Watz et al. Respiratory Research (2020) 21:87
https://doi.org/10.1186/s12931-020-01349-5

Respiratory Research

LETTER TO THE EDITOR Open Access

Letter to the editor: indacaterol/glycopyrronium/mometasone furoate compared with salmeterol/fluticasone propionate in patients with asthma: a randomized controlled cross-over study

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Abstract

Indacaterol (IND; 150 μg), glycopyrronium (GLY; 50 μg) and mometasone furoate (MF; 160 μg [high-dose ICS] and 80 μg [medium-dose ICS]) have been formulated as a once-daily (o.d.) fixed-dose combination treatment delivered via the Breezhaler® device for the treatment of patients with asthma. In this randomized ($n = 116$), double-blind, double-dummy, active comparator-controlled, three-period cross-over study we evaluated the benefit of o.d. IND/GLY/MF versus twice daily (b.i.d.) salmeterol/fluticasone propionate combination (SFC; 50/500 μg; high-dose ICS) treatment (NCT03063086). Overall, 107 patients completed the study. The study met its primary objective by demonstrating superiority of o.d. IND/GLY/MF at medium and high-dose ICS over b.i.d. SFC (high-dose ICS) in peak FEV_1 after 21 days of treatment (+ 172 mL with high-dose and + 159 mL with medium-dose IND/GLY/MF versus SFC, $p < 0.0001$ for each comparison). We also observed that a higher percentage of patients did not need rescue medicine with IND/GLY/MF (high-dose ICS, 58%; medium-dose ICS, 52%) compared with SFC (45%) during the last week of each treatment period. Study treatments were well-tolerated with no relevant differences in tolerability between both IND/GLY/MF doses and SFC. In conclusion, both doses of IND/GLY/MF provided superior lung function benefits compared with twice-daily, standard-of-care SFC at the highest approved dose.

Trial registration: ClinicalTrials.gov, (Identifier: NCT03063086),
EudraCT start date: May 11, 2017; First patient first visit / study initiation date: May 31, 2017.

Keywords: Indacaterol, Glycopyrronium, Mometasone Furoate, Asthma

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To the Editor:

The combination of an inhaled corticosteroid (ICS) plus a long-acting β2-agonist (LABA) is considered standard-of-care therapy for patients with moderate-to-severe asthma (GINA step 3/4/5) [1]. However, some patients remain inadequately controlled despite using LABA/ICS combination treatments [2, 3]. Adding a long-acting muscarinic antagonist (LAMA) on top of LABA/ICS (medium- or high-dose ICS) can help to improve asthma outcomes in these patients [1, 4, 5].

The combination of the LABA indacaterol acetate (IND) and the LAMA glycopyrronium bromide (GLY) is presently available as once daily (o.d.) treatment for patients with chronic obstructive pulmonary disease (COPD). Recently, IND/GLY has been formulated in combination with the ICS mometasone furoate (MF) delivered via dry powder inhalation device (Breezhaler®) for the treatment of asthma.

We conducted a phase II multi-center study to investigate lung function parameters and rescue medication use with IND/GLY/MF compared with salmeterol/fluticasone propionate combination (SFC) in adults with asthma (NCT03063086). The primary study objective was to demonstrate superiority in peak bronchodilator effect of o.d. IND/GLY/MF (150/50/160 μg [high-dose ICS]; 150/50/80 μg [medium-dose ICS]) compared with twice-daily (b.i.d.) SFC (50/500 μg; high-dose ICS) after 21 days of treatment.

