**Online Supplement**

# Lung function improvements following inhaled indacaterol/glycopyrronium/mometasone furoate are independent of dosing time in asthma patients: a randomized trial

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## Full inclusion and exclusion criteria

Inclusion criteria

- Patients with a documented physician diagnosis of asthma and who additionally met the following criteria:
  - patients receiving daily treatment with an inhaled corticosteroid at a low or medium daily dose
  - on a stable regimen for at least 4 weeks prior to screening
- Pre-bronchodilator forced expiratory volume in one second ($FEV_1$) ≥60% and <100% of the predicted normal value for the patient during screening.
- Patients who demonstrated an increase in $FEV_1$ of ≥12% and ≥200 mL after administration of 400 µg salbutamol/360 µg albuterol (or equivalent dose) at screening. All patients were required to perform a reversibility test at screening.
- At screening, and baseline (day 1 pre-dose time) of the first treatment period, vital signs (systolic and diastolic blood pressure and pulse rate) were assessed in the sitting position and again in the standing position. Sitting and standing vital signs had to be within the following ranges:
  - oral body temperature 35.0–37.5 °C
  - systolic blood pressure 90–159 mmHg
  - diastolic blood pressure 50–99 mmHg
  - pulse rate 40–90 beats per minute
- Hypertensive patients must have been on stable antihypertensive therapy for at least 4 weeks prior to screening to be included in the trial.

Exclusion criteria

- Contra-indicated for treatment with, or having a history of reactions/hypersensitivity to any drugs of a similar class.
- Patients who had an asthma attack/exacerbation requiring systemic steroids, hospitalization, or emergency room visit within 1 year of screening.
- Patients who were previously intubated for a severe asthma attack/exacerbation.

- Patients with a history of clinically relevant bronchoconstriction upon repeated forced expiratory manoeuvres.
- History of paradoxical bronchospasm in response to inhaled medicines.
- Patients who during the run-in period prior to randomization required the use of ≥12 puffs/24 h of rescue medication for 48 h (over two consecutive days) or who had a decline in peak expiratory flow (PEF) from the reference PEF of ≥30% for 6 consecutive scheduled PEF readings.
- Patients who did not maintain regular day/night, waking/sleeping cycles (e.g. night shift workers).
- Current smokers and patients who had smoked or inhaled tobacco products within the 6-month period prior to screening, or who had a smoking history of greater than 10 pack years (Note: one pack is equivalent to 20 cigarettes. 10 pack years = 1 pack/day x 10 years or pack/day x 20 years).

## Patient numbering, treatment assignment, and randomization

*Patient numbering*

Each patient was uniquely identified by a 7-digit patient number, which was comprised of the site number assigned by Novartis and a sequential number assigned by the investigator at screening. Once assigned to the patient, the patient number was not re-used. This number was the definitive, unique identifier for the patient and was used to identify the patient throughout the study for all data collected, sample labels, etc. Upon signing the informed consent form, the patient was assigned the next sequential number by the investigator. The investigator or his/her staff contacted the Interactive Response Technology (IRT) and provided the requested identifying information of the patient to register them into the IRT.

*Treatment assignment, and randomization*

Randomized treatment was assigned to individual patients by way of a randomization number, which was in the range of 5101–5137. After randomizing 35 patients, two patients met eligibility criteria for randomization on the same day. Consequently, after confirming with the clinical trial team that the randomization system is able to accommodate an additional patient than planned, both the patients were randomized. This resulted in randomizing 37 patients instead of the planned 36 patients.

The randomization number was only used to identify which treatment sequence the patients were randomized to receive. The patient number assigned to the patient at screening remained the unique identifier for the patient throughout the study. The investigator entered the screening number that was kept throughout the study in the electronic case report form (eCRF). The randomization numbers were generated using the following procedure to ensure that treatment assignment remained unbiased and concealed from patients and investigator staff: a patient randomization list was produced by the IRT provider using a validated system that automated the random assignment of patient numbers to randomization numbers. These randomization numbers were linked to the different treatment arms, which in turn were linked to the medication numbers. The randomization scheme for patients was reviewed and approved by a member of the Randomization Office.

*Treatment blinding*

Patients, investigators and the sponsor remained blinded to study treatment throughout the study. The identity of the treatments was concealed by the use of study drugs that were all identical in packaging, labeling, schedule of administration, appearance, and odor. No emergency unblinding occurred during the study.

