IND–GLY was greater than the 182 mL improvement observed with medium-dose MF–IND (p<0·001) and the 194 mL improvement observed with high-dose MF–IND (p<0·001) on day 1 (appendix 1 p 19). Compared with both doses of MF–IND–GLY (p<0·001), the improvement in FEV_1 with high-dose FLU–SAL was slower and peaked at 157 mL (1 h post-dose; appendix 1 p 19). The difference in post-dose FEV_1 at 1 h was maintained throughout the study (appendix 1 p 32). Improvements in trough FVC and $FEF_{25–75\%}$ with either dose of MF–IND–GLY versus respective doses of MF–IND and FLU–SAL were seen at week 26 and maintained until week 52 (appendix 1 p 32).

All treatment groups showed large (almost double the minimal clinically important difference [MCID]) improvements from baseline in ACQ-7 score, but the study did not meet the key secondary endpoint of superiority of either dose of MF–IND–GLY versus the respective dose of MF–IND in ACQ-7 score after 26 weeks (figure 4A). Differential improvements in ACQ-7 scores, however, were observed for both doses of MF–IND–GLY versus high-dose FLU–SAL at week 26 (–0·084 [p=0·038] for medium-dose and –0·086 [p=0·034] for high-dose). There was no loss of effect of the treatments on ACQ-7 up to 52 weeks (appendix 1 pp 20–21). A higher proportion of patients achieved the MCID (≥0·5-point improvement from baseline) with high-dose MF–IND–GLY versus high-dose FLU–SAL at weeks 4, 12, and 52 (appendix 1 p 33). Treatment differences for change from baseline in ACQ-5 score were generally consistent with those for ACQ-7 (appendix 1 p 22).

Over 52 weeks, MF–IND–GLY reduced the annualised rate of moderate or severe exacerbations by 13% (p=0·17; medium-dose) and 15% (p=0·12; high-dose), severe