This confirmatory study had a randomized, double-blind, double-dummy, active-comparator-controlled, crossover design with three consecutive study periods of 21 treatment days each. Eligible patients were randomized to receive o.d. IND/GLY/MF (high-dose ICS; 160 μg MF), o.d. IND/GLY/MF (medium-dose ICS; 80 μg MF) and b.i.d. SFC (high-dose ICS) in one of six treatment sequences. 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. Written informed consent was obtained from each patient before conducting any study

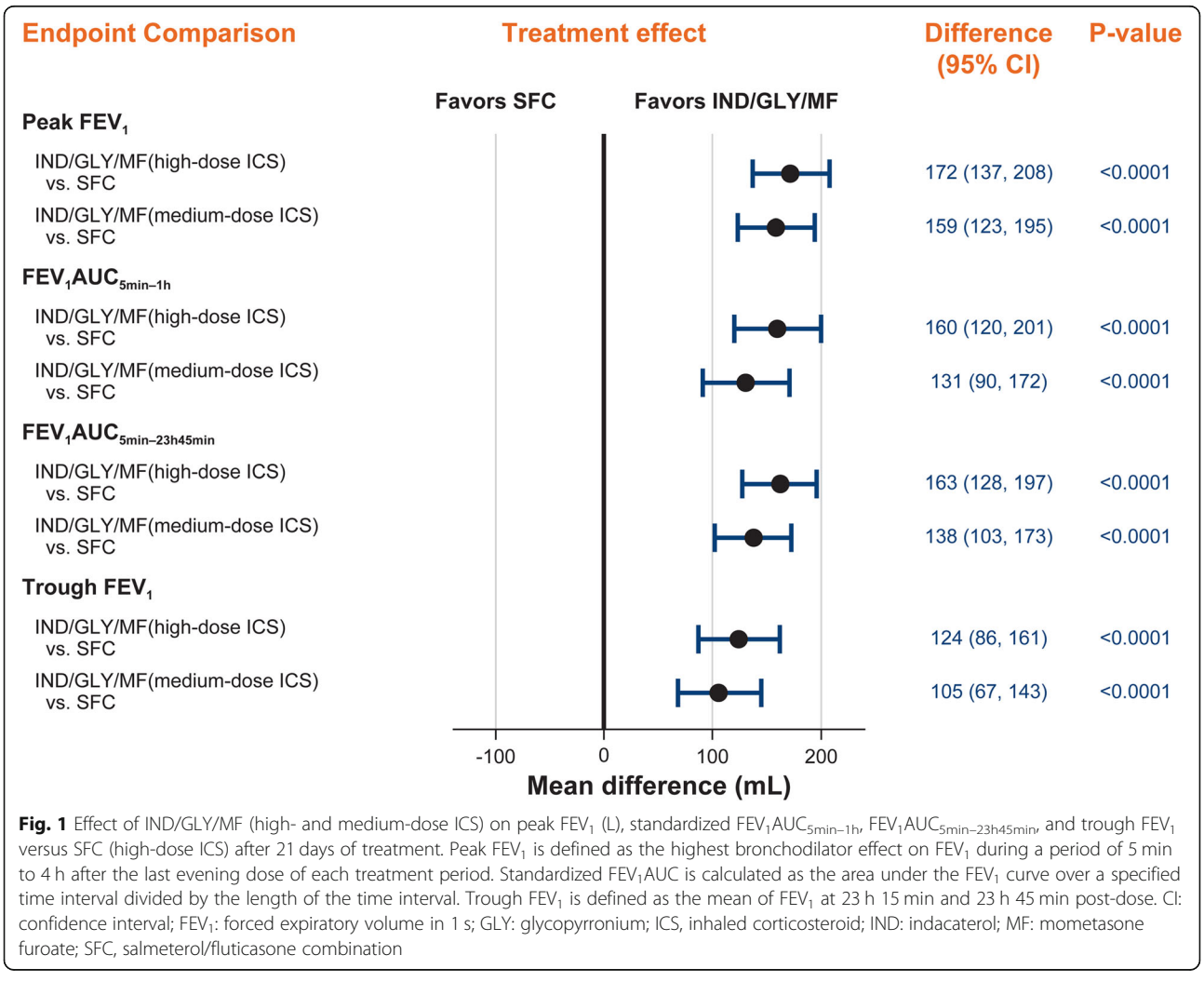

Fig. 1 Effect of IND/GLY/MF (high- and medium-dose ICS) on peak FEV_1 (L), standardized $FEV_1AUC_{5min–1h}$, $FEV_1AUC_{5min–23h45min}$, and trough FEV_1 versus SFC (high-dose ICS) after 21 days of treatment. Peak FEV_1 is defined as the highest bronchodilator effect on FEV_1 during a period of 5 min to 4 h after the last evening dose of each treatment period. Standardized FEV_1AUC is calculated as the area under the FEV_1 curve over a specified time interval divided by the length of the time interval. Trough FEV_1 is defined as the mean of FEV_1 at 23 h 15 min and 23 h 45 min post-dose. CI: confidence interval; FEV_1: forced expiratory volume in 1 s; GLY: glycopyrronium; ICS, inhaled corticosteroid; IND: indacaterol; MF: mometasone furoate; SFC, salmeterol/fluticasone combination

specific procedures. Some results from this study have been previously reported in abstracts [6, 7].

Male and female patients with a documented physician diagnosis of asthma for a period of ≥12 months and who were previously treated with LABA/ICS combinations for ≥3 months and at a stable medium- or high-dose ICS for ≥1 month prior to screening were eligible to enrol. All patients had a pre-bronchodilator forced expiratory volume in 1 s (FEV_1) < 80% of the predicted normal value (after withholding bronchodilators) and an FEV_1 increase ≥12% and ≥ 200 mL after administration of 400 μg salbutamol/360 μg albuterol (or equivalent dose) at screening. Key exclusion