The Combination of Indacaterol/Glycopyrronium/Mometasone Furoate is Superior to High-Dose Salmeterol/Fluticasone Propionate in Improving Lung Function in Patients with Asthma

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Introduction

- The combination of an inhaled corticosteroid (ICS) plus a long-acting β_2-agonist (LABA), e.g. salmeterol/fluticasone, is considered standard-of-care therapy (SoC) for patients with moderate-to-severe asthma, GINA step 3/4.
- Despite the ample availability of SoC therapies, there remains a high prevalence of inadequately controlled asthma worldwide[1, 2].
- Adding a long-acting muscarinic antagonist (LAMA) can provide further benefit for patients with inadequately controlled asthma despite the use of ICS and LABAs[3].
- In this study, indacaterol (IND, LABA), glycopyrronium (GLY, LAMA) and mometasone furoate (MF, ICS) have been formulated as a once-daily (o.d.) fixed-dose combination therapy (IND/GLY/MF) delivered via the Breezhaler® inhalation device for treatment of asthma.
- We conducted this study to investigate the lung function benefits of o.d. IND/GLY/MF (high- and medium-dose ICS) compared with twice-daily (b.i.d.) SoC salmeterol/fluticasone propionate 50/500 µg.

Methods

Objectives

- **Primary**: To demonstrate superiority in peak bronchodilator effect of o.d. IND/GLY/MF, at doses of 150/50/**160** µg and 150/50/**80** µg, compared with salmeterol/fluticasone 50/500 µg b.i.d., after 3 weeks of treatment in patients with asthma.
- **Secondary**:
  - To evaluate the bronchodilator effect of each dose of IND/GLY/MF compared with salmeterol/fluticasone 50/500 µg b.i.d. by measuring the standardized forced expiratory volume in 1 second (FEV_1) area under the curve (AUC) after 3 weeks of treatment ($FEV_1AUC_{5min\text{-}1h}$ and $FEV_1AUC_{5min\text{-}23h45min}$).
  - To evaluate safety and tolerability of IND/GLY/MF.
- **Exploratory**: To evaluate the bronchodilator effect of each dose of IND/GLY/MF compared with salmeterol/fluticasone 50/500 µg b.i.d on pre-medication morning and evening peak expiratory flow rate (a.m./p.m. PEF) over the last week of treatment in each treatment period.

Study design

- This was a randomized, double-blind, double-dummy, active comparator-controlled, three-period crossover trial with 21 treatment days per treatment period in 116 adults with moderate-to-severe asthma (NCT03063086; **Figure 1**).
- Patients received o.d. IND/GLY/MF (150/50/**160** µg, high-dose ICS; 150/50/**80** µg, medium-dose ICS) and b.i.d. salmeterol/fluticasone (50/500 µg).
- This study was conducted in accordance with the Declaration of Helsinki and was approved by the Independent Ethics Committees of participating sites. Informed consent was obtained from each patient in writing before conducting any study specific procedures.

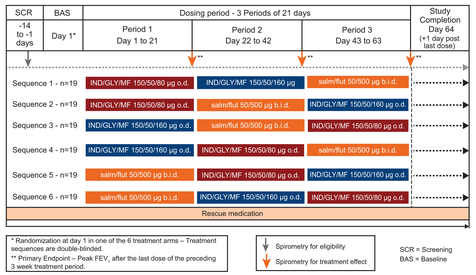
Key inclusion criteria

- Male and female patients aged between 18 and 75 years with asthma and who had been treated with ICS and LABA combinations for at least 3 months and at a stable medium- or high-dose ICS for at least 1 month prior to screening.
- Pre-bronchodilator FEV_1 of <80% of the predicted normal value at Screening Visit 1.
- 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 corticosteroids, hospitalization, or emergency room visit within 1 year prior to the study.
- Current (or within the 6 months prior to Visit 1) and past heavy smokers (>10 pack years).
- Patients who discontinued LAMA therapy in the past for any safety, tolerability or perceived lack of efficacy reason.