## Study design

*Treatment period Day 1*

On Day 1 of each treatment period, patients attended the site for an outpatient visit in the afternoon (approximately 1 to 2 h before the first scheduled evening dose) and Day 1 pre-dose assessments were performed. Patients were evaluated for randomization eligibility (only at treatment period 1), and trained/retrained on the use of the Breezhaler® inhalation device. Only the evening dose was inhaled onsite (at approximately 19:00 h) on Day 1 under the guidance and supervision of site personnel.

*Treatment period Day 2 to Day 13*

The first morning dose of each treatment period was administered on Day 2 of each treatment period. Patients self-administered the study drug from Day 2 to Day 13 of each treatment period at home. Patients were instructed to take the study drug in the morning (at approximately 07:00 h) and in the evening (at approximately 19:00 h) and to record their pre-treatment morning and

evening PEF throughout the study in a patient e-diary. Site staff were recommended to call the patient once per week during the treatment and washout periods to verify the patient's well-being and to ensure that none of the study discontinuation criteria were met.

*Treatment period Day 14 and Day 15*

Patients visited the site on the morning of Day 14 of each treatment period to inhale the morning dose of study drug or placebo under the guidance and supervision of site staff. Site personnel also reviewed PEF measurements and rescue medication intake as well as study drug compliance by checking the patient's e-diary. Patients were retrained on the use of the Breezhaler® inhalation device under the guidance of site personnel. Patients were then admitted in the afternoon of Day 14 of treatment period 1 and treatment period 2 (approximately 4 h prior to Day 14 assessments) to ensure that the patients did not take any rescue medication within 4 h prior to the start of spirometry assessments. The last evening dose of study drug or placebo on Day 14 (at approximately 19:00 h) and morning dose on Day 15 (at approximately 07:00 h) was inhaled under the guidance and supervision of site personnel. Spirometry was performed from Day 14 starting before the evening dose (at approximately -5 min in relation to planned evening dosing time, i.e. at approximately 19:00 h) and then every 3 h after administration of the evening dose until 24 h after the Day 14 evening dose, i.e. until approximately 19:00 h on Day 15. After completion of the spirometry assessments and the last Day 15 visit assessment, the patients were discharged and started the washout period of 14 to 21 days' duration.

*Washout period*

The treatment periods were separated by washout periods of 14 to 21 days duration. Washout periods started from the evening of Day 15 of treatment periods 1 and 2. During the washout period, patients were instructed to continue measuring PEF, and to register PEF measurements and rescue medication intake in the patient e-diary. Site personnel continued to call the patient weekly to check the patient's well-being. Procedures in treatment periods 2 and 3 were identical to the procedures of treatment period 1 apart from:

- Eligibility check, which occurred only prior to randomization on Day 1 of treatment period 1.
- At the end of treatment period 3, the patients completed the end of study visit assessments instead of entering into a washout period.

*Study completion*

At the end of the last treatment period (treatment period 3), patients were discharged from the site after completing study completion evaluations (1–7 days following the last dose). All patients had a safety follow-up call 30 days after their last visit.

## Concomitant and rescue medication

At Day 1 of the run-in period, all patients were instructed to discontinue their previous asthma medications and were provided with a short-acting $\beta_2$-agonist (100 µg salbutamol/90 µg albuterol, or equivalent dose) as rescue medication on an "as-needed" basis. Rescue medication was withheld for at least 4 hours prior to spirometry assessments. Prohibited asthma medications during the treatment period included long-acting anticholinergic agents (other than the study drug); short-acting anticholinergics; fixed combinations of long-acting $\beta_2$-agonists and inhaled corticosteroids; long-acting $\beta_2$-agonists (other than the study drug); short-acting $\beta_2$-agonists (other than those prescribed as rescue medication in the study); theophylline and other xanthines; and inhaled (other than the study drug), parenteral, or oral corticosteroids.

## Statistical analysis

Sample size calculation: to ensure that at least 30 patients would complete the study, 36 patients were planned to be enrolled assuming a dropout rate of up to 20% and assuming equal assignment to the six sequences. With a sample size of 30 completers, ie - 5 patients per sequence, a two-sided 90% confidence interval for the difference (between IND/GLY/MF morning dosing, IND/GLY/MF evening dosing and placebo in weighted mean $FEV_1$ over 24 h) after 2 weeks of treatment had an interval that extended no more than 88 mL from the observed difference in means. This calculation assumed a within-patient standard deviation of 200 mL in weighted mean $FEV_1$ over 24 h ($AUC_{0–24h}$).