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2. SYNOPSIS

Name of Sponsor/Company: Lupin Research Inc.	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product: Beclometasone Dipropionate/ Formoterol Fumarate Dihydrate Inhalation Solution, 200/6 mcg	Volume:	
Name of Active Ingredient: Beclometasone dipropionate and formoterol fumarate dihydrate	Page:	

Title of Study:

BDPFF-AS-101: An Open-Label, Randomised, 4-Period, 4-Treatment, 4-Sequence, Crossover, Single-Dose Bioequivalence Study to Compare the Pharmacokinetic and Safety Profiles Following 2 Inhalations Each of Lupin Beclometasone Dipropionate/Formoterol Fumarate Dihydrate 200/6 mcg per Actuation Pressurised Inhalation Solution and FOSTAIR® 200/6 mcg per Actuation Pressurised Inhalation Solution, With and Without Charcoal Block, Administered in Healthy Volunteers Under Fasting Conditions

Investigators and Study Centres:

[redacted]

Publication (Reference):

Not applicable

Study Period:

First Subject Screened: 30-Apr-2019
First Subject Dosed: 15-May-2019
Last Subject Dosed: 27-Jul-2019
Last Subject Visit: 27-Sep-2019

Phase of Development:

1 (Pharmacokinetic [PK] Bioequivalence Study)

Objectives:

Primary Objective

The primary objectives of the study were to:

- assess and compare the PK profiles of beclometasone-17-monopropionate (17-BMP) and formoterol following 2 inhalations from (i) Lupin beclometasone dipropionate/formoterol fumarate dihydrate 200/6 mcg per actuation pressurised inhalation solution (BDP/FF 200/6 mcg) and (ii) FOSTAIR 200/6 mcg per actuation pressurised inhalation solution (FOSTAIR 200/6 mcg) without charcoal block.
- assess and compare the PK profiles of formoterol following administration of BDP/FF 200/6 mcg and FOSTAIR 200/6 mcg with charcoal block.

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Secondary Objectives

The secondary objectives of this study were to:

- assess and compare the PK profiles of BDP following 2 inhalations from BDP/FF 200/6 mcg and FOSTAIR 200/6 mcg without charcoal block.
- evaluate the safety and tolerability of Lupin BDP/FF 200/6 mcg and FOSTAIR 200/6 mcg.

Methodology:

This was a single-centre, open-label, randomised, 4-period, 4-treatment, 4-sequence, crossover, single-dose bioequivalence study with and without charcoal block in healthy subjects, aged 18–45 years.

The study consisted of a Screening visit and 4 single-dose treatment periods each comprised of a 4-day/3-night (concurrent) inpatient stay:

- Screening visit – Screening assessments up to 21 days prior to treatment period 1, Day -1. Subjects were screened by the following procedures: screening consent form, informed consent document (ICD), inclusion/exclusion criteria, demographic data, body mass index (BMI), medical/medication history, physical examination, 12-lead electrocardiogram (ECG) (supine, following 5 minutes of rest), vital signs (sitting blood pressure and pulse rate; after approximately 5 minutes of rest), urine pregnancy test for all females, clinical laboratory tests (non-fasting), urine drug screen including cotinine test (either urine or breath test), alcohol breath test, Aerosol Inhalation Monitor (AIM™) device training, and placebo (HFA-134a) pressurised inhalation solution training.
- Treatment period 1 – Final eligibility; AIM device and placebo (HFA-134a) pressurised inhalation solution training on Day -1; study medication administration with pre- and post-dose PK assessments for determining plasma levels for the relevant analytes prior to and following dosing; followed by a 20 (+3) day washout period.
- Treatment period 2 – Final eligibility; AIM device and placebo (HFA-134a) pressurised inhalation solution training on Day -1; study medication administration with pre- and post-dose PK assessments for determining plasma levels for the relevant analytes prior to and following dosing; followed by a 20 (+3) day washout period.
- Treatment period 3 – Final eligibility; AIM device and placebo (HFA-134a) pressurised inhalation solution training on Day -1; study medication administration with pre- and post-dose PK assessments for determining plasma levels for the relevant analytes prior to and following dosing; followed by a 20 (+3) day washout period.
- Treatment period 4 – Final eligibility; AIM device and placebo (HFA-134a) pressurised inhalation solution training on Day -1; final study medication administration with pre- and post-dose PK assessments for determining plasma levels for the relevant analytes prior to and following dosing after the last blood sample collection (End of Study [EOS]).

The duration of subject participation from the screening period through the EOS visit at treatment period 4 check-out was approximately 13 weeks.

