ORIGINAL ARTICLE
ASTHMA

# Lung function improvements following inhaled indacaterol/glycopyrronium/mometasone furoate are independent of dosing time in asthma patients: a randomised trial

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ABSTRACT Once-daily asthma treatment should prevent night-time deterioration, irrespective of the time of dosing. IND/GLY/MF, a fixed-dose combination of inhaled indacaterol acetate (IND, long-acting $\beta_2$-agonist (LABA)), glycopyrronium bromide (GLY, long-acting muscarinic antagonist) and mometasone furoate (MF, inhaled corticosteroid (ICS)) delivered by Breezhaler, is indicated in adult asthma patients inadequately controlled on LABA/ICS.

A randomised, double-blind, placebo-controlled, three-period, crossover, phase II study was performed to investigate the bronchodilator effect of IND/GLY/MF (150/50/80 µg) dosed morning and evening *versus* placebo in patients with mild-moderate asthma. The primary end-point was weighted mean forced expiratory volume in 1 s ($FEV_1$) over 24 h following 14 days of IND/GLY/MF dosed a.m. and p.m. *versus* placebo. Secondary end-points included the effect of dosing time on peak expiratory flow (PEF) and safety/tolerability.

Of 37 randomised patients (age 18–72 years; 21 male, 16 female) 34 completed all three treatment periods. At screening, median (range) pre-bronchodilator $FEV_1$ was 75.8% (60–96%). Patients were using stable low- (83.8%) or medium-dose (16.2%) ICS. Morning and evening dosing of IND/GLY/MF improved $FEV_1$ (area under the curve from 0 to 24 h) by 610 mL (90% CI 538–681 mL) and 615 mL (90% CI 544–687 mL), respectively, *versus* placebo. Mean PEF over 14 days increased by 70.7 $L{\cdot}min^{-1}$ (90% CI 60.5–80.9 $L{\cdot}min^{-1}$) following a.m. dosing, and by 59.7 $L{\cdot}min^{-1}$ (90% CI 49.5–69.9 $L{\cdot}min^{-1}$) following p.m. dosing of IND/GLY/MF *versus* placebo. IND/GLY/MF demonstrated a safety profile comparable with placebo.

Once-daily inhaled IND/GLY/MF was well tolerated and provided sustained lung function improvements over 24 h, irrespective of a.m. or p.m. dosing, in patients with mild–moderate asthma.

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**This randomised study found single-inhaler indacaterol/glycopyrronium/mometasone furoate improved respiratory parameters $FEV_1$ and PEF in asthma patients, and showed similar efficacy when taken once daily in the morning or evening** https://bit.ly/3fH0I1K

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This study is registered at www.clinicaltrials.gov with identifier number NCT03108027 and at www.clinicaltrialsregister.eu with identifier number 2017-000644-17. Novartis is committed to sharing with qualified external researchers, access to patient-level data and supporting clinical documents from eligible studies. These requests are reviewed and approved by an independent review panel on the basis of scientific merit. All data provided is anonymised to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations. This trial data availability is according to the criteria and process described on www.clinicalstudydatarequest.com.

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## Introduction

Despite the availability of combination inhaled corticosteroid (ICS) and long-acting $\beta_2$-agonist (LABA) therapies, many patients worldwide are impacted by uncontrolled asthma with clinically relevant symptoms, bronchoconstriction and exacerbations. Inadequately controlled asthma is associated with a poorer quality of life, daily activity limitations, higher risk of exacerbations and a disproportionately high use of healthcare resources [1, 2].

The Global Initiative for Asthma (GINA) suggests the addition of a long-acting muscarinic antagonist (LAMA) (tiotropium) for patients with asthma who remain uncontrolled despite treatment with a combination of an ICS with a LABA [3]. There is mounting evidence that add-on LAMA therapy to LABA/ICS can provide additional benefit in terms of fewer exacerbations and improved lung function compared with patients receiving LABA/ICS therapy alone [4, 5]. Therefore, single-inhaler LABA/LAMA/ICS fixed-dose combinations are being developed for patients with asthma.

Increased circadian variation is a hallmark of uncontrolled asthma, with symptoms, airway hyperresponsiveness and airway obstruction worsening at night [6]. Airway eosinophils were shown to correlate significantly with circadian rhythm in induced sputum from patients with mild–moderate asthma, with a peak influx at 04:00 h, which also coincided with peak sputum eotaxin concentrations [7]. In addition, there is circadian rhythmic variability in a proportion of exhaled volatile organic compounds over 24 h [8]. Drugs with a 24-h action should prevent night-time lung function deterioration, irrespective of the time of administration. However, studies have shown that for some inhaled therapies, time of administration can affect drug efficacy over a 24-h period [9, 10].

IND/GLY/MF is an inhaled combination which is approved in the European Union and other countries worldwide, for once-daily treatment of asthma, inadequately controlled by LABA/ICS. This therapy combines sustained bronchodilation by indacaterol acetate (IND, a LABA) and glycopyrronium bromide (GLY, a LAMA) with anti-inflammatory properties of mometasone furoate (MF, an ICS). The fixed-dose combination is delivered with the Breezhaler inhalation device. The Breezhaler device provides feedback on correct delivery [11] and is currently used to deliver a range of medicines in asthma (*e.g.* budesonide) and COPD, including IND, GLY and IND/GLY.