Figure 1. Study design



Assessments

- Spirometry measurements followed the American Thoracic Society/European Respiratory Society guidelines[4] and were performed at screening and at the end of each treatment period, at pre-dose, and at specific time points until 24 h post-dose.
- Peak FEV_1 bronchodilator effect was assessed using peak (defined as the highest bronchodilator effect on FEV_1 during a period of 5 min to 4h after the last evening dose of each treatment period).
- Standardized FEV_1AUC was calculated as the area under the FEV_1 curve over a specified time interval divided by the length of the specified time interval.
- Patients were provided with a PEF-meter and a patient e-diary for recording the PEF measurements twice daily from Screening through the End of Study visit and rescue medication use.

Results

Demographics and clinical characteristics (Table 1)

- Of 116 randomized patients, 107 patients completed the study. The most common reasons for discontinuation was occurrence of AEs (n = 4; see Safety Results). Other reasons included patient decision, physician decision, non-compliance with study treatment, and technical problems.
- Patient demographics and baseline characteristics are depicted in **Table 1**.

Table 1. Demographic and clinical baseline characteristics (safety analysis set)

	Total (N = 116)
Demographics	
Median age, years (min, max)	52.0 (18, 76)
Male, n (%)	61 (52.6)
BMI, kg/m², mean (SD)	27.2 (5.51)
Clinical characteristics	
Pre-bronchodilator FEV_1 (L), mean (SD)	2.2 (0.74)
Post-bronchodilator FEV_1 (L), mean (SD)	2.6 (0.81)
Mean predicted FEV_1 pre-dose, % (min, max)	62.2 (25, 82)
Reversibility (L), mean (SD)	0.5 (0.24)
Mean reversibility, % (min, max)	23.9 (12, 86)
Use of prior asthma medication, n (%)	
ICS/LABA/LAMA	10 (8.6)
ICS/LABA	105 (90.5)
ICS	1 (0.9)
ICS dose at screening, n (%)	
Low-dose	11 (9.5)
Medium-dose	86 (74.1)
High-dose	19 (16.4)
Baseline Morning PEF (L/min), mean (SD)	354.4 (122.53)
Baseline Evening PEF (L/min), mean (SD)	373.5 (121.7)

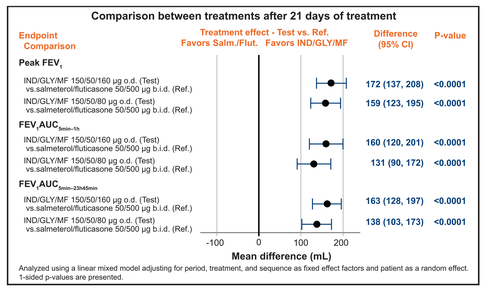
*The study population included patients from Europe (Germany [N=62], Bulgaria [N=25], Romania [N=9], The Netherlands [N=8], and United Kingdom [N=4]) and Asia (China [N=8])

BMI: body mass index; FEV_1: forced expiratory volume in 1 second; ICS: inhaled corticosteroids; LABA: long-acting β_2-agonist; LAMA: long-acting muscarinic antagonists; PEF: peak expiratory flow; SD: standard deviation.

Primary efficacy results: effect of IND/GLY/MF on peak FEV_1

- The study met its primary objective by demonstrating superiority (statistically significant and clinically meaningful improvement) of both IND/GLY/MF doses over salmeterol/fluticasone 50/500 µg b.i.d. in terms of peak FEV_1 improvement after 21 days of treatment (**Figure 2**).

Figure 2. Effect of IND/GLY/MF (150/50/160 and 150/50/80 µg o.d.) on peak FEV_1 (L) and standardized $FEV_1AUC_{5min\text{-}1h}$ and $FEV_1AUC_{5min\text{-}23h45min}$ versus salmeterol/fluticasone 50/500 µg b.i.d.