criteria included current smokers or patients who had smoked tobacco products within 6 months prior to Visit 1 or who had a smoke history of greater than 10 pack years; patients who had an asthma exacerbation requiring systemic steroids, hospitalisation, or emergency room visit within 6 weeks prior to the study; and patients with a history of chronic lung diseases other than asthma.

From screening to the end of the study, patients were asked to record study medication intake, peak expiratory flow (PEF; a.m. and p.m.) and rescue medication use (short-acting β2-agonist [SABA], MDI; 100 μg salbutamol/90 μg albuterol) in an electronic diary (data from last week of each treatment period was pre-specified to be used for evaluation of PEF and rescue medication use). Spirometry measurements followed the American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines [8].

The sample size of this study was 116 randomized patients (52.6% male; mean age: 49.5 years [range: 18–76 years]), of which 107 patients completed the study. Adverse events (AEs) were the most common reason for discontinuation (3.4%). Other reasons included non-compliance with study treatment (1.7%), and patient and physician decision (both 0.9%). At baseline, mean pre-bronchodilator FEV_1 was 2.2 L (range: 0.8–4.5 L), mean predicted FEV_1 pre-bronchodilator was 62.2% (range: 25–82%pred.), mean SABA reversibility was 23.9% (range: 12–86%), and 90.5% of patients used LABA/ICS as prior medication (8.6% LABA/LAMA/ICS; 0.9% ICS only). Of 116 randomized patients, 86 were on medium-dose ICS at screening, 19 were on high-dose ICS, and 11 were on low-dose ICS; this gives an indication of the asthma severity of the study population.

The primary objective was met showing superiority of IND/GLY/MF at both ICS doses over SFC in peak FEV_1 after 21 days of treatment (Fig. 1: 172 mL [95% CI: 137, 208; high-dose ICS]; 159 mL [95% CI: 123, 195; medium-dose ICS]; $p < 0.0001$). Similarly, on day 21 IND/GLY/MF (high- and medium-dose ICS) showed a