The aim of this phase II study was to investigate the bronchodilator effect of once-daily inhaled IND/GLY/MF (150 µg of indacaterol acetate, 50 µg of glycopyrronium bromide and 80 µg of mometasone furoate (medium dose)) when administered in the morning or in the evening compared with placebo in patients with uncontrolled asthma. The individual components of IND/GLY/MF have demonstrated a sustained 24-h duration of action as mono- or combination therapies [12, 13]. Therefore, we hypothesised that IND/GLY/MF would demonstrate sustained lung function benefits irrespective of the time of dosing. In addition, the safety and tolerability of the fixed-dose combination *versus* placebo was evaluated.

## Methods

### *Participants and study design*

Study participants were males and females with asthma aged ⩾18 years who were receiving a stable daily regimen of low- or medium-dose ICS (as defined by GINA [14]) for ⩾4 weeks prior to screening. Eligible patients had a pre-bronchodilator forced expiratory volume in 1 s ($FEV_1$) ⩾60%–<100% of the predicted normal value and demonstrated an $FEV_1$ increase of ⩾12% and ⩾200 mL after administration of 400 µg salbutamol/360 µg albuterol (or equivalent dose) at screening. Patients who had an asthma exacerbation requiring systemic corticosteroids, hospitalisation or emergency room visit within 1 year prior to the study were excluded. Current smokers and patients who had smoked or inhaled tobacco products within the 6-month period prior to screening, or who had a smoking history of ⩾10 pack-years, were also excluded. Details of inclusion and exclusion criteria are available in the supplementary material.

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The study had a randomised, double-blind, placebo-controlled, six-sequence, three-period crossover design and was conducted in six European centres (https://clinicaltrials.gov/ct2/show/NCT03108027) between June 26, 2017 and February 24, 2018. Prior to study enrolment, there was a 14-day screening period, followed by a 14-day unblinded run-in period where patients were instructed to discontinue their previous asthma medications and were provided with short-acting $\beta_2$-agonist (SABA; 100 µg salbutamol/90 µg albuterol, or another SABA at matching dose strength) as rescue medication. Eligible patients were subsequently randomised to one of the six treatment sequences all consisting of three treatment periods with a minimum duration of 14 days each (maximum 18 days), separated by a 14–21-day washout period (figure 1a). The final treatment period was followed by a study completion evaluation visit after 1–7 days. The total duration of the study was 13–19 weeks for each patient. The study was ended after the last patient completed follow-up.

For the overall relatively short study duration in patients with mild to moderate asthma it was considered acceptable to have a placebo period/control without ICS background. The run-in period made sure that subjects were able to tolerate not taking ICS for a short, defined period of time. Patients who could not tolerate ICS withdrawal were not randomised.

At the end of the run-in period, patients were randomised in a ratio of 1:1:1:1:1:1 (Williams design) to one of six treatment sequences (table 1); each sequence consisted of three double-blind treatment periods of 14–18 days (in different orders) as follows. IND/GLY/MF evening dose (A): placebo (a.m.) and IND/GLY/MF (p.m.); IND/GLY/MF morning dose (B): IND/GLY/MF (a.m.) and placebo (p.m.); placebo (C): placebo (a.m.) and placebo (p.m.)

The dose strength of IND/GLY/MF administered in this trial was 150 µg IND, 50 µg GLY and 80 µg MF, which is the medium dose of MF delivered with the Breezhaler device (corresponding to MF 400 µg delivered with the Twisthaler inhalation device). More information on the study design including treatment sequences and methods is available in the supplementary material.

The patient randomisation list was produced by the interactive response technology provider using a validated system that automated the random assignment of patient numbers to randomisation numbers. All patients gave written informed consent. This study was conducted in accordance with the Declaration of Helsinki and was approved by the independent ethics committees of the participating sites.

### *Study objectives*

The primary objective of this study was to investigate the effect of dosing time (morning or evening) on the bronchodilator effect of once-daily inhaled IND/GLY/MF (150/50/80 µg; medium-dose strength of MF) compared with placebo. This was assessed using weighted mean $FEV_1$ over 24 h (area under the curve from 0 to 24 h ($AUC_{0-24h}$)) following 14 days of treatment with IND/GLY/MF dosed in the morning, IND/GLY/MF dosed in the evening, and placebo, as the primary end-point.