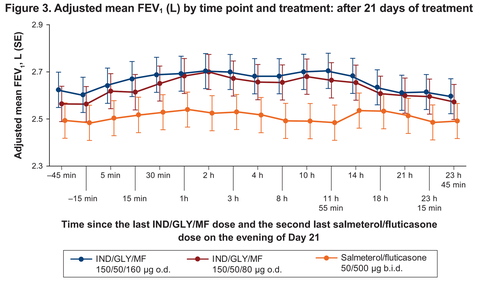


CI: confidence interval; FEV_1: forced expiratory volume in 1 second; IND: indacaterol; GLY: glycopyrronium; MF: mometasone furoate.

Secondary efficacy endpoints: standardized FEV_1AUC at various time points, and FEV_1 measurements over 24 h

- Compared with salmeterol/fluticasone 50/500 µg b.i.d., both IND/GLY/MF doses induced improvements in standardized FEV_1 AUC across different time intervals (**Figure 2**; p<0.0001 for all comparisons).
- IND/GLY/MF high and medium doses showed a superior treatment effect compared with salmeterol/fluticasone on mean FEV_1 at all timepoints (P<0.0001; **Figure 3**).
- At the last time point:
  - IND/GLY/MF (high-dose ICS) increased FEV_1 105 mL more than salmeterol/fluticasone (95% CI: 64, 147).
  - IND/GLY/MF (medium-dose ICS) increased FEV_1 81 mL more than salmeterol/fluticasone (95% CI: 39, 123).

Figure 3. Adjusted mean FEV_1 (L) by time point and treatment: after 21 days of treatment

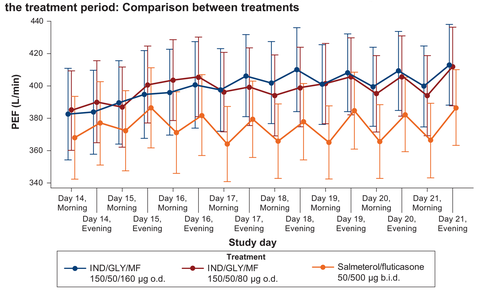


FEV_1: forced expiratory volume in 1 second; IND: indacaterol; GLY: glycopyrronium; MF: mometasone furoate; SE: standard error.

Exploratory efficacy endpoints: pre-medication evening and pre-medication morning PEF

- After 21 days of treatment, both doses of o.d. IND/GLY/MF showed a superior treatment effect compared with salmeterol/fluticasone 50/500 µg b.i.d. in mean PEF of 29 L/min (95% CI: 22, 35) for the high dose and of 24 L/min (95% CI: 18, 31) for the medium dose (P<0.0001 for comparisons of both IND/GLY/MF doses vs. salmeterol/fluticasone). **Figure 4** illustrates PEF over the last week of treatment for all 3 treatments, demonstrating a consistently higher pre-dose morning and evening PEF with IND/GLY/MF compared with salmeterol/fluticasone.

Figure 4. Mean (95% CI*) morning/evening PEF (L/min) between Days 14 and 21 within the treatment period: Comparison between treatments



Study day is calculated relative to start of treatment period
In case of rescue medication intake during 24 h spirometry assessment, observations after rescue medication intake are excluded from the analysis. All spirometry assessments are excluded from the analysis in case of rescue medication intake within 6 hours prior to spirometry assessments.

CI: confidence interval; IND: indacaterol; GLY: glycopyrronium; MF: mometasone furoate; PEF: peak expiratory flow.

*The CIs are based on estimated variance involving between subject effect. For a cross-over study, these CIs cannot be used for comparing two treatments

