2 SYNOPSIS

Title of Study:	A randomized, single blind, 3-period, 3-treatment, single-dose, crossover study to assess the relative bioavailability of BGF MDI CCI and BGF MDI CCI compared with BGF MDI HFA in healthy subjects	
Study Numbers:	Parexel Study No.: Pxl245780 Sponsor Study No.: D5985C00001	
Investigational Medicinal Products:	Test Products: Budesonide/glycopyrronium/formoterol (BGF) metered dose inhaler (MDI) formulated with 2 different propellants Treatment A: CCI Treatment B: CCI Reference Product: Budesonide/glycopyrronium/formoterol (BGF) metered dose inhaler (MDI) formulated with reference propellant Treatment C: HFA (HFA propellant)	
Indication Studied:	Chronic Obstructive Pulmonary Disease (COPD)	
Development Phase:	Phase 1	
Sponsor:	AstraZeneca AB 151 85 Södertälje Sweden	
Principal Investigator:	Dr David Han	
Study Center:	Parexel Early Phase Clinical Unit - Los Angeles	
Publication:	None	
Study Duration:	First subject first visit: 19 Oct 2020	Last subject last visit: 17 May 2021

Study Objectives:

Primary objective:

To evaluate the relative bioavailabilities between the test formulations and the reference formulation for fixed dose combinations (FDCs) of budesonide, glycopyrronium, and formoterol when administered as budesonide, glycopyrronium, and formoterol (BGF) metered dose inhaler (MDI) with 3 different propellants.

Secondary objectives:

To determine the pharmacokinetic (PK) parameters of BGF when administered as 3 different propellant formulations.

To assess the safety and tolerability of a combination of BGF when administered as single doses in 3 different propellant formulations in healthy subjects.

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Study Design:

This study was a randomized, single blind, 3-period, 3-treatment, single-dose, single-center, crossover study. The study included the assessment of PK properties of BGF MDI formulated with 3 different propellants: CCI - Treatment A (test), CCI - Treatment B (test), and hydrofluoroalkane (HFA) - Treatment C (reference).

The study comprised of:

- Screening period: up to 28 days prior to first dosing.
- Three treatment periods of maximum 3 days each: subjects were resident from the morning of the day before the first dosing with BGF MDI (Day -1) in Treatment Period 1, throughout all treatment and washout periods up to discharge on Day 2 of Treatment Period 3.
- Follow-up: within 3 to 7 days after the last administration of BGF MDI.

There was a washout period of 3 to 7 days between each dose.

Each subject received 3 single-dose treatments of BGF MDI (1 dose CCI [Treatment A]; 1 dose CCI [Treatment B] and 1 dose HFA [Treatment C]), following an overnight fast of at least 8 hours.

Study Subjects:

Planned for Inclusion:	Randomized:	Completed Study:
Approximately 48 subjects	47 subjects	47 subjects

Main Inclusion Criteria:

Healthy, non-smoking male subjects aged 18 to 60 years with suitable veins for cannulation or repeated venepuncture. Subjects had to have a body mass index (BMI) between 18 and 30 kg/m^2, inclusive and weigh at least 50 kg and no more than 100 kg, inclusive. Subjects had to have a forced expiratory volume in one second (FEV1) ≥ 80% of the predicted value regarding age, height, and ethnicity at the screening visit.

Investigational Medicinal Products:

Formulations:	Strength/Concentrations:	Batch/Manufacturing Lot Numbers:	Expiry Dates:
Treatment A: BGF MDI CCI (test)	CCI	CCI	June 2021
Treatment B: BGF MDI CCI (test)	CCI	CCI	June 2021
Treatment C: BGF MDI HFA (reference)	CCI	CCI	June 2023

Duration of Study:

Each subject was to be involved in the study for up to 53 days.

Treatment Compliance:

Dosing took place at the Parexel Early Phase Clinical Unit in Los Angeles. The administration of all investigational medicinal products (IMPs) was recorded in Parexel's electronic source data capturing and information management system (ClinBase™). Compliance was assured by direct supervision and witnessing of IMP administration.

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Criteria for Evaluation:

Pharmacokinetic Parameters:

- Primary PK parameters: Cmax, AUCinf, and AUClast for test and reference treatment
- Secondary PK parameters: tmax, t½λz, MRT, λz, CL/F, Vz/F, TRCmax, TRAUCinf, and TRAUClast.