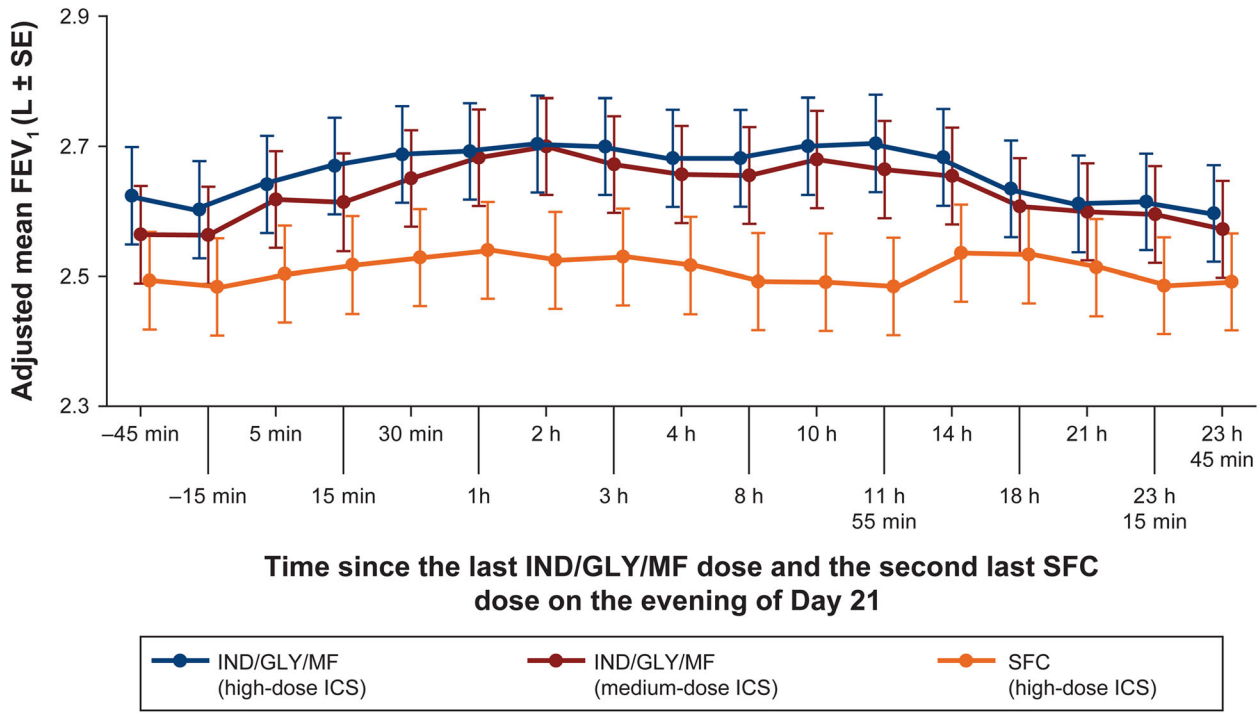

Fig. 2 Adjusted mean FEV_1 (L) by time point and treatment: after 21 days of treatment. $p < 0.001$ for comparisons between IND/GLY/MF (high and medium-dose ICS) and SFC (high-dose ICS) treatments at each time point after − 45 min ($p < 0.001$ for IND/GLY/MF [high-dose ICS] and $p < 0.05$ for IND/GLY/MF [medium-dose ICS] versus SFC at − 45 min). FEV_1: forced expiratory volume in 1 s; GLY: glycopyrronium; IND: indacaterol; MF: mometasone furoate; SE: standard error; SFC, salmeterol/fluticasone combination

superior treatment effect on mean FEV_1 at all time points compared with SFC (Fig. 2). Both IND/GLY/MF doses also improved standardized $FEV_1AUC_{5min\text{-}1h}$ and $FEV_1AUC_{5min\text{-}23h45min}$ versus SFC ($p < 0.0001$; Fig. 1) and showed a superior treatment effect compared with SFC on mean PEF measurements (least square mean difference of 29 L/min [95% CI: 22, 35; $P < 0.0001$] with high-dose ICS and 24 L/min [95% CI: 18, 31; $P < 0.0001$] with medium-dose ICS versus SFC).

Furthermore, we observed that a higher percentage of patients did not need rescue medicine with IND/GLY/MF (high-dose ICS, 58%; medium-dose ICS, 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 than with SFC (95% CI: 1.7, 5.0; $p = 0.018$). Similarly, the odds ratio (95% CI) was 1.7 (0.8, 3.4; $p = 0.153$) for IND/GLY/MF (medium-dose ICS) versus SFC.

