A Review of the Unique Drug Development Strategy of Indacaterol Acetate/Glycopyrronium Bromide/Mometasone Furoate: A First-in-Class, Once-Daily, Single-Inhaler, Fixed-Dose Combination Treatment for Asthma

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ABSTRACT

A novel, once-daily (o.d.), fixed-dose combination (FDC) of indacaterol acetate (IND), glycopyrronium bromide (GLY), and mometasone furoate (MF), delivered by the inhaler Breezhaler® device, is the first long-acting beta2-adrenergic agonist/long-acting muscarinic antagonist/inhaled corticosteroid (LABA/LAMA/ICS) therapy to be approved for maintenance treatment of asthma in adults inadequately controlled on LABA/ICS. The approval of IND/GLY/MF in the European Union (EU) also included an optional electronic sensor and smartphone (or other suitable device) application, making it the first “digital companion” that can be prescribed with an asthma medication. As a result, the European Medicines Agency included this approval as one of the “outstanding contributions to public health” (for Pneumology/Allergology) in their 2020 highlights report. Alongside IND/GLY/MF, an o.d. LABA/ICS FDC, IND/MF, was also developed and approved. This review outlines the unique strategy used in the accelerated development of IND/GLY/MF that combined various approaches: (1) selecting individual components with established efficacy/safety, (2) bridging doses to optimize efficacy/safety of IND/GLY/MF and IND/MF delivered via the Breezhaler® device, (3) developing IND/GLY/MF and IND/MF in parallel, and (4) submission for regulatory approval before formal completion of the pivotal phase III studies. IND/GLY/MF and IND/MF were combined in a single-development plan (PLATINUM program), which comprised four phase III studies: QUARTZ and PALLADIUM evaluated IND/MF while IRIDIUM and ARGON evaluated IND/GLY/MF. A unique feature was the inclusion of two LABA/ICS comparators in the pivotal IRIDIUM study—IND/MF as an internal comparator, and high-dose salmeterol xinafoate/fluticasone propionate (SAL/FLU) as a marketed comparator. In the ARGON study, IND/GLY/MF was compared against o.d. tiotropium (via Respimat®) plus twice-daily (b.i.d.) high-dose SAL/FLU (via Diskus®). As a result of this development strategy, the development and approval of IND/GLY/MF was accelerated by ca. 4 years as against what would be expected from a traditional approach, novel data were generated, and a unique optional digital companion was approved in the EU.

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A fixed-dose combination of indacaterol acetate (IND), glycopyrronium bromide (GLY), and mometasone furoate (MF), delivered by the inhaler Breezhaler® device, is the first once-daily, long-acting beta2-adrenergic agonist/long-acting muscarinic antagonist/inhaled corticosteroid (LABA/LAMA/ICS) therapy to be approved for maintenance treatment of inadequately controlled asthma in adults inadequately controlled on LABA/ICS.

The approval of IND/GLY/MF in the European Union also includes an optional electronic sensor and smartphone (or other suitable device) application (app) that together provide inhalation confirmation, medication reminders, and access to patient objective data (disease-related symptoms and rescue medication use) to support therapeutic decisions, making it the first “digital companion” that can be prescribed with an asthma medication. As a result, the European Medicines Agency (EMA) has listed IND/GLY/MF Breezhaler® as one of the “outstanding contributions to public health” in its 2020 highlights report (for Pneumology/Allergology) [4]. In this review, we describe the unique strategy used in the accelerated development of IND/GLY/MF, alongside the corresponding LABA/ICS FDC (IND/MF), which was developed in parallel, for the treatment of inadequately controlled asthma. This novel approach to drug development could be of interest to anyone involved in developing new safe and effective medicines, including academic researchers, pharmaceutical companies, and health authorities.

DIGITAL FEATURES

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UNMET NEEDS FOR MORE EFFECTIVE, EASY-TO-USE ASTHMA TREATMENTS

Patients with inadequately controlled asthma are at an increased risk of exacerbations,
hospitalizations, or death [5–7]. In general, ICS-based therapies are the cornerstone of treatment options in asthma. The Global Initiative for Asthma (GINA) 2021 strategy recommends the addition of a LABA to medium- or high-dose ICS as the preferred controller treatment option for patients at steps 4 and 5 [8]. However, despite treatment with LABA/ICS, some patients may still have persistent uncontrolled asthma. There are limited treatment options in these patients; therefore LAMA may be considered as an add-on therapy [8].

