CLINICAL STUDY REPORT

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

Phase 1

Study BDPFF-AS-101

Sponsor
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Study Initiation Date (first subject screened):	**30 April 2019**
Study Completion Date (last subject completed):	**27 September 2019**
Report Approval Date:	**23 April 2020**

The conduct of this study with regard to Good Clinical Practice is addressed in Appendix 16.1.8.

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:	
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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.

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:	

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%.

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:	

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%.

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:	

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%.

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:	

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

3. TABLE OF CONTENTS

3.1. List of Tables Presented in the Text

3.2. List of Figures Presented in the Text

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Full Name
17-BMP	beclometasone-17-monopropionate
AE	adverse event
AIM™	Aerosol Inhalation Monitor
ALT	alanine aminotransferase
AMP	amphetamine
ANOVA	analysis of variance
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC_{0-t}	area under the plasma concentration versus time curve from time zero (0) to the time of the last quantifiable concentration
$AUC_{0-\infty}$	area under the plasma concentration versus time curve from time zero (0) to infinity
$AUC_{\%Extrap\ obs}$	the percent of area extrapolated for calculation of $AUC_{0-\infty}$
BAR	barbiturates
BDP	beclometasone dipropionate
BID	twice daily
BLQ	below the limit of quantification
BMI	body mass index
BZD	benzodiazepines
cAMP	cyclic-3′,5′-adenosine monophosphate
CFC	chlorofluorocarbons
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum observed plasma concentration
COC	cocaine
COPD	chronic obstructive pulmonary disease
COT	cotinine
CRF	case report form
CV%	percent coefficient of variation
cAMP	cyclic-3′,5′-adenosine monophosphate
CYP3A4	cytochrome P450 3A4 enzyme
CYP450	cytochrome P450
ECG	electrocardiogram

Abbreviation	Full Name
EOS	End of Study
ET	Early Termination
FAS	Full Analysis Set
FDA	Food and Drug Administration
FEV_1	forced expiratory volume in 1 second
FEV_1%	percent forced expiatory volume in 1 second
GCP	Good Clinical Practice
GLSM	geometric least squares mean
GMR	geometric mean ratio
HFA	hydrofluoroalkane
HIV	human immunodeficiency virus
ICD	informed consent document
ICF	informed consent form
ICH	International Council on Harmonisation
ICMR	Indian Council of Medical Research
IEC	independent ethics committee
IRB	institutional review board
IUD	intrauterine device
K_{el}	first order rate constant associated with the terminal (log-linear) portion of the curve
LABA	long-acting β-agonist
LSM	least-squares means
Max	maximum
MDI	metered-dose inhaler
MedDRA	Medical Dictionary for Regulatory Activities
Min	minimum
N	number of subjects
n	number of subjects in the category
NA	not applicable
OPI	opiates
OTC	over-the-counter
PI	Principal Investigator
PK	pharmacokinetic(s)
PT	Preferred Term
QA	quality assurance

Abbreviation	Full Name
R^2	coefficient of determination
RBC	red blood cell
RLD	reference listed drug
RPR	rapid plasma reagin
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	System Organ Class
$t_{½}$	apparent terminal elimination half-life
TEAE	treatment-emergent adverse event
THC	tetrahydrocannabinol
t_{max}	time to maximum observed plasma concentration
TPHA	*Treponema pallidum* haemagglutination assay
UK	United Kingdom
US(A)	United States (of America)
VDRL	Venereal Disease Research Laboratory
WBC	white blood cell
WHO	World Health Organization

5. ETHICS

5.1. Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

Before the study was initiated, Amendment 01 (dated 22 March 2019) was the first version of the protocol submitted to the independent ethics committee (IEC) which was approved on 02 April 2019. Copies of the protocol and amendments are provided in Appendix 16.1.1.

The name and address of the IEC consulted, with their assurance numbers or committee chairpersons, is provided in Appendix 16.1.3.

5.2. Ethical Conduct of the Study

This study was conducted in conformance with the principles of the Declaration of Helsinki. This study was conducted in full accordance with the International Council on Harmonisation (ICH) Guideline E6: Good Clinical Practice (GCP), and the Indian Council of Medical Research (ICMR) Ethical Guidelines for Biomedical Research on Human Subjects (2006). Essential study documents are currently archived in accordance with applicable regulations.

The Investigator was responsible for performing the study in accordance with the protocol, ICH guidelines, and GCP; and for collecting, recording, and reporting the data accurately and properly. Agreement of the Principal Investigator (PI) to conduct and administer this study in accordance with the protocol was documented in separate study agreements with the Sponsor, and other forms completed as required by national authorities in the country where the study centre is located.

The PI was responsible for the conduct and administration of the study at the centre and for contacts with study centre management, the institutional review board (IRB), and local authorities. Signatures of the PI and/or the Sponsor's responsible medical officer are provided in Appendix 16.1.5.

5.3. Subject Information and Consent

A properly executed, written informed consent form (ICF), in compliance with the Declaration of Helsinki, ICH GCP, the United States (US) Code of Federal Regulations (CFR) for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), and ICMR regulations was obtained before entering a subject in the study and before any protocol-specified tests or evaluations were performed. Written and/or oral information about the study (general screening and study specific procedures) was provided to all subjects in a language understandable by the subjects. The information included an adequate explanation of the aims, methods, anticipated benefits, potential hazards, and insurance arrangements in force. It was explained to the subjects that they were free to refuse entry into the study, and free to withdraw from the study at any time without prejudice to future treatment.

Each subject's willingness to participate in the study was documented in writing in a consent form that was signed and dated by the subject. The Investigator retained the original consent forms, and copies were given to the subjects.

Copies of the sample ICF and any other written information provided to the subjects are provided in Appendix 16.1.3.

6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

The administrative structure of the study was as follows:

Study Administrative Structure

Sponsored by	Lupin Research Inc. Harborplace Tower 111 S. Calvert Street, 21st Floor Baltimore, MD 21202 USA
Conducted by	Lupin Bioresearch Center [redacted]
Clinical supplies managed by	[redacted]
Clinical supplies manufactured by	[redacted]

Study Administrative Structure (Continued)

Local clinical laboratory	Lupin Bioresearch Center [redacted]
Pharmacokinetic sample analyses	Lupin Bioresearch Center [redacted]
Monitored by	[redacted]
Sponsor Medical Expert	
Sponsor Local Clinical Management	
Sponsor's Representative	
Study Director	

Study Administrative Structure (Continued)

Principal Investigator	[redacted]
Clinical Investigator	
Pharmacokinetic Investigator	
Bioanalytical Investigator	
Biostatistician	
Medical writer(s)	
Study initiation date (first subject screened)	30-Apr-2019
Study completion date (last subject completed)	27-Sep-2019

This study was performed at a single study centre by 1 Investigator, with 112 subjects randomly assigned to 1 of 4 treatment sequences.

A list of Investigators and other important participants in the study, including documentation of their qualifications, is provided in Appendix 16.1.4.

7. INTRODUCTION

Asthma is a chronic disease of the airways, characterised by airway constriction and inflammation, often manifested through episodic attacks. In the United Kingdom (UK), 5.4 million people are affected by asthma, with children constituting 1.1 million, or nearly 20% of those affected (Asthma UK 2018). Although asthma prevalence in the UK has plateaued since the late 1990's, the UK continues to have one of the highest rates in Europe; it is reported that on average 3 people die per day due to asthma. In 2016 alone (the most recent data available), there were 1,410 deaths from asthma (Asthma UK 2018). Asthma is also a cost burden on the UK healthcare system, with around £1 billion spent annually by the National Health Service (NHS) in the treatment of asthma (Asthma UK 2018).

Asthma is a chronic inflammatory disease of the bronchial tract characterised by reversible airway obstruction and bronchial hyper-responsiveness (GINA 2018, NHLBI 2007). This chronic inflammatory process is manifested by airway infiltration by inflammatory cells, denudation of airway epithelium, subepithelial deposition of collagen, and hyperplasia of smooth muscle cells, goblet cells, and submucosal glands. Chronic inflammation in the airways may lead to permanent structural changes. These changes can result in permanent airflow limitation, a process known as airway remodelling. Symptoms of asthma include wheezing, shortness of breath, chest tightness, and coughing with symptoms often worse at night and in the early morning.

The goals of asthma therapy include the following: control chronic and nocturnal symptoms, maintain normal activity levels (including exercise), maintain near normal pulmonary function, prevent acute episodes of asthma, minimise emergency room visits and hospitalisations, and avoid adverse effects of asthma medications (NHLBI 2007). The therapeutic use of a combination of inhaled corticosteroid and an inhaled long-acting β-agonist (LABA) for the treatment of asthma has been well established, offering advantages in both lung function improvement, as well as important clinical outcomes over the individual components alone (Gibson 2007).

Pressurised inhalation solutions/metered-dose inhalers (MDIs) allow patients who require therapy for various airway diseases to deliver these therapies directly via inhalation. This route of administration is desirable, because it optimises local effects while minimising systemic effects. Currently, these inhalers are widely used by patients for treatment of airway disease due to asthma.

Several different therapies are available in pressurised inhalation solution inhalers/MDIs. These include controller therapies such as inhaled corticosteroids in combination with a LABA. FOSTAIR® (Chiesi), a reference listed drug (RLD) for the fixed combination of beclometasone dipropionate (BDP) (a corticosteroid) and formoterol fumarate dihydrate (a LABA), is a pressurised inhalation solution, and is marketed in 2 different strengths of the BDP component, 100 micrograms (mcg) and 200 mcg, each combined with 6 mcg of formoterol fumarate dihydrate, per actuation. The low strength product is indicated in the regular treatment of asthma, maintenance and reliever therapy, where use of a combination product is appropriate and in the symptomatic treatment of severe chronic obstructive pulmonary disease (COPD) with a history of repeated exacerbations. The high strength product is indicated in the regular maintenance treatment of asthma, where use of a combination product is appropriate. FOSTAIR

was approved in the UK in November 2007. Because of the prevalence and costs associated with asthma, less expensive treatment options are being developed to help limit the costs associated with disease management and help improve access to quality therapy.

Lupin Research Inc. has developed a generic formulation of BDP and formoterol fumarate dihydrate pressurised inhalation solution to be a substitutable product for FOSTAIR 200/6 mcg per actuation pressurised inhalation solution, the RLD.

Beclometasone Dipropionate (BDP)

While the precise mechanism of corticosteroid action on asthma is not known, inflammation is an important component in the pathogenesis of asthma. Corticosteroids have been shown to have a wide range of inhibitory effects on multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, and cytokines) involved in inflammation and in the asthmatic response. These anti-inflammatory actions of corticosteroids may contribute to their efficacy in asthma.

Beclometasone dipropionate, a dipropionate ester of a synthetic glucocorticoid (corticosteroid) with immunomodulating properties, is a pro-drug with weak glucocorticoid receptor binding affinity. In vivo, after cell surface receptor attachment and cell entry, it is hydrolysed via esterase enzymes to an active metabolite beclometasone 17-monopropionate (17-BMP), which has a more potent anti-inflammatory activity compared to the pro-drug. Beclometasone enters the nucleus where it binds to and activates specific nuclear receptors, resulting in an altered gene expression and inhibition of proinflammatory cytokine production.

First approved for use (in the US) as a single agent in 1976, BDP is employed topically and in aerosol forms as an anti-inflammatory agent. Its potent anti-inflammatory activity has been shown to reduce both swelling and irritation in the lungs, which has led to its aerosol form being used in the treatment of asthma.

Formoterol Fumarate Dihydrate

Formoterol fumarate dihydrate is a selective LABA. Inhaled formoterol fumarate dihydrate acts locally in the lungs as a bronchodilator. In vitro studies have shown that formoterol has more than 200-fold greater agonist activity at β_2-receptors than at β_1-receptors.

The pharmacologic effects of β_2-adrenoceptor agonist drugs, including formoterol, are at least in part attributable to stimulation of intracellular adenyl cyclase, the enzyme that catalyses the conversion of adenosine triphosphate (ATP) to cyclic-3′,5′-adenosine monophosphate (cAMP). Increased cAMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

7.1. Clinical Experience with Beclometasone Dipropionate, Beclometasone-17-Monopropionate, and Formoterol Fumarate Dihydrate

Information in this section is extracted from Summaries of Product Characteristics (SmPCs) for:

FOSTAIR 100/6 mcg per actuation pressurised inhalation solution (FOSTAIR 100/6 SmPC 2018),
FOSTAIR 200/6 mcg per actuation pressurised inhalation solution (FOSTAIR 200/6 SmPC 2018).

7.1.1. Pharmacological Properties

7.1.1.1. Asthma

7.1.1.1.1. Clinical Efficacy for FOSTAIR Maintenance Therapy

In clinical trials in adults, the addition of formoterol to BDP improved asthma symptoms and lung function and reduced exacerbations.

In a 24-week study the effect on lung function of FOSTAIR was at least equal to that of the free combination of BDP and formoterol and exceeded that of BDP alone.

7.1.1.1.2. Clinical Efficacy for FOSTAIR Maintenance and Reliever Therapy

In a 48-week parallel group study involving 1701 adult patients with un-controlled moderate to severe asthma, the efficacy of FOSTAIR administered as maintenance (1 inhalation twice daily [BID]) and reliever therapy (up to a total of 8 puffs per day) was compared to FOSTAIR administered as maintenance therapy (1 inhalation BID) plus as needed salbutamol. The results demonstrated that FOSTAIR used as maintenance and reliever therapy significantly prolonged the time to first severe exacerbation (severe exacerbations were defined as deterioration in asthma resulting in hospitalisation or emergency room treatment, or resulting in the need for systemic steroids for more than 3 days) when compared with FOSTAIR used as maintenance plus as needed salbutamol ($p < 0.001$ for both Intent-to-Treat [ITT] and Per Protocol [PP] populations). The rate of severe asthma exacerbations per patients/year was significantly reduced in the maintenance and reliever therapy group compared to salbutamol group: 0.1476 versus 0.2239, respectively (statistically significant reduction: $p < 0.001$). Patients in the FOSTAIR maintenance and reliever group achieved a clinically meaningful improvement in asthma control. The mean number of inhalations/day of reliever medication and the proportion of patients using reliever medication decreased similarly in both groups.

In another clinical study, a single dose of FOSTAIR 100/6 mcg provided a quick bronchodilation effect and a rapid relief from dyspnoea symptoms similar to that of salbutamol 200 mcg/dose in asthmatic patients when methacholine challenge is used to induce bronchoconstriction.

7.1.1.2. Chronic Obstructive Pulmonary Disease

In two (2) 48-week studies, the effects on lung function and the rate of exacerbation (defined as courses of oral steroids and/or course of antibiotics and/or hospitalisations) in patients with severe COPD (percent forced expiatory volume in 1 second [FEV_1%] between 30–50%) was evaluated.

One pivotal trial showed a significant improvement in lung function (primary endpoint change in pre-dose forced expiratory volume in 1 second [FEV_1]) compared to formoterol after 12 weeks of treatment (adjusted mean difference between FOSTAIR and formoterol: 69 mL) as well as at each clinic visit during the whole treatment period (48 weeks). The study demonstrated that the mean number of exacerbations per patient/year (exacerbation rate, co-primary endpoint) was statistically significantly reduced with FOSTAIR as compared with formoterol treatment (adjusted mean rate 0.80 compared with 1.12 in the formoterol group, adjusted ratio 0.72, $p < 0.001$) over a 48 week treatment period in a total of 1199 patients with severe COPD. In addition, FOSTAIR statistically significantly prolonged the time to first exacerbation

compared to formoterol. The superiority of FOSTAIR versus formoterol was also confirmed in terms of exacerbation rate in subgroups of patients taking or not taking tiotropium bromide (around 50% in each treatment arm) as concomitant medication.

The other pivotal study, which was a 3-arm, randomised, parallel group study in 718 patients, confirmed the superiority of FOSTAIR versus formoterol treatment in terms of change in pre-dose FEV_1 at the end of treatment (48 weeks) and demonstrated the non-inferiority of FOSTAIR compared to budesonide/formoterol fixed dose combination on the same parameter.

7.1.2. Pharmacokinetic Properties

The systemic exposure to the active substances BDP and formoterol in the fixed combination FOSTAIR have been compared to the single components.

In a pharmacokinetic (PK) study conducted in healthy subjects treated with a single dose of FOSTAIR fixed combination (4 puffs of 100/6 mcg) or a single dose of BDP chlorofluorocarbons (CFC) (4 puffs of 250 mcg) and formoterol hydrofluoroalkane (HFA) [4 puffs of 6 mcg], the area under the plasma concentration versus time curve (AUC) of 17-BMP and its maximum observed plasma concentration (C_{max}) were 35% and 19% lower, respectively, with the fixed combination than with non-extrafine BDP CFC formulation; in contrast, the rate of absorption was more rapid (0.5 vs 2 hours) with the fixed combination compared to non-extrafine BDP CFC formulation alone.

For formoterol, C_{max} was similar after administration of the fixed or the extemporary combination and the systemic exposure was slightly higher after administration of FOSTAIR than with the extemporary combination.

There was no evidence of PK or pharmacodynamic (systemic) interactions between BDP and formoterol.

The use of Aerochamber Plus® spacer increased the lung delivery of BDP active metabolite 17-BMP and formoterol by 41% and 45%, respectively, in comparison to the use of standard actuator in a study conducted in healthy volunteers. The total systemic exposure was unchanged for formoterol, reduced by 10% for 17-BMP and increased for unchanged BDP.

A lung deposition study conducted in stable COPD patients, healthy volunteers, and asthmatic patients, demonstrated that on average 33% of the nominal dose is deposited into the lung of COPD patients compared to 34% in healthy subjects and 31% in asthmatic patients. Beclometasone 17-monopropionate and formoterol plasma exposures were comparable across the 3 groups during the 24 hours following the inhalation. The total exposure of BDP was higher in COPD patients compared to the exposure in asthmatic patients and healthy volunteers.

7.1.2.1. Beclometasone Dipropionate

7.1.2.1.1. Absorption, Distribution, and Biotransformation

Inhaled BDP is rapidly absorbed through the lungs; prior to absorption there is extensive conversion to its active metabolite 17-BMP via esterase enzymes that are found in most tissues. The systemic availability of the active metabolite arises from lung (36 %) and from gastrointestinal absorption of the swallowed dose. The bioavailability of swallowed BDP is negligible, however, pre-systemic conversion to 17-BMP results in 41% of the dose being

absorbed as the active metabolite. There is an approximately linear increase in systemic exposure with increasing inhaled dose.

The absolute bioavailability following inhalation is approximately 2% and 62% of the nominal dose for unchanged BDP and 17-BMP, respectively.

Following intravenous dosing, the disposition of BDP and its active metabolite are characterised by high plasma clearance (150 and 120 L/h, respectively), with a small volume of distribution at steady state for BDP (20 L) and larger tissue distribution for its active metabolite (424 L).

Plasma protein binding is moderately high.

7.1.2.1.2. Elimination

Faecal excretion is the major route of BDP elimination mainly as polar metabolites. The renal excretion of BDP and its metabolites is negligible. The terminal elimination half-lives are 0.5 and 2.7 hours for BDP and 17-BMP, respectively.

7.1.2.1.3. Special Populations (Hepatic/Renal Impairment)

The pharmacokinetics of BDP in patients with renal or hepatic impairment have not been studied; however, as BDP undergoes a very rapid metabolism via esterase enzymes present in intestinal fluid, serum, lungs, and liver, to originate the more polar products beclometasone-21-monopropionate, 17-BMP, and beclometasone, hepatic impairment is not expected to modify the pharmacokinetics and safety profile of BDP. As BDP or its metabolites were not traced in the urine, an increase in systemic exposure is not envisaged in patients with renal impairment.

7.1.2.2. Formoterol

7.1.2.2.1. Absorption and Distribution

Following inhalation, formoterol is absorbed from both the lung and from the gastrointestinal tract. The fraction of an inhaled dose that is swallowed after administration with an MDI may range between 60–90%. At least 65% of the fraction that is swallowed is absorbed from the gastrointestinal tract. Peak plasma concentrations of unchanged drug occur within 0.5 to 1 hour after oral administration. Plasma protein binding of formoterol is 61–64% with 34% bound to albumin. There was no saturation of binding in the concentration range attained with therapeutic doses. The elimination half-life determined after oral administration is 2–3 hours. Absorption of formoterol is linear following inhalation of 12 to 96 µg of formoterol fumarate dihydrate.

7.1.2.2.2. Biotransformation

Formoterol is widely metabolised, and the prominent pathway involves direct conjugation at the phenolic hydroxyl group. Glucuronide acid conjugate is inactive. The second major pathway involves O-demethylation followed by conjugation at the phenolic 2′-hydroxyl group. Cytochrome P450 (CYP450) isoenzymes CYP2D6, CYP2C19, and CYP2C9 are involved in the O-demethylation of formoterol. Liver appears to be the primary site of metabolism. Formoterol does not inhibit CYP450 enzymes at therapeutically relevant concentrations.

7.1.2.2.3. Elimination

The cumulative urinary excretion of formoterol after single inhalation from a dry powder inhaler increased linearly in the 12–96 µg dose range. On average, 8% and 25% of the dose was excreted as unchanged and total formoterol, respectively. Based on plasma concentrations measured following inhalation of a single 120 µg dose by 12 healthy subjects, the mean terminal elimination half-life was determined to be 10 hours. The (R,R)- and (S,S)-enantiomers represented about 40% and 60% of unchanged drug excreted in the urine, respectively. The relative proportion of the two enantiomers remained constant over the dose range studied and there was no evidence of relative accumulation of one enantiomer over the other after repeated dosing.

After oral administration (40 to 80 µg), 6% to 10% of the dose was recovered in urine as unchanged drug in healthy subjects; up to 8% of the dose was recovered as the glucuronide.

A total 67% of an oral dose of formoterol is excreted in urine (mainly as metabolites) and the remainder in the faeces. The renal clearance of formoterol is 150 mL/min.

7.1.2.2.4. Special Populations (Hepatic/Renal Impairment)

To date, Lupin has not completed any clinical studies with beclometasone dipropionate/formoterol fumarate dihydrate 200/6 mcg per actuation pressurised inhalation solution.

7.2. Study Purpose

Lupin Research Inc. has developed beclometasone dipropionate/formoterol fumarate dihydrate pressurised inhalation solution as a substitutable product for FOSTAIR, the RLD.

The purpose of the study described herein was to assess and compare the PK profiles of 17-BMP, BDP, and formoterol following administration of beclometasone dipropionate/ formoterol fumarate dihydrate pressurised inhalation solution combination products as 2 inhalations from 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), with and without charcoal block. Safety profiles observed for the products were also evaluated.

8. STUDY OBJECTIVES

8.1. 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.

8.2. Secondary Objective

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.

9. INVESTIGATIONAL PLAN

9.1. Overall Study Design and Plan: Description

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.

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.

The Time and Events Schedule that was utilised in this study is included in Table 5, with further details on the timing of specific procedures/assessments provided in the protocol.

Study information is provided in Appendix 16.1, with the protocol and protocol amendments in Appendix 16.1.1 and a sample case report form (CRF) in Appendix 16.1.2.

9.2. Discussion of Study Design, Including the Choice of Control Groups

For comparison of PK, the study design was based on the pertinent guidelines for bioavailability (i.e., FDA Guidance on Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations, Revision 1 dated March 2003, Guidance for Industry: Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs – General Considerations, March 2014, and European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP): Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr). London, 20 January 2010). In this study, an open-label, randomised, 4-period, 4-treatment, 4-sequence, crossover design was chosen to assess the PK profiles following a single orally-administered dose of beclometasone dipropionate/formoterol fumarate dihydrate combination products, administered as 2 inhalations from Lupin BDP/FF 200/6 mcg (total dose = 400/12 mcg), and from FOSTAIR 200/6 mcg manufactured by Chiesi Limited (total dose = 400/12 mcg), with and without charcoal block. The dosage of 2 inhalations of beclometasone dipropionate/formoterol fumarate dihydrate 200/6 mcg (total dose = 400/12 mcg) was chosen to achieve sufficient plasma levels to characterise the PK profiles of 17-BMP, BDP, and formoterol. The crossover design had been selected to minimise the variability by using subjects as their own control, with sufficient washout between each treatment.

The determination of sample size is described in Section 9.7.2. Because the objectives of the study were to assess the PK profile of three analytes (i.e., 17-BMP, BDP, and formoterol), and PK measures are not subject to bias, an open-label design was appropriate.

9.3. Selection of Study Population

A total of 112 healthy male and female subjects (28 subjects per treatment sequence), aged 18–45 years, were enrolled to ensure that a minimum of 94 subjects completed all treatment periods and all critical assessments. Recruitment for the study sought to include representation from both genders within the study population without regard to a predetermined gender ratio or equal distribution of genders across sequences. However, either gender could not represent more than 70% of the study population. The recruitment of males and females was made throughout the study. The study was conducted in multiple cohorts due to subject recruitment.

Note: Two (02) additional subjects (X1 and X2) were enrolled at the time of treatment period 1 check-in for each cohort depending on the availability of the eligible subjects. Any subject withdrawn/dropped out from the study before dosing at check-in was to be replaced from the additional subjects.

9.3.1. Inclusion Criteria

Subjects were eligible for enrolment if all the following inclusion criteria applied:

1. Able to give signed written informed consent prior to study entry.
2. Male or female 18 to 45 years of age (inclusive) at the Screening visit.

3. 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.
4. Female subjects of:
   - non-childbearing potential, were:
     - premenarche, or
     - ≥1 year post-menopausal (no menstrual period for at least 12 consecutive months without any other medical cause), or
     - surgically sterile by history (tubal ligation, oophorectomy, hysteroscopic sterilisation, or hysterectomy), or
     - diagnosed as infertile by history and not undergoing treatment to reverse infertility
   - childbearing potential and sexually active, were not pregnant, breastfeeding, or attempting to become pregnant for 4 weeks before the Screening visit, throughout the duration of the study, and 30 days after the subject's last study-related visit (for eligible subjects only, if applicable); had a negative serum pregnancy test; and committed to using a consistent and acceptable method of birth control as defined below for the duration of the study:
     - systemic or vaginal contraception used for ≥1 month prior to screening, including birth control pills, transdermal patch (e.g., EVRA® or equivalent), vaginal ring (e.g., NUVARING® or equivalent), levonorgestrel implant (e.g., NORPLANT® or equivalent), or injectable progesterone (e.g., DEPO-PROVERA® or equivalent)
     - double barrier methods (condoms, cervical cap, diaphragm, or vaginal contraceptive film with spermicide)
     - intrauterine device (IUD) with a low failure rate <1% per year (the use of copper IUDs was excluded)
     - monogamous with a vasectomised male partner or exclusively had same-sex partners
   - childbearing potential and not sexually active, and committed to using a consistent and acceptable method of birth control as defined above for the duration of the study, in the event the subject became sexually active.

   Sexually active male subjects committed to an acceptable method of birth control for the duration of the study or exclusively had same-sex partners.

   Additionally, all subjects and their partners were required to use 2 types of contraception, one of which was a barrier method, such as a condom.
5. Body mass index (BMI) of ≥18.5 to ≤30 kg/m^2 and a body weight ≥50 kg. BMI is calculated as follows: weight (kg)/height (m)^2.
6. Resting sitting pulse rate of ≥50 to ≤99 beats per minute (bpm), and blood pressure of ≤130/80 mmHg.

7. Non-smoker and had not used tobacco products (i.e., cigarettes, cigars, pipe tobacco, Gutkha) for at least 1 year prior to the Screening visit and had a maximum smoking history of ten pack-years (i.e., the equivalent of one pack per day for ten years).
8. In good general health and free of any concomitant conditions or treatments that could have interfered with study conduct, influenced the interpretation of study observations/results, or placed the subject at increased risk during the study (e.g., subject was not able to follow instructions required for proper inhalation technique).
9. Demonstrated proper inhalation technique using the AIM. Subjects were able to get a reading of "good" technique within the first 5 attempts and then a second "good" reading within 3 additional attempts.

9.3.2. Exclusion Criteria

Subjects who met any of the following exclusion criteria were not enrolled:

1. History or current evidence of a 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 adequately treated basal cell carcinoma]) that in the medical judgement of the Investigator would put the safety of the subject at risk through participation or that could affect the pharmacokinetic or safety analysis if the disease/condition worsened during the study.
2. History of a respiratory infection or disorder (including, but not limited to bronchitis, pneumonia, the common cold, acute or chronic sinusitis, flu) within 30 days preceding the Screening visit.
3. 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.
4. Female subjects were pregnant or lactating, planned to become pregnant, or donate gametes (ova) during the study period or for 30 days after the subject's last study-related visit (for eligible subjects only, if applicable). Eligible female and male subjects who were unwilling to employ appropriate contraceptive measures to ensure that pregnancy would not occur during the study were excluded. Any subject who became pregnant during the study was to be withdrawn from the study.
5. Positive test result for urine pregnancy (all females) at the Screening visit.
6. History or presence of a positive test for human immunodeficiency virus (HIV), hepatitis B, hepatitis C infection, or syphilis.
7. Random plasma glucose >199 mg/dL at the Screening visit.
8. Clinically significant abnormalities on the 12-lead ECG at the Screening visit (in the Investigator's opinion).

9. Presence of any disease or condition known to interfere with the absorption, distribution, metabolism, or excretion of drugs.
10. Occurrence of any injury or localised infection in the mouth or pharynx (e.g., oral thrush).
11. Unable to demonstrate proper inhalation techniques involved in using the inhaler.
12. Used an inhaled/topical corticosteroid within 30 days prior to Screening visit or a systemic/oral corticosteroid, any biologic therapy/treatment with monoclonal antibodies within 60 days of the Screening visit.
13. Non-vaccinated exposure to or active infection with chickenpox or measles within 21 days of the Screening visit.
14. Exposure to any investigational drug within 90 days prior to dosing.
15. Used medications that are cytochrome P450 3A4 (CYP3A4) inhibitors (e.g., ritonavir, ketoconazole, itraconazole) within 30 days prior to the Screening visit.
16. 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.
17. History of difficulty with donating blood.
18. History of alcohol or drug abuse within 2 years preceding the Screening visit.
19. Positive test for alcohol or drugs of abuse (including cotinine) at screening and within 24 hours prior to receiving study drug.
20. Used prohibited medications within the prescribed withdrawal periods of the protocol.
21. Presence, by history, and/or symptoms, signs suggestive of ocular disturbances, including glaucoma, cataracts, or ocular herpes simplex.
22. Vulnerable subject (e.g., persons kept in detention).
23. Piercings of the tongue, lips, or mouth.
24. Loose dentures or denture abnormalities like protruding teeth.
25. An employee of the investigational site or an immediate relative of an employee of the centre.

9.3.3. Removal of Subjects from Therapy or Assessment

Subjects could withdraw consent and/or be discontinued by the Investigator and/or Sponsor for any reason at any time. A subject could withdraw or be withdrawn for any of the following reasons:

1. Death
2. Adverse Event (AE)/Serious Adverse Event (SAE)
3. Subject withdrawal of consent
4. Request of primary care physician or Investigator
5. Protocol deviation/non-compliance

6. Pregnancy
7. Use of a prohibited concomitant medication
8. Failed to return/lost to follow-up
9. Cross participation in another study

If a subject was withdrawn due to an AE, he/she was to be followed until the event resolved, resolved with sequelae, was otherwise explained by a medical condition, follow-up was not possible (documented), or the subject died. All attempts to follow up were to be documented. Discontinuation of subjects due to AEs, including those due to abnormal laboratory results, were to be promptly reported to the Sponsor.

The date that the subject was withdrawn from the study and the reason for discontinuation was to be recorded in the CRF. If there were multiple reasons for early discontinuation, the worst-case scenario was to be chosen.

If a subject was lost to follow-up (failed to return for study visits), a reasonable effort was to be made to determine why the subject failed to return. This information was to be documented on the CRF. When a subject was withdrawn from the study (regardless of the cause), all EOS evaluations were to be performed.

In addition to the above, a subject could withdraw his/her consent at any time, without giving any reason. The Investigator or study personnel were to obtain the possible reason for his/her withdrawal and were to help the subject complete other study-related requirements. The subject withdrawal during the study was to be handled as per in-house standard operating procedures (SOPs) with adequate documentation.

9.4. Treatments

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.

9.4.1. Treatments Administered

The following treatments were administered in a, 4-period, 4-treatment, 4-sequence, crossover design (Table 1):

Table 1: Beclometasone Dipropionate and Formoterol Fumarate Dihydrate Treatments

Treatment	Dose	Route of administration	Duration of treatment
Test Product (Treatment A) Beclometasone dipropionate/formoterol fumarate dihydrate 200/6 mcg per actuation pressurised inhalation solution (Lupin BDP/FF 200/6 mcg)	2 inhalations Total dose = 400/12 mcg	Oral inhalation	Single dose
Reference Product (Treatment B) FOSTAIR 200/6 micrograms per actuation pressurised inhalation solution (FOSTAIR 200/6 mcg)	2 inhalations Total dose = 400/12 mcg	Oral inhalation	Single dose
Test Product (Treatment C) Beclometasone dipropionate/formoterol fumarate dihydrate 200/6 mcg per actuation pressurised inhalation solution (Lupin BDP/FF 200/6 mcg) with concomitant oral charcoal* administration	2 inhalations Total dose = 400/12 mcg	Oral inhalation	Single dose
Reference Product (Treatment D) FOSTAIR 200/6 micrograms per actuation pressurised inhalation solution (FOSTAIR 200/6 mcg) with concomitant oral charcoal* administration	2 inhalations Total dose = 400/12 mcg	Oral inhalation	Single dose

* Charcodote® or equivalent (5 g activated charcoal suspended in 25 mL water).

Information regarding the batches of study drug that were used in this study is provided in Appendix 16.1.6 and in Table 2.

9.4.2. Identity of Investigational Product(s)

The investigational products used in this study are described in Table 2.

Test Product

Beclometasone dipropionate (BDP), one active component of Lupin BDP/FF 200/6 mcg, is a synthetic glucocorticoid having the chemical name (8S,9R,10S,11S,13S,14S,16S,17R)-9-chloro-11-hydroxy-10,13,16-trimethyl-3-oxo-17-[2-(propionyloxy)acetyl]-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a] phenanthrene-17-yl propionate. Beclometasone dipropionate is a white to creamy white powder with a molecular weight of 521.042 g/mol and an empirical formula of $C_{28}H_{37}ClO_7$. It is slightly soluble in water, very soluble in chloroform, and freely soluble in acetone and in alcohol. The other active component of Lupin BDP/FF 200/6 mcg is formoterol fumarate dihydrate, a selective β_2-andrenergic bronchodilator. Formoterol fumarate dihydrate is a white to slightly yellow powder with a molecular weight of 840.9 g/mol, and the empirical formula is $(C_{19}H_{24}N_2O_4)_2 \cdot C_4H_4O_4 \cdot 2H_2O$. It is freely soluble in glacial acetic acid, soluble in methanol, sparingly soluble in ethanol and isopropanol, slightly soluble in water, and practically insoluble in acetone, ethyl acetate, and diethyl ether.

[redacted]

Reference Product

FOSTAIR 200/6 mcg consists of the drugs BDP and formoterol fumarate dihydrate and has a dose counter providing 120 metered doses (marketed by Chiesi Limited).

Table 2: Investigational Products and Components

Identifying parameters	Test Product (Treatment A and Treatment C)	Reference Product (Treatment B and Treatment D)
Product name	Lupin BDP/FF 200/6 mcg (without and with oral charcoal)	FOSTAIR 200/6 mcg (without and with oral charcoal)
Manufacturer's name	[redacted]	
Canister		
Valve		
Actuator and Cap		
Manufacturing of Finished Product		
Batch no./Lot no.		
Manufacturing date	07 February 2019	Unknown
Expiry date/use by	08 February 2020	August 2020

Source: Data on File, Appendix 16.1.6.

9.4.2.1. Ancillary Supplies

Training placebo (HFA-134a) pressurised inhalers containing only propellant with no active drug (Lot number: [redacted] were provided by Lupin for the purpose of device specific training and stored at controlled room temperature below 25°C.

Charcodote (200 mg/mL activated charcoal suspension in purified water) was provided in a 250 mL polyethylene bottle containing 250 mL of suspension (50 g activated charcoal) and stored at controlled room temperature below 25°C. For the purposes of this study, each

bottle provided approximately 10 doses (Lot number: [redacted]). Charcodote is marketed by Teva UK Limited in the UK.

Designated study personnel provided inhalation training using the AIM device to ensure the subjects demonstrated proper inhalation technique.

No additional supplies were provided by Lupin Research Inc. for this study.

9.4.3. Method of Assigning Subjects to Treatment Sequences

Study medication was administered to subjects who signed and dated an ICD who met the study entry criteria and who demonstrated proper use of the AIM device and training placebo (HFA-134a) pressurised inhaler were randomised to treatment. Subjects were randomised to treatment on Day -1 of treatment period 1 and were required to demonstrate proper use of the AIM device and placebo (HFA-134a) pressurised inhaler at each treatment period. A total of 112 subjects were randomised to 1 of 4 treatment sequences (ABDC, BCAD, CDBA, or DACB) in accordance with the randomisation schedule generated in advance of the study start. The randomisation schedule included additional subject numbers in the event that additional subjects were needed.

The order of receiving the test and reference formulations for each subject during the treatment periods of the study was determined according to the randomisation schedule (generated using SAS [SAS Institute Inc., USA] version 9.4). Randomisation occurred in blocks using PROC PLAN such that the design was balanced. Equal allocation of subjects to each treatment sequence was ensured. The randomisation schedule was created by Lupin Bioresearch Center (LBC), approved by Lupin Research Inc., and kept under controlled access. The personnel involved in dispensing the study drug and verifying dispensed study drugs were accountable for ensuring compliance to the randomisation schedule.

The study personnel at the analytical lab involved in the sample analysis were kept blinded from the randomisation code during the entire study.

The randomisation scheme and codes are provided in Appendix 16.1.7.

9.4.4. Selection of Doses in the Study

The recommended dose of FOSTAIR 200/6 mcg per actuation pressurised inhalation solution is 2 inhalations. Lupin selected 2 inhalations of the Lupin BDP/FF 200/6 mcg test formulation (total dose = 400/12 mcg) to achieve sufficient plasma levels to characterise the PK profiles of the drugs in order to establish bioequivalence of the test and reference products.

9.4.5. Selection and Timing of Dose for Each Subject

At the Screening visit, and on Day -1 of all treatment periods, designated study personnel provided inhalation training using the AIM device to ensure subjects' proper use of a tested training placebo (HFA-134a) pressurised inhaler. Subjects needed to demonstrate the proper study medication procedures using a placebo (HFA-134a) pressurised inhaler. Demonstration of proper use of the inhaler was documented at each treatment visit in the CRF.

Subjects began an overnight fast (at least 8 hours) on Day -1 of each treatment period and continued to fast until approximately 4 hours after the study medication was administered on Day 0 between the hours of 07:00 and 09:00 (±30 minutes) per the randomisation schedule.

For treatments utilizing co-administration of activated charcoal (i.e., Treatments C and D), subjects received a suspension of 5 g of activated charcoal in 25 mL of water (25 mL of activated charcoal suspension contains 5 g of activated charcoal) 2 minutes before self-administering the dose of study medication, and at 0.50, 60, 120, and 240 minutes after dose inhalation. Immediately following the administration of charcoal, 25 mL of water was then added to the cup and swirled to rinse any charcoal that adhered to the sides of the cup. The subject drank the 25 mL water rinse, thoroughly rinsing their mouth before swallowing the rinse. Charcoal was to be administered at the scheduled times, but a time deviation window of ±30 seconds was allowed. Administration of activated charcoal occurred based on the start time of the second inhalation. The schedule of charcoal administration is presented below in Table 3.

Table 3: Schedule of Charcoal Administration

	Day 0 of Treatment Periods 1–4 for Subjects Assigned to Treatments C and D				
Timepoint (minutes)[1]	**-2**	**0.5**	**60**	**120**	**240**
Administer charcoal	X	X	X	X	X
Amount administered (g)	5	5	5	5	5

[1] Relative to 0-hour dose time defined as time of first inhalation for the -2 minute timepoint, and as the time of second inhalation for all subsequent timepoints.

On Day -1 of all treatment periods, study medication was tested by trained study staff for use within 24 hours of dosing in a well-ventilated area away from the subjects, dosing, and PK sampling areas.

Each subject used 1 inhaler in each treatment period. Each inhaler was used only once (excluding placebo [HFA-134a] pressurised training inhalers). Each study medication administration (i.e., dosing) was monitored for any detectable inconsistencies from the instructions provided and observed deviations were detailed and documented in the CRF.

The first and second study medication administration times were recorded. The time that the first inhalation of study medication was administered was considered the actual dose administration time. All subsequent study scheduled times were relative to that actual dose administration time. Study medication (2 inhalations from the assigned pressurised inhalation solution) was subject self-administered no more than 15 minutes after the pre-dose PK blood sample collection.

Study medications were administered with the subject in a seated position. After the first inhalation, the second inhalation of study medication was to be administered 30 (±10) seconds later so that both inhalations were administered within a period of approximately 90 seconds. The subject rinsed their mouth with approximately 100 mL of water and spit it out immediately following the second inhalation. Subjects were instructed not to swallow the water. All dose administrations occurred between the hours of 07:00 and 09:00 hours. The earliest dosing (first

inhalation) took place at 08:00:02, while the latest occurred at 09:13:07 (Appendix 16.2.5, Listing 16.2.5.4).

9.4.6. Blinding

This was an open-label study; therefore, treatment was not blinded. All study medications were administered in an open-label manner and packaged in its marketed configuration (where applicable).

The study personnel at the analytical lab involved in the sample analysis were kept blinded from the randomisation code during the entire study.

9.4.7. Prior and Concomitant Therapy

Medications (including vitamins, herbal medicine, home remedies, and over-the-counter [OTC] medications) and therapies used within 90 days before the Screening visit through the EOS/Early Termination (ET) visit were recorded in the CRF and coded using WHODrug Global B3 Format, March 1, 2019 with descriptors from the Anatomical Therapeutic Chemical (ATC) classification system.

9.4.7.1. Prohibited Medications

The particular therapies listed in Table 4 were prohibited and could not be taken during the specific times listed and thereafter, and could not be taken within the appropriate time period.

Table 4: Disallowed Previous Medications

Type of Medication	Days Since Screening Visit
Any other investigational drug	90 days
Anti-immunoglobulin E (IgE) therapy (omalizumab)	60 days
Systemic/inhaled corticosteroids	60 days
Intranasal/topical corticosteroids	30 days
Leukotriene modifiers	30 days
Inhaled short or long-acting β_2-agonists	30 days
Oral β_2-agonists	30 days
Theophylline	30 days
Monoamine oxidase inhibitors	30 days
Tricyclic antidepressants	30 days
Anticonvulsants	30 days
β-adrenergic receptor blocking agents	30 days
Stimulants (e.g., methylphenidate, amphetamines)	30 days
Cromones	30 days
Anticholinergics	30 days
CYP3A4 inhibitors (e.g., ritonavir, ketoconazole)	30 days
Non-potassium sparing diuretics	14 days
Vitamins	14 days
Herbal and dietary supplements	14 days

Type of Medication	Days Since Screening Visit
Long acting antihistamines (e.g., CLARITIN® [loratadine], CLARINEX® [desloratadine], ZYRTEC® [cetirizine HCl], ALLEGRA® [fexofenadine])	10 days
OTC cough and cold preparations or sleep aids containing antihistamines	10 days
Topical/Oral/Nasal decongestants (e.g., oxymetazoline, pseudoephedrine, tetrahydrozoline)	7 days
AIROZIN® (OTC food supplement/diet to reduce leukotrienes)	7 days
Inhaled/Oral/Intranasal anticholinergics	7 days
Short acting antihistamines including intranasal and ocular antihistamines	3 days

The administration of any additional medication (including OTC and vitamins) was to be clearly documented both in the source documents and the CRF. No medication, other than the study medication and allowed medications, were to be taken during the study.

Other concomitant medications could be used for the treatment of an AE (e.g., paracetamol, aspirin, or ibuprofen), provided they did not threaten subject safety. Such administration was to be clearly documented and cross-referenced with the AE in the CRF and could require discontinuation of the study medication and withdrawal of the subject from the study if the medication was prohibited.

All other prohibited therapies were to be discontinued according to the protocol specified periods. These medications could only be discontinued if the Investigator decided that discontinuing subjects from therapy was the best course of action for the subject. These medications and therapies could not be discontinued for the sole purpose of making a subject eligible for enrolment into the study.

Subjects were not permitted to enter the study if they were receiving any prohibited concomitant medication or medication which could not be discontinued. If administration of any prohibited medication became necessary during the study for medical reasons, the subject was to be withdrawn from further study participation.

9.4.7.2. Restrictions

9.4.7.2.1. Dietary and Other Restrictions

Subjects were served dinner on the day of admission. Subjects began an overnight fast of at least 8 hours on Day -1 of all treatment periods and continued to fast until approximately 4 hours after study medication administration on Day 0. Subjects were permitted to have non-mineral water at room temperature ad libitum up until 1 hour before study dosing, and could resume room temperature non-mineral water intake 1 hour post-dose. A normal diet and meal schedule resumed following the morning fast. On Day 0 (the day of study medication administration) in all treatment periods, no breakfast was served. Meals were served as follows (all times are approximate):

Meal	Day 0	Day 1	Day 2
Breakfast	None	24 hours post-dose	48 hours post-dose
Lunch	4 hours post-dose	28 hours post-dose	
Evening Snack	8 hours post-dose	32 hours post-dose	
Dinner	12 hours post-dose	36 hours post-dose	

Subjects were instructed to abstain from consuming caffeine and/or xanthine products (e.g., coffee, tea, chocolate, and caffeine-containing sodas, colas, etc.) for at least 24 hours prior to dosing during study confinement; alcohol and its products, foods and beverages known to inhibit CYP3A4 (e.g., red wine, grapefruit products, Seville oranges and marmalade) were prohibited for at least 24 hours prior to dosing and during study confinement. Subjects were not to have an unusual diet, for whatever reason (e.g., low salt) for 3 weeks prior to dosing and throughout the study. Smoking or consuming tobacco/tobacco-containing products/Gutkha in the previous 1 year prior to screening and throughout the study was prohibited.

Compliance assessment to the above restrictions was performed at screening, prior to check-in of each treatment period, and EOS. Urine screens for drugs of abuse (tetrahydrocannabinol [cannabinoids]-THC, amphetamine-AMP, barbiturates-BAR, cocaine-COC, benzodiazepines-BZD, cotinine-COT, and opiates-OPI) were performed during screening and on the day of check-in (Day -1) of each treatment period.

9.4.7.2.2. Restricted Activities

Subjects abstained from strenuous exercise for 48 hours prior to blood sample collection for clinical laboratory tests at the Screening and EOS visits. Subjects were requested to remain seated during the first hour after study medication administration except for study required procedures, due to the frequent blood draws.

Subjects could participate in light recreational activities (e.g., reading, watching television, walking, carom, chess, etc.) during each treatment period.

9.4.8. Treatment Compliance

A single dose administration of 2 inhalations from the study medication was self-administered by each subject in clinic during all treatment periods according to the randomisation schedule. Study drug was administered according to the randomisation schedule under the supervision of designated study personnel (including the Quality Assurance [QA] auditor and Monitor). Study personnel ensured that the proper dose of the study drug was administered, and that proper administration procedures were followed. The date, time, and treatment administered were recorded in the CRF for each subject during each treatment period.

9.5. Pharmacokinetic and Safety Variables

9.5.1. Pharmacokinetic and Safety Measurements Assessed and Flow Chart

Safety and PK measurements were made according to the Time and Events Schedule in the protocol (Table 5).

Table 5: Time and Events Schedule

Assessments	Screening visit [a]	Treatment Periods 1, 2, 3, and 4				End of Study (EOS) [b]
		Day –1	Day 0	Day 1	Day 2	
Screening consent form	X					
Study specific ICD	X					
Inclusion/Exclusion criteria check	X	X				
Demography	X					
Screening compliance check	X					
Medical/Medication history	X					
Physical examination [c]	X	X			X	X
12-lead ECG (supine)	X					X
Vital signs (seated) [d]	X	X	X	X	X	X
BMI (height and weight)	X					
Urine pregnancy test (if applicable)	X					
Serum pregnancy test (if applicable)		X				X
Clinical laboratory tests [e]	X					X
HIV, hepatitis, syphilis tests	X					
Urine drug screen including cotinine test [f]	X	X				
Alcohol breath test	X	X				
AIM device training [g]	X	X				
Placebo (HFA-134a) pressurised inhalation solution training [g]	X	X				
Randomisation [h]		X				
Inpatient stay [i]		X----------X				
Compliance health check		X				
Inhaler testing [j]		X				
Study medication administration [k]			X			
PK blood sample collection [l]			X	X	X	
Charcoal administration [l]			X			
Cough frequency assessment [m]			X			
Concomitant medication monitoring	X----------X					
Adverse event monitoring	X----------X					

Abbreviations: AE = adverse event; AIM = Aerosol Inhalation Monitor, BMI = Body Mass Index; ECG = electrocardiogram; EOS = End of Study; HIV = human immunodeficiency virus; ICD = informed consent document; PK = pharmacokinetic.

