Lung function normalisation with indacaterol/glycopyrronium/mometasone furoate in patients with asthma

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Introduction

- The combination of an inhaled corticosteroid (ICS) plus a long-acting β_2-agonist (LABA) is considered standard-of-care therapy for patients with moderate-to-severe asthma[1]
- For patients who remain uncontrolled despite treatment with a combination of a medium- or high-dose ICS plus a LABA, one suggestion in the Global Initiative for Asthma (GINA) report is addition of a long-acting muscarinic antagonist (LAMA)[1]
- 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® device for treatment of asthma
- Two Phase II studies were conducted to investigate:
  - the lung function benefits of o.d. IND/GLY/MF (high- and medium-dose ICS) compared with twice-daily (b.i.d.) high-dose ICS salmeterol/fluticasone propionate combination (SFC) (Study B2208);
  - the effect of dosing time (morning or evening) on the lung function benefits of o.d. IND/GLY/MF (medium-dose ICS) compared with placebo (Study B2209)
- The B2208 study met its primary objective by demonstrating that mean peak forced expiratory volume in 1 second (FEV_1) increased with fixed-dose combination IND/GLY/MF (high-dose ICS) by 172 mL (95% CI, 137 to 208) and IND/GLY/MF (medium-dose ICS) by 159 mL (95% CI, 123 to 195) compared with high-dose ICS SFC after 21 days of treatment[2]
- The B2209 study met its primary objective showing that both morning and evening dosing of IND/GLY/MF (medium-dose ICS) provided statistically significant and similar improvements in FEV_1 compared with placebo after 14 days of treatment. Least squares mean difference in FEV_1 over 24 hours (AUC_{0-24h}) was 610 mL (90% CI, 538 to 681) and 615 mL (90% CI, 544 to 687) for morning and evening dosing, respectively, versus placebo[3]
- Here we present results from the two studies on the effect of IND/GLY/MF on the proportion of patients achieving normalisation of lung function and on rescue medication use versus SFC and placebo

Methods

Study design

- Both B2208 and B2209 studies had a randomised, double-blind, 3-treatment, 3-period, 6-sequence crossover design

B2208

- This was an active-comparator-controlled study with 21 treatment days per treatment period (NCT03063086)
- Patients received o.d. IND/GLY/MF (150/50/160 µg, high-dose ICS and 150/50/80 µg, medium-dose ICS) and b.i.d. SFC (50/500 µg)
- Patients who had an asthma exacerbation requiring systemic steroids, hospitalisation, or emergency room visit within 6 weeks prior to the study were excluded

B2209

- This was a placebo-controlled study with 3 treatment periods of 14 days each (NCT03108027); treatment periods were separated by washout periods of 14–21 days
- The three treatments were: IND/GLY/MF 150/50/80 µg in the evening, IND/GLY/MF 150/50/80 µg in the morning, and placebo
- B2209 included patients with asthma aged ≥18 years, with an FEV_1 ≥60%–<100% of the predicted normal value at screening, and receiving stable daily low- or medium-dose ICS for ≥4 weeks prior to screening
- Patients who had an asthma exacerbation requiring systemic steroids, hospitalisation, or emergency room visit within 1 year prior to the study were excluded

Assessments (B2208 and B2209)

- 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
- Near-normal lung function was defined as FEV_1 [$AUC_{(0-24h)}$] ≥80% of predicted normal (% pred.) at the end of the treatment period and normal lung function as FEV_1 [$AUC_{(0-24h)}$] >90% pred. at the end of the treatment period
- Patients were provided with an electronic diary to record study assessments, including rescue medication use, from screening through to End of Study visit. Rescue medication use over the last week of each treatment period was assessed

Results

Demographics and clinical characteristics

- In B2208, 116 patients were randomised of whom 107 completed the study.
- In B2209, 37 patients were eligible and could be randomised; 34 completed the study.
- Patient demographics and baseline characteristics for both studies are listed in **Table 1**

Table 1. Demographic and clinical baseline characteristics (B2208 and B2209)