Poor treatment adherence is also a risk factor for future exacerbations in patients with asthma, independent of symptom control [8]. Some of the known barriers to adherence to inhaled treatment include complicated dosing regimens, improper use of inhalers, and misunderstanding of the role of controller medications that contribute to poor treatment outcomes. It is critical to note that the use of multiple and often different devices represents a significant burden for patients with asthma [9]. The availability of LABA/LAMA/ICS or LABA/ICS in a single inhaler to be used as an o.d. regimen may thus offer advantages in terms of improved adherence. This, in turn, may help in achieving better asthma control; indeed, better adherence and improved patient compliance to medication has been observed with o.d. dosing [10–12].

Another potential treatment option for patients with severe asthma is the use of biologics, especially in patients who are symptomatic despite treatment with LABA/ICS. However, the high cost of biologic therapy along with access challenges limits their widespread clinical use [8, 13]. Thus, there is a clear unmet need for the development of new affordable and effective medicines that provide better treatment options to patients with inadequately controlled asthma [14].

**APPROACH TO AN ACCELERATED AND UNIQUE DRUG DEVELOPMENT STRATEGY**

IND/GLY/MF, the first-in-class LABA/LAMA/ICS for asthma, equipped with the first digital companion (optional electronic sensor and a smartphone [or other suitable device] app) that can be prescribed alongside a treatment for uncontrolled asthma in the EU, and IND/MF, a LABA/ICS FDC, are o.d., single-inhaler FDCs envisioned to provide effective treatment options for patients with asthma that offer increased potential for treatment adherence and improved outcomes [2, 3].

A unique development strategy for IND/GLY/MF was devised to accelerate the drug development process and, thereby, its availability for patients. Novel approaches of this development strategy included (1) selecting individual components with established efficacy and safety profiles, (2) bridging doses to optimize efficacy and safety of IND/GLY/MF and IND/MF delivered via the Breezhaler® device, (3) developing IND/GLY/MF and IND/MF in parallel, in contrast to the traditional sequential approach for developing combination medicines (i.e., first LABA/ICS, followed by LABA/LAMA/ICS), and (4) submission for approval before the pivotal phase III studies had formally completed. These aspects are discussed in detail in the sections below.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

**Selecting Individual Components with Established Efficacy and Safety Profiles**

Indacaterol (IND), an ultra-LABA with a fast onset of action and sustained bronchodilator effect delivered by the Breezhaler® device, is approved at o.d. doses of 150 µg and 300 µg for the treatment of chronic obstructive pulmonary disease (COPD) [15, 16]. Glycopyrronium (GLY), a LAMA that provides 24-h bronchodilation with fast onset of action delivered via the Breezhaler® device, is approved at an o.d. dose of 50 µg for the treatment of COPD [17]. An FDC of IND and GLY, delivered via the Breezhaler® device, is approved for the treatment of COPD [18]. Although IND and GLY were already approved for the treatment of COPD,
these molecules also demonstrated efficacy in patients with asthma [19, 20]. Mometasone furoate (MF), a potent corticosteroid delivered via the Twisthaler® device, is approved at doses of 200 μg o.d., 400 μg o.d., and 400 μg twice daily (b.i.d.) for the treatment of asthma [21–23]. On the basis of this evidence, IND, GLY, and MF were considered as potential molecules for IND/GLY/MF FDC. Moreover, the selection of these three individual components provided flexibility in making use of the available toxicology, pharmacology, and preclinical data, thereby paving a way directly to clinical studies.

**Dose-Finding Strategy and Dose-Bridging Approach**

IND (acetate salt) 150 μg o.d. was considered an optimal dose to advance to phase III studies for IND/GLY/MF and IND/MF [24]. No alterations in fine particle mass of IND in either of the combinations meant that no dose adjustments were necessary [25]. The dose of GLY selected for IND/GLY/MF is the approved dose for COPD—50 μg o.d. delivered via the Breezhaler® device [26].