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Subjects meeting all entry inclusion criteria and none of the exclusion criteria were randomised to 1 of 4 treatment sequences (ABDC, BCAD, CDBA, or DACB) consisting of the following 4 treatments:

- **Treatment A**: Lupin BDP/FF 200/6 mcg – 2 inhalations
- **Treatment B**: FOSTAIR 200/6 mcg – 2 inhalations
- **Treatment C**: Lupin BDP/FF 200/6 mcg with oral charcoal – 2 inhalations
- **Treatment D**: FOSTAIR 200/6 mcg with oral charcoal – 2 inhalations

At the Screening visit and on Day -1 of each treatment period, procedures for using the AIM device and training placebo (HFA-134a) pressurised inhaler were reviewed and the subject's ability to use the device and inhaler correctly were documented. Only those subjects who demonstrated proper use of the AIM device and placebo (HFA-134a) pressurised inhaler were eligible to continue in the study. During treatment periods 1–4, each subject took 2 inhalations from the inhalation solution to which they were randomised. The functionality of the inhaler was tested by releasing the first 3 actuations. Actuations 4 and 5 were used for dosing and PK assessments during treatment periods 1–4. Treatment periods were separated by a 20 (+3) day washout period between treatment administrations.

For treatments utilizing co-administration of activated charcoal, a suspension of 5 g activated charcoal in 25 mL of water (25 mL of activated charcoal suspension contains 5 g of activated charcoal) was administered 2 minutes before and 0.5, 60, 120, and 240 minutes after dose inhalation. Charcoal was administered at the scheduled times, but a time deviation window of ±30 seconds was allowed. Charcoal was utilised to block gastrointestinal absorption of any swallowed drug from entering the systemic compartment. Beclometasone did not require a charcoal block study. Only formoterol was assessed following charcoal block to fulfil the needs of the regulatory agency.

During each treatment period, a total of 20 blood samples (10 mL for the pre-dose sample and 07 mL for all post-dose samples for subjects who received Treatments A or B, and 05 mL for the pre-dose sample and 04 mL for all post-dose samples for subjects receiving Treatments C or D) were obtained pre-dose (within 15 minutes of study medication administration), and at 0.03 (2 minutes), 0.06 (4 minutes), 0.10 (6 minutes), 0.13 (8 minutes), 0.18 (11 minutes), 0.25 (15 minutes), 0.33 (20 minutes), 0.50 (30 minutes), 0.75 (45 minutes), 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, 12.0, 16.0, 24.0, and 36.0 hours post-dose.

Plasma samples from treatment periods where Treatments A or B (treatments without charcoal block) were administered were assayed for plasma BDP, 17-BMP, and formoterol. Plasma samples from treatment periods where Treatments C or D (treatments with charcoal) were administered were assayed for formoterol only.

Safety was monitored by clinical laboratory tests and 12-lead ECGs at the Screening visit and at the EOS visit; physical examinations at the Screening visit, at check-in and check-out of each treatment period, and at the EOS visit; vital signs measurements and adverse event (AE) assessments were used to monitor safety throughout the study from the Screening visit until the EOS visit (including all treatment periods). Special training/reminders were provided to the medical/clinical staff in the clinical research unit (CRU) to ensure capture of all relevant AEs, such as cough, wheezing, bronchospasm, and throat/larynx irritation (paying particular attention to any signs of local irritation). A staff administered cough frequency assessment was completed evaluating the subject's frequency of cough 2 minutes following the start of dosing in each treatment period to assess any potential immediate local effects.

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Number of Subjects (Planned and Analysed):

The study had a planned enrolment of 112 subjects. A total of 112 subjects were randomised to one of four treatment sequences, with 102 completing the study. A summary of the analysis populations by treatment and total are provided in the table below.

	Treatment				
	Test Product	Reference Product	Test Product	Reference Product	
Analysis Population, n (%)	Lupin BDP/FF 200/6 mcg (Treatment A)	FOSTAIR 200/6 mcg (Treatment B)	Lupin BDP/FF 200/6 mcg with Oral Charcoal (Treatment C)	FOSTAIR 200/6 mcg with Oral Charcoal (Treatment D)	Total, N
Safety Analysis Set	107 (95.5)	106 (94.6)	108 (96.4)	109 (97.3)	112
Full Analysis Set	105 (93.8)	105 (93.8)	105 (93.8)	105 (93.8)	108
PK Analysis Set	97 (86.6)	97 (86.6)	88 (78.6)	88 (78.6)	104

Diagnosis and Main Criteria for Inclusion:

All subjects enrolled in this study were deemed by the Investigator to be normal, healthy volunteers who met all inclusion and none of the exclusion criteria.