Safety Variables:

- Adverse events (AEs)/Serious adverse events (SAEs).
- Vital signs (systolic and diastolic blood pressure, pulse rate, body temperature, oxygen saturation, and respiratory rate).
- Twelve-lead safety and digital electrocardiograms (ECGs) as well as cardiac telemetry
- Physical examination.
- Laboratory assessments (hematology, clinical chemistry and urinalysis)
- Spirometry.
- Taste assessment.

Statistical Methods:

Determination of Sample Size:

This was a pilot PK study to determine the relative bioavailabilities between 2 test formulations of BGF MDI with next generation propellants (NGPs) compared with the current formulation with HFA propellant. Therefore, no sample size calculation was performed.

It was expected that 48 healthy subjects (number of subjects were increased from 24 to 48 as per protocol amendment 2 to account for replacement subjects due to a dosing deviation involving the first 23 subjects) were to be randomized to a 6 sequence Williams design for 3 periods and 3 treatments: ABC, BCA, CAB, ACB, BAC and CBA, in order to ensure at least 20 evaluable subjects at the end of the last treatment period.

Subjects were considered evaluable if they had an evaluable PK profile, ie, (1) received active treatment, (2) did not significantly violate protocol inclusion or exclusion criteria, or deviate significantly from the protocol, and (3) did not have unavailable or incomplete data which may have influenced the PK analysis.

Presentation and Analysis of Pharmacokinetic Data:

All PK concentrations, parameter summaries and statistical analyses were presented for the PK Analysis Set, unless otherwise specified. The PK concentration and parameter listings were presented for the Safety Analysis Set and included all reportable individual PK results. Individual PK concentration and parameter data for any subjects not included in the PK Analysis Set or excluded from the descriptive summary tables, figures and/or inferential statistical analyses were included in the listings and flagged with an appropriate footnote.

The test treatments, Treatments A and B (BGF MDI CCI and BGF MDI CCI, respectively), were separately compared to the reference treatment, Treatment C (BGF MDI HFA), for each analyte. The statistical analyses were performed using a linear mixed effects analysis of variance model, using the natural logarithm of Cmax, AUCinf, and AUClast as the response variables, with sequence, and period, treatment as fixed effects and subject nested within sequence as random effect. Transformed back from the logarithmic scale, geometric means together with the intra-subject coefficient of variation confidence intervals (CIs) (2-sided 95%) for Cmax, AUCinf, and AUClast were estimated and presented. In addition, ratios of geometric means together with CIs (2-sided 90%) were estimated and presented.

Additionally, the median difference in untransformed tmax between the test treatments and the reference treatment for each analyte and the corresponding 90% CIs for the median differences, for each analyte were calculated using the non-parametric Hodges Lehmann method.

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Presentation and Analysis of Safety and Eligibility Data:

Safety data (scheduled and unscheduled) were presented in the data listings. Continuous variables were summarized using descriptive statistics (n, mean, standard deviation [SD], minimum, median, maximum) by treatment. Categorical variables were summarized in frequency tables (frequency and proportion) by treatment, if applicable. The analysis of the safety variables was based on the Safety Analysis Set.

Adverse events were summarized by Preferred Term (PT) and System Organ Class (SOC) using Medical Dictionary for Regulatory Activities (MedDRA) vocabulary. Furthermore, listings of SAEs and AEs that led to withdrawal were made and the number of subjects who had any AEs, SAEs, AEs that led to withdrawal, and AEs with severe intensity were summarized. Adverse events that occurred before dosing were reported separately.

Tabulations and listings of data for vital signs, clinical laboratory tests, digital ECGs, and 12-lead safety ECGs (listings only), telemetry (listings only), and spirometry were presented. Results from the taste assessment were presented separately in listings only. Any new or aggravated clinically relevant abnormal medical physical examination finding compared to the baseline assessment was reported as an AE. Data were summarized for the observed values at each scheduled assessment, together with the corresponding changes from the baseline when baseline was defined. Clinical laboratory data were reported in the units provided by the clinical laboratory for the Safety Review Committee (SRC) meeting, and in Système International (SI) units in the Clinical Study Report (CSR).

