2 SYNOPSIS

Title of Study:	A Phase I, Randomized, Double-blind, Single-dose, Partial replicate, 3-way Cross-over Study to Assess the Lung Exposure Bioequivalence of Budesonide, Glycopyrronium, and Formoterol Delivered by BGF MDI HFO Compared with BGF MDI HFA	
Study Numbers:	Parexel Study No.: PXL266498 Sponsor Study No.: D5985C00005	
Study Interventions:	Test Product: Budesonide, glycopyrronium, and formoterol fumarate (BGF) metered-dose inhaler (MDI) formulated with hydrofluoroolefin (HFO) propellant. Reference Product: BGF MDI formulated with hydrofluoroalkane (HFA) propellant.	
Indication(s) Studied:	COPD (chronic obstructive pulmonary disease)	
Development Phase:	Phase I	
Sponsor:	AstraZeneca AB 151 85 Södertälje Sweden	
Principal Investigator:	PPD	
Study Center:	Parexel Early Phase Clinical Unit Baltimore Harbor Hospital 3001 S. Hanover St. Baltimore, MD 21225 United States of America (USA)	
Publications:	None	
Study Duration:	First participant first visit: 29 July 2022	Last participant last visit: 11 April 2023

Study Objectives:

Primary Objective:

- To assess the bioequivalence of the lung exposure of BGF administered as BGF MDI HFO compared with BGF MDI HFA.

Secondary Objectives:

- To characterize the pharmacokinetic (PK) profiles of BGF administered as BGF MDI HFO and BGF MDI HFA with oral activated charcoal.
- To assess the safety and tolerability of single doses of BGF MDI HFO and BGF MDI HFA with oral activated charcoal in healthy participants.

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Study Design:

This study was a Phase I, randomized, double-blind, single-dose, single-center, partial-replicate, 3-way cross-over study. The study included the assessment of PK and safety of BGF MDI in healthy participants (male or female) after administration of BGF MDI HFO (test) and BGF MDI HFA (reference) with oral activated charcoal.

The study comprised of:

- A screening period up to 28 days prior to first dosing.
- Three Treatment Periods: participants were resident at the Clinical Unit from the morning on the day before dosing with BGF MDI (Day -1 of Treatment Period 1), until 24 hours (h) following the final dose (Day 2 of Treatment Period 3) with a washout period of 3 to 7 days between each dose.
- Follow-up: final outpatient safety Follow-up Phone Call within 3 to 7 days after the last administration of BGF MDI in Treatment Period 3.

Each participant received 3 single-dose treatments of BGF MDI following an overnight fast of at least 8 h. Participants received treatments in 1 of 3 possible treatment sequences: ABB, BAB, or BBA. The reference formulation was administered during 2 of the 3 Treatment Periods to estimate intra-participant variability.

Study Participants:

Planned for Inclusion:	**Randomized:**	**Completed Study:**
96 participants	108 participants	103 participants

Main Inclusion Criteria:

1 Provision of signed and dated, written informed consent prior to any study specific procedures.

2 Healthy non-smoking male and/or female participants 18 to 60 years of age with suitable veins for cannulation or repeated venipuncture.

3 Females must have had a negative pregnancy test at screening and on admission to the unit, must not have been lactating, confirmed at screening and fulfill the criteria detailed in the Section 4.2.1 of the clinical study protocol (CSP) (Appendix 16.1.1).

4 Had a body mass index -between 18 and 35 kg/m^2, inclusive and weighed at least 50 kg and no more than 120 kg inclusive.

5 Participants must have had a forced expiratory volume in the first second (FEV_1) ≥ 80% of the predicted normal value and an FEV_1/forced vital capacity > 70% regarding age, height, and ethnicity at the Screening Visit.

6 Participant had to demonstrate proper inhalation technique and had the ability to properly use an MDI device after training.

Study Interventions:

Arm name:	**BGF MDI HFO:**	**BGF MDI HFA:**
Intervention name:	BGF pressurized inhalation suspension, HFO (test)	BGF pressurized inhalation suspension, HFA (reference)
Type:	Combination product	Combination product
Dose formulation:	MDI	MDI
Unit dose strength(s) (Delivered dose):	160/7.2/4.8 µg per actuation	160/7.2/4.8 µg per actuation

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Dosage level:	4 inhalations	4 inhalations
Route of administration:	Oral inhalation	Oral inhalation
Use:	Experimental	Comparator
Study intervention and Non-investigational Medicinal Product:	Study intervention	Study intervention
Sourcing:	Provided centrally by the Sponsor	Provided centrally by the Sponsor
Batch/Manufacturing Lot Number:	Lot number: CCI (Blinded lot) Bulk lot: CCI	Lot number: CCI (Blinded lot) Bulk lot: CCI
Expiry Date:	01 January 2024	01 October 2024

Duration of Treatment:

Each participant was to be involved in the study for up to 55 days.