Time and Events Schedule, continued

a. All assessments were conducted within 21 days of admission to treatment period 1, Day -1. A screening consent form was reviewed with and signed by potential subjects before any evaluations and procedures took place. A study-specific ICD was given to all subjects on the day of screening for this study. The study specific informed consent was completed before any study procedures took place.
b. The EOS assessments were completed on Day 2 of treatment period 4 or upon Early Termination (ET) from the study. Electrocardiography (ECG) and vital signs measurements were completed before any clinical laboratory blood sample collections.
c. Physical examinations and compliance health checks were conducted at screening, at check-in and check-out of each treatment period, and EOS.
d. Vital signs (sitting blood pressure and pulse rate; after approximately 5 minutes of rest) were measured during screening; Day -1 at check-in; Day 0 prior to dosing, and at 2, 4, 6, and 12 hours post-dose; Day 1 at 24, and 36 hours post-dose; and on Day 2 prior to discharge from each period. A window of ±40 minutes from the scheduled time point was permitted for post-dose vital signs measurements at 2, 4, 6, 12, 24, and 36 hours. Subjects were required to have clinically acceptable vital signs prior to check-in of each period.
e. Clinical laboratory tests at screening were collected in the non-fasting state and at the EOS visit in the fasting state.
f. Results of urine drug screen including cotinine test (either urine or breath test) and alcohol test were required to be available prior to dosing on Day 0 of each treatment period.
g. At screening and upon admission to each treatment period (Day -1), procedures for the Aerosol Inhalation Monitor (AIM) and training placebo (HFA-134a) pressurised inhaler use were reviewed and the subject's ability to use the device and inhaler correctly documented.
h. Randomise upon entry to treatment period 1 for subjects who met study entry criteria and demonstrated proper AIM and training placebo (HFA-134a) pressurised inhaler use.
i. Subjects could be discharged from treatment periods 1, 2, and 3 after the 48-hour PK blood sample collection. Discharge from treatment period 4 could occur after completion of EOS assessments.
j. Placebo (HFA-134a) pressurised inhalers were to be tested within 24 hours of dosing in a well-ventilated area away from the subjects, dosing, and PK sampling areas.
k. The study medication was administered between 07:00 and 09:00 (±30 minutes) on Day 0 of each treatment period. Subjects were permitted to have non-mineral water at room temperature ad libitum (at liberty) until 1 hour before study dosing and could resume room temperature non-mineral water intake 1-hour post-dose. After the first inhalation, the second inhalation of study medication was to be administered 30 (±10) seconds later so that both inhalations were administered within a period of approximately 90 seconds. The subject rinsed his/her mouth with approximately 100 mL of water and spit it out immediately following the second inhalation. Subjects were instructed not to swallow the water.
l. See Table 3 for the schedule of charcoal administration and Table 5 of the protocol (Appendix 16.1.1) for the schedule of PK blood sampling collection times.
m. Cough frequency assessment was completed through 2 minutes after dosing.

9.5.1.1. Pharmacokinetic Measurements

The primary PK variables of this study were 17-BMP (without charcoal) and formoterol (with and without charcoal) area under the plasma concentration versus time curve from time zero (0) to the time of the last quantifiable concentration (AUC_{0-t}), and maximum observed plasma concentration (C_{max}) following each treatment. See Section 9.5.4 for details.

9.5.1.2. Safety Measurements

Individual safety data including reported AEs, physical (medical) examination results, vital signs measurements, 12-lead ECG overall interpretation, and clinical laboratory test results were used to evaluate the safety profile of the study treatments. Body weight and height measurements were recorded only at the Screening visit. Repeats and unscheduled visits were included in the listings.

Safety and tolerability endpoints included the following:

- The frequency of treatment-emergent adverse events (TEAEs) during and between on-site treatment-evaluation visits
- The nature, incidence, severity, and causality of spontaneously reported and elicited AEs
- The frequency of cough through 2 minutes after dosing
- Change from baseline in vital signs (blood pressure and pulse rate)
- Clinical laboratory test results (haematology, biochemistry, serology, and urine analysis results) and change from baseline in laboratory values
- Change from baseline in 12-lead ECG results
- Change from baseline in physical examination results

The following treatment intervals assignments were used for reporting the safety data:

- **Pre-dose** – From the time the subject provided informed consent until immediately prior to the start of the first inhalation in treatment period 1.
- **Period 1 Treatment** – From the start of the first inhalation in treatment period 1 until immediately prior to the first inhalation in treatment period 2 (or until checkout for subjects who discontinued prior to treatment period 2).
- **Period 2 Treatment** – From the start of the first inhalation in treatment period 2 until immediately prior to the first inhalation in treatment period 3 (or until checkout for subjects who discontinued prior to treatment period 3).
- **Period 3 Treatment** – From the start of the first inhalation in treatment period 3 until immediately prior to the first inhalation in treatment period 4 (or until checkout for subjects who discontinued prior to treatment period 4).
- **Period 4 Treatment** – From the start of the first inhalation in treatment period 4 until checkout.
- **End of Study** – From subject checkout through the end of study safety assessment.

The Safety Analysis Set was used for reporting safety data.

Due to the sampling schedule (i.e., Screening and EOS visits only; see Time and Events Schedule in Table 5), TEAEs associated with laboratory results or ECGs were assigned to the most recent treatment received prior to the sample draw/procedure.

9.5.1.2.1. Adverse Events (AEs)

Adverse events were recorded from the time a subject signed the ICF through the duration of the study. The Investigator's verbatim term for the AE was mapped to the System Organ Class (SOC) and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) version 22.0.

All AE summary tables included only TEAEs and were summarised by SOC and PT using frequency counts and percentages of subjects experiencing the AE and the number of incidences reported. A subject was only counted once per SOC and PT within a treatment.

Severity of an AE was graded as 'Mild', 'Moderate', or 'Severe'. If a subject had multiple events occurring in the same SOC or same PT, then the event with the maximum intensity (e.g., severe) was considered in summary analyses.

Causal relationship of an AE to study medication was classified by the Investigator as 'Certainly related', 'Probably related', 'Possibly related', 'Unlikely related', 'Conditionally related', 'Unclassifiable', or 'Not Applicable'. If a subject had multiple events occurring in the same SOC or same PT, the event with the highest association (e.g., a single subject with 2 events of headache; one with a possible relationship, and the other with a probable relationship; only the 'probable' event was included in the table) to study medication was summarised.

An AE was reported as 'related' to study medication if the causal relation to study medication was graded as 'Certainly related', 'Probably related', 'Possibly related', 'Conditionally related', or 'Unclassifiable'; otherwise it was considered 'Not related'.

Adverse events are presented in decreasing order of the incidences at SOC level and within each SOC, in decreasing order of the incidences at the PT level.

An overall summary of AEs is presented, with summary tables presenting the following, when applicable:

- All TEAEs
- TEAEs by severity grade
- TEAEs by relationship to study drug
- Serious TEAEs
- Serious study medication related TEAEs
- TEAEs resulting in death
- Study medication related TEAEs resulting in death
- TEAEs leading to study drug discontinuation
- Study medication related TEAEs resulting in study drug discontinuation

Individual AEs are provided in listings by subject. The listings include the onset date/time and date/time of resolution (when available), severity, association with the study treatment, outcome, action taken, treatment of AE administered at the site, whether or not it was an SAE, and whether or not it was a TEAE.

Subjects were monitored throughout the study for AEs, and were instructed to inform the study personnel, study physician, or nurses of any AE that may have occurred during the study. Subjects were also queried throughout their visits in the clinic regarding any adverse effects they may have experienced. Cough events which occurred within 2 minutes of dosing were captured on the cough frequency assessment only. Cough events which occurred after 2 minutes were to be recorded as AEs.

9.5.1.2.2. Safety Laboratory Tests

The clinical laboratory tests performed during this study are listed in Table 6.

Serum chemistry, haematology, and urinalysis were performed at the Screening visit and at the EOS/ET visit (Day 2 of treatment period 4 or upon early discharge from the study).

Urine drug screen including cotinine test and alcohol breath test, was performed at screening and on Day -1 of each treatment period. Other tests, including HIV, Syphilis test (Venereal Disease Research Laboratory [VDRL] rapid plasma reagin [RPR]/*Treponema pallidum* haemagglutination assay [TPHA]), and hepatitis serology, were performed at screening only.

A urine pregnancy test (females only) was performed at the Screening visit, with a serum pregnancy test performed on Day -1 of each treatment period and at the EOS/ET visit.

Table 6: Clinical Laboratory Tests Performed During the Study

Serum Chemistry	Haematology	Urinalysis
Screening visit and End of Study Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Alkaline phosphatase Albumin Total bilirubin Sodium Potassium Total protein Calcium Bicarbonate Blood urea nitrogen (BUN) Creatinine Glucose Chloride Total cholesterol **Screening visit** HIV1 antibody (Ab) and antigen (Ag), and HIV2 Ab Hepatitis B (HBsAg) Hepatitis C (Hep C Ab) Syphilis (VDRL [RPR]/TPHA) Urine pregnancy test (β-HCG) for females of childbearing potential **Day -1 of each Treatment Period and EOS** Serum pregnancy test	**Screening visit and End of Study** Haemoglobin Haematocrit Erythrocyte (i.e., red blood cell [RBC]) count Platelet count Total leucocytes (white blood cell [WBC]) count with differential count • Neutrophils • Monocytes • Eosinophils • Lymphocytes • Basophils	**Screening visit and End of Study** pH Protein Glucose Ketones Bilirubin Nitrite Blood Leucocytes Specific gravity Urobilinogen Microscopic examination • RBCs • WBCs • Epithelial cells • Casts (hyaline casts, granular casts, bacteria, cellular casts) • Crystals • Other Findings **Screening visit and Day -1 of each Treatment Period** Urine Drug Screen including cotinine test Alcohol breath test

Individual laboratory results including haematology, serum chemistry, urinalysis, and serology results, as well as urine scan of drugs of abuse, breath alcohol test (BAT), and cotinine test were presented in listings. Urine and serum pregnancy test results for female subjects were also listed. Repeats and unscheduled visits were included in the listings. A listing of individual out of range laboratory results was also produced for serum chemistry, haematology, and urine analysis parameters.

Laboratory parameters (haematology and serum chemistry) were summarised by overall subjects using descriptive statistics (number of subjects in the category [n], mean, standard deviation [SD], median, minimum [Min], and maximum [Max]) 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.

Laboratory results with normal reference ranges are presented in Appendix 16.2.8, Listing 16.2.8.2 (serum chemistry), Listing 16.2.8.3 (haematology), and Listing 16.2.8.4 (urinalysis).

9.5.1.2.3. Vital Signs Measurements

Vital signs were measured at the timepoints indicated in Table 5 after 5 minutes of rest and consisted of sitting systolic blood pressure, diastolic blood pressure, and radial pulse. Although body temperature and respiratory rate were collected, the data were not reported in tables and listings.

Individual vital signs including diastolic blood pressure, systolic blood pressure, temperature, and radial pulse were listed by parameter, treatment, and study day. Repeats and unscheduled visits were included in the listings but were not used in the summaries. Vital signs could be taken at times other than those specified in the study task flow chart, if deemed necessary. Height, weight, and BMI were measured at the Screening visit only.

Change from baseline was derived for vital signs. Baseline was defined as the last observation prior to the first inhalation in each treatment period including rechecks and unscheduled assessments. Change from baseline was derived by taking the Day 2 (check-out) results in each treatment period and subtracting the corresponding baseline result.

Vital signs and change from baseline values were summarised by treatment and study day using the n, mean, SD, median, Min, and Max.

9.5.1.2.4. 12-Lead Electrocardiograms

Electrocardiograms were conducted at the Screening and EOS visits. The ECG parameters heart rate (HR), PR, QRS, QT, and corrected QT interval (QTc) intervals were summarised by overall subjects using descriptive statistics (n, mean, SD, median, Min, and Max) 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.

Additionally, shift tables were produced. The shift tables were generated 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.

Individual ECG parameters were presented in listings which includes repeats and unscheduled assessments. The listings also included whether the ECG was indicated as normal, abnormal not clinically significant/abnormal clinically significant by the Investigator.

9.5.1.2.5. Physical Examinations

Physical examinations were conducted at screening, at check-in and check-out of each treatment period, and at the EOS/ET visit. The abnormal physical examination findings were summarised at baseline and as a shift from baseline to the end of the study. Abnormal physical examination findings were presented in listings.

9.5.1.2.6. Cough Assessment

Cough frequency assessment was completed through 2 minutes after dosing in each treatment period, and counts were summarised by treatment using the n, mean, SD, median, Min, and Max. Cough assessment findings were presented in listings.

9.5.1.2.7. Concomitant Medication

The World Health Organization (WHO) WHODrug Global B3 Format, March 1, 2019 was used to classify prior and concomitant medications by active ingredient and WHO Anatomical Therapeutic Chemical (ATC) classification of ingredients.

9.5.1.3. Efficacy Measurements

Efficacy was not measured in this study.

9.5.2. Appropriateness of Measurements

The safety measures used are standard for most clinical studies and follow the recommendations in the ICH guidelines. The assessments for determining the plasma concentrations were appropriate to determine the PK of the study medication.

9.5.3. Drug Concentration Measurements

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.

The following deviation windows were permitted: 2–6 minutes ±15 seconds; 8–45 minutes ±1 minute; 1–7 hours ±3 minutes; 8–16 hours ±5 minutes; 24–36 hours ±10 minutes. The actual time the samples were collected was recorded in the CRF.

A total of approximately 20 blood samples for PK analysis were obtained per subject during each treatment period. Blood samples were collected via an indwelling cannula (when possible) or direct venepuncture. Therefore, the total blood collected (including samples for routine clinical laboratory evaluations at the Screening and EOS visits, and for PK analysis [including discarded heparinised blood]) was approximately 488 mL for male subjects and 496 for female subjects, collected over the subject's participation in the study.

Blood samples for PK analysis were collected using di-potassium ethylenediaminetetraacetic acid (K_2EDTA) tubes and centrifuged at 3,800 ±20 revolutions per minute (rpm) at 10 ±2°C for 10 minutes. The plasma was harvested from each tube, decanted equally into previously labelled

polypropylene tubes, and frozen immediately at -75 ±10°C or lower. The plasma aliquots were maintained in the frozen state until analysed.

A validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) method was used to analyse the samples for concentrations of BDP, 17-BMP, and formoterol at Lupin Bioresearch Center [redacted] . The lower limit of quantitation (LLOQ) of the assay for BDP was 5.019 pg/mL, for 17-BMP was 25.079 pg/mL, and for formoterol was 0.410 pg/mL. Details of the analytical method are presented in the bioanalytical report.

For the bioanalytical report, see Bioanalytical Report of Beclometasone Dipropionate and Bioanalytical Report of Formoterol for Study BDPFF-AS-101.

9.5.4. Pharmacokinetic Variables

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.

9.5.4.1. Beclometasone dipropionate, Beclometasone-17-monopropionate, and Formoterol Plasma Concentrations

Individual BDP (without charcoal), 17-BMP (without charcoal), and formoterol (with and without charcoal) plasma concentrations were listed and summarised by treatment and planned timepoint using descriptive statistics (number of subjects [n] with non-missing concentrations, mean, SD, percent coefficient of variation [CV%], median, Min, and Max). The listing also includes the actual time of the sample collection from the time of the first inhalation.

Figures of mean and mean (±SD) BDP (without charcoal), 17-BMP (without charcoal), and formoterol (with and without charcoal) plasma concentrations versus time using nominal time were presented on a linear and semi-logarithmic scale using all timepoints. Figures of mean BDP (without charcoal), 17-BMP (without charcoal), and formoterol (with and without charcoal) plasma concentrations versus time using nominal time from pre-dose to 2 hours post-dose were presented on a linear and semi-logarithmic scale. Individual BDP (without charcoal), 17-BMP (without charcoal), and formoterol (with and without charcoal) plasma concentration versus actual time plots were also presented on the linear and semi-logarithmic scale using all timepoints as well as from pre-dose to 2 hours.

9.5.4.2. Assessment of Pharmacokinetic Parameters

Subject BDP (without charcoal), 17-BMP (without charcoal), and formoterol (with and without charcoal) plasma concentration versus time profiles were used to derive the PK parameters. All concentration values below the limit of quantification (BLQ) were set to zero (0) in the calculation of summary statistics. For the calculation of PK parameters, concentrations that were BLQ were treated as zero (0) before the first quantifiable concentration and as missing after the first quantifiable concentration. Any missing samples were reported as 'Missing' and treated as missing for PK parameter and concentration summary calculations. Subjects for whom there were insufficient data to calculate the PK parameters were included in the summarization of PK concentration and excluded from PK parameter summary and the statistical analysis.

The first order rate constant associated with the terminal (log-linear) portion of the curve (K_{el}) was determined using linear regression composed of at least 3 data points of the log-concentration. The K_{el} was not assigned if 1) the terminal elimination phase was not apparent, 2) if time to maximum observed plasma concentration (t_{max}) was one of the 3 last data points, or 3) if the coefficient of determination (R^2) value was less than 0.8. In cases where the K_{el} interval was not assigned, the values of apparent terminal elimination half-life ($t_{½}$), area under the plasma concentration versus time curve from time zero (0) to infinity ($AUC_{0-\infty}$), and the percent of area extrapolated for calculation of $AUC_{0-\infty}$ ($AUC_{\%Extrap\ obs}$) were considered not calculable and were not reported. Subjects with lack of any measurable concentrations or very low plasma concentrations for reference treatments (B and D) could be excluded. A subject was considered to have very low plasma concentration if the AUC_{0-t} was less than 5% of reference treatment (B and D) geometric mean AUC_{0-t} (which was to be calculated without inclusion of data from outlying subject). If for any subject the pre-dose concentration appeared to be >5% of the C_{max} in any period, the concentration data for that subject in the specified period was to be excluded from statistical analyses. If over 20% of the area under the curve was extrapolated beyond the last measurable value, then $AUC_{0-\infty}$ could be considered missing for that subject and treatment period.

9.5.4.3. 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)

9.5.4.4. 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)

- 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)

9.6. Data Quality Assurance

Data handling, including data quality assurance, was conducted according to the regulatory guidelines (e.g., ICH GCP). Documentation of interlaboratory standardization methods is provided in Appendix 16.1.10.

A summary of auditing activities is provided in Appendix 16.1.8.

9.7. Statistical Methods Planned in the Protocol and Determination of Sample Size

9.7.1. Statistical and Analytical Plans

A copy of the Statistical Analysis Plan (SAP), dated 12 July 2019, is provided in Appendix 16.1.9. All data listings, summaries, figures, and statistical analyses were generated using SAS® version 9.4. Tables, figures, and listings were finalised on 19 February 2020.

9.7.1.1. Analysis Populations

Three (3) populations/analysis sets were defined for analysis purposes as described below.

9.7.1.1.1. Full Analysis Set

The Full Analysis Set (FAS) includes randomised subjects who received at least 1 dose of investigational product and had at least 1 evaluable PK parameter. Subjects excluded from the FAS either for Treatment A or Treatment B, also had any data from the corresponding test or reference treatment excluded (the same was true for subjects excluded from the FAS either for Treatment C or Treatment D). In this population, treatment was assigned based upon the treatment subjects actually received regardless of the treatment to which they were randomised. The FAS was used for supportive analyses of the PK endpoints.

9.7.1.1.2. PK Analysis Set

The PK Analysis Set includes randomised subjects who received at least 1 dose of study medication with sufficient data to calculate the PK parameters C_{max} or AUC_{0-t} from any treatment period prior to experiencing a major protocol deviation. A subject could be excluded from the PK Analysis Set for one or more than one treatment period if a protocol violation occurred and was classified as major. Subjects excluded from the PK Analysis Set either for Treatment A or Treatment B, also had any data from the corresponding test or reference treatment excluded (the same was true for subjects excluded from the PK Analysis Set either for Treatment C or Treatment D). Subjects were analysed under the treatment they actually received, as opposed to the treatment to which they were randomised. The PK Analysis Set was the primary analysis set for analyses of the PK endpoints.

9.7.1.1.3. Safety Analysis Set

The Safety Analysis Set includes all randomised subjects who received at least 1 dose of study medication. In this analysis set, treatment was assigned based upon the treatment subjects actually received regardless of the treatment to which they were randomised. The Safety Analysis Set was used for all analyses of safety data.

9.7.1.2. Descriptive Statistics

The number of subjects (n) with non-missing concentrations, mean, SD, CV%, median, Min, and Max were calculated by treatment for all PK parameters.

9.7.1.3. Analysis of Variance (ANOVA)

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. The PK Analysis Set was the primary population for analyses of the PK parameters. The FAS was used to evaluate the impact on the analysis results due to exclusion of subjects from the PK Analysis Set. Therefore, statistical analyses were carried out using the PK Analysis Set as well as the FAS.

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 primary comparisons were A versus B for 17-BMP (without charcoal) and formoterol (without charcoal), and C versus D for formoterol (with charcoal). The geometric mean ratios (GMRs) between Lupin BDP/FF 200/6 mcg will be considered bioequivalent to FOSTAIR 200/6 mcg if 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%.

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

9.7.1.4. Ratio Analysis

The 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 AUC_{0-t} and C_{max} 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) AUC_{0-t} and C_{max} fell within 80.00–125.00%, the respective test product was considered bioequivalent to the reference product.

The relative bioavailability of the test products versus the reference product were estimated by the GMRs.

9.7.1.5. Intra-subject Variability

The intra-subject CV% was computed for PK parameters and AUC_{0-t} and C_{max} for 17-BMP and formoterol.

9.7.2. Determination of Sample Size

A sample size of 94 subjects was estimated to provide an overall power of at least 90% to demonstrate bioequivalence, defined as the 90% CI for the geometric mean test-to-reference AUC_{0-t} ratio and the test-to-reference C_{max} ratio for 17-BMP (without charcoal) and formoterol (with and without charcoal) being contained within 80.00–125.00%. This assumed the underlying test/reference ratios would be in the range of 93–107.5% and intrasubject CV%s of 19% and 26% for AUC_{0-t} and C_{max} of 17-BMP (without charcoal) and 27% and 30% for AUC_{0-t} and C_{max} of formoterol (with and without charcoal), respectively. For the 6 primary comparisons: Test versus Reference for 17-BMP AUC_{0-t} (without charcoal), 17-BMP C_{max} (without charcoal), formoterol AUC_{0-t} (with charcoal), formoterol C_{max} (with charcoal), formoterol AUC_{0-t} (without charcoal), and formoterol C_{max} (without charcoal), the power for each primary comparison is 0.9999, 0.9909, 0.9867, 0.9675, 0.9867, and 0.9675, respectively. Assuming that AUC_{0-t} and C_{max} for plasma 17-BMP (without charcoal) and formoterol (with and without charcoal) would be statistically independent, the overall power is the product of the powers for each of the 6 comparisons.

Estimating a drop-out rate of 15%, approximately 112 subjects (28 subjects per sequence) were to be enrolled in this study to ensure that a minimum of 94 subjects completed all dosing periods and critical assessments.

A total of 112 subjects were enrolled in the study.

9.8. Changes in the Conduct of the Study or Planned Analyses

The study was conducted according to the clinical study protocol dated 13 February 2019. One protocol amendment was issued for this study (prior to any subject being dosed):

Amendment 01, dated 22 March 2019:

- Revised the PK sampling schedule from 23 to 20 samples, revised sample volumes, and revised total blood volume collected during the study
- Corrected that urine pregnancy test (if applicable) was to be collected at the Screening visit, and serum pregnancy test (if applicable) was to be collected on Day -1 of each treatment period and at EOS

- Added additional administrative information to the bioanalytical procedures in Appendix 3
- Revised information for the Bioanalytical Investigator and the Local Safety Monitor

The final study protocol and amendment are provided in Appendix 16.1.1.

There was 1 study-wide deviation from the protocol's planned conduct:

- The protocol sought to enroll no more than 70% of the subjects from either gender. However, the final enrollment of 82 male subjects represented 73.2% of the Safety Population.

10. STUDY SUBJECTS

10.1. Disposition of Subjects

The first subject signed informed consent (first subject first visit) on 30 April 2019, with the first subject receiving study drug on 15 May 2019. The study completed (last subject last visit) on 27 September 2019.

Subject disposition is summarised in Table 7. A total of 112 subjects were enrolled and randomised to one of four treatment sequences, with 102 completing the study.

There were 9 subjects who discontinued from the study, thereby not receiving all assigned treatments:

- Subject [redacted] (randomised to treatment sequence CDBA) discontinued due to an AE of urinary tract infection after treatment period 3, and therefore did not receive Treatment A in period 4.
- Subject [redacted] (randomised to treatment sequence BCAD) withdrew consent (withdrawal by subject) after treatment period 3, and therefore did not receive Treatment D in period 4.
- Subject [redacted] (randomised to treatment sequence ABDC) was discontinued due to "other, withdrawn on medical grounds due to difficulty in cannulation" after the first two PK sample draws in treatment period 1, and therefore did not receive Treatments B, D, and C in periods 2, 3, and 4, respectively.
- Subject [redacted] (randomised to treatment sequence CDBA) was discontinued due to a protocol violation (prohibitory substances consumed/found during frisking) during treatment period 3 prior to study drug administration, and therefore did not receive Treatments B and A in periods 3 and 4, respectively.
- Subject [redacted] (randomised to treatment sequence DACB) withdrew consent (withdrawal by subject) after treatment period 1, and therefore did not receive Treatments A, C, and B in periods 2, 3, and 4, respectively.
- Subject [redacted] (randomised to treatment sequence ABDC) was discontinued due to a protocol violation (breath alcohol test positive) at treatment period 4 check-in, and therefore did not receive Treatment C in period 4.
- Subject [redacted] (randomised to treatment sequence DACB) was discontinued due to an AE of influenza like illness after treatment period 3, and therefore did not receive Treatment B in period 4.
- Subject [redacted] randomised to treatment sequence CDBA) withdrew consent (withdrawal by subject) after treatment period 1, and therefore did not receive Treatments D, B, and A in periods 2, 3, and 4, respectively.
- Subject [redacted] (randomised to treatment sequence DACB) was discontinued due to a protocol violation (breath alcohol test positive) at treatment period 2 check-in, and therefore did not receive Treatments A, C, and B in periods 2, 3, and 4, respectively.

In addition, Subject [redacted] (randomised to treatment sequence CDBA) was discontinued due to an AE of pyrexia on Day 1 of treatment period 4 (prior to the 36 hour PK sample draw; the preceding samples were used to calculate PK parameters for treatment period 4).

Table 7: Summary of Subject Disposition

Category	Treatment Sequence				Total
	ABDC n (%)	BCAD n (%)	CDBA n (%)	DACB n (%)	N
Enrolled	28 (100.0)	28 (100.0)	28 (100.0)	28 (100.0)	112
Completed	26 (92.9)	27 (96.4)	24 (85.7)	25 (89.3)	102
Discontinued	2 (7.1)	1 (3.6)	4 (14.3)	3 (10.7)	10
Adverse event	0	0	2 (7.1)	1 (3.6)	3
Withdrawal by subject	0	1 (3.6)	1 (3.6)	1 (3.6)	3
Protocol violation	1 (3.6)	0	1 (3.6)	1 (3.6)	3
Other	1 (3.6)	0	0	0	1

Abbreviation: N = number of subjects; n = number of subjects in the category.

Note: Percentages were based on the total number of subjects enrolled to each treatment sequence.

Screen failures were not captured in the study database. All study-specific screen failure data were recorded as part of the site's source documentation.

Treatment A = Test Product: Lupin BDP/FF 200/6 mcg – 2 inhalations for a total dose of 400/12 mcg.
Treatment B = Reference Product: FOSTAIR 200/6 mcg – 2 inhalations for a total dose of 400/12 mcg.
Treatment C = Test Product: Lupin BDP/FF 200/6 mcg with oral charcoal – 2 inhalations for a total dose of 400/12 mcg.
Treatment D = Reference Product: FOSTAIR 200/6 mcg with oral charcoal – 2 inhalations for a total dose of 400/12 mcg.

Source: Table 14.1.1.1.

Details of subject disposition are provided in Appendix 16.2.1, Listing 16.2.1. Screen failures were not captured in the study database. All study-specific screen failure data were recorded as part of the site's source documentation.

10.2. Protocol Deviations

Protocol deviations were discussed at the protocol deviation meeting (prior to database lock) to classify the deviations into the category of "major" or "minor" (BDPFF-AS-101 Data Review Meeting Minutes dated 01 October 2019, Appendix 16.1.9). Protocol deviations were defined as "major" if they were likely to affect the primary PK endpoint variables. All other protocol deviations were regarded as "minor". Subjects with major protocol deviations who were excluded from the PK Analysis Set either for Treatment A or Treatment B, also had any data from the corresponding test or reference treatment excluded (the same was true for subjects with major protocol deviations who were excluded from the PK Analysis Set either for Treatment C or Treatment D).

Protocol deviations by subject are provided in Appendix 16.2.2, Listing 16.2.2, and are summarised by treatment and total in Table 8. A total of 98 subjects had 403 protocol deviations, of which 32 were considered major and 371 were considered minor.

Of the deviations, there were PK blood sample collection deviations in 78 (69.6%) subjects; deviations related to drug administration observations in 56 (50.0%) subjects; charcoal administration deviations in 19 (17.0%) subjects; deviations related to protocol non-compliance in 3 (2.7%) subjects; drug administration deviations in 2 (1.8%) subjects; and a sample processing deviation in 1 (0.9%) subject.

Additionally, 1 study-wide deviation is addressed in Section 9.8.

Table 8: Summary of Protocol Deviations by Treatment (Safety Analysis Set)

Deviation Reason, n (%), D	Treatment				Total (N = 112)
	Lupin BDP/FF 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg (Treatment A) (N = 107)	FOSTAIR 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg (Treatment B) (N = 106)	Lupin BDP/FF 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg with Oral Charcoal (Treatment C) (N = 108)	FOSTAIR 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg with Oral Charcoal (Treatment D) (N = 109)	
Subjects with at least 1 deviation	51 (47.7), 94	50 (47.2), 88	52 (48.1), 111	52 (47.7), 110	98 (87.5), 403
Blood sample collection deviation	34 (31.8), 69	44 (41.5), 81	30 (27.8), 51	42 (38.5), 73	78 (69.6), 274
Charcoal administration deviation	0	0	11 (10.2), 25	8 (7.3), 22	19 (17.0), 47
Drug administration deviation	1 (0.9), 1	0	1 (0.9), 1	0	2 (1.8), 2
Drug administration observations	24 (22.4), 24	7 (6.6), 7	33 (30.6), 33	12 (11.0), 12	56 (50.0), 76
Protocol non-compliance	0	0	0	3 (2.8), 3	3 (2.7), 3
Sample processing deviation	0	0	1 (0.9), 1	0	1 (0.9), 1
Major Protocol Deviations	8 (7.5), 8	0	15 (13.9), 15	8 (7.3), 9	27 (24.1), 32
Blood sample collection deviation	0	0	0	1 (0.9), 2	1 (0.9), 2
Drug administration observations	8 (7.5), 8	0	15 (13.9), 15	4 (3.7), 4	24 (21.4), 27
Protocol non-compliance	0	0	0	3 (2.8), 3	3 (2.7), 3

Abbreviation: D = number of deviations.
Note: Subjects with protocol deviations in more than one treatment were only counted once in total.
Source: Table 14.3.8.

There were 32 major protocol deviations in 27 subjects, which are presented in Table 9. Of these, there were 27 deviations related to drug administration observations in 24 subjects, 3 deviations related to protocol non-compliance in 3 subjects, and 2 blood sample collection deviations in 1 subject.

Table 9: Major Protocol Deviations

Subject Number	Treatment/ Treatment Period	Deviation Type	Deviation Description
[redacted]	Treatment C: Lupin BDP/FF 200/6 mcg with Oral Charcoal (treatment period 1)	Drug administration observations	Small aerosol cloud was observed from the canister at the time of 1st inhalation during dosing. Large aerosol cloud was observed from the canister at the time of 2nd inhalation during dosing.
[redacted]	Treatment A: Lupin BDP/FF 200/6 mcg (treatment period 1)	Drug administration observations	Small aerosol cloud was observed from the canister at the time of 1st inhalation during dosing. Large aerosol cloud was observed from the canister at the time of 2nd inhalation during dosing.
[redacted]	Treatment C: Lupin BDP/FF 200/6 mcg with Oral Charcoal (treatment period 1)	Drug administration observations	Large aerosol cloud was observed from the canister at the time of 1st inhalation during dosing. Large aerosol cloud was observed from the canister at the time of 2nd inhalation during dosing.
[redacted]	Treatment A: Lupin BDP/FF 200/6 mcg (treatment period 2)	Drug administration observations	Large aerosol cloud was observed from the canister at the time of 1st inhalation during dosing.
[redacted]	Treatment C: Lupin BDP/FF 200/6 mcg with Oral Charcoal (treatment period 1)	Drug administration observations	Small aerosol cloud was observed from the canister at the time of 1st inhalation during dosing. Large aerosol cloud was observed from the canister at the time of 2nd inhalation during dosing.
[redacted]	Treatment C: Lupin BDP/FF 200/6 mcg with Oral Charcoal (treatment period 1)	Drug administration observations	Small aerosol cloud was observed from the canister at the time of 1st inhalation during dosing. Small aerosol cloud was observed from the canister at the time of 2nd inhalation during dosing.
[redacted]	Treatment D: FOSTAIR 200/6 mcg with Oral Charcoal (treatment period 1)	Drug administration observations	Large aerosol cloud was observed from the canister at the time of 2nd inhalation during dosing.
[redacted]	Treatment D: FOSTAIR 200/6 mcg with Oral Charcoal (treatment period 1)	Drug administration observations	Small aerosol cloud was observed from the canister at the time of 1st inhalation during dosing. Small aerosol cloud was observed from the canister at the time of 2nd inhalation during dosing.
[redacted]	Treatment C: Lupin BDP/FF 200/6 mcg with Oral Charcoal (treatment period 3)	Drug administration observations	Small aerosol cloud was observed from canister at the time of 1st inhalation during dosing. Small aerosol cloud was observed from the canister at the time of 2nd inhalation during dosing. Canister pressed but not released immediately at the time of 2nd inhalation during dosing.

Subject Number	Treatment/ Treatment Period	Deviation Type	Deviation Description
[redacted]	Treatment A: Lupin BDP/FF 200/6 mcg (treatment period 1)	Drug administration observations	Large aerosol cloud was observed from the canister at the time of 2nd inhalation during dosing.
[redacted]	Treatment C: Lupin BDP/FF 200/6 mcg with Oral Charcoal (treatment period 4)	Drug administration observations	Large aerosol cloud was observed from the canister at the time of 1st inhalation during dosing. Small aerosol cloud was observed from the canister at the time of 2nd inhalation during dosing.
[redacted]	Treatment A: Lupin BDP/FF 200/6 mcg (treatment period 3)	Drug administration observations	Small aerosol cloud was observed from the canister at the time of 1st inhalation during dosing. Small aerosol cloud was observed from the canister at the time of 2nd inhalation during dosing.
[redacted]	Treatment C: Lupin BDP/FF 200/6 mcg with Oral Charcoal (treatment period 2)	Drug administration observations	Small aerosol cloud was observed from the canister at the time of 1st inhalation during dosing. Small aerosol cloud was observed from the canister at the time of 2nd inhalation during dosing.
[redacted]	Treatment A: Lupin BDP/FF 200/6 mcg (treatment period 1)	Drug administration observations	Small aerosol cloud was observed from the canister at the time of 1st inhalation during dosing. Small aerosol cloud was observed from the canister at the time of 2nd inhalation during dosing.
[redacted]	Treatment D: FOSTAIR 200/6 mcg with Oral Charcoal (treatment period 3)	Protocol non-compliance	Prohibitory substances were consumed/found during frisking.
[redacted]	Treatment C: Lupin BDP/FF 200/6 mcg with Oral Charcoal (treatment period 2)	Drug administration observations	Small aerosol cloud was observed from the canister at the time of 1st inhalation during dosing. Small aerosol cloud was observed from the canister at the time of 2nd inhalation during dosing.
[redacted]	Treatment C: Lupin BDP/FF 200/6 mcg with Oral Charcoal (treatment period 3)	Drug administration observations	Large aerosol cloud was observed from the canister at the time of 1st inhalation during dosing.
[redacted]	Treatment C: Lupin BDP/FF 200/6 mcg with Oral Charcoal (treatment period 1)	Drug administration observations	Small aerosol cloud was observed from the canister at the time of 1st inhalation during dosing. Small aerosol cloud was observed from the canister at the time of 2nd inhalation during dosing.
[redacted]	Treatment C: Lupin BDP/FF 200/6 mcg with Oral Charcoal (treatment period 4)	Drug administration observations	Small aerosol cloud was observed from the canister at the time of 1st inhalation during dosing. Small aerosol cloud was observed from the canister at the time of 2nd inhalation during dosing.

Subject Number	Treatment/ Treatment Period	Deviation Type	Deviation Description
[redacted]	Treatment C: Lupin BDP/FF 200/6 mcg with Oral Charcoal (treatment period 1)	Drug administration observations	Small aerosol cloud was observed from the canister at the time of 1st inhalation during dosing. Large aerosol cloud was observed from the canister at the time of 2nd inhalation during dosing.
[redacted]	Treatment A: Lupin BDP/FF 200/6 mcg (treatment period 4)	Drug administration observations	Small aerosol cloud was observed from the canister at the time of 2nd inhalation during dosing. Large aerosol cloud was observed from the canister at the time of 1st inhalation during dosing.
[redacted]	Treatment D: FOSTAIR 200/6 mcg with Oral Charcoal (treatment period 3)	Blood sample collection deviation	The 0.06 hour post-dose PK blood draw was not done due to cannula being blocked and difficulty in finding the vein.
[redacted]	Treatment D: FOSTAIR 200/6 mcg with Oral Charcoal (treatment period 3)	Blood sample collection deviation	The 0.10 hour post-dose PK blood draw was not done due to cannula being blocked and difficulty in finding the vein.
[redacted]	Treatment D: FOSTAIR 200/6 mcg with Oral Charcoal (treatment period 4)	Protocol non-compliance	Breath alcohol test positive (value: 30.4) during check-in.
[redacted]	Treatment A: Lupin BDP/FF 200/6 mcg (treatment period 4)	Drug administration observations	Small aerosol cloud was observed from the canister at the time of 1st inhalation during dosing. Small aerosol cloud was observed from the canister at the time of 2nd inhalation during dosing.
[redacted]	Treatment D: FOSTAIR 200/6 mcg with Oral Charcoal (treatment period 2)	Drug administration observations	Large aerosol cloud was observed from the canister at the time of 1st inhalation during dosing.
[redacted]	Treatment C: Lupin BDP/FF 200/6 mcg with Oral Charcoal (treatment period 4)	Drug administration observations	Small aerosol cloud was observed from the canister at the time of 1st and 2nd inhalation during dosing. Subject did not breathe in steadily at the time of 1st and 2nd inhalation during dosing.
[redacted]	Treatment C: Lupin BDP/FF 200/6 mcg with Oral Charcoal (treatment period 1)	Drug administration observations	Small aerosol cloud was observed from the canister at the time of 1st inhalation during dosing. Small aerosol cloud was observed from the canister at the time of 2nd inhalation during dosing.
[redacted]	Treatment A: Lupin BDP/FF 200/6 mcg (treatment period 1)	Drug administration observations	Large aerosol cloud was observed from the canister at the time of 1st inhalation during dosing.
[redacted]	Treatment D: FOSTAIR 200/6 mcg with Oral Charcoal (treatment period 2)	Protocol non-compliance	Breath alcohol test positive (value: 43.8) during check-in.

Subject Number	Treatment/ Treatment Period	Deviation Type	Deviation Description
[redacted]	Treatment C: Lupin BDP/FF 200/6 mcg with Oral Charcoal (treatment period 1)	Drug administration observations	Small aerosol cloud was observed from the canister at the time of 1st inhalation during dosing. Small aerosol cloud was observed from the canister at the time of 2nd inhalation during dosing.
[redacted]	Treatment D: FOSTAIR 200/6 mcg with Oral Charcoal (treatment period 3)	Drug administration observations	Small aerosol cloud was observed from the canister at the time of 1st inhalation during dosing. Small aerosol cloud was observed from the canister at the time of 2nd inhalation during dosing.

Source: Appendix 16.2.2, Listing 16.2.2; BDPFF-AS-101 Data Review Meeting Minutes dated 01 October 2019, Appendix 16.1.9.

When looking at the number of aerosol clouds observed and the relative imbalance across the test and reference products, one possibility is that by subjects not properly coordinating inhalation with actuation and thereby effectively blocking the actuator mouthpiece when a spray is fired, this led to the spray evaporating inside the main body of the actuator and then escaping from the actuator top opening. The evaporation of aerosol spray, which contains ethanol, may be less complete inside the test product (Treatment A or Treatment C) actuator than the reference product (Treatment B or Treatment D) actuator. This could lead to a tendency to observe aerosol cloud from the test product more so than the reference product.

11. PHARMACOKINETICS

11.1. Data Sets Analysed

Three population/analysis sets were defined for analysis purposes in Section 9.7.1.1, and are summarised in Table 10.

Subjects who withdrew early from the study (Section 10.1) and did not provide evaluable data for Treatment A or Treatment B, the test and reference treatment respectively for the without charcoal comparison, were excluded from the FAS for both Treatment A and Treatment B (these include Subjects [redacted]). Also, subjects who withdrew early from the study and did not provide evaluable data for Treatment C or Treatment D, the test and reference treatment respectively for the with charcoal comparison, were excluded from the FAS for both Treatment C and Treatment D (these include Subjects [redacted]).

Subjects who had a major protocol deviation (Table 9) or withdrew early from the study and did not provide evaluable data for Treatment A or Treatment B, the test and reference treatment respectively for the without charcoal comparison, were excluded from the PK Analysis Set for both Treatment A and Treatment B (these include Subjects [redacted]). Also, subjects who had a major protocol deviation or withdrew early from the study and did not provide evaluable data for Treatment C or Treatment D, the test and reference treatment respectively for the with charcoal comparison, were excluded from the PK Analysis Set for both Treatment C and Treatment D (these include Subjects [redacted]. Additionally, Subject [redacted] was excluded from the PK Analysis Set for both Treatment C and Treatment D due to the inability to quantify all formoterol samples, resulting in no data points for estimation of PK parameters.

Subjects excluded from the PK Analysis Set are presented in Appendix 16.2.3, Listing 16.2.3.

Table 10: Summary of Analysis Sets by Treatment

Analysis Set	Treatment				Total N
	Lupin BDP/FF 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg (Treatment A) n (%)	FOSTAIR 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg (Treatment B) n (%)	Lupin BDP/FF 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg with Oral Charcoal (Treatment C) n (%)	FOSTAIR 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg with Oral Charcoal (Treatment D) 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

Note: Percentages are based on the total number of subjects in the Safety Analysis Set.
Source: Table 14.1.4.

11.2. Demographic and Other Baseline Characteristics

11.2.1. Demographic Characteristics

The demographic data (sex, race, ethnicity, age, weight, height, BMI) for subjects by treatment sequence and overall are summarised in Table 11. Overall, more subjects were male (73.2%) than female (26.8%). All subjects included in the study were of Asian race and of unknown descent. Overall, the average age of the subjects was 28.4 years. The average weight, height, and BMI were 63.92 kg, 164.4 cm, and 23.73 kg/m^2, respectively.

No inferential analyses were performed on the demographic data.

Demographic data for the FAS are summarised in post-text Table 14.1.2.3, and in post-text Table 14.1.2.2 for the PK Analysis Set. Individual subject demographic data are provided in Appendix 16.2.4, Listing 16.2.4.1.

Table 11: Summary of Demographic Characteristics by Treatment Sequence and Overall (Safety Analysis Set)

Characteristic	Treatment Sequence				Overall (N = 112)
	ABDC (N=28)	BCAD (N=28)	CDBA (N=28)	DACB (N=28)	
Sex, n (%)					
Male	21 (75.0)	20 (71.4)	21 (75.0)	20 (71.4)	82 (73.2)
Female	7 (25.0)	8 (28.6)	7 (25.0)	8 (28.6)	30 (26.8)
Race, n (%)					
Asian	28 (100.0)	28 (100.0)	28 (100.0)	28 (100.0)	112 (100.0)
Ethnicity, n (%)					
Unknown	28 (100.0)	28 (100.0)	28 (100.0)	28 (100.0)	112 (100.0)
Age (years)					
Mean (SD)	28.5 (5.7)	29.1 (5.0)	28.3 (6.0)	27.6 (6.2)	28.4 (5.7)
Median (Min, Max)	30 (21, 42)	29 (19, 40)	29 (18, 39)	27 (20, 44)	28 (18, 44)
Weight (kg)					
Mean (SD)	64.02 (7.06)	61.45 (7.22)	64.04 (9.06)	66.19 (8.44)	63.92 (8.06)
Median (Min, Max)	64.4 (51.5, 74.2)	62.8 (50.2, 75.5)	64.1 (50.3, 83.1)	64.6 (54.1, 84.9)	63.2 (50.2, 84.9)
Height (cm)					
Mean (SD)	165.2 (8.6)	164.5 (8.2)	164.5 (9.0)	163.4 (8.6)	164.4 (8.5)
Median (Min, Max)	166 (146, 181)	164 (145, 180)	168 (144, 175)	166 (144, 180)	165 (144, 181)
BMI (kg/m^2)					
Mean (SD)	23.57 (3.05)	22.78 (2.92)	23.68 (2.89)	24.90 (3.45)	23.73 (3.14)
Median (Min, Max)	23.5 (18.7, 29.8)	22.5 (18.6, 29.9)	23.7 (18.7, 29.2)	24.9 (18.6, 29.8)	23.4 (18.6, 29.9)

Note: Percentages were based on the number of subjects randomised to each treatment sequence, and overall.

Treatment A = Test Product: Lupin BDP/FF 200/6 mcg – 2 inhalations for a total dose of 400/12 mcg.
Treatment B = Reference Product: FOSTAIR 200/6 mcg – 2 inhalations for a total dose of 400/12 mcg.
Treatment C = Test Product: Lupin BDP/FF 200/6 mcg with oral charcoal – 2 inhalations for a total dose of 400/12 mcg.
Treatment D = Reference Product: FOSTAIR 200/6 mcg with oral charcoal – 2 inhalations for a total dose of 400/12 mcg.

Source: Table 14.1.2.1.

11.2.2. Other Baseline Characteristics

Individual subject eligibility for all enrolled subjects is presented in Appendix 16.2.5, Listing 16.2.5.2.

Screen failures were not captured in the study database. All study-specific screen failure data were recorded as part of the site's source documentation.

11.2.2.1. Medical History, Electrocardiography, and Physical Examination Findings

No subject had any clinically relevant medical history, ECG, or physical examination findings at baseline.

Medical history findings are summarised in post-text Table 14.1.6, and individual medical and surgical history is provided in Appendix 16.2.4, Listing 16.2.4.2. Electrocardiogram baseline data are summarised in post-text Table 14.3.6.1, ECG overall interpretation at baseline in post-text Table 14.3.6.2, and individual ECG parameters and overall interpretation are presented in Appendix 16.2.10, Listing 16.2.10.2. Abnormal physical examination findings at baseline are summarised in post-text Table 14.1.5 (also reference Appendix 16.1.1, Note to File re: Data Table 14.1.5 Error, dated 27-Feb-2020). Individual abnormal physical examinations are provided in Appendix 16.2.10, Listing 16.2.10.1.

11.2.2.2. Prior and Concomitant Therapy

Prior to being enrolled in the study, no subject reported prior medication use or any history of ongoing medication at the time of the Screening visit.

Concomitant medications that were administered after the first dose of study drug are as follows:

- Subject [redacted] (sequence CDBA) was administered ferrous ascorbate (equivalent to elemental iron + folic acid) for haemoglobin decreased in treatment period 4.
- Subject [redacted] (sequence CDBA) was administered dexamethasone, tramadol, paracetamol, norfloxacin lactic acid bacillus, ranitidine, and diclofenac for urinary tract infection in treatment period 3; and ferrous ascorbate + folic acid + zinc for haemoglobin decreased in treatment period 3.
- Subject [redacted] (sequence BCAD) was administered norfloxacin for urine analysis abnormal in treatment period 4.
- Subject [redacted] (sequence CDBA) was administered paracetamol for pharyngitis in treatment period 3.
- Subject [redacted] sequence ABDC) was administered an oral rehydration solution (ORS) for diarrhoea in treatment period 4.
- Subject [redacted] (sequence DACB) was administered paracetamol (intravenous and oral), and paracetamol + chlorpheniramine maleate + phenylephrine for influenza like illness in treatment period 3.
- Subject [redacted] (sequence CDBA) was administered paracetamol for pyrexia in treatment period 4.

- Subject [redacted] (sequence CDBA) was administered lactobacillus for diarrhoea in treatment period 1.
- Subject [redacted] (sequence ABDC) was administered paracetamol + ibuprofen for swelling arm in treatment period 3.

None of the concomitant medications are expected to alter PK of study drug. Prior and concomitant medications are summarised by therapeutic class and preferred term in post-text Table 14.3.9, and provided by subject in Appendix 16.2.9, Listing 16.2.9.1.

11.2.2.3. Other Screening and Baseline Observations

Individual substance use history is provided in Appendix 16.2.4, Listing 16.2.4.3.

Results of urine drug screen (Appendix 16.2.8, Listing 16.2.8.6), urine cotinine tests (Appendix 16.2.8, Listing 16.2.8.7), and breath alcohol tests (Appendix 16.2.8, Listing 16.2.8.8) were negative for all enrolled subjects.

Results of all serological tests (HIV, Hepatitis B and C virus, and syphilis) were negative for all subjects (Appendix 16.2.8, Listing 16.2.8.5).

Results of urine pregnancy tests were negative for all female subjects at the Screening visit, and serum pregnancy tests were negative for all female subjects at check-in on Day -1 of treatment periods 1, 2, 3, and 4, and at EOS (Appendix 16.3).

All subjects demonstrated proper inhaler technique using the AIM device and the training placebo (HFA-134a) pressurised inhalation solution at the Screening visit and on Day -1 of treatment periods 1, 2, 3, and 4 (Appendix 16.2.8, Listing 16.2.5.3).

11.3. Measurements of Treatment Compliance

For information on measurements of treatment compliance, please refer to Section 9.4.8.

Subjects were trained using the AIM device, and their ability to achieve a "good" reading was confirmed to ensure the subjects demonstrated proper inhalation technique.

Subjects were also provided training on a placebo (HFA-134a) pressurised inhalation solution containing only propellant with no active drug prior to administration of the study drug in each treatment period. Demonstration of proper inhalation technique was documented at each treatment visit.