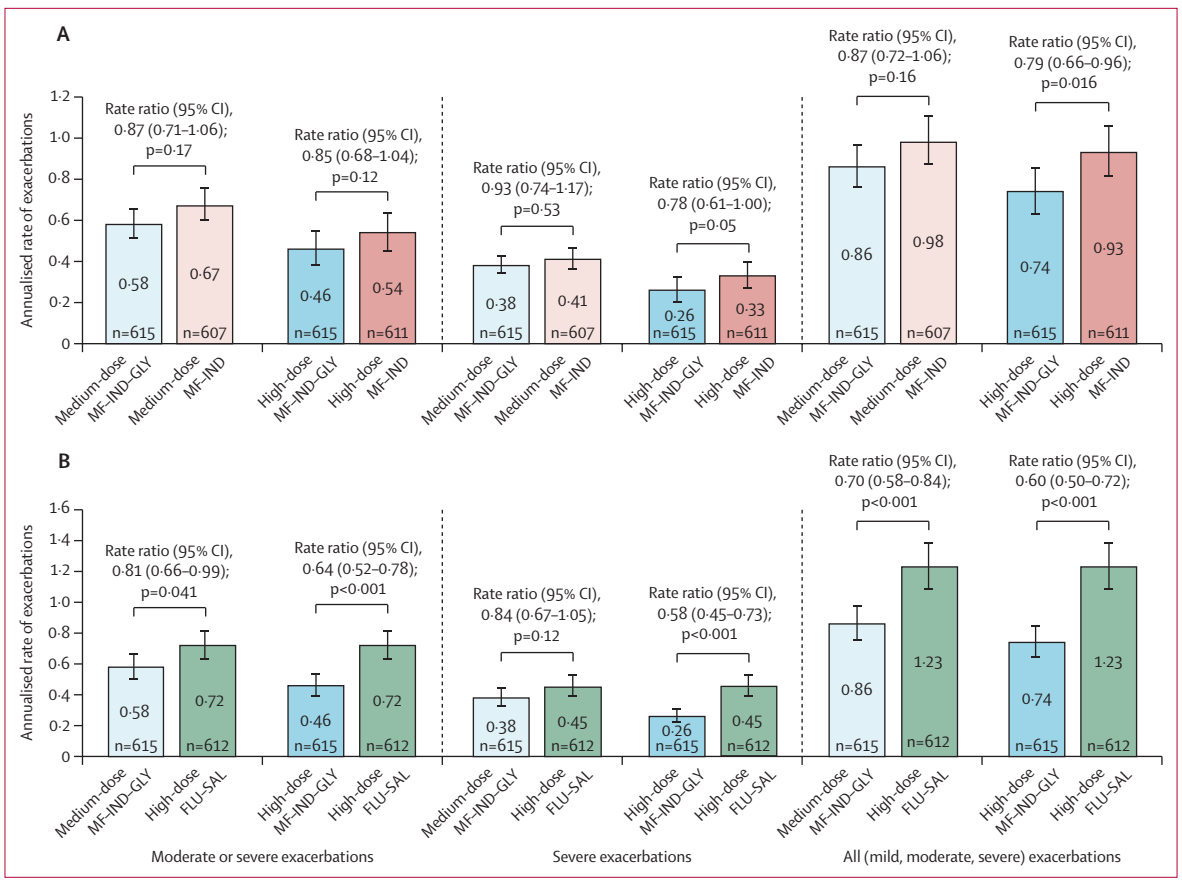

Figure 5: **Annualised rate of exacerbations at week 52 in the full analysis set**
Annualised rate of exacerbations with MF–IND–GLY versus MF–IND (A) and FLU–SAL (B). Data are presented as annualised rate (95% CI); error bars represent 95% CI. Patients received medium-dose MF–IND–GLY (80 µg, 150 µg, 50 µg) once daily; or high-dose MF–IND–GLY (160 µg, 150 µg, 50 µg) once daily; or medium-dose MF–IND (160 µg, 150 µg) once daily; or high-dose MF–IND (320 µg, 150 µg) once daily; or high-dose FLU–SAL (500 µg, 50 µg) twice daily. Definitions of mild, moderate, and severe exacerbations are provided in the main text. FLU–SAL=fluticasone–salmeterol. MF–IND=mometasone–indacaterol. MF–IND–GLY=mometasone–indacaterol–glycopyrronium.

exacerbations by 7% (p=0·53) and 22% (p=0·050), and all exacerbations (mild, moderate, and severe) by 13% (p=0·16) and 21% (p=0·016) compared with medium-dose and high-dose MF–IND (figure 5A). Reductions in exacerbations were also greater with medium-dose and high-dose MF–IND–GLY compared with high-dose FLU–SAL: 19% (p=0·041) and 36% (p<0·001) for moderate or severe exacerbations, 16% (p=0·12) and 42% (p<0·001) for severe exacerbations, and 30% (p<0·001) and 40% (p<0·001) for all exacerbations (figure 5B). The proportions of patients with mild, moderate, or severe, or severe exacerbations are tabulated in appendix 1 (p 34).

The time to first moderate or severe, or severe exacerbation was slightly longer with MF–IND–GLY versus the respective doses of MF–IND, and more so versus FLU–SAL (appendix 1 pp 23–24, 35).

The change from baseline in evening PEF with medium-dose and high-dose MF–IND–GLY during weeks 1–52 was greater than that with the respective doses of MF–IND once daily (15·0 L/min for medium-dose and 17·5 L/min for high-dose) and high-dose FLU–SAL twice daily (25·8 L/min and 29·5 L/min; all p<0·001; figure 6 and appendix 1 p 25). Similarly, clinically meaningful improvements were seen in mean morning PEF with MF–IND–GLY versus MF–IND and FLU–SAL (all p<0·001; appendix 1 p 25).

The reductions in the mean daily number of puffs of rescue medication and percentage of rescue medication-free days with both doses of MF–IND–GLY were similar to the respective doses of MF–IND and to FLU–SAL over 52 weeks (appendix 1 pp 36–37). Reductions in total daily asthma symptom scores, percentage of asthma symptom-free days, and percentage of nights with no night-time awakenings were similar across all treatment groups over 52 weeks (appendix 1 pp 36–37). Clinically meaningful improvements in the standardised AQLQ-S scores from baseline were observed for all treatment groups over 52 weeks, with no meaningful differences between the treatments (appendix 1 pp 36–37).