- **Inclusion Criteria**

  Healthy male and female subjects 18–45 years of age (inclusive) who were able to provide written informed consent; assessed as healthy during screening within 21 days prior to administration of first dose of study drug based on medical history, physical examination findings, laboratory evaluations, and 12-lead ECG; female subjects were of 1) non-childbearing potential or 2) childbearing potential and not pregnant (negative serum pregnancy test), breastfeeding, or attempting to become pregnant, and committed to using a consistent and acceptable method of birth control for the duration of the study; sexually active male subjects committed to an acceptable method of birth control for the duration of the study or exclusively had same-sex partners; all subjects agreed to use 2 types of contraception, one of which was a barrier method (e.g., condom); body mass index (BMI) ≥18.5 to ≤30 kg/m^2 and body weight ≥50 kg; resting sitting pulse rate of ≥50 to ≤99 beats per minute and blood pressure of ≤130/80 mmHg; non-smoker for at least 1 year prior to the Screening visit and maximum smoking history of ten-pack years; in good general health free of any concomitant conditions or treatments that could interfere with study conduct, influence interpretation of study observations/results, or put subject at increased risk; demonstrated proper inhalation technique using the AIM with a "good" technique within the first 5 attempts and a second "good" reading within 3 additional attempts.

- **Exclusion Criteria**

  History or current evidence of cardiovascular, hepatic, renal, pulmonary, neurologic, endocrine, fungal, or other major systemic disease (e.g., congestive heart failure, uncontrolled coronary artery disease, known aortic aneurysm, myocardial infarction, cardiac dysrhythmia, uncontrolled hypertension, chronic constipation, uncontrolled diabetes mellitus, chronic obstructive pulmonary disease, stroke, malignancy [excluding basal cell carcinoma]) that, in the medical judgement of the Investigator, would put the safety of

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the subject at risk through participation or that could affect the pharmacokinetic or safety analysis if the disease/condition worsened during the study; history of a respiratory infection or disorder within 30 days preceding the Screening visit; known or suspected hypersensitivity or idiosyncratic reaction to any steroid, including beclometasone, any β_2-agonist including formoterol fumarate dihydrate, or to any ingredients used in the beclometasone dipropionate and formoterol fumarate dihydrate pressurised inhalation solution; pregnant or lactating, planned to become pregnant, donate gametes during the study or for 30 days after last study visit, or unwilling to employ appropriate contraceptive measures to ensure pregnancy would not occur during the study; positive test result for urine pregnancy at the Screening visit; positive result for human immunodeficiency virus (HIV), hepatitis B, hepatitis C, or syphilis; random plasma glucose >199 mg/dL at the Screening visit; clinically significant abnormalities, in the Investigator's opinion, on the 12-lead ECG at the Screening visit; presence of any disease or condition known to interfere with the absorption, distribution, metabolism, or excretion of drugs; occurrence of any injury or localised infection in the mouth or pharynx (e.g., oral thrush); unable to demonstrate proper inhalation techniques using the inhaler; use of an inhaled/topical corticosteroid within 30 days prior to screening, or systemic/oral corticosteroids or biologic therapy/treatment with monoclonal antibodies within 60 days of the Screening visit, investigational drug within 90 days prior to dosing, or used medications that are cytochrome P4503A4 (CYP3A4) inhibitors within 30 days prior to screening; non-vaccinated exposure to or active infection with chickenpox or measles within 21 days of the Screening visit; donated plasma or blood within 90 days prior to the Screening visit, or planned to donate plasma or blood within 30 days following study completion; history of difficulty with donating blood; history of alcohol or drug abuse within 2 years preceding the Screening visit; positive alcohol or drugs of abuse test (including cotinine) at screening and within 24 hours prior to receiving study drug; used prohibited medications within the prescribed withdrawal periods of the protocol; presence, by history, and/or symptoms, signs suggestive of ocular disturbances; vulnerable subjects; piercings of the tongue, lips, or mouth; loose dentures or denture abnormalities; employee of the investigational site, or an immediate relative of an employee of the centre.

Test Product, Dose and Mode of Administration, Batch (Lot) Numbers:

Test Product: Beclometasone dipropionate/formoterol fumarate dihydrate 200/6 mcg per actuation pressurised inhalation solution

Manufacturer: [redacted]

Mode of Administration: Oral pressurised inhalation solution

Dose: Single dose of 2 inhalations (total dose of 400 mcg beclometasone dipropionate/ 12 mcg formoterol fumarate dihydrate)

Batch Number: [redacted]

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Reference Therapy, Dose and Mode of Administration, Batch (Lot) Number:

Reference Product (R): FOSTAIR 200/6 micrograms per actuation pressurised inhalation solution
Manufacturer: [redacted]
Mode of Administration: Oral pressurised inhalation solution
Dose: Single dose of 2 inhalations (total dose of 400 mcg beclometasone dipropionate/ 12 mcg formoterol fumarate dihydrate)
Batch Number: [redacted]

Duration of Treatment:

Each subject participated in the study for approximately 13 weeks. Participation included a screening period of up to 21 days and 4 treatment periods, each consisting of a 4-day/3-night inpatient stay. Treatment periods were separated by a 20(+3) day washout period between treatment administrations.