During the development process, the device used for delivery of drugs is as critical as the active pharmaceutical ingredients. IND and GLY have been approved for inhalation via the Breezhaler® device, whereas MF is approved for inhalation via the Twisthaler® device [15, 17, 23]. Therefore, a stepwise bridging approach was implemented to facilitate the bridging of MF doses from Twisthaler® to Breezhaler® and in IND/GLY/MF and IND/MF formulations [27, 28]. MF at doses of 80, 160, and 320 μg delivered via the Breezhaler® device was assessed to be comparable to MF 200, 400, and 800 μg (two inhalations of 400 μg) delivered via the Twisthaler® device (Table 1), and these adjusted doses were confirmed via a pharmacokinetic/pharmacodynamic study program at different MF dose levels [27–30]. The confirmed doses of MF were then used for the IND/MF FDC. As a result of a pharmaceutical interaction within the IND/GLY/MF formulation, there was an increase in the MF fine particle mass in this FDC compared to the same nominal MF dose in IND/MF. Hence, MF 80 μg o.d. (medium-dose strength) and 160 μg o.d. (high-dose strength) in the IND/GLY/MF formulation provided comparable ICS efficacy/dose strength to MF 160 μg o.d. (medium-dose strength) and 320 μg o.d. (high-dose strength) in the IND/MF formulation, respectively; the low-dose strength of MF in IND/GLY/MF was not developed. The comparable fine particle mass is expected to result in comparable delivery of MF to the lung and comparable systemic MF exposure between the corresponding doses of IND/GLY/MF and IND/MF [28].

**Benefits of Using the Breezhaler® Device**

Breezhaler® is a capsule-based unit-dose dry powder inhaler (DPI) with low airflow resistance, which makes it easier for patients with

| Table 1 | Doses of MF as monotherapy and as fixed-dose combination used in the clinical development program for IND/GLY/MF and IND/MF |
|---------|----------------------------------------------------|---------------------------------|-------------------------------------------------|
|         | Monotherapy                                        | IND/MF                          | IND/GLY/MF                                      |
| MF      | Via Twisthaler® [30]                               | Via Breezhaler® [38]             | Via Breezhaler® [36]                            |
| Dose level (strength) | Low 200 μg                                        | 80 μg                           | Not developed                                   |
|         | Medium 400 μg                                      | 160 μg                          | 80 μg                                           |
|         | High 800 μg                                        | 320 μg                          | 160 μg                                          |

MF 800 μg is administered as two inhalations of MF 400 μg

GLY glycopyrronium bromide, IND indacaterol acetate, MF mometasone furoate

△ Adis
bronchial asthma of varying airway obstruction to achieve the inhalation flow rate required for lung deposition of the medication [31]. Evidence suggests that DPIs have a lower carbon footprint than metered dose inhalers (MDIs) that use potent greenhouse gases as propellents [32]. As Breezhaler® is a DPI free from hydrofluoroalkane/chlorofluorocarbon propellants (HFA/CFC), it is considered to have a reduced carbon footprint and thereby a low impact on the environment [3]. A “cradle-to-grave” carbon footprint study conducted on two Breezhaler® inhaled combinations (IND/GLY/MF and IND/MF FDCs) reported a low carbon footprint with the assessed Breezhaler®, in line with the literature on DPIs [33, 34].

Inclusion of an Optional Electronic Sensor and Application for the IND/GLY/MF Breezhaler®

The IND/GLY/MF Breezhaler® included an optional electronic sensor linked to a paired smartphone (or other suitable device) app (Propeller Health). Both the sensor and app send patients reminders to take their prescribed doses. The app records and stores data (Fig. 1) that the patient can share with their clinician to help inform their treatment plan [3]. Inhalation of the medication through the Breezhaler® device triggers the sensor to recognize, record, and wirelessly transmit time and date of medication usage to the patient’s mobile app and to the healthcare provider’s web app. This passive system helps patients monitor the use of their Breezhaler® inhaler. Additionally, the patient can input their disease-related symptoms and rescue medication use in the app. This information supports patient understanding of their asthma and helps build engagement with their treatment plan and clinician [3]. IND/GLY/MF was submitted and received for regulatory approval as a package with the electronic sensor and app in the EU [3].

Acceleration Steps in Phase III Program

IND/GLY/MF and IND/MF were combined in a single-development plan (PLATINUM program), rather than the traditional sequential approach of evaluation of efficacy and safety of LABA/ICS first followed by LABA/LAMA/ICS. The PLATINUM program included four clinical trials, namely QUARTZ, PALLADIUM, IRIDIUM, and ARGON. The first two studies evaluated IND/MF whereas the last two evaluated IND/GLY/MF [35–38]. In the IRIDIUM study, medium- and high-doses of IND/MF, as well as high-dose salmeterol xinafoate/fluticasone propionate (SAL/FLU), were evaluated as comparators to IND/GLY/MF (Table 2). We estimate that this combined parallel approach (PALLADIUM and IRIDIUM studies in parallel) helped in accelerating the development and approval of IND/GLY/MF by ca. 4 years compared to the traditional sequential approach for developing combination medicines. Moreover, Novartis sought agreement from regulatory authorities for parallel development and that a single pivotal study for each of the FDCs could be acceptable, provided that the results are statistically compelling and clinically relevant. Hence, one robust clinical study was designed for IND/GLY/MF and one for IND/MF, with both studies being conducted in parallel. Clinical study data related to IND/GLY/MF and IND/MF were submitted for regulatory approval while both pivotal PALLADIUM and IRIDIUM