The overall incidence of adverse events was similar across the treatment groups. The most frequently observed adverse events by preferred terms are shown in

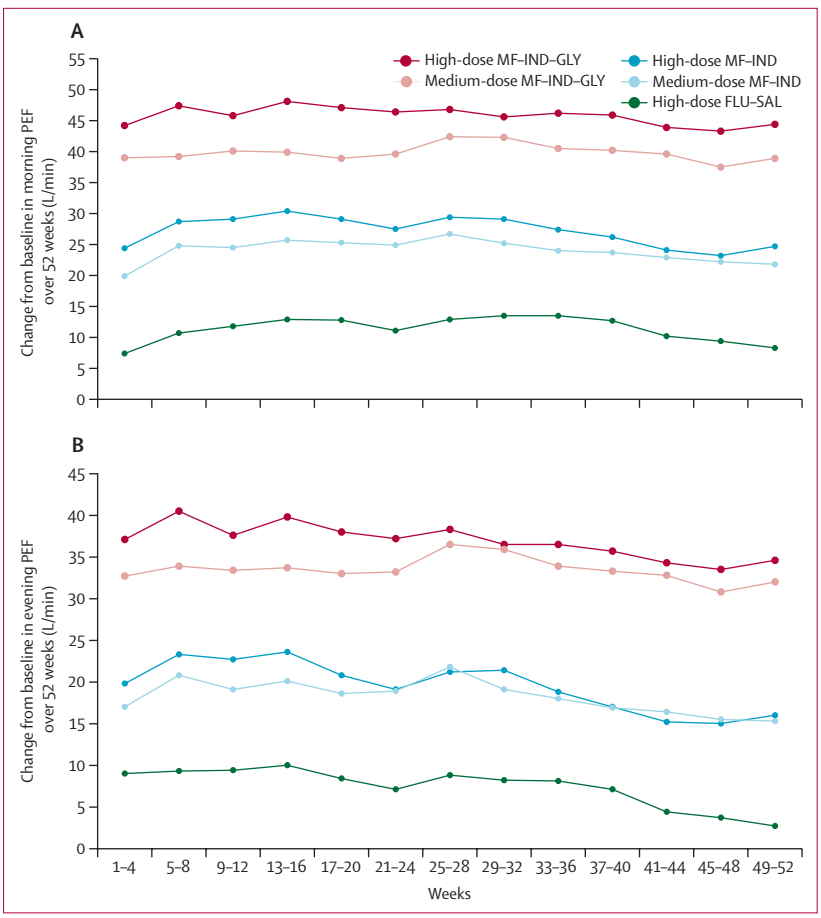

Figure 6: **Change from baseline in morning and evening PEF at 4-weekly intervals up to week 52 in the full analysis set**

Change in morning PEF (A) and evening PEF (B) with MF–IND–GLY, MF–IND, and FLU–SAL. Data are presented as least squares mean. Patients received medium-dose MF–IND–GLY (80 µg, 150 µg, 50 µg) once daily; or high-dose MF–IND–GLY (160 µg, 150 µg, 50 µg) once daily; or medium-dose MF–IND (160 µg, 150 µg) once daily; or high-dose MF–IND (320 µg, 150 µg) once daily; or high-dose FLU–SAL (500 µg, 50 µg) twice daily. FLU–SAL=fluticasone–salmeterol. MF–IND=mometasone–indacaterol. MF–IND–GLY=mometasone–indacaterol–glycopyrronium. PEF=peak expiratory flow.

table 2. Asthma exacerbation was the most commonly reported adverse event. The incidence rates of adverse events suspected to be treatment-related were generally low and similar across treatment groups. The incidence of serious adverse events was low and similar across treatment groups, with asthma exacerbation being the most frequently reported; cholelithiasis, pneumonia, lower respiratory tract infection, and pulmonary embolism were the other most frequently reported serious adverse events. Asthma exacerbation was the most common adverse event leading to permanent discontinuation of study treatment in any treatment group, with no difference between the groups. Adjudicated MACE outcomes were reported in 13 patients; none of these outcomes was considered to be related to study treatment by the study investigators (appendix 1 p 38).

Seven deaths were reported: one aortic dissection with medium-dose MF–IND–GLY; one aortic dissection (during 30-day follow-up after study treatment completion) and one sudden death with high-dose MF–IND–GLY; one train accident, one lymphoma, and two sudden deaths (one in a patient with multiple, severe cardiovascular comorbidities) with high-dose MF–IND. None of the deaths was considered by the reporting investigator to be related to the study drugs. No discernible pattern was evident between MACE events and any specific treatment group.