Details of individual investigational product administration times are provided in Appendix 16.2.5, Listing 16.2.5.4, and charcoal administration data are provided in Appendix 16.2.5, Listing 16.2.5.5. All subjects received assigned treatments per the randomisation schedule according to the protocol under supervision of the clinical staff and QA auditor.

Meal times are presented in Appendix 16.2.5, Listing 16.2.5.8. All meals were identical during each treatment period and were provided as planned after study drug administration.

There were 76 deviations related to drug administration observations in 56 subjects, 47 charcoal administration deviations in 19 subjects, and 2 drug administration deviations in 2 subjects.

Additionally, there were 274 PK blood sample collection deviations in 78 subjects, 3 deviations related to protocol non-compliance in 3 subjects, and 1 sample processing deviation in 1 subject.

Refer to Section 10.2 for a summary of protocol deviations.

11.4. Pharmacokinetic Results and Tabulations of Individual Subject Data

11.4.1. Analysis of Pharmacokinetics

11.4.1.1. Analysis of Pharmacokinetics for Beclometasone-17-Monopropionate (17-BMP)

The bioanalysis was performed at Lupin Bioresearch Center [redacted] as described in Section 9.5.3. The PK parameters of 17-BMP were determined by noncompartmental methods using Phoenix® WinNonlin® version 8.0 (Pharsight Corporation, USA).

Primary analyses of the PK parameters are based upon the PK Analysis Set. The FAS was used as the supportive analysis set for PK analyses of 17-BMP.

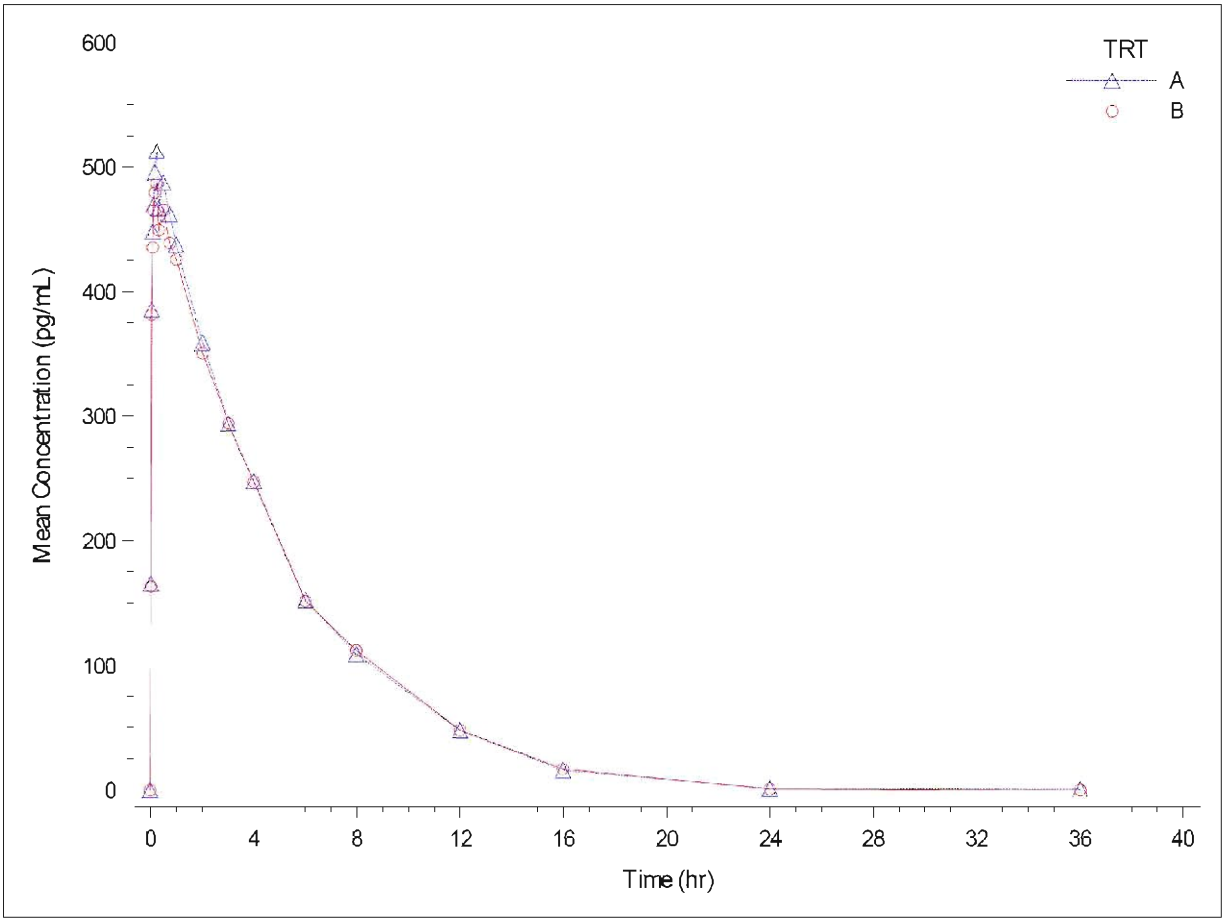
11.4.1.1.1. Plasma Concentration Data for 17-BMP

Plasma concentrations of 17-BMP for individual subjects in the FAS are provided in Appendix 16.2.5, Listing 16.2.5.9.1 for the test product Lupin BDP/FF 200/6 mcg (Treatment A), and in Appendix 16.2.5, Listing 16.2.5.9.2 for the reference product FOSTAIR 200/6 mcg (Treatment B). Figures of Treatment A and Treatment B 17-BMP concentration versus time profiles for 0–36 hours for individual subjects are presented on a linear scale and a semi-log scale for the FAS in Appendix 16.2.6, Figure 16.2.6.5.1 and Appendix 16.2.6, Figure 16.2.6.5.2, respectively, and for 0–2 hours in Appendix 16.2.6, Figure 16.2.6.5.3 and Appendix 16.2.6, Figure 16.2.6.5.4. Individual PK blood sample collection times are provided in Appendix 16.2.5, Listing 16.2.5.7.

Summary statistics for 17-BMP plasma concentration data for Treatments A and B are presented in post-text Table 14.2.1.1 for the PK Analysis Set, and in post-text Table 14.2.1.2 for the FAS.

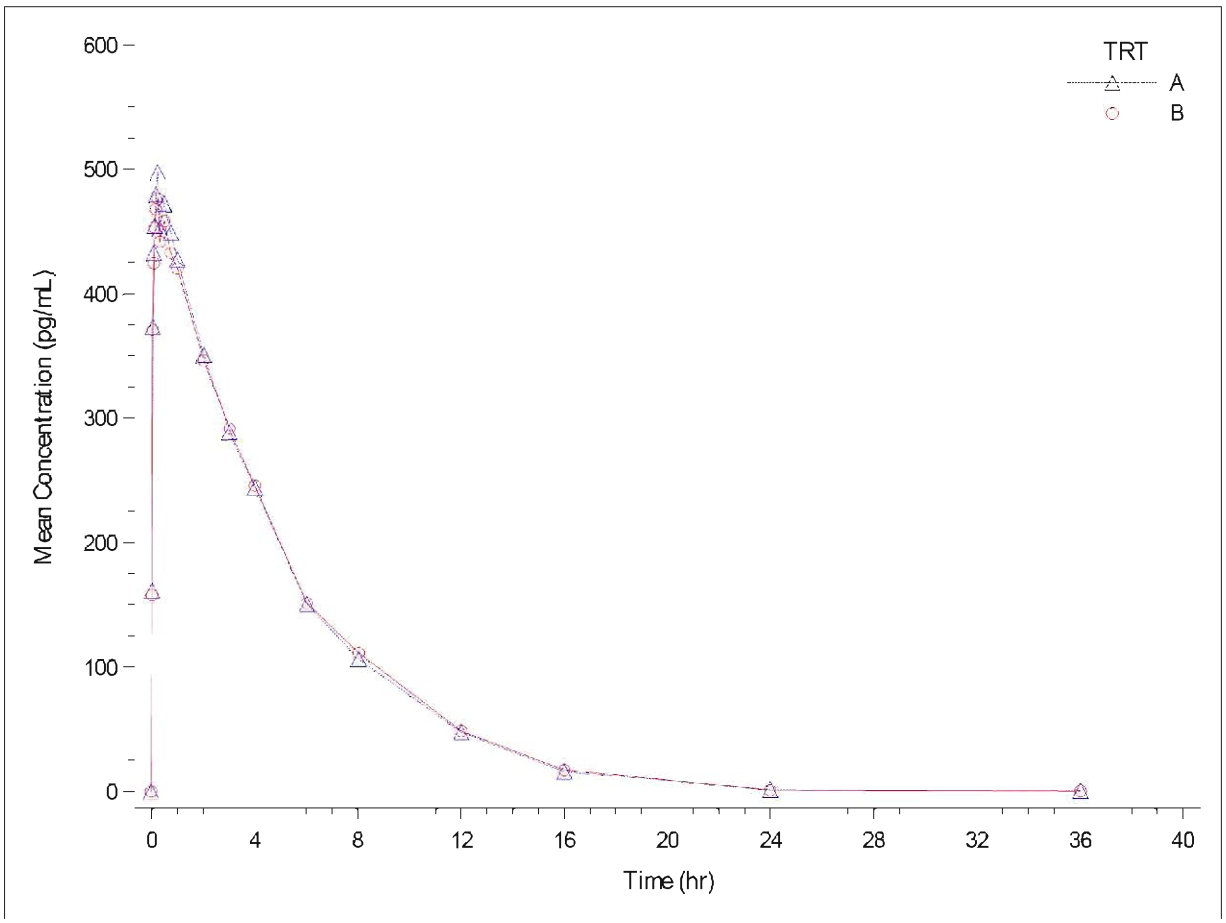
For Treatments A and B, the mean observed plasma concentration of 17-BMP versus time profiles are presented for 0–36 hours in Figure 1 and Figure 2 for the PK Analysis Set and the FAS, respectively, and for 0–2 hours in Figure 3 and Figure 4 for the PK Analysis Set and the FAS, respectively. On average, the mean observed 17-BMP plasma concentrations for the test product Lupin BDP/FF 200/6 mcg (Treatment A) were similar to the reference product FOSTAIR 200/6 mcg (Treatment B) for both the PK Analysis Set and the FAS.

Figure 1: Arithmetic Mean 17-BMP Plasma Concentration versus Time Profiles by Treatment, 0–36 Hours (Linear Scale) (PK Analysis Set)



Note: For the calculation of summary statistics, values that were below the limit of quantification (BLQ) were treated as zero (0).
The following subjects were excluded from the PK Analysis Set for both Treatments A and B (see Section 11.1 for details): Subjects [redacted].
Treatment A = Test Product: Lupin BDP/FF 200/6 mcg – 2 inhalations for a total dose of 400/12 mcg.
Treatment B = Reference Product: FOSTAIR 200/6 mcg – 2 inhalations for a total dose of 400/12 mcg.
Source: Figure 14.2.2.1.1.

Figure 2: Arithmetic Mean 17-BMP Plasma Concentration versus Time Profiles by Treatment, 0–36 Hours (Linear Scale) (FAS)



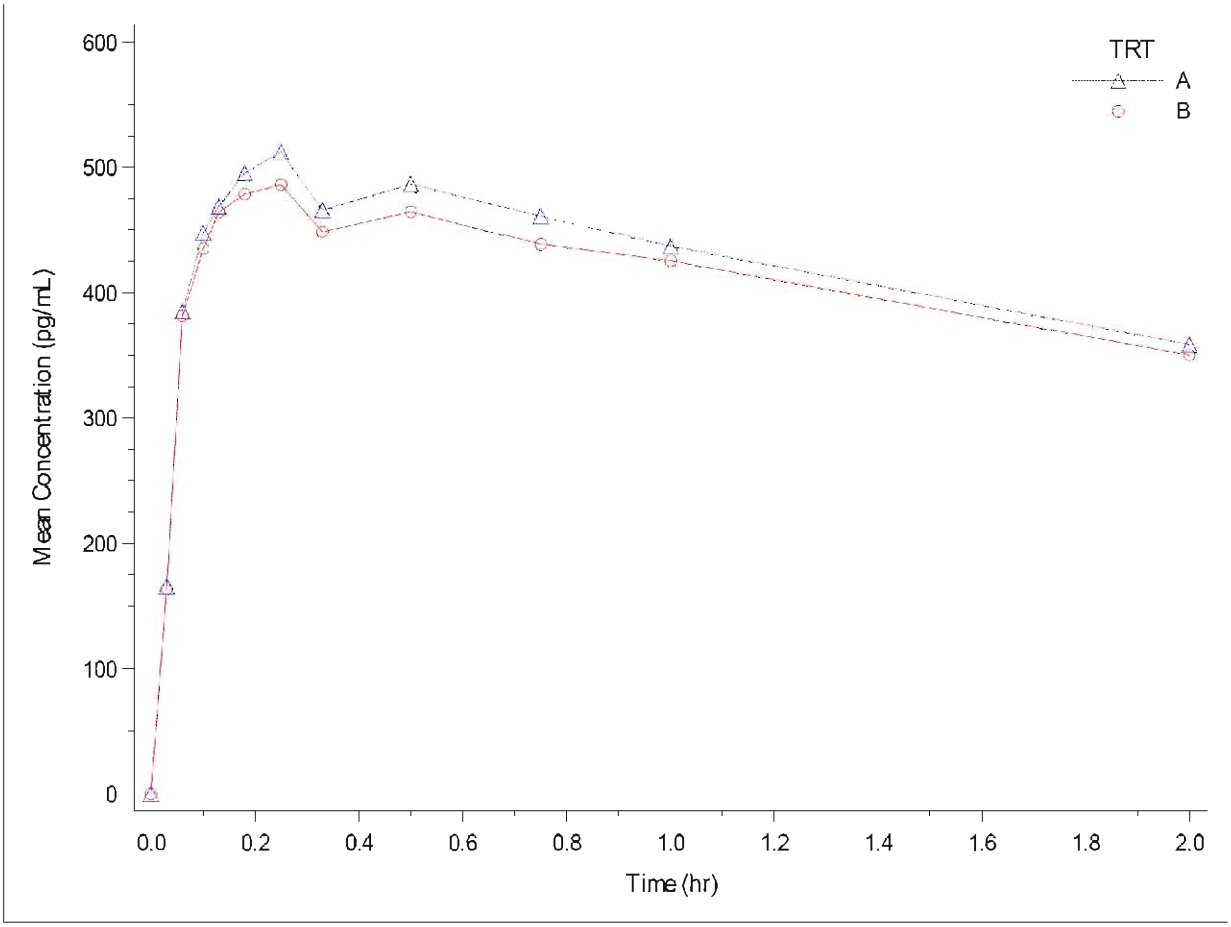
Note: For the calculation of summary statistics, values that were below the limit of quantification (BLQ) were treated as zero (0).

The following subjects were excluded from the FAS for both Treatments A and B (see Section 11.1 for details):
Subjects [redacted].

Treatment A = Test Product: Lupin BDP/FF 200/6 mcg – 2 inhalations for a total dose of 400/12 mcg.
Treatment B = Reference Product: FOSTAIR 200/6 mcg – 2 inhalations for a total dose of 400/12 mcg.

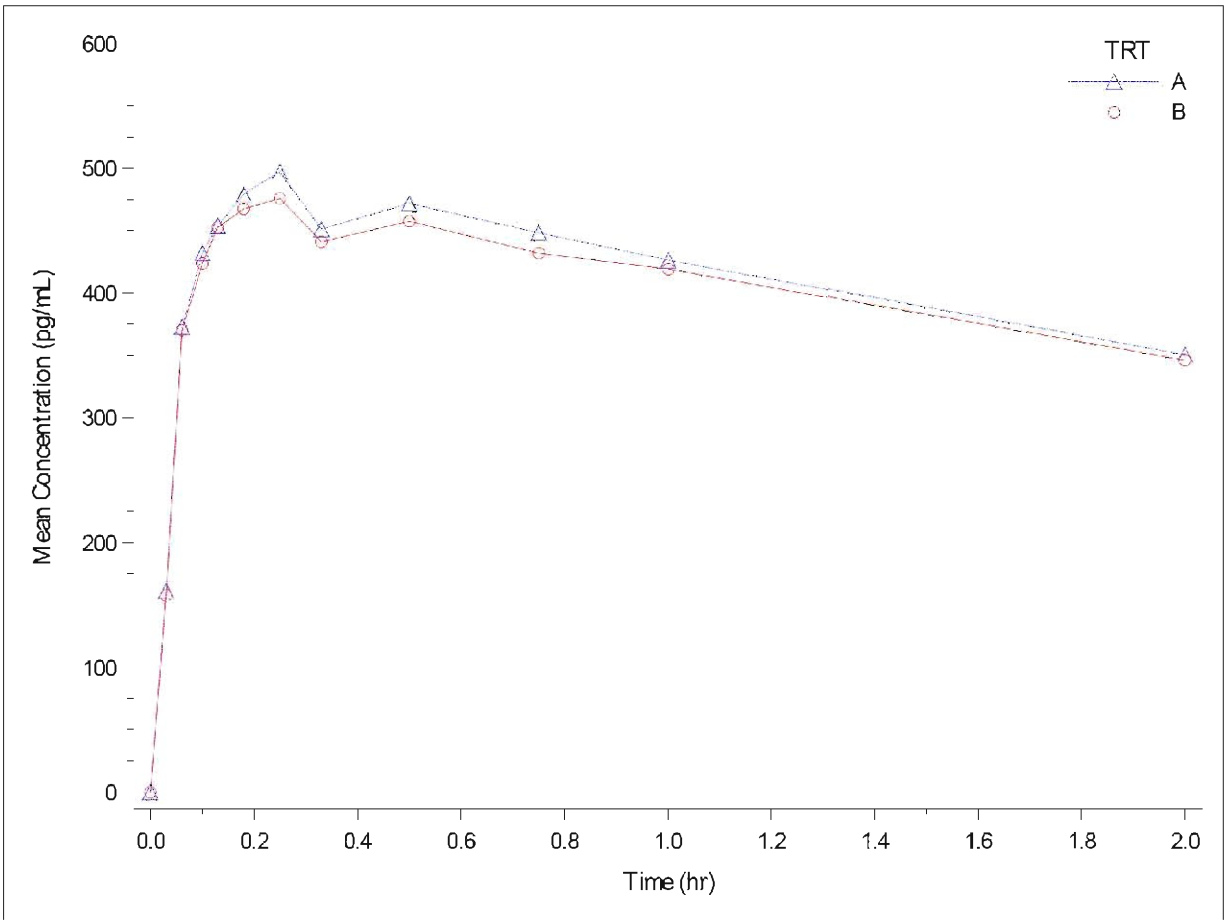
Source: Figure 14.2.2.1.7.

Figure 3: Arithmetic Mean 17-BMP Plasma Concentration versus Time Profiles by Treatment, 0–2 Hours (Linear Scale) (PK Analysis Set)



Note: For the calculation of summary statistics, values that were below the limit of quantification (BLQ) were treated as zero (0).
The following subjects were excluded from the PK Analysis Set for both Treatments A and B (see Section 11.1 for details):
Subjects [redacted]
Treatment A = Test Product: Lupin BDP/FF 200/6 mcg – 2 inhalations for a total dose of 400/12 mcg.
Treatment B = Reference Product: FOSTAIR 200/6 mcg – 2 inhalations for a total dose of 400/12 mcg.
Source: Figure 14.2.2.1.5.

Figure 4: Arithmetic Mean 17-BMP Plasma Concentration versus Time Profiles by Treatment, 0–2 Hours (Linear Scale) (FAS)



Note: For the calculation of summary statistics, values that were below the limit of quantification (BLQ) were treated as zero (0).

The following subjects were excluded from the FAS for both Treatments A and B (see Section 11.1 for details):
Subjects [redacted].

Treatment A = Test Product: Lupin BDP/FF 200/6 mcg – 2 inhalations for a total dose of 400/12 mcg.
Treatment B = Reference Product: FOSTAIR 200/6 mcg – 2 inhalations for a total dose of 400/12 mcg.

Source: Figure 14.2.2.1.11.

11.4.1.1.2. Pharmacokinetic Parameter Data for 17-BMP

Plasma 17-BMP PK parameters for individual subjects are provided in Appendix 16.2.6, Listing 16.2.6.2.1 (Treatment A) and Appendix 16.2.6, Listing 16.2.6.2.2 (Treatment B) for the FAS. Treatment A versus Treatment B arithmetic ratios of 17-BMP PK parameters for individual subjects are provided in Appendix 16.2.6, Listing 16.2.6.4.1, Listing 16.2.6.4.2, and Listing 16.2.6.4.3 for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$, respectively. Summary statistics for Treatment A versus Treatment B arithmetic ratios are presented for the PK Analysis Set in Appendix 16.2.6, Listing 16.2.6.4.13, Listing 16.2.6.4.14, and Listing 16.2.6.4.15 for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$, respectively; and for the FAS in Appendix 16.2.6, Listing 16.2.6.4.25, Listing 16.2.6.4.26, and Listing 16.2.6.4.27. Details of the results of the statistical methods used in this study are provided in Appendix 16.1.9.

Summary statistics of the PK parameter data for 17-BMP are presented in Table 12 for the PK Analysis Set.

The geometric mean plasma C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ of 17-BMP were similar after inhalation with Treatment A (533.0313 pg/mL, 2306.4954 pg×hr/mL, and 2621.4820 pg×hr/mL, respectively) and Treatment B (523.2420 pg/mL, 2309.9321 pg×hr/mL, and 2605.4783 pg×hr/mL, respectively) 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.

Table 12: Summary of PK Parameters for 17-BMP Following Oral Inhalation Administration of Study Drug, by Treatment (PK Analysis Set)

Parameter (unit)	Statistic	Treatments	
		Lupin BDP/FF 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg (Treatment A)	FOSTAIR 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg (Treatment B)
C_{max} (pg/mL)	N	97	97
	Mean (SD)	602.9960 (307.4615)	579.7414 (266.5610)
	CV%	50.99	45.98
	Geometric mean	533.0313	523.2420
AUC_{0-t} (pg×hr/mL)	N	97	97
	Mean (SD)	2518.3756 (1068.0521)	2486.6713 (961.2931)
	CV%	42.41	38.66
	Geometric mean	2306.4954	2309.9321
$AUC_{0-\infty}$ (pg×hr/mL)	N	92	92
	Mean (SD)	2793.6792 (1053.3647)	2749.1034 (953.1493)
	CV%	37.71	34.67
	Geometric mean	2621.4820	2605.4783

Parameter (unit)	Statistic	Treatments	
		Lupin BDP/FF 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg (Treatment A)	FOSTAIR 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg (Treatment B)
t_{max} (hour)	N	97	97
	Mean (SD)	0.4804 (0.5792)	0.4862 (0.8682)
	Median	0.255	0.254
	Min, Max	0.060, 4.008	0.060, 8.003
$t_{½}$ (hour)	N	95	95
	Mean (SD)	3.8680 (0.9524)	3.7421 (0.8213)
	Median	3.677	3.625
	Min, Max	2.453, 7.660	2.224, 6.865
K_{el} (1/hour)	N	95	95
	Mean (SD)	0.1884 (0.0397)	0.1931 (0.0385)
	Median	0.189	0.191
	Min, Max	0.090, 0.283	0.101, 0.312
$AUC_{\%Extrap\ obs}$ (%)	N	95	95
	Mean (SD)	8.9057 (4.3363)	8.3022 (3.7311)
	Median	7.669	7.612
	Min, Max	3.276, 27.211	3.423, 24.335

Note: For profiles where R^2 <0.8 in the calculation of K_{el} (Subjects [redacted] for Treatment A, and Subjec[redacted] for Treatment B), the interval was not assigned and the values of $AUC_{0-\infty}$, $t_{½}$, and $AUC_{\%Extrap\ obs}$ reported as missing and not included in the calculation of summary statistics.

The following subjects were excluded from the PK Analysis Set for both Treatments A and B (see Section 11.1 for details): Subjects [redacted].

Source: Table 14.2.1.7.

Summary statistics of the PK parameter data for 17-BMP are presented in Table 13 for the FAS. The results for the FAS were comparable to those of the PK Analysis Set.

The geometric mean plasma C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ of 17-BMP were similar after inhalation with Treatment A (513.0491 pg/mL, 2253.8320 pg×hr/mL, and 2580.0087 pg×hr/mL, respectively) and Treatment B (508.9718 pg/mL, 2289.9579 pg×hr/mL, and 2581.7652 pg×hr/mL, respectively) for the FAS.

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

The median $t_{½}$ was 3.712 hours for Treatment A and 3.643 hours for Treatment B.

The median K_{el} was 0.187 $hour^{-1}$ for Treatment A and 0.190 $hour^{-1}$ for Treatment B.

Table 13: Summary of PK Parameters for 17-BMP Following Oral Inhalation Administration of Study Drug, by Treatment (FAS)

Parameter (unit)	Statistic	Treatments	
		Lupin BDP/FF 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg (Treatment A)	FOSTAIR 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg (Treatment B)
C_{max} (pg/mL)	N	105	105
	Mean (SD)	582.9229 (305.2909)	565.4190 (264.5807)
	CV%	52.37	46.79
	Geometric mean	513.0491	508.9718
AUC_{0-t} (pg×hr/mL)	N	105	105
	Mean (SD)	2464.2827 (1057.3434)	2465.6708 (955.8570)
	CV%	42.91	38.77
	Geometric mean	2253.8320	2289.9579
$AUC_{0-\infty}$ (pg×hr/mL)	N	99	99
	Mean (SD)	2748.1564 (1038.2325)	2728.1241 (954.4193)
	CV%	37.78	34.98
	Geometric mean	2580.0087	2581.7652
t_{max} (hour)	N	105	105
	Mean (SD)	0.4712 (0.5643)	0.4924 (0.8369)
	Median	0.254	0.254
	Min, Max	0.060, 4.008	0.060, 8.003
$t_{½}$ (hour)	N	103	103
	Mean (SD)	3.8544 (0.9390)	3.7389 (0.7939)
	Median	3.712	3.643
	Min, Max	2.028, 7.660	2.224, 6.865
K_{el} (1/hour)	N	103	103
	Mean (SD)	0.1892 (0.0414)	0.1928 (0.0373)
	Median	0.187	0.190
	Min, Max	0.090, 0.342	0.101, 0.312
$AUC_{\%Extrap\ obs}$ (%)	N	103	103
	Mean (SD)	9.0936 (4.4223)	8.3967 (3.7109)
	Median	7.714	7.695
	Min, Max	3.276, 27.211	3.423, 24.335

Note: For profiles where R^2 <0.8 in the calculation of K_{el} (Subjects [redacted] for Treatment A, and Subject [redacted] for Treatment B), the interval was not assigned and the values of $AUC_{0-\infty}$, $t_{½}$, and $AUC_{\%Extrap\ obs}$ reported as missing and not included in the calculation of summary statistics.

The following subjects were excluded from the FAS for both Treatments A and B (see Section 11.1 for details):
Subjects [redacted]

Source: Table 14.2.1.8.

For Treatment A, there were 4 subjects with $AUC_{\%Extrap\ obs}$ >20% (Subjects [redacted] and 111; Appendix 16.2.6, Listing 16.2.6.2.1). For Treatment B, there was 1 subject with $AUC_{\%Extrap\ obs}$ >20% (Subject 003; Appendix 16.2.6, Listing 16.2.6.2.2). The analysis of $AUC_{0-\infty}$ for both the PK Analysis Set and the FAS excluded subjects from both the test and reference treatments in treatment periods where $AUC_{\%Extrap\ obs}$ was >20%for either test or reference.

11.4.1.1.3. Statistical Analysis of Pharmacokinetic Parameters for 17-BMP

11.4.1.1.3.1. PK Analysis Set

The ANOVA model described in Section 9.7.1.3 was performed on the primary PK parameters (C_{max} and AUC_{0-t}) to assess the bioequivalence criteria of 17-BMP for Lupin BDP/FF 200/6 mcg (Treatment A) versus FOSTAIR 200/6 mcg (Treatment B). The ANOVA results including the GMR and 90% CI for 17-BMP C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ PK parameters are presented in Table 14 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%.

Table 14: Summary of Statistical Comparisons of Plasma 17-BMP Pharmacokinetic Parameters C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ (PK Analysis Set)

Parameter (unit)	Lupin BDP/FF 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg (Treatment A) GLSM	FOSTAIR 200/6 mcg (2 inhalations) Total Dose = 400/12 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

The following subjects were excluded from the PK Analysis Set for both Treatments A and B (see Section 11.1 for details): Subjects [redacted]

Source: Table 14.2.1.13.

11.4.1.1.3.2. Full Analysis Set

The ANOVA results including the GMR and 90% CI for 17-BMP C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ PK parameters for Lupin BDP/FF 200/6 mcg (Treatment A) versus FOSTAIR 200/6 mcg (Treatment B) are presented in Table 15 for the FAS and were similar to the PK Analysis Set.

Treatment A GLSM was essentially the same as Treatment B for 17-BMP C_{max} and $AUC_{0-\infty}$, respectively, and was approximately 2% lower 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%.

Table 15: Summary of Statistical Comparisons of Plasma 17-BMP Pharmacokinetic Parameters C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ (FAS)

Parameter (unit)	Lupin BDP/FF 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg (Treatment A)	FOSTAIR 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg (Treatment B)	GMR (90% CI) A vs B	Intrasubject CV% A vs B
	GLSM	GLSM		
C_{max} (pg/mL)	511.6943	509.8596	100.36 (94.64, 106.43)	25.96
AUC_{0-t} (pg×hr/mL)	2251.3619	2290.3890	98.30 (93.41, 103.44)	22.47
$AUC_{0-\infty}$ (pg×hr/mL)	2576.9916	2582.3048	99.79 (95.40, 104.39)	19.08

The following subjects were excluded from the FAS for both Treatments A and B (see Section 11.1 for details):
Subjects [redacted]
Source: Table 14.2.1.14.

11.4.1.2. Analysis of Pharmacokinetics for Formoterol

The bioanalysis was performed at Lupin Bioresearch Center [redacted] as described in Section 9.5.3. The PK parameters of formoterol were determined by noncompartmental methods using Phoenix® WinNonlin® version 8.0 (Pharsight Corporation, USA).

Primary analyses of the PK parameters are based upon the PK Analysis Set. The FAS was used as the supportive analysis set for PK analyses of formoterol.

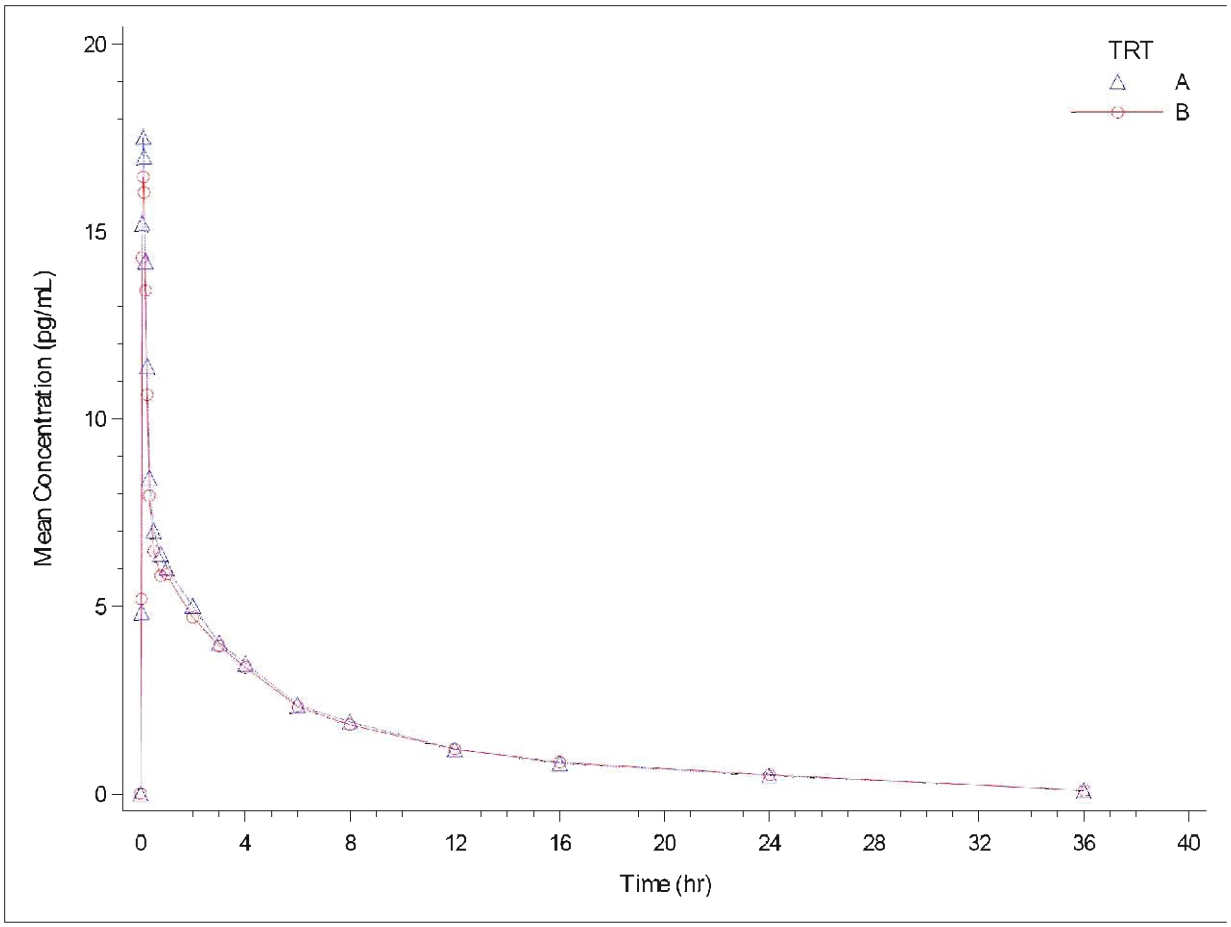
11.4.1.2.1. Plasma Concentration Data for Formoterol

Plasma concentrations of formoterol for individual subjects in the FAS are provided in Appendix 16.2.5, Listing 16.2.5.9.3 for the test product Lupin BDP/FF 200/6 mcg (Treatment A), Appendix 16.2.5, Listing 16.2.5.9.4 for the reference product FOSTAIR 200/6 mcg (Treatment B), Appendix 16.2.5, Listing 16.2.5.9.5 for the test product Lupin BDP/FF 200/6 mcg with oral charcoal (Treatment C), and in Appendix 16.2.5, Listing 16.2.5.9.6 for the reference product FOSTAIR 200/6 mcg with oral charcoal (Treatment D). Figures of Treatment A and Treatment B formoterol concentration versus time profiles for 0–36 hours for individual subjects are presented on a linear scale and a semi-log scale for the FAS in Appendix 16.2.6, Figure 16.2.6.5.5 and Appendix 16.2.6, Figure 16.2.6.5.6, respectively; and for 0–2 hours in Appendix 16.2.6, Figure 16.2.6.5.7 and Appendix 16.2.6, Figure 16.2.6.5.8. Figures of Treatment C and Treatment D formoterol with oral charcoal concentration versus time profiles for 0–36 hours for individual subjects are presented on a linear scale and a semi-log scale for the FAS in Appendix 16.2.6, Figure 16.2.6.5.9 and Appendix 16.2.6, Figure 16.2.6.5.10, respectively; and for 0–2 hours in Appendix 16.2.6, Figure 16.2.6.5.11 and Appendix 16.2.6, Figure 16.2.6.5.12. Individual PK blood sample collection times are provided in Appendix 16.2.5, Listing 16.2.5.7.

Summary statistics for formoterol plasma concentration data for Treatments A, B, C, and D are presented in post-text Table 14.2.1.3 for the PK Analysis Set, and in post-text Table 14.2.1.4 for the FAS.

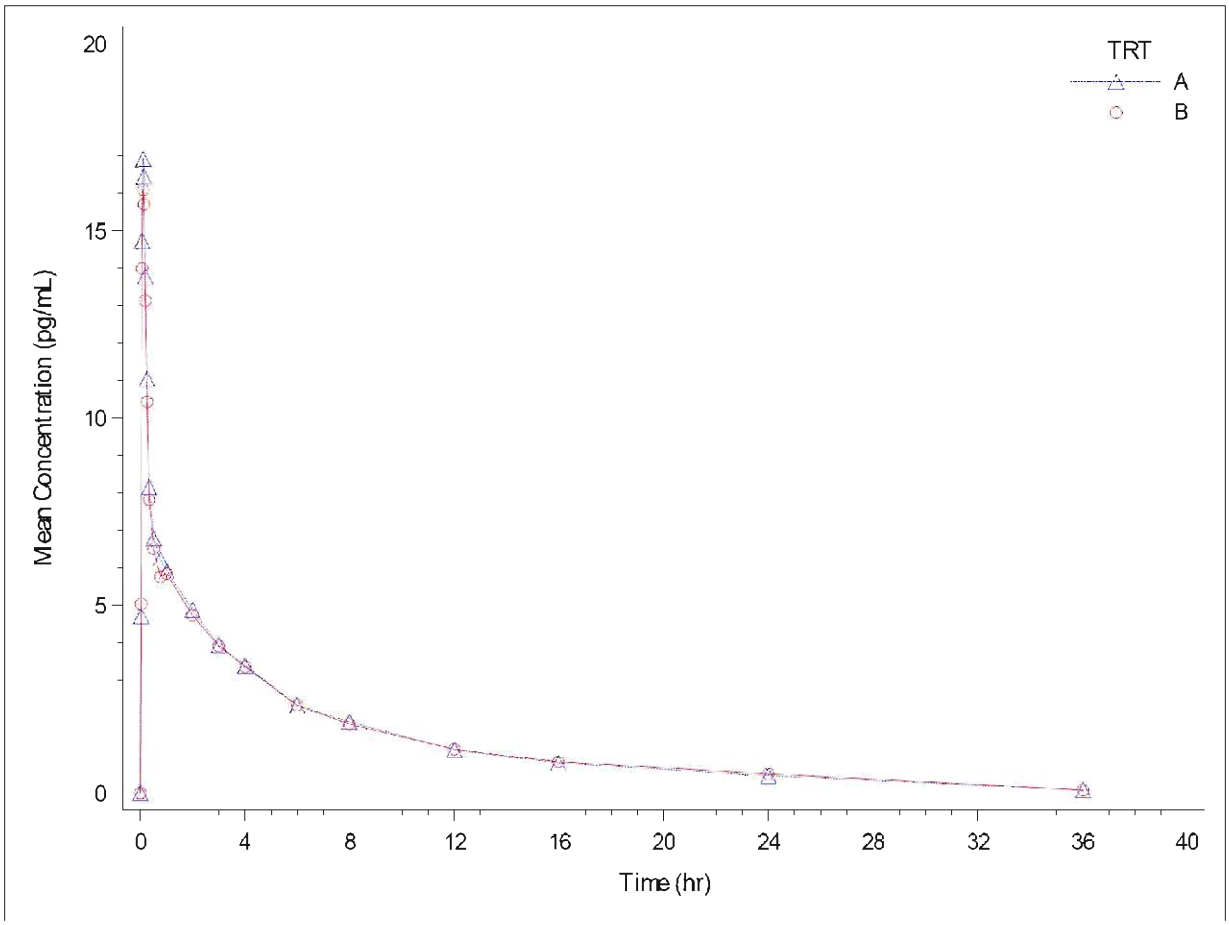
For Treatments A and B, the mean observed plasma concentration of formoterol versus time profiles are presented for 0–36 hours in Figure 5 and Figure 6 for the PK Analysis Set and the FAS, respectively, and for 0–2 hours in Figure 7 and Figure 8 for the PK Analysis Set and the FAS, respectively. On average, the mean observed formoterol plasma concentrations for the test product Lupin BDP/FF 200/6 mcg (Treatment A) were similar to the reference product FOSTAIR 200/6 mcg (Treatment B) for both the PK Analysis Set and the FAS.

Figure 5: Arithmetic Mean Formoterol Plasma Concentration versus Time Profiles by Treatment, 0–36 Hours (Linear Scale) (PK Analysis Set)



Note: For the calculation of summary statistics, values that were below the limit of quantification (BLQ) were treated as zero (0).
The following subjects were excluded from the PK Analysis Set for both Treatments A and B (see Section 11.1 for details): Subjects [redacted].
Treatment A = Test Product: Lupin BDP/FF 200/6 mcg – 2 inhalations for a total dose of 400/12 mcg.
Treatment B = Reference Product: FOSTAIR 200/6 mcg – 2 inhalations for a total dose of 400/12 mcg.
Source: Figure 14.2.2.2.1.

Figure 6: Arithmetic Mean Formoterol Plasma Concentration versus Time Profiles by Treatment, 0–36 Hours (Linear Scale) (FAS)



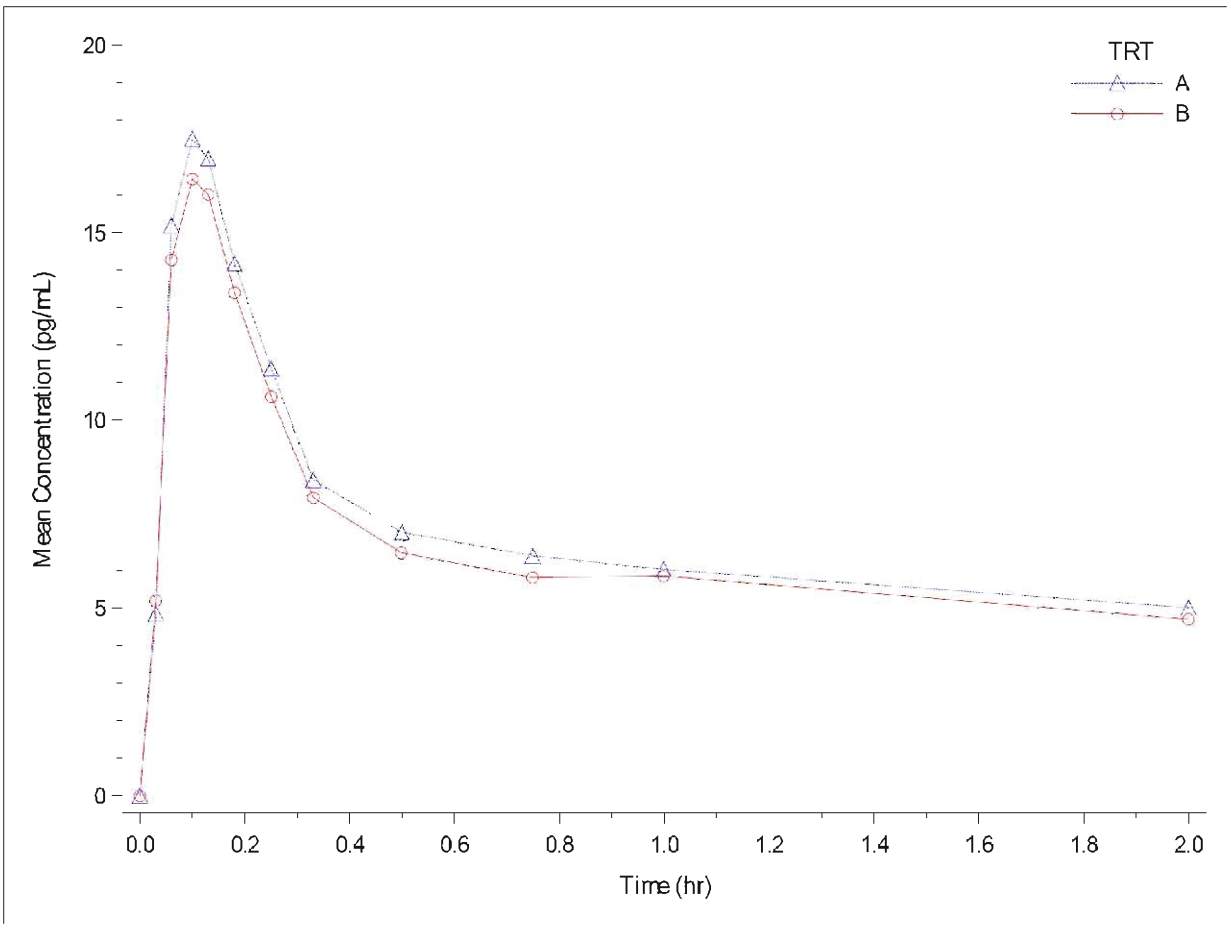
Note: For the calculation of summary statistics, values that were below the limit of quantification (BLQ) were treated as zero (0).

The following subjects were excluded from the FAS for both Treatments A and B (see Section 11.1 for details):
Subjects [redacted].

Treatment A = Test Product: Lupin BDP/FF 200/6 mcg – 2 inhalations for a total dose of 400/12 mcg.
Treatment B = Reference Product: FOSTAIR 200/6 mcg – 2 inhalations for a total dose of 400/12 mcg.

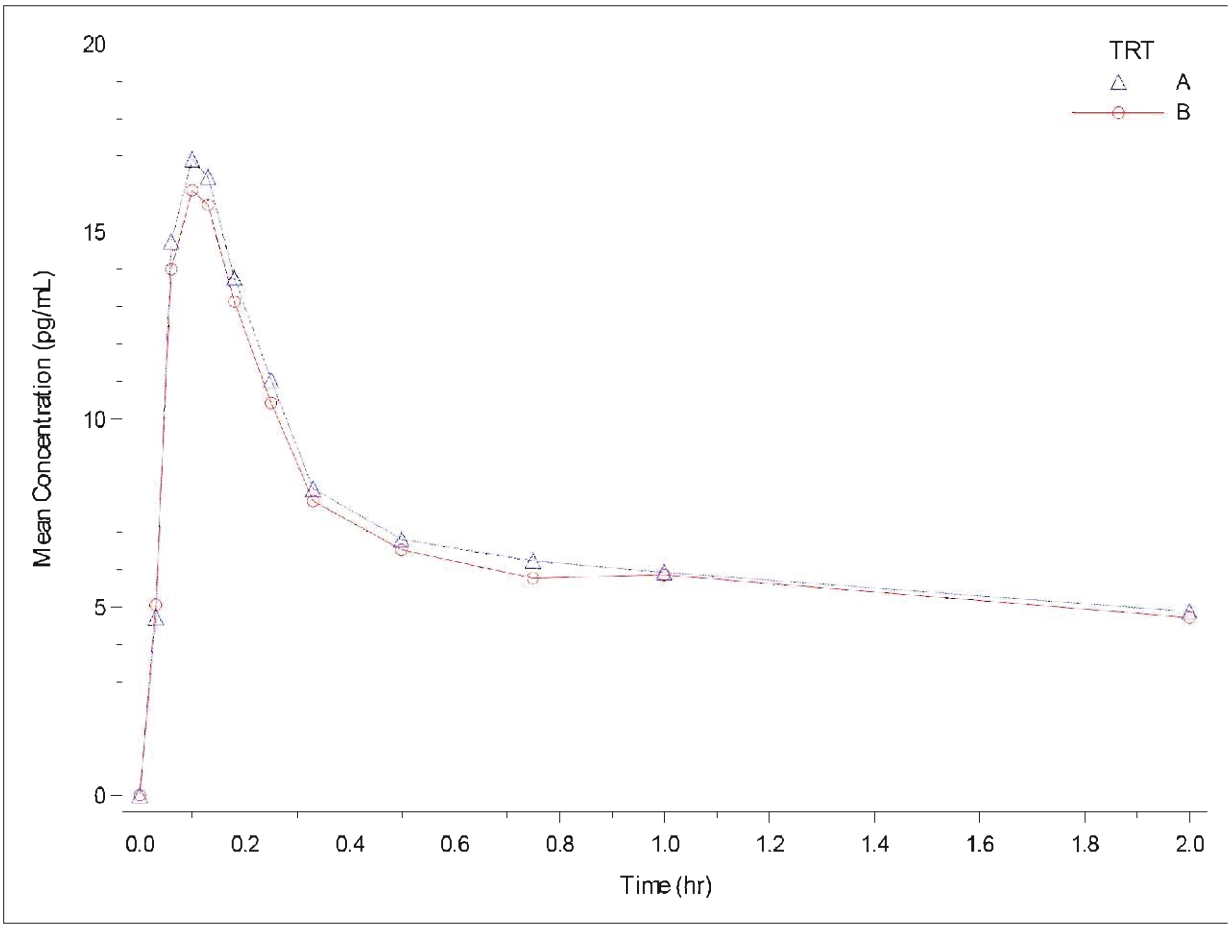
Source: Figure 14.2.2.2.7.

Figure 7: Arithmetic Mean Formoterol Plasma Concentration versus Time Profiles by Treatment, 0–2 Hours (Linear Scale) (PK Analysis Set)



Note: For the calculation of summary statistics, values that were below the limit of quantification (BLQ) were treated as zero (0).
The following subjects were excluded from the PK Analysis Set for both Treatments A and B (see Section 11.1 for details):
Subjects [redacted]
Treatment A = Test Product: Lupin BDP/FF 200/6 mcg – 2 inhalations for a total dose of 400/12 mcg.
Treatment B = Reference Product: FOSTAIR 200/6 mcg – 2 inhalations for a total dose of 400/12 mcg.
Source: Figure 14.2.2.2.5.

