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Lung Function Normalisation with Indacaterol Acetate/ Glycopyrronium Bromide/Mometasone Furoate in Patients with Asthma

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To the Editor,

In patients with asthma, low forced expiratory volume in 1 second (FEV₁) values represent objectively measurable, strong independent predictors of a future risk of exacerbations [1–3]. Thus, an important treatment outcome in patients with asthma is to achieve normal or near-normal lung function.

The Global Initiative for Asthma 2020 recommends treatment with medium-dose inhaled corticosteroids (ICS) with long-acting β_2 -agonists (LABA) as the preferred controller for patients with asthma at step 4 and high-dose ICS with LABA for step 5 [1]. However, some patients remain inadequately controlled despite treatment with LABA/ICS medium- or high-dose. Add-on treatment with a long-acting muscarinic antagonist (LAMA) can provide further benefits in these patients [4–6]. Indacaterol acetate/glycopyrronium bromide/mometasone furoate (IND/GLY/MF), delivered via Breezhaler[®], is a novel once-daily treatment.

The LABA/LAMA/ICS combination is approved for the maintenance treatment of asthma [7].

In this post-hoc analysis of data from two multicentre trials, we compared the effect of treatment interventions on lung function in a responder analysis. Normal lung function was defined as FEV₁ area under the curve from 0 to 24 h [AUC_(0–24h)] \geq 90% of predicted normal after treatment and near-normal lung function was defined as FEV₁ [AUC_(0–24h)] \geq 80% of predicted normal after treatment. We report results from a responder analysis evaluating the percentage of patients achieving normal or near-normal lung function with IND/GLY/MF compared with salmeterol xinafoate/fluticasone propionate (SAL/FLU) or placebo from two phase II studies (CQVM149B2208 [7], NCT03063086; CQVM149B2209 [8], NCT03108027).

CQVM149B2208 (hereafter referred to as B2208) was a randomised, double-blind, double-dummy, active-controlled, three-period (21 days each), six-sequence crossover study in patients with moderate-to-severe asthma. Eligible patients were randomised to one of the six possible

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treatment sequences, to receive IND/GLY/MF high-dose ICS (150/50/160 µg) or IND/GLY/MF medium-dose ICS (150/50/80 µg) once daily delivered via Breezhaler® or SAL/FLU high-dose ICS (50/500 µg) twice daily delivered via Accuhaler®, for 21 days in each of the three treatment periods.

CQVM149B2209 (hereafter referred to as B2209) was a randomised, double-blind, placebo-controlled, three-period (14 days each), six-sequence crossover study in patients with mild-to-moderate asthma. Eligible patients were randomised to one of the six possible treatment sequences, to receive IND/GLY/MF medium-dose once daily in the evening or morning, delivered via Breezhaler® or placebo via a matching inhaler, for 14 days in each of the three treatment periods.

Male and female patients (aged ≥ 18 years) with a pre-bronchodilator FEV₁ of < 80% of the predicted value were included in the B2208 study, and those with a pre-bronchodilator FEV₁ of ≥ 60% and < 100% of the predicted value were included in the B2209 study. Both studies included patients with an FEV₁ increase of ≥ 12% and > 200 mL after administration of 400 µg of salbutamol or 360 µg of albuterol. Patients with an asthma exacerbation requiring systemic steroids, hospitalisation or an emergency room visit within 6 weeks prior to the study were excluded. Detailed information on the study designs and patient criteria is described in the respective publications [7, 8]. Patients included in the B2209 study had less severe lung function impairment with a pre-bronchodilator FEV₁ between 60 and 100% of the predicted value at screening. As the “near-normal” cut-off of ≥ 80% falls in the middle of the range required at inclusion, some patients were already above it, and therefore the criterion to assess improvement was raised to ≥ 90% (“normal”). However, the B2208 study included patients with FEV₁ < 80% at screening, therefore achieving “near-normal” lung function could be assessed in B2208.

In the B2208 study, both IND/GLY/MF high-dose and medium-dose demonstrated greater improvements in peak FEV₁ vs SAL/FLU after 21 days of treatment. IND/GLY/MF at both ICS doses provided greater improvements in trough FEV₁ and forced vital capacity AUC_{0–24h} compared with SAL/FLU. Mean forced expiratory flow at 25–75% also improved with IND/GLY/MF high-dose and medium-dose (1.71 L/s and 1.70 L/s, respectively) compared with SAL/FLU (1.54 L/s).

Similarly, in the B2209 study, medium-dose IND/GLY/MF showed greater improvement in FEV₁ (AUC_{0–24h}) for both morning and evening administrations vs placebo after 14 days of treatment [8]. Greater improvements in trough FEV₁ were also seen with medium-dose IND/GLY/MF, regardless of the time of administration (morning or evening), and provided substantial improvements in forced vital capacity (AUC_{0–24h}) compared with placebo.