The effects on the primary endpoint of trough FEV_1 with medium-dose and high-dose MF–IND–GLY versus the respective MF–IND doses were consistent across subgroups defined by baseline characteristics (age, sex, race, pre-bronchodilator FEV_1 % predicted, exacerbation history, previous asthma therapy, and baseline ACQ-7 score; appendix 1 pp 26–27). The improvement in trough FEV_1 was comparable between medium-dose and high-dose MF–IND–GLY at week 26, again with a similar trend observed for the various subgroups (appendix 1 p 28). The reduction in moderate or severe exacerbations with medium-dose and high-dose MF–IND–GLY versus respective doses of MF–IND were consistent across defined subgroups (appendix 1 pp 29–30). In a post-hoc analysis, doubling the ICS dose from medium-dose to high-dose MF–IND–GLY reduced the rate of moderate or severe exacerbations, which was consistent across various subgroups (appendix 1 p 31).

Discussion

The IRIDIUM study showed that the addition of the LAMA glycopyrronium to a medium-dose or high-dose MF–IND combination provides significant improvements in trough FEV_1 over 26 weeks. The study also showed greater improvements with both doses of MF–IND–GLY versus high-dose FLU–SAL, a well-established ICS–LABA combination. These improvements in trough FEV_1 versus MF–IND and FLU–SAL were observed as early as day 2 and were maintained through to week 52.

The significant improvements in trough FEV_1, as observed with MF–IND–GLY versus MF–IND, are in line with those observed in the TRIMARAN and TRIGGER studies,[25] in which glycopyrronium was administered in a twice-daily regimen of beclometasone dipropionate–formoterol fumarate–glycopyrronium (BDP–FF–GLY). In the present study, at week 26, the differences in trough FEV_1 with medium-dose and high-dose MF–IND–GLY were 76 and 65 mL versus the respective doses of MF–IND; these were 57 and 73 mL in the earlier-mentioned studies with a twice-daily treatment regimen.[25] In two replicate PrimoTinA asthma studies in patients with poorly controlled asthma, the addition of tiotropium to the high-dose ICS–LABA treatment resulted in improvements of 88 mL and 111 mL in trough FEV_1 versus placebo add-on to high-dose ICS–LABA at week 24.[8] By comparison, in our study, improvements in trough FEV_1 were 99 mL with medium-dose and 119 mL with high-dose MF–IND–GLY versus high-dose

	Medium-dose MF–IND–GLY (n=617), exp=575·9 years	High-dose MF–IND–GLY (n=616), exp=583·8 years	Medium-dose MF–IND (n=608), exp=573·2 years	High-dose MF–IND (n=613), exp=578·9 years	High-dose FLU–SAL (n=618), exp=575·6 years
Patients with ≥1 adverse event	460 (174·2)	458 (163·3)	453 (163·8)	454 (169·0)	487 (193·9)
Asthma	248 (57·4)	247 (56·1)	268 (65·0)	256 (60·1)	309 (79·4)
Nasopharyngitis	77 (14·4)	64 (11·7)	64 (11·9)	73 (13·7)	83 (15·7)
Bronchitis	48 (8·8)	49 (8·8)	44 (8·0)	46 (8·3)	55 (10·0)
Upper respiratory tract infection	45 (8·2)	33 (5·9)	48 (8·8)	52 (9·4)	52 (9·5)
Headache	30 (5·4)	23 (4·0)	34 (6·1)	24 (4·3)	25 (4·4)
Viral upper respiratory tract infection	31 (5·5)	21 (3·7)	27 (4·8)	38 (6·8)	47 (8·6)
Respiratory tract infection viral	17 (3·0)	18 (3·1)	29 (5·2)	11 (1·9)	22 (3·9)
Upper respiratory tract infection bacterial	22 (3·9)	17 (2·9)	28 (5·0)	27 (4·8)	29 (5·2)
Patient with ≥1 adverse event suspected to be study drug-related	46 (8·4)	51 (9·2)	42 (7·6)	38 (6·9)	51 (9·3)
Patient with ≥1 serious adverse event	49 (8·8)	46 (8·2)	38 (6·8)	52 (9·3)	39 (7·0)
Asthma	15 (2·6)	9 (1·6)	8 (1·4)	12 (2·1)	9 (1·6)
Pneumonia	2 (0·3)	3 (0·5)	3 (0·5)	1 (0·2)	5 (0·9)
Lower respiratory tract infection	1 (0·2)	1 (0·2)	1 (0·2)	3 (0·5)	2 (0·3)
Cholelithiasis	0	3 (0·5)	1 (0·2)	0	1 (0·2)
Pulmonary embolism	0	1 (0·2)	0	3 (0·5)	0
Patient with ≥1 adverse event leading to permanent discontinuation of study drug	25 (4·3)	13 (2·2)	19 (3·3)	18 (3·1)	21 (3·7)
Asthma exacerbation	8 (1·4)	3 (0·5)	12 (2·1)	6 (1·0)	10 (1·7)
Death	1 (0·2)	2 (0·3)	0	4 (0·7)	0
Cancer	0	0	0	1 (0·2)	0
Cardiovascular	1 (0·2)	2 (0·3)	0	2 (0·3)	0
Accidental	0	0	0	1 (0·2)	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 µg, 150 µg, 50 µg) once daily; or high-dose MF–IND–GLY (160 µg, 150 µg, 50 µg) once daily; or medium-dose MF–IND (160 µg, 150 µg) once daily; or high-dose MF–IND (320 µg, 150 µg) once daily; or high-dose FLU–SAL (500 µg, 50 µg) twice daily. 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.