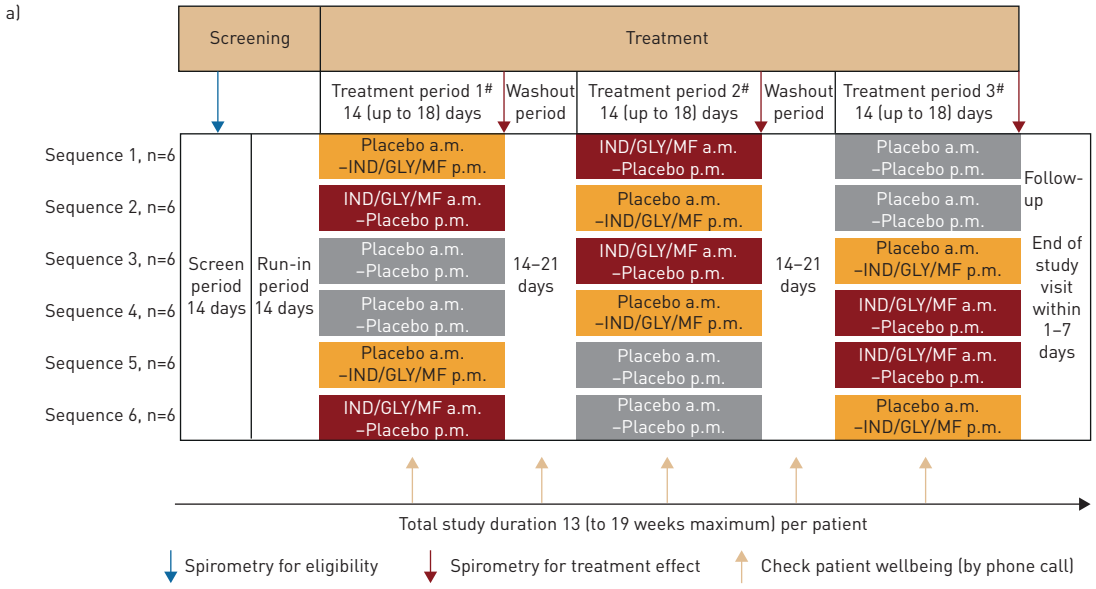
Secondary objectives were to evaluate the effect of IND/GLY/MF dosing time on peak expiratory flow (PEF) rate from day 2 to day 14 during the three treatment periods and with serial measurement during the 24 h spirometry profiling assessment on day 14 of each treatment period. In addition, the safety and tolerability of IND/GLY/MF were assessed.

### *Study treatment and assessments*

On day 1 of each treatment period, patients attended the site for an outpatient visit in the afternoon (~1–2 h before the first scheduled p.m. dose) and day 1 pre-dose assessments were performed. Patients were evaluated for randomisation eligibility (only at treatment period 1) and trained/re-trained on the use of the Breezhaler inhalation device. Patients were instructed to take IND/GLY/MF or placebo in the morning (at ~07:00 h) and in the evening (at ~19:00 h) and to record their pre-treatment morning and evening PEF throughout the study in a patient e-diary.

Spirometry measurements followed the American Thoracic Society/European Respiratory Society guidelines [15]. Patients were provided with a combined electronic PEF-meter and e-diary for recording trough (pre-dose) PEF measurements each morning and evening throughout the entire study. $FEV_1$ measurements were taken 5 min before the evening dose on day 14, then +3 h, +6 h, +9 h, +12 h, +15 h, +18 h, +21 h and +23 h 55 min (timing from the day 14 post-evening dose). Spirometry was performed on day 14 prior to and 3 h after study drug administration and on day 15, 6–12 h after the last dose of IND/GLY/MF.

All patients were provided with rescue medication (SABA; 100 µg salbutamol/90 µg albuterol or equivalent dose) at day 1 of the run-in period and were instructed to use it on an "as-needed" basis only. SABA use was recorded twice daily throughout the entire study.