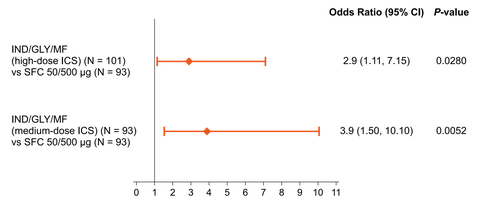
	B2208 (N = 116)	B2209 (N = 37)
Demographics		
Median age, years (range)	52 (18, 76)	46 (18, 72)
Male, n (%)	61 (52.6)	21 (56.8)
BMI, kg/m², mean (SD)	27.2 (5.51)	26.2 (4.67)
Baseline clinical characteristics		
Pre-bronchodilator FEV_1 (L), mean (SD)	2.2 (0.74)	2.9 (0.72)
Predicted FEV_1 pre-dose (%), mean (SD)	62.2 (11.62)	75.8 (9.04)
Reversibility (%), mean (SD)	23.9 (12.61)	18.9 (7.83)
Use of prior asthma medication, n (%)		
LABA/LAMA/ICS	10 (8.6)	–†
LABA/ICS	105 (90.5)	–†
ICS	1 (0.9)	–†
Screening ICS dose category, n (%)		
Low dose	11 (9.5)	31 (83.8)
Medium dose	86 (74.1)	6 (16.2)
High dose	19 (16.4)	–

†Prior medication usage in B2209 captured for ICS dose category only.
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 receptor antagonist; SD, standard deviation

Effect of IND/GLY/MF treatment on normalisation of lung function

- In B2208, 45% and 47% of patients on high- or medium-ICS dose IND/GLY/MF, respectively, achieved near-normal lung function (FEV_1 [$AUC_{(0-24h)}$] ≥80% pred.) versus 34% with high-dose ICS SFC ($P < 0.05$ for both comparisons)
- For patients with moderate-to-severe disease (B2208), the odds of achieving near-normal lung function increased by:
  - 2.9 times when treated with IND/GLY/MF (high-dose ICS) versus high-dose ICS SFC ($P = 0.0280$);
  - 3.9 times when treated with IND/GLY/MF (medium-dose ICS) versus high-dose ICS SFC ($P = 0.0052$) (**Figure 1**)
- For patients with mild-to-moderate asthma severity (B2209), the likelihood of achieving normal lung function (FEV_1 [$AUC_{(0-24h)}$] >90% pred.) substantially increased with IND/GLY/MF (medium-dose ICS) compared with placebo. This was irrespective of dose timing (morning or evening). The percentage of patients who achieved normal lung function on IND/GLY/MF (medium-dose ICS) after morning dosing was 45%, and after evening dosing was 48%, compared with 7% on placebo

Figure 1. Patients with moderate-to-severe asthma were more likely to achieve near-normal lung function (FEV_1 [$AUC_{(0-24h)}$] ≥80% pred.) when treated with IND/GLY/MF compared with SFC (B2208)



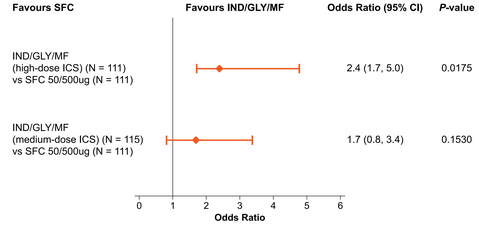
Responder in a treatment period is defined as achieving >80% $AUC_{(0-24h)}$ of pred. FEV_1 at the end of period. Responder (yes/no) is analyzed using a logistic regression with treatment, sequence, period as factors having fixed effects, baseline pre-bronchodilatory pred. FEV_1% as covariate having fixed effect and subject having random effect.

GLY, glycopyrronium; IND, indacaterol; MF, mometasone furoate; SFC, salmeterol/fluticasone

Effect of IND/GLY/MF treatment on rescue medication use

- In B2208, a higher percentage of patients did not need rescue medication in the last week of treatment with IND/GLY/MF (high-dose ICS, 58%; medium-dose 52%) compared with SFC (45%)
- The odds of being free from rescue medication with IND/GLY/MF (high-dose ICS) was 2.4 times higher compared with SFC (95% CI, 1.7 to 5.0; $P = 0.0175$). Similarly, the odds ratio (OR) with IND/GLY/MF (medium-dose ICS) was 1.7 (95% CI, 0.8 to 3.4; $P = 0.153$) (**Figure 2**)

Figure 2. Patients with asthma who were treated with IND/GLY/MF were more likely to be rescue-medication free in the last week of treatment compared with those on SFC (B2208)

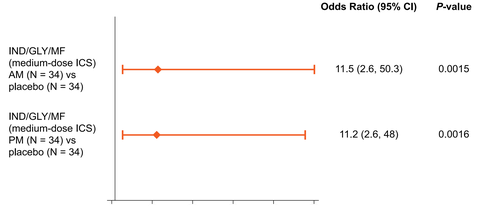


Responder (not using rescue medication in last 7 days of treatment period) is analysed using a logistic regression with treatment, sequence, period as factors having fixed effects and subject having random effect.