Criteria for Evaluation:

Pharmacokinetics (PK)

All BDP, 17-BMP, and formoterol PK parameters were determined using the non-compartmental model of Phoenix® WinNonlin® version 8.0 and summarised using SAS® version 9.4.

Primary Pharmacokinetic Parameters

The primary PK endpoints included:

- area under the plasma concentration versus time curve from time zero (0) to the time of the last quantifiable concentration (AUC_{0-t}) for 17-BMP (without charcoal) and formoterol (with and without charcoal)
- maximum observed plasma concentration (C_{max}) for 17-BMP (without charcoal) and formoterol (with and without charcoal)

Secondary Pharmacokinetic Parameters

The secondary PK endpoints included:

- area under the plasma concentration versus time curve from time zero (0) to the time of the last quantifiable concentration (AUC_{0-t}) for BDP (without charcoal)
- maximum observed plasma concentration (C_{max}) for BDP (without charcoal)
- area under the plasma concentration versus time curve from time zero (0) to infinity ($AUC_{0-\infty}$) for BDP (without charcoal), 17-BMP (without charcoal), and formoterol (with and without charcoal)
- time to maximum observed plasma concentration (t_{max}) for BDP (without charcoal), 17-BMP (without charcoal), and formoterol (with and without charcoal)
- first order rate constant associated with the terminal (log-linear) portion of the curve (K_{el}) for BDP (without charcoal), 17-BMP (without charcoal), and formoterol (with and without charcoal)
- apparent terminal elimination half-life ($t_{½}$) for BDP (without charcoal), 17-BMP (without charcoal), and formoterol (with and without charcoal)

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- the percent of area extrapolated for calculation of $AUC_{0-\infty}$ ($AUC_{\%Extrap\ obs}$) for BDP (without charcoal), 17-BMP (without charcoal), and formoterol (with and without charcoal)

Safety

Safety was assessed by evaluating reported AEs, cough assessment, changes in physical (medical) examination results, vital signs measurements, 12-lead ECG overall interpretations, and clinical laboratory test results.

Statistical Methods:

Pharmacokinetics

All BDP, 17-BMP, and formoterol PK endpoints were summarised by treatment. The PK Analysis Set was the primary population for analyses of the PK endpoints. The Full Analysis Set (FAS) was used for supportive analyses of the PK endpoints.

Primary PK Analyses:

- The primary PK parameters to assess bioequivalence of Lupin beclometasone dipropionate/formoterol fumarate dihydrate 200/6 mcg per actuation pressurised inhalation solution (BDP/FF 200/6 mcg) and FOSTAIR 200/6 mcg per actuation pressurised inhalation solution (FOSTAIR 200/6 mcg) are 17-BMP AUC_{0-t} and C_{max} without charcoal block and formoterol AUC_{0-t} and C_{max} with and without charcoal block. Comparisons of AUC_{0-t} and C_{max} between test versus reference were carried out using a parametric analysis of variance (ANOVA) model with terms for cohort, sequence, sequence * cohort, subject (sequence * cohort), period (cohort), and treatment as fixed effects. Separate models were used for 17-BMP using Treatment A and Treatment B only, and for formoterol using Treatments A, B, C, and D.
- The geometric mean ratios (GMRs) and 90% confidence interval (CI) for the ratios of the test versus reference products were calculated for 17-BMP and formoterol AUC_{0-t} and C_{max} by taking the antilog of the estimated difference between the least-squares means (LSMs) for each comparison and corresponding 90% CIs. The primary comparisons of interest were Treatment A (Lupin BDP/FF 200/6 mcg) versus Treatment B (FOSTAIR 200/6 mcg) for 17-BMP (without charcoal), Treatment A (Lupin BDP/FF 200/6 mcg) versus Treatment B (FOSTAIR 200/6 mcg) for formoterol (without charcoal), Treatment C (Lupin BDP/FF 200/6 mcg) versus Treatment D (FOSTAIR 200/6 mcg) for formoterol (with charcoal). The ratios were of the form Test/Reference. The GMRs were expressed as a percentage of the reference treatment.
- Two one-sided tests for bioequivalence were performed using 90% CIs for the ratio of geometric means between drug formulations to assess bioequivalence criteria for C_{max} and AUC_{0-t} for 17-BMP (without charcoal) and formoterol (with and without charcoal). If the 90% CIs for the GMRs for 17-BMP (without charcoal) and formoterol (with and without charcoal) C_{max} and AUC_{0-t} fell within 80.00–125.00%, the respective test product was considered bioequivalent to the reference product.

Secondary PK Analyses:

- Pairwise comparisons of t_{max} and $t_{½}$ between treatments were based on the Wilcoxon signed rank test.
- The secondary PK parameter $AUC_{0-\infty}$ was assessed using the same methodology described above for C_{max} and AUC_{0-t}.