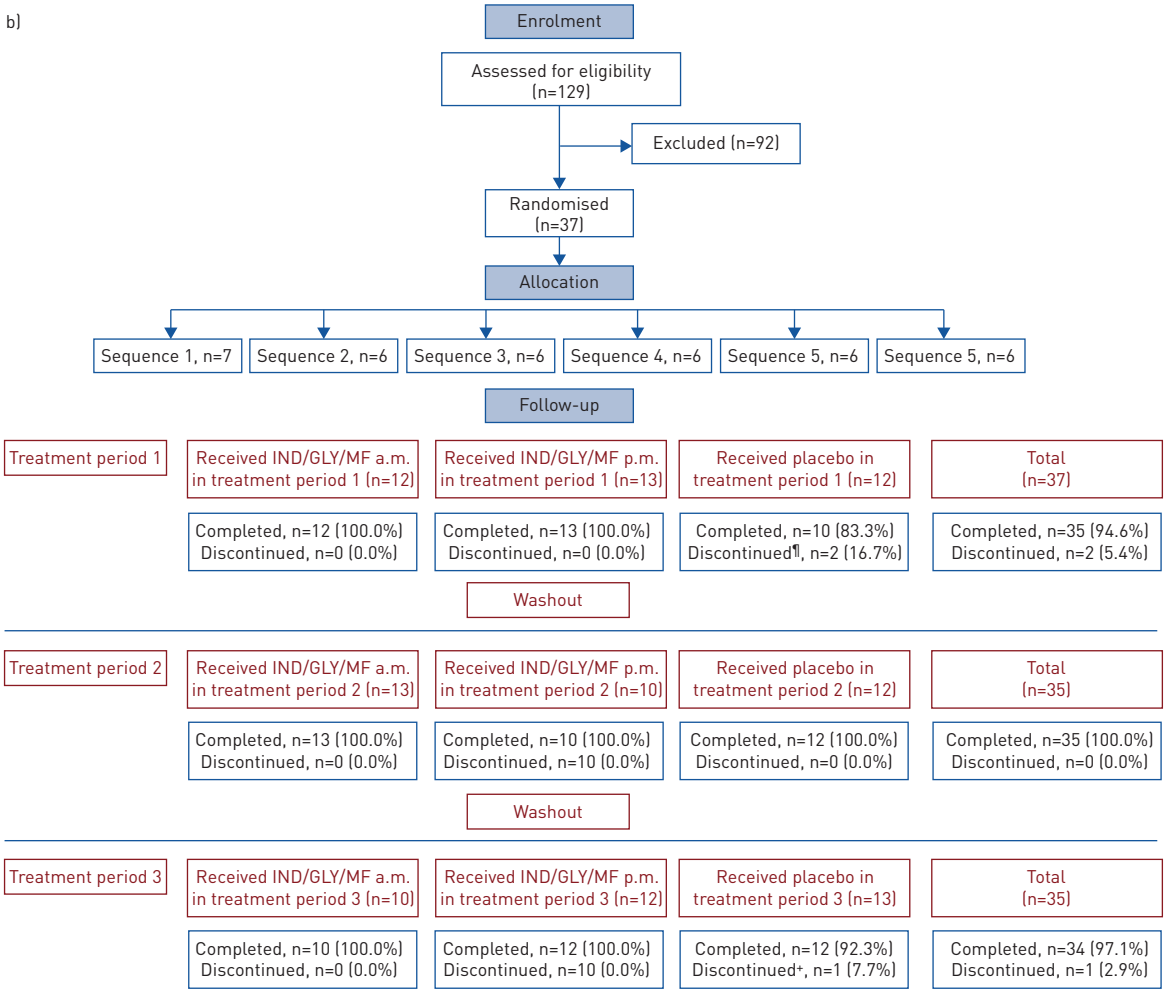




FIGURE 1 Study design and participant inclusion. a) Study design. This was a randomised, placebo-controlled, double-blind, six-sequence, three-period, crossover study. b) Study disposition. Of 129 screened for enrolment in this study, 37 patients were randomised to one of six treatment sequences (each consisting of three treatment periods) in an allocation ratio of 1:1:1:1:1:1. For each sequence, a) six patients were planned to be randomised; b) as 37 patients were randomised, sequence 1 contained seven patients. 34 patients completed all three treatment periods. IND: indacaterol acetate; GLY: glycopyrronium bromide; MF: mometasone furoate. #: primary end-point mean forced expiratory volume in 1 s ($FEV_1$) (L) (area under the curve from 0 to 24 h); ¶: two patients discontinued from the study during treatment period 1 due to subject/guardian decision; +: one patient experienced an asthma exacerbation and discontinued from the study on the first day of treatment period 3.

TABLE 1 Definition of treatment sequences

| | Treatment period 1 | Treatment period 2 | Treatment period 3 |
|---|---|---|---|
| **1** | A | B | C |
| **2** | B | A | C |
| **3** | C | B | A |
| **4** | C | A | B |
| **5** | A | C | B |
| **6** | B | C | A |

A: indacaterol acetate (IND)/glycopyrronium bromide (GLY)/mometasone furoate (MF) evening dose: placebo (a.m.) and IND/GLY/MF (p.m.); B: IND/GLY/MF morning dose: IND/GLY/MF (a.m.) and placebo (p.m.); C: placebo: placebo (a.m.) and placebo (p.m.).

Adherence to the intake of study drug and the need of rescue medication at home was monitored closely by reviewing the patient e-diary in which all patients were instructed to record the details pertaining to administration each day in the morning and in the evening. In addition, compliance was assessed by the investigator and/or study personnel at each visit using capsule counts and information provided by the patient.

### *Statistical analysis*

The safety analysis set included all patients who received at least one dose of IND/GLY/MF and descriptive safety statistics are presented. The pharmacodynamic (PD) analysis set included all patients with any available PD data, who received any dose of study drug and experienced no protocol deviations with relevant impact on PD data. The primary and secondary analyses included all patients in the PD analysis set.

The primary variable was the weighted mean $FEV_1$ over 24 h ($AUC_{0-24h}$) following 14 days of treatment with IND/GLY/MF dosed in the morning, IND/GLY/MF dosed in the evening and placebo. The weighted mean (least square (LS) mean) was calculated as the $AUC_{0-24h}$ divided by the time interval (time of the first observation − time of the last observation) for each patient. The primary variable was determined for each patient on day 14 of each treatment using the linear trapezoidal rule. Data for the primary and secondary end-points were analysed using a linear mixed model. The model included period, treatment (IND/GLY/MF morning, IND/GLY/MF evening, placebo) and sequence as fixed effect factors. The patient effect was assumed to be random. The Kenward–Roger approximation was used to estimate denominator degrees of freedom. From these analyses, point estimates and their associated 90% confidence intervals were constructed for each treatment. The difference between adjusted LS means and the corresponding two-sided 90% confidence interval for a.m. dose *versus* placebo, p.m. dose *versus* placebo and a.m. *versus* p.m. dosing were also evaluated within the linear mixed model.

