Indacaterol/glycopyrronium/mometasone furoate combination consistently shows lung function benefits 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 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 the secondary lung function endpoint (trough FEV_1, forced vital capacity [FVC] average) results from the two studies

Methods

Study designs

- 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)
- The study included patients with asthma aged between 18 and 75 years who had been treated with ICS plus LABA combinations for at least 3 months and at a stable ICS dose for at least 1 month prior to screening, and had a pre-bronchodilator FEV_1 of <80% of predicted normal
- 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.
- Trough FEV_1 was defined as the mean of FEV_1 at 23 h 15 min and 23 h 45 min post-dose from the last evening dose of each period, i.e., on Day 21 (B2208)
- In B2209:
  - morning (AM dose) trough FEV_1 is defined as the FEV_1 measurement at Day 15, +12 h (timing from the post-evening dose on Day 14) before Day 15 AM dose;
  - evening (PM dose) trough FEV_1 (L) is defined as the FEV_1 measurement at Day 15, +23 h 55 min (timing from the post-evening dose on Day 14)
- Standardised FVC [$AUC_{(0-24h)}$] is derived as a weighted average of repeated measurements of FVC at fixed time intervals relative to last evening dose of the treatment period

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)

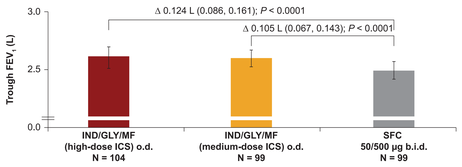
	B2208 (N = 116)	B2209 (N = 37)
Demographics		
Median age, years (range)	52 (18, 76)	46 (18, 72)
Male, n (%)	61 (52.6)	21 (56.8)
BMI, kg/m², mean (SD)	27.2 (5.51)	26.2 (4.67)
Baseline clinical characteristics		
Pre-bronchodilator FEV_1 (L), mean (SD)	2.2 (0.74)	2.9 (0.72)
Predicted FEV_1 pre-dose (%), 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 corticosteroid; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic receptor antagonist; SD, standard deviation

Superior treatment effect of IND/GLY/MF versus SFC on trough FEV_1

- In B2208, IND/GLY/MF (both high- and medium-dose ICS) showed superior treatment effect (least squares mean difference) versus SFC on trough FEV_1 (124 mL [95% CI, 86 to 161] and 105 mL [95% CI, 67 to 143], respectively, both $P < 0.0001$) in patients with moderate-to-severe asthma after 21 days (**Figure 1**)
- In B2209, in a less severe asthma patient population, the mean improvement in trough FEV_1 by IND/GLY/MF (medium-dose ICS) was 544 mL versus placebo after 14 days (95% CI, 460 to 628 mL; $P < 0.0001$) (**Figure 2**)

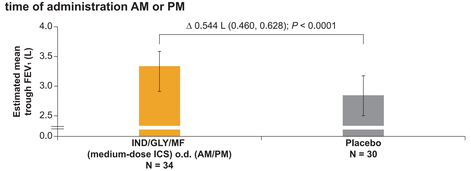
Figure 1. Compared with SFC, trough FEV_1 (L) was increased with IND/GLY/MF (high- and medium-dose ICS) o.d. in patients with moderate-to-severe asthma (B2208)



Test conducted at one-sided 2.5% level. N: number of patients with non-missing value of trough FEV_1 (mL). Trough FEV_1 analyzed using a linear mixed model with treatment, period, sequence as factors having fixed effects while subject has a random effect

FEV_1, forced expiratory volume in 1 second; GLY, glycopyrronium; IND, indacaterol; MF, mometasone furoate; SFC, salmeterol fluticasone

Figure 2. Trough FEV_1 (L) was increased with IND/GLY/MF (medium-dose ICS) o.d. versus placebo in patients with mild-to-moderate asthma (B2209), irrespective of time of administration AM or PM