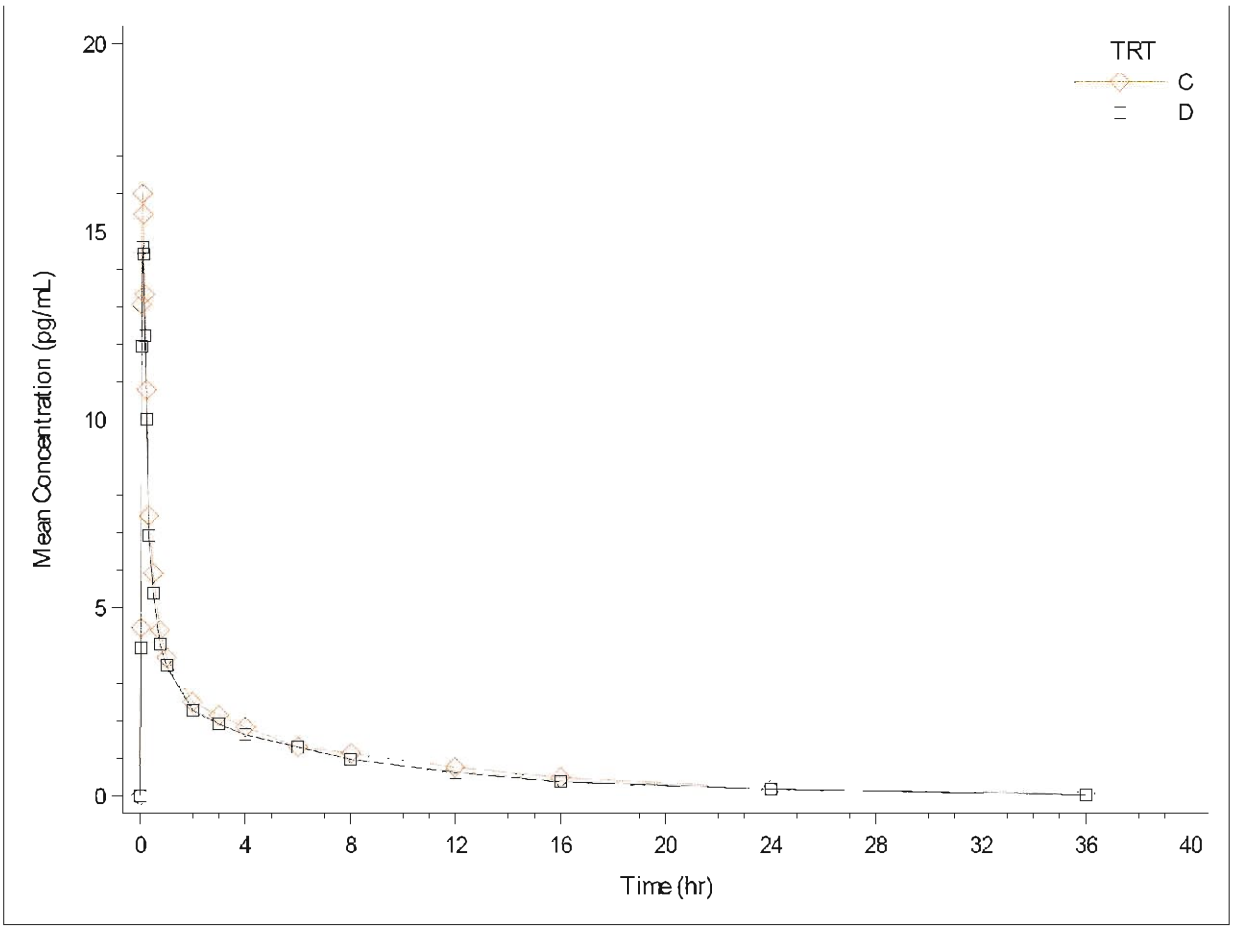
Figure 8: Arithmetic Mean Formoterol Plasma Concentration versus Time Profiles by Treatment, 0–2 Hours (Linear Scale) (FAS)



Note: For the calculation of summary statistics, values that were below the limit of quantification (BLQ) were treated as zero (0).
The following subjects were excluded from the FAS for both Treatments A and B (see Section 11.1 for details):
Subjects [redacted]
Treatment A = Test Product: Lupin BDP/FF 200/6 mcg – 2 inhalations for a total dose of 400/12 mcg.
Treatment B = Reference Product: FOSTAIR 200/6 mcg – 2 inhalations for a total dose of 400/12 mcg.
Source: Figure 14.2.2.2.11.

For Treatments C and D, the mean observed plasma concentration of formoterol with oral charcoal versus time profiles are presented for 0–36 hours in Figure 9 and Figure 10 for the PK Analysis Set and the FAS, respectively, and for 0–2 hours in Figure 11 and Figure 12 for the PK Analysis Set and the FAS, respectively. On average, the mean observed formoterol plasma concentrations for the test product Lupin BDP/FF 200/6 mcg with oral charcoal (Treatment C) were similar to the reference product FOSTAIR 200/6 mcg with oral charcoal (Treatment D) for both the PK Analysis Set and the FAS.

Figure 9: Arithmetic Mean Formoterol Plasma Concentration versus Time Profiles by Treatment, With Oral Charcoal, 0–36 Hours (Linear Scale) (PK Analysis Set)



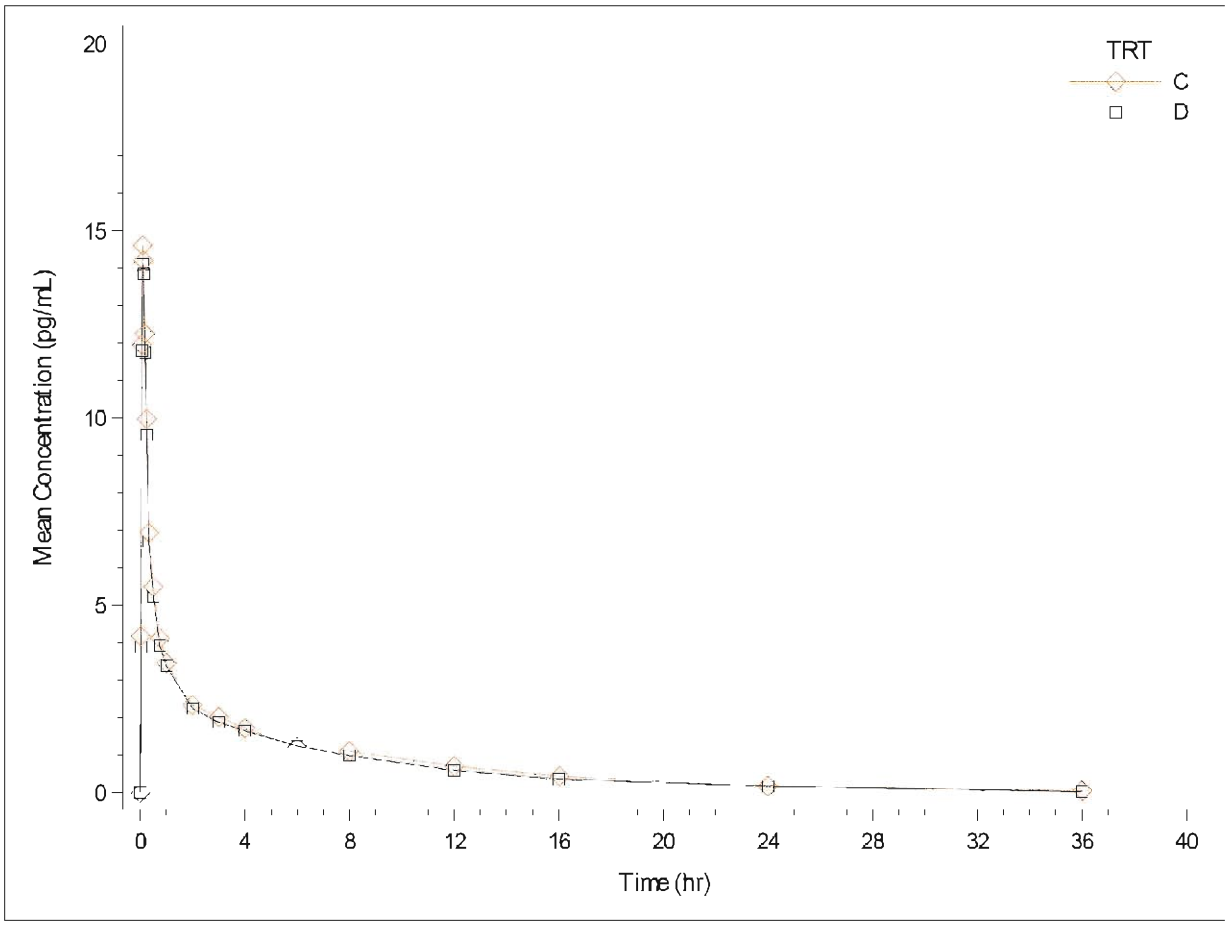
Note: For the calculation of summary statistics, values that were below the limit of quantification (BLQ) were treated as zero (0).

The following subjects were excluded from the PK Analysis Set for both Treatments C and D (see Section 11.1 for details): Subjects [redacted] Additionally, Subjec[redacted] was excluded from the PK Analysis Set for both Treatments C and D due to the inability to quantify all formoterol samples.

Treatment C = Test Product: Lupin BDP/FF 200/6 mcg with oral charcoal – 2 inhalations for a total dose of 400/12 mcg.
Treatment D = Reference Product: FOSTAIR 200/6 mcg with oral charcoal – 2 inhalations for a total dose of 400/12 mcg.

Source: Figure 14.2.2.2.13.

Figure 10: Arithmetic Mean Formoterol Plasma Concentration versus Time Profiles by Treatment, With Oral Charcoal, 0–36 Hours (Linear Scale) (FAS)

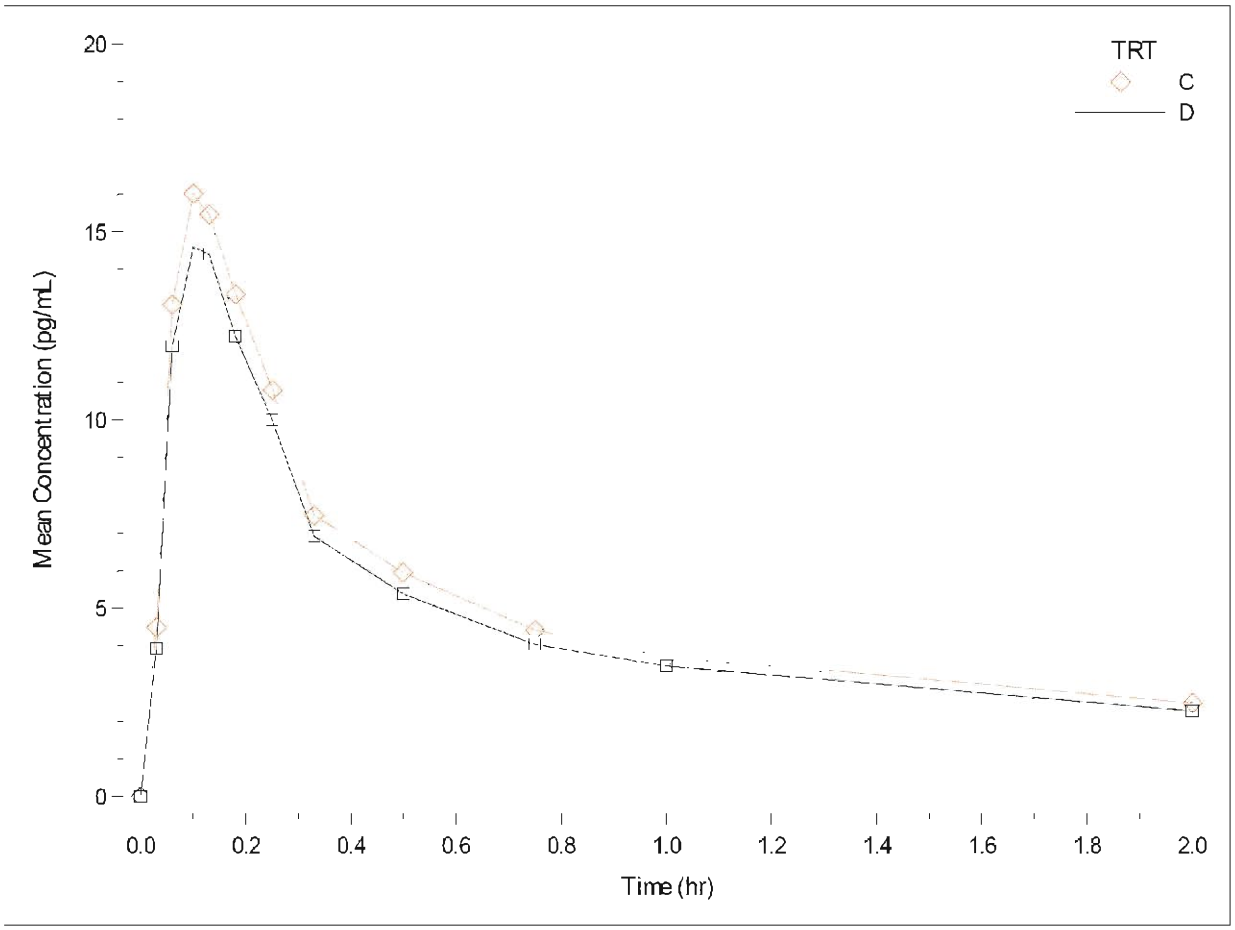


Note: For the calculation of summary statistics, values that were below the limit of quantification (BLQ) were treated as zero (0).

The following subjects were excluded from the FAS for both Treatments C and D (see Section 11.1 for details):
Subjects [redacted]

Treatment C = Test Product: Lupin BDP/FF 200/6 mcg with oral charcoal – 2 inhalations for a total dose of 400/12 mcg.
Treatment D = Reference Product: FOSTAIR 200/6 mcg with oral charcoal – 2 inhalations for a total dose of 400/12 mcg.
Source: Figure 14.2.2.2.19.

Figure 11: Arithmetic Mean Formoterol Plasma Concentration versus Time Profiles by Treatment, With Oral Charcoal, 0–2 Hours (Linear Scale) (PK Analysis Set)

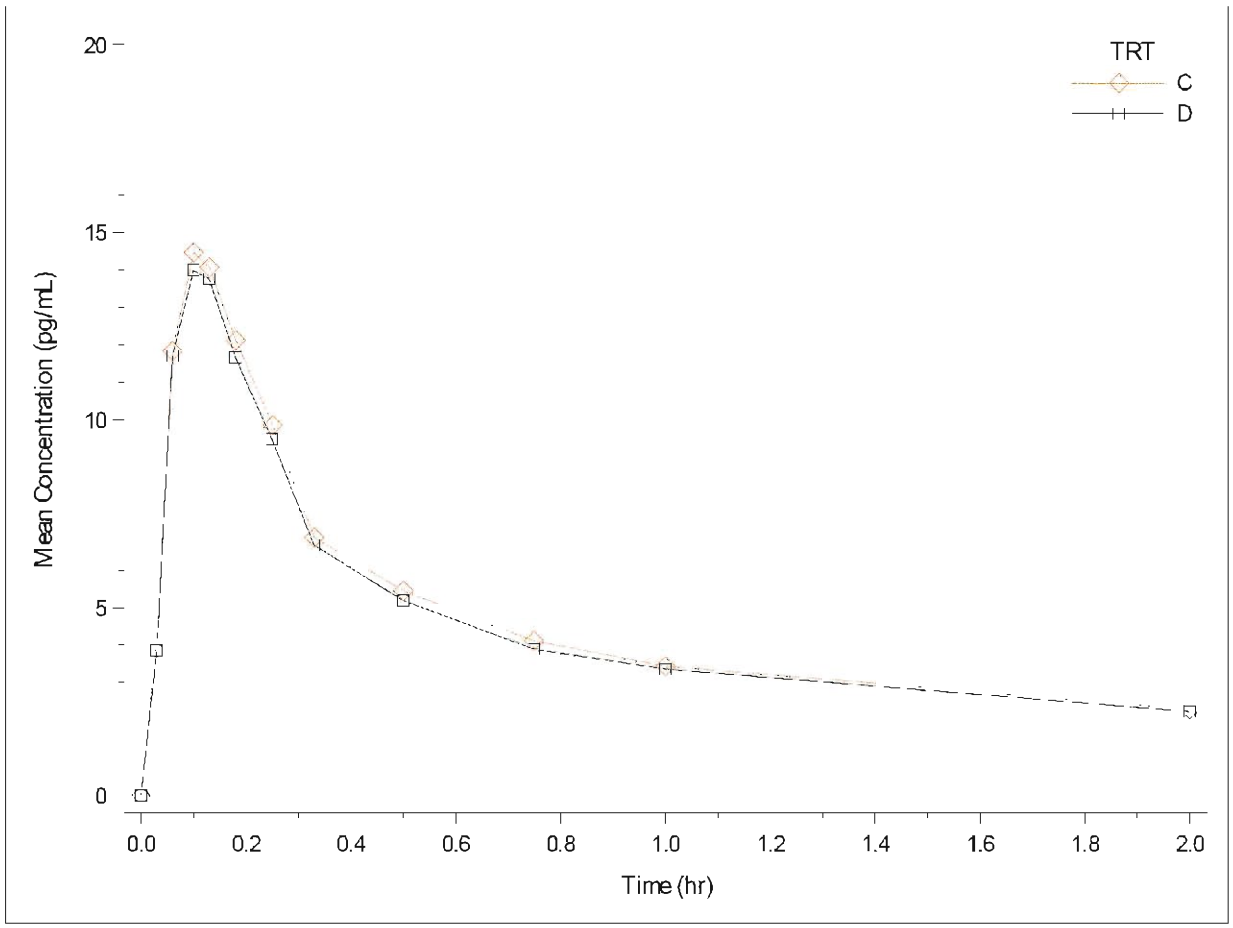


Note: For the calculation of summary statistics, values that were below the limit of quantification (BLQ) were treated as zero (0).

The following subjects were excluded from the PK Analysis Set for both Treatments C and D (see Section 11.1 for details): Subjects [redacted] Additionally, Subject [redacted] was excluded from the PK Analysis Set for both Treatments C and D due to the inability to quantify all formoterol samples.

Treatment C = Test Product: Lupin BDP/FF 200/6 mcg with oral charcoal – 2 inhalations for a total dose of 400/12 mcg.
Treatment D = Reference Product: FOSTAIR 200/6 mcg with oral charcoal – 2 inhalations for a total dose of 400/12 mcg.
Source: Figure 14.2.2.2.17.

Figure 12: Arithmetic Mean Formoterol Plasma Concentration versus Time Profiles by Treatment, With Oral Charcoal, 0–2 Hours (Linear Scale) (FAS)



Note: For the calculation of summary statistics, values that were below the limit of quantification (BLQ) were treated as zero (0).
The following subjects were excluded from the FAS for both Treatments C and D (see Section 11.1 for details):
Subjects [redacted]
Treatment C = Test Product: Lupin BDP/FF 200/6 mcg with oral charcoal – 2 inhalations for a total dose of 400/12 mcg.
Treatment D = Reference Product: FOSTAIR 200/6 mcg with oral charcoal – 2 inhalations for a total dose of 400/12 mcg.
Source: Figure 14.2.2.2.23.

11.4.1.2.2. Pharmacokinetic Parameter Data for Formoterol

Plasma formoterol PK parameters for individual subjects are provided in Appendix 16.2.6, Listing 16.2.6.2.3 (Treatment A), Appendix 16.2.6, Listing 16.2.6.2.4 (Treatment B), Appendix 16.2.6, Listing 16.2.6.2.5 (Treatment C), and Appendix 16.2.6, Listing 16.2.6.2.6 (Treatment D) for the FAS. Treatment A versus Treatment B arithmetic ratios of formoterol PK parameters for individual subjects are provided in Appendix 16.2.6, Listing 16.2.6.4.4, Listing 16.2.6.4.5, and Listing 16.2.6.4.6 for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$, respectively, and for Treatment C versus Treatment D in Appendix 16.2.6, Listing 16.2.6.4.7, Listing 16.2.6.4.8, and Listing 16.2.6.4.9. Summary statistics for Treatment A versus Treatment B arithmetic ratios

for these parameters are presented for the PK Analysis Set in Appendix 16.2.6, Listing 16.2.6.4.16, Listing 16.2.6.4.17, and Listing 16.2.6.4.18 for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$, respectively, and for Treatment C versus Treatment D in Appendix 16.2.6, Listing 16.2.6.4.19, Listing 16.2.6.4.20, and Listing 16.2.6.4.21. Summary statistics for Treatment A versus Treatment B arithmetic ratios for these parameters are presented for the FAS in Appendix 16.2.6, Listing 16.2.6.4.28, Listing 16.2.6.4.29, and Listing 16.2.6.4.30 for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$, respectively, and for Treatment C versus Treatment D in Appendix 16.2.6, Listing 16.2.6.4.31, Listing 16.2.6.4.32, and Listing 16.2.6.4.33. Details of the results of the statistical methods used in this study are provided in Appendix 16.1.9.

Summary statistics of the PK parameter data for formoterol without and with oral charcoal are presented in Table 16 for the PK Analysis Set.

Treatment A and Treatment B

The geometric mean plasma C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ of formoterol were similar after inhalation with Treatment A (16.1488 pg/mL, 44.2892 pg×hr/mL, and 52.9804 pg×hr/mL, respectively) and Treatment B (15.3967 pg/mL, 43.0548 pg×hr/mL, and 51.6039 pg×hr/mL, respectively) 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

The geometric mean plasma C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ of formoterol with oral charcoal were similar after inhalation with Treatment C (15.0207 pg/mL, 23.1549 pg×hr/mL, and 39.1843 pg×hr/mL, respectively) and Treatment D (13.6418 pg/mL, 20.8757 pg×hr/mL, and 35.6846 pg×hr/mL, respectively) 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.

Table 16: Summary of PK Parameters for Formoterol Following Oral Inhalation Administration of Study Drug, by Treatment, Without and With Oral Charcoal (PK Analysis Set)

Parameter (unit)	Statistics	Treatments			
		Lupin BDP/FF 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg (Treatment A)	FOSTAIR 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg (Treatment B)	Lupin BDP/FF 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg with Oral Charcoal (Treatment C)	FOSTAIR 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg with Oral Charcoal (Treatment D)
C_{max} (pg/mL)	N	97	97	88	88
	Mean (SD)	18.3924 (8.7472)	17.4271 (8.3431)	16.7410 (7.6773)	15.2828 (7.4185)
	CV%	47.56	47.87	45.86	48.54
	Geometric mean	16.1488	15.3967	15.0207	13.6418
AUC_{0-t} (pg×hr/mL)	N	97	97	88	88
	Mean (SD)	48.2820 (18.8251)	46.7734 (17.9951)	28.0978 (16.2823)	25.0775 (14.3769)
	CV%	38.99	38.47	57.95	57.33
	Geometric mean	44.2892	43.0548	23.1549	20.8757
$AUC_{0-\infty}$ (pg×hr/mL)	N	66	66	29	29
	Mean (SD)	56.4531 (20.1010)	54.4086 (18.2098)	41.6203 (16.8839)	38.0143 (14.2674)
	CV%	35.61	33.47	40.57	37.53
	Geometric mean	52.9804	51.6039	39.1843	35.6846
t_{max} (hour)	N	97	97	88	88
	Mean (SD)	0.1217 (0.0960)	0.1456 (0.1810)	0.1168 (0.0326)	0.1130 (0.0298)
	Median	0.103	0.104	0.103	0.103
	Min, Max	0.062, 0.756	0.061, 1.008	0.031, 0.251	0.060, 0.185

Parameter (unit)	Statistics	Treatments			
		Lupin BDP/FF 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg (Treatment A)	**FOSTAIR 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg (Treatment B)**	**Lupin BDP/FF 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg with Oral Charcoal (Treatment C)**	**FOSTAIR 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg with Oral Charcoal (Treatment D)**
$t_{½}$ (hour)	N	84	84	64	64
	Mean (SD)	8.4519 (3.9162)	8.1116 (3.4785)	8.5123 (11.4657)	7.2817 (2.7094)
	Median	7.500	7.189	6.668	7.443
	Min, Max	2.758, 21.137	2.544, 25.751	1.209, 96.111	2.848, 17.309
K_{el} (1/hour)	N	84	84	64	64
	Mean (SD)	0.0989 (0.0431)	0.0981 (0.0367)	0.1166 (0.0760)	0.1104 (0.0467)
	Median	0.092	0.097	0.104	0.093
	Min, Max	0.033, 0.251	0.027, 0.272	0.007, 0.573	0.040, 0.243
$AUC_{\%Extrap\ obs}$ (%)	N	84	84	64	64
	Mean (SD)	12.9039 (5.1135)	13.6242 (5.1504)	19.2548 (10.3401)	19.8249 (7.1693)
	Median	11.621	12.531	16.963	18.519
	Min, Max	3.841, 26.387	5.248, 36.833	6.816, 63.691	8.445, 40.999

Note: For profiles where R^2 <0.8 in the calculation of K_{el} (Subjects [redacted] for Treatment A; Subjects [redacted] for Treatment B; Subjects [redacted] for Treatment C; and Subjects [redacted] for Treatment D), the interval was not assigned and the values of $AUC_{0-\infty}$, $t_{½}$, and $AUC_{\%Extrap\ obs}$ reported as missing and not included in the calculation of summary statistics.

The following subjects were excluded from the PK Analysis Set for both Treatments A and B (see Section 11.1 for details):
Subjects [redacted].

The following subjects were excluded from the PK Analysis Set for both Treatments C and D (see Section 11.1 for details):
Subjects [redacted] Additionally, Subject [redacted] was excluded from the PK Analysis Set for both Treatments C and D due to the inability to quantify all formoterol samples.

Source: Table 14.2.1.9.

Summary statistics of the PK parameter data for formoterol without and with oral charcoal are presented in Table 17 for the FAS. The results for the FAS were comparable to those of the PK Analysis Set.

Treatment A and Treatment B

The geometric mean plasma C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ of formoterol were similar after inhalation with Treatment A (15.6282 pg/mL, 43.1559 pg×hr/mL, and 51.1830 pg×hr/mL, respectively) and Treatment B (15.1636 pg/mL, 42.9946 pg×hr/mL, and 51.3240 pg×hr/mL, respectively) for the FAS.

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

The median $t_{½}$ was 7.238 hours for Treatment A and 7.245 hours for Treatment B.

The median K_{el} was 0.096 $hour^{-1}$ for Treatment A and 0.096 $hour^{-1}$ for Treatment B.

Treatment C and Treatment D

The geometric mean plasma C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ of formoterol with oral charcoal were similar after inhalation with Treatment C (13.1858 pg/mL, 19.9572 pg×hr/mL, and 37.1042 pg×hr/mL, respectively) and Treatment D (12.8039 pg/mL, 19.2168 pg×hr/mL, and 36.1122 pg×hr/mL, respectively) for the FAS.

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

The median $t_{½}$ was 6.632 hours for Treatment C and 7.207 hours for Treatment D.

The median K_{el} was 0.105 $hour^{-1}$ for Treatment C and 0.097 $hour^{-1}$ for Treatment D.

Table 17: Summary of PK Parameters for Formoterol Following Oral Inhalation Administration of Study Drug, by Treatment, Without and With Oral Charcoal (FAS)

Parameter (unit)	Statistics	Treatments			
		Lupin BDP/FF 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg (Treatment A)	FOSTAIR 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg (Treatment B)	Lupin BDP/FF 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg with Oral Charcoal (Treatment C)	FOSTAIR 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg with Oral Charcoal (Treatment D)
C_{max} (pg/mL)	N	105	105	105	105
	Mean (SD)	17.8201 (8.6738)	17.1021 (8.1547)	15.3436 (7.8557)	14.7270 (7.6233)
	CV%	48.67	47.68	51.20	51.76
	Geometric mean	15.6282	15.1636	13.1858	12.8039
AUC_{0-t} (pg×hr/mL)	N	105	105	105	105
	Mean (SD)	47.1426 (18.7743)	46.6317 (17.8273)	25.9854 (16.0637)	24.4683 (15.4230)
	CV%	39.82	38.23	61.82	63.03
	Geometric mean	43.1559	42.9946	19.9572	19.2168
$AUC_{0-\infty}$ (pg×hr/mL)	N	73	73	33	33
	Mean (SD)	54.7562 (20.1416)	54.1711 (18.2086)	39.7743 (16.8154)	39.1602 (16.5128)
	CV%	36.78	33.61	42.28	42.17
	Geometric mean	51.1830	51.3240	37.1042	36.1122
t_{max} (hour)	N	105	105	105	105
	Mean (SD)	0.1212 (0.0928)	0.1467 (0.1778)	0.1153 (0.0326)	0.1106 (0.0309)
	Median	0.103	0.104	0.103	0.103
	Min, Max	0.062, 0.756	0.061, 1.008	0.031, 0.251	0.032, 0.185

Parameter (unit)	Statistics	Treatments			
		Lupin BDP/FF 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg (Treatment A)	**FOSTAIR 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg (Treatment B)**	**Lupin BDP/FF 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg with Oral Charcoal (Treatment C)**	**FOSTAIR 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg with Oral Charcoal (Treatment D)**
$t_{½}$ (hour)	N	91	91	78	78
	Mean (SD)	8.2300 (3.8570)	8.1165 (3.3871)	8.0436 (10.5594)	7.1941 (3.0971)
	Median	7.238	7.245	6.632	7.207
	Min, Max	2.758, 21.137	2.544, 25.751	0.544, 96.111	0.266, 18.241
K_{el} (1/hour)	N	91	91	78	78
	Mean (SD)	0.1013 (0.0429)	0.0976 (0.0362)	0.1503 (0.1892)	0.1440 (0.2861)
	Median	0.096	0.096	0.105	0.097
	Min, Max	0.033, 0.251	0.027, 0.272	0.007, 1.274	0.038, 2.604
$AUC_{\%Extrap\ obs}$ (%)	N	91	91	78	78
	Mean (SD)	12.8114 (5.0528)	13.5314 (5.0339)	20.9950 (12.2229)	20.4779 (7.9884)
	Median	11.157	12.483	17.777	18.932
	Min, Max	3.841, 26.387	5.248, 36.833	6.816, 75.577	6.758, 48.435

Note: For profiles where R^2 <0.8 in the calculation of K_{el} (Subjects [redacted] for Treatment A; Subjects [redacted] for Treatment B; Subjects [redacted] for Treatment C; and Subjects [redacted] for Treatment D), the interval was not assigned and the values of $AUC_{0-\infty}$, $t_{½}$, and $AUC_{\%Extrap\ obs}$ reported as missing and not included in the calculation of summary statistics.

The following subjects were excluded from the FAS for both Treatments A and B (see Section 11.1 for details):
Subjects [redacted].

The following subjects were excluded from the FAS for both Treatments C and D (see Section 11.1 for details):
Subjects [redacted]

Source: Table 14.2.1.10.

For Treatment A, there were 17 subjects with AUC >20% (Subjects [redacted]; Appendix 16.2.6, Listing 16.2.6.2.3). For Treatment B, there were 15 subjects with AUC >20% (Subjects [redacted] Appendix 16.2.6, Listing 16.2.6.2.4). For Treatment C, there were 54 subjects with $AUC_{\%Extrap\ obs}$ >20% (Subjects [redacted] Appendix 16.2.6, Listing 16.2.6.2.5). For Treatment D, there were 55 subjects with $AUC_{\%Extrap\ obs}$ >20% (Subjects [redacted] Appendix 16.2.6, Listing 16.2.6.2.6). The analysis of $AUC_{0-\infty}$ for both the PK Analysis Set and the FAS excluded subjects from both the test and reference treatments in treatment periods where $AUC_{\%Extrap\ obs}$ was >20% for either test or reference.

11.4.1.2.3. Statistical Analysis of Pharmacokinetic Parameters for Formoterol

11.4.1.2.3.1. PK Analysis Set

The ANOVA model described in Section 9.7.1.3 was performed on the primary PK parameters (C_{max} and AUC_{0-t}) to assess the bioequivalence criteria of formoterol for Lupin BDP/FF 200/6 mcg (Treatment A) versus FOSTAIR 200/6 mcg (Treatment B), and Lupin BDP/FF 200/6 mcg with oral charcoal (Treatment C) versus FOSTAIR 200/6 mcg with oral charcoal (Treatment D). The ANOVA results including the GMR and 90% CI for formoterol C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ PK parameters are presented in Table 18 for the PK Analysis Set.

Treatment A versus Treatment B

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 versus Treatment D

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%.

Table 18: 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)	Treatments			
	Lupin BDP/FF 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg (Treatment A)	FOSTAIR 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg (Treatment B)	Lupin BDP/FF 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg with Oral Charcoal (Treatment C)	FOSTAIR 200/6 mcg (2 inhalations) Total Dose = 400/12 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

The following subjects were excluded from the PK Analysis Set for both Treatments A and B (see Section 11.1 for details):
Subjects [redacted].

The following subjects were excluded from the PK Analysis Set for both Treatments C and D (see Section 11.1 for details):
Subjects [redacted]. Additionally, Subject [redacted] was excluded from the PK Analysis Set for both Treatments C and D due to the inability to quantify all formoterol samples.

Source: Table 14.2.1.15.

11.4.1.2.3.2. Full Analysis Set

The ANOVA results including the GMR and 90% CI for formoterol C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ PK parameters for Lupin BDP/FF 200/6 mcg (Treatment A) versus FOSTAIR 200/6 mcg (Treatment B), and Lupin BDP/FF 200/6 mcg with oral charcoal (Treatment C) versus FOSTAIR 200/6 mcg with oral charcoal (Treatment D) are presented in Table 19 for the FAS and were similar to the PK Analysis Set.

Treatment A versus Treatment B

Treatment A GLSM was approximately 2% and 1% higher than Treatment B for formoterol C_{max} and AUC_{0-t}, respectively, and essentially the same for $AUC_{0-\infty}$.

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 versus Treatment D

Treatment C GLSM was approximately 2%, 4%, and 1% 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%.

Table 19: Summary of Statistical Comparisons of Plasma Formoterol Pharmacokinetic Parameters C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$, Without and With Oral Charcoal (FAS)

Parameter (unit)	Treatments			
	Lupin BDP/FF 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg (Treatment A)	FOSTAIR 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg (Treatment B)	Lupin BDP/FF 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg with Oral Charcoal (Treatment C)	FOSTAIR 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg with Oral Charcoal (Treatment D)
	GLSM	GLSM	GLSM	GLSM
C_{max} (pg/mL)	15.4592	15.1944	13.2594	13.0454
AUC_{0-t} (pg×hr/mL)	43.2375	42.7802	20.7643	19.9351
$AUC_{0-\infty}$ (pg×hr/mL)	47.4633	47.3764	28.6863	28.5341

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)	101.74 (94.75, 109.25)	101.64 (95.14, 108.59)	30.71
AUC_{0-t} (pg×hr/mL)	101.07 (90.48, 112.89)	104.16 (93.99, 115.43)	49.30
$AUC_{0-\infty}$ (pg×hr/mL)	100.18 (91.74, 109.40)	100.53 (92.63, 109.11)	37.08

The following subjects were excluded from the FAS for both Treatments A and B (see Section 11.1 for details):
Subjects [redacted]
The following subjects were excluded from the FAS for both Treatments C and D (see Section 11.1 for details):
Subjects [redacted]
Source: Table 14.2.1.16.

11.4.1.3. Analysis of Pharmacokinetics for Beclometasone Dipropionate (BDP)

The bioanalysis was performed at Lupin Bioresearch Center [redacted] as described in Section 9.5.3. The PK parameters of BDP were determined by noncompartmental methods using Phoenix® WinNonlin® version 8.0 (Pharsight Corporation, USA).

Primary analyses of the PK parameters are based upon the PK Analysis Set. The FAS was used as the supportive analysis set for PK analyses of BDP.

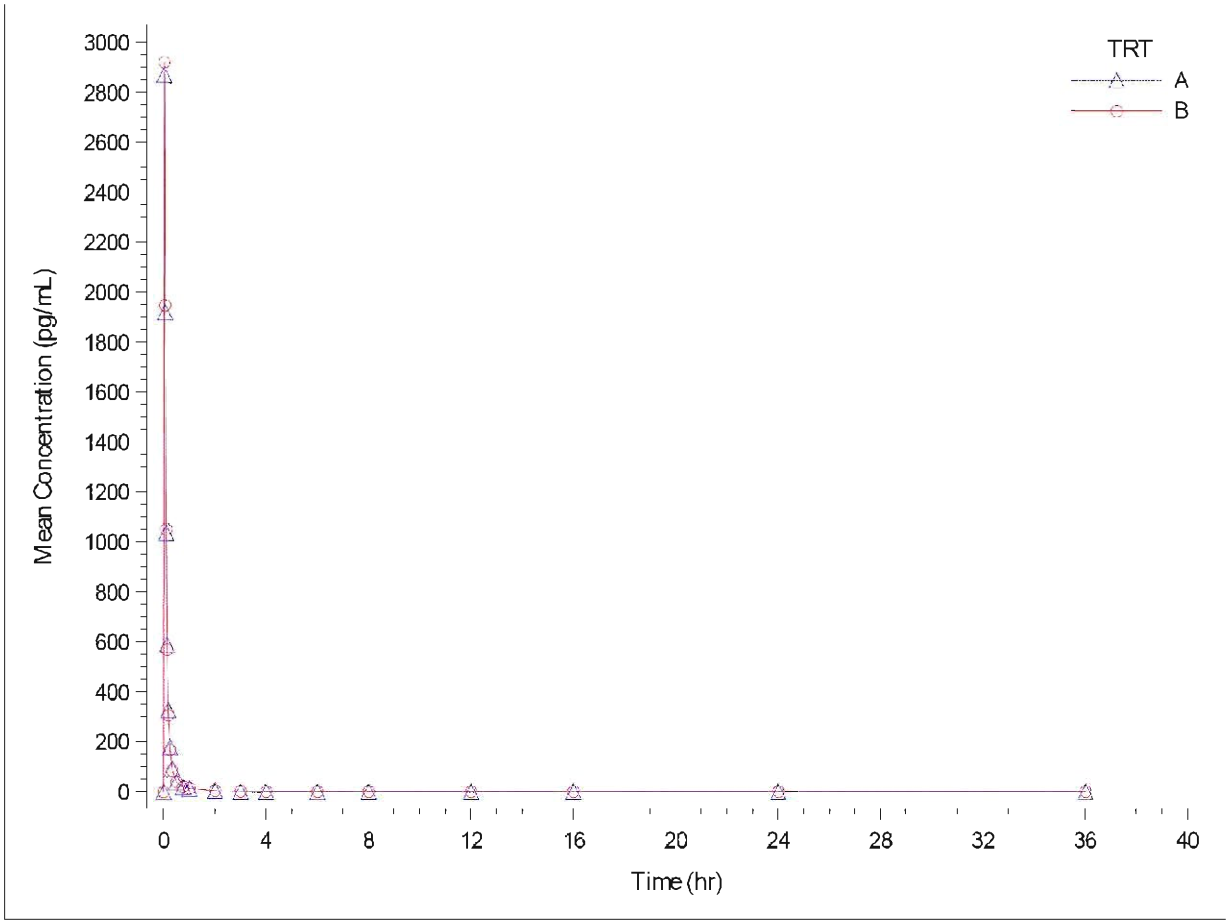
11.4.1.3.1. Plasma Concentration Data for BDP

Plasma concentrations of BDP for individual subjects in the FAS are provided in Appendix 16.2.5, Listing 16.2.5.9.7 for the test product Lupin BDP/FF 200/6 mcg (Treatment A), and in Appendix 16.2.5, Listing 16.2.5.9.8 for the reference product FOSTAIR 200/6 mcg (Treatment B). Figures of Treatment A and Treatment B BDP concentration versus time profiles for 0–36 hours for individual subjects are presented on a linear scale and a semi-log scale for the FAS in Appendix 16.2.6, Figure 16.2.6.5.17 and Appendix 16.2.6, Figure 16.2.6.5.18, respectively, and for 0–2 hours in Appendix 16.2.6, Figure 16.2.6.5.19 and Appendix 16.2.6, Figure 16.2.6.5.20. Individual PK blood sample collection times are provided in Appendix 16.2.5, Listing 16.2.5.7.

Summary statistics for BDP plasma concentration data for Treatments A and B are presented in post-text Table 14.2.1.5 for the PK Analysis Set, and in post-text Table 14.2.1.6 for the FAS.

For Treatments A and B, the mean observed plasma concentration of BDP versus time profiles are presented for 0–36 hours in Figure 13 and Figure 14 for the PK Analysis Set and the FAS, respectively, and for 0–2 hours in Figure 15 and Figure 16 for the PK Analysis Set and the FAS, respectively. On average, the mean observed BDP plasma concentrations for the test product Lupin BDP/FF 200/6 mcg (Treatment A) were similar to the reference product FOSTAIR 200/6 mcg (Treatment B) for both the PK Analysis Set and the FAS.

Figure 13: Arithmetic Mean BDP Plasma Concentration versus Time Profiles by Treatment, 0–36 Hours (Linear Scale) (PK Analysis Set)



Note: For the calculation of summary statistics, values that were below the limit of quantification (BLQ) were treated as zero (0).

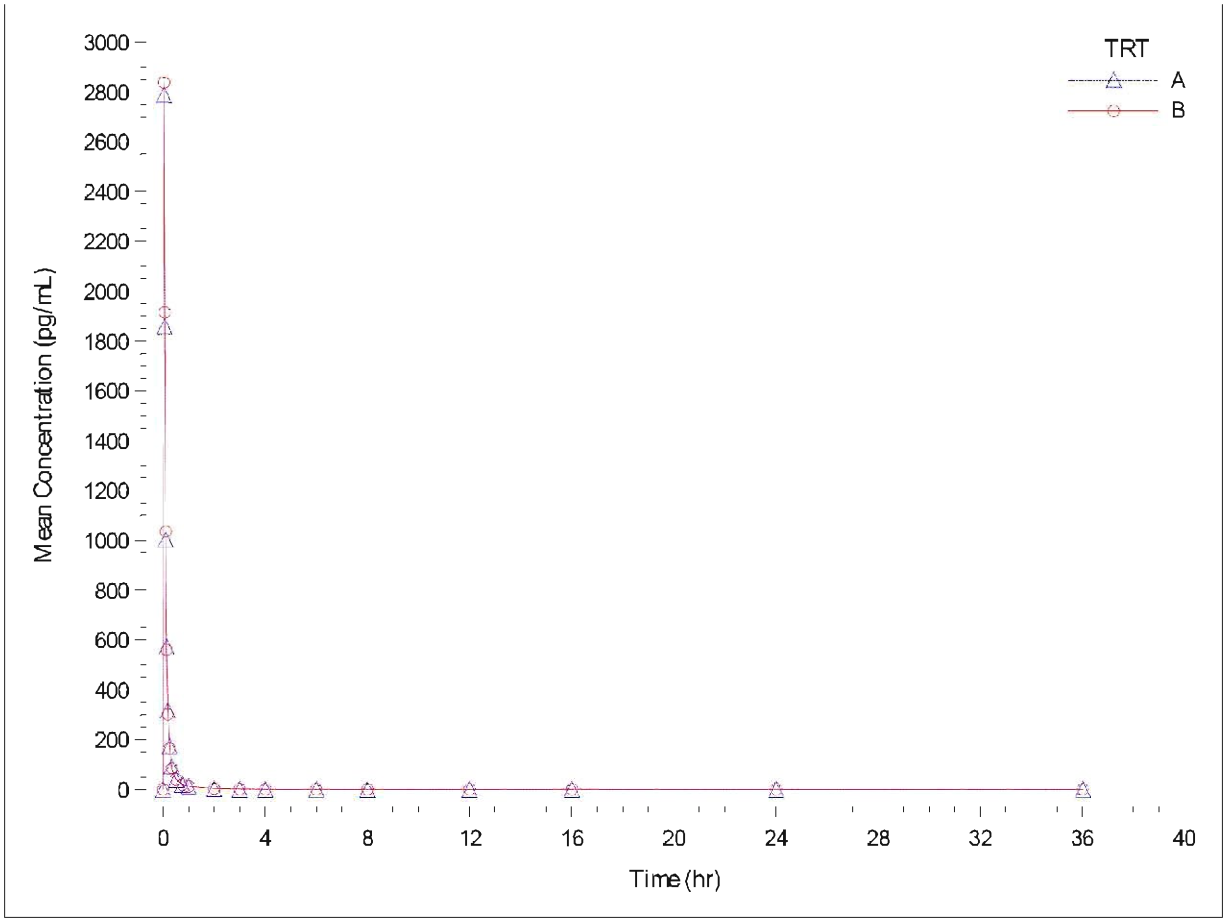
The following subjects were excluded from the PK Analysis Set for both Treatments A and B (see Section 11.1 for details): Subjects [redacted].

Treatment A = Test Product: Lupin BDP/FF 200/6 mcg – 2 inhalations for a total dose of 400/12 mcg.

Treatment B = Reference Product: FOSTAIR 200/6 mcg – 2 inhalations for a total dose of 400/12 mcg.

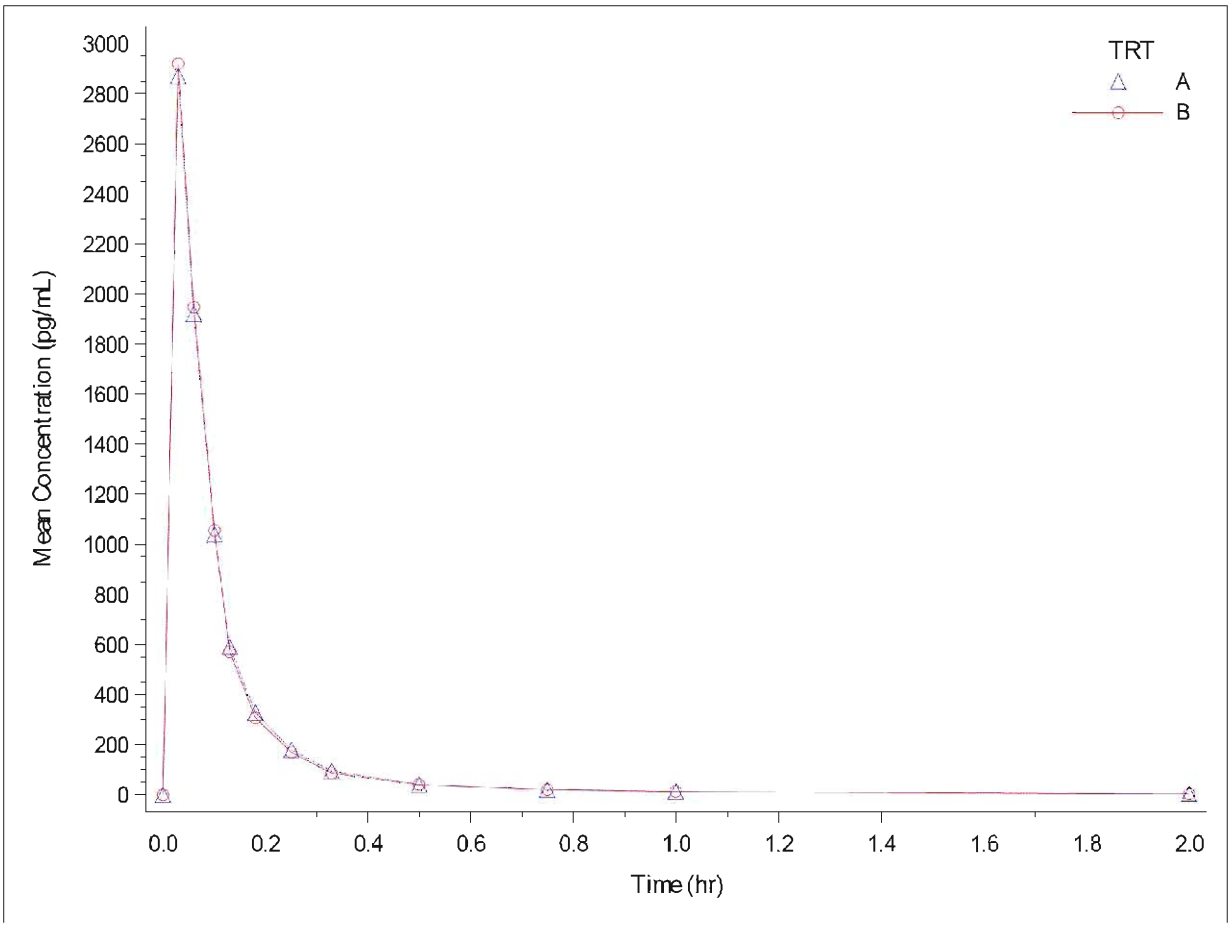
Source: Figure 14.2.2.3.1.

Figure 14: Arithmetic Mean BDP Plasma Concentration versus Time Profiles by Treatment, 0–36 Hours (Linear Scale) (FAS)



Note: For the calculation of summary statistics, values that were below the limit of quantification (BLQ) were treated as zero (0).
The following subjects were excluded from the FAS for both Treatments A and B (see Section 11.1 for details):
Subjects [redacted]
Treatment A = Test Product: Lupin BDP/FF 200/6 mcg – 2 inhalations for a total dose of 400/12 mcg.
Treatment B = Reference Product: FOSTAIR 200/6 mcg – 2 inhalations for a total dose of 400/12 mcg.
Source: Figure 14.2.2.3.7.