The sample size calculation is described in the supplementary material.

Statistical analyses were performed by Novartis Institutes for Biomedical Research, Switzerland and Novartis Healthcare, India using SAS software (version 9.4; SAS Institute, Cary, NC, USA).

## Results

### *Participant characteristics*

Of 129 patients screened for inclusion, 37 eligible patients were randomised to one of the six treatment sequences. Of the 37 eligible patients randomised in this study, 35 patients completed treatment period 1 (figure 1b). Two patients receiving placebo discontinued the study (subject/guardian decision) during treatment period 1 on day 1 and day 14, respectively. All 35 patients who entered treatment period 2 completed the treatment period as planned. Of the 35 patients who completed treatment period 2, 34 patients entered and completed treatment period 3. One patient receiving placebo discontinued the study prior to entering treatment period 3 due to an asthma exacerbation (figure 1b).

Patient demographics and baseline characteristics are summarised in table 2.

At baseline, all patients were receiving maintenance daily treatment with low- (83.8%) or medium-dose (16.2%) ICS (table 2). Patients had a mean±SD pre-dose $FEV_1$ 75.8±9.04% of predicted normal (table 2). Mean reversibility to SABA was 18.9% (range 12–52%) (table 2).

TABLE 2 Baseline participant demographics and characteristics (pharmacodynamics analysis set)

| | |
|---|---|
| **Participants** | 37 |
| **Age years** | 46.0 (18–72) |
| **Male** | 21 (56.8) |
| **Body mass index kg·m$^{-2}$** | 26.2±4.67 |
| **Blood eosinophils ×10$^{9}$ cells·L$^{-1}$** | 0.242±0.1588 |
| **Race** | |
| White | 35 (94.6) |
| Other | 2 (5.4) |
| **Screening ICS category** | |
| Low-dose | 31 (83.8) |
| Medium-dose | 6 (16.2) |
| **Pre-bronchodilator $FEV_1$ L** | 2.9±0.72 |
| **Post-bronchodilator $FEV_1$ L** | 3.4±0.81 |
| **$FEV_1$ pre-dose % predicted** | 75.8 (60–96) |
| **Reversibility L** | 0.5±0.21 |
| **Reversibility %** | 18.9 (12–52) |
| **Baseline morning# PEF L·min$^{-1}$** | 422.4±107.42 |
| **Baseline evening# PEF L·min$^{-1}$** | 454.9±107.51 |

Data are presented as n, mean (range), n (%) or mean±SD. ICS: inhaled corticosteroids; $FEV_1$: forced expiratory volume in 1 s; PEF: peak expiratory flow. #: morning and evening PEF are defined as the first adequate results prior to dosing for each time point.

### *Efficacy outcomes*

#### *Effect of IND/GLY/MF dosing time on $FEV_1$ ($AUC_{0–24h}$)*

14 days of IND/GLY/MF treatment significantly improved weighted mean $FEV_1$ ($AUC_{0–24h}$) compared with placebo, irrespective of time of dosing. LS weighted mean $FEV_1$ ($AUC_{0–24h}$) after 14 days of IND/GLY/MF a.m. dosing was 3.43 L (90% CI 3.172–3.689 L), and 3.44 L (90% CI 3.178–3.694 L) after 14 days of IND/GLY/MF p.m. dosing. Patients receiving placebo for 14 days had a substantially lower weighted mean $FEV_1$ ($AUC_{0–24h}$) of 2.82 L (90% CI 2.562–3.080 L). This was consistent with a LS means difference of 610 mL (90% CI 538–681 mL) with a.m. dosing of IND/GLY/MF and 615 mL (90% CI 544–687 mL) with p.m. dosing of IND/GLY/MF *versus* placebo (figure 2).

A negligible difference in weighted mean $FEV_1$ ($AUC_{0–24h}$) was observed between IND/GLY/MF morning and evening dose (–6 mL, 90% CI –76–65 mL; <1%).

*Post hoc* analyses directly compared 24 h post-dose $FEV_1$ (trough $FEV_1$) between IND/GLY/MF a.m. and p.m. dosing after 14 days of treatment. No difference was observed in mean 24 h post-dose $FEV_1$ between IND/GLY/MF morning and evening dosing (8.7 mL, 90% CI −60.4–77.8 mL).