GLY, glycopyrronium; IND, indacaterol; MF, mometasone furoate; SFC, salmeterol/fluticasone

- In B2209, a higher percentage of patients did not need rescue medication in the last week of treatment with IND/GLY/MF (morning medium-dose ICS, 71%; evening medium-dose ICS, 71%) compared with placebo (29%). The OR of being rescue-medication free with morning medium-dose IND/GLY/MF versus placebo was 11.5 (95% CI 2.6, 50.3; $P = 0.0015$) (**Figure 3**). Evening results were almost identical

Figure 3. Compared with placebo, patients with asthma who were treated with IND/GLY/MF were more likely to be rescue-medication free in the last week of treatment (B2209)



Responder (not using rescue medication in the last 7 days of treatment period) is analyzed using a logistic regression with treatment, sequence, period as factors having fixed effects and subject having random effect.

GLY, glycopyrronium; IND, indacaterol; MF, mometasone furoate

Safety

- In B2208, all study treatments were well tolerated and there were no relevant differences in tolerability between IND/GLY/MF (high- and medium-dose ICS) and SFC after 21 days of treatment
- In B2209, all treatments were well tolerated. Overall the safety and tolerability profiles of morning and evening dosing of IND/GLY/MF were comparable and similar to placebo after 14 days of treatment
- Adverse events (AEs) occurring in more than 5% of patients in either study are shown in **Table 2a** and **2b**. There were no serious AEs, no deaths or new safety findings for IND/GLY/MF in either study. In both studies, the majority of AEs were mild or moderate in severity

Table 2a. Incidence of treatment-emergent AEs by preferred term affecting >5% of patients (safety analysis set) (B2208)

Preferred term	IND/GLY/MF (high-dose ICS) (N = 112) n (%)	IND/GLY/MF (medium-dose ICS) (N = 115) n (%)	SFC 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; GLY, glycopyrronium; IND, indacaterol; MF, mometasone furoate; SFC, salmeterol fluticasone

Table 2b. Incidence of treatment-emergent AEs by preferred term affecting >5% of patients (safety analysis set) (B2209)

Preferred term	IND/GLY/MF AM (N = 35) n (%)	IND/GLY/MF PM (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; GLY, glycopyrronium; IND, indacaterol; MF, mometasone furoate

Conclusions

- The B2208 study demonstrated that mean peak FEV_1 increased with IND/GLY/MF (high-dose ICS) by 172 mL (95% CI, 137 to 208) and IND/GLY/MF (medium-dose ICS) by 159 mL (95% CI, 123 to 195) compared with high-dose ICS salmeterol/fluticasone after 21 days of treatment. IND/GLY/MF is delivered via the Breezhaler® device
- The B2209 study showed that both morning and evening dosing of IND/GLY/MF (medium-dose ICS) provided statistically significant and similar improvements in FEV_1 compared with placebo after 14 days of treatment
- Nearly half of patients achieved normal or near-normal lung function with IND/GLY/MF, irrespective of morning or evening once-daily dosing
- The odds of achieving near-normal (or normal) lung function statistically increased by at least 2.9 times when treated with IND/GLY/MF versus high-dose ICS salmeterol/fluticasone or placebo
- Patients with asthma were more likely to be rescue-medication free with IND/GLY/MF compared with high-dose ICS salmeterol/fluticasone or placebo
- The odds of being rescue-medication free statistically increased by at least 2 times when patients were treated with IND/GLY/MF (high-dose ICS) versus high-dose ICS salmeterol/fluticasone and by 11 times versus placebo
- These results provide further evidence of the benefits provided by IND/GLY/MF (both high- and medium-dose ICS) on patients' lung function and symptoms (using rescue medication use as surrogate) compared with placebo and with active control by a standard-of-care treatment (salmeterol/fluticasone) at the highest approved daily dose

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