Table 2: **Adverse events, serious adverse events, and deaths in the safety set**

FLU–SAL. A fast onset of action was observed with both doses of MF–IND–GLY, with at least 50 mL improvements in FEV_1 versus both doses of MF–IND, and at least 114 mL improvement versus FLU–SAL, observed as early as 5 min on day 1 and sustained at all timepoints across 52 weeks.

Improvements in lung function were further confirmed by clinically meaningful improvements in evening and morning PEF changes, when adding glycopyrronium to medium-dose and high-dose MF–IND. In the PALLADIUM study,[18] the fixed-dose combination of MF–IND was associated with improvements in evening and morning PEF compared with mometasone alone (23–30 L/min). The present study showed further improvements in PEF with MF–IND–GLY. In the studies by Virchow and colleagues,[25] BDP–FF–GLY twice daily showed an improvement of 8–9 L/min in morning PEF versus BDP–FF. In two replicate PrimoTinA asthma studies,[8] the addition of tiotropium to a high-dose ICS–LABA combination showed improvements in morning and evening PEF ranging from 14 to 24 L/min compared with high-dose ICS–LABA. Asthma studies have suggested that improvements in PEF of 15–20 L/min from baseline are clinically relevant;[26,27] the improvements versus FLU–SAL of 26–35 L/min observed in our study were greater than these clinically relevant changes.

Our study did not meet its key secondary endpoint of superiority in ACQ-7 score at week 26 for either dose of MF–IND–GLY versus the respective dose of MF–IND, at least in part because of large improvements (almost twice the MCID) in ACQ-7 with all treatments. These results are in line with previous studies evaluating ICS–LABA–LAMA versus ICS–LABA from single inhalers[25] or separate inhalers.[8] As seen in many other studies, we observed a considerable Hawthorne effect, reflecting a change in patient behaviour when participating in a trial. This Hawthorne effect might be greater in randomised, active-controlled trials where it is not ethical to have placebo and therefore all patients are receiving active treatment, which

has been observed particularly for patient-reported outcomes such as ACQ and AQLQ.[28] The lack of treatment difference in these parameters between treatments containing bronchodilators has been encountered in many studies of severe asthma when evaluating the addition of drugs to already effective regimens. This observation might reflect the fact that these patient-reported outcomes were initially validated in milder patients in which placebo comparators were used.[29]

Nevertheless, greater improvements in ACQ-7 score were observed with high-dose MF–IND–GLY versus high-dose FLU–SAL at week 52 in the present study, accompanied by a greater proportion of patients achieving an MCID improvement in ACQ-7. The proportion of patients achieving the MCID in ACQ-7 score at weeks 26 and 52 with medium-dose and high-dose MF–IND–GLY was greater than the proportion achieving MCID in ACQ-7 with BDP–FF–GLY in the studies by Virchow and colleagues.[25] An alternative way of assessing asthma control is by looking at mild exacerbations in our study (defined as worsening of symptoms, increase in rescue medication use, or decrease in PEF as captured by e-Diary). Although the improvements in ACQ-7 scores were similar across the treatment groups, a lower percentage of mild exacerbations was shown with medium-dose (13·5%) and high-dose (14·8%) MF–IND–GLY compared with high-dose FLU–SAL (19·4%).