Figure 15: Arithmetic Mean BDP Plasma Concentration versus Time Profiles by Treatment, 0–2 Hours (Linear Scale) (PK Analysis Set)



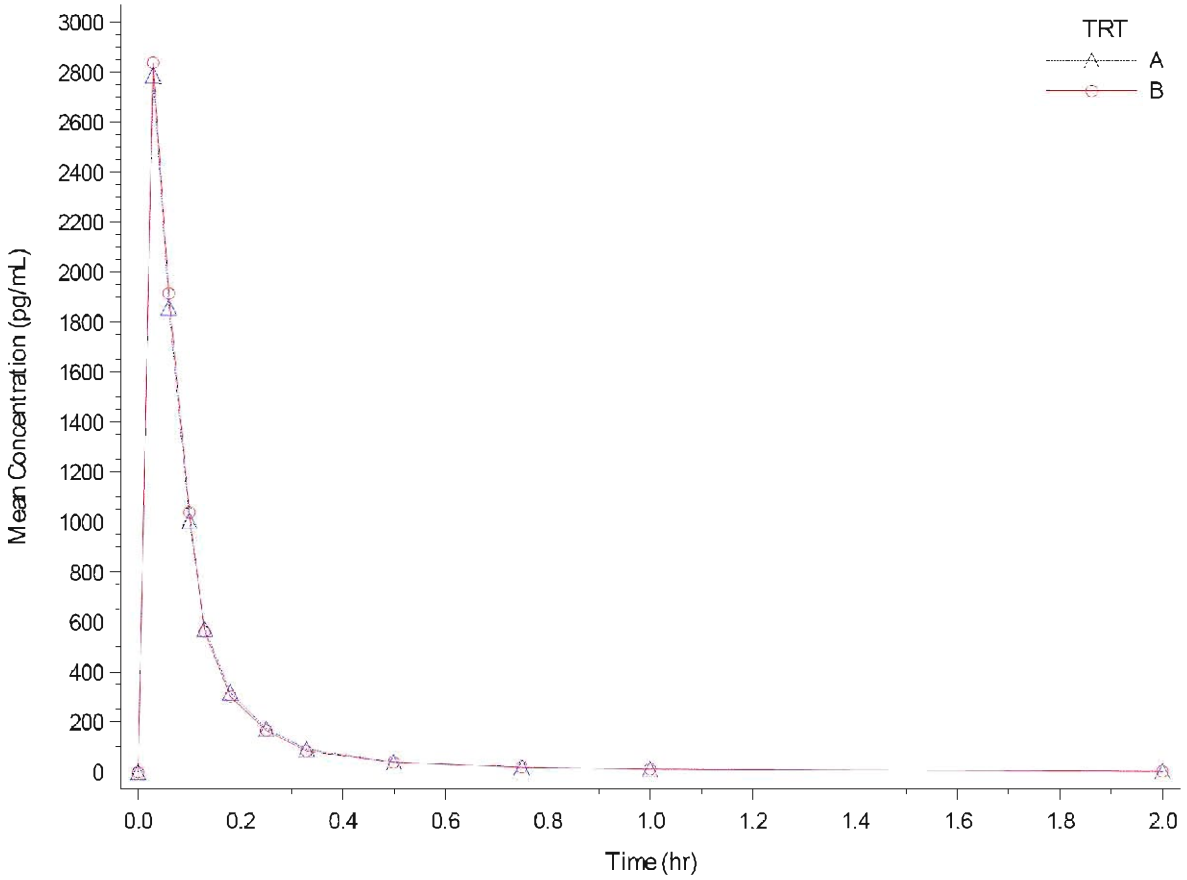
Note: For the calculation of summary statistics, values that were below the limit of quantification (BLQ) were treated as zero (0).

The following subjects were excluded from the PK Analysis Set for both Treatments A and B (see Section 11.1 for details): Subjects [redacted]

Treatment A = Test Product: Lupin BDP/FF 200/6 mcg – 2 inhalations for a total dose of 400/12 mcg.
Treatment B = Reference Product: FOSTAIR 200/6 mcg – 2 inhalations for a total dose of 400/12 mcg.

Source: Figure 14.2.2.3.5.

Figure 16: Arithmetic Mean BDP Plasma Concentration versus Time Profiles by Treatment, 0–2 Hours (Linear Scale) (FAS)



Note: For the calculation of summary statistics, values that were below the limit of quantification (BLQ) were treated as zero (0).
The following subjects were excluded from the FAS for both Treatments A and B (see Section 11.1 for details):
Subjects [redacted]
Treatment A = Test Product: Lupin BDP/FF 200/6 mcg – 2 inhalations for a total dose of 400/12 mcg.
Treatment B = Reference Product: FOSTAIR 200/6 mcg – 2 inhalations for a total dose of 400/12 mcg.
Source: Figure 14.2.2.3.11.

11.4.1.3.2. Pharmacokinetic Parameter Data for BDP

Plasma BDP PK parameters for individual subjects are provided in Appendix 16.2.6, Listing 16.2.6.2.7 (Treatment A) and Appendix 16.2.6, Listing 16.2.6.2.8 (Treatment B) for the FAS. Treatment A versus Treatment B arithmetic ratios of BDP PK parameters for individual subjects are provided in Appendix 16.2.6, Listing 16.2.6.4.10, Listing 16.2.6.4.11, and Listing 16.2.6.4.12 for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$, respectively. Summary statistics for Treatment A versus Treatment B arithmetic ratios for these parameters are presented for the PK Analysis Set in Appendix 16.2.6, Listing 16.2.6.4.22, Listing 16.2.6.4.23, and Listing 16.2.6.4.24 for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$, respectively; and for the FAS in Appendix 16.2.6,

Listing 16.2.6.4.34, Listing 16.2.6.4.35, and Listing 16.2.6.4.36. Details of the results of the statistical methods used in this study are provided in Appendix 16.1.9.

Summary statistics of the PK parameter data for BDP are presented in Table 20 for the PK Analysis Set.

The geometric mean plasma C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ of BDP were similar after inhalation with Treatment A (2361.8720 pg/mL, 234.6115 pg×hr/mL, and 244.1335 pg×hr/mL, respectively) and Treatment B (2427.2848 pg/mL, 243.2328 pg×hr/mL, and 257.9951 pg×hr/mL, respectively) 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.

Table 20: Summary of PK Parameters for BDP Following Oral Inhalation Administration of Study Drug, by Treatment (PK Analysis Set)

Parameter (unit)	Statistic	Treatments	
		Lupin BDP/FF 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg (Treatment A)	FOSTAIR 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg (Treatment B)
C_{max} (pg/mL)	N	97	97
	Mean (SD)	3011.6444 (2419.0212)	3010.5315 (2279.2760)
	CV%	80.32	75.71
	Geometric mean	2361.8720	2427.2848
AUC_{0-t} (pg×hr/mL)	N	97	97
	Mean (SD)	282.3162 (191.5901)	282.9575 (188.8517)
	CV%	67.86	66.74
	Geometric mean	234.6115	243.2328
$AUC_{0-\infty}$ (pg×hr/mL)	N	76	76
	Mean (SD)	289.9633 (196.8895)	301.0003 (204.3515)
	CV%	67.90	67.89
	Geometric mean	244.1335	257.9951
t_{max} (hour)	N	97	97
	Mean (SD)	0.0436 (0.0166)	0.0415 (0.0134)
	Median	0.034	0.034
	Min, Max	0.030, 0.103	0.031, 0.102
$t_{½}$ (hour)	N	76	76
	Mean (SD)	0.5143 (0.5750)	0.4248 (0.2952)
	Median	0.330	0.295
	Min, Max	0.110, 3.697	0.072, 1.206

Parameter (unit)	Statistic	Treatments	
		Lupin BDP/FF 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg (Treatment A)	FOSTAIR 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg (Treatment B)
K_{el} (1/hour)	N	76	76
	Mean (SD)	2.2057 (1.2959)	2.4659 (1.5876)
	Median	2.101	2.355
	Min, Max	0.187, 6.289	0.575, 9.577
$AUC_{\%Extrap\ obs}$ (%)	N	76	76
	Mean (SD)	2.3261 (2.2337)	1.8332 (1.0444)
	Median	1.872	1.537
	Min, Max	0.477, 16.017	0.498, 4.973

Note: For profiles where R^2 <0.8 in the calculation of K_{el} (Subjects [redacted] for Treatment A, and Subjects [redacted] for Treatment B), the interval was not assigned and the values of $AUC_{0-\infty}$, $t_{½}$, and $AUC_{\%Extrap\ obs}$ reported as missing and not included in the calculation of summary statistics.

The following subjects were excluded from the PK Analysis Set for both Treatments A and B (see Section 11.1 for details): Subjects [redacted].

Source: Table 14.2.1.11.

Summary statistics of the PK parameter data for BDP are presented in Table 21 for the FAS. The results for the FAS were comparable to those of the PK Analysis Set.

The geometric mean plasma C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ of BDP were similar after inhalation with Treatment A (2299.6737 pg/mL, 227.0742 pg×hr/mL, and 234.1919 pg×hr/mL, respectively) and Treatment B (2364.7801 pg/mL, 237.9251 pg×hr/mL, and 251.1561 pg×hr/mL, respectively) for the FAS.

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.

Table 21: Summary of PK Parameters for BDP Following Oral Inhalation Administration of Study Drug, by Treatment (FAS)

Parameter (unit)	Statistic	Treatments	
		Lupin BDP/FF 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg (Treatment A)	FOSTAIR 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg (Treatment B)
C_{max} (pg/mL)	N	105	105
	Mean (SD)	2919.7152 (2357.4310)	2928.5474 (2228.0476)
	CV%	80.74	76.08
	Geometric mean	2299.6737	2364.7801

Parameter (unit)	Statistic	Treatments	
		Lupin BDP/FF 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg (Treatment A)	FOSTAIR 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg (Treatment B)
AUC_{0-t} (pg×hr/mL)	N	105	105
	Mean (SD)	273.6672 (187.9112)	276.9778 (185.2846)
	CV%	68.66	66.90
	Geometric mean	227.0742	237.9251
$AUC_{0-\infty}$ (pg×hr/mL)	N	83	83
	Mean (SD)	279.4741 (193.1161)	293.6171 (200.0948)
	CV%	69.10	68.15
	Geometric mean	234.1919	251.1561
t_{max} (hour)	N	105	105
	Mean (SD)	0.0432 (0.0163)	0.0417 (0.0135)
	Median	0.034	0.034
	Min, Max	0.030, 0.103	0.031, 0.102
$t_{½}$ (hour)	N	84	84
	Mean (SD)	0.5745 (0.8976)	0.4225 (0.2914)
	Median	0.330	0.295
	Min, Max	0.110, 6.996	0.072, 1.206
K_{el} (1/hour)	N	84	84
	Mean (SD)	2.2113 (1.2958)	2.4525 (1.5451)
	Median	2.101	2.355
	Min, Max	0.099, 6.289	0.575, 9.577
$AUC_{\%Extrap\ obs}$ (%)	N	84	84
	Mean (SD)	2.5570 (2.9207)	1.8799 (1.0638)
	Median	1.890	1.560
	Min, Max	0.477, 20.529	0.498, 4.973

Note: For profiles where R^2 <0.8 in the calculation of K_{el} (Subjects [redacted] for Treatment A, and Subjects [redacted] for Treatment B), the interval was not assigned and the values of $AUC_{0-\infty}$, $t_{½}$, and $AUC_{\%Extrap\ obs}$ reported as missing and not included in the calculation of summary statistics.

The following subjects were excluded from the FAS for both Treatments A and B (see Section 11.1 for details): Subjects [redacted].

Source: Table 14.2.1.12.

For Treatment A, there were 3 subjects with $AUC_{\%Extrap\ obs}$ >20% (Subjects [redacted] Appendix 16.2.6, Listing 16.2.6.2.7). For Treatment B, there were 2 subjects with $AUC_{\%Extrap\ obs}$ >20% (Subjects [redacted] Appendix 16.2.6, Listing 16.2.6.2.8). The analysis of $AUC_{0-\infty}$ for both the PK Analysis Set and the FAS excluded subjects from both the test and reference treatments in treatment periods where $AUC_{\%Extrap\ obs}$ was >20% for either test or reference.

11.4.1.3.3. Statistical Analysis of Pharmacokinetic Parameters for BDP

11.4.1.3.3.1. PK Analysis Set

The ANOVA model described in Section 9.7.1.3 was performed on the primary PK parameters (C_{max} and AUC_{0-t}) to assess the bioequivalence criteria of BDP for Lupin BDP/FF 200/6 mcg (Treatment A) versus FOSTAIR 200/6 mcg (Treatment B). The ANOVA results including the GMR and 90% CI for BDP C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ PK parameters are presented in Table 22 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%.

Table 22: Summary of Statistical Comparisons of Plasma BDP Pharmacokinetic Parameters C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ (PK Analysis Set)

Parameter (unit)	Lupin BDP/FF 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg (Treatment A) GLSM	FOSTAIR 200/6 mcg (2 inhalations) Total Dose = 400/12 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

The following subjects were excluded from the PK Analysis Set for both Treatments A and B (see Section 11.1 for details):
Subjects [redacted].
Source: Table 14.2.1.17.

11.4.1.3.3.2. Full Analysis Set

The ANOVA results including the GMR and 90% CI for BDP C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ PK parameters for Lupin BDP/FF 200/6 mcg (Treatment A) versus FOSTAIR 200/6 mcg (Treatment B) are presented in Table 23 for the FAS and were similar to the PK Analysis Set.

Treatment A GLSM was approximately 4%, 5%, and 7% 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%.

Table 23: Summary of Statistical Comparisons of Plasma BDP Pharmacokinetic Parameters C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ (FAS)

Parameter (unit)	Lupin BDP/FF 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg (Treatment A) GLSM	FOSTAIR 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg (Treatment B) GLSM	GMR (90% CI) A vs B	Intrasubject CV% A vs B
C_{max} (pg/mL)	2294.8945	2380.0569	96.42 (89.20, 104.22)	34.84
AUC_{0-t} (pg×hr/mL)	226.8572	238.9945	94.92 (89.02, 101.21)	28.48
$AUC_{0-\infty}$ (pg×hr/mL)	235.3075	252.6729	93.13 (86.99, 99.70)	26.66

The following subjects were excluded from the FAS for both Treatments A and B (see Section 11.1 for details):
Subjects [redacted]
Source: Table 14.2.1.18.

11.4.2. Statistical/Analytical Issues

11.4.2.1. Adjustments for Covariates

No adjustments for covariates or prognostic factors were used in any of the analyses for this study.

11.4.2.2. Handling of Dropouts or Missing Data

Subjects who withdrew or who were discontinued were not replaced. Any missing samples were reported as "missing" and not included in the PK and statistical analysis.

11.4.2.3. Interim Analyses and Data Monitoring

This section is not applicable. No interim analyses were conducted.

11.4.2.4. Multicentre Studies

This section is not applicable.

11.4.2.5. Multiple Comparisons/Multiplicity

No adjustments were made for multiple comparisons.

11.4.2.6. Use of a "Pharmacokinetic Subset" of Subjects

Pharmacokinetic analyses were performed using the PK Analysis Set of subjects.

11.4.2.7. Active-Control Studies Intended to Show Equivalence

See Section 9.7.1.3 for statistical analysis and assessment of bioequivalence criteria.

11.4.2.8. Examination of Subgroups

This section is not applicable.

11.4.3. Tabulation of Individual Response Data

The individual data for PK parameters are displayed in Appendix 16.2.6.

11.4.4. Drug Dose, Drug Concentration, and Relationships to Response

This section is not applicable.

11.4.5. Drug-Drug and Drug-Disease Interactions

This section is not applicable.

11.4.6. By-Subject Displays

Individual subject concentrations are displayed in Appendix 16.2.5, and individual subject PK parameters are displayed in Appendix 16.2.6.

11.4.7. Pharmacokinetic Conclusions

11.4.7.1. Primary Endpoint Comparisons

Lupin BDP/FF 200/6 mcg (Treatment A) versus FOSTAIR 200/6 mcg (Treatment B) for 17-BMP

The 17-BMP relative bioavailability for Lupin BDP/FF 200/6 mcg (Treatment A) compared to FOSTAIR 200/6 mcg (Treatment B) as measured by the test to reference ratios of the GLSM of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were 102.44, 100.13, and 100.78, respectively, for the PK Analysis Set.

The 90% CI for the GMRs of C_{max} (96.47–108.79%), AUC_{0-t} (95.10–105.42%), and $AUC_{0-\infty}$ (96.18–105.60%) for 17-BMP fell within the bioequivalence limits of 80.00–125.00%.

Lupin BDP/FF 200/6 mcg (Treatment A) versus FOSTAIR 200/6 mcg (Treatment B) for Formoterol

The formoterol relative bioavailability for Lupin BDP/FF 200/6 mcg (Treatment A) compared to FOSTAIR 200/6 mcg (Treatment B) as measured by the test to reference ratios of the GLSM of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were 105.14, 102.73, and 101.52, respectively, for the PK Analysis Set.

The 90% CI for the GMRs of C_{max} (98.67–112.03%), AUC_{0-t} (94.21–112.03%), and $AUC_{0-\infty}$ (95.30–108.15%) for formoterol fell within the bioequivalence limits of 80.00–125.00%.

Lupin BDP/FF 200/6 mcg with Oral Charcoal (Treatment C) versus FOSTAIR 200/6 mcg with Oral Charcoal (Treatment D) for Formoterol

The formoterol relative bioavailability for Lupin BDP/FF 200/6 mcg with oral charcoal (Treatment C) compared to FOSTAIR 200/6 mcg with oral charcoal(Treatment D) as measured by the test to reference ratios of the GLSM of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were 110.43, 111.59, and 104.90, respectively, for the PK Analysis Set.

The 90% CI for the GMRs of C_{max} (103.48–117.85%), AUC_{0-t} (102.12–121.93%), and $AUC_{0-\infty}$ (98.32–111.92%) for formoterol (with oral charcoal) fell within the bioequivalence limits of 80.00–125.00%.

Bioequivalence

As the 90% CI for the GMRs of C_{max} and AUC_{0-t} for 17-BMP (without oral charcoal) 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.

11.4.7.2. Secondary Endpoint Comparison

11.4.7.2.1. Lupin BDP/FF 200/6 mcg (Treatment A) versus FOSTAIR 200/6 mcg (Treatment B) for BDP

The BDP relative bioavailability for Lupin BDP/FF 200/6 mcg (Treatment A) compared to FOSTAIR 200/6 mcg (Treatment B) as measured by the test to reference ratios of the GLSM of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were 97.61, 97.22, and 96.12, respectively, for the PK Analysis Set.

The 90% CI for the GMRs of C_{max} (89.81–106.09%), AUC_{0-t} (90.97–103.91%), and $AUC_{0-\infty}$ (89.58–103.14%) for BDP fell within the bioequivalence limits of 80.00–125.00%.

12. SAFETY EVALUATION

Adverse events were recorded from the time a subject signed the ICF and throughout the entire duration of the study. Non-treatment-emergent adverse events were AEs occurring prior to the start of the first inhalation in treatment period 1, while TEAEs were AEs occurring after the start of the first inhalation in treatment period 1.

12.1. Extent of Exposure

Investigational Product Administration data is displayed by subject in Appendix 16.2.5, Listing 16.2.5.4.

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

Of those subjects randomised, 107 received Treatment A, 106 subjects received Treatment B, 108 subjects received Treatment C, and 109 subjects received Treatment D. Information regarding subjects who did not receive either Treatment A, Treatment B, Treatment C, or Treatment D is detailed in Section 10.1.

12.2. Adverse Events

All AEs for subjects in the Safety Analysis Set are listed in Appendix 16.2.7, Listing 16.2.7.3 and summarised in post-text Table 14.3.1.1, post-text Table 14.3.1.2, post-text Table 14.3.1.3, and post-text Table 14.3.1.4.

No deaths or SAEs occurred in this study.

12.2.1. Brief Summary of Adverse Events

An overview of TEAEs is presented in Table 24.

Table 24: Overview of Subjects with Treatment-Emergent Adverse Events (Safety Analysis Set)

Treatment-Emergent Adverse Event (TEAE) Category, n (%), E	Treatment				Overall (N = 112)
	Lupin BDP/FF 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg (Treatment A) (N = 107)	FOSTAIR 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg (Treatment B) (N = 106)	Lupin BDP/FF 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg with Oral Charcoal (Treatment C) (N = 108)	FOSTAIR 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg with Oral Charcoal (Treatment D) (N = 109)	
At least 1 TEAE	9 (8.4), 11	8 (7.5), 14	12 (11.1), 18	8 (7.3), 12	37 (33.0), 55
At least 1 Serious TEAE	0	0	0	0	0
At least 1 Drug-Related TEAE	7 (6.5), 9	2 (1.9), 3	7 (6.5), 12	5 (4.6), 8	21 (18.8), 32
At least 1 Drug-Related, Serious TEAE	0	0	0	0	0
At least 1 TEAE Leading to Study Drug Discontinuation	0	0	0	0	0
At least 1 TEAE Leading to Study Discontinuation	1 (0.9), 1	1 (0.9), 1	1 (0.9), 1	0	3 (2.7), 3
At least 1 Drug-Related TEAE Leading to Study Discontinuation	1 (0.9), 1	0	0	0	1 (0.9), 1
Any TEAE leading to Death	0	0	0	0	0

Abbreviations: E = number of events.
Source: Table 14.3.1.1.

All AEs were considered TEAEs, as they occurred after the first study drug administration in treatment period 1.

A total of 55 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. 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.

The incidence of TEAEs was low and there was no discernible effect due to treatment.

There were no SAEs or deaths in the study.

12.2.2. Display of Adverse Events

All TEAEs are summarized by SOC and PT in Table 25, and by severity and relationship to study drug in Table 26.

Table 25: Treatment-Emergent Adverse Event Frequency by Treatment – Number of Subjects Reporting the Event (% of Subjects Dosed) (Safety Analysis Set)

System Organ Class Preferred Term, n (%), E	Treatment				Overall (N = 112)
	Lupin BDP/FF 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg (Treatment A) (N = 107)	FOSTAIR 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg (Treatment B) (N = 106)	Lupin BDP/FF 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg with Oral Charcoal (Treatment C) (N = 108)	FOSTAIR 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg with Oral Charcoal (Treatment D) (N = 109)	
At least 1 TEAE	9 (8.4), 11	8 (7.5), 14	12 (11.1), 18	8 (7.3), 12	37 (33.0), 55
Cardiac disorders	1 (0.9), 1	0	1 (0.9), 1	1 (0.9), 1	3 (2.7), 3
Sinus bradycardia	0	0	1 (0.9), 1	0	1 (0.9), 1
Sinus tachycardia	0	0	0	1 (0.9), 1	1 (0.9), 1
Ventricular extrasystoles	1 (0.9), 1	0	0	0	1 (0.9), 1
Gastrointestinal disorders	0	0	2 (1.9), 2	0	2 (1.8), 2
Diarrhoea	0	0	2 (1.9), 2	0	2 (1.8), 2
General disorders and administration site conditions	1 (0.9), 1	1 (0.9), 1	1 (0.9), 1	0	3 (2.7), 3
Influenza like illness	0	0	1 (0.9), 1	0	1 (0.9), 1
Pyrexia	1 (0.9), 1	0	0	0	1 (0.9), 1
Swelling arm	0	1 (0.9), 1	0	0	1 (0.9), 1
Infections and infestations	1 (0.9), 1	2 (1.9), 2	0	0	3 (2.7), 3
Pharyngitis	1 (0.9), 1	1 (0.9), 1	0	0	2 (1.8), 2
Urinary tract infection	0	1 (0.9), 1	0	0	1 (0.9), 1
Investigations	7 (6.5), 8	6 (5.7), 11	9 (8.3), 14	8 (7.3), 11	30 (26.8), 44
Alanine aminotransferase increased	2 (1.9), 2	1 (0.9), 1	1 (0.9), 1	0	4 (3.6), 4
Aspartate aminotransferase increased	0	1 (0.9), 1	1 (0.9), 1	1 (0.9), 1	3 (2.7), 3

System Organ Class Preferred Term, n (%), E	Treatment				Overall (N = 112)
	Lupin BDP/FF 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg (Treatment A) (N = 107)	FOSTAIR 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg (Treatment B) (N = 106)	Lupin BDP/FF 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg with Oral Charcoal (Treatment C) (N = 108)	FOSTAIR 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg with Oral Charcoal (Treatment D) (N = 109)	
Blood albumin decreased	0	1 (0.9), 1	0	0	1 (0.9), 1
Blood alkaline phosphatase increased	1 (0.9), 1	0	3 (2.8), 3	1 (0.9), 1	5 (4.5), 5
Blood glucose increased	1 (0.9), 1	1 (0.9), 1	1 (0.9), 1	2 (1.8), 2	5 (4.5), 5
Blood potassium increased	1 (0.9), 1	1 (0.9), 1	1 (0.9), 1	2 (1.8), 2	5 (4.5), 5
Eosinophil count increased	0	0	2 (1.9), 2	0	2 (1.8), 2
Haemoglobin decreased	1 (0.9), 1	1 (0.9), 1	0	0	2 (1.8), 2
Lymphocyte count decreased	0	0	1 (0.9), 1	0	1 (0.9), 1
Neutrophil count decreased	1 (0.9), 1	0	0	1 (0.9), 1	2 (1.8), 2
Neutrophil count increased	0	1 (0.9), 1	1 (0.9), 1	0	2 (1.8), 2
Platelet count decreased	0	0	1 (0.9), 1	0	1 (0.9), 1
Urine analysis abnormal	0	3 (2.8), 3	2 (1.9), 2	4 (3.7), 4	9 (8.0), 9
White blood cell count decreased	1 (0.9), 1	0	0	0	1 (0.9), 1
White blood cell count increased	0	1 (0.9), 1	0	0	1 (0.9), 1

Note: Adverse events were classified according to MedDRA Version 22.0.
Percentages were based on the number of subjects (N) in each treatment and overall.
Each subject was only counted once per Preferred Term and once per System Organ Class.
Source: Table 14.3.1.2.

Table 26: Treatment-Emergent Adverse Events by Treatment, Severity, and Relationship to Drug – Number of Subjects Reporting the Event (Safety Analysis Set)

System Organ Class Preferred Term, n (%)	Treatment	Number of Subjects					
		Subjects with TEAEs	Severity/Intensity			Relationship to Study Drug	
			Mild	Moderate	Severe	Related	Not Related
Cardiac disorders	A	1	1	0	0	1	0
	C	1	1	0	0	0	1
	D	1	1	0	0	1	0
Sinus bradycardia	C	1	1	0	0	0	1
Sinus tachycardia	D	1	1	0	0	1	0
Ventricular extrasystoles	A	1	1	0	0	1	0
Gastrointestinal disorders	C	1	0	2	0	0	2
Diarrhoea	C	1	0	2	0	0	2
General disorders and administration site conditions	A	1	0	1	0	1	0
	B	1	0	1	0	0	1
	C	1	0	1	0	0	1
Influenza like illness	C	1	0	1	0	0	1
Pyrexia	A	1	0	1	0	1	0
Swelling arm	B	1	0	1	0	0	1
Infections and infestations	A	1	1	0	0	0	1
	B	2	0	2	0	1	1
Pharyngitis	A	1	1	0	0	0	1
	B	1	0	1	0	1	0
Urinary tract infection	B	1	0	1	0	0	1
Investigations	A	7	6	1	0	6	1
	B	6	5	1	0	1	5
	C	9	9	0	0	7	2
	D	8	7	1	0	5	3
Alanine aminotransferase increased	A	2	2	0	0	2	0
	B	1	1	0	0	0	1
	C	1	1	0	0	1	0
Aspartate aminotransferase increased	B	1	1	0	0	0	1
	C	1	1	0	0	1	0
	D	1	1	0	0	1	0
Blood albumin decreased	B	1	1	0	0	0	1

System Organ Class Preferred Term, n (%)	Treatment	Number of Subjects					
		Subjects with TEAEs	Severity/Intensity			Relationship to Study Drug	
			Mild	Moderate	Severe	Related	Not Related
Blood alkaline phosphatase increased	A	1	1	0	0	1	0
	C	3	3	0	0	3	0
	D	1	1	0	0	1	0
Blood glucose increased	A	1	1	0	0	1	0
	B	1	1	0	0	0	1
	C	1	1	0	0	1	0
	D	2	2	0	0	2	0
Blood potassium increased	A	1	1	0	0	1	0
	B	1	1	0	0	0	1
	C	1	1	0	0	1	0
	D	2	2	0	0	2	0
Eosinophil count increased	C	2	2	0	0	2	0
Haemoglobin decreased	A	1	0	1	0	0	1
	B	1	0	1	0	0	1
Lymphocyte count decreased	C	1	1	0	0	1	0
Neutrophil count decreased	A	1	1	0	0	1	0
	D	1	1	0	0	1	0
Neutrophil count increased	B	1	1	0	0	1	0
	C	1	1	0	0	1	0
Platelet count decreased	C	1	1	0	0	1	0
Urine analysis abnormal	B	3	3	0	0	0	3
	C	2	2	0	0	0	2
	D	4	3	1	0	0	4
White blood cell count decreased	A	1	1	0	0	1	0
White blood cell count increased	B	1	1	0	0	1	0

System Organ Class Preferred Term, n (%)	Treatment	Number of Subjects					
		Subjects with TEAEs	Severity/Intensity			Relationship to Study Drug	
			Mild	Moderate	Severe	Related	Not Related
Number of Subjects by Treatment							
Treatment A	(n = 107)	9	7	2	0	7	2
Treatment B	(n = 106)	8	5	3	0	2	6
Treatment C	(n = 108)	12	9	3	0	7	5
Treatment D	(n = 109)	8	7	1	0	5	3
Overall	(N = 112)	37	28	9	0	21	16

Note: Adverse events were classified according to MedDRA Version 22.0.

Each subject was only counted once per Preferred Term and once per System Organ Class.
If any AE occurred more than once, the highest severity or relationship to study medication was used for summary tabulation.
An AE with a missing severity designation would have been summarised as a severe AE.

Related: Certainly related, Probably related, Possibly related, Conditionally related, Unclassifiable; else considered Not Related.

Source: Table 14.3.1.3, Table 14.3.1.4, Appendix 16.1.1, Note to File regarding Data Table 14.3.1.3 and Table 14.3.1.4 Errors, dated 06-Mar-2020.

12.2.3. Analysis of Adverse Events

A total of 55 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 (Section 9.5.1.2.2 and Section 9.5.1.2.4); therefore, a meaningful comparison of incidence or relationship to study drug between treatments for these TEAEs is precluded.

None of the adverse events not associated with laboratory findings were considered unexpected for the treatment.

12.2.4. Listing of Adverse Events by Subject

The listing of TEAEs by subject is presented in Appendix 16.2.7, Listing 16.2.7.3.

12.3. Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

12.3.1. Listing of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

12.3.1.1. Deaths

No deaths occurred during the study.

12.3.1.2. Other Serious Adverse Events

There were no other SAEs reported during this study.

12.3.1.3. Other Significant Adverse Events

There were 3 subjects withdrawn from the study due to a TEAE:

- Subject [redacted] sequence CDBA) discontinued study as the result of a moderate urinary tract infection deemed unlikely to be related to treatment after reference product FOSTAIR 200/6 mcg (Treatment B) administration, and did not subsequently receive the test product Lupin BDP/FF 200/6 mcg (Treatment A)
- Subject [redacted] (sequence DACB) discontinued study as the result of a moderate influenza like illness deemed unlikely to be related to treatment after test product Lupin BDP/FF 200/6 mcg with oral charcoal (Treatment C) administration, and did not subsequently receive the reference product FOSTAIR 200/6 mcg (Treatment B)
- Subject [redacted] (sequence CDBA) discontinued study as the result of moderate pyrexia deemed possibly related to study treatment after test product Lupin BDP/FF 200/6 mcg (Treatment A) administration

12.3.2. Narratives of Deaths, Other Serious Adverse Events, and Certain Other Significant Adverse Events

See Section 14.3.3 for narratives for the subjects who were withdrawn from the study due to TEAEs.

12.3.3. Analysis and Discussion of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

There were no deaths, or other SAEs during the study. See Section 14.3.3 for narratives for the subjects who were withdrawn from the study due to TEAEs.

12.4. Clinical Laboratory Evaluation

12.4.1. Listing of Individual Laboratory Measurements by Subject and Each Abnormal Laboratory Value

Listings of individual subject laboratory results are indicated in the table below (Appendix 16.2.8) for samples obtained. Any clinically significant out of range values were designated as "yes" by the Clinical Investigator.

Title of Listing	Listing Number
Potentially Clinically Significant Abnormal Laboratory Results, Safety Analysis Set	16.2.8.1
Clinical Laboratory Results – Serum Chemistry, Safety Analysis Set	16.2.8.2
Clinical Laboratory Results – Hematology, Safety Analysis Set	16.2.8.3
Clinical Laboratory Results – Urinalysis, Safety Analysis Set	16.2.8.4
Clinical Laboratory Results – Other (Serology), Safety Analysis Set	16.2.8.5
Clinical Laboratory Results – Urine Drug Screen, Safety Analysis Set	16.2.8.6
Clinical Laboratory Results – Cotinine, Safety Analysis Set	16.2.8.7
Clinical Laboratory Results – Breath Alcohol Test, Safety Analysis Set	16.2.8.8

12.4.2. Evaluation of Each Laboratory Parameter

12.4.2.1. Laboratory Values Over Time

Laboratory samples (serum chemistry, hematology, and urinalysis) were collected at the Screening visit and EOS (Day 2 of treatment period 4) as designated in Section 9.5.1.2.2. Clinical laboratory summary and changes from baseline are summarized in post-text Table 14.3.4.4 (serum chemistry) and in post-text Table 14.3.4.5 (hematology), and shifts from baseline are presented in post-text Table 14.3.4.6 (serum chemistry) and in post-text Table 14.3.4.7 (hematology).

12.4.2.2. Individual Subject Changes

Individual subject laboratory results are provided in Appendix 16.2.8. Out-of-range results are summarized in post-text Table 14.3.4.1 (serum chemistry), post-text Table 14.3.4.2 (hematology), and post-text Table 14.3.4.3 (urinalysis). Clinically significant changes in laboratory results that were associated with TEAEs occurred in 15 subjects for serum chemistry, 9 subjects for hematology, and 9 subjects for urinalysis (see Section 12.4.2.3).

12.4.2.3. Individual Clinically Significant Abnormalities

Clinically significant results are presented in post-text Table 14.3.4.1 (serum chemistry), post-text Table 14.3.4.2 (hematology), and post-text Table 14.3.4.3 (urinalysis).

Table 27 summarizes clinically significant laboratory abnormalities reported as AEs. Due to the sampling schedule (i.e., Screening and EOS visits only), association of the clinically significant out-of-range value with a specific study drug (i.e., Lupin BDP/FF 200/6 mcg without or with oral charcoal administration, or FOSTAIR 200/6 mcg without or with oral charcoal administration) cannot be reasonably determined.

Table 27: Summary of Clinically Significant Laboratory Abnormalities by Subject

Subject Number	Laboratory Parameter	Reference Range	Screening Result	Worst End of Study Result	Increase or Decrease	Severity	Relationship to Study Drug	Outcome
[redacted]	Urine occult blood	Negative	Negative	1+	increase	mild	unlikely	recovered/resolved
	Urine leukocytes	0–5/HPF	1/HPF	60/HPF	increase	mild	unlikely	recovered/resolved
	Urine erythrocytes	0–2/HPF	0/HPF	10/HPF	increase	mild	unlikely	recovered/resolved
	Urine epithelial cells	0–5/HPF	2/HPF	40/HPF	increase	mild	unlikely	recovered/resolved
	Urine bacteria	Nil	Negative	Positive	increase	mild	unlikely	recovered/resolved
[redacted]	Urine leukocytes	0–5/HPF	1/HPF	8/HPF	increase	mild	unlikely	recovered/resolved
	Urine bacteria	Nil	Negative	Positive	increase	mild	unlikely	recovered/resolved
[redacted]	Haemoglobin	12.0–15.0 g/dL	11.3 g/dL	9.8 g/dL	decrease	moderate	unlikely	recovered/resolved
[redacted]	AST	<35 U/L	54.8 U/L	73.0 U/L	increase	mild	unlikely	ongoing
	ALT	<35 U/L	66.6 U/L	82.5 U/L	increase	mild	unlikely	ongoing
[redacted]	Albumin	3.5–5.2 g/dL	4.00 g/dL	2.93 g/dL	decrease	mild	unlikely	ongoing
	Blood glucose	70–199 mg/dL (random)	96.9 mg/dL	NA	increase	mild	unlikely	ongoing
		70–99 mg/dL (fasting)	NA	141.8 mg/dL				
	Potassium	3.50–5.10 mmol/L	5.2 mmol/L	5.8 mmol/L	increase	mild	unlikely	ongoing
	Haemoglobin	12.0–15.0 g/dL	11.8 g/dL	9.9 g/dL	decrease	moderate	unlikely	ongoing
[redacted]	Urine leukocytes	0–5/HPF	2/HPF	80/HPF	increase	moderate	unlikely	recovered/resolved
	Urine bacteria	Nil	Negative	Positive	increase	moderate	unlikely	recovered/resolved
[redacted]	Alkaline phosphatase	30–120 U/L	120 U/L	168 U/L	increase	mild	possibly	recovered/resolved
[redacted]	Blood glucose	70–199 mg/dL (random)	89.1 mg/dL	NA	increase	mild	possibly	ongoing
		70–99 mg/dL (fasting)	NA	151.8 mg/dL				
	Urine protein	Negative	Negative	1+	increase	mild	unlikely	ongoing
	Urine leukocytes	0–5/HPF	2/HPF	60/HPF	increase	mild	unlikely	ongoing
	Urine epithelial cells	0–5/HPF	2/HPF	30/HPF	increase	mild	unlikely	ongoing
	Urine bacteria	Nil	Negative	Positive	increase	mild	unlikely	ongoing

Subject Number	Laboratory Parameter	Reference Range	Screening Result	Worst End of Study Result	Increase or Decrease	Severity	Relationship to Study Drug	Outcome
[redacted]	Urine leukocytes	0–5/HPF	1/HPF	20/HPF	increase	mild	unlikely	recovered/resolved
	Urine epithelial cells	0–5/HPF	2/HPF	10/HPF	increase	mild	unlikely	recovered/resolved
	Urine bacteria	Nil	Negative	Positive	increase	mild	unlikely	recovered/resolved
[redacted]	Urine protein	Negative	Negative	1+	increase	mild	unlikely	recovered/resolved
	Urine occult blood	Negative	Negative	3+	increase	mild	unlikely	recovered/resolved
	Urine bilirubin	Negative	Negative	1+	increase	mild	unlikely	recovered/resolved
[redacted]	Blood glucose	70–199 mg/dL (random)	83.0 mg/dL	NA	increase	mild	possibly	ongoing
		70–99 mg/dL (fasting)	NA	149.5 mg/dL				
[redacted]	Blood glucose	70–199 mg/dL (random)	114.6 mg/dL	NA	increase [a]	mild	possibly	recovered/resolved
		70–99 mg/dL (fasting)	NA	110.7 mg/dL				
	Alkaline phosphatase	30–120 U/L	102 U/L	140 U/L	increase	mild	possibly	recovered/resolved
	AST	<35 U/L	23.6 U/L	91.7 U/L	increase	mild	possibly	recovered/resolved
	ALT	<35 U/L	51.6 U/L	137.2 U/L	increase	mild	possibly	recovered/resolved
[redacted]	Alkaline phosphatase	30–120 U/L	87 U/L	160 U/L	increase	mild	possibly	ongoing
[redacted]	Urine occult blood	Negative	Negative	1+	increase	mild	unlikely	recovered/resolved
	Urine epithelial cells	0–5/HPF	2/HPF	8/HPF	increase	mild	unlikely	recovered/resolved
	Urine glucose	Negative	Negative	1+	increase	mild	unlikely	recovered/resolved
[redacted]	Potassium	3.50–5.10 mmol/L	4.3 mmol/L	5.5 mmol/L	increase	mild	possibly	recovered/resolved
[redacted]	Platelets	150–400 × 10^3/µL	228 × 10^3/µL	114 × 10^3/µL	decrease	mild	possibly	recovered/resolved
[redacted]	Leukocytes	4.0–11.0 × 10^3/µL	5.3 × 10^3/µL	3.5 × 10^3/µL	decrease	mild	possibly	recovered/resolved
	Neutrophils, absolute	2.00–7.00 × 10^3/µL	2.14 × 10^3/µL [b]	1.51 × 10^3/µL	decrease	mild	possibly	recovered/resolved
[redacted]	Eosinophils	1–6%	1.9%	18%	increase	mild	possibly	recovered/resolved
[redacted]	Potassium	3.50–5.10 mmol/L	4.5 mmol/L	5.5 mmol/L	increase	mild	possibly	recovered/resolved
[redacted]	ALT	<50 U/L	43.7 U/L	92.2 U/L	increase	mild	possibly	ongoing

Subject Number	Laboratory Parameter	Reference Range	Screening Result	Worst End of Study Result	Increase or Decrease	Severity	Relationship to Study Drug	Outcome
[redacted]	Potassium	3.50–5.10 mmol/L	5.3 mmol/L	5.6 mmol/L	increase	mild	possibly	ongoing
	Lymphocytes	20–40%	36.6%	15%	decrease	mild	possibly	ongoing
	Neutrophils	40–75%	52.4%	76%	increase	mild	possibly	ongoing
[redacted]	Alkaline phosphatase	30–120 U/L	134 U/L	162 U/L	increase	mild	possibly	recovered/resolved
	Blood glucose	70–199 mg/dL (random)	100.8 mg/dL	NA	increase	mild	possibly	recovered/resolved
		70–99 mg/dL (fasting)	NA	139.8 mg/dL				
	AST	<50 U/L	23.1 U/L	70.2 U/L	increase	mild	possibly	recovered/resolved
[redacted]	Leukocytes	4.0–11.0 × 10^3/µL	8.4 × 10^3/µL	17.4 × 10^3/µL	increase	mild	possibly	ongoing
	Neutrophils	40–75%	58.6%	77%	increase	mild	possibly	ongoing
[redacted]	Potassium	3.50–5.10 mmol/L	4.6 mmol/L	5.6 mmol/L	increase	mild	possibly	recovered/resolved
[redacted]	Neutrophils	40–75%	52.6%	37.6%	decrease	mild	possibly	recovered/resolved
[redacted]	Alkaline phosphatase	30–120 U/L	125 U/L	171 U/L	increase	mild	possibly	ongoing
[redacted]	ALT	<50 U/L	47.5 U/L	67.7 U/L	increase	mild	possibly	ongoing
[redacted]	Urine occult blood	Negative	Negative	1+	increase	mild	unlikely	recovered/resolved
	Urine epithelial cells	0–5/HPF	3/HPF	10/HPF	increase	mild	unlikely	recovered/resolved
[redacted]	Urine leukocytes	0–5/HPF	1/HPF	20/HPF	increase	mild	unlikely	ongoing
[redacted]	Eosinophils	1–6%	7.7%	13.3%	increase	mild	possibly	recovered/resolved

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; HPF = high-powered field; NA = not applicable.

Note: The urinalysis findings for each subject were reported as a grouped AE of "urine analysis abnormal".

a. Random blood glucose for Subject [redacted] was within the normal range at screening. Fasting blood glucose was above the upper limit of normal at End of Study, and is therefore marked as "increase" (which also corresponds to the adverse event term "blood glucose increased").

b. Absolute neutrophil count was not performed for Subject [redacted] at screening. Value is calculated based on the leukocyte result of 5.3 × 10^3/µL and neutrophil percent of 40.3%.

Source: Table 14.3.4.1, Table 14.3.4.2, Table 14.3.4.3; Appendix 16.2.7, Listing 16.2.7.3; Appendix 16.2.8, Listing 16.2.8.2, Listing 16.2.8.3, Listing 16.2.8.4.

12.5. Vital Signs, Physical Findings, and Other Observations Related to Safety

Vital signs, electrocardiogram, and physical examination findings by subject are provided in Appendix 16.2.10 and indicated in the table below.

Title of Listing	Listing Number
Vital Signs Normal Ranges	16.2.8.9.1
Vital Signs, Safety Analysis Set	16.2.8.9.2
Abnormal Physical Examination Findings, Safety Analysis Set	16.2.10.1
ECG Parameters and Overall Interpretation, Safety Analysis Set	16.2.10.2

12.5.1. Vital Signs Assessments

Vital signs measurements were collected during screening, during each treatment period (on Day -1 at check-in; on Day 0 prior to dosing, and at 2, 4, 6, and 12 hours post-dose; Day 1 at 24, and 36 hours post-dose; and Day 2 prior to discharge from each treatment period), and at the EOS visit. The EOS assessments were completed on Day 2 of treatment period 4 or upon early termination from the study. The vital signs summary and change from baseline results are presented in post-text Table 14.3.5. There were no clinically meaningful changes in vital signs, and no subjects reported TEAEs associated with vital signs measurements.

12.5.2. Physical Examinations

Physical examinations were performed at the Screening visit, during each treatment period on Day -1 (check-in), and on Day 2 (check-out). The EOS assessments were completed on Day 2 of treatment period 4 or upon early termination from the study. Physical examination findings at baseline are presented in post-text Table 14.1.5 (also reference Appendix 16.1.1, Note to File re: Data Table 14.1.5 Error, dated 27-Feb-2020), and physical examination findings shifts from baseline to EOS are presented in post-text Table 14.3.7. Two TEAEs related to physical examination findings were reported: mild pharyngitis (Subject [redacted]), and moderate swelling arm (Subject [redacted]). Both events recovered and were considered by the Investigator as unlikely to be related to treatment.

12.5.3. Electrocardiography (ECG)

An ECG was performed at the Screening visit and at the EOS visit. The EOS assessments were completed on Day 2 of treatment period 4 or upon early termination from the study. The ECG summary and change from baseline results are presented in post-text Table 14.3.6.1, and ECG findings shift from baseline data are presented post-text Table 14.3.6.2. Three transient TEAEs related to ECGs were reported: mild sinus tachycardia (Subject [redacted] mild ventricular extrasystoles (Subject [redacted], and mild sinus bradycardia (Subject [redacted]). All 3 events recovered upon same-day repeat testing; the sinus bradycardia was considered by the Investigator as unlikely to be related to treatment, and the sinus tachycardia and ventricular extrasystoles were considered by the Investigator to possibly be related to treatment.

12.5.4. Cough Assessment

Cough frequency assessment was completed through 2 minutes after dosing in each treatment period, and is summarized in Table 28. 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.

Following the treatments without oral charcoal, the percentage of subjects who did not cough during the 2-minute post-dosing interval was similar between Treatments A and B (95.3% and 98.1%, respectively). A total of 5 (4.7%) subjects coughed following Treatment A: 3 coughs in 2 (1.9%) subjects, and 2, 4, or 5 coughs in 1 (0.9%) subject each. A total of 2 (1.9%) subjects coughed following Treatment B: 1 or 2 coughs in 1 (0.9%) subject each.

Following the treatments with oral charcoal, the percentage of subjects who did not cough during the 2-minute post-dosing interval was slightly lower in Treatment C than in Treatment D (86.1% and 93.6%, respectively). A total of 15 (13.9%) subjects coughed following Treatment C: 2 coughs in 7 (6.5%) subjects, 1 cough in 6 (5.6%) subjects, and 3 or 4 coughs in 1 (0.9%) subject each. A total of 7 (6.4%) subjects coughed following Treatment D: 1 cough in 5 (4.6%) subjects, and 2 coughs in 2 (1.8%) subjects.

No subjects experienced >5 coughs during the 2-minute post-dosing interval for any treatment.

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).

Table 28: Summary of Cough Assessment (Safety Analysis Set)

Cough Category, n (%)	Treatment				Overall (N = 112)
	Lupin BDP/FF 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg (Treatment A) (N = 107)	FOSTAIR 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg (Treatment B) (N = 106)	Lupin BDP/FF 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg with Oral Charcoal (Treatment C) (N = 108)	FOSTAIR 200/6 mcg (2 inhalations) Total Dose = 400/12 mcg with Oral Charcoal (Treatment D) (N = 109)	
Subjects with no coughs	102 (95.3)	104 (98.1)	93 (86.1)	102 (93.6)	91 (81.2)
Subjects with ≥1 cough	5 (4.7)	2 (1.9)	15 (13.9)	7 (6.4)	21 (18.8)
Subjects by actual number of coughs observed					
1	0	1 (0.9)	6 (5.6)	5 (4.6)	7 (6.3)
2	1 (0.9)	1 (0.9)	7 (6.5)	2 (1.8)	9 (8.0)
3	2 (1.9)	0	1 (0.9)	0	2 (1.8)
4	1 (0.9)	0	1 (0.9)	0	2 (1.8)
5	1 (0.9)	0	0	0	1 (0.9)

Source: Table 14.3.10.

12.6. Safety Conclusions

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 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 (Section 9.5.1.2.2 and Section 9.5.1.2.4); 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 deemed 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 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).

13. DISCUSSION AND OVERALL CONCLUSIONS

[redacted]

The purpose of this study was to assess and compare the PK profiles of 17-BMP, BDP, and formoterol following administration of beclometasone dipropionate/formoterol fumarate dihydrate pressurised inhalation solution combination products as 2 inhalations from Lupin BDP/FF 200/6 mcg and FOSTAIR 200/6 mcg in this open-label, randomised, 4-period, 4-treatment, 4-sequence, crossover design in healthy subjects, ages 18 to 45 years, under fasting conditions. The study design was based on the FDA Guidance on Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations, Revision 1 dated March 2003, Guidance for Industry: Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs – General Considerations, March 2014, and European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP): Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr). London, 20 January 2010.

13.1. Pharmacokinetic Conclusions

The primary objective of the study was to assess and compare the PK profiles of 17-BMP and formoterol following 2 inhalations from Lupin BDP/FF 200/6 mcg (Treatment A) and FOSTAIR 200/6 mcg (Treatment B) without charcoal block; and to assess and compare the PK profiles of formoterol following administration of Lupin BDP/FF 200/6 mcg and FOSTAIR 200/6 mcg with charcoal block (Treatments C and D, respectively) in healthy subjects ages 18–45 years, under fasting conditions.

Lupin BDP/FF 200/6 mcg (Treatment A) versus FOSTAIR 200/6 mcg (Treatment B) for 17-BMP

- 17-BMP appeared rapidly in plasma following administration of the test product Lupin BDP/FF 200/6 mcg (Treatment A) and the reference product FOSTAIR 200/6 mcg (Treatment B). 17-BMP mean concentrations were similar between the two products.
- The mean $t_{½}$ was similar for Treatment A (3.8680 hours) and Treatment B (3.7421 hours).
- The intrasubject CV%s are 25.38%, 21.66%, and 18.99% for 17-BMP C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$, respectively.
- The 17-BMP relative bioavailability for Lupin BDP/FF 200/6 mcg (Treatment A) compared to FOSTAIR 200/6 mcg (Treatment B) as measured by the test to reference ratios of the GLSM of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were 102.44, 100.13, and 100.78, respectively, for the PK Analysis Set.
- The 90% CI for the GMRs of C_{max} (96.47–108.79%), AUC_{0-t} (95.10–105.42%), and $AUC_{0-\infty}$ (96.18–105.60%) for 17-BMP fell within the bioequivalence limits of 80.00–125.00%.

