The Efficacy of the Combination Indacaterol/Glycopyrronium/Mometasone Furoate is Independent of Time of Dosing in Patients with Asthma

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Introduction

- Global Initiative for Asthma (GINA) guidelines suggest the addition of a long-acting muscarinic antagonist (LAMA) (tiotropium) for patients with asthma who remain uncontrolled despite treatment with a combination of a medium- or high-dose inhaled corticosteroid (ICS) with a long-acting β_2-agonist (LABA) [1].
- Currently, no LABA/LAMA/ICS fixed-dose combination is available for patients with asthma.
- Asthma is characterized by diurnal variation; in some patients symptoms may worsen and lung function may decrease during the night [2].
- Drugs with a 24-hour duration of 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-hour period [3, 4].
- IND/GLY/MF is an inhaled combination currently under development for once-daily treatment of asthma. This therapy combines comprehensive bronchodilation by indacaterol acetate (IND, a LABA) and glycopyrronium bromide (GLY, a LAMA) with the anti-inflammatory efficacy of mometasone furoate (MF), an ICS.
- This fixed-dose combination is delivered using the Breezhaler® inhalation device. The Breezhaler® device provides feedback for confirmation of correct delivery and is used to deliver a range of medicines in asthma (e.g. budesonide) and COPD, including IND, GLY, and IND/GLY.
- The components of IND/GLY/MF have demonstrated a sustained 24-hour duration of action as mono- or combination therapies [5-7]. Therefore, we hypothesized that IND/GLY/MF would demonstrate sustained lung function benefits irrespective of the time of dosing.

Methods

Objectives

- Primary: 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 forced expiratory volume in 1 second (FEV_1) over 24 hours (AUC_{0-24h}) following 14 days of treatment with IND/GLY/MF dosed in the morning or the evening, or placebo.
- Secondary: to evaluate the effect of the time of IND/GLY/MF dosing on peak expiratory flow (PEF) rate from Day 2 to Day 14 during the treatment periods.
- Safety and tolerability were also assessed.

Study design

- This was a randomized, double-blind, placebo-controlled, six-sequence, three-period crossover, Phase II study in patients with asthma at 6 European centers (NCT03108027). The study consisted of a 14-day screening period, a 14-day run-in period, and three treatment periods with a minimum duration of 14 days each (maximum 18 days), which were punctuated by washout periods of 14–21 days (**Figure 1**).
- Patients were randomized to one of six treatment sequences and each sequence consisted of 3 double-blind treatment periods. The 3 treatments were: **A. IND/GLY/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.); and **C. Placebo:** placebo (a.m.) and placebo (p.m.). Randomization was done according to a Williams design for 3 treatments and 3 periods (six sequences).
- This study was conducted in accordance with the Declaration of Helsinki and was approved by the Independent Ethics Committees of the participating sites and written informed consent was obtained from all participants.

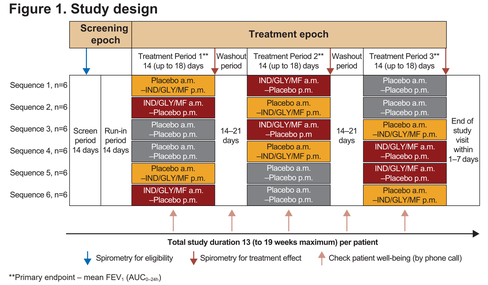
Key inclusion criteria:

- Patients with asthma aged ≥18 years receiving stable daily low- or medium-dose ICS (defined by GINA) for ≥4 weeks prior to screening
- FEV_1 >60%–<100% of the predicted normal value at screening
- FEV_1 increase ≥12% and ≥200 mL after administration of 400 µg salbutamol/360 µg albuterol (or equivalent dose) at screening

Key exclusion criteria:

- Patients who had an asthma exacerbation requiring systemic steroids, hospitalization, or emergency room visit within 1 year prior to the study

Figure 1. Study design



**Primary endpoint – mean FEV_1 (AUC_{0-24h})

Assessments

- Spirometry measurements followed the American Thoracic Society/European Respiratory Society guidelines [8]. Patients were provided with a PEF-meter and e-diary for recording trough (pre-dose) PEF measurements each morning and evening throughout the entire study.
- Morning and evening FEV_1 and PEF were analyzed by time of day. Morning assessments were performed 24 h after the last morning dose and 12 h after the last evening dose. Analogously, evening assessments were performed 24 h after the last evening dose and 12 h after the last morning dose, always shortly before inhalation of the next dose.