High-dose MF–IND–GLY treatment resulted in a reduction of 15% in the rate of moderate or severe exacerbations, and 22% in the rate of severe exacerbations, versus high-dose MF–IND. In previous studies,[25] BDP–FF–GLY reduced the rate of moderate and severe exacerbations by 12% in the TRIGGER study and 15% in the TRIMARAN study, and severe exacerbations by 23% (pooled data) versus BDP–FF. The advantage of treatment with high-dose MF–IND–GLY versus high-dose FLU–SAL was large, with reductions of 36% in moderate or severe exacerbations and 42% in severe exacerbations, providing evidence for benefits in exacerbation reduction compared with a standard-of-care. These results with once-daily single inhaler therapy are consistent with results from two long-term studies[8] that evaluated the addition of tiotropium to ICS–LABA in patients with poorly controlled asthma. In analyses of time to first exacerbation, medium-dose MF–IND–GLY reduced the risk of severe exacerbations by 22% and high-dose by 32% versus high-dose FLU–SAL, as compared with a 21% reduction in risk of severe exacerbations with a tiotropium add-on to ICS–LABA.[8]

The primary objective of this study was to assess the effect on trough FEV_1 of adding glycopyrronium to two doses of MF–IND. Many other comparisons between the five groups are of great interest, among them the effects of adding a LAMA versus increasing the ICS dose on FEV_1 and exacerbations. Compared with high doses of MF–IND and FLU–SAL, adding glycopyrronium to medium-dose or high-dose MF–IND provided significantly higher trough FEV_1. Additional post-hoc analyses, for which the study was not powered, suggest that the rate of moderate-to-severe exacerbations was similar with medium-dose MF–IND–GLY and high-dose MF–IND, and was lower compared with high-dose FLU–SAL (prespecified endpoint). This suggests that in patients with asthma, poorly controlled on ICS–LABA, treatment with medium-dose MF–IND–GLY instead of high-dose ICS–LABA—ie, using a lower ICS dose—might be considered a valid treatment option. When comparing ICS dose strength in the MF–IND–GLY treatment groups, doubling the ICS dose seemed to provide additional benefit in terms of exacerbation reduction. The difference in trough FEV_1 between medium and high doses of ICS in ICS–LABA–LAMA would be expected to be modest, which was the case in our study. Further studies involving direct comparison between different doses of ICS in the ICS–LABA–LAMA combination are required to validate these outomes. Overall, the numerically largest effects on both FEV_1 and exacerbations were observed with the addition of LAMA and increase in the ICS dose.

The improvements in FEV_1 and moderate-to-severe exacerbation rates shown with the addition of glycopyrronium to MF–IND were independent of the prespecified factors age, sex, race, pre-bronchodilator FEV_1 % predicted, exacerbation history, previous asthma therapy, and baseline ACQ-7. These results are in line with the PrimoTinA asthma studies.[8]

Once-daily medium-dose and high-dose MF–IND–GLY were generally well tolerated. The most frequently reported adverse events and serious adverse events leading to treatment discontinuation across treatment groups were asthma exacerbations, similar to findings of the PALLADIUM study.[18] Seven deaths were reported during the study; none of these was related to asthma or deemed to be related to the treatments being evaluated. Two patients died owing to aortic dissection, but no clear relation to the drugs under study could be established. These two patients were aged over 60 years with coexisting cardiovascular risk factors, including hypertension. Adjudicated MACE outcomes were reported in 13 patients. Most of these patients had cardiovascular-related medical histories, which could potentially have been associated with MACE. No new safety findings were reported with either dose of MF–IND–GLY versus MF–IND and FLU–SAL, indicating no incremental risks with the addition of a LAMA. This finding is in line with results of other trials in patients with asthma, in which use of a LAMA add-on to ICS–LABA did not contribute to additional safety concerns.[7–9,25,30] Furthermore, there was no evidence of increased risk of adverse events typically associated with ICS use (pneumonia, candidiasis, infection, etc) in the high-dose MF–IND–GLY group compared with the medium-dose group.

To our knowledge, this is the first study to evaluate a once-daily dosing of the ICS–LABA–LAMA combination

MF–IND–GLY in a single inhaler versus a comparator ICS–LABA combination and a well-established ICS–LABA combination, FLU–SAL, in patients with asthma inadequately controlled on medium-dose and high-dose ICS–LABA.

Once-daily dosing from a single device to deliver multiple inhaled medications might potentially improve adherence to treatment, as observed in other respiratory diseases,[10–13] which might lead to better disease control, although there is little evidence to support this proposal. Use of a single inhaler device also facilitates step-up from ICS–LABA therapy in the same device, if required.