Lupin BDP/FF 200/6 mcg (Treatment A) versus FOSTAIR 200/6 mcg (Treatment B) for Formoterol

- Formoterol appeared rapidly in plasma following administration of the test product Lupin BDP/FF 200/6 mcg (Treatment A) and the reference product FOSTAIR 200/6 mcg (Treatment B). Formoterol mean concentrations were similar between the two products.
- The mean $t_{½}$ was similar for Treatment A (8.4519 hours) and Treatment B (8.1116 hours).
- The intrasubject CV%s are 26.75%, 37.03%, and 22.00% for 17-BMP C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$, respectively.
- The formoterol relative bioavailability for Lupin BDP/FF 200/6 mcg (Treatment A) compared to FOSTAIR 200/6 mcg (Treatment B) as measured by the test to reference ratios of the GLSM of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were 105.14, 102.73, and 101.52, respectively, for the PK Analysis Set.
- The 90% CI for the GMRs of C_{max} (98.67–112.03%), AUC_{0-t} (94.21–112.03%), and $AUC_{0-\infty}$ (95.30–108.15%) for formoterol fell within the bioequivalence limits of 80.00–125.00%.

Lupin BDP/FF 200/6 mcg with Oral Charcoal (Treatment C) versus FOSTAIR 200/6 mcg with Oral Charcoal (Treatment D) for Formoterol

- Formoterol appeared rapidly in plasma following administration of the test product Lupin BDP/FF 200/6 mcg with oral charcoal (Treatment C) and the reference product FOSTAIR 200/6 mcg with oral charcoal (Treatment D). Formoterol (with oral charcoal) mean concentrations were similar between the two products.
- The mean $t_{½}$ was longer for Treatment C (8.5123 hours) compared to Treatment D (7.2817 hours).
- The formoterol relative bioavailability for Lupin BDP/FF 200/6 mcg with oral charcoal (Treatment C) compared to FOSTAIR 200/6 mcg with oral charcoal(Treatment D) as measured by the test to reference ratios of the GLSM of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were 110.43, 111.59, and 104.90, respectively, for the PK Analysis Set.
- The 90% CI for the GMRs of C_{max} (103.48–117.85%), AUC_{0-t} (102.12–121.93%), and $AUC_{0-\infty}$ (98.32–111.92%) for formoterol (with oral charcoal) fell within the bioequivalence limits of 80.00–125.00%.

13.2. Safety Conclusions

- A total of 55 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 deemed 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 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).

13.3. Overall Conclusions

PK Conclusions

- 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 Conclusions

- 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.

14. TABLES AND FIGURES REFERRED TO BUT NOT INCLUDED IN THE TEXT

14.1. Demographic Data Summary Tables

This section contains the following tables:

Number	Title
14.1.1.1	Summary of Disposition
14.1.2.1	Summary of Demographic Characteristics by Sequence and Overall, Safety Analysis Set
14.1.2.2	Summary of Demographic Characteristics by Sequence and Overall, PK Analysis Set
14.1.2.3	Summary of Demographic Characteristics by Sequence and Overall, FAS
14.1.3	Summary of Demographic Characteristics by Treatment and Overall, PK Analysis Set
14.1.4	Summary of Analysis Populations by Treatment
14.1.5	Abnormal Physical Examination Findings at Baseline, Safety Analysis Set
14.1.6	Medical History, FAS

Table 14.1.1.1. Summary of Disposition

	Sequence				
Category	**ABDC n (%)**	**BCAD n (%)**	**CDBA n (%)**	**DACB n (%)**	**Total**
Enrolled	28 (100.0)	28 (100.0)	28 (100.0)	28 (100.0)	112
Completed	26 (92.9)	27 (96.4)	24 (85.7)	25 (89.3)	102
Discontinued	2 (7.1)	1 (3.6)	4 (14.3)	3 (10.7)	10
Adverse Event	0	0	2 (7.1)	1 (3.6)	3
Withdrawal By Subject	0	1 (3.6)	1 (3.6)	1 (3.6)	3
Protocol Violation	1 (3.6)	0	1 (3.6)	1 (3.6)	3
Other	1 (3.6)	0	0	0	1
Source: Listing 16.2.1					

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
Table Generation 03FEB2020 at 4:43 PM by Table 14.1.1.1.sas

Table 14.1.2.1. Summary of Demographic Characteristics by Sequence and Overall, Safety Analysis Set

		Treatment Sequence				
Characteristics	**Statistic**	**ABDC (N=28)**	**BCAD (N=28)**	**CDBA (N=28)**	**DACB (N=28)**	**Overall (N=112)**
Sex						
Male	n (%)	21 (75.0)	20 (71.4)	21 (75.0)	20 (71.4)	82 (73.2)
Female	n (%)	7 (25.0)	8 (28.6)	7 (25.0)	8 (28.6)	30 (26.8)
Race						
Asian	n (%)	28 (100.0)	28 (100.0)	28 (100.0)	28 (100.0)	112 (100.0)
Ethnicity						
Unknown	n (%)	28 (100.0)	28 (100.0)	28 (100.0)	28 (100.0)	112 (100.0)
Age (yr)	N	28	28	28	28	112
	Mean	28.5	29.1	28.3	27.6	28.4
	SD	5.7	5.0	6.0	6.2	5.7
	Minimum	21	19	18	20	18
	Median	30	29	29	27	28
	Maximum	42	40	39	44	44
	CV	20.11	17.34	21.36	22.37	20.13
Weight (kg)	N	28	28	28	28	112
	Mean	64.02	61.45	64.04	66.19	63.92
	SD	7.06	7.22	9.06	8.44	8.06
	Minimum	51.5	50.2	50.3	54.1	50.2

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
Table Generation 03FEB2020 at 4:50 PM by Table 14.1.2.1.sas

Table 14.1.2.1. Summary of Demographic Characteristics by Sequence and Overall, Safety Analysis Set

		Treatment Sequence				
Characteristics	**Statistic**	**ABDC (N=28)**	**BCAD (N=28)**	**CDBA (N=28)**	**DACB (N=28)**	**Overall (N=112)**
	Median	64.4	62.8	64.1	64.6	63.2
	Maximum	74.2	75.5	83.1	84.9	84.9
	CV	11.02	11.74	14.15	12.75	12.61
Height (cm)	N	28	28	28	28	112
	Mean	165.2	164.5	164.5	163.4	164.4
	SD	8.6	8.2	9.0	8.6	8.5
	Minimum	146	145	144	144	144
	Median	166	164	168	166	165
	Maximum	181	180	175	180	181
	CV	5.21	4.97	5.45	5.25	5.17
BMI (kg/m^2)	N	28	28	28	28	112
	Mean	23.57	22.78	23.68	24.90	23.73
	SD	3.05	2.92	2.89	3.45	3.14
	Minimum	18.7	18.6	18.7	18.6	18.6
	Median	23.5	22.5	23.7	24.9	23.4
	Maximum	29.8	29.9	29.2	29.8	29.9
	CV	12.93	12.83	12.21	13.85	13.22

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
Table Generation 03FEB2020 at 4:50 PM by Table 14.1.2.1.sas

Table 14.1.2.2. Summary of Demographic Characteristics by Sequence and Overall, PK Analysis Set

		Treatment Sequence				
Characteristics	**Statistic**	**ABDC (N=26)**	**BCAD (N=27)**	**CDBA (N=25)**	**DACB (N=26)**	**Overall (N=104)**
Sex						
Male	n (%)	21 (80.8)	20 (74.1)	19 (76.0)	18 (69.2)	78 (75.0)
Female	n (%)	5 (19.2)	7 (25.9)	6 (24.0)	8 (30.8)	26 (25.0)
Race						
Asian	n (%)	26 (100.0)	27 (100.0)	25 (100.0)	26 (100.0)	104 (100.0)
Ethnicity						
Unknown	n (%)	26 (100.0)	27 (100.0)	25 (100.0)	26 (100.0)	104 (100.0)
Age (yr)	N	26	27	25	26	104
	Mean	28.2	29.0	28.3	27.7	28.3
	SD	5.9	5.1	6.3	6.4	5.9
	Minimum	21	19	18	20	18
	Median	28	28	29	27	28
	Maximum	42	40	39	44	44
	CV	20.78	17.68	22.12	23.11	20.68
Weight (kg)	N	26	27	25	26	104
	Mean	64.48	61.06	64.70	66.85	64.24
	SD	7.08	7.06	9.18	8.34	8.10
	Minimum	51.5	50.2	50.3	55.1	50.2

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
Table Generation 14FEB2020 at 11:40 AM by Table 14.1.2.2.sas

Table 14.1.2.2. Summary of Demographic Characteristics by Sequence and Overall, PK Analysis Set

		Treatment Sequence				
Characteristics	**Statistic**	**ABDC (N=26)**	**BCAD (N=27)**	**CDBA (N=25)**	**DACB (N=26)**	**Overall (N=104)**
	Median	65.4	62.7	64.2	66.3	63.5
	Maximum	74.2	75.5	83.1	84.9	84.9
	CV	10.99	11.56	14.18	12.48	12.62
Height (cm)	N	26	27	25	26	104
	Mean	166.2	164.7	165.0	163.4	164.8
	SD	8.1	8.3	9.2	8.9	8.5
	Minimum	146	145	144	144	144
	Median	167	164	168	166	166
	Maximum	181	180	175	180	181
	CV	4.86	5.01	5.55	5.44	5.17
BMI (kg/m^2)	N	26	27	25	26	104
	Mean	23.47	22.57	23.81	25.15	23.74
	SD	3.04	2.76	3.03	3.44	3.17
	Minimum	18.7	18.6	18.7	18.6	18.6
	Median	23.5	22.3	24.1	25.3	23.6
	Maximum	29.8	29.9	29.2	29.8	29.9

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
Table Generation 14FEB2020 at 11:40 AM by Table 14.1.2.2.sas

Table 14.1.2.2. Summary of Demographic Characteristics by Sequence and Overall, PK Analysis Set

		Treatment Sequence				
Characteristics	**Statistic**	**ABDC (N=26)**	**BCAD (N=27)**	**CDBA (N=25)**	**DACB (N=26)**	**Overall (N=104)**
	CV	12.97	12.22	12.73	13.68	13.36

Source: Listing 16.2.4.1
[redacted] was withdrawn due to adverse events and did not receive Treatment A
[redacted] voluntarily withdrew consent and did not receive Treatments D
[redacted] and 067 were excluded due to major protocol deviations from A and C
[redacted] was withdrawn on medical grounds due to difficulty in cannulation and did not receive Treatments B, D and C
[redacted] was withdrawn due to protocol violation and did not receive Treatments B and A
[redacted] voluntarily withdrew consent and did not receive Treatments A, C and B
[redacted] was withdrawn due to protocol violation did not receive Treatment C
[redacted] voluntarily withdrew consent and did not receive Treatments D, B and A
[redacted] was withdrawn due to failure to comply with protocol requirements and did not receive Treatments A, C and B

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
Table Generation 14FEB2020 at 11:40 AM by Table 14.1.2.2.sas

Table 14.1.2.3. Summary of Demographic Characteristics by Sequence and Overall, FAS

		Treatment Sequence				
Characteristics	**Statistic**	**ABDC (N=27)**	**BCAD (N=28)**	**CDBA (N=27)**	**DACB (N=26)**	**Overall (N=108)**
Sex						
Male	n (%)	21 (77.8)	20 (71.4)	20 (74.1)	18 (69.2)	79 (73.1)
Female	n (%)	6 (22.2)	8 (28.6)	7 (25.9)	8 (30.8)	29 (26.9)
Race						
Asian	n (%)	27 (100.0)	28 (100.0)	27 (100.0)	26 (100.0)	108 (100.0)
Ethnicity						
Unknown	n (%)	27 (100.0)	28 (100.0)	27 (100.0)	26 (100.0)	108 (100.0)
Age (yr)	N	27	28	27	26	108
	Mean	28.4	29.1	28.3	27.7	28.4
	SD	5.8	5.0	6.1	6.4	5.8
	Minimum	21	19	18	20	18
	Median	29	29	29	27	28
	Maximum	42	40	39	44	44
	CV	20.44	17.34	21.76	23.11	20.43
Weight (kg)	N	27	28	27	26	108
	Mean	64.34	61.45	64.46	66.85	64.22
	SD	6.99	7.22	8.94	8.34	8.03
	Minimum	51.5	50.2	50.3	55.1	50.2

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
Table Generation 03FEB2020 at 5:07 PM by Table 14.1.2.3.sas

Table 14.1.2.3. Summary of Demographic Characteristics by Sequence and Overall, FAS

		Treatment Sequence				
Characteristics	**Statistic**	**ABDC (N=27)**	**BCAD (N=28)**	**CDBA (N=27)**	**DACB (N=26)**	**Overall (N=108)**
	Median	65.2	62.8	64.2	66.3	63.5
	Maximum	74.2	75.5	83.1	84.9	84.9
	CV	10.86	11.74	13.88	12.48	12.50
Height (cm)	N	27	28	27	26	108
	Mean	165.5	164.5	164.8	163.4	164.6
	SD	8.7	8.2	9.0	8.9	8.6
	Minimum	146	145	144	144	144
	Median	167	164	168	166	166
	Maximum	181	180	175	180	181
	CV	5.23	4.97	5.45	5.44	5.21
BMI (kg/m^2)	N	27	28	27	26	108
	Mean	23.62	22.78	23.76	25.15	23.81
	SD	3.09	2.92	2.92	3.44	3.17
	Minimum	18.7	18.6	18.7	18.6	18.6
	Median	23.5	22.5	23.8	25.3	23.6
	Maximum	29.8	29.9	29.2	29.8	29.9

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
Table Generation 03FEB2020 at 5:07 PM by Table 14.1.2.3.sas

Table 14.1.2.3. Summary of Demographic Characteristics by Sequence and Overall, FAS

		Treatment Sequence				
Characteristics	**Statistic**	**ABDC (N=27)**	**BCAD (N=28)**	**CDBA (N=27)**	**DACB (N=26)**	**Overall (N=108)**
	CV	13.10	12.83	12.28	13.68	13.31

Source: Listing 16.2.4.1
Subject no. [redacted] was withdrawn on medical grounds due to difficulty in cannulation and did not receive Treatments B, D and C
Subject no[redacted] voluntarily withdrew consent and did not receive Treatments A, C and B
Subject no[redacted] voluntarily withdrew consent and did not receive Treatments D, B and A
Subject no. [redacted] was withdrawn due to failure to comply with protocol requirements and did not receive Treatments A, C and B

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
Table Generation 03FEB2020 at 5:07 PM by Table 14.1.2.3.sas

Table 14.1.3. Summary of Demographic Characteristics by Treatment and Overall, PK Analysis Set

Characteristics	Statistic	Treatment A (N=97)	Treatment B (N=97)	Treatment C (N=88)	Treatment D (N=88)	Overall (N=104)
Sex						
Male	n (%)	73 (75.3)	73 (75.3)	68 (77.3)	68 (77.3)	78 (75.0)
Female	n (%)	24 (24.7)	24 (24.7)	20 (22.7)	20 (22.7)	26 (25.0)
Race						
Asian	n (%)	97 (100.0)	97 (100.0)	88 (100.0)	88 (100.0)	104 (100.0)
Ethnicity						
Unknown	n (%)	97 (100.0)	97 (100.0)	88 (100.0)	88 (100.0)	104 (100.0)
Age Group						
18-40 years	n (%)	96 (99.0)	96 (99.0)	86 (97.7)	86 (97.7)	102 (98.1)
41-64 years	n (%)	1 (1.0)	1 (1.0)	2 (2.3)	2 (2.3)	2 (1.9)
Age (yr)	N	97	97	88	88	104
	Mean	28.4	28.4	28.2	28.2	28.3
	SD	5.7	5.7	5.9	5.9	5.9
	Minimum	18	18	18	18	18
	Median	28	28	28	28	28
	Maximum	44	44	44	44	44
	CV	19.94	19.94	20.86	20.86	20.68
Weight (kg)	N	97	97	88	88	104
	Mean	63.77	63.77	64.70	64.70	64.24

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
Table Generation 03FEB2020 at 6:12 PM by Table 14.1.3.sas

Table 14.1.3. Summary of Demographic Characteristics by Treatment and Overall, PK Analysis Set

Characteristics	Statistic	Treatment A (N=97)	Treatment B (N=97)	Treatment C (N=88)	Treatment D (N=88)	Overall (N=104)
	SD	7.68	7.68	8.24	8.24	8.10
	Minimum	50.2	50.2	50.2	50.2	50.2
	Median	63.2	63.2	64.1	64.1	63.5
	Maximum	81.9	81.9	84.9	84.9	84.9
	CV	12.04	12.04	12.73	12.73	12.62
Height (cm)	N	97	97	88	88	104
	Mean	164.8	164.8	165.3	165.3	164.8
	SD	8.4	8.4	8.3	8.3	8.5
	Minimum	144	144	144	144	144
	Median	165	165	167	167	166
	Maximum	181	181	181	181	181
	CV	5.11	5.11	5.01	5.01	5.17
BMI (kg/m^2)	N	97	97	88	88	104
	Mean	23.56	23.56	23.75	23.75	23.74
	SD	3.07	3.07	3.13	3.13	3.17
	Minimum	18.6	18.6	18.6	18.6	18.6
	Median	23.4	23.4	23.6	23.6	23.6
	Maximum	29.9	29.9	29.9	29.9	29.9

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
Table Generation 03FEB2020 at 6:12 PM by Table 14.1.3.sas

Table 14.1.3. Summary of Demographic Characteristics by Treatment and Overall, PK Analysis Set

Characteristics	Statistic	Treatment A (N=97)	Treatment B (N=97)	Treatment C (N=88)	Treatment D (N=88)	Overall (N=104)
	CV	13.03	13.03	13.17	13.17	13.36

Source: Listing 16.2.4.1
Subject no. [redacted] was withdrawn due to adverse events and did not receive Treatment A
Subject no. [redacted] voluntarily withdrew consent and did not receive Treatments D
Subject no. [redacted] was withdrawn on medical grounds due to difficulty in cannulation and did not receive Treatments B, D and C
Subject no[redacted] did not have any measurable formoterol concentrations following administration of Treatment C and therefore was excluded from Treatment C and D
Subject no. [redacted] was withdrawn due to protocol violation and did not receive Treatments B and A
Subject no. [redacted] voluntarily withdrew consent and did not receive Treatments A, C and B
Subject no. [redacted] was withdrawn due to protocol violation did not receive Treatment C
Subject no. [redacted] was withdrawn due to adverse events and did not receive Treatment B
Subject no. [redacted] voluntarily withdrew consent and did not receive Treatments D, B and A
Subject no[redacted] was withdrawn due to failure to comply with protocol requirements and did not receive Treatments A, C and B
Subject no. [redacted] were excluded due to major protocol deviations for Treatments A & B
Subject no. [redacted] were excluded due to major protocol deviations for Treatments C & D

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
Table Generation 03FEB2020 at 6:12 PM by Table 14.1.3.sas

Table 14.1.4. Summary of Analysis Population by Treatment

Visit	Treatment A n (%)	Treatment B n (%)	Treatment C n (%)	Treatment D n (%)	Total
Safety Analysis Set	107 (95.5)	106 (94.6)	108 (96.4)	109 (97.3)	112
FAS	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

Percentages are based on the total number of subjects in the Safety Analysis Set
Source: Listing 16.2.3 and 16.2.4.1

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
Table Generation 04FEB2020 at 10:56 AM by Table 14.1.4.sas

Table 14.1.5 Abnormal Physical Examination Findings at Baseline, Safety Analysis Set

Category **n (%)**	**Overall** **(N=112)**
Subject with a physical examination	112 (100)
Subject with at least 1 abnormal finding	3 (2.7)
General Examination	2 (1.8)
HEENT	1 (0.9)

Source: Listing 16.2.10.1
H.E.E.N.T - Head or Eyes or Ear or Nose or Throat

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
Table Generation 04FEB2020 at 9:32 AM by Table 14.1.5.sas

Table 14.1.6 Medical History, FAS

No medical history items were reported.

14.2. Pharmacokinetic Data Summary Tables

This section contains the following tables:

Table 14.2.1.1 Summary of 17-BMP Plasma Concentrations (pg/mL) by Treatment, PK Analysis Set (without charcoal)

Treatment		0.00	0.03	0.06	0.10	0.13	0.18	0.25	0.33	0.50	0.75
A	N	97	96	97	96	97	97	97	97	97	97
	Mean	0.0000	165.5410	384.9160	447.3937	468.7058	495.3051	512.0226	466.0820	486.5646	461.0801
	SD	0.0000	163.2069	280.0452	257.7544	266.3829	283.9599	271.8721	238.8114	225.9634	206.7339
	Min	0.000	0.000	0.000	26.468	45.514	58.401	63.506	53.772	75.219	80.426
	Median	0.000	129.201	302.658	380.713	393.047	423.913	449.453	426.315	454.787	432.007
	Max	0.000	833.166	1507.450	1234.487	1460.419	1804.949	1755.844	1431.596	1452.967	1240.729
	CV%	.	98.59	72.75	57.61	56.83	57.33	53.10	51.24	46.44	44.84
	Geometric Mean	.	.	.	376.8159	399.1059	423.4692	443.4944	405.0740	433.2101	413.7575
B	N	97	97	97	97	97	97	97	97	97	97
	Mean	0.0000	163.2895	381.0700	434.6375	464.0774	478.5452	486.0035	448.5293	464.5774	438.1582
	SD	0.0000	166.7694	249.2499	241.3190	230.9429	231.4656	217.5353	221.3745	224.6307	192.2140
	Min	0.000	0.000	0.000	34.025	39.144	35.432	42.917	39.703	52.475	55.776
	Median	0.000	113.067	327.241	426.307	441.675	440.598	463.189	435.770	427.383	426.622
	Max	0.000	1334.641	1525.364	1421.351	1399.371	1370.710	1192.548	1656.268	1734.133	1479.537
	CV%	.	102.13	65.41	55.52	49.76	48.37	44.76	49.36	48.35	43.87
	Geometric Mean	.	.	.	369.2037	404.1635	420.1875	431.5254	395.7854	413.1383	396.6257

For the calculation of summary statistics, values that are below the limit of quantitation (BLQ) are treated as zero (0)
* .= Missing
Source: 16.2.5.9.1 and 16.2.5.9.2

Treatment A: Lupin BDP/FF 200/6 mcg-2 inhalations
Treatment B: FOSTAIR 200/6 mcg-2 inhalations
Table Generation: 03FEB2020 at 8:12 PM by Table 14.2.1.1.sas

Table 14.2.1.1 Summary of 17-BMP Plasma Concentrations (pg/mL) by Treatment, PK Analysis Set (without charcoal)

Subject no. [redacted] was withdrawn on medical grounds due to difficulty in cannulation and did not receive drug administration in periods 2, 3 and 4 (Treatments B, D and C, respectively)
Subject no[redacted] was withdrawn due to adverse events and did not receive drug administration in period 4 (Treatment A)
Subject no[redacted] was withdrawn due to adverse events and did not receive drug administration in period 4 (Treatment B)
Subject no. [redacted] was withdrawn due to protocol violation and did not receive drug administration in periods 3 and 4 (Treatments B and A respectively)
Subject no[redacted] voluntarily withdrew consent and did not receive drug administration in periods 2, 3 and 4 (Treatments A, C and B respectively)
Subject no. [redacted] voluntarily withdrew consent and did not receive drug administration in periods 2, 3 and 4 (Treatments D, B and A respectively)
Subject no. [redacted] was withdrawn due to failure to comply with protocol requirements and did not receive drug administration in periods 2, 3 and 4 (Treatments A, C and B respectively)
Subject no. [redacted] were excluded due to major protocol deviations for Treatment A & B

Treatment A: Lupin BDP/FF 200/6 mcg-2 inhalations
Treatment B: FOSTAIR 200/6 mcg-2 inhalations
Table Generation: 03FEB2020 at 8:12 PM by Table 14.2.1.1.sas

Table 14.2.1.1 Summary of 17-BMP Plasma Concentrations (pg/mL) by Treatment, PK Analysis Set (without charcoal)

Treatment		1.0	2.0	3.0	4.0	6.0	8.0	12.0	16.0	24.0	36.0
A	N	97	97	97	97	97	97	97	97	97	96
	Mean	436.8145	358.3757	293.8276	247.6212	152.3313	108.4558	47.7314	15.5139	1.2625	0.5936
	SD	181.7865	142.8737	108.1401	95.5888	61.8279	45.6740	23.9349	20.7398	6.3146	5.8164
	Min	88.735	88.578	84.727	73.983	42.029	28.886	0.000	0.000	0.000	0.000
	Median	417.785	344.156	279.358	236.513	140.510	100.470	44.030	0.000	0.000	0.000
	Max	956.486	947.628	655.001	601.706	425.497	324.347	143.989	97.611	43.809	56.989
	CV%	41.62	39.87	36.80	38.60	40.59	42.11	50.14	133.69	500.16	979.80
	Geometric Mean	396.6258	331.2314	274.3066	230.4981	140.7983	100.2183	.	.	.	.
B	N	97	97	97	97	97	97	97	97	97	97
	Mean	425.0281	349.9272	293.9598	246.9352	151.4512	111.2025	48.0227	16.5581	0.7047	0.0000
	SD	178.5378	127.6868	109.1089	84.5182	54.9581	41.1241	23.1858	19.5009	5.0038	0.0000
	Min	65.675	71.109	63.689	59.356	39.625	38.144	0.000	0.000	0.000	0.000
	Median	429.164	343.346	290.129	251.141	151.366	107.690	46.855	0.000	0.000	0.000
	Max	1339.121	983.136	831.308	615.100	422.714	324.232	154.315	93.049	41.782	0.000
	CV%	42.01	36.49	37.12	34.23	36.29	36.98	48.28	117.77	710.08	.
	Geometric Mean	386.6481	327.2779	275.2626	232.6762	142.0871	104.5504	.	.	.	.

For the calculation of summary statistics, values that are below the limit of quantitation (BLQ) are treated as zero (0)
* .= Missing
Source: 16.2.5.9.1 and 16.2.5.9.2

Treatment A: Lupin BDP/FF 200/6 mcg-2 inhalations
Treatment B: FOSTAIR 200/6 mcg-2 inhalations
Table Generation: 03FEB2020 at 8:12 PM by Table 14.2.1.1.sas

Table 14.2.1.1 Summary of 17-BMP Plasma Concentrations (pg/mL) by Treatment, PK Analysis Set (without charcoal)

Subject no[redacted] was withdrawn on medical grounds due to difficulty in cannulation and did not receive drug administration in periods 2, 3 and 4 (Treatments B, D and C, respectively)
Subject no[redacted] was withdrawn due to adverse events and did not receive drug administration in period 4 (Treatment A)
Subject no[redacted] was withdrawn due to adverse events and did not receive drug administration in period 4 (Treatment B)
Subject no[redacted] was withdrawn due to protocol violation and did not receive drug administration in periods 3 and 4 (Treatments B and A respectively)
Subject no[redacted] voluntarily withdrew consent and did not receive drug administration in periods 2, 3 and 4 (Treatments A, C and B respectively)
Subject no.[redacted] voluntarily withdrew consent and did not receive drug administration in periods 2, 3 and 4 (Treatments D, B and A respectively)
Subject no.[redacted] was withdrawn due to failure to comply with protocol requirements and did not receive drug administration in periods 2, 3 and 4 (Treatments A, C and B respectively)
Subject no.[redacted] were excluded due to major protocol deviations for Treatment A & B

Treatment A: Lupin BDP/FF 200/6 mcg-2 inhalations
Treatment B: FOSTAIR 200/6 mcg-2 inhalations
Table Generation: 03FEB2020 at 8:12 PM by Table 14.2.1.1.sas

Table 14.2.1.2 Summary of 17-BMP Plasma Concentrations (pg/mL) by Treatment, FAS (without charcoal)

Treatment		0.00	0.03	0.06	0.10	0.13	0.18	0.25	0.33	0.50	0.75
A	N	105	104	105	104	105	105	105	105	105	105
	Mean	0.0000	161.0314	372.5773	432.0520	453.6139	478.7279	496.6096	451.1411	471.5260	448.1238
	SD	0.0000	158.3143	274.2902	255.7056	263.3343	281.2147	268.9321	237.3058	225.7457	205.4716
	Min	0.000	0.000	0.000	26.468	45.514	58.401	63.506	53.772	75.219	80.426
	Median	0.000	126.779	294.979	366.459	378.375	421.204	431.659	418.644	440.775	410.551
	Max	0.000	833.166	1507.450	1234.487	1460.419	1804.949	1755.844	1431.596	1452.967	1240.729
	CV%	.	98.31	73.62	59.18	58.05	58.74	54.15	52.60	47.88	45.85
	Geometric Mean	.	.	.	362.1951	385.2374	407.5490	429.1627	390.6578	417.8710	401.3136
B	N	105	105	105	105	105	105	105	105	105	105
	Mean	0.0000	157.5889	370.1282	423.7024	452.3056	467.0398	475.3804	440.9636	457.2838	431.8642
	SD	0.0000	162.5390	244.2613	237.6310	229.4343	230.4305	217.0626	219.6305	221.9872	189.8331
	Min	0.000	0.000	0.000	34.025	39.144	35.432	42.917	39.703	52.475	55.776
	Median	0.000	111.422	315.524	397.378	435.275	434.217	444.827	428.092	426.096	417.021
	Max	0.000	1334.641	1525.364	1421.351	1399.371	1370.710	1192.548	1656.268	1734.133	1479.537
	CV%	.	103.14	65.99	56.08	50.73	49.34	45.66	49.81	48.54	43.96
	Geometric Mean	.	.	.	360.2677	393.0987	409.0733	421.1020	388.7743	406.6722	391.3672

For the calculation of summary statistics, values that are below the limit of quantitation (BLQ) are treated as zero (0)
* .= Missing
Source: 16.2.5.9.1 and 16.2.5.9.2

Treatment A: Lupin BDP/FF 200/6 mcg-2 inhalations
Treatment B: FOSTAIR 200/6 mcg-2 inhalations
Table Generation: 03FEB2020 at 8:17 PM by Table 14.2.1.2.sas

Table 14.2.1.2 Summary of 17-BMP Plasma Concentrations (pg/mL) by Treatment, FAS (without charcoal)

Subject no. [redacted] was withdrawn on medical grounds due to difficulty in cannulation and did not receive drug administration in periods 2, 3 and 4 (Treatments B, D and C, respectively)
Subject no. [redacted] was withdrawn due to adverse events and did not receive drug administration in period 4 (Treatment A)
Subject no. [redacted] was withdrawn due to adverse events and did not receive drug administration in period 4 (Treatment B)
Subject no. [redacted] was withdrawn due to protocol violation and did not receive drug administration in periods 3 and 4 (Treatments B and A respectively)
Subject no[redacted] voluntarily withdrew consent and did not receive drug administration in periods 2, 3 and 4 (Treatments A, C and B respectively)
Subject no. [redacted] voluntarily withdrew consent and did not receive drug administration in periods 2, 3 and 4 (Treatments D, B and A respectively)
Subject no. [redacted] was withdrawn due to failure to comply with protocol requirements and did not receive drug administration in periods 2, 3 and 4 (Treatments A, C and B respectively)

Treatment A: Lupin BDP/FF 200/6 mcg-2 inhalations
Treatment B: FOSTAIR 200/6 mcg-2 inhalations
Table Generation: 03FEB2020 at 8:17 PM by Table 14.2.1.2.sas

Table 14.2.1.2 Summary of 17-BMP Plasma Concentrations (pg/mL) by Treatment, FAS (without charcoal)

Treatment		1.0	2.0	3.0	4.0	6.0	8.0	12.0	16.0	24.0	36.0
A	N	105	105	105	105	105	105	105	104	104	103
	Mean	426.4544	350.1207	288.5183	243.8005	150.3159	106.2407	47.0080	15.3737	1.1775	0.5533
	SD	180.3055	141.7484	107.2144	94.1489	60.9439	45.4591	24.0379	20.4472	6.1046	5.6153
	Min	88.735	88.578	84.727	73.983	42.029	28.886	0.000	0.000	0.000	0.000
	Median	406.888	338.479	273.831	227.991	139.413	98.618	44.030	0.000	0.000	0.000
	Max	956.486	947.628	655.001	601.706	425.497	324.347	143.989	97.611	43.809	56.989
	CV%	42.28	40.49	37.16	38.62	40.54	42.79	51.14	133.00	518.41	1014.89
	Geometric Mean	386.9039	323.0919	269.2257	227.0324	138.9566	97.7344	.	.	.	.
B	N	105	105	105	105	105	105	105	105	105	105
	Mean	419.3858	345.7596	291.0665	245.3228	151.1175	111.0694	48.0046	16.7391	0.6510	0.0000
	SD	176.2802	127.4912	107.7800	84.1474	55.4999	40.9633	23.3494	19.5582	4.8112	0.0000
	Min	65.675	71.109	63.689	59.356	39.625	38.144	0.000	0.000	0.000	0.000
	Median	419.393	336.422	284.253	244.240	150.308	107.690	46.855	0.000	0.000	0.000
	Max	1339.121	983.136	831.308	615.100	422.714	324.232	154.315	93.049	41.782	0.000
	CV%	42.03	36.87	37.03	34.30	36.73	36.88	48.64	116.84	739.05	.
	Geometric Mean	381.9807	323.0591	272.7675	231.2170	141.5660	104.3900	.	.	.	.

For the calculation of summary statistics, values that are below the limit of quantitation (BLQ) are treated as zero (0)
* .= Missing
Source: 16.2.5.9.1 and 16.2.5.9.2

Treatment A: Lupin BDP/FF 200/6 mcg-2 inhalations
Treatment B: FOSTAIR 200/6 mcg-2 inhalations
Table Generation: 03FEB2020 at 8:17 PM by Table 14.2.1.2.sas

Table 14.2.1.2 Summary of 17-BMP Plasma Concentrations (pg/mL) by Treatment, FAS (without charcoal)

Subject no[redacted] was withdrawn on medical grounds due to difficulty in cannulation and did not receive drug administration in periods 2, 3 and 4 (Treatments B, D and C, respectively)
Subject no. [redacted] was withdrawn due to adverse events and did not receive drug administration in period 4 (Treatment A)
Subject no. [redacted] was withdrawn due to adverse events and did not receive drug administration in period 4 (Treatment B)
Subject no[redacted] was withdrawn due to protocol violation and did not receive drug administration in periods 3 and 4 (Treatments B and A respectively)
Subject no[redacted] voluntarily withdrew consent and did not receive drug administration in periods 2, 3 and 4 (Treatments A, C and B respectively)
Subject no. [redacted] voluntarily withdrew consent and did not receive drug administration in periods 2, 3 and 4 (Treatments D, B and A respectively)
Subject no[redacted] was withdrawn due to failure to comply with protocol requirements and did not receive drug administration in periods 2, 3 and 4 (Treatments A, C and B respectively)

Treatment A: Lupin BDP/FF 200/6 mcg-2 inhalations
Treatment B: FOSTAIR 200/6 mcg-2 inhalations
Table Generation: 03FEB2020 at 8:17 PM by Table 14.2.1.2.sas

Table 14.2.1.3 Summary of Formoterol Plasma Concentrations (pg/mL) by Treatment, PK Analysis Set (with and without charcoal)

Treatment		0.00	0.03	0.06	0.10	0.13	0.18	0.25	0.33	0.50	0.75
A	N	97	96	97	96	97	97	97	97	97	97
	Mean	0.0000	4.8314	15.1896	17.4906	16.9621	14.1688	11.3773	8.4076	7.0019	6.3791
	SD	0.0000	4.0144	7.9380	8.5842	8.4534	7.0687	5.5168	4.0094	3.2341	2.9472
	Min	0.000	0.000	0.657	1.065	1.521	1.423	1.356	1.196	0.966	0.902
	Median	0.000	3.316	13.740	15.312	15.272	12.867	10.495	7.927	6.650	6.008
	Max	0.000	18.308	34.412	45.942	46.345	37.636	28.332	19.969	16.709	14.605
	CV%	.	83.09	52.26	49.08	49.84	49.89	48.49	47.69	46.19	46.20
	Geometric Mean	.	.	12.8782	15.1458	14.6286	12.2253	9.8986	7.3515	6.1569	5.5971
B	N	97	97	97	97	97	97	97	97	97	97
	Mean	0.0000	5.1803	14.2666	16.4151	16.0055	13.3914	10.6175	7.9310	6.4540	5.7986
	SD	0.0000	4.3740	7.6242	8.1639	7.5613	6.7238	5.0687	3.8690	2.9701	2.4907
	Min	0.000	0.000	0.932	1.473	1.505	1.143	0.985	0.751	0.851	1.076
	Median	0.000	4.123	12.869	15.205	15.360	12.659	10.111	7.538	6.241	5.529
	Max	0.000	21.914	43.041	47.959	45.398	37.477	29.205	21.051	17.094	13.573
	CV%	.	84.44	53.44	49.73	47.24	50.21	47.74	48.78	46.02	42.95
	Geometric Mean	.	.	12.2172	14.2400	14.0039	11.6352	9.3155	6.9429	5.7379	5.2377

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
Table Generation: 03FEB2020 at 8:52 PM by Table 14.2.1.3.sas

Table 14.2.1.3 Summary of Formoterol Plasma Concentrations (pg/mL) by Treatment, PK Analysis Set (with and without charcoal)

Treatment		0.00	0.03	0.06	0.10	0.13	0.18	0.25	0.33	0.50	0.75
C	N	88	88	88	88	88	88	88	88	88	88
	Mean	0.0000	4.4853	13.0622	16.0033	15.4524	13.3314	10.7958	7.4530	5.9267	4.4229
	SD	0.0000	5.5042	7.3249	7.8833	7.3833	5.8398	5.0709	3.2439	2.9006	1.9863
	Min	0.000	0.000	1.864	2.300	2.518	2.170	1.698	1.166	0.883	0.652
	Median	0.000	3.285	12.127	15.094	14.771	12.442	10.053	7.213	5.321	4.513
	Max	0.000	36.599	42.081	50.205	50.756	33.049	32.007	17.732	17.383	12.071
	CV%	.	122.72	56.08	49.26	47.78	43.81	46.97	43.52	48.94	44.91
	Geometric Mean	.	.	11.0072	14.0925	13.8012	12.0083	9.6645	6.7018	5.2255	3.9477
D	N	88	88	88	88	88	88	88	88	88	88
	Mean	0.0000	3.9300	11.9593	14.5927	14.4068	12.2344	10.0149	6.9158	5.3784	4.0408
	SD	0.0000	3.5352	6.2661	7.4290	7.1440	5.9944	4.9975	3.2466	2.6263	2.0577
	Min	0.000	0.000	2.650	4.173	4.111	3.339	3.160	2.099	1.510	1.240
	Median	0.000	2.916	10.510	13.088	13.166	11.275	8.897	6.412	5.002	3.707
	Max	0.000	17.129	35.745	39.450	38.115	33.074	26.069	18.361	14.246	11.929
	CV%	.	89.95	52.39	50.91	49.59	49.00	49.90	46.94	48.83	50.92
	Geometric Mean	.	.	10.3941	12.8862	12.7886	10.8907	8.9065	6.1899	4.7818	3.5830

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
Table Generation: 03FEB2020 at 8:52 PM by Table 14.2.1.3.sas

Table 14.2.1.3 Summary of Formoterol Plasma Concentrations (pg/mL) by Treatment, PK Analysis Set (with and without charcoal)

For the calculation of summary statistics, values that are below the limit of quantitation (BLQ) are treated as zero (0)
* .= Missing
Source: Listings 16.2.5.9.3, 16.2.5.9.4, 16.2.5.9.5 and 16.2.5.9.6
Subject no. [redacted] was withdrawn on medical grounds due to difficulty in cannulation and did not receive drug administration in periods 2, 3 and 4 (Treatments B, D and C, respectively)
Subject no[redacted] was withdrawn due to adverse events and did not receive drug administration in period 4 (Treatment A)
Subject no. [redacted]was withdrawn due to adverse events and did not receive drug administration in period 4 (Treatment B)
Subject no. [redacted] was withdrawn due to protocol violation and did not receive drug administration in periods 3 and 4 (Treatments B and A respectively)
Subject no. [redacted] was withdrawn due to protocol violation did not receive drug administration in period 4 (Treatment C)
Subject no[redacted] voluntarily withdrew consent and did not receive drug administration in period 4 (Treatments D)
Subject no. [redacted] did not have any measurable formoterol concentrations following administration of Treatment C and therefore was excluded from Treatment C and D
Subject no. [redacted] voluntarily withdrew consent and did not receive drug administration in periods 2, 3 and 4 (Treatments A, C and B respectively)
Subject no. [redacted] voluntarily withdrew consent and did not receive drug administration in periods 2, 3 and 4 (Treatments D, B and A respectively)
Subject no[redacted] was withdrawn due to failure to comply with protocol requirements and did not receive drug administration in periods 2, 3 and 4 (Treatments A, C and B respectively)
Subject no. [redacted] were excluded due to major protocol deviations from A vs B calculation
Subject no. [redacted] were excluded due to major protocol deviations from C vs D calculation

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
Table Generation: 03FEB2020 at 8:52 PM by Table 14.2.1.3.sas

Table 14.2.1.3 Summary of Formoterol Plasma Concentrations (pg/mL) by Treatment, PK Analysis Set (with and without charcoal)

Treatment		1.0	2.0	3.0	4.0	6.0	8.0	12.0	16.0	24.0	36.0
A	N	97	97	97	97	97	97	97	97	97	96
	Mean	6.0166	5.0086	4.0155	3.4667	2.3497	1.9043	1.1748	0.8022	0.4785	0.0847
	SD	2.5337	1.7678	1.6451	1.5132	0.8304	0.7591	0.5207	0.3634	0.3493	0.2425
	Min	1.104	1.622	1.007	1.200	0.689	0.583	0.000	0.000	0.000	0.000
	Median	5.805	4.789	3.622	3.179	2.250	1.849	1.145	0.781	0.500	0.000
	Max	12.423	10.462	10.242	9.152	5.089	4.986	3.810	2.476	1.642	1.521
	CV%	42.11	35.30	40.97	43.65	35.34	39.86	44.33	45.30	72.99	286.47
	Geometric Mean	5.3955	4.7009	3.7017	3.1849	2.2043	1.7594	.	.	.	.
B	N	97	97	97	97	97	97	97	97	97	97
	Mean	5.8417	4.7001	3.9374	3.3655	2.3103	1.8217	1.1809	0.8272	0.4981	0.0809
	SD	2.5926	1.7283	1.3983	1.1471	0.8903	0.6581	0.4371	0.9148	0.4675	0.3300
	Min	1.110	1.623	0.967	1.267	0.614	0.453	0.000	0.000	0.000	0.000
	Median	5.805	4.546	3.774	3.235	2.165	1.768	1.139	0.767	0.515	0.000
	Max	14.837	11.064	7.861	8.296	5.253	4.827	2.870	9.054	3.139	2.652
	CV%	44.38	36.77	35.51	34.08	38.53	36.13	37.01	110.60	93.84	407.74
	Geometric Mean	5.2538	4.3995	3.6833	3.1769	2.1484	1.7059	.	.	.	.

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
Table Generation: 03FEB2020 at 8:52 PM by Table 14.2.1.3.sas

Table 14.2.1.3 Summary of Formoterol Plasma Concentrations (pg/mL) by Treatment, PK Analysis Set (with and without charcoal)

Treatment		1.0	2.0	3.0	4.0	6.0	8.0	12.0	16.0	24.0	36.0
C	N	88	88	88	88	88	88	88	88	88	88
	Mean	3.6973	2.4818	2.1339	1.8259	1.3037	1.1389	0.7371	0.4727	0.1772	0.0598
	SD	1.7673	1.2861	1.1727	1.0162	0.6623	0.6452	0.5415	0.5496	0.2946	0.2746
	Min	0.581	0.424	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	Median	3.509	2.358	1.929	1.817	1.261	1.068	0.720	0.490	0.000	0.000
	Max	10.995	8.311	7.782	6.960	3.948	3.709	3.010	4.444	1.353	2.154
	CV%	47.80	51.82	54.96	55.66	50.81	56.65	73.47	116.27	166.20	458.93
	Geometric Mean	3.2731	2.1674	.	.	.	.	.	.	.	.
D	N	88	88	88	88	88	88	88	88	88	88
	Mean	3.4643	2.2700	1.9116	1.6258	1.2995	0.9753	0.6199	0.3747	0.1754	0.0273
	SD	1.7313	1.1694	0.9288	0.8678	1.0694	0.5573	0.4078	0.4159	0.3155	0.1564
	Min	0.953	0.616	0.436	0.479	0.000	0.000	0.000	0.000	0.000	0.000
	Median	3.184	2.067	1.821	1.519	1.248	0.944	0.569	0.427	0.000	0.000
	Max	10.244	6.400	4.784	5.218	9.421	2.948	1.722	2.255	1.310	1.208
	CV%	49.98	51.52	48.59	53.38	82.29	57.15	65.78	111.01	179.95	574.11
	Geometric Mean	3.0576	1.9989	1.6936	1.4191	.	.	.	.	.	.

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
Table Generation: 03FEB2020 at 8:52 PM by Table 14.2.1.3.sas

Table 14.2.1.3 Summary of Formoterol Plasma Concentrations (pg/mL) by Treatment, PK Analysis Set (with and without charcoal)

For the calculation of summary statistics, values that are below the limit of quantitation (BLQ) are treated as zero (0)
* .= Missing
Source: Listings 16.2.5.9.3, 16.2.5.9.4, 16.2.5.9.5 and 16.2.5.9.6
Subject no. [redacted] was withdrawn on medical grounds due to difficulty in cannulation and did not receive drug administration in periods 2, 3 and 4 (Treatments B, D and C, respectively)
Subject no. [redacted] was withdrawn due to adverse events and did not receive drug administration in period 4 (Treatment A)
Subject no. [redacted] was withdrawn due to adverse events and did not receive drug administration in period 4 (Treatment B)
Subject no. [redacted] was withdrawn due to protocol violation and did not receive drug administration in periods 3 and 4 (Treatments B and A respectively)
Subject no. [redacted] was withdrawn due to protocol violation did not receive drug administration in period 4 (Treatment C)
Subject no. [redacted] voluntarily withdrew consent and did not receive drug administration in period 4 (Treatments D)
Subject no. [redacted] did not have any measurable formoterol concentrations following administration of Treatment C and therefore was excluded from Treatment C and D
Subject no. [redacted] voluntarily withdrew consent and did not receive drug administration in periods 2, 3 and 4 (Treatments A, C and B respectively)
Subject no. [redacted] voluntarily withdrew consent and did not receive drug administration in periods 2, 3 and 4 (Treatments D, B and A respectively)
Subject no. [redacted] was withdrawn due to failure to comply with protocol requirements and did not receive drug administration in periods 2, 3 and 4 (Treatments A, C and B respectively)
Subject no. [redacted] were excluded due to major protocol deviations from A vs B calculation
Subject no. [redacted] were excluded due to major protocol deviations from C vs D calculation

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
Table Generation: 03FEB2020 at 8:52 PM by Table 14.2.1.3.sas

Table 14.2.1.4 Summary of Formoterol Plasma Concentrations (pg/mL) by Treatment, FAS (with and without charcoal)

Treatment		0.00	0.03	0.06	0.10	0.13	0.18	0.25	0.33	0.50	0.75
A	N	105	104	105	104	105	105	105	105	105	105
	Mean	0.0000	4.7125	14.7199	16.9073	16.4350	13.7607	11.0401	8.1493	6.7881	6.2225
	SD	0.0000	3.9130	7.8294	8.5156	8.3655	6.9847	5.4593	3.9829	3.2212	2.9073
	Min	0.000	0.000	0.657	1.065	1.521	1.423	1.356	1.196	0.966	0.902
	Median	0.000	3.316	12.956	14.267	14.659	12.583	10.206	7.436	6.335	5.946
	Max	0.000	18.308	34.412	45.942	46.345	37.636	28.332	19.969	16.709	14.605
	CV%	.	83.03	53.19	50.37	50.90	50.76	49.45	48.87	47.45	46.72
	Geometric Mean	.	.	12.4968	14.6244	14.1717	11.8734	9.6029	7.1114	5.9539	5.4654
B	N	105	105	105	105	105	105	105	105	105	105
	Mean	0.0000	5.0441	13.9826	16.0784	15.6916	13.1236	10.4286	7.8226	6.5101	5.7648
	SD	0.0000	4.2857	7.4407	7.9840	7.4113	6.5894	4.9768	3.7896	3.0539	2.4607
	Min	0.000	0.000	0.932	1.473	1.505	1.143	0.985	0.751	0.851	1.076
	Median	0.000	4.027	12.561	15.060	15.174	12.564	9.986	7.222	6.241	5.529
	Max	0.000	21.914	43.041	47.959	45.398	37.477	29.205	21.051	17.094	13.573
	CV%	.	84.96	53.21	49.66	47.23	50.21	47.72	48.44	46.91	42.68
	Geometric Mean	.	.	12.0320	14.0043	13.7817	11.4413	9.1788	6.8794	5.7857	5.2130

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
Table Generation: 03FEB2020 at 9:04 PM by Table 14.2.1.4.sas

Table 14.2.1.4 Summary of Formoterol Plasma Concentrations (pg/mL) by Treatment, FAS (with and without charcoal)

Treatment		0.00	0.03	0.06	0.10	0.13	0.18	0.25	0.33	0.50	0.75
C	N	105	105	105	105	105	105	105	105	105	105
	Mean	0.0000	4.1768	11.9443	14.5841	14.1818	12.2343	9.9632	6.9306	5.4945	4.1281
	SD	0.0000	5.1546	7.3075	8.0284	7.4841	6.0366	5.1442	3.2959	2.9121	2.0096
	Min	0.000	0.000	0.806	0.567	0.759	0.609	0.553	0.530	0.000	0.000
	Median	0.000	3.100	10.238	13.946	13.175	11.331	9.268	6.629	4.895	4.036
	Max	0.000	36.599	42.081	50.205	50.756	33.049	32.007	17.732	17.383	12.071
	CV%	.	123.41	61.18	55.05	52.77	49.34	51.63	47.56	53.00	48.68
	Geometric Mean	.	.	9.6354	12.2406	12.1470	10.5232	8.5561	6.0308	.	.
D	N	105	105	105	105	105	105	105	105	105	105
	Mean	0.0000	3.8778	11.8046	14.0984	13.8608	11.7536	9.5473	6.7133	5.2271	3.9158
	SD	0.0000	3.7010	6.4347	7.6028	7.3532	6.1231	5.0537	3.4517	2.8318	2.1628
	Min	0.000	0.000	1.362	1.336	1.104	0.824	0.711	0.513	0.466	0.000
	Median	0.000	2.682	10.181	12.214	12.164	10.811	8.470	5.944	4.796	3.505
	Max	0.000	19.403	35.745	39.450	38.115	33.074	26.069	18.451	16.212	11.929
	CV%	.	95.44	54.51	53.93	53.05	52.10	52.93	51.42	54.18	55.23
	Geometric Mean	.	.	10.0718	12.1334	11.9707	10.1743	8.2527	5.8451	4.5100	.