Results

Patient demographics and clinical characteristics

- Of 129 patients screened for inclusion, 37 eligible patients were randomized to one of six treatment sequences in a ratio of 1:1:1:1:1:1 (**Figure 1**).
- Patient demographics and baseline characteristics are depicted in **Table 1**.

Table 1. Patient demographics and baseline characteristics

Parameter	All (n=37)
Median age, years (min, max)	46.0 (18,72)
Male, n (%)	21 (56.8)
Body mass index, kg/m²	26.2 (4.7)
ICS dose at screening, n (%)	
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)
Mean predicted FEV_1 pre-dose, % (min, max)	75.8 (60, 96)
Reversibility, L	0.5 (0.21)
Mean reversibility, % (min, max)	18.9 (12, 52)
Baseline morning PEF, L/min	422.4 (107.42)
Baseline evening PEF, L/min	454.9 (107.51)

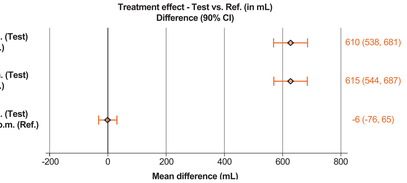
All values shown are mean (SD) unless otherwise stated. FEV_1: forced expiratory volume in 1 second; ICS: inhaled corticosteroids; n: number of patients contributing to the analysis; PEF: peak expiratory flow.

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

- Assessment of the primary endpoint showed a substantial improvement in FEV_1 (AUC_{0-24h}) for both IND/GLY/MF morning and evening dosing compared with placebo. Least squares (LS) means weighted mean FEV_1 (AUC_{0-24h}) after 14 days of IND/GLY/MF dosed in the morning was 3.43 L (90% CI: 3.172, 3.689), and 3.44 L (90% CI: 3.178, 3.694) after 14 days of IND/GLY/MF dosed in the evening (LS means difference of 610 mL [90% CI: 538, 681] and 615 mL [90% CI: 544, 687], respectively vs. placebo) (**Figure 2**).
- A negligible difference in weighted mean FEV_1 over 24 hours (AUC_{0-24h}) was observed between IND/GLY/MF morning and evening dose (–6 mL [90% CI: –76, 65]).

Figure 2. Effect of morning or evening dosing of IND/GLY/MF on weighted mean FEV_1 ($AUC_{0–24h}$) versus placebo

Parameters were analyzed using a mixed model adjusting for period, treatment, and sequence as fixed effect factors and patient as a random effect. CI: confidence interval; Ref: Reference



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

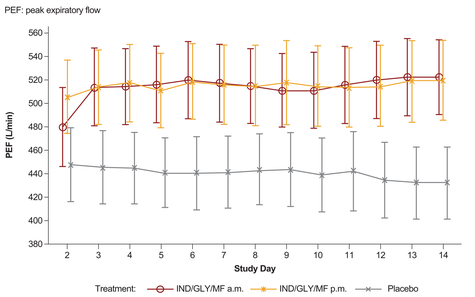
- Mean morning PEF (measured pre-dose on the morning of Day 15 of each treatment period) was significantly improved by IND/GLY/MF dosed in the morning and the evening (LS means difference 72.1 L/min [90% CI: 61.3, 82.9] and 86.9 L/min [90% CI: 76.1, 97.8], respectively versus placebo) (**Table 2**).
- 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 [90% CI: 61.9, 84.2]) and evening dose (58.7 L/min [90% CI: 47.5, 69.9]) versus placebo (**Table 2**).
- There were negligible differences in overall PEF values between morning and evening dosing (vs. 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 [90% CI: –25.6, –4.1]). Analogously, pre-dose PEF was higher in the evening with morning dosing than with evening dosing (+14.4 L/min [90% CI: 3.3, 25.5]).
- A line chart depicting mean overall PEF values from Day 2 to 14 is shown in **Figure 3**.