Treatment Compliance:

Dosing took place at the Parexel Early Phase Clinical Unit in Baltimore. The administration of all study intervention was recorded in ClinBase™. Compliance was assured by direct supervision and witnessing the self-administration of study intervention.

Criteria for Evaluation:

Pharmacokinetic Parameters:

- Primary PK parameters: Cmax, AUCinf, and AUClast for test and reference treatments.
- Secondary PK parameters: tmax, λz, t½λz, MRTinf, CL/F, and Vz/F.

Safety Variables:

- Adverse events (AEs)/Serious adverse events (SAEs),
- Vital signs (systolic and diastolic blood pressure, pulse rate, body temperature, and respiratory rate),
- 12-lead electrocardiograms,
- Physical examination,
- Laboratory assessments (hematology, clinical chemistry, and urinalysis).

Statistical Methods:

Determination of Sample Size:

This was a sample size study based on the precision in estimating the primary PK parameters AUCinf, AUClast, and Cmax of BGF MDI HFA.

Among the analytes, glycopyrronium has the highest Cmax intra-participant coefficient of variation at CCI %, estimated from a previous single-dose BGF spacer study in healthy volunteers. In studies with higher intra-participant variability larger absolute differences between the logarithmic means were observed and so a true geometric mean ratio (GMR) of CCI was assumed. Given these assumptions, a sample size of 96 participants provided 90% probability of obtaining a 90% confidence interval (CI) within the expanded limits of 69.84% to 143.19% for Cmax or the fixed limits of 80% to 125% for AUClast and AUCinf, and a GMR estimate within the bounds of 80% to 125%. To account for a 10% dropout rate, 108 participants were to be randomized to achieve at least 96 evaluable participants.

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The number of participant identifiers generated for the study accounted for the number of randomized participants per the sample size calculation (number of participants [N] = 108). For this study, a total of 108 participant identifiers were randomized to 1 of 3 possible treatment sequences: ABB, BAB, BBA.

Presentation and Analysis of Pharmacokinetic Data:

Plasma concentrations for each analyte (budesonide, glycopyrronium, and formoterol) were listed by treatment occasion, participant, and time point. Plasma concentrations were also summarized by treatment occasion and for each analyte using protocol scheduled times and appropriate descriptive statistics.

For each analyte, individual plasma concentrations versus actual time were plotted in linear and semi-logarithmic scale with all treatment occasions overlaid on the same plot and separate plots for each participant. Combined individual plasma concentration versus actual times were plotted in linear and semi-logarithmic scale for each treatment occasion and analyte. Geometric mean plasma concentration (± geometric standard deviation) versus nominal sampling time were plotted in linear and semi-logarithmic (no standard deviation [SD] presented) scale with all treatment occasions overlaid on the same figure.

Plasma PK parameters were listed and summarized using descriptive statistics for each treatment occasion and analyte. Where possible, the following descriptive statistics were presented: number of participants (n), geometric mean, geometric coefficient of variation (gCV%), arithmetic mean, arithmetic SD, median, minimum (min), and maximum (max). For tmax, only n, median, min, and max were presented.

Additionally, the statistical analysis was performed for the PK analysis set. PK parameters were calculated using non-compartmental analysis.

Bioequivalence was assessed between test treatment BGF MDI HFO and reference treatment BGF MDI HFA, based on the PK analysis set using average bioequivalence (ABE), average bioequivalence with expanded limits (ABEL), or reference-scaled average bioequivalence (RSABE).

Presentation and Analysis of Safety Data:

All safety data (scheduled and unscheduled) were presented in the data listings. Continuous variables were summarized using descriptive statistics (n, mean, SD, min, median, and max) by treatment group. Categorical variables were summarized in frequency tables (frequency and proportion) by treatment/dose group. The analysis of the safety variables was based on the safety analysis set.

AEs were coded by preferred term and System Organ Class using the latest version of the Medical Dictionary for Regulatory Activities available at the time of clinical data lock. An overview of AEs was presented for each treatment, summarizing the number and percentage of participants with any AE, any SAE, any SAE with outcome of death, any AE leading to discontinuation of study intervention (DAE), any possibly related AE, and any possibly related SAE. Separate AE tables were provided taking into consideration relationship as assessed by the Investigator, max intensity, seriousness, death, and DAE. AEs that occur before dosing were reported separately.