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
Table Generation: 03FEB2020 at 9:04 PM by Table 14.2.1.4.sas

Table 14.2.1.4 Summary of Formoterol Plasma Concentrations (pg/mL) by Treatment, FAS (with and without charcoal)

For the calculation of summary statistics, values that are below the limit of quantitation (BLQ) are treated as zero (0)
* .= Missing
For the calculation of summary statistics, values that are below the limit of quantitation (BLQ) are treated as zero (0)
* .= Missing
Source: Listings 16.2.5.9.3, 16.2.5.9.4, 16.2.5.9.5 and 16.2.5.9.6
Subject no. [redacted] was withdrawn on medical grounds due to difficulty in cannulation and did not receive drug administration in periods 2, 3 and 4 (Treatments B, D and C, respectively)
Subject no. [redacted] was withdrawn due to adverse events and did not receive drug administration in period 4 (Treatment A)
Subject no. [redacted] was withdrawn due to adverse events and did not receive drug administration in period 4 (Treatment B)
Subject no. [redacted] was withdrawn due to protocol violation and did not receive drug administration in periods 3 and 4 (Treatments B and A respectively)
Subject no. [redacted] was withdrawn due to protocol violation did not receive drug administration in period 4 (Treatment C)
Subject no. [redacted] voluntarily withdrew consent and did not receive drug administration in period 4 (Treatments D)
Subject no. [redacted] did not have any measurable formoterol concentrations following administration of Treatment C and therefore was excluded from Treatment C and D
Subject no. [redacted] voluntarily withdrew consent and did not receive drug administration in periods 2, 3 and 4 (Treatments A, C and B respectively)
Subject no[redacted] voluntarily withdrew consent and did not receive drug administration in periods 2, 3 and 4 (Treatments D, B and A respectively)
Subject no. [redacted] was withdrawn due to failure to comply with protocol requirements and did not receive drug administration in periods 2, 3 and 4 (Treatments A, C and B respectively)

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
Table Generation: 03FEB2020 at 9:04 PM by Table 14.2.1.4.sas

Table 14.2.1.4 Summary of Formoterol Plasma Concentrations (pg/mL) by Treatment, FAS (with and without charcoal)

Treatment		1.0	2.0	3.0	4.0	6.0	8.0	12.0	16.0	24.0	36.0
A	N	105	105	105	105	105	105	105	104	104	103
	Mean	5.9173	4.8860	3.9419	3.4033	2.3244	1.8938	1.1550	0.7894	0.4550	0.0789
	SD	2.4947	1.7827	1.6139	1.4836	0.8313	0.7885	0.5098	0.3567	0.3525	0.2350
	Min	1.104	1.622	1.007	1.200	0.689	0.583	0.000	0.000	0.000	0.000
	Median	5.742	4.703	3.604	3.172	2.237	1.781	1.140	0.757	0.490	0.000
	Max	12.423	10.462	10.242	9.152	5.089	4.986	3.810	2.476	1.642	1.521
	CV%	42.16	36.49	40.94	43.59	35.77	41.64	44.14	45.19	77.48	297.86
	Geometric Mean	5.3105	4.5647	3.6398	3.1305	2.1778	1.7403	.	.	.	.
B	N	105	105	105	105	105	105	105	105	105	105
	Mean	5.8486	4.7283	3.9231	3.3677	2.3269	1.8347	1.1709	0.8186	0.5026	0.0748
	SD	2.5731	1.7404	1.3783	1.1649	0.9479	0.6874	0.4291	0.8821	0.4905	0.3178
	Min	1.110	1.623	0.967	1.267	0.614	0.453	0.000	0.000	0.000	0.000
	Median	5.805	4.546	3.774	3.235	2.165	1.749	1.139	0.762	0.515	0.000
	Max	14.837	11.064	7.861	8.296	5.751	4.827	2.870	9.054	3.139	2.652
	CV%	43.99	36.81	35.13	34.59	40.74	37.46	36.65	107.76	97.60	425.04
	Geometric Mean	5.2707	4.4206	3.6763	3.1756	2.1509	1.7128	.	.	.	.

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
Table Generation: 03FEB2020 at 9:04 PM by Table 14.2.1.4.sas

Table 14.2.1.4 Summary of Formoterol Plasma Concentrations (pg/mL) by Treatment, FAS (with and without charcoal)

Treatment		1.0	2.0	3.0	4.0	6.0	8.0	12.0	16.0	24.0	36.0
C	N	105	105	105	105	105	105	105	105	105	105
	Mean	3.4630	2.3142	1.9970	1.7078	1.2196	1.0778	0.6863	0.4201	0.1575	0.0501
	SD	1.7729	1.2856	1.1539	1.0026	0.6595	0.6624	0.5222	0.5253	0.2800	0.2521
	Min	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	Median	3.132	2.189	1.883	1.665	1.112	0.978	0.654	0.479	0.000	0.000
	Max	10.995	8.311	7.782	6.960	3.948	3.709	3.010	4.444	1.353	2.154
	CV%	51.19	55.55	57.78	58.71	54.08	61.46	76.08	125.04	177.75	502.78
	Geometric Mean	.	.	.	.	.	.	.	.	.	.
D	N	105	105	105	105	105	105	105	105	105	105
	Mean	3.3825	2.2436	1.8749	1.6511	1.2434	0.9842	0.5872	0.3524	0.1650	0.0276
	SD	1.9126	1.3292	1.0016	1.0863	1.0246	0.6956	0.4220	0.4075	0.3056	0.1507
	Min	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	Median	3.034	1.999	1.743	1.493	1.164	0.927	0.561	0.422	0.000	0.000
	Max	11.673	8.495	4.784	7.244	9.421	3.733	1.722	2.255	1.310	1.208
	CV%	56.54	59.24	53.42	65.79	82.40	70.67	71.87	115.61	185.17	546.58
	Geometric Mean	.	.	.	.	.	.	.	.	.	.

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
Table Generation: 03FEB2020 at 9:04 PM by Table 14.2.1.4.sas

Table 14.2.1.4 Summary of Formoterol Plasma Concentrations (pg/mL) by Treatment, FAS (with and without charcoal)

For the calculation of summary statistics, values that are below the limit of quantitation (BLQ) are treated as zero (0)
* .= Missing
For the calculation of summary statistics, values that are below the limit of quantitation (BLQ) are treated as zero (0)
* .= Missing
Source: Listings 16.2.5.9.3, 16.2.5.9.4, 16.2.5.9.5 and 16.2.5.9.6
Subject no. [redacted] was withdrawn on medical grounds due to difficulty in cannulation and did not receive drug administration in periods 2, 3 and 4 (Treatments B, D and C, respectively)
Subject no. [redacted] was withdrawn due to adverse events and did not receive drug administration in period 4 (Treatment A)
Subject no. [redacted] was withdrawn due to adverse events and did not receive drug administration in period 4 (Treatment B)
Subject no. [redacted] was withdrawn due to protocol violation and did not receive drug administration in periods 3 and 4 (Treatments B and A respectively)
Subject no. [redacted] was withdrawn due to protocol violation did not receive drug administration in period 4 (Treatment C)
Subject no. [redacted] voluntarily withdrew consent and did not receive drug administration in period 4 (Treatments D)
Subject no. [redacted] did not have any measurable formoterol concentrations following administration of Treatment C and therefore was excluded from Treatment C and D
Subject no. [redacted] voluntarily withdrew consent and did not receive drug administration in periods 2, 3 and 4 (Treatments A, C and B respectively)
Subject no. [redacted] voluntarily withdrew consent and did not receive drug administration in periods 2, 3 and 4 (Treatments D, B and A respectively)
Subject no[redacted] was withdrawn due to failure to comply with protocol requirements and did not receive drug administration in periods 2, 3 and 4 (Treatments A, C and B respectively)

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
Table Generation: 03FEB2020 at 9:04 PM by Table 14.2.1.4.sas

Table 14.2.1.5 Summary of BDP Plasma Concentrations (pg/mL) by Treatment, PK Analysis Set (without charcoal)

Treatment		0.00	0.03	0.06	0.10	0.13	0.18	0.25	0.33	0.50	0.75
A	N	97	96	97	96	97	97	97	97	97	97
	Mean	0.0000	2868.2207	1918.9670	1036.1244	588.8169	326.8503	178.6365	93.1083	39.2387	19.6096
	SD	0.0000	2515.0401	1379.6675	694.1322	383.0472	233.1106	130.6184	76.8984	27.1618	13.2205
	Min	0.000	257.762	131.069	110.448	49.149	41.062	22.552	13.778	6.087	0.000
	Median	0.000	2165.291	1611.920	903.376	505.469	271.307	146.075	67.858	30.981	16.775
	Max	0.000	15068.120	8907.603	4283.483	2046.203	1279.193	753.886	523.540	159.325	96.675
	CV%	.	87.69	71.90	66.99	65.05	71.32	73.12	82.59	69.22	67.42
	Geometric Mean	.	2087.5134	1566.7722	857.7747	478.2504	261.8933	142.9565	72.1396	32.0272	.
B	N	97	97	97	97	97	97	97	97	97	97
	Mean	0.0000	2917.9768	1946.0841	1050.6610	568.4815	305.4726	168.2855	85.0791	39.3581	19.4567
	SD	0.0000	2325.8853	1370.0919	727.4337	379.9089	222.7571	136.0918	65.9103	30.7831	15.3386
	Min	0.000	190.719	202.254	104.932	41.637	28.436	17.709	6.930	6.192	0.000
	Median	0.000	2291.352	1650.275	886.451	480.948	237.587	135.594	70.136	33.037	16.396
	Max	0.000	15471.840	8827.148	4117.320	2113.632	1313.344	1059.601	518.320	260.778	128.577
	CV%	.	79.71	70.40	69.24	66.83	72.92	80.87	77.47	78.21	78.83
	Geometric Mean	.	2270.6159	1614.8648	857.6756	468.7261	247.4556	134.7076	68.3532	32.1186	.

For the calculation of summary statistics, values that are below the limit of quantitation (BLQ) are treated as zero (0)
* .= Missing
Source: 16.2.5.9.7 and 16.2.5.9.8

Treatment A: Lupin BDP/FF 200/6 mcg-2 inhalations
Treatment B: FOSTAIR 200/6 mcg-2 inhalations
Table Generation: 03FEB2020 at 9:10 PM by Table 14.2.1.5.sas

Table 14.2.1.5 Summary of BDP Plasma Concentrations (pg/mL) by Treatment, PK Analysis Set (without charcoal)

Subject no. [redacted] was withdrawn on medical grounds due to difficulty in cannulation and did not receive drug administration in periods 2, 3 and 4 (Treatments B, D and C, respectively)
Subject no. [redacted] was withdrawn due to adverse events and did not receive drug administration in period 4 (Treatment A)
Subject no [redacted] was withdrawn due to adverse events and did not receive drug administration in period 4 (Treatment B)
Subject no. [redacted] was withdrawn due to protocol violation and did not receive drug administration in periods 3 and 4 (Treatments B and A respectively)
Subject no. [redacted] voluntarily withdrew consent and did not receive drug administration in periods 2, 3 and 4 (Treatments A, C and B respectively)
Subject no. [redacted] voluntarily withdrew consent and did not receive drug administration in periods 2, 3 and 4 (Treatments D, B and A respectively)
Subject no. [redacted] was withdrawn due to failure to comply with protocol requirements and did not receive drug administration in periods 2, 3 and 4 (Treatments A, C and B respectively)
Subject no. [redacted] were excluded due to major protocol deviations for Treatment A & B

Treatment A: Lupin BDP/FF 200/6 mcg-2 inhalations
Treatment B: FOSTAIR 200/6 mcg-2 inhalations
Table Generation: 03FEB2020 at 9:10 PM by Table 14.2.1.5.sas

Table 14.2.1.5 Summary of BDP Plasma Concentrations (pg/mL) by Treatment, PK Analysis Set (without charcoal)

Treatment		1.0	2.0	3.0	4.0	6.0	8.0	12.0	16.0	24.0	36.0
A	N	97	96	97	97	97	97	97	97	97	96
	Mean	11.9898	3.0224	0.6277	0.1086	0.0000	0.0550	0.0837	0.3005	0.0950	0.0000
	SD	8.0023	4.1588	2.0177	0.7528	0.0000	0.5418	0.8247	2.4780	0.9358	0.0000
	Min	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	Median	11.594	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	Max	57.082	17.975	10.190	5.392	0.000	5.336	8.122	23.887	9.217	0.000
	CV%	66.74	137.60	321.46	692.98	.	984.89	984.89	824.68	984.89	.
	Geometric Mean	.	.	.	.	.	.	.	.	.	.
B	N	97	97	97	97	97	97	97	97	97	97
	Mean	12.0619	2.9460	0.9095	0.2092	0.0793	0.0000	0.0000	0.0000	0.0685	0.2274
	SD	9.6677	4.3480	2.3958	1.1985	0.7811	0.0000	0.0000	0.0000	0.6744	2.2397
	Min	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	Median	10.592	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	Max	81.134	22.286	10.871	8.507	7.693	0.000	0.000	0.000	6.642	22.058
	CV%	80.15	147.59	263.43	572.79	984.89	.	.	.	984.89	984.89
	Geometric Mean	.	.	.	.	.	.	.	.	.	.

For the calculation of summary statistics, values that are below the limit of quantitation (BLQ) are treated as zero (0)
* .= Missing
Source: 16.2.5.9.7 and 16.2.5.9.8

Treatment A: Lupin BDP/FF 200/6 mcg-2 inhalations
Treatment B: FOSTAIR 200/6 mcg-2 inhalations
Table Generation: 03FEB2020 at 9:10 PM by Table 14.2.1.5.sas

Table 14.2.1.5 Summary of BDP Plasma Concentrations (pg/mL) by Treatment, PK Analysis Set (without charcoal)

Subject no[redacted] was withdrawn on medical grounds due to difficulty in cannulation and did not receive drug administration in periods 2, 3 and 4 (Treatments B, D and C, respectively)
Subject no. [redacted] was withdrawn due to adverse events and did not receive drug administration in period 4 (Treatment A)
Subject no. [redacted] was withdrawn due to adverse events and did not receive drug administration in period 4 (Treatment B)
Subject no. [redacted] was withdrawn due to protocol violation and did not receive drug administration in periods 3 and 4 (Treatments B and A respectively)
Subject no. [redacted] voluntarily withdrew consent and did not receive drug administration in periods 2, 3 and 4 (Treatments A, C and B respectively)
Subject no[redacted] voluntarily withdrew consent and did not receive drug administration in periods 2, 3 and 4 (Treatments D, B and A respectively)
Subject no. [redacted] was withdrawn due to failure to comply with protocol requirements and did not receive drug administration in periods 2, 3 and 4 (Treatments A, C and B respectively)
Subject no. [redacted] were excluded due to major protocol deviations for Treatment A & B

Treatment A: Lupin BDP/FF 200/6 mcg-2 inhalations
Treatment B: FOSTAIR 200/6 mcg-2 inhalations
Table Generation: 03FEB2020 at 9:10 PM by Table 14.2.1.5.sas

Table 14.2.1.6 Summary of BDP Plasma Concentrations (pg/mL) by Treatment, FAS (without charcoal)

Treatment		0.00	0.03	0.06	0.10	0.13	0.18	0.25	0.33	0.50	0.75
A	N	105	104	105	104	105	105	105	105	105	105
	Mean	0.0000	2784.8326	1856.8990	1002.3413	572.3100	317.6458	173.3985	90.1726	38.0086	19.1033
	SD	0.0000	2443.7539	1353.7643	684.3696	378.4214	229.1154	128.0261	74.8111	26.5581	12.9073
	Min	0.000	257.762	131.069	110.448	49.149	41.062	22.552	13.778	6.087	0.000
	Median	0.000	2092.214	1579.240	862.500	467.676	255.260	140.820	67.858	29.231	15.886
	Max	0.000	15068.120	8907.603	4283.483	2046.203	1279.193	753.886	523.540	159.325	96.675
	CV%	.	87.75	72.90	68.28	66.12	72.13	73.83	82.96	69.87	67.57
	Geometric Mean	.	2049.3831	1508.6152	823.2741	462.3007	253.6141	138.5607	70.0818	31.0506	.
B	N	105	105	105	105	105	105	105	105	105	105
	Mean	0.0000	2834.1966	1912.8961	1034.5690	559.4065	301.7792	165.7915	83.0478	38.6831	19.0661
	SD	0.0000	2275.6690	1342.4745	715.8866	374.9279	219.0398	133.4328	64.2811	29.8694	14.8520
	Min	0.000	190.719	202.254	104.932	41.637	28.436	17.709	6.930	6.192	0.000
	Median	0.000	2255.698	1605.674	880.222	454.311	237.264	135.071	70.057	32.880	16.389
	Max	0.000	15471.840	8827.148	4117.320	2113.632	1313.344	1059.601	518.320	260.778	128.577
	CV%	.	80.29	70.18	69.20	67.02	72.58	80.48	77.40	77.22	77.90
	Geometric Mean	.	2205.9025	1589.6437	845.1006	461.1142	245.0994	132.8284	66.8690	31.7710	.

For the calculation of summary statistics, values that are below the limit of quantitation (BLQ) are treated as zero (0)
* .= Missing
Source: 16.2.5.9.7 and 16.2.5.9.8

Treatment A: Lupin BDP/FF 200/6 mcg-2 inhalations
Treatment B: FOSTAIR 200/6 mcg-2 inhalations
Table Generation: 03FEB2020 at 9:14 PM by Table 14.2.1.6.sas

Table 14.2.1.6 Summary of BDP Plasma Concentrations (pg/mL) by Treatment, FAS (without charcoal)

Subject no. [redacted] was withdrawn on medical grounds due to difficulty in cannulation and did not receive drug administration in periods 2, 3 and 4 (Treatments B, D and C, respectively)
Subject no. [redacted] was withdrawn due to adverse events and did not receive drug administration in period 4 (Treatment A)
Subject no [redacted] was withdrawn due to adverse events and did not receive drug administration in period 4 (Treatment B)
Subject no [redacted] was withdrawn due to protocol violation and did not receive drug administration in periods 3 and 4 (Treatments B and A respectively)
Subject no [redacted] voluntarily withdrew consent and did not receive drug administration in periods 2, 3 and 4 (Treatments A, C and B respectively)
Subject no. [redacted] voluntarily withdrew consent and did not receive drug administration in periods 2, 3 and 4 (Treatments D, B and A respectively)
Subject no. [redacted] was withdrawn due to failure to comply with protocol requirements and did not receive drug administration in periods 2, 3 and 4 (Treatments A, C and B respectively)

Treatment A: Lupin BDP/FF 200/6 mcg-2 inhalations
Treatment B: FOSTAIR 200/6 mcg-2 inhalations
Table Generation: 03FEB2020 at 9:14 PM by Table 14.2.1.6.sas

Table 14.2.1.6 Summary of BDP Plasma Concentrations (pg/mL) by Treatment, FAS (without charcoal)

Treatment		1.0	2.0	3.0	4.0	6.0	8.0	12.0	16.0	24.0	36.0
A	N	105	104	105	105	105	105	105	104	104	103
	Mean	11.6994	2.7899	0.5798	0.1004	0.0000	0.0508	0.1302	0.2803	0.0886	0.0000
	SD	7.8221	4.0752	1.9458	0.7238	0.0000	0.5207	0.9555	2.3935	0.9038	0.0000
	Min	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	Median	10.703	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	Max	57.082	17.975	10.190	5.392	0.000	5.336	8.122	23.887	9.217	0.000
	CV%	66.86	146.07	335.57	721.28	.	1024.70	734.00	854.04	1019.80	.
	Geometric Mean	.	.	.	.	.	.	.	.	.	.
B	N	105	105	105	105	105	105	105	105	105	105
	Mean	11.8433	2.8442	0.8402	0.1933	0.0733	0.0000	0.0000	0.0000	0.0633	0.2101
	SD	9.4223	4.2633	2.3146	1.1528	0.7508	0.0000	0.0000	0.0000	0.6482	2.1526
	Min	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	Median	10.592	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	Max	81.134	22.286	10.871	8.507	7.693	0.000	0.000	0.000	6.642	22.058
	CV%	79.56	149.90	275.48	596.40	1024.70	.	.	.	1024.70	1024.70
	Geometric Mean	.	.	.	.	.	.	.	.	.	.

For the calculation of summary statistics, values that are below the limit of quantitation (BLQ) are treated as zero (0)
* .= Missing
Source: 16.2.5.9.7 and 16.2.5.9.8

Treatment A: Lupin BDP/FF 200/6 mcg-2 inhalations
Treatment B: FOSTAIR 200/6 mcg-2 inhalations
Table Generation: 03FEB2020 at 9:14 PM by Table 14.2.1.6.sas

Table 14.2.1.6 Summary of BDP Plasma Concentrations (pg/mL) by Treatment, FAS (without charcoal)

Subject no[redacted] was withdrawn on medical grounds due to difficulty in cannulation and did not receive drug administration in periods 2, 3 and 4 (Treatments B, D and C, respectively)
Subject no. [redacted] was withdrawn due to adverse events and did not receive drug administration in period 4 (Treatment A)
Subject no. [redacted] was withdrawn due to adverse events and did not receive drug administration in period 4 (Treatment B)
Subject no[redacted] was withdrawn due to protocol violation and did not receive drug administration in periods 3 and 4 (Treatments B and A respectively)
Subject no. [redacted] voluntarily withdrew consent and did not receive drug administration in periods 2, 3 and 4 (Treatments A, C and B respectively)
Subject no[redacted] voluntarily withdrew consent and did not receive drug administration in periods 2, 3 and 4 (Treatments D, B and A respectively)
Subject no. [redacted] was withdrawn due to failure to comply with protocol requirements and did not receive drug administration in periods 2, 3 and 4 (Treatments A, C and B respectively)

Treatment A: Lupin BDP/FF 200/6 mcg-2 inhalations
Treatment B: FOSTAIR 200/6 mcg-2 inhalations
Table Generation: 03FEB2020 at 9:14 PM by Table 14.2.1.6.sas

Table 14.2.1.7 Summary of 17-BMP Pharmacokinetic Parameters by Treatment, PK Analysis Set (without charcoal)

Treatment		C_{max} (pg/mL)	AUC_{0-t} (pg*hr/mL)	AUC_{0-inf} (pg*hr/mL)	t_{max} (hr)	$t_{1/2}$ (hr)	K_{el} (1/hr)	$AUC\_{\%Extrap\_obs}$ (%)
A	N	97	97	92	97	95	95	95
	Mean	602.9960	2518.3756	2793.6792	0.4804	3.8680	0.1884	8.9057
	SD	307.4615	1068.0521	1053.3647	0.5792	0.9524	0.0397	4.3363
	Min	118.168	520.908	1187.896	0.060	2.453	0.090	3.276
	Median	532.247	2396.372	2663.482	0.255	3.677	0.189	7.669
	Max	1804.949	6498.443	6939.916	4.008	7.660	0.283	27.211
	CV%	50.99	42.41	37.71	120.57	24.62	21.06	48.69
	Geometric Mean	533.0313	2306.4954	2621.4820	0.2996	3.7678	0.1840	8.0421
B	N	97	97	92	97	95	95	95
	Mean	579.7414	2486.6713	2749.1034	0.4862	3.7421	0.1931	8.3022
	SD	266.5610	961.2931	953.1493	0.8682	0.8213	0.0385	3.7311
	Min	124.208	507.478	1036.431	0.060	2.224	0.101	3.423
	Median	554.044	2495.522	2803.615	0.254	3.625	0.191	7.612
	Max	1734.133	7077.594	7335.351	8.003	6.865	0.312	24.335
	CV%	45.98	38.66	34.67	178.55	21.95	19.92	44.94
	Geometric Mean	523.2420	2309.9321	2605.4783	0.2810	3.6628	0.1893	7.6264

Source: Listings 16.2.6.2.1 and 16.2.6.2.2
Subjects [redacted] were excluded from AUC_{0-inf}, $t_{1/2}$, K_{el} and $AUC_{\%Extrap\_obs}$ due to R2<0.8 for Treatment A
Subject [redacted] was excluded from AUC_{0-inf}, $t_{1/2}$, K_{el} and $AUC\_{\%Extrap\_obs}$ due to R2<0.8 for Treatment B

Treatment A: Lupin BDP/FF 200/6 mcg-2 inhalations
Treatment B: FOSTAIR 200/6 mcg-2 inhalations
Table Generation: 03FEB2020 at 9:19 PM by Table 14.2.1.7.sas

Table 14.2.1.7 Summary of 17-BMP Pharmacokinetic Parameters by Treatment, PK Analysis Set (without charcoal)

Subjects [redacted] were excluded from AUC_{0-inf} due to 20% of the AUC is extrapolated beyond the last measurable value for Treatment A
Subject [redacted] was excluded from AUC_{0-inf} due to 20% of the AUC is extrapolated beyond the last measurable value for Treatment B
Subject no. [redacted] was withdrawn on medical grounds due to difficulty in cannulation and did not receive drug administration in periods 2, 3 and 4 (Treatments B, D and C, respectively)
Subject no. [redacted] was withdrawn due to adverse events and did not receive drug administration in period 4 (Treatment A)
Subject no. [redacted] was withdrawn due to adverse events and did not receive drug administration in period 4 (Treatment B)
Subject no [redacted] was withdrawn due to protocol violation and did not receive drug administration in periods 3 and 4 (Treatments B and A respectively)
Subject no. [redacted] voluntarily withdrew consent and did not receive drug administration in periods 2, 3 and 4 (Treatments A, C and B respectively)
Subject no. [redacted] voluntarily withdrew consent and did not receive drug administration in periods 2, 3 and 4 (Treatments D, B and A respectively)
Subject no. [redacted] was withdrawn due to failure to comply with protocol requirements and did not receive drug administration in periods 2, 3 and 4 (Treatments A, C and B respectively)
Subject no. [redacted] were excluded due to major protocol deviations for Treatment A & B

Treatment A: Lupin BDP/FF 200/6 mcg-2 inhalations
Treatment B: FOSTAIR 200/6 mcg-2 inhalations
Table Generation: 03FEB2020 at 9:19 PM by Table 14.2.1.7.sas

Table 14.2.1.8 Summary of 17-BMP Pharmacokinetic Parameters by Treatment, FAS (without charcoal)

Treatment		C_{max} (pg/mL)	AUC_{0-t} (pg*hr/mL)	AUC_{0-inf} (pg*hr/mL)	t_{max} (hr)	$t_{1/2}$ (hr)	K_{el} (1/hr)	$AUC\_{\%Extrap\_obs}$ (%)
A	N	105	105	99	105	103	103	103
	Mean	582.9229	2464.2827	2748.1564	0.4712	3.8544	0.1892	9.0936
	SD	305.2909	1057.3434	1038.2325	0.5643	0.9390	0.0414	4.4223
	Min	118.168	520.908	1187.896	0.060	2.028	0.090	3.276
	Median	508.786	2344.820	2584.258	0.254	3.712	0.187	7.714
	Max	1804.949	6498.443	6939.916	4.008	7.660	0.342	27.211
	CV%	52.37	42.91	37.78	119.77	24.36	21.88	48.63
	Geometric Mean	513.0491	2253.8320	2580.0087	0.2953	3.7545	0.1847	8.2056
B	N	105	105	99	105	103	103	103
	Mean	565.4190	2465.6708	2728.1241	0.4924	3.7389	0.1928	8.3967
	SD	264.5807	955.8570	954.4193	0.8369	0.7939	0.0373	3.7109
	Min	124.208	507.478	1036.431	0.060	2.224	0.101	3.423
	Median	543.591	2488.808	2759.356	0.254	3.643	0.190	7.695
	Max	1734.133	7077.594	7335.351	8.003	6.865	0.312	24.335
	CV%	46.79	38.77	34.98	169.98	21.23	19.32	44.19
	Geometric Mean	508.9718	2289.9579	2581.7652	0.2946	3.6647	0.1892	7.7270

Source: Listings 16.2.6.2.1 and 16.2.6.2.2
Subjects [redacted] were excluded from AUC_{0-inf}, $t_{1/2}$, K_{el} and $AUC_{\%Extrap\_obs}$ due to R2<0.8 for Treatment A
Subject [redacted] was excluded from AUC_{0-inf}, $t_{1/2}$, K_{el} and $AUC\_{\%Extrap\_obs}$ due to R2<0.8 for Treatment B

Treatment A: Lupin BDP/FF 200/6 mcg-2 inhalations
Treatment B: FOSTAIR 200/6 mcg-2 inhalations
Table Generation: 03FEB2020 at 9:22 PM by Table 14.2.1.8.sas

Table 14.2.1.8 Summary of 17-BMP Pharmacokinetic Parameters by Treatment, FAS (without charcoal)

Subjects [redacted] were excluded from $AUC_{0\text{-}inf}$ due to 20% of the AUC is extrapolated beyond the last measurable value for Treatment A
Subject [redacted] was excluded from $AUC_{0\text{-}inf}$ due to 20% of the AUC is extrapolated beyond the last measurable value for Treatment B
Subject no. [redacted] was withdrawn on medical grounds due to difficulty in cannulation and did not receive drug administration in periods 2, 3 and 4 (Treatments B, D and C, respectively)
Subject no. [redacted] was withdrawn due to adverse events and did not receive drug administration in period 4 (Treatment A)
Subject no. [redacted] was withdrawn due to adverse events and did not receive drug administration in period 4 (Treatment B)
Subject no [redacted] was withdrawn due to protocol violation and did not receive drug administration in periods 3 and 4 (Treatments B and A respectively)
Subject no. [redacted] voluntarily withdrew consent and did not receive drug administration in periods 2, 3 and 4 (Treatments A, C and B respectively)
Subject no. [redacted] voluntarily withdrew consent and did not receive drug administration in periods 2, 3 and 4 (Treatments D, B and A respectively)
Subject no. [redacted] was withdrawn due to failure to comply with protocol requirements and did not receive drug administration in periods 2, 3 and 4 (Treatments A, C and B respectively)

Treatment A: Lupin BDP/FF 200/6 mcg-2 inhalations
Treatment B: FOSTAIR 200/6 mcg-2 inhalations
Table Generation: 03FEB2020 at 9:22 PM by Table 14.2.1.8.sas

Table 14.2.1.9 Summary of Formoterol Pharmacokinetic Parameters by Treatment, PK Analysis Set (with and without charcoal)

Treatment		C_{max} (pg/mL)	AUC_{0-t} (pg*hr/mL)	AUC_{0-inf} (pg*hr/mL)	t_{max} (hr)	$t_{1/2}$ (hr)	K_{el} (1/hr)	$AUC\_\%Extrap\_obs$ (%)
A	N	97	97	66	97	84	84	84
	Mean	18.3924	48.2820	56.4531	0.1217	8.4519	0.0989	12.9039
	SD	8.7472	18.8251	20.1010	0.0960	3.9162	0.0431	5.1135
	Min	2.697	10.073	19.376	0.062	2.758	0.033	3.841
	Median	16.728	46.455	51.839	0.103	7.500	0.092	11.621
	Max	46.345	97.185	111.435	0.756	21.137	0.251	26.387
	CV%	47.56	38.99	35.61	78.90	46.33	43.62	39.63
	Geometric Mean	16.1488	44.2892	52.9804	0.1093	7.6835	0.0902	11.9405
B	N	97	97	66	97	84	84	84
	Mean	17.4271	46.7734	54.4086	0.1456	8.1116	0.0981	13.6242
	SD	8.3431	17.9951	18.2098	0.1810	3.4785	0.0367	5.1504
	Min	2.373	10.611	24.897	0.061	2.544	0.027	5.248
	Median	16.723	46.998	52.842	0.104	7.189	0.097	12.531
	Max	47.959	111.974	130.609	1.008	25.751	0.272	36.833
	CV%	47.87	38.47	33.47	124.26	42.88	37.42	37.80
	Geometric Mean	15.3967	43.0548	51.6039	0.1154	7.5450	0.0919	12.8017

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
Table Generation: 15FEB2020 at 10:35 AM by Table 14.2.1.9.sas

Table 14.2.1.9 Summary of Formoterol Pharmacokinetic Parameters by Treatment, PK Analysis Set (with and without charcoal)

Treatment		C_{max} (pg/mL)	AUC_{0-t} (pg*hr/mL)	AUC_{0-inf} (pg*hr/mL)	t_{max} (hr)	$t_{1/2}$ (hr)	K_{el} (1/hr)	$AUC\_\%Extrap\_obs$ (%)
C	N	88	88	29	88	64	64	64
	Mean	16.7410	28.0978	41.6203	0.1168	8.5123	0.1166	19.2548
	SD	7.6773	16.2823	16.8839	0.0326	11.4657	0.0760	10.3401
	Min	2.523	1.685	21.317	0.031	1.209	0.007	6.816
	Median	15.720	26.734	37.675	0.103	6.668	0.104	16.963
	Max	50.756	99.236	109.159	0.251	96.111	0.573	63.691
	CV%	45.86	57.95	40.57	27.93	134.70	65.21	53.70
	Geometric Mean	15.0207	23.1549	39.1843	0.1123	6.8337	0.1014	17.4397
D	N	88	88	29	88	64	64	64
	Mean	15.2828	25.0775	38.0143	0.1130	7.2817	0.1104	19.8249
	SD	7.4185	14.3769	14.2674	0.0298	2.7094	0.0467	7.1693
	Min	4.173	4.852	13.686	0.060	2.848	0.040	8.445
	Median	13.732	23.500	36.483	0.103	7.443	0.093	18.519
	Max	39.450	74.741	86.677	0.185	17.309	0.243	40.999
	CV%	48.54	57.33	37.53	26.34	37.21	42.33	36.16
	Geometric Mean	13.6418	20.8757	35.6846	0.1089	6.7834	0.1022	18.6107

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
Table Generation: 15FEB2020 at 10:35 AM by Table 14.2.1.9.sas

Table 14.2.1.9 Summary of Formoterol Pharmacokinetic Parameters by Treatment, PK Analysis Set (with and without charcoal)

Treatment		C_{max} (pg/mL)	AUC_{0-t} (pg*hr/mL)	AUC_{0-inf} (pg*hr/mL)	t_{max} (hr)	$t_{1/2}$ (hr)	K_{el} (1/hr)	$AUC\_\%Extrap\_obs$ (%)

Source: Listings 16.2.6.2.3, 16.2.6.2.4, 16.2.6.2.5 and 16.2.6.2.6
Subjects [redacted] were excluded from AUC_{0-inf}, $t_{1/2}$, K_{el} and $AUC\_\%Extrap\_obs$ due to R2<0.8 for Treatment A
Subjects [redacted] were excluded from AUC_{0-inf}, $t_{1/2}$, K_{el} and $AUC_{\%Extrap\_obs}$ due to R2<0.8 for Treatment B
Subjects [redacted] were excluded from AUC_{0-inf}, $t_{1/2}$, K_{el} and $AUC_{\%Extrap\_obs}$ due to R2<0.8 for Treatment C
Subjects [redacted] were excluded from AUC_{0-inf}, $t_{1/2}$, K_{el} and $AUC_{\%Extrap\_obs}$ due to R2<0.8 for Treatment D
Subjects [redacted] were excluded from AUC_{0-inf} due to 20% of the AUC is extrapolated beyond the last measurable value for Treatment A
Subjects [redacted] were excluded from AUC_{0-inf} due to 20% of the AUC is extrapolated beyond the last measurable value for Treatment B
Subjects [redacted] were excluded from AUC_{0-inf} due to 20% of the AUC is extrapolated beyond the last measurable value for Treatment C
Subjects [redacted] were excluded from AUC_{0-inf} due to 20% of the AUC is extrapolated beyond the last measurable value for Treatment D
Subject no. [redacted] was withdrawn on medical grounds due to difficulty in cannulation and did not receive drug administration in periods 2, 3 and 4 (Treatments B, D and C, respectively)
Subject no. [redacted] was withdrawn due to adverse events and did not receive drug administration in period 4 (Treatment A)
Subject no. [redacted] was withdrawn due to adverse events and did not receive drug administration in period 4 (Treatment B)
Subject no. [redacted] was withdrawn due to protocol violation and did not receive drug administration in periods 3 and 4 (Treatments B and A respectively)
Subject no. [redacted] was withdrawn due to protocol violation did not receive drug administration in period 4 (Treatment C)

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
Table Generation: 15FEB2020 at 10:35 AM by Table 14.2.1.9.sas

Table 14.2.1.9 Summary of Formoterol Pharmacokinetic Parameters by Treatment, PK Analysis Set (with and without charcoal)

Subject no[redacted] voluntarily withdrew consent and did not receive drug administration in period 4 (Treatments D)
Subject no.[redacted] did not have any measurable formoterol concentrations following administration of Treatment C and therefore was excluded from Treatment C and D
Subject no.[redacted] voluntarily withdrew consent and did not receive drug administration in periods 2, 3 and 4 (Treatments A, C and B respectively)
Subject no.[redacted] voluntarily withdrew consent and did not receive drug administration in periods 2, 3 and 4 (Treatments D, B and A respectively)
Subject no.[redacted] was withdrawn due to failure to comply with protocol requirements and did not receive drug administration in periods 2, 3 and 4 (Treatments A, C and B respectively)
Subject no[redacted] were excluded due to major protocol deviations from A vs B calculation
Subject no.[redacted] were excluded due to major protocol deviations from C vs D calculation

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
Table Generation: 15FEB2020 at 10:35 AM by Table 14.2.1.9.sas

Table 14.2.1.10 Summary of Formoterol Pharmacokinetic Parameters by Treatment, FAS (with and without charcoal)

Treatment		C_{max} (pg/mL)	AUC_{0-t} (pg*hr/mL)	AUC_{0-inf} (pg*hr/mL)	t_{max} (hr)	$t_{1/2}$ (hr)	K_{el} (1/hr)	$AUC\_\%Extrap\_obs$ (%)
A	N	105	105	73	105	91	91	91
	Mean	17.8201	47.1426	54.7562	0.1212	8.2300	0.1013	12.8114
	SD	8.6738	18.7743	20.1416	0.0928	3.8570	0.0429	5.0528
	Min	2.697	10.073	19.376	0.062	2.758	0.033	3.841
	Median	16.021	44.844	51.185	0.103	7.238	0.096	11.157
	Max	46.345	97.185	111.435	0.756	21.137	0.251	26.387
	CV%	48.67	39.82	36.78	76.55	46.87	42.37	39.44
	Geometric Mean	15.6282	43.1559	51.1830	0.1094	7.4808	0.0927	11.8724
B	N	105	105	73	105	91	91	91
	Mean	17.1021	46.6317	54.1711	0.1467	8.1165	0.0976	13.5314
	SD	8.1547	17.8273	18.2086	0.1778	3.3871	0.0362	5.0339
	Min	2.373	10.611	24.897	0.061	2.544	0.027	5.248
	Median	16.343	46.433	52.223	0.104	7.245	0.096	12.483
	Max	47.959	111.974	130.609	1.008	25.751	0.272	36.833
	CV%	47.68	38.23	33.61	121.21	41.73	37.03	37.20
	Geometric Mean	15.1636	42.9946	51.3240	0.1164	7.5710	0.0916	12.7431

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
Table Generation: 15FEB2020 at 10:38 AM by Table 14.2.1.10.sas

Table 14.2.1.10 Summary of Formoterol Pharmacokinetic Parameters by Treatment, FAS (with and without charcoal)

Treatment		C_{max} (pg/mL)	AUC_{0-t} (pg*hr/mL)	AUC_{0-inf} (pg*hr/mL)	t_{max} (hr)	$t_{1/2}$ (hr)	K_{el} (1/hr)	$AUC\_\%Extrap\_obs$ (%)
C	N	105	105	33	105	78	78	78
	Mean	15.3436	25.9854	39.7743	0.1153	8.0436	0.1503	20.9950
	SD	7.8557	16.0637	16.8154	0.0326	10.5594	0.1892	12.2229
	Min	0.806	0.201	14.308	0.031	0.544	0.007	6.816
	Median	14.185	22.381	36.489	0.103	6.632	0.105	17.777
	Max	50.756	99.236	109.159	0.251	96.111	1.274	75.577
	CV%	51.20	61.82	42.28	28.30	131.28	125.89	58.22
	Geometric Mean	13.1858	19.9572	37.1042	0.1108	6.2388	0.1111	18.6448
D	N	105	105	33	105	78	78	78
	Mean	14.7270	24.4683	39.1602	0.1106	7.1941	0.1440	20.4779
	SD	7.6233	15.4230	16.5128	0.0309	3.0971	0.2861	7.9884
	Min	1.362	0.351	13.686	0.032	0.266	0.038	6.758
	Median	12.986	22.570	36.483	0.103	7.207	0.097	18.932
	Max	39.450	74.741	86.677	0.185	18.241	2.604	48.435
	CV%	51.76	63.03	42.17	27.92	43.05	198.68	39.01
	Geometric Mean	12.8039	19.2168	36.1122	0.1059	6.4468	0.1075	19.0519

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
Table Generation: 15FEB2020 at 10:38 AM by Table 14.2.1.10.sas

Table 14.2.1.10 Summary of Formoterol Pharmacokinetic Parameters by Treatment, FAS (with and without charcoal)

Treatment		C_{max} (pg/mL)	AUC_{0-t} (pg*hr/mL)	AUC_{0-inf} (pg*hr/mL)	t_{max} (hr)	$t_{1/2}$ (hr)	K_{el} (1/hr)	$AUC\_{\%Extrap\_obs}$ (%)

Source: Listings 16.2.6.2.3, 16.2.6.2.4, 16.2.6.2.5 and 16.2.6.2.6
Subjects [redacted] were excluded from AUC_{0-inf}, $t_{1/2}$, K_{el} and $AUC\_{\%Extrap\_obs}$ due to R2<0.8 for Treatment A
Subjects [redacted] were excluded from AUC_{0-inf}, $t_{1/2}$, K_{el} and $AUC_{\%Extrap\_obs}$ due to R2<0.8 for Treatment B
Subjects [redacted] were excluded from AUC_{0-inf}, $t_{1/2}$, K_{el} and $AUC_{\%Extrap\_obs}$ due to R2<0.8 for Treatment C
Subjects [redacted] were excluded from AUC_{0-inf}, $t_{1/2}$, K_{el} and $AUC_{\%Extrap\_obs}$ due to R2<0.8 for Treatment D
Subjects [redacted] were excluded from AUC_{0-inf} due to 20% of the AUC is extrapolated beyond the last measurable value for Treatment A
Subjects [redacted] were excluded from AUC_{0-inf} due to 20% of the AUC is extrapolated beyond the last measurable value for Treatment B
Subjects [redacted] were excluded from AUC_{0-inf} due to 20% of the AUC is extrapolated beyond the last measurable value for Treatment C
Subjects [redacted] were excluded from AUC_{0-inf} due to 20% of the AUC is extrapolated beyond the last measurable value for Treatment D
Subject no. [redacted] was withdrawn on medical grounds due to difficulty in cannulation and did not receive drug administration in periods 2, 3 and 4 (Treatments B, D and C, respectively)
Subject no. [redacted] was withdrawn due to adverse events and did not receive drug administration in period 4 (Treatment A)
Subject no. [redacted] was withdrawn due to adverse events and did not receive drug administration in period 4 (Treatment B)
Subject no. [redacted] was withdrawn due to protocol violation and did not receive drug administration in periods 3 and 4 (Treatments B and A respectively)
Subject no. [redacted] was withdrawn due to protocol violation did not receive drug administration in period 4 (Treatment C)

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
Table Generation: 15FEB2020 at 10:38 AM by Table 14.2.1.10.sas

Table 14.2.1.10 Summary of Formoterol Pharmacokinetic Parameters by Treatment, FAS (with and without charcoal)

Subject no. [redacted] voluntarily withdrew consent and did not receive drug administration in period 4 (Treatments D)
Subject no. [redacted] did not have any measurable formoterol concentrations following administration of Treatment C and therefore was excluded from Treatment C and D
Subject no. [redacted] voluntarily withdrew consent and did not receive drug administration in periods 2, 3 and 4 (Treatments A, C and B respectively)
Subject no. [redacted] voluntarily withdrew consent and did not receive drug administration in periods 2, 3 and 4 (Treatments D, B and A respectively)
Subject no. [redacted] was withdrawn due to failure to comply with protocol requirements and did not receive drug administration in periods 2, 3 and 4 (Treatments A, C and B respectively)

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
Table Generation: 15FEB2020 at 10:38 AM by Table 14.2.1.10.sas

Table 14.2.1.11 Summary of BDP Pharmacokinetic Parameters, PK Analysis Set (without charcoal)

Treatment		C_{max} (pg/mL)	AUC_{0-t} (pg*hr/mL)	AUC_{0-inf} (pg*hr/mL)	t_{max} (hr)	$t_{1/2}$ (hr)	K_{el} (1/hr)	$AUC\_\%Extrap\_obs$ (%)
A	N	97	97	76	97	76	76	76
	Mean	3011.6444	282.3162	289.9633	0.0436	0.5143	2.2057	2.3261
	SD	2419.0212	191.5901	196.8895	0.0166	0.5750	1.2959	2.2337
	Min	324.835	42.378	61.518	0.030	0.110	0.187	0.477
	Median	2392.851	231.902	248.745	0.034	0.330	2.101	1.872
	Max	15068.124	1202.396	1208.162	0.103	3.697	6.289	16.017
	CV%	80.32	67.86	67.90	38.20	111.80	58.75	96.02
	Geometric Mean	2361.8720	234.6115	244.1335	0.0411	0.3825	1.8118	1.8633
B	N	97	97	76	97	76	76	76
	Mean	3010.5315	282.9575	301.0003	0.0415	0.4248	2.4659	1.8332
	SD	2279.2760	188.8517	204.3515	0.0134	0.2952	1.5876	1.0444
	Min	202.254	53.611	54.258	0.031	0.072	0.575	0.498
	Median	2462.614	233.451	257.570	0.034	0.295	2.355	1.537
	Max	15471.847	1432.603	1442.477	0.102	1.206	9.577	4.973
	CV%	75.71	66.74	67.89	32.35	69.50	64.38	56.97
	Geometric Mean	2427.2848	243.2328	257.9951	0.0398	0.3426	2.0226	1.5903

Treatment A: Lupin BDP/FF 200/6 mcg-2 inhalations
Treatment B: FOSTAIR 200/6 mcg-2 inhalations
Table Generation: 04FEB2020 at 9:13 AM by Table 14.2.1.11.sas

Table 14.2.1.11 Summary of BDP Pharmacokinetic Parameters, PK Analysis Set (without charcoal)

Treatment		C_{max} (pg/mL)	AUC_{0-t} (pg*hr/mL)	AUC_{0-inf} (pg*hr/mL)	t_{max} (hr)	$t_{1/2}$ (hr)	K_{el} (1/hr)	$AUC\_{\%Extrap\_obs}$ (%)

Source: Listings 16.2.6.2.7 and 16.2.6.2.8
Subjects [redacted] were excluded from AUC_{0-inf}, $t_{1/2}$, K_{el} and $AUC\_{\%Extrap\_obs}$ due to R2<0.8 for Treatment A
Subjects [redacted] were excluded from AUC_{0-inf}, $t_{1/2}$, K_{el} and $AUC_{\%Extrap\_obs}$ due to R2<0.8 for Treatment B
Subjects [redacted] were excluded from AUC_{0-inf} due to 20% of the AUC is extrapolated beyond the last measurable value for Treatment A
Subjects [redacted] were excluded from AUC_{0-inf} due to 20% of the AUC is extrapolated beyond the last measurable value for Treatment B
Subject no. [redacted] was withdrawn on medical grounds due to difficulty in cannulation and did not receive drug administration in periods 2, 3 and 4 (Treatments B, D and C, respectively)
Subject no. [redacted] was withdrawn due to adverse events and did not receive drug administration in period 4 (Treatment A)
Subject no [redacted] was withdrawn due to adverse events and did not receive drug administration in period 4 (Treatment B)
Subject no. [redacted] was withdrawn due to protocol violation and did not receive drug administration in periods 3 and 4 (Treatments B and A respectively)
Subject no. [redacted] voluntarily withdrew consent and did not receive drug administration in periods 2, 3 and 4 (Treatments A, C and B respectively)
Subject no [redacted] voluntarily withdrew consent and did not receive drug administration in periods 2, 3 and 4 (Treatments D, B and A respectively)
Subject no. [redacted] was withdrawn due to failure to comply with protocol requirements and did not receive drug administration in periods 2, 3 and 4 (Treatments A, C and B respectively)
Subject no. [redacted] were excluded due to major protocol deviations for Treatment A & B