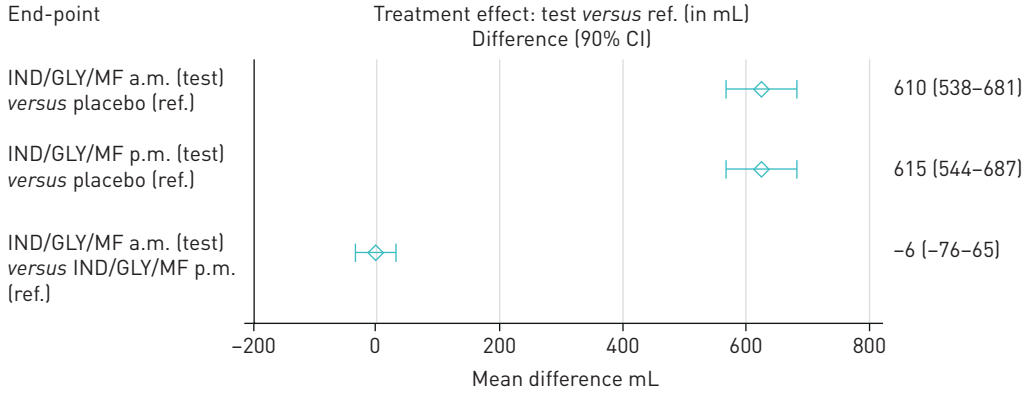



FIGURE 2 Effect of morning or evening dosing of inhaled indacaterol acetate (IND)/glycopyrronium bromide (GLY)/mometasone furoate (MF) on weighted mean forced expiratory volume in 1 s ($FEV_1$) (area under the curve from 0 to 24 h ($AUC_{0–24h}$)) *versus* placebo (pharmacodynamics (PD) analysis set). Comparison of morning or evening dosing of IND/GLY/MF on weighted mean $FEV_1$ (mL) ($AUC_{0–24h}$) with placebo in the PD analysis set. Parameters were analysed using a mixed model adjusting for period, treatment and sequence as fixed effect factors, and patient as a random effect. Data are presented as least squares means treatment difference (90% CI) compared with placebo. ref: reference.

TABLE 3 Comparison of peak expiratory flow (PEF) measured in the morning and evening after 14 days of treatment (pharmacodynamics analysis set)

| | PEF L·min$^{-1}$ | |
|---|---|---|
| | LS means (90% CI) | LS means difference (90% CI) |
| **Morning mean** | | |
| IND/GLY/MF a.m. *versus* placebo[#] | 489.6 (456.2–523.1) *versus* 417.5 (384.1–450.9) | 72.1 (61.3–82.9) |
| IND/GLY/MF p.m. *versus* placebo[#] | 504.4 (471.0–537.9) *versus* 417.5 (384.1–450.9) | 86.9 (76.1–97.8) |
| IND/GLY/MF a.m. *versus* IND/GLY/MF p.m. | 489.6 (456.2–523.1) *versus* 504.4 (471.0–537.9) | −14.8 (−25.6–−4.1) |
| **Evening mean** | | |
| IND/GLY/MF a.m. *versus* placebo[#] | 522.0 (488.7–555.4) *versus* 449.0 (415.7–482.3) | 73.1 (61.9–84.2) |
| IND/GLY/MF p.m. *versus* placebo[#] | 507.7 (474.3–541.0) *versus* 449.0 (415.7–482.3) | 58.7 (47.5–69.9) |
| IND/GLY/MF a.m. *versus* IND/GLY/MF p.m. | 522.0 (488.7–555.4) *versus* 507.7 (474.3–541.0) | 14.4 (3.3–25.5) |

n=35, unless otherwise stated. Morning PEF assessments were performed 24 h after the last morning dose and 12 h after the last evening dose. Analogously, the evening PEF assessments were performed 24 h after the last evening dose and 12 h after the last morning dose. LS: least squares; IND: indacaterol acetate; GLY: glycopyrronium bromide; MF: mometasone furoate. [#]: n=36.

*Effect of dosing time of IND/GLY/MF on PEF*

Mean morning PEF (measured pre-dose on the morning of day 15 of each treatment period) was significantly improved by IND/GLY/MF dosed in the morning and the evening (LS means difference 72.1 L·min$^{-1}$ (90% CI 61.3–82.9 L·min$^{-1}$) and 86.9 L·min$^{-1}$ (90% CI 76.1–97.8 L·min$^{-1}$), respectively *versus* placebo) (table 3).

Similarly, mean evening PEF (measured on the evening of day 15 of each treatment period) was significantly improved by IND/GLY/MF morning dose (LS means difference 73.1 L·min$^{-1}$, 90% CI 61.9–84.2 L·min$^{-1}$) and evening dose (58.7 L·min$^{-1}$, 90% CI 47.5–69.9 L·min$^{-1}$) *versus* placebo (table 3).

There were negligible differences in overall PEF values between morning and evening dosing (*versus* placebo) (figure 3). With IND/GLY/MF dosed in the morning, the next morning pre-dose PEF was lower compared with dosing in the evening (−14.8 L·min$^{-1}$, 90% CI −25.6–−4.1 L·min$^{-1}$). Analogously, pre-dose PEF was higher in the evening with morning dosing than with evening dosing (+14.4 L·min$^{-1}$, 90% CI 3.3–25.5 L·min$^{-1}$).