In the B2208 study, 44.6% and 47.3% of patients taking IND/GLY/MF high- and medium-dose, respectively, achieved near-normal lung function compared with 33.7% of patients taking SAL/FLU (Fig. 1a). In the B2209 study, 47.0% of patients taking IND/GLY/MF medium-dose achieved normal lung function vs 6.7% patients

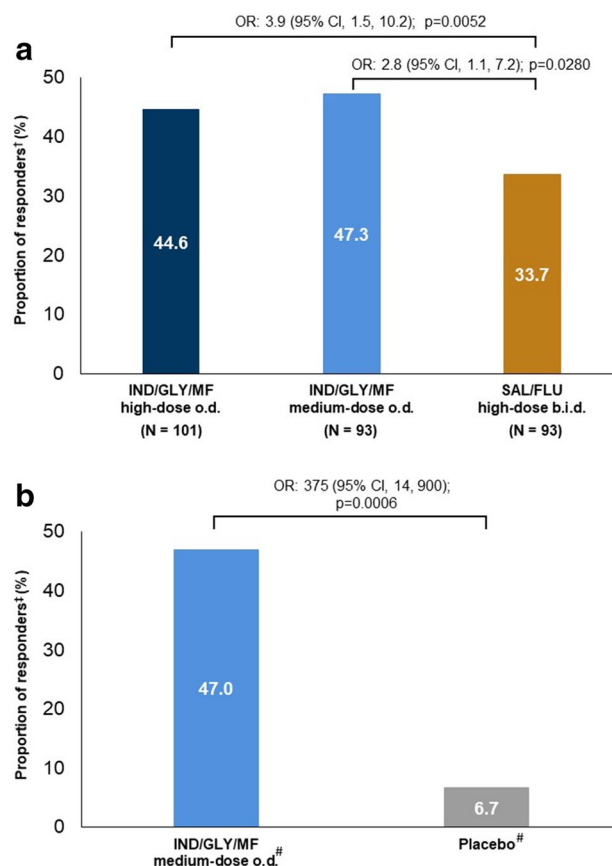


Fig. 1 Lung function normalisation with indacaterol acetate/glycopyrronium bromide/mometasone furoate (IND/GLY/MF) in patients with asthma. **a** Near-normal lung function (forced expiratory volume in 1 second area under the curve from 0 to 24 hours [FEV₁ AUC_(0–24h)] ≥ 80% predicted) with IND/GLY/MF high-dose and medium-dose vs salmeterol/fluticasone (SAL/FLU) high-dose and **b** normal lung function (FEV₁ AUC_(0–24h) ≥ 90% predicted) with IND/GLY/MF medium-dose vs placebo. *A.M.* morning, *b.i.d.* twice daily, *CI* confidence interval, *o.d.* once daily, *OR* odds ratio, *P.M.* evening. [#]*N* = 33 and *N* = 31 patients were included in the o.d. IND/GLY/MF medium-dose *A.M.* and *P.M.* groups, respectively; *N* = 30 patients were included in the placebo group. Responders' data presented here represent the mean of percentage responders from IND/GLY/MF medium-dose *A.M.* and *P.M.* groups. [†]Response for a treatment period is defined as achieving AUC_(0–24h) of predicted FEV₁ ≥ 80% after the end of the treatment period in B2208. [‡]Response for a treatment period is defined as achieving AUC_(0–24h) of predicted FEV₁ ≥ 90% after the end of the treatment period in B2209. Responder (yes/no) is analysed using a logistic regression with treatment, sequence, period as factors having fixed effects, baseline pre-bronchodilator % predicted FEV₁ as a covariate having a fixed effect and subject having a random effect

receiving placebo (Fig. 1b). This was irrespective of the time of dose (morning or evening), as the percentage of patients who achieved normal lung function with medium-dose IND/GLY/MF at morning and evening administrations was 45.2% and 48.5%, respectively, compared with 6.7% receiving placebo.

Studies in asthma suggest that improvements in the peak expiratory flow (PEF) of 15–20 L/min are clinically relevant and perceptible by patients [9, 10]. The lung function normalisation outcomes, which were achieved with IND/GLY/MF vs SAL/FLU and placebo, were complemented by a greater proportion of patients achieving clinically meaningful improvement in PEF with IND/GLY/MF vs these comparators. In the B2208 study, 63.6% and 63.2% of patients taking IND/GLY/MF high-dose and medium-dose, respectively, had an improvement of ≥ 20 L/min in PEF vs 31.0% of patients taking SAL/FLU. In the B2209 study, a greater percentage of patients treated with IND/GLY/MF medium-dose (91.0% and 84.4% for morning and evening doses, respectively) had an improvement of ≥ 20 L/min in PEF vs placebo (11.4%).