Safety

- Study treatments (IND/GLY/MF 150/50/**160** µg o.d., IND/GLY/MF 150/50/**80** µg o.d., and salmeterol/fluticasone 50/500 µg b.i.d.) were well-tolerated and there were no relevant differences in tolerability between IND/GLY/MF doses and salmeterol/fluticasone 50/500 µg b.i.d. after 21 days of treatment.
- The most common adverse events (AEs) reported in ≥5% patients were headache (18.1%), nasopharyngitis (12.1%), cough (9.5%), and dysphonia (9.5%; **Table 2**). There were no serious AEs, no deaths or new safety findings for IND/GLY/MF.
- In total, 41 (35.3%) patients were reported with AEs of mild severity and 29 (25.0%) patients with moderate severity. Two severe AEs were reported during the study: fatigue and gastrointestinal infection, which were reported while receiving IND/GLY/MF 150/50/**80** µg o.d. and salmeterol/fluticasone 50/500 µg b.i.d. treatment, respectively.
- Four patients discontinued the study treatment/study due to AEs (three AEs were reported [tachyarrhythmia, diarrhea, and asthma exacerbation] while patients received IND/GLY/MF 150/50/**80** µg o.d. treatment and one AE was reported [asthma exacerbation] while the patient received salmeterol/fluticasone 50/500 µg b.i.d. treatment).

Table 2. Incidence of treatment-emergent AEs by preferred term affecting ≥5% of patients (safety analysis set)

Preferred term	IND/GLY/MF 150/50/160 µg (N=112) n (%)	IND/GLY/MF 150/50/80 µg (N=115) n (%)	salmeterol/fluticasone 50/500 µg b.i.d. (N=111) n (%)	Total (N=116) n (%)
Number of patients with ≥1 AE	37 (33.0)	33 (28.7)	42 (37.8)	72 (62.1)
Headache	10 (8.9)	10 (8.7)	13 (11.7)	21 (18.1)
Nasopharyngitis	3 (2.7)	7 (6.1)	4 (3.6)	14 (12.1)
Cough	5 (4.5)	3 (2.6)	3 (2.7)	11 (9.5)
Dysphonia	6 (5.4)	1 (0.9)	6 (5.4)	11 (9.5)

AE: adverse event; N: number of patients studied; n: number of patients with at least one adverse event in the category.

Discussion and Conclusions

- Once-daily inhaled IND/GLY/MF, at both high and medium-doses of ICS MF, provided superior lung function benefits compared with twice-daily salmeterol/fluticasone at the highest approved dose (50/500 µg b.i.d.) and was well-tolerated with a similar safety profile observed for all treatments.
- There was a numerically slightly higher lung function benefit with IND/GLY/MF 150/50/**160** µg vs salmeterol/fluticasone than with IND/GLY/MF 150/50/**80** µg for all lung function endpoints. For peak FEV_1, $FEV_1AUC_{5min\text{-}1hour}$, and $FEV_1AUC_{5min\text{-}23h45min}$ the estimated mean differences between the two doses of IND/GLY/MF were 13 mL (95%CI: -22.9, 48.9), 29.1 mL (95%CI: -10.4, 68.6), and 25 mL (95%CI: -8.9, 59) in favor of the higher dose, respectively. The study was not powered to establish a dose differentiation.
- Both doses of IND/GLY/MF improved morning and evening PEF in the last treatment week versus salmeterol/fluticasone 50/500 µg b.i.d. PEF is measured twice daily every day and is therefore a reliable, consistent and accurate measure of lung function variation with a strong correlation to symptoms. Studies in patients with asthma suggest that improvements in PEF of 15 to 20 L/min are clinically relevant and perceptible by the patient[5,6].
- Cross-study comparisons have substantial limitations due to differences between the studies (e.g. treatment duration, disease severity of patient populations, background LABA/ICS therapy, and study design). In the presented study, mean peak FEV_1 increases with fixed-dose combination IND/GLY/MF were 159 mL (95% CI: 123, 195) with the medium-dose ICS and 172 mL (95% CI:137, 208) with the high-dose ICS compared with LABA/ICS high-dose therapy. In a previous study with a different study design and patient population, a loose triple combination of tiotropium (Respimat) 5 µg as add-on to LABA plus high-dose ICS increased mean peak FEV_1 by 110 mL (95% CI: 63, 158)[7].
- The results provide, to the best of our knowledge, the first evidence that a LABA/LAMA/ICS fixed-dose combination (here IND/GLY/MF) at medium- and high-dose ICS can provide substantial lung function benefit over high-dose standard-of-care salmeterol/fluticasone in patients with moderate-to-severe asthma.

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