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- The secondary PK parameters t_{max}, $t_{½}$, K_{el}, $AUC_{0-\infty}$, and $AUC_{\%Extrap\ obs}$ were summarised by analyte and treatment.

Safety

The Safety Analysis Set was used for the safety endpoints. Safety endpoints included the overall incidence of AEs, as well as the incidence of serious adverse events (SAEs), drug-related AEs, and AEs leading to withdrawal, which were summarised by treatment and by Medical Dictionary for Regulatory Activities (MedDRA® version 22.0) System Organ Class (SOC) and Preferred Term (PT). Adverse events with an onset date between treatment periods were assigned to the last treatment received.

Clinical laboratory results were summarised by overall subjects using descriptive statistics for observed and change from baseline values for the Screening and EOS visits. If a repeat of a scheduled assessment was performed, the repeat value was used in summaries for screening. Additionally, shift tables were produced. The shift tables were based on the classification of laboratory results (i.e., normal and abnormal) at the EOS visit compared to the grading of baseline results.

Electrocardiogram parameters were summarised by overall subjects using descriptive statistics for observed and change from baseline values for the Screening and EOS visits. Additionally, shift tables were produced comparing the frequency of normal and abnormal (i.e., abnormal not clinically significant and abnormal clinically significant) results at the EOS visit compared to the grading of the results at baseline.

Vital signs and change from baseline values were summarised by treatment and study day using descriptive statistics.

Cough frequency assessment was completed through 2 minutes after dosing in each treatment period, and values were summarised by treatment using descriptive statistics.

Due to the sampling schedule (i.e., Screening and EOS visits only), TEAEs associated with laboratory results or ECGs were assigned to the most recent treatment received prior to the sample draw/procedure.

SUMMARY OF RESULTS

Pharmacokinetics

Pharmacokinetic Parameter Data for 17-BMP

As presented in the table below, the geometric mean plasma C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ of 17-BMP were similar after inhalation with Treatment A and Treatment B for the PK Analysis Set.

The median t_{max} was 0.255 hours for Treatment A and 0.254 hours for Treatment B.

The median $t_{½}$ was 3.677 hours for Treatment A and 3.625 hours for Treatment B.

The median K_{el} was 0.189 $hour^{-1}$ for Treatment A and 0.191 $hour^{-1}$ for Treatment B.

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Summary of PK Parameters for 17-BMP Following Oral Inhalation Administration of Study Drug, by Treatment (PK Analysis Set)

Pharmacokinetic Parameter	Test Product Lupin BDP/FF 200/6 mcg (Treatment A)	N	Reference Product FOSTAIR 200/6 mcg (Treatment B)	N
C_{max} (pg/mL) [a]	533.0313 (50.99)	97	523.2420 (45.98)	97
AUC_{0-t} (pg×hr/mL) [a]	2306.4954 (42.41)	97	2309.9321 (38.66)	97
$AUC_{0-\infty}$ (pg×hr/mL) [a]	2621.4820 (37.71)	92	2605.4783 (34.67)	92
t_{max} (hour) [b]	0.255 (0.060, 4.008)	97	0.254 (0.060, 8.003)	97
$t_{½}$ (hour) [b]	3.677 (2.453, 7.660)	95	3.625 (2.224, 6.865)	95
K_{el} ($hour^{-1}$) [b]	0.189 (0.090, 0.283)	95	0.191 (0.101, 0.312)	95
$AUC_{\%Extrap\ obs}$ [c]	8.9057 (4.3363)	95	8.3022 (3.7311)	95

Abbreviations: CV% = percent coefficient of variation; N = number of subjects; SD = standard deviation.

[a] Presented as geometric mean (CV%).

[b] Presented as median (minimum, maximum).

[c] Presented as arithmetic mean (SD).

Source: Table 14.2.1.7.

Pharmacokinetic Parameter Data for Formoterol

Treatment A and Treatment B (Without Oral Charcoal)

As presented in the table below, the geometric mean plasma C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ of formoterol were similar after inhalation with Treatment A and Treatment B for the PK Analysis Set.

The median t_{max} was 0.103 hours for Treatment A and 0.104 hours for Treatment B.

The median $t_{½}$ was 7.500 hours for Treatment A and 7.189 hours for Treatment B.

The median K_{el} was 0.092 $hour^{-1}$ for Treatment A and 0.097 $hour^{-1}$ for Treatment B.

Treatment C and Treatment D (With Oral Charcoal)

As presented in the table below, the geometric mean plasma C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ of formoterol were similar after inhalation with Treatment C and Treatment D for the PK Analysis Set.

The median t_{max} was 0.103 hours for Treatment C and 0.103 hours for Treatment D.

The median $t_{½}$ was 6.668 hours for Treatment C and 7.443 hours for Treatment D.