The IRIDIUM study was a large 52-week, double-blind study in patients with diverse geographical background. It also had a well known active comparator, FLU–SAL, which was assessed masked with a double-dummy technique. The study has some notable limitations. In a five-group study, multiple comparisons are interesting, and would ideally be adjusted for multiplicity; however, this would require a significantly larger number of patients, which is not feasible in a phase 3 setting. Since the primary question was about the addition of glycopyrronium to ICS–LABA in terms of lung function and ACQ-7 score, the study was subsequently not powered to provide conclusive answers for the other comparisons and endpoints. As in most regulatory studies in asthma, patient selection included beta-mimetic reversibility. Patients with at least one exacerbation in the previous year were included in the study; however, approximately 80% of patients had only one exacerbation in the previous year. This is a carefully controlled study and therefore not necessarily reflective of a real-world setting.

The once-daily combination therapy of medium-dose and high-dose MF–IND–GLY, from a single inhaler, significantly improved lung function versus the respective once-daily MF–IND doses and twice-daily high-dose FLU–SAL, a well established ICS–LABA combination. Both doses of MF–IND–GLY showed similarly large improvements in asthma control from baseline, with no difference between any of the treatments. The annualised rate of exacerbations was numerically lower with MF–IND–GLY versus the ICS–LABA comparators. Medium-dose MF–IND–GLY showed greater improvements in trough FEV_1 and exacerbation rates versus twice-daily FLU–SAL, at a reduced steroid dose. The combination MF–IND–GLY was well tolerated at both doses, indicating no incremental risks versus MF–IND and FLU–SAL.

Contributors

The study was designed by HAMK, A-MT, and PD'A. MH and CL contributed to conduct of the study. Data were acquired by HAMK, JM, KRC, and RNvZ-S, and analysed by AP and XS. All authors contributed equally to the interpretation of data. HAMK is the principal investigator for this study. All authors contributed to the intellectual content of the manuscript and approved the final version for publication.

Declaration of interests

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 GlaxoSmithKline and Boehringer Ingelheim, and a grant from Chiesi, outside of the submitted work. All were paid to his institution. JM reports grants and personal fees from Novartis, during the conduct of the study, grants and personal fees from Sanofi, and personal fees from AstraZeneca and ImmunoTek. KRC reports grants and personal fees from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Grifols, Novartis, Regeneron, Sanofi, and Takeda, grants from Vertex, and personal fees from CSL Behring, Inhibrx, and Kamada, all outside of the submitted work . RNvZ-S reports personal fees from Aspen–GSK, AstraZeneca, Cipla, Merck Sharp & Dohme, Novartis, Pfizer, and Roche, outside of the submitted work. MH and A-MT are employees of Novartis Pharma. CL, AP, XS, and PD'A are employees of Novartis Pharmaceuticals.

Data sharing

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. For any such request, email peter.dandrea@novartis.com. All data provided are anonymised to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations.

Acknowledgments

The study was funded by Novartis Pharmaceuticals, East Hanover. We thank the investigators and patients at the investigative sites for their support during the conduct of the study. Under the direction of authors, Vatsal Vithlani and Claire Twomey (professional medical writers; Novartis) assisted in the preparation of this article in accordance with the third edition of Good Publication Practice guidelines.

References

1 GINA. Global strategy for asthma management and prevention 2019. https://ginasthma.org/wpcontent/ (accessed Dec 17, 2019).
2 Bateman ED, Boushey HA, Bousquet J, et al. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma controL study. *Am J Respir Crit Care Med* 2004; **170:** 836–44.
3 Partridge MR, Dal Negro RW, Olivieri D. Understanding patients with asthma and COPD: insights from a European study. *Prim Care Respir J* 2011; **20:** 315–23.
4 Demoly P, Paggiaro P, Plaza V, et al. Prevalence of asthma control among adults in France, Germany, Italy, Spain and the UK. *Eur Respir Rev* 2009; **18:** 105–12.
5 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; **1:** CD011721.
6 Munoz-Cano R, Torrego A, Bartra J, et al. Follow-up of patients with uncontrolled asthma: clinical features of asthma patients according to the level of control achieved (the COAS study). *Eur Respir J* 2017; **49:** 1501885.
7 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.
8 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.
9 Ohta K, Ichinose M, Tohda Y, et al. Long-term once-daily tiotropium respimat(R) 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.
10 Stoloff SW, Stempel DA, Meyer J, Stanford RH, Carranza Rosenzweig JR. Improved refill persistence with fluticasone propionate and salmeterol in a single inhaler compared with other controller therapies. *J Allergy Clin Immunol* 2004; **113:** 245–51.
11 Melani AS, Bonavia M, Cilenti V, et al. Inhaler mishandling remains common in real life and is associated with reduced disease control. *Respir Med* 2011; **105:** 930–38.
12 Woodcock A, Vestbo J, Bakerly ND, et al. Effectiveness of fluticasone furoate plus vilanterol on asthma control in clinical practice: an open-label, parallel group, randomised controlled trial. *Lancet* 2017; **390:** 2247–55.
13 Saini SD, Schoenfeld P, Kaulback K, Dubinsky MC. Effect of medication dosing frequency on adherence in chronic diseases. *Am J Manag Care* 2009; **15:** e22–33.