Any new or aggravated clinically relevant abnormal medical physical examination finding compared to the baseline assessment was reported as an AE. For vital signs, data was summarized for the observed values at each scheduled assessment, together with the corresponding changes (and/or percentage change) from the baseline when baseline was defined.

Out-of-range values for safety laboratory were flagged in individual listings.

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Protocol Deviations:

Overall, important protocol deviations were reported for 14 (13.3%) participants; 2 (1.9%) participants in Treatment A, 8 (7.6%) participants in Treatment B (Replicate 1), and 5 (4.8%) participants in Treatment B (Replicate 2).

All these important protocol deviations were dosing deviations, where the participants did not demonstrate proper inhalation technique or did not use the device properly. Due to the protocol deviations, participants were excluded from the PK analysis set in the relevant Treatment Period, but none of the participants were excluded from the safety analysis set.

Pharmacokinetic Results:

- Lung exposure, assessed by US approach, to budesonide from BGF MDI HFO was bioequivalent to BGF MDI HFA, with GMRs and 90% CIs of 104.24% (95.78%, 113.44%), 106.87% (99.30%, 115.01%), and 107.76% (100.35%, 115.72%) for Cmax, AUClast, and AUCinf, respectively.
- Lung exposure, assessed by European Union (EU) approach, to budesonide from BGF MDI HFO was bioequivalent to BGF MDI HFA, with GMRs and 90% CIs of 103.12% (94.44%, 112.60%), and 106.10% (98.39%, 114.41%) for Cmax and AUClast, respectively.
- Lung exposure, assessed by US approach, to glycopyrronium from BGF MDI HFO was bioequivalent to BGF MDI HFA, with GMRs and 90% CIs of 93.45% (84.31%, 103.58%), 102.02% (89.12%, 116.79%), and 112.22% (92.27%, 136.49%) for Cmax, AUClast, and AUCinf, respectively.
- Lung exposure, assessed by EU approach, to glycopyrronium from BGF MDI HFO was bioequivalent to BGF MDI HFA, with GMRs and 90% CIs of 93.39% (85.29%, 102.26%), and 97.02% (84.18%, 111.82%) for Cmax and AUClast, respectively.
- Lung exposure, assessed by US approach, to formoterol from BGF MDI HFO was bioequivalent to BGF MDI HFA, with GMRs and 90% CIs of 100.14% (91.90%, 109.11%), 107.76% (94.91%, 122.36%), and 101.45% (91.76%, 112.15%) for Cmax, AUClast, and AUCinf, respectively.
- Lung exposure, assessed by EU approach, to formoterol from BGF MDI HFO was bioequivalent to BGF MDI HFA, with GMRs and 90% CIs of 99.70% (91.44%, 108.71%), and 105.74% (92.59%, 120.75%) for Cmax and AUClast, respectively.
- Budesonide, glycopyrronium, and formoterol all had high (> 40%) inter-participant variability (gCV%) for the PK parameters across treatments.
- Within participant variability (%gCV) determined in Treatment B was moderate to high:
  - Cmax: 43% for budesonide, 41% for glycopyrronium and formoterol in both US and EU approaches.
  - AUClast: 35% for budesonide, 75% for glycopyrronium, and 67% for formoterol in both US and EU approaches.
  - AUCinf: 34% for budesonide, 86% for glycopyrronium, and 47% for formoterol in the US approach.

Safety Results:

- A single dose treatment of BGF MDI HFO and BGF MDI HFA with oral activated charcoal was well tolerated in healthy participants.
- The frequency of AEs was similar between the BGF MDI HFO and BGF MDI HFA treatment groups.
- There were no new or unexpected safety findings in any of the individual participants across the 3-way cross-over treatment groups.

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Conclusion:

Lung exposure to budesonide, glycopyrronium, and formoterol was bioequivalent for BGF MDI HFO compared with the reference product, BGF MDI HFA, for both US and EU analysis approaches.

A single dose of BGF MDI HFO with oral activated charcoal was well tolerated in healthy participants with a similar safety profile as BGF MDI HFA.

Overall Impact of COVID-19

The Coronavirus disease of 2019 (COVID-19) pandemic was not judged to meaningfully impact the overall quality of the study, including the conduct, data, and interpretation of results.

Version and Date of Report: Final 1.0, 07 November 2023

This study was conducted in compliance with International Council for Harmonisation Good Clinical Practice guidelines.