Table 2. Comparison of PEF measured in the morning and evening after 14 days of treatment

LS means (90% CI)			LS means difference (90% CI)
Morning average PEF (L/min)			
IND/GLY/MF a.m. (n=35) 489.6 (456.2, 523.1)	vs.	Placebo (n=36) 417.5 (384.1, 450.9)	72.1 (61.3, 82.9)
IND/GLY/MF p.m. (n=35) 504.4 (471.0, 537.9)	vs.	Placebo (n=36) 417.5 (384.1, 450.9)	86.9 (76.1, 97.8)
IND/GLY/MF a.m. (n=35) 489.6 (456.2, 523.1)	vs.	IND/GLY/MF p.m. (n=35) 504.4 (471.0, 537.9)	–14.8 (–25.6, –4.1)
Evening average PEF (L/min)			
IND/GLY/MF a.m. (n=35) 522.0 (488.7, 555.4)	vs.	Placebo (n=36) 449.0 (415.7, 482.3)	73.1 (61.9, 84.2)
IND/GLY/MF p.m. (n=35) 507.7 (474.3, 541.0)	vs.	Placebo (n=36) 449.0 (415.7, 482.3)	58.7 (47.5, 69.9)
IND/GLY/MF a.m. (n=35) 522.0 (488.7, 555.4)	vs.	IND/GLY/MF p.m. (n=35) 507.7 (474.3, 541.0)	14.4 (3.3, 25.5)

CI: confidence interval; LS: least squares; n: number of patients contributing to the analysis; PEF: peak expiratory flow.

Figure 3. Mean overall PEF (L/min) (90% CI) over Days 2–14 by treatment



Note: if a treatment period for an individual patient exceeded 14 days, the patient's PEF values contributed only up to Day 14 for the respective period

Safety and tolerability

- Overall, the safety and tolerability profiles of IND/GLY/MF were comparable between morning and evening dosing and were similar to placebo.
- A total of 79 adverse events (AEs) were reported in 32 (87%) patients during the study; the majority of AEs reported were of mild or moderate severity and were self-limiting.
- AEs were reported by 18 patients (51%) receiving IND/GLY/MF morning dose, 23 patients (66%) on IND/GLY/MF evening dose, and 18 (50%) receiving placebo.
- The most frequent AEs were headache (27%), nasopharyngitis (22%), and oropharyngeal pain (19%). The AEs which occurred in more than 5% of patients are shown in **Table 3**.
- Two patients experienced a severe AE (one bacterial food poisoning and one influenza); these were deemed unrelated to the study treatment by the investigator. There were no serious AEs, deaths, or new safety findings for IND/GLY/MF in this study.

Table 3. Incidence of treatment-emergent AEs by preferred term affecting >5% of patients (safety analysis set)

Preferred term	IND/GLY/MF morning (N=35) n (%)	IND/GLY/MF evening (N=35) n (%)	Placebo (N=36) n (%)	Total (N=37) n (%)
Number of patients with ≥1 AE	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)

AE: adverse event; N: number of patients studied; n: number of patients with at least one adverse event in the category. Values shown are n (%).

Discussion and Conclusions

- Both morning and evening dosing of once-daily IND/GLY/MF (110/50/80 µg) for 14–18 days provided significant and similar improvements in FEV_1 and PEF compared with placebo. These results support the use of once-daily LABA/LAMA/ICS in patients with asthma.
- Adherence to treatment is a key element of sustained asthma control. While once-daily administration has been suggested to improve therapy adherence, a patient may have a preferred time of the day to take his or her medication. Flexibility of dosing irrespective of the time of day may hence further support treatment adherence. Based on the present data, IND/GLY/MF provides this flexibility.
- 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 combination effects can be considered. For vilanterol/fluticasone furoate, increases of 377 mL and 422 mL in FEV_1 (AUC_{0-24h}) following morning and evening dose, respectively versus placebo were observed [9]. The LAMA umeclidinium additionally provided increases in FEV_1 (AUC_{0-24h}) over placebo between 68–121 mL in asthma patients [10]. Since comparing observations across studies carries limitations (e.g. differences in drugs used, treatment duration, patient populations), the authors caution against the over-interpretation of cross-study observations.
- PEF is measured twice daily every day and is therefore a very reliable, consistent, and accurate measure of lung function variation with some correlation to symptoms, even for patients who cannot perform full spirometry manoeuvers.
- The PEF improvements vs. placebo observed with IND/GLY/MF in this study are well above the range (15 to 20 L/min) suggested to be clinically relevant and perceptible by the patient [11, 12]. The consistency in PEF over the treatment period suggests good and stable lung function control with IND/GLY/MF in patients with asthma.
- Once-daily inhaled IND/GLY/MF provides consistent and substantial lung function benefits over the entire 24-hour dosing interval, irrespective of whether patients receive IND/GLY/MF in the morning or evening. There is no discernible, clinically meaningful difference between the IND/GLY/MF dosing regimens investigated in this study.

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