Furthermore, lung function normalisation with IND/GLY/MF was complemented by a greater proportion of patients with no rescue medication use with IND/GLY/MF vs SAL/FLU and placebo. In the B2208 study, a higher percentage of patients treated with IND/GLY/MF high-dose (58%) did not require rescue medication compared with patients treated with SAL/FLU (45%) [odds ratio: 2.4; 95% confidence interval [CI] 1.7–5.0; $p = 0.018$]; a similar trend was also observed with IND/GLY/MF medium-dose (52%; OR: 1.7; 95% CI 0.8–3.4; $p = 0.1530$) vs SAL/FLU [7]. A substantial proportion of patients did not require rescue medication with either morning (67.6%; OR: 11.07; 95% CI 3.08–39.81; $p = 0.0015$) or evening (70.6%; OR: 11.96; 95% CI 3.45–41.39; $p = 0.0016$) administration of IND/GLY/MF medium-dose compared with placebo in the B2209 study. Regardless of the timing of administration, for a given patient, the odds of being “rescue medication free” were higher when treated with IND/GLY/MF medium-dose compared with placebo.

Lung function normalisation can be assessed by improvements in FEV₁ (AUC_{0–24h}), supported by improvements observed in other lung function parameters. Another important goal of asthma treatment is to eliminate or reduce the need for rescue medication [2].

Overall, results from B2208 and B2209 studies demonstrated greater improvements in lung function with IND/GLY/MF compared with SAL/FLU and placebo, respectively. These improvements in lung function translated into more patients achieving normal or near-normal lung function with IND/GLY/MF compared with SAL/FLU and placebo. In addition, patients were more likely to be rescue

medication free with IND/GLY/MF compared with high-dose SAL/FLU or placebo.

A responder analysis based on the ability to achieve normal lung function helps to translate clinical trial results into clinically useful terms. However, at least one limitation of this approach must be noted. Neither B2208 nor B2209 studies allowed us to define the best achievable lung function, an alternative and acceptable endpoint in the clinical setting if remodelling prevents the achievement of population-predicted normal values.

In summary, results from this responder analysis, based on the lung function normalisation and reduction in rescue medication use, provide further evidence on benefits of IND/GLY/MF in patients with asthma and support the use of this LABA/LAMA/ICS combination in patients who are inadequately controlled on LABA/ICS.

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Declarations

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Conflicts of interest Kenneth R. Chapman reports grants and personal fees from AstraZeneca, Boehringer Ingelheim, Grifols, GlaxoSmithKline, Sanofi, Regeneron, Novartis and Takeda. Kenneth R. Chapman also received personal fees from CSL Behring, Inhibrx and Kamada, and grants from Vertex, outside the submitted work. Henrik Watz reports grants, personal fees and non-financial support from Novartis, during the conduct of the study; grants, personal fees and non-financial support from AZ, BerlinChemie/Menarini, GlaxoSmithKline, Chiesi, Bayer and Takeda, outside the submitted work. Dave Singh reports personal fees from AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, Genentech, GlaxoSmithKline, Glenmark, Gossamerbio, Menarini, Mundipharma, Novartis, Peptinnovate, Pfizer, Pulmatrix, Theravance and Verona, outside the submitted work. Jens M. Hohlfeld reports grants from Novartis during the conduct of the study. Jens M. Hohlfeld also reports personal fees from Boehringer Ingelheim, Merck & Co, Inc., Novartis and HAL; and grants from AstraZeneca AB, Novartis, Janssen Pharmaceutica NV, ALK, Boehringer Ingelheim, LETI, GlaxoSmithKline, Sanofi-Aventis, Astellas Pharma and Allergopharma, outside the submitted work. In the past 3 years, Zuzana Diamanat acted as the Research Director at QPS-NL, an institution that received research support from several bio-pharmaceutical companies, especially within respiratory field: Patara Pharma (now Respivant), Novartis, Foresee Pharmaceuticals. Furthermore, Zuzana Diamanat received honoraria or speaker fees for serving on advisory boards or acting as a consultant from ALK, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, HAL Allergy, Merck Sharp & Dohme and Sanofi-Genzyme-Regeneron. In addition, Zuzana Diamanat also acts as an advisor for BMR BV, which holds patents for several respiratory indications. Ieuan Jones and

Ivan Nikolaev are employees of Novartis. Hanns-Christian Tillmann is an employee of Novartis Institutes for Biomedical Research and owns Novartis shares.

Ethics approval The study was conducted in accordance with the Declaration of Helsinki and was approved by the independent ethics committees of participating sites in Europe and China.

Consent to participate Written informed consent was obtained from each patient before conducting any study-specific procedures.

Consent for publication Not applicable.

Availability of data and material 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 are anonymized to respect the privacy of patients who have participated in the study in line with applicable laws and regulations. This study data availability is according to the criteria and process described on www.clinicalstudydatarequest.com.

Code availability Not applicable.

Authors' contributions KRC, IJ, HCT and IN conceptualised this responder analysis. HW, DS, JHM, ZD and HCT designed the studies. HW, DS, JHM and ZD were responsible for data acquisition. IJ was involved in the extraction of the data and statistical analyses. All the authors were involved in the interpretation of the results and the writing and critical revision of the manuscript with the support of professional medical writers mentioned in the Acknowledgements section. All authors provided final approval on the version to be submitted.

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