Overall, study treatments were well-tolerated with no clinically relevant differences in AE rates (IND/GLY/MF [high-dose ICS]: 33.0%; IND/GLY/MF [medium-dose ICS]: 28.7%; SFC: 37.8%). The most commonly reported AEs included headache (IND/GLY/MF [high-dose ICS], 8.9%; IND/GLY/MF [medium-dose ICS], 8.7%; SFC, 11.7%), nasopharyngitis (2.7, 6.1, and 3.6%, respectively), cough (4.5, 2.6, and 2.7%, respectively), and dysphonia (5.4, 0.9, and 5.4%, respectively). Four (3.4%) patients discontinued the study due to AEs (tachyarrhythmia, diarrhea, asthma exacerbation during IND/GLY/MF [medium-dose ICS] treatment, and asthma exacerbation during SFC treatment). There were no serious AEs or new safety findings in the study.

In a previous study, with a different design and patient population, the open combination of tiotropium (Respimat®) 5 μg as add-on to LABA/ICS (high-dose ICS) increased mean peak FEV_1 by 110 mL (95% CI: 63, 158) at week 24 compared with LABA/ICS (high-dose ICS) plus placebo [9]. In the present study, we report a least square mean peak FEV_1 treatment difference of 172 mL and 159 mL for IND/GLY/MF high- and medium-dose ICS, respectively, when compared with SFC. Cross-study comparisons have substantial limitations due to differences in study design, treatment duration, and patient populations, therefore the authors caution against over-interpretation.

Although the lack of monitoring of asthma symptoms can be perceived as a limitation of this study, the decreased use of rescue medication during treatment with IND/GLY/MF versus SFC provides a signal for improved asthma control while on IND/GLY/MF.

While several studies with LABA/LAMA/ICS combination therapy in asthma are presently ongoing, our data provide evidence that a fixed-dose, once-daily treatment with IND/GLY/MF at medium- and high-dose ICS improves outcomes in patients with moderate-to-severe asthma in comparison to twice-daily high-dose ICS SFC.

Abbreviations

AE: Adverse events; ATS: American Thoracic Society; b.i.d.: twice-daily; CI: Confidence interval; COPD: Chronic obstructive pulmonary disease; ERS: European Respiratory Society; FEV_1: Forced expiratory volume in 1 s; GLY: Glycopyrronium bromide; ICS: Inhaled corticosteroid; IND: Indacaterol acetate; LABA: long-acting β_2-agonist; LAMA: Long-acting muscarinic antagonist; MF: Mometasone furoate; o.d.: Once daily; PEF: Peak expiratory flow; SABA: Short-acting β_2-agonist; SFC: Salmeterol/fluticasone propionate combination

Acknowledgements

The authors wish to thank Arnab Sarkar and Sampath Kalluri (Novartis Healthcare Pvt. Ltd.) for providing statistical support and Áine Abautret-Daly of Novartis Product Lifecycle Services (Dublin, Ireland) for providing scientific writing support for this article, which was funded by Novartis Pharma AG, Basel, Switzerland in accordance with Good Publication Practice (GPP3) guidelines (http://www.ismpp.org/gpp3). Dave Singh is supported by the National Institute for Health Research (NIHR) Manchester Biomedical Research Centre (BRC).

Authors' contributions

HW, JMH, DS, PP, IJ, HCT conceived and designed the study. HW, JMH, DS, JB, ZD, JL, SH, KAE performed the study and collected data. The data were analyzed by IJ, and all authors revised the manuscript for intellectual content and approved it for publication.

Funding

This clinical trial was funded by Novartis Pharma AG, Basel, Switzerland (Clinical trial registration: NCT03063086; EUDRA-CT no: 2016–005164-34).

Availability of data and materials

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 is 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.

Ethics approval and consent to participate

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. Written informed consent was obtained from each patient before conducting any study specific procedures.

Consent for publication

Not applicable.