Fig. 1 The Breezhaler® device with the Propeller Health® sensor and smartphone app. Image © Propeller Health
studies were ongoing, accelerating the regulatory filing by ca. 7 months. This was made possible by the fact that although both studies were of 52 weeks’ duration, both primary and key secondary endpoints were measured and analyzed at week 26. This accelerated strategy supported regulatory submission by allowing for full analysis of the primary endpoint (trough FEV₁), key secondary endpoints (ACQ-7), and other important secondary endpoints related to lung function and asthma control, including exacerbations while the study was ongoing, but after all patients completed at least 26 weeks of treatment. The studies continued until 52 weeks under the direction of a separate, fully blinded study team in order to maintain the integrity of the study data and subsequently analyze the remaining time points beyond 26 weeks, including long-term safety. This approach meant that, by the time of regulatory submission, the initial registration dossier contained more than 85% of the expected final data but after all patients completed at least 26 weeks of treatment. Approximately 64% of patients had completed the full 52-week treatment period, ca. 30% had variable exposure between 26 and 52 weeks, whereas the remaining ca. 6% had discontinued the treatment prematurely. Importantly, the submitted registration dossier contained fully adequate safety exposure per International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines. Additionally, the remainder of the data from the fully completed studies was submitted to Health Authorities at a later stage during the marketing authorization process.

Table 2 Overview of the PLATINUM phase 3 clinical development program

| Study (NCT number)   | Study duration (weeks) | Study treatment arms                                                                 | N   |
|---------------------|------------------------|--------------------------------------------------------------------------------------|-----|
| QUARTZ (NCT02892344) | 12                     | IND/MF low-dose (150/80 µg o.d.) via Breezhaler® MF low-dose (200 µg o.d.) via Twistrhaler® | 398 |
| PALLADIUM (NCT02554786) | 52                    | IND/MF medium-dose (150/160 µg o.d.) via Breezhaler® IND/MF high-dose (150/320 µg o.d.) via Breezhaler® MF medium-dose (400 µg o.d.) via Twistrhaler® MF high-dose (800 µg [400 µg b.i.d.]) via Twistrhaler® | 439 |
| IRIDIUM (NCT02571777) | 52                    | IND/GLY/MF medium-dose (150/50/80 µg o.d.) via Breezhaler® IND/GLY/MF high-dose (150/50/160 µg o.d.) via Breezhaler® IND/MF medium-dose (150/160 µg o.d.) via Breezhaler® IND/MF high-dose (150/320 µg o.d.) via Breezhaler® SAL/FLU high-dose (50/500 µg b.i.d.) via Diskus® | 620 |
| ARGON (NCT03158311)  | 24                     | IND/GLY/MF medium-dose (150/50/80 µg o.d.) via Breezhaler® IND/GLY/MF high-dose (150/50/160 µg o.d.) via Breezhaler® IND/MF medium-dose (150/160 µg o.d.) via Breezhaler® IND/MF high-dose (150/320 µg o.d.) via Breezhaler® SAL/FLU high-dose (50/500 µg b.i.d.) via Diskus® + TIO 5 µg o.d. via Respimat® | 474 |

*b.i.d.* twice daily, *FLU* fluticasone propionate, *GLY* glycopyrronium bromide, *IND* indacaterol acetate, *MF* mometasone furoate, *N* number of patients randomized to study treatment, *o.d.* once daily, *SAL* salmeterol xinafoate, *TIO* tiotropium
application review to enable them to consider the full study data in the decision process.

**Inclusion of an Additional Comparator in Phase III Studies: IRIDIUM and ARGON**

Another important feature in the development strategy of IND/GLY/MF was the inclusion of two different LABA/ICS comparators. In the pivotal phase III IRIDIUM study, IND/MF was selected as an internal comparator against IND/GLY/MF to demonstrate the additional benefit of GLY [36], in line with CHMP combination guidance (EMA/CHMP/158268/2017). In addition, SAL/FLU was used as a marketed comparator, since it enabled demonstration of the effects of IND/GLY/MF and IND/MF together against SAL/FLU, a widely used treatment of asthma [36].