The median K_{el} was 0.104 $hour^{-1}$ for Treatment C and 0.093 $hour^{-1}$ for Treatment D.

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Summary of PK Parameters for Formoterol Following Oral Inhalation Administration of Study Drug, by Treatment, Without and With Oral Charcoal (PK Analysis Set)

Pharmacokinetic Parameters	Test Product Lupin BDP/FF 200/6 mcg (Treatment A)	N	Reference Product FOSTAIR 200/6 mcg (Treatment B)	N	Test Product Lupin BDP/FF 200/6 mcg with Oral Charcoal (Treatment C)	N	Reference Product FOSTAIR 200/6 mcg with Oral Charcoal (Treatment D)	N
C_{max} (pg/mL) [a]	16.1488 (47.56)	97	15.3967 (47.87)	97	15.0207 (45.86)	88	13.6418 (48.54)	88
AUC_{0-t} (pg×hr/mL) [a]	44.2892 (38.99)	97	43.0548 (38.47)	97	23.1549 (57.95)	88	20.8757 (57.33)	88
$AUC_{0-\infty}$ (pg×hr/mL) [a]	52.9804 (35.61)	66	51.6039 (33.47)	66	39.1843 (40.57)	29	35.6846 (37.53)	29
t_{max} (hour) [b]	0.103 (0.062, 0.756)	97	0.104 (0.061, 1.008)	97	0.103 (0.031, 0.251)	88	0.103 (0.060, 0.185)	88
$t_{½}$ (hour) [b]	7.500 (2.758, 21.137)	84	7.189 (2.544, 25.751)	84	6.668 (1.209, 96.111)	64	7.443 (2.848, 17.309)	64
K_{el} ($hour^{-1}$) [b]	0.092 (0.033, 0.251)	84	0.097 (0.027, 0.272)	84	0.104 (0.007, 0.573)	64	0.093 (0.040, 0.243)	64
$AUC_{\%Extrap\ obs}$ (%) [c]	12.9039 (5.1135)	84	13.6242 (5.1504)	84	19.2548 (10.3401)	64	19.8249 (7.1693)	64

[a] Presented as geometric mean (CV%).
[b] Presented as median (minimum, maximum).
[c] Presented as arithmetic mean (SD).
Source: Table 14.2.1.9.

Pharmacokinetic Parameter Data for BDP

As presented in the table below, the geometric mean plasma C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ of BDP were similar after inhalation with Treatment A and Treatment B for the PK Analysis Set.

The median t_{max} was 0.034 hours for Treatment A and 0.034 hours for Treatment B.

The median $t_{½}$ was 0.330 hours for Treatment A and 0.295 hours for Treatment B.

The median K_{el} was 2.101 $hour^{-1}$ for Treatment A and 2.355 $hour^{-1}$ for Treatment B.

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Summary of PK Parameters for BDP Following Oral Inhalation Administration of Study Drug, by Treatment (PK Analysis Set)

Pharmacokinetic Parameter	Test Product Lupin BDP/FF 200/6 mcg (Treatment A)	N	Reference Product FOSTAIR 200/6 mcg (Treatment B)	N
C_{max} (pg/mL) [a]	2361.8720 (80.32)	97	2427.2848 (75.71)	97
AUC_{0-t} (pg×hr/mL) [a]	234.6115 (67.86)	97	243.2328 (66.74)	97
$AUC_{0-\infty}$ (pg×hr/mL) [a]	244.1335 (67.90)	76	257.9951 (67.89)	76
t_{max} (hour) [b]	0.034 (0.030, 0.103)	97	0.034 (0.031, 0.102)	97
$t_{½}$ (hour) [b]	0.330 (0.110, 3.697)	76	0.295 (0.072, 1.206)	76
K_{el} ($hour^{-1}$) [b]	2.101 (0.187, 6.289)	76	2.355 (0.575, 9.577)	76
$AUC_{\%Extrap\ obs}$ [c]	2.3261 (2.2337)	76	1.8332 (1.0444)	76

[a] Presented as geometric mean (CV%).
[b] Presented as median (minimum, maximum).
[c] Presented as arithmetic mean (SD).
Source: Table 14.2.1.11.

Primary Endpoint

Statistical Analysis of Pharmacokinetic Parameters for 17-BMP

The results of the statistical analyses of the PK parameters for 17-BMP are presented in the table below for the PK Analysis Set.

Treatment A geometric least squares mean (GLSM) was approximately 2% and 1% higher than Treatment B for 17-BMP C_{max} and $AUC_{0-\infty}$, respectively, and essentially the same for AUC_{0-t}.

For Treatment A versus Treatment B, the 90% CI of the GMR for 17-BMP primary PK parameters of C_{max} and AUC_{0-t} fell within the bioequivalence limits of 80.00–125.00%.