Out of range values for safety laboratory assessments were flagged in individual listings as well as summarized descriptively using agreed standard reference ranges and/or extended reference ranges (eg, AstraZeneca, program, or laboratory ranges).

Protocol Deviations:

In total, important protocol deviations were reported for 26 (55.3%) subjects during the study:

- For Treatment A CCI : 23 (48.9%) subjects were reported with other important protocol deviations (subject did not self dose with the inhaler as outlined in the protocol. Nurse administered the dose).
- For Treatment B CCI : 23 (48.9%) subjects were reported with other important protocol deviations (subject did not self dose with the inhaler as outlined in the protocol. Nurse administered the dose) and 2 (4.3%) subjects did not receive the full dose expected due to issues during inhalation.
- For Treatment C (HFA propellant): 23 (48.9%) subjects were reported with other important protocol deviations (subject did not self dose with the inhaler as outlined in the protocol. Nurse administered the dose) and 1 (2.1%) subject did not receive the full dose expected due to issues during inhalation.

The number of subjects were increased from 24 to 48 as per protocol amendment 2 to account for replacement subjects due to a dosing deviation involving the first 23 subjects.

There were 23 subjects excluded from the PK Analysis Set due to protocol deviations reported.

No important protocol deviations related to COVID-19 were reported during the study.

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Pharmacokinetic Results:

- Systemic exposure to budesonide from BGF MDI CCI was comparable to BGF MDI HFA, with GMRs and 90% CIs of 111.7% (91.01%, 137.1%), 104.7% (91.95%, 119.2%) and 107.2% (94.53%, 121.9%) for Cmax, AUCinf and AUClast, respectively
- Systemic exposure to budesonide from BGF MDI CCI was comparable to BGF MDI HFA, with GMRs and 90% CIs of 98.78% (78.67%, 124.0%), 98.03% (83.33%, 115.3%) and 98.80% (84.59%, 115.4%) for Cmax, AUCinf and AUClast, respectively.
- Systemic exposure to glycopyrronium from BGF MDI CCI was comparable to BGF MDI HFA, with GMRs and 90% CIs of 108.3% (85.50%, 137.3%) and 106.1% (86.18%, 130.6%) for Cmax and AUClast, respectively.
- Systemic exposure to glycopyrronium from BGF MDI CCI was comparable to BGF MDI HFA, with GMRs and 90% CIs of 94.88% (74.69%, 120.5%) and 99.71% (80.84%, 123.0%) for Cmax and AUClast, respectively.
- Systemic exposure to formoterol from BGF MDI CCI was comparable to BGF MDI HFA, with GMRs and 90% CIs of 109.1% (97.02%, 122.7%), 96.00% (70.33%, 131.0%) and 98.13% (86.44%, 111.4%) for Cmax, AUCinf and AUClast, respectively.
- Systemic exposure to formoterol from BGF MDI CCI was comparable to BGF MDI HFA, with GMRs and 90% CIs of 100.1% (83.78%, 119.5%), 116.7% (86.31%, 157.8%) and 107.0% (88.82%, 128.9%) for Cmax, AUCinf and AUClast, respectively.

Safety Results:

- There were no deaths, SAEs, or AEs that led to the discontinuation of the IMP reported during this study.
- No new safety signals were observed, no clinically relevant trends were observed for vital signs, physical examination, laboratory results, spirometry and taste assessment, and no abnormal clinically significant 12-lead safety and digital ECG, as well as cardiac telemetry findings were reported.
- The combination of budesonide, glycopyrronium, and formoterol when administered as single doses in 3 different propellant formulations demonstrated an acceptable safety profile and was well tolerated in the studied population.

Discussion and Conclusion:

Systemic exposure to budesonide, glycopyrronium, and formoterol was similar for BGF MDI CCI compared with the reference product, BGF MDI HFA.

Systemic exposure to budesonide, glycopyrronium, and formoterol was similar for BGF MDI CCI compared with the reference product, BGF MDI HFA.

There was no indication of meaningful differences between the products in this taste assessment.

The combination of budesonide, glycopyrronium, and formoterol when administered as single doses in 3 different propellant formulations demonstrated an acceptable safety profile and was well tolerated in the studied population.

Version and Date of Report: Final 1.0, 28 September 2021

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