Similarly, the ARGON study was designed to compare the effect of o.d. IND/GLY/MF FDC versus concurrent administration of b.i.d. high-dose SAL/FLU (via Diskus®) and o.d. tiotropium (TIO [via Respimat®]) [35].

Figure 2 shows the timeline plot depicting the single-development plan for IND/GLY/MF and IND/MF that accelerated approval of IND/GLY/MF by ca. 4 years. Table 3 summarizes the unique approach adopted for clinical development to approval of the two FDCs.

**CLINICAL OVERVIEW**

The efficacy and safety of IND/GLY/MF was evaluated in the IRIDIUM and ARGON studies under the phase III PLATINUM program.

**IND/GLY/MF: Data from IRIDIUM and ARGON Studies**

The IRIDIUM study established the benefits of IND/GLY/MF versus internal comparator IND/MF and the widely used standard-of-care SAL/FLU, whereas the ARGON study demonstrated the effects of o.d. single-inhaler (Breezhaler®) IND/GLY/MF versus concurrent administration of two approved treatments: b.i.d. high-dose SAL/FLU via Diskus® and o.d. TIO via Respimat® in patients with inadequately controlled asthma [35, 36].

**IRIDIUM (NCT02571777)**

The primary endpoint results showed that IND/GLY/MF medium-dose and high-dose (delivered via the Breezhaler® device) demonstrated superiority in improving trough forced expiratory volume in 1 s (FEV1) over IND/MF medium-dose ($\Delta 76 \text{ mL} \ [95\% \text{ CI } 41–111] ; \ p < 0.001$) and high-dose ($\Delta 65 \text{ mL} \ [95\% \text{ CI } 31–99] ; \ p < 0.001$), respectively (both doses delivered via the Breezhaler® device) at week 26 (Fig. 3a) [36]. IND/GLY/MF medium-dose ($\Delta 99 \text{ mL} \ [95\% \text{ CI } 64–133] ; \ p < 0.001$) and high-dose ($\Delta 119 \text{ mL} \ [95\% \text{ CI } 85–154] ; \ p < 0.001$) showed greater improvements in trough FEV1 at week 26 compared with SAL/FLU high-dose (delivered via Diskus®; Fig. 3a) [36]. Improvements were sustained at week 52. Furthermore, IND/GLY/MF showed greater improvement in evening and morning peak expiratory flow (PEF) than IND/MF and SAL/FLU over 52 weeks. The key secondary endpoint was improvement in Asthma Control Questionnaire (ACQ-7) score for IND/GLY/MF versus IND/MF at week 26. Although both treatments delivered clinically meaningful improvements from baseline in this measure, the key secondary endpoint was not met. However, differential improvements were observed with both doses of IND/GLY/MF versus SAL/FLU high-dose at week 26 [36]. The annualized rate of moderate or severe exacerbations, severe exacerbations, and all exacerbations decreased with IND/GLY/MF medium- and high-dose versus the corresponding dose of IND/MF [36]. Substantial reductions (36–42%) in moderate-to-severe and severe asthma exacerbation rates were observed with IND/GLY/MF high-dose compared with SAL/FLU high-dose, and even numerical reductions were observed with IND/GLY/MF medium-dose compared with SAL/FLU high-dose (Fig. 4a,b) [36]. The reduction in rescue medication use and daily asthma symptom scores and improvement in asthma quality-of-life questionnaire (AQLQ) scores were comparable between the IND/GLY/MF versus IND/MF or SAL/FLU groups [36]. Safety findings were
consistent with the known safety profiles of LABA, LAMA, and ICS drug classes in asthma [36, 39].