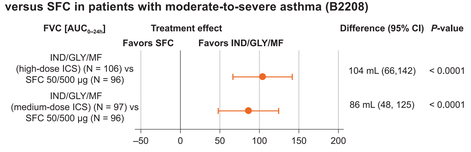
Effect of IND/GLY/MF medium dose (regardless of time of administration AM or PM), is estimated from a model adjusting for treatment (IND/GLY/MF/ Placebo), time of assessment (AM or PM trough), period, sequence as fixed factor, subject as random effect, with an unstructured correlation matrix to account for correlation between morning and evening trough FEV_1 of the same patient in a period

FEV_1, forced expiratory volume in 1 second; GLY, glycopyrronium; IND, indacaterol; MF, mometasone furoate

Superior treatment effect of IND/GLY/MF versus SFC on FVC [AUC_{0-24h}]

- In B2208, IND/GLY/MF (high- and medium-dose ICS) improved FVC [AUC_{0-24h}] compared with SFC by 104 mL (95% CI, 66 to 142, $P < 0.0001$) and 86 mL (95% CI, 48 to 125, $P < 0.0001$), respectively, after 21 days of treatment (**Figure 3**)

Figure 3. IND/GLY/MF (high- and medium-dose ICS) improved FVC [AUC_{0-24h}] versus SFC in patients with moderate-to-severe asthma (B2208)

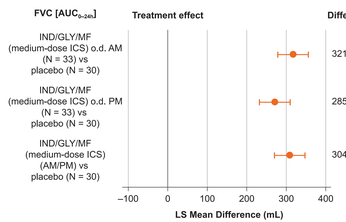


Standardised FVC [AUC_{0-24h}] is analyzed using a linear mixed effects model with treatment, sequence, period as fixed effects and subject as a random effects. Profiles of patients using rescue medication during 24h spirometry or within 6h prior to 24h spirometry are completely excluded from the AUC derivation (and hence do not contribute to analysis)

AUC, area under the curve; FVC, forced vital capacity; GLY, glycopyrronium; IND, indacaterol; MF, mometasone furoate; SFC, salmeterol fluticasone

- In B2209, a mean increase of 304 mL in FVC [AUC_{0-24h}] was seen versus placebo (95% CI, 243 to 364 mL; $P < 0.0001$) after 14 days of treatment irrespective of time of dosing (**Figure 4**)

Figure 4. IND/GLY/MF (medium-dose ICS) improved FVC [AUC_{0-24h}] versus placebo in patients with mild-to-moderate asthma (B2209)



Standardised FVC [AUC_{0-24h}] is analyzed using a linear mixed effects model with treatment, sequence, period as fixed effects and subject as a random effects. Effect of IND/GLY/MF, regardless of time of administration, on FVC [AUC_{0-24h}] is provided based on the model (model based averaging of morning/ evening dose effect, rather than averaging patient outcomes), Profiles of patients using rescue medication during 24h spirometry or within 6h prior to 24h spirometry are completely excluded from the AUC derivation (and hence do not contribute to analysis)

AUC, area under the curve; FVC, forced vital capacity; 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
- The data newly presented here confirms the lung function benefits across a variety of lung function parameters. A once daily fixed-dose LABA/LAMA/ICS combination (here IND/GLY/MF) at both medium- and high-dose ICS can provide substantial lung function benefit over a high-dose ICS standard-of-care (here salmeterol/fluticasone) in patients with moderate-to-severe asthma
- Substantial and statistically significant lung function benefits were observed with IND/GLY/MF (medium-dose ICS) irrespective of morning or evening dosing
- Once-daily IND/GLY/MF was well tolerated with a safety profile comparable with SFC and placebo
- Once-daily IND/GLY/MF consistently showed clinically relevant and statistically significant improvements in lung function compared with the highest approved daily dose of twice-daily salmeterol/fluticasone and placebo in patients with asthma across all severities in two separate Phase II studies

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