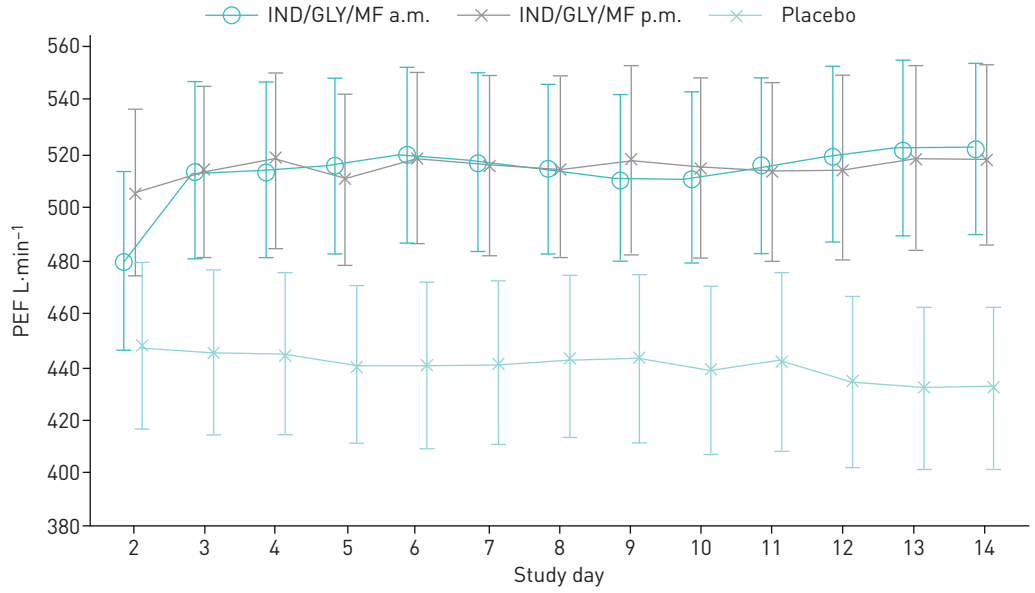



FIGURE 3 Effect of indacaterol acetate (IND)/glycopyrronium bromide (GLY)/mometasone furoate (MF) on overall mean peak expiratory flow (L·min$^{-1}$) (90% CI) over days 2–14 by treatment (pharmacodynamics analysis set). Parameters were calculated using a mixed-effects model including period, treatment (IND/GLY/MF morning, IND/GLY/MF evening, placebo), and sequence as fixed effects. Note: if a treatment period for an individual patient exceeded 14 days, the patient's peak expiratory flow (PEF) values contributed only up to day 14 for the respective period.

### *Safety and tolerability*

Safety and tolerability were assessed in the safety analysis set (n=37). No serious adverse events, deaths or new safety findings for IND/GLY/MF were reported during this study. The incidence of treatment-emergent adverse events affecting >5% of patients by treatment group is available in table 4. The safety and tolerability profiles of IND/GLY/MF were comparable between a.m. and p.m. dosing and were similar to placebo (table 4). Two patients discontinued in the placebo period due to subject/guardian decision and one patient discontinued during a washout period due to an asthma exacerbation of moderate severity.

Two patients experienced an adverse event graded as severe: one bacterial food poisoning (day 15 during the IND/GLY/MF p.m. dosing period) and one case of influenza (day 9 during IND/GLY/MF p.m. dosing period). These were deemed unrelated to the study treatment by the investigator and did not lead to discontinuation of the patients from the study.

Rescue medication use details are available for 35 patients. The number of patients who did not take rescue medication (SABA) in the last 7 days in the respective periods were 24 (71%) with IND/GLY/MF morning dosing, 24 (71%) with IND/GLY/MF evening dosing and 10 (29%) with placebo. The odds ratio of being rescue medication free with morning dosing *versus* placebo was 11.5 (95% CI 2.6–50.3; p=0.0015). Evening dosing results were almost identical.

## Discussion and conclusions

The results of this study show that once-daily IND/GLY/MF at 150 µg of indacaterol acetate, 50 µg of glycopyrronium bromide and 80 µg of mometasone furoate (medium ICS dose category) delivered with the Breezhaler device elicits substantial and sustained bronchodilation in patients with asthma receiving ICS at baseline after 14–18 days of treatment, irrespective of the time of dosing (a.m. or p.m.). In addition, the fixed combination was well tolerated overall. These data support the once-daily use of IND/GLY/MF as treatment in patients with asthma.

Evidence generated from randomised controlled trials is supportive of the use of LABA/LAMA/ICS in the treatment of patients with poorly controlled asthma despite the use of ICS and LABA [16]. Tiotropium was tested as an add-on to LABA/ICS treatment in two replicate studies, showing that addition of tiotropium 5 µg (*via* the Respimat inhalation device) resulted in significant changes in peak $FEV_1$ from baseline compared with placebo (increases of 86±34 mL and 154±32 mL) in patients with a mean baseline $FEV_1$ of 62% predicted [17]. In the 52-week TRIMARAN and TRIGGER studies, twice-daily inhalations of formoterol fumarate (FF)/glycopyrronium (G)/beclometasone dipropionate (BDP) from a single device showed significant improvements of 57 mL and 73 mL in pre-dose $FEV_1$, respectively, *versus* FF/BDP [18]. The individual lung function contribution of the LABA indacaterol and the LAMA glycopyrronium were not investigated in this clinical trial. To put results into perspective, it is helpful to consider that in large phase 3 trials that investigated IND/MF *versus* MF alone and IND/GLY/MF *versus* IND/MF adding IND to MF increased trough $FEV_1$ by 132–211 mL after 26 weeks of treatment [19] and adding GLY to IND/MF increased it by an additional 65–76 mL [20].