**Table 3** Unique approach adopted from clinical development to approval of IND/GLY/MF and IND/MF

| Development sequence | Unique clinical development strategy for IND/GLY/MF | Typical clinical development strategy for combination therapies |
|----------------------|-----------------------------------------------------|------------------------------------------------------------------|
|                      | Parallel development: IND/GLY/MF and IND/MF in parallel; this accelerated development of IND/GLY/MF by ca. 4 years | Stepwise: e.g., first dual combination then triple combination |
| Phase III comparator | Two comparators: IND/MF as internal comparator; SAL/FLU as marketed comparator | One comparator: internal comparator (dual combination) |
| Submission to regulatory authorities | Submission while studies were ongoing (accelerated approval process by ca. 7 months), with long-term safety provided through variable exposure periods | Submission only upon completion of clinical trial program |
| Digital companion | Incorporation in initial Marketing Authorization Application | Not part of Marketing Authorization Application (either not submitted at all, or submitted after approval) |

*IND* indacaterol acetate, *FLU* fluticasone propionate, *GLY* glycopyrronium bromide, *MF* mometasone furoate, *SAL* salmeterol xinafoate

**ARGON (NCT03158311)** Once-daily IND/GLY/MF medium-dose ($\Delta - 0.038$; $p < 0.001$) and high-dose ($\Delta 0.073$;
both doses delivered via the Breezhaler® device) met the primary endpoint, demonstrating non-inferiority to concurrent administration of two existing inhaled medications: b.i.d. SAL/FLU high-dose (delivered via Diskus®) plus o.d. TIO (delivered via Respimat®) in improving AQLQ score at week 24 [35]. Greater improvements in trough FEV$_1$, forced vital capacity, ACQ-7 scores, evening and morning PEF and St. George’s Respiratory Questionnaire (SGRQ) score were observed at week 24 with IND/GLY/MF high-dose compared with SAL/FLU high-dose plus TIO, while comparable benefits were seen with IND/GLY/MF medium-dose versus SAL/FLU high-dose plus TIO but with a lower ICS dose treatment (Fig. 3b) [35]. The rate of all exacerbations and moderate or severe exacerbations...
was comparable between either doses of IND/GLY/MF versus SAL/FLU high-dose plus TIO (Fig. 4c) [35]. The safety profile with IND/GLY/MF was comparable to that of SAL/FLU high-dose plus TIO [35, 39].

**SUMMARY**

The limited availability of treatment options in the severe asthma population underscores the need for innovative development strategies to bring new medications to patients. Taken together with lengthy timelines for a traditional “sequential” development program, these challenges led us to utilize a novel strategy that accelerated the development of o.d. IND/GLY/MF by ca. 4 years, thereby enabling earlier patient access to this treatment. Despite being an accelerated development plan, this strategy maintained a robust pivotal study design to allow for thorough assessment of efficacy as well as safety. As a result, o.d. IND/GLY/MF delivered via Breezhaler® became the first LABA/LAMA/ICS FDC to be approved as a maintenance treatment in patients with asthma inadequately controlled with LABA/ICS [3, 40]. Moreover, for the first time, an optional digital companion, comprising an electronic sensor and app that provide inhalation confirmation, medication reminders, and access to objective data to better support therapeutic decisions is also covered under approval by the European Commission [3]. In parallel, IND/MF, an o.d. LABA/ICS delivered via the Breezhaler® device and an optional digital companion, designed to simplify the use and optimize medication adherence by patients, it is hoped that these

![Fig. 4](https://example.com/fig4.jpg) Annualized rate of exacerbations with: 

- **a** IND/GLY/MF versus IND/MF over 52 weeks (IRIDIUM),
- **b** IND/GLY/MF versus SAL/FLU over 52 weeks (IRIDIUM),
- **c** IND/GLY/MF versus SAL/FLU + TIO over 24 weeks (ARGON).

Data are presented as annualized rates. *p ≤ 0.05. IND/GLY/MF medium-dose, IND/GLY/MF 150/50/80 µg o.d.; IND/GLY/MF high-dose, IND/GLY/MF 150/50/160 µg o.d.; IND/MF medium-dose, IND/MF 150/160 µg o.d.; IND/MF high-dose, IND/MF 150/320 µg o.d.; SAL/FLU high-dose, SAL/FLU 50/500 µg b.i.d.; TIO, TIO 5 µg o.d. b.i.d., twice daily; CI, confidence interval; FLU, fluticasone propionate; GLY, glycopyrronium bromide; IND, indacaterol acetate; MF, mometasone furoate; o.d., once daily; SAL, salmeterol xinafoate; TIO, tiotropium. 

a, b Reprinted from *Lancet Respir Med.* Kerstjens HAM et al., 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, vol 8, pp 1000–1012. Copyright 2020, with permission from Elsevier. 

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medicines can help contribute toward meeting some of the unmet needs in asthma healthcare.

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**Compliance with Ethics Guidelines.** This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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