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Name of Finished Product: Beclometasone Dipropionate/ Formoterol Fumarate Dihydrate Inhalation Solution, 200/6 mcg	Volume:	
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Summary of Statistical Comparisons of Plasma 17-BMP Pharmacokinetic Parameters C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ (PK Analysis Set)

Parameter (unit)	Test Product Lupin BDP/FF 200/6 mcg (Treatment A) GLSM	Reference Product FOSTAIR 200/6 mcg (Treatment B) GLSM	GMR (90% CI) A vs B	Intrasubject CV% A vs B
C_{max} (pg/mL)	534.3078	521.5587	102.44 (96.47, 108.79)	25.38
AUC_{0-t} (pg×hr/mL)	2304.7341	2301.7928	100.13 (95.10, 105.42)	21.66
$AUC_{0-\infty}$ (pg×hr/mL)	2623.5814	2603.3801	100.78 (96.18, 105.60)	18.99

Source: Table 14.2.1.13.

Statistical Analysis of Pharmacokinetic Parameters for Formoterol

The results of the statistical analyses of the PK parameters for formoterol are presented in the table below for the PK Analysis Set.

Treatment A and Treatment B (Without Oral Charcoal)

Treatment A GLSM was approximately 5%, 3%, and 2% higher than Treatment B for formoterol C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$, respectively.

For Treatment A versus Treatment B, the 90% CI of the GMR for formoterol primary PK parameters of C_{max} and AUC_{0-t} fell within the bioequivalence limits of 80.00–125.00%.

Treatment C and Treatment D (With Oral Charcoal)

Treatment C GLSM was approximately 10%, 12%, and 5% higher than Treatment D for formoterol C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$, respectively.

For Treatment C versus Treatment D, the 90% CI of the GMR for formoterol primary PK parameters of C_{max} and AUC_{0-t} fell within the bioequivalence limits of 80.00–125.00%.

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Summary of Statistical Comparisons of Plasma Formoterol Pharmacokinetic Parameters C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$, Without and With Oral Charcoal (PK Analysis Set)

Parameter (unit)	Test Product Lupin BDP/FF 200/6 mcg (Treatment A)	Reference Product FOSTAIR 200/6 mcg (Treatment B)	Test Product Lupin BDP/FF 200/6 mcg with Oral Charcoal (Treatment C)	Reference Product FOSTAIR 200/6 mcg with Oral Charcoal (Treatment D)
	GLSM	GLSM	GLSM	GLSM
C_{max} (pg/mL)	16.0682	15.2830	14.6351	13.2526
AUC_{0-t} (pg×hr/mL)	44.1205	42.9461	23.5434	21.0990
$AUC_{0-\infty}$ (pg×hr/mL)	52.4552	51.6675	43.5534	41.5183

Parameter (unit)	GMR (90% CI) Treatment A vs Treatment B (without Oral Charcoal)	GMR (90% CI) Treatment C vs Treatment D (with Oral Charcoal)	Intrasubject CV%
C_{max} (pg/mL)	105.14 (98.67, 112.03)	110.43 (103.48, 117.85)	26.75
AUC_{0-t} (pg×hr/mL)	102.73 (94.21, 112.03)	111.59 (102.12, 121.93)	37.03
$AUC_{0-\infty}$ (pg×hr/mL)	101.52 (95.30, 108.15)	104.90 (98.32, 111.92)	22.00

Source: Table 14.2.1.15.

As the 90% CI for the GMRs of C_{max} and AUC_{0-t} for 17-BMP and formoterol (with and without oral charcoal) fell within the bioequivalence limits of 80.00–125.00%, the test product Lupin BDP/FF 200/6 mcg is considered bioequivalent to the reference product FOSTAIR 200/6 mcg in this study.

Secondary Endpoint

Statistical Analysis of Pharmacokinetic Parameters for BDP

The results of the statistical analyses of the PK parameters for BDP are presented in the table below for the PK Analysis Set.

Treatment A GLSM was approximately 2%, 3%, and 4% lower than Treatment B for BDP C_{max} AUC_{0-t}, and $AUC_{0-\infty}$, respectively.

For Treatment A versus Treatment B, the 90% CI of the GMR for BDP primary PK parameters of C_{max} and AUC_{0-t} fell within the bioequivalence limits of 80.00–125.00%.

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Summary of Statistical Comparisons of Plasma BDP Pharmacokinetic Parameters C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ (PK Analysis Set)

Parameter (unit)	Test Product Lupin BDP/FF 200/6 mcg (Treatment A) GLSM	Reference Product FOSTAIR 200/6 mcg (Treatment B) GLSM	GMR (90% CI) A vs B	Intrasubject CV% A vs B
C_{max} (pg/mL)	2363.9272	2421.7765	97.61 (89.81, 106.09)	35.68
AUC_{0-t} (pg×hr/mL)	235.4247	242.1470	97.22 (90.97, 103.91)	28.19
$AUC_{0-\infty}$ (pg×hr/mL)	245.7612	255.6832	96.12 (89.58, 103.14)	25.88

Source: Table 14.2.1.17.