Competing interests

HW reports grants from Novartis during the conduct of the study; and personal fees from AZ, BerlinChemie, Boehringer Ingelheim, GSK, Novartis, Takeda, and Chiesi outside the submitted work. JMH reports grants from Novartis during the conduct of the study. JMH 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 (GSK), Sanofi-Aventis, Astellas Pharma, and Allergopharma, outside the submitted work. DS reports personal fees from Novartis during the conduct of the study; and personal fees from AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, Genentech, GlaxoSmithKline, Glenmark, Menarini, Mundipharma, Novartis, Peptinnovate, Pfizer, Pulmatrix, Theravance, and Verona outside the submitted work. JB reports other from Novartis during the conduct of the study; other from AstraZeneca, Novartis, Boehringer, Chiesi, and Pearl Therapeutics outside the submitted work; and is a 50% share-holder and managing director full-time of Insaf Respiratory Research Institute, which received the compensations listed above. Apart from academic affiliations, ZD acts as Executive and Scientific Medical Director at a phase I/II pharmacological unit (QPS-NL), which performs clinical studies for pharmaceutical companies, including Novartis. In the past 3 years, ZD

received honoraria, consultancy or speaker fees, personal fees and other from Astrazeneca, ALK, Aquilon, Boehringer Ingelheim, CSL, HAL Allergy, MSD, Sanofi-Genzyme. JL has nothing to disclose. SH is a Principal Investigator at Jilin University First Hospital, which received funding from Novartis Pharma AG for the conduct of this study; Jilin University First Hospital, has received funding from other pharmaceutical companies for conduct of clinical trials outside the submitted work. KAE is an Investigator at QPS, a CRO that received funding from Novartis Pharma AG for the conduct of the study; QPS has received funding from various pharmaceutical companies for the conduct of clinical studies outside the submitted work. IJ and PP are employees of Novartis. HCT is an employee of Novartis Institutes for Biomedical Research and owns Novartis shares.

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Received: 23 December 2019 Accepted: 1 April 2020
Published online: 15 April 2020

References

1. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. 2019. Available from: http://ginasthma.org/gina-reports/.
2. Price D, Fletcher M, van der Molen T. Asthma control and management in 8,000 European patients: the REcognise asthma and LInk to symptoms and experience (REALISE) survey. NPJ Prim Care Respir Med. 2014;24:14009.
3. Bateman ED, Boushey HA, Bousquet J, Busse WW, Clark TJ, Pauwels RA, et al. Can guideline-defined asthma control be achieved? The gaining optimal asthma ControL study. Am J Respir Crit Care Med. 2004;170(8):836–44.
4. Aalbers R, Park HS. Positioning of long-acting muscarinic antagonists in the Management of Asthma. Allergy, Asthma Immunol Res. 2017;9(5):386–93.
5. Virchow JC, Kuna P, Paggiaro P, Papi A, Singh D, Corre S, et al. Single inhaler extrafine triple therapy in uncontrolled asthma: two randomised, double-blind, parallel group, controlled trials (TRIMARAN and TRIGGER). Lancet. 2019;394(10210):1737–49.
6. Watz H, Hohlfeld JM, Singh D, Beier J, Scholz V, Diamant Z, et al. The Combination of Indacaterol/Glycopyrronium/Mometasone Furoate Is Superior to High-Dose Salmeterol/Fluticasone Propionate in Improving Lung Function in Patients with Asthma. Am J Respir Crit Care Med. 2019; 199:A7081.
7. Chapman KR, Watz H, Beier J, Singh D, Hohlfeld JM, Diamant Z, et al. Lung function normalization with indacaterol/glycopyrronium/mometasone furoate in patients with asthma. Eur Respir J. 2019;54(suppl 63):PA2539.
8. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J. 2005;26:319–38.
9. Kerstjens HA, Moroni-Zentgraf P, Tashkin DP, Dahl R, Paggiaro P, Vandewalker M, et al. Tiotropium improves lung function, exacerbation rate, and asthma control, independent of baseline characteristics including age, degree of airway obstruction, and allergic status. Respir Med. 2016;117:198–206.

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