14 Cazzola M, Molimard M. The scientific rationale for combining long-acting beta2-agonists and muscarinic antagonists in COPD. *Pulm Pharmacol Ther* 2010; **23:** 257–67.

15 Blais CM, Davis BE, Cockcroft DW. The effect of glycopyrronium and indacaterol, as monotherapy and in combination, on the methacholine dose-response curve of mild asthmatics: a randomized three-way crossover study. *Respir Res* 2017; **18:** 146.

16 Derendorf H, Nave R, Drollmann A, Cerasoli F, Wurst W. Relevance of pharmacokinetics and pharmacodynamics of inhaled corticosteroids to asthma. *Eur Respir J* 2006; **28:** 1042–50.

17 Fish JE, Karpel JP, Craig TJ, et al. Inhaled mometasone furoate reduces oral prednisone requirements while improving respiratory function and health-related quality of life in patients with severe persistent asthma. *J Allergy Clin Immunol* 2000; **106:** 852–60.

18 van Zyl-Smit RN, Krüll M, Gessner C, et al. Once-daily mometasone plus indacaterol versus mometasone or twice-daily fluticasone plus salmeterol in patients with inadequately controlled asthma (PALLADIUM): a randomised, double-blind, triple-dummy, controlled phase 3 study. *Lancet Respir Med* 2020; published online July 9. https://doi.org/10.1016/S2213-2600(20)30178-8.

19 Kornmann O, Mucsi J, Kolosa N, et al. Efficacy and safety of inhaled once-daily low-dose indacaterol acetate/mometasone furoate in patients with inadequately controlled asthma: phase III randomised QUARTZ study findings. *Respir Med* 2020; **161:** 105809.

20 Vaidya S, Khindri S, Robinson J, et al. Pharmacokinetics (PK) of single doses of mometasone furoate (MF) delivered via the Breezhaler® (BH) and Twisthaler® (TH) devices in healthy subjects. *Eur Respir J* 2012; **40:** 2145 (abstr).

21 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.

22 Beier J, Watz H, Scholz V, et al. The efficacy of the combination indacaterol/glycopyrronium/mometasone furoate is independent of time of dosing in patients with asthma. *Am J Respir Crit Care Med* 2019; **199** (abstr).

23 EMA. Guideline on the clinical investigation of medicinal products for the treatment of asthma. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-medicinal-products-treatment-asthma_en.pdf (accessed June 3, 2020).

24 Maurer W, Glimm E, Bretz F. Multiple and repeated testing of primary, coprimary, and secondary hypotheses. *Stat Biopharm Res* 2011; **3:** 336–52.24

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

26 Reddel HK, Taylor DR, Bateman ED, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *Am J Respir Crit Care Med* 2009; **180:** 59–99.

27 Santanello NC, Zhang J, Seidenberg B, Reiss TF, Barber BL. What are minimal important changes for asthma measures in a clinical trial? *Eur Respir J* 1999; **14:** 23–27.

28 Braunholtz DA, Edwards SJ, Lilford RJ. Are randomized clinical trials good for us (in the short term)? Evidence for a "trial effect". *J Clin Epidemiol* 2001; **54:** 217–24.

29 Bateman ED, Esser D, Chirila C, et al. Magnitude of effect of asthma treatments on Asthma Quality of Life Questionnaire and Asthma Control Questionnaire scores: systematic review and network meta-analysis. *J Allergy Clin Immunol* 2015; **136:** 914–22.

30 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.