Safety

The results of the study showed that Lupin BDP/FF 200/6 mcg without and with oral charcoal (Treatment A and Treatment C, respectively), and FOSTAIR 200/6 mcg without and with oral charcoal (Treatment B and Treatment D, respectively) were safe and well tolerated.

A total of 55 treatment-emergent adverse events (TEAEs) were reported in 37 (33.0%) subjects: 9 (8.4%) subjects on Lupin BDP/FF 200/6 mcg (Treatment A), 8 (7.5%) subjects on FOSTAIR 200/6 mcg (Treatment B), 12 (11.1%) subjects on Lupin BDP/FF 200/6 mcg with oral charcoal (Treatment C), and 8 (7.3%) subjects on FOSTAIR 200/6 mcg with oral charcoal (Treatment D). All TEAEs were considered mild or moderate in severity. The most common SOC was Investigations, with TEAEs in 30 (26.8%) subjects overall, with the other SOCs occurring in <3% of subjects. The percentage of subjects with TEAEs considered related to treatment was 18.8%. Due to the sampling schedule (i.e., Screening and EOS visits only), TEAEs associated with laboratory results or ECGs were assigned to the most recent treatment received prior to the sample draw/procedure; therefore, a meaningful comparison of incidence or relationship to study drug between treatments for these TEAEs is precluded.

There were no SAEs or deaths, and 3 subjects were withdrawn from the study due to a TEAE: Subject [redacted] due to a moderate urinary tract infection considered unlikely to be related to treatment after receiving FOSTAIR 200/6 mcg (Treatment B) in treatment period 3; Subject [redacted] due to a moderate influenza like illness deemed unlikely related to treatment after receiving Lupin BDP/FF 200/6 mcg with oral charcoal (Treatment C) in treatment period 3; and Subject [redacted] due to moderate pyrexia deemed possibly related to study treatment after receiving Lupin BDP/FF 200/6 mcg (Treatment A).

Two physical examination findings were reported as TEAEs, which resolved by the EOS visit; and 3 transient ECG findings at the EOS visit which resolved upon repeat ECG were reported as TEAEs. There were no clinically relevant treatment-related findings observed for vital signs measurements.

Overall, 21 (18.8%) subjects had at least 1 cough during the 2-minute post-dosing interval; of those subjects who coughed, the most prevalent categorical number of coughs was 2, occurring in 9 (8.0%) subjects. The incidence

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of cough was slightly higher after administration of the test product without and with oral charcoal (Treatment A and Treatment C, respectively) than the reference product without or with oral charcoal (Treatment B and Treatment D, respectively), although the difference was not considered clinically meaningful. The administration of oral charcoal (2 minutes before the first inhalation and 30 seconds after the second inhalation) was associated with a ≥3-fold higher incidence of subjects experiencing cough during the 2-minute post-dosing interval (5 [4.7%] subjects in Treatment A vs 15 [13.9%] subjects in Treatment C; 2 [1.9%] subjects in Treatment B vs 7 [6.4%] subjects in Treatment D). None of the coughs were considered to have clinical consequence by the Investigator. There were no cough events noted after 2 minutes in any treatment period (which would have been reported as TEAEs).

CONCLUSIONS

Pharmacokinetics

The test formulation of Lupin BDP/FF 200/6 mcg without oral charcoal (Treatment A) resulted in a similar rate and extent of absorption for 17-BMP and formoterol compared to the reference product FOSTAIR 200/6 mcg without oral charcoal (Treatment B).

The test formulation of Lupin BDP/FF 200/6 mcg with oral charcoal (Treatment C) resulted in a similar rate and extent of absorption for formoterol compared to the reference product FOSTAIR 200/6 mcg with oral charcoal (Treatment D).

The 90% CI for the GMRs of AUC_{0-t} and C_{max} for 17-BMP (without charcoal) and formoterol (with and without charcoal) are all contained within 80.00–125.00%. Therefore, Lupin BDP/FF 200/6 mcg is bioequivalent to FOSTAIR 200/6 mcg.

Safety

Single orally inhaled doses (2 inhalations, total dose = 400/12 mcg) of the test product Lupin BDP/FF 200/6 mcg and the reference product FOSTAIR 200/6 mcg manufactured by [redacted] were safe and well tolerated in healthy male and female subjects, ages 18–45 years.

The overall safety profile of 2 inhalations of Lupin BDP/FF 200/6 mcg was similar and consistent with the prescribing information for 2 inhalations for FOSTAIR 200/6 mcg. No new safety concerns were identified following treatment.

Date of the Report: 23 April 2020 Final