Adherence to treatment is a key element of sustained asthma control. While once-daily dosing has been suggested to improve adherence [21], a patient may prefer a (flexible) time of the day to take his or her

TABLE 4 Incidence of treatment-emergent adverse events by preferred MedDRA term affecting >5% of patients (safety analysis set)

| | IND/GLY/MF a.m. | IND/GLY/MF p.m. | Placebo | Total |
|---|---|---|---|---|
| **Patients** | 35 | 35 | 36 | 37 |
| **Number of patients with ⩾1 adverse event** | 18 (51.4) | 23 (65.7) | 18 (50.0) | 32 (86.5) |
| **Headache** | 5 (14.3) | 3 (8.6) | 7 (19.4) | 10 (27.0) |
| **Nasopharyngitis** | 2 (5.7) | 2 (5.7) | 5 (13.9) | 8 (21.6) |
| **Oropharyngeal pain** | 3 (8.6) | 4 (11.4) | 2 (5.6) | 7 (18.9) |
| **Cough** | 1 (2.9) | 2 (5.7) | 1 (2.8) | 4 (10.8) |
| **Dysphonia** | 2 (5.7) | 3 (8.6) | 1 (2.8) | 4 (10.8) |
| **Asthma** | 1 (2.9) | 1 (2.9) | 1 (2.8) | 3 (8.1) |
| **Throat clearing** | 1 (2.9) | 1 (2.9) | 0 (0.0) | 2 (5.4) |

Data are presented as n or n (%). MedDRA: Medical Dictionary for Regulatory Activities; IND: indacaterol acetate; GLY: glycopyrronium bromide; MF: mometasone furoate.

medication. Hence, flexibility of dosing, irrespective of the time of day, may further support adherence. Based on the present data, IND/GLY/MF allows this flexibility. In this study, the 2-week run-in period allowed for an assessment of likely study adherence since patients used short-acting rescue medication only, and ensured that those who could not tolerate withdrawal from ICS for a short period of time were not randomised. Since the increases in $FEV_1$ as the primary outcome with morning and evening dosing of IND/GLY/MF *versus* placebo were substantial and comparable, it is reasonable to assume that adherence was high. The formulation of fixed-dose LABA/LAMA/ICS combinations in a single device may have contributed to a good level of adherence [16].

To benchmark the presented increases in $FEV_1$ ($AUC_{0-24h}$) of >600 mL with IND/GLY/MF over placebo, previous reports for LABA/ICS fixed-dose combination effects can be considered. For vilanterol/fluticasone furoate administered using a dry-powder inhaler, increases of 377 mL and 422 mL in $FEV_1$ ($AUC_{0-24h}$) following morning and evening dose, respectively, over 14 days *versus* placebo were observed in a similar population of asthmatic patients aged 18–70 years with $FEV_1$ of ⩾60% pred [22]. Furthermore, when these increases are added to those observed in adult asthmatics with baseline $FEV_1$ of 60–85% pred, the LAMA umeclidinium dosed at 5.6, 31.25, 62.5, 125 or 250 µg once daily, or 15.6 or 31.25 µg twice daily, administered for 14 days (range 68–121 mL for increase in $FEV_1$ ($AUC_{0-24h}$) over placebo) [23], improvements appeared to be less than those achieved with IND/GLY/MF in the present study. Since comparing observations across studies carries limitations (*e.g.* differences in drugs and doses used, treatment duration, patient populations), the authors caution against the over-interpretation of these cross-study observations.

PEF is measured twice daily every day and is therefore a reliable, consistent and accurate measure of lung function variation with some correlation to symptoms, even for patients who cannot perform full spirometry manoeuvres. The PEF improvements *versus* placebo observed with IND/GLY/MF in this study are well above the range (15–20 $L \cdot min^{-1}$) suggested to be clinically relevant and perceptible by the patient [24, 25]. The consistency in PEF over the treatment period suggests good and stable lung function control with IND/GLY/MF in patients with asthma.

The safety and tolerability profile of IND/GLY/MF was similar to placebo. The two severe adverse events of influenza and food poisoning that occurred during this study were deemed unrelated to the study drug by the investigator, and there were no serious adverse events, deaths or new safety findings reported. One patient discontinued the study during the placebo period due to an asthma exacerbation which was treated with prednisolone.

Potential limitations to this study include the relatively short duration of treatment, participants being limited to those with mild to moderate asthma which differs from the labelled indication of IND/GLY/MF, and the rate of adherence to study medication which was self-reported *via* an electronic diary. While 14 days of treatment cannot give a reliable estimate of asthma control sustained benefits were demonstrated over each IND/GLY/MF treatment period as evidenced by substantial, consistent, and constant PEF improvements compared to placebo (figure 3). Although lack of data on asthma control status can be perceived as a limitation, it should be noted that this is a comparatively small study embedded in the overall development programme of IND/GLY/MF, the results of which have been published previously [19, 20, 26].

Overall, these results demonstrate that IND/GLY/MF is effective irrespective of time of dosing, and therefore, that this fixed-dose combination can be administered effectively and safely either in the morning or the evening.

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