Treatment A: Lupin BDP/FF 200/6 mcg-2 inhalations
Treatment B: FOSTAIR 200/6 mcg-2 inhalations
Table Generation: 04FEB2020 at 9:13 AM by Table 14.2.1.11.sas

Table 14.2.1.12 Summary of BDP Pharmacokinetic Parameters, FAS (without charcoal)

Treatment		C_{max} (pg/mL)	AUC_{0-t} (pg*hr/mL)	AUC_{0-inf} (pg*hr/mL)	t_{max} (hr)	$t_{1/2}$ (hr)	K_{el} (1/hr)	$AUC\_\%Extrap\_obs$ (%)
A	N	105	105	83	105	84	84	84
	Mean	2919.7152	273.6672	279.4741	0.0432	0.5745	2.2113	2.5570
	SD	2357.4310	187.9112	193.1161	0.0163	0.8976	1.2958	2.9207
	Min	324.835	42.378	61.518	0.030	0.110	0.099	0.477
	Median	2291.505	218.696	238.187	0.034	0.330	2.101	1.890
	Max	15068.124	1202.396	1208.162	0.103	6.996	6.289	20.529
	CV%	80.74	68.66	69.10	37.78	156.25	58.60	114.23
	Geometric Mean	2299.6737	227.0742	234.1919	0.0409	0.3870	1.7909	1.9518
B	N	105	105	83	105	84	84	84
	Mean	2928.5474	276.9778	293.6171	0.0417	0.4225	2.4525	1.8799
	SD	2228.0476	185.2846	200.0948	0.0135	0.2914	1.5451	1.0638
	Min	202.254	53.611	54.258	0.031	0.072	0.575	0.498
	Median	2437.173	226.058	250.304	0.034	0.295	2.355	1.560
	Max	15471.847	1432.603	1442.477	0.102	1.206	9.577	4.973
	CV%	76.08	66.90	68.15	32.42	68.98	63.00	56.59
	Geometric Mean	2364.7801	237.9251	251.1561	0.0400	0.3424	2.0243	1.6328

Treatment A: Lupin BDP/FF 200/6 mcg-2 inhalations
Treatment B: FOSTAIR 200/6 mcg-2 inhalations
Table Generation: 04FEB2020 at 9:15 AM by Table 14.2.1.12.sas

Table 14.2.1.12 Summary of BDP Pharmacokinetic Parameters, FAS (without charcoal)

Treatment		C_{max} (pg/mL)	AUC_{0-t} (pg*hr/mL)	AUC_{0-inf} (pg*hr/mL)	t_{max} (hr)	$t_{1/2}$ (hr)	K_{el} (1/hr)	$AUC_{\_\%Extrap\_obs}$ (%)

Source: Listings 16.2.6.2.7 and 16.2.6.2.8
Subjects [redacted] were excluded from AUC_{0-inf}, $t_{1/2}$, K_{el} and $AUC_{\_\%Extrap\_obs}$ due to R2<0.8 for Treatment A
Subjects [redacted] were excluded from AUC_{0-inf}, $t_{1/2}$, K_{el} and $AUC_{\%Extrap\_obs}$ due to R2<0.8 for Treatment B
Subjects [redacted] were excluded from AUC_{0-inf} due to 20% of the AUC is extrapolated beyond the last measurable value for Treatment A
Subjects [redacted] were excluded from AUC_{0-inf} due to 20% of the AUC is extrapolated beyond the last measurable value for Treatment B
Subject no [redacted] was withdrawn on medical grounds due to difficulty in cannulation and did not receive drug administration in periods 2, 3 and 4 (Treatments B, D and C, respectively)
Subject no. [redacted] was withdrawn due to adverse events and did not receive drug administration in period 4 (Treatment A)
Subject no [redacted] was withdrawn due to adverse events and did not receive drug administration in period 4 (Treatment B)
Subject no [redacted] was withdrawn due to protocol violation and did not receive drug administration in periods 3 and 4 (Treatments B and A respectively)
Subject no [redacted] voluntarily withdrew consent and did not receive drug administration in periods 2, 3 and 4 (Treatments A, C and B respectively)
Subject no [redacted] voluntarily withdrew consent and did not receive drug administration in periods 2, 3 and 4 (Treatments D, B and A respectively)
Subject no [redacted] was withdrawn due to failure to comply with protocol requirements and did not receive drug administration in periods 2, 3 and 4 (Treatments A, C and B respectively)

Treatment A: Lupin BDP/FF 200/6 mcg-2 inhalations
Treatment B: FOSTAIR 200/6 mcg-2 inhalations
Table Generation: 04FEB2020 at 9:15 AM by Table 14.2.1.12.sas

Table 14.2.1.13 Summary of Statistical Comparisons of Plasma 17-BMP Pharmacokinetic Parameters C_{max}, AUC_{0-t}, and AUC_{0-inf} PK Analysis Set (without charcoal)

	Geometric LSM			
Parameter	**Treatment A**	**Treatment B**	**Geometric Mean Ratio (90% Confidence Interval) (%)**	**Intra-subject CV%**
Cmax (pg/mL)	534.3078	521.5587	102.44 [96.47,108.79]	25.38
AUC0-t (pg*hr/mL)	2304.7341	2301.7928	100.13 [95.10,105.42]	21.66
AUC0-inf (pg*hr/mL)	2623.5814	2603.3801	100.78 [96.18,105.60]	18.99

Source: Listings 16.2.6.2.1 and 16.2.6.2.2
Subjects [redacted] were excluded from AUC_{0-inf}, $t_{1/2}$, K_{el} and $AUC\_{\%Extrap\_obs}$ due to R2<0.8 for Treatment A
Subject [redacted] was excluded from AUC_{0-inf}, $t_{1/2}$, K_{el} and $AUC\_{\%Extrap\_obs}$ due to R2<0.8 for Treatment B
Subjects [redacted] were excluded from AUC_{0-inf} due to 20% of the AUC is extrapolated beyond the last measurable value for Treatment A
Subject [redacted] was excluded from AUC_{0-inf} due to 20% of the AUC is extrapolated beyond the last measurable value for Treatment B
Subject no. [redacted] was withdrawn on medical grounds due to difficulty in cannulation and did not receive drug administration in periods 2, 3 and 4 (Treatments B, D and C, respectively)
Subject no [redacted] was withdrawn due to adverse events and did not receive drug administration in period 4 (Treatment A)
Subject no [redacted] was withdrawn due to adverse events and did not receive drug administration in period 4 (Treatment B)
Subject no [redacted] was withdrawn due to protocol violation and did not receive drug administration in periods 3 and 4 (Treatments B and A respectively)
Subject no [redacted] voluntarily withdrew consent and did not receive drug administration in periods 2, 3 and 4 (Treatments A, C and B respectively)
Subject no. [redacted] voluntarily withdrew consent and did not receive drug administration in periods 2, 3 and 4 (Treatments D, B and A respectively)
Subject no. [redacted] was withdrawn due to failure to comply with protocol requirements and did not receive drug administration in periods 2, 3 and 4 (Treatments A, C and B respectively)
Subject no. [redacted] were excluded due to major protocol deviations for Treatment A & B

Treatment A: Lupin BDP/FF 200/6 mcg-2 inhalations
Treatment B: FOSTAIR 200/6 mcg-2 inhalations
Table Generation: 04FEB2020 at 10:06 AM by Table 14.2.1.13.sas

Table 14.2.1.14 Summary of Statistical Comparisons of Plasma 17-BMP Pharmacokinetic Parameters C_{max}, AUC_{0-t}, and AUC_{0-inf} FAS (without charcoal)

	Geometric LSM			
Parameter	**Treatment A**	**Treatment B**	**Geometric Mean Ratio (90% Confidence Interval) (%)**	**Intra-subject CV%**
Cmax (pg/mL)	511.6943	509.8596	100.36 [94.64,106.43]	25.96
AUC0-t (pg*hr/mL)	2251.3619	2290.3890	98.30 [93.41,103.44]	22.47
AUC0-inf (pg*hr/mL)	2576.9916	2582.3048	99.79 [95.40,104.39]	19.08

Source: Listings 16.2.6.2.1 and 16.2.6.2.2
Subjects [redacted] were excluded from AUC_{0-inf}, $t_{1/2}$, K_{el} and $AUC\_{\%Extrap\_obs}$ due to R2<0.8 for Treatment A
Subject [redacted] was excluded from AUC_{0-inf}, $t_{1/2}$, K_{el} and $AUC\_{\%Extrap\_obs}$ due to R2<0.8 for Treatment B
Subjects [redacted] were excluded from AUC_{0-inf} due to 20% of the AUC is extrapolated beyond the last measurable value for Treatment A
Subject [redacted] was excluded from AUC_{0-inf} due to 20% of the AUC is extrapolated beyond the last measurable value for Treatment B
Subject no. [redacted] was withdrawn on medical grounds due to difficulty in cannulation and did not receive drug administration in periods 2, 3 and 4 (Treatments B, D and C, respectively)
Subject no [redacted] was withdrawn due to adverse events and did not receive drug administration in period 4 (Treatment A)
Subject no [redacted] was withdrawn due to adverse events and did not receive drug administration in period 4 (Treatment B)
Subject no. [redacted] was withdrawn due to protocol violation and did not receive drug administration in periods 3 and 4 (Treatments B and A respectively)
Subject no. [redacted] voluntarily withdrew consent and did not receive drug administration in periods 2, 3 and 4 (Treatments A, C and B respectively)
Subject no [redacted] voluntarily withdrew consent and did not receive drug administration in periods 2, 3 and 4 (Treatments D, B and A respectively)
Subject no. [redacted] was withdrawn due to failure to comply with protocol requirements and did not receive drug administration in periods 2, 3 and 4 (Treatments A, C and B respectively)

Treatment A: Lupin BDP/FF 200/6 mcg-2 inhalations
Treatment B: FOSTAIR 200/6 mcg-2 inhalations
Table Generation: 04FEB2020 at 10:10 AM by Table 14.2.1.14.sas

Table 14.2.1.15 Summary of Statistical Comparisons of Plasma Formoterol Pharmacokinetic Parameters C_{max}, AUC_{0-t}, and AUC_{0-inf} PK Analysis Set (with and without charcoal)

	Geometric LSM			
Parameter	**Treatment A**	**Treatment B**	**Treatment C**	**Treatment D**
Cmax (pg/mL)	16.0682	15.2830	14.6351	13.2526
AUC0-t (pg*hr/mL)	44.1205	42.9461	23.5434	21.0990
AUC0-inf (pg*hr/mL)	52.4552	51.6675	43.5534	41.5183

Parameter	**Geometric Mean Ratio (90% Confidence Interval) (%) A vs B (without charcoal)**	**Geometric Mean Ratio (90% Confidence Interval) (%) C vs D (with charcoal)**	**Intra-subject CV%**
Cmax (pg/mL)	105.14 [98.67,112.03]	110.43 [103.48,117.85]	26.75
AUC0-t (pg*hr/mL)	102.73 [94.21,112.03]	111.59 [102.12,121.93]	37.03
AUC0-inf (pg*hr/mL)	101.52 [95.30,108.15]	104.90 [98.32,111.92]	22.00

Source: Listings 16.2.6.2.3, 16.2.6.2.4, 16.2.6.2.5 and 16.2.6.2.6
Subjects [redacted] were excluded from AUC_{0-inf}, $t_{1/2}$, K_{el} and $AUC_{\%Extrap\_obs}$ due to R2<0.8 for Treatment A
Subjects [redacted] were excluded from AUC_{0-inf}, $t_{1/2}$, K_{el} and $AUC_{\%Extrap\_obs}$ due to R2<0.8 for Treatment B
Subjects [redacted] were excluded from AUC_{0-inf}, $t_{1/2}$, K_{el} and $AUC_{\%Extrap\_obs}$ due to R2<0.8 for Treatment C
Subjects [redacted] were excluded from AUC_{0-inf}, $t_{1/2}$, K_{el} and $AUC_{\%Extrap\_obs}$ due to R2<0.8 for Treatment D

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
Table Generation: 04FEB2020 at 10:14 AM by Table 14.2.1.15.sas

Table 14.2.1.15 Summary of Statistical Comparisons of Plasma Formoterol Pharmacokinetic Parameters C_{max}, AUC_{0-t}, and AUC_{0-inf} PK Analysis Set (with and without charcoal)

Subjects [redacted] were excluded from AUC_{0-inf} due to 20% of the AUC is extrapolated beyond the last measurable value for Treatment A
Subjects [redacted] were excluded from AUC_{0-inf} due to 20% of the AUC is extrapolated beyond the last measurable value for Treatment B
Subjects [redacted] were excluded from AUC_{0-inf} due to 20% of the AUC is extrapolated beyond the last measurable value for Treatment C
Subjects [redacted] were excluded from AUC_{0-inf} due to 20% of the AUC is extrapolated beyond the last measurable value for Treatment D
Subject no. [redacted] was withdrawn on medical grounds due to difficulty in cannulation and did not receive drug administration in periods 2, 3 and 4 (Treatments B, D and C, respectively)
Subject no. [redacted] was withdrawn due to adverse events and did not receive drug administration in period 4 (Treatment A)
Subject no. [redacted] was withdrawn due to adverse events and did not receive drug administration in period 4 (Treatment B)
Subject no [redacted] was withdrawn due to protocol violation and did not receive drug administration in periods 3 and 4 (Treatments B and A respectively)
Subject no. [redacted] was withdrawn due to protocol violation did not receive drug administration in period 4 (Treatment C)
Subject no. [redacted] voluntarily withdrew consent and did not receive drug administration in period 4 (Treatments D)
Subject no. [redacted] did not have any measurable formoterol concentrations following administration of Treatment C and therefore was excluded from Treatment C and D
Subject no. [redacted] voluntarily withdrew consent and did not receive drug administration in periods 2, 3 and 4 (Treatments A, C and B respectively)
Subject no. [redacted] voluntarily withdrew consent and did not receive drug administration in periods 2, 3 and 4 (Treatments D, B and A respectively)
Subject no. [redacted] was withdrawn due to failure to comply with protocol requirements and did not receive drug administration in periods 2, 3 and 4 (Treatments A, C and B respectively)
Subject no. [redacted] were excluded due to major protocol deviations from A vs B calculation
Subject no. [redacted] were excluded due to major protocol deviations from C vs D calculation

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
Table Generation: 04FEB2020 at 10:14 AM by Table 14.2.1.15.sas

Table 14.2.1.16 Summary of Statistical Comparisons of Plasma Formoterol Pharmacokinetic Parameters C_{max}, AUC_{0-t}, and AUC_{0-inf} FAS (with and without charcoal)

	Geometric LSM			
Parameter	**Treatment A**	**Treatment B**	**Treatment C**	**Treatment D**
Cmax (pg/mL)	15.4592	15.1944	13.2594	13.0454
AUC0-t (pg*hr/mL)	43.2375	42.7802	20.7643	19.9351
AUC0-inf (pg*hr/mL)	47.4633	47.3764	28.6863	28.5341

Parameter	**Geometric Mean Ratio (90% Confidence Interval) (%) A vs B (without charcoal)**	**Geometric Mean Ratio (90% Confidence Interval) (%) C vs D (with charcoal)**	**Intra-subject CV%**
Cmax (pg/mL)	101.74 [94.75,109.25]	101.64 [95.14,108.59]	30.71
AUC0-t (pg*hr/mL)	101.07 [90.48,112.89]	104.16 [93.99,115.43]	49.30
AUC0-inf (pg*hr/mL)	100.18 [91.74,109.40]	100.53 [92.63,109.11]	37.08

Source: Listings 16.2.6.2.3, 16.2.6.2.4, 16.2.6.2.5 and 16.2.6.2.6
Subjects [redacted] were excluded from AUC_{0-inf}, $t_{1/2}$, K_{el} and AUC $_{\%Extrap\ obs}$ due to R2<0.8 for Treatment A
Subjects [redacted] were excluded from AUC_{0-inf}, $t_{1/2}$, K_{el} and AUC $_{\%Extrap\ obs}$ due to R2<0.8 for Treatment B
Subjects [redacted] were excluded from AUC_{0-inf}, $t_{1/2}$, K_{el} and AUC $_{\%Extrap\ obs}$ due to R2<0.8 for Treatment C
Subjects [redacted] were excluded from AUC_{0-inf}, $t_{1/2}$, K_{el} and $AUC_{\_\%Extrap\_obs}$ due to R2<0.8 for Treatment D

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
Table Generation: 04FEB2020 at 10:27 AM by Table 14.2.1.16.sas

Table 14.2.1.16 Summary of Statistical Comparisons of Plasma Formoterol Pharmacokinetic Parameters C_{max}, AUC_{0-t}, and AUC_{0-inf} FAS (with and without charcoal)

Subjects [redacted] were excluded from AUC_{0-inf} due to 20% of the AUC is extrapolated beyond the last measurable value for Treatment A
Subjects [redacted] were excluded from AUC_{0-inf} due to 20% of the AUC is extrapolated beyond the last measurable value for Treatment B
Subjects [redacted] were excluded from AUC_{0-inf} due to 20% of the AUC is extrapolated beyond the last measurable value for Treatment C
Subjects [redacted] were excluded from AUC_{0-inf} due to 20% of the AUC is extrapolated beyond the last measurable value for Treatment D
Subject no [redacted] was withdrawn on medical grounds due to difficulty in cannulation and did not receive drug administration in periods 2, 3 and 4 (Treatments B, D and C, respectively)
Subject no. [redacted] was withdrawn due to adverse events and did not receive drug administration in period 4 (Treatment A)
Subject no. [redacted] was withdrawn due to adverse events and did not receive drug administration in period 4 (Treatment B)
Subject no. [redacted] was withdrawn due to protocol violation and did not receive drug administration in periods 3 and 4 (Treatments B and A respectively)
Subject no. [redacted] was withdrawn due to protocol violation did not receive drug administration in period 4 (Treatment C)
Subject no [redacted] voluntarily withdrew consent and did not receive drug administration in period 4 (Treatments D)
Subject no. [redacted] did not have any measurable formoterol concentrations following administration of Treatment C and therefore was excluded from Treatment C and D
Subject no. [redacted] voluntarily withdrew consent and did not receive drug administration in periods 2, 3 and 4 (Treatments A, C and B respectively)
Subject no. [redacted] voluntarily withdrew consent and did not receive drug administration in periods 2, 3 and 4 (Treatments D, B and A respectively)
Subject no. [redacted] was withdrawn due to failure to comply with protocol requirements and did not receive drug administration in periods 2, 3 and 4 (Treatments A, C and B respectively)

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
Table Generation: 04FEB2020 at 10:27 AM by Table 14.2.1.16.sas

Table 14.2.1.17 Summary of Statistical Comparisons of Plasma BDP Pharmacokinetic Parameters C_{max}, AUC_{0-t}, and AUC_{0-inf} PK Analysis Set (without charcoal)

	Geometric LSM			
Parameter	**Treatment A**	**Treatment B**	**Geometric Mean Ratio (90% Confidence Interval) (%)**	**Intra-subject CV%**
Cmax (pg/mL)	2363.9272	2421.7765	97.61 [89.81,106.09]	35.68
AUC0-t (pg*hr/mL)	235.4247	242.1470	97.22 [90.97,103.91]	28.19
AUC0-inf (pg*hr/mL)	245.7612	255.6832	96.12 [89.58,103.14]	25.88

Source: Listings 16.2.6.2.7 and 16.2.6.2.8
Subjects [redacted] were excluded from AUC_{0-inf}, $t_{1/2}$, K_{el} and $AUC\_{\%Extrap\_obs}$ due to R2<0.8 for Treatment A
Subjects [redacted] were excluded from AUC_{0-inf}, $t_{1/2}$, K_{el} and $AUC\_{\%Extrap\_obs}$ due to R2<0.8 for Treatment B
Subjects [redacted] were excluded from AUC_{0-inf} due to 20% of the AUC is extrapolated beyond the last measurable value for Treatment A
Subjects [redacted] were excluded from AUC_{0-inf} due to 20% of the AUC is extrapolated beyond the last measurable value for Treatment B
Subject no. [redacted] was withdrawn on medical grounds due to difficulty in cannulation and did not receive drug administration in periods 2, 3 and 4 (Treatments B, D and C, respectively)
Subject no. [redacted] was withdrawn due to adverse events and did not receive drug administration in period 4 (Treatment A)
Subject no. [redacted] was withdrawn due to adverse events and did not receive drug administration in period 4 (Treatment B)
Subject no [redacted] was withdrawn due to protocol violation and did not receive drug administration in periods 3 and 4 (Treatments B and A respectively)
Subject no. [redacted] voluntarily withdrew consent and did not receive drug administration in periods 2, 3 and 4 (Treatments A, C and B respectively)
Subject no [redacted] voluntarily withdrew consent and did not receive drug administration in periods 2, 3 and 4 (Treatments D, B and A respectively)
Subject no. [redacted] was withdrawn due to failure to comply with protocol requirements and did not receive drug administration in periods 2, 3 and 4 (Treatments A, C and B respectively)
Subject no [redacted] were excluded due to major protocol deviations for Treatment A & B

Treatment A: Lupin BDP/FF 200/6 mcg-2 inhalations
Treatment B: FOSTAIR 200/6 mcg-2 inhalations
Table Generation: 04FEB2020 at 10:36 AM by Table 14.2.1.17.sas

Table 14.2.1.18 Summary of Statistical Comparisons of Plasma BDP Pharmacokinetic Parameters C_{max}, AUC_{0-t}, and AUC_{0-inf} FAS (without charcoal)

	Geometric LSM			
Parameter	**Treatment A**	**Treatment B**	**Geometric Mean Ratio (90% Confidence Interval) (%)**	**Intra-subject CV%**
Cmax (pg/mL)	2294.8945	2380.0569	96.42 [89.20,104.22]	34.84
AUC0-t (pg*hr/mL)	226.8572	238.9945	94.92 [89.02,101.21]	28.48
AUC0-inf (pg*hr/mL)	235.3075	252.6729	93.13 [86.99,99.70]	26.66

Source: Listings 16.2.6.2.7 and 16.2.6.2.8
Subjects [redacted] were excluded from AUC_{0-inf}, $t_{1/2}$, K_{el} and $AUC\_\%Extrap\_obs$ due to R2<0.8 for Treatment A
Subjects [redacted] were excluded from
AUC_{0-inf}, $t_{1/2}$, K_{el} and $AUC\_\%Extrap\_obs$ due to R2<0.8 for Treatment B
Subjects [redacted] were excluded from AUC_{0-inf} due to 20% of the AUC is extrapolated beyond the last measurable value for Treatment A
Subjects [redacted] were excluded from AUC_{0-inf} due to 20% of the AUC is extrapolated beyond the last measurable value for Treatment B
Subject no. [redacted] was withdrawn on medical grounds due to difficulty in cannulation and did not receive drug
administration in periods 2, 3 and 4 (Treatments B, D and C, respectively)
Subject no. [redacted] was withdrawn due to adverse events and did not receive drug administration in period 4 (Treatment A)
Subject no [redacted] was withdrawn due to adverse events and did not receive drug administration in period 4 (Treatment B)
Subject no [redacted] was withdrawn due to protocol violation and did not receive drug administration in periods 3 and 4 (Treatments B and A respectively)
Subject no. [redacted] voluntarily withdrew consent and did not receive drug administration in periods 2, 3 and 4 (Treatments A, C and B respectively)
Subject no. [redacted] voluntarily withdrew consent and did not receive drug administration in periods 2, 3 and 4 (Treatments D, B and A respectively)
Subject no. [redacted] was withdrawn due to failure to comply with protocol requirements and did not receive drug
administration in periods 2, 3 and 4 (Treatments A, C and B respectively)

Treatment A: Lupin BDP/FF 200/6 mcg-2 inhalations
Treatment B: FOSTAIR 200/6 mcg-2 inhalations
Table Generation: 04FEB2020 at 10:36 AM by Table 14.2.1.18.sas

Table 14.2.1.19 Nonparametric Statistical Comparison of 17-BMP Pharmacokinetic Parameters t_{max} and $t_{½}$, PK Analysis Set (without charcoal)

Pharmacokinetic Parameter	Treatment Comparison	Treatment Difference Test - Reference	90% Confidence Interval
$t_{1/2}$ (hr)	A-B	0.0215	-0.05 - 0.199
t_{max} (hr)	A-B	0.0020	-0.019 - 0.063

The confidence interval was constructed using Walsh averages and the appropriate quantile of the Wilcoxon Signed Ranks Test statistic.
Source: Listings 16.2.6.2.1 and 16.2.6.2.2
Subjects [redacted] were excluded from $t_{1/2}$ due to R2<0.8 for Treatment A
Subject [redacted] was excluded from $t_{1/2}$ due to R2<0.8 for Treatment B
Subject no. [redacted] was withdrawn on medical grounds due to difficulty in cannulation and did not receive drug administration in periods 2, 3 and 4 (Treatments B, D and C, respectively)
Subject no [redacted] was withdrawn due to adverse events and did not receive drug administration in period 4 (Treatment A)
Subject no. [redacted] was withdrawn due to adverse events and did not receive drug administration in period 4 (Treatment B)
Subject no. [redacted] was withdrawn due to protocol violation and did not receive drug administration in periods 3 and 4 (Treatments B and A respectively)
Subject no. [redacted] voluntarily withdrew consent and did not receive drug administration in periods 2, 3 and 4 (Treatments A, C and B respectively)
Subject no. [redacted] voluntarily withdrew consent and did not receive drug administration in periods 2, 3 and 4 (Treatments D, B and A respectively)
Subject no. [redacted] was withdrawn due to failure to comply with protocol requirements and did not receive drug administration in periods 2, 3 and 4 (Treatments A, C and B respectively)
Subject no. [redacted] were excluded due to major protocol deviations for Treatment A & B

Treatment A: Lupin BDP/FF 200/6 mcg-2 inhalations
Treatment B: FOSTAIR 200/6 mcg-2 inhalations
Table Generation: 04FEB2020 at 10:45 AM by Table 14.2.1.19.sas

Table 14.2.1.20 Nonparametric Statistical Comparison of 17-BMP Pharmacokinetic Parameters t_{max} and $t_{½}$, FAS (without charcoal)

Pharmacokinetic Parameter	Treatment Comparison	Treatment Difference Test - Reference	90% Confidence Interval
$t_{1/2}$ (hr)	A-B	0.0170	-0.0525 - 0.187
t_{max} (hr)	A-B	0.0010	-0.035 - 0.0495

The confidence interval was constructed using Walsh averages and the appropriate quantile of the Wilcoxon Signed Ranks Test statistic.
Source: Listings 16.2.6.2.1 and 16.2.6.2.2
Subjects [redacted] were excluded from $t_{1/2}$ due to R2<0.8 for Treatment A
Subject [redacted] was excluded from $t_{1/2}$ due to R2<0.8 for Treatment B
Subject no. [redacted] was withdrawn on medical grounds due to difficulty in cannulation and did not receive drug administration in periods 2, 3 and 4 (Treatments B, D and C, respectively)
Subject no. [redacted] was withdrawn due to adverse events and did not receive drug administration in period 4 (Treatment A)
Subject no. [redacted] was withdrawn due to adverse events and did not receive drug administration in period 4 (Treatment B)
Subject no. [redacted] was withdrawn due to protocol violation and did not receive drug administration in periods 3 and 4 (Treatments B and A respectively)
Subject no. [redacted] voluntarily withdrew consent and did not receive drug administration in periods 2, 3 and 4 (Treatments A, C and B respectively)
Subject no. [redacted] voluntarily withdrew consent and did not receive drug administration in periods 2, 3 and 4 (Treatments D, B and A respectively)
Subject no. [redacted] was withdrawn due to failure to comply with protocol requirements and did not receive drug administration in periods 2, 3 and 4 (Treatments A, C and B respectively)

Treatment A: Lupin BDP/FF 200/6 mcg-2 inhalations
Treatment B: FOSTAIR 200/6 mcg-2 inhalations
Table Generation: 04FEB2020 at 10:46 AM by Table 14.2.1.20.sas

Table 14.2.1.21 Nonparametric Statistical Comparison of Formoterol Pharmacokinetic Parameters t_{max} and $t_{½}$, PK Analysis Set (with and without charcoal)

Pharmacokinetic Parameter	Treatment Comparison	Treatment Difference Test - Reference	90% Confidence Interval
$t_{1/2}$ (hr)	A-B	0.3690	-0.3075 - 0.945
	C-D	0.0405	-0.3825 - 0.687
t_{max} (hr)	A-B	-0.0010	-0.0135 - 0.000
	C-D	0.0000	-0.001 - 0.014

The confidence interval was constructed using Walsh averages and the appropriate quantile of the Wilcoxon Signed Ranks Test statistic.
Source: Listings 16.2.6.2.3, 16.2.6.2.4, 16.2.6.2.5 and 16.2.6.2.6
Subjects [redacted] were excluded from $t_{1/2}$ due to R2<0.8 for Treatment A
Subjects [redacted] were excluded from $t_{1/2}$ due to R2<0.8 for Treatment B
Subjects [redacted] were excluded from $t_{1/2}$ due to R2<0.8 for Treatment C
Subjects [redacted] were excluded from $t_{1/2}$ due to R2<0.8 for Treatment D
Subject no [redacted] was withdrawn on medical grounds due to difficulty in cannulation and did not receive drug administration in periods 2, 3 and 4 (Treatments B, D and C, respectively)
Subject no. [redacted] was withdrawn due to adverse events and did not receive drug administration in period 4 (Treatment A)
Subject no. [redacted] was withdrawn due to adverse events and did not receive drug administration in period 4 (Treatment B)
Subject no. [redacted] was withdrawn due to protocol violation and did not receive drug administration in periods 3 and 4 (Treatments B and A respectively)
Subject no. [redacted] was withdrawn due to protocol violation did not receive drug administration in period 4 (Treatment C)
Subject no. [redacted] voluntarily withdrew consent and did not receive drug administration in period 4 (Treatments D)
Subject no. [redacted] did not have any measurable formoterol concentrations following administration of Treatment C and therefore was excluded from Treatment C and D
Subject no. [redacted] voluntarily withdrew consent and did not receive drug administration in periods 2, 3 and 4 (Treatments A, C and B respectively)
Subject no. [redacted] voluntarily withdrew consent and did not receive drug administration in periods 2, 3 and 4 (Treatments D, B and A respectively)
Subject no. [redacted] was withdrawn due to failure to comply with protocol requirements and did not receive drug administration in periods 2, 3 and 4 (Treatments A, C and B respectively)
Subject no. [redacted] were excluded due to major protocol deviations from A vs B calculation

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
Table Generation: 04FEB2020 at 10:49 AM by Table 14.2.1.21.sas

Table 14.2.1.21 Nonparametric Statistical Comparison of Formoterol Pharmacokinetic Parameters t_{max} and $t_{½}$, PK Analysis Set (with and without charcoal)

Subject no. [redacted] were excluded due to major protocol deviations from C vs D calculation

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
Table Generation: 04FEB2020 at 10:49 AM by Table 14.2.1.21.sas

Table 14.2.1.22 Nonparametric Statistical Comparison of Formoterol Pharmacokinetic Parameters t_{max} and $t_{½}$, FAS (with and without charcoal)

Pharmacokinetic Parameter	Treatment Comparison	Treatment Difference Test - Reference	90% Confidence Interval
$t_{1/2}$ (hr)	A-B	0.1850	-0.5005 - 0.639
	C-D	-0.1840	-0.507 - 0.577
t_{max} (hr)	A-B	-0.0010	-0.013 - 0.0005
	C-D	0.0000	-0.0005 - 0.014

The confidence interval was constructed using Walsh averages and the appropriate quantile of the Wilcoxon Signed Ranks Test statistic.
Source: Listings 16.2.6.2.3, 16.2.6.2.4, 16.2.6.2.5 and 16.2.6.2.6
Subjects [redacted] were excluded from $t_{1/2}$ due to R2<0.8 for Treatment A
Subjects [redacted] were excluded from $t_{1/2}$ due to R2<0.8 for Treatment B
Subjects [redacted] were excluded from $t_{1/2}$ due to R2<0.8 for Treatment C
Subjects [redacted] were excluded from $t_{1/2}$ due to R2<0.8 for Treatment D
Subject no. [redacted] was withdrawn on medical grounds due to difficulty in cannulation and did not receive drug administration in periods 2, 3 and 4 (Treatments B, D and C, respectively)
Subject no. [redacted] was withdrawn due to adverse events and did not receive drug administration in period 4 (Treatment A)
Subject no. [redacted] was withdrawn due to adverse events and did not receive drug administration in period 4 (Treatment B)
Subject no. [redacted] was withdrawn due to protocol violation and did not receive drug administration in periods 3 and 4 (Treatments B and A respectively)
Subject no [redacted] was withdrawn due to protocol violation did not receive drug administration in period 4 (Treatment C)
Subject no. [redacted]3 voluntarily withdrew consent and did not receive drug administration in period 4 (Treatments D)
Subject no. [redacted] did not have any measurable formoterol concentrations following administration of Treatment C and therefore was excluded from Treatment C and D
Subject no. [redacted] voluntarily withdrew consent and did not receive drug administration in periods 2, 3 and 4 (Treatments A, C and B respectively)
Subject no. [redacted] voluntarily withdrew consent and did not receive drug administration in periods 2, 3 and 4 (Treatments D, B and A respectively)
Subject no. [redacted] was withdrawn due to failure to comply with protocol requirements and did not receive drug administration in periods 2, 3 and 4 (Treatments A, C and B respectively)

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
Table Generation: 04FEB2020 at 10:52 AM by Table 14.2.1.22.sas

Table 14.2.1.23 Nonparametric Statistical Comparison of BDP Pharmacokinetic Parameters t_{max} and $t_{½}$, PK Analysis Set (without charcoal)

Pharmacokinetic Parameter	Treatment Comparison	Treatment Difference Test - Reference	90% Confidence Interval
$t_{1/2}$ (hr)	A-B	0.0160	-0.045 - 0.091
t_{max} (hr)	A-B	0.0000	-0.0005 - 0.001

The confidence interval was constructed using Walsh averages and the appropriate quantile of the Wilcoxon Signed Ranks Test statistic.
Source: Listings 16.2.6.2.7 and 16.2.6.2.8
Subjects [redacted] were excluded from $t_{1/2}$ due to R2<0.8 for Treatment A
Subjects [redacted] were excluded from $t_{1/2}$ due to R2<0.8 for Treatment B
Subject no [redacted] was withdrawn on medical grounds due to difficulty in cannulation and did not receive drug administration in periods 2, 3 and 4 (Treatments B, D and C, respectively)
Subject no. [redacted] was withdrawn due to adverse events and did not receive drug administration in period 4 (Treatment A)
Subject no. [redacted] was withdrawn due to adverse events and did not receive drug administration in period 4 (Treatment B)
Subject no. [redacted] was withdrawn due to protocol violation and did not receive drug administration in periods 3 and 4 (Treatments B and A respectively)
Subject no. [redacted] voluntarily withdrew consent and did not receive drug administration in periods 2, 3 and 4 (Treatments A, C and B respectively)
Subject no [redacted] voluntarily withdrew consent and did not receive drug administration in periods 2, 3 and 4 (Treatments D, B and A respectively)
Subject no. [redacted] was withdrawn due to failure to comply with protocol requirements and did not receive drug administration in periods 2, 3 and 4 (Treatments A, C and B respectively)
Subject no. [redacted] were excluded due to major protocol deviations for Treatment A & B

Treatment A: Lupin BDP/FF 200/6 mcg-2 inhalations
Treatment B: FOSTAIR 200/6 mcg-2 inhalations
Table Generation: 04FEB2020 at 10:53 AM by Table 14.2.1.23.sas

Table 14.2.1.24 Nonparametric Statistical Comparison of BDP Pharmacokinetic Parameters t_{max} and $t_{½}$, FAS (without charcoal)

Pharmacokinetic Parameter	Treatment Comparison	Treatment Difference Test - Reference	90% Confidence Interval
$t_{1/2}$ (hr)	A-B	0.0190	-0.0345 - 0.091
t_{max} (hr)	A-B	0.0000	-0.0005 - 0.001

The confidence interval was constructed using Walsh averages and the appropriate quantile of the Wilcoxon Signed Ranks Test statistic.
Source: Listings 16.2.6.2.7 and 16.2.6.2.8
Subjects [redacted] were excluded from $t_{1/2}$ due to R2<0.8 for Treatment A
Subjects [redacted] were excluded from $t_{1/2}$ due to R2<0.8 for Treatment B
Subject no. [redacted] was withdrawn on medical grounds due to difficulty in cannulation and did not receive drug administration in periods 2, 3 and 4 (Treatments B, D and C, respectively)
Subject no. [redacted] was withdrawn due to adverse events and did not receive drug administration in period 4 (Treatment A)
Subject no. [redacted] was withdrawn due to adverse events and did not receive drug administration in period 4 (Treatment B)
Subject no. [redacted] was withdrawn due to protocol violation and did not receive drug administration in periods 3 and 4 (Treatments B and A respectively)
Subject no [redacted] voluntarily withdrew consent and did not receive drug administration in periods 2, 3 and 4 (Treatments A, C and B respectively)
Subject no. [redacted] voluntarily withdrew consent and did not receive drug administration in periods 2, 3 and 4 (Treatments D, B and A respectively)
Subject no. [redacted] was withdrawn due to failure to comply with protocol requirements and did not receive drug administration in periods 2, 3 and 4 (Treatments A, C and B respectively)

Treatment A: Lupin BDP/FF 200/6 mcg-2 inhalations
Treatment B: FOSTAIR 200/6 mcg-2 inhalations
Table Generation: 04FEB2020 at 10:55 AM by Table 14.2.1.24.sas

14.3. Safety Data Summary Tables

14.3.1. Display of Adverse Events

This section contains the following tables:

Number	Title
14.3.1.1	Overall Adverse Events, Safety Analysis Set
14.3.1.2	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term, Safety Analysis Set
14.3.1.3	Treatment-Emergent Adverse Events by Severity Grade, System Organ Class, and Preferred Term, Safety Analysis Set
14.3.1.4	Treatment-Emergent Adverse Events by Relationship to Study Drug, System Organ Class, and Preferred Term, Safety Analysis Set

Table 14.3.1.1. Overall Adverse Events, Safety Analysis Set

	Treatment				
	Treatment A (N=107) n (%), E	**Treatment B (N=106) n (%), E**	**Treatment C (N=108) n (%), E**	**Treatment D (N=109) n (%), E**	**Overall (N=112) n (%), E**
TEAE	9 (8.4), 11	8 (7.5), 14	12 (11.1), 18	8 (7.3), 12	37 (33.0), 55
Non TEAE	0	0	0	0	0
Severe TEAE[a]	0	0	0	0	0
Serious TEAE	0	0	0	0	0
Study Drug related TEAE[b]	7 (6.5), 9	2 (1.9), 3	7 (6.5), 12	5 (4.6), 8	21 (18.8), 32
Study Drug related Serious TEAE[b]	0	0	0	0	0
Expected TEAE	3 (2.8), 3	2 (1.9), 2	1 (0.9), 1	2 (1.8), 3	8 (7.1), 9
TEAE leading to study drug discontinuation	0	0	0	0	0
Drug related TEAE leading to study drug discontinuation[b]	0	0	0	0	0
TEAE leading to study discontinuation	1 (0.9), 1	1 (0.9), 1	1 (0.9), 1	0	3 (2.7), 3
Drug related TEAE leading to study discontinuation[b]	1 (0.9), 1	0	0	0	1 (0.9), 1
TEAE leading to death	0	0	0	0	0

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
Table Generation 04FEB2020 at 9:36 AM by Table 14.3.1.1.sas

Table 14.3.1.1. Overall Adverse Events, Safety Analysis Set

	Treatment				
	Treatment A (N=107) n (%), E	**Treatment B (N=106) n (%), E**	**Treatment C (N=108) n (%), E**	**Treatment D (N=109) n (%), E**	**Overall (N=112) n (%), E**
Drug related TEAE leading to death	0	0	0	0	0

Listing Reference: 16.2.7.3
TEAE = Treatment-Emergent Adverse Event, SAE = Serious Adverse Event
Note: Percentages are based on the number of subjects (N) in each treatment.
n (%) = number and percentage of subjects in the category; E = Number of AEs; TEAE = Treatment-Emergent Adverse Event
[a] The severity of an AE is graded as Mild, Moderate, or Severe. If any AE occurs more than once, the highest severity is summarized. An AE with a missing severity designation is summarized as a severe AE.
[b] Study medication related adverse events include those adverse events with relationship classified as 'Certainly related', 'Probably related', 'Possibly related', 'Conditionally related', or Unclassifiable, else considered as 'not related'. If any AE occurs more than once, the highest relationship to study medication is used for summary tabulation. Missing relationship for an AE is considered 'related' to study medication.

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
Table Generation 04FEB2020 at 9:36 AM by Table 14.3.1.1.sas

Table 14.3.1.2. Treatment-Emergent Adverse Events by System Organ Class and Preferred Term, Safety Analysis Set

	Treatment				
System Organ Class Preferred Term [a]	**A (N=107) n (%), E**	**B (N=106) n (%), E**	**C (N=108) n (%), E**	**D (N=109) n (%), E**	**Overall (N=112) n (%), E**
Subject with at least 1 TEAE	9 (8.4), 11	8 (7.5), 14	12 (11.1), 18	8 (7.3), 12	37 (33.0), 55
CARDIAC DISORDERS	1 (0.9), 1	0	1 (0.9), 1	1 (0.9), 1	3 (2.7), 3
Sinus bradycardia	0	0	1 (0.9), 1	0	1 (0.9), 1
Sinus tachycardia	0	0	0	1 (0.9), 1	1 (0.9), 1
Ventricular extrasystoles	1 (0.9), 1	0	0	0	1 (0.9), 1
GASTROINTESTINAL DISORDERS	0	0	2 (1.9), 2	0	2 (1.8), 2
Diarrhoea	0	0	2 (1.9), 2	0	2 (1.8), 2
GENERAL DISORDERS AND ADMINISTRATION	1 (0.9), 1	1 (0.9), 1	1 (0.9), 1	0	3 (2.7), 3
Influenza like illness	0	0	1 (0.9), 1	0	1 (0.9), 1
Pyrexia	1 (0.9), 1	0	0	0	1 (0.9), 1
Swelling arm	0	1 (0.9), 1	0	0	1 (0.9), 1
INFECTIONS AND INFESTATIONS	1 (0.9), 1	2 (1.9), 2	0	0	3 (2.7), 3
Pharyngitis	1 (0.9), 1	1 (0.9), 1	0	0	2 (1.8), 2
Urinary tract infection	0	1 (0.9), 1	0	0	1 (0.9), 1
INVESTIGATIONS	7 (6.5), 8	6 (5.7), 11	9 (8.3), 14	8 (7.3), 11	30 (26.8), 44
Alanine aminotransferase increased	2 (1.9), 2	1 (0.9), 1	1 (0.9), 1	0	4 (3.6), 4

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
Table Generation 04FEB2020 at 9:43 AM by Table 14.3.1.2.sas

Table 14.3.1.2. Treatment-Emergent Adverse Events by System Organ Class and Preferred Term, Safety Analysis Set

	Treatment				
System Organ Class Preferred Term [a]	**A (N=107) n (%), E**	**B (N=106) n (%), E**	**C (N=108) n (%), E**	**D (N=109) n (%), E**	**Overall (N=112) n (%), E**
Aspartate aminotransferase increased	0	1 (0.9), 1	1 (0.9), 1	1 (0.9), 1	3 (2.7), 3
Blood albumin decreased	0	1 (0.9), 1	0	0	1 (0.9), 1
Blood alkaline phosphatase increased	1 (0.9), 1	0	3 (2.8), 3	1 (0.9), 1	5 (4.5), 5
Blood glucose increased	1 (0.9), 1	1 (0.9), 1	1 (0.9), 1	2 (1.8), 2	5 (4.5), 5
Blood potassium increased	1 (0.9), 1	1 (0.9), 1	1 (0.9), 1	2 (1.8), 2	5 (4.5), 5
Eosinophil count increased	0	0	2 (1.9), 2	0	2 (1.8), 2
Haemoglobin decreased	1 (0.9), 1	1 (0.9), 1	0	0	2 (1.8), 2
Lymphocyte count decreased	0	0	1 (0.9), 1	0	1 (0.9), 1
Neutrophil count decreased	1 (0.9), 1	0	0	1 (0.9), 1	2 (1.8), 2
Neutrophil count increased	0	1 (0.9), 1	1 (0.9), 1	0	2 (1.8), 2
Platelet count decreased	0	0	1 (0.9), 1	0	1 (0.9), 1
Urine analysis abnormal	0	3 (2.8), 3	2 (1.9), 2	4 (3.7), 4	9 (8.0), 9
White blood cell count decreased	1 (0.9), 1	0	0	0	1 (0.9), 1

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
Table Generation 04FEB2020 at 9:43 AM by Table 14.3.1.2.sas

Table 14.3.1.2. Treatment-Emergent Adverse Events by System Organ Class and Preferred Term, Safety Analysis Set

	Treatment				
System Organ Class Preferred Term [a]	**A (N=107) n (%), E**	**B (N=106) n (%), E**	**C (N=108) n (%), E**	**D (N=109) n (%), E**	**Overall (N=112) n (%), E**
White blood cell count increased	0	1 (0.9), 1	0	0	1 (0.9), 1

Listing Reference: 16.2.7.3
Notes: Percentages are based on the number of subjects (N) in each treatment and overall
Each subject will only be counted once per Preferred Term and once per System Organ Class.
n(%)=number and percentage of subjects in the category; E = Number of AEs, TEAE= Treatment-Emergent Adverse Event
[a] All adverse events as described by the investigators (verbatim term) were coded using MedDRA version 22.0

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
Table Generation 04FEB2020 at 9:43 AM by Table 14.3.1.2.sas

Table 14.3.1.3. Treatment-Emergent Adverse Events by Severity Grade, System Organ Class, and Preferred Term, Safety Analysis Set

		Treatment				
System Organ Class Preferred Term [a]	**Severity Grades[b]**	**A (N=107) n (%), E**	**B (N=106) n (%), E**	**C (N=108) n (%), E**	**D (N=109) n (%), E**	**Overall (N=112) n (%), E**
Subject with at least 1 TEAE	Mild	7 (6.5), 9	6 (5.7), 10	10 (9.3), 15	7 (6.4), 11	30 (26.8), 45
	Moderate	2 (1.9), 2	3 (2.8), 4	3 (2.8), 3	1 (0.9), 1	9 (8.0), 10
	Severe	0	0	0	0	0
CARDIAC DISORDERS	Mild	1 (0.9), 1	0	1 (0.9), 1	1 (0.9), 1	3 (2.7) ,3
	Moderate	0	0	0	0	0
	Severe	0	0	0	0	0
Sinus bradycardia	Mild	0	0	1 (0.9), 1	0	1 (0.9), 1
	Moderate	0	0	0	0	0
	Severe	0	0	0	0	0
Sinus tachycardia	Mild	0	0	0	1 (0.9), 1	1 (0.9), 1
	Moderate	0	0	0	0	0
	Severe	0	0	0	0	0
Ventricular extrasystoles	Mild	1 (0.9), 1	0	0	0	1 (0.9), 1
	Moderate	0	0	0	0	0
	Severe	0	0	0	0	0

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
Table Generation 14FEB2020 at 11:23 AM by Table 14.3.1.3.sas

Table 14.3.1.3. Treatment-Emergent Adverse Events by Severity Grade, System Organ Class, and Preferred Term, Safety Analysis Set

		Treatment				
System Organ Class Preferred Term [a]	**Severity Grades[b]**	**A (N=107) n (%), E**	**B (N=106) n (%), E**	**C (N=108) n (%), E**	**D (N=109) n (%), E**	**Overall (N=112) n (%), E**
GASTROINTESTINAL DISORDERS	Mild	0	0	0	0	0
	Moderate	0	0	2 (1.9), 2	0	2 (1.8) ,2
	Severe	0	0	0	0	0
Diarrhoea	Mild	0	0	0	0	0
	Moderate	0	0	2 (1.9), 2	0	2 (1.8), 2
	Severe	0	0	0	0	0
GENERAL DISORDERS AND ADMINISTRATION	Mild	0	0	0	0	0
	Moderate	1 (0.9), 1	1 (0.9), 1	1 (0.9), 1	0	3 (2.7) ,3
	Severe	0	0	0	0	0
Influenza like illness	Mild	0	0	0	0	0
	Moderate	0	0	1 (0.9), 1	0	1 (0.9), 1
	Severe	0	0	0	0	0
Pyrexia	Mild	0	0	0	0	0
	Moderate	1 (0.9), 1	0	0	0	1 (0.9), 1
	Severe	0	0	0	0	0

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
Table Generation 14FEB2020 at 11:23 AM by Table 14.3.1.3.sas

Table 14.3.1.3. Treatment-Emergent Adverse Events by Severity Grade, System Organ Class, and Preferred Term, Safety Analysis Set

		Treatment				
System Organ Class Preferred Term [a]	**Severity Grades[b]**	**A (N=107) n (%), E**	**B (N=106) n (%), E**	**C (N=108) n (%), E**	**D (N=109) n (%), E**	**Overall (N=112) n (%), E**
Swelling arm	Mild	0	0	0	0	0
	Moderate	0	1 (0.9), 1	0	0	1 (0.9), 1
	Severe	0	0	0	0	0
INFECTIONS AND INFESTATIONS	Mild	1 (0.9), 1	0	0	0	1 (0.9) ,1
	Moderate	0	2 (1.9), 2	0	0	2 (1.8) ,2
	Severe	0	0	0	0	0
Pharyngitis	Mild	1 (0.9), 1	0	0	0	1 (0.9), 1
	Moderate	0	1 (0.9), 1	0	0	1 (0.9), 1
	Severe	0	0	0	0	0
Urinary tract infection	Mild	0	0	0	0	0
	Moderate	0	1 (0.9), 1	0	0	1 (0.9), 1
	Severe	0	0	0	0	0
INVESTIGATIONS	Mild	6 (5.6), 7	6 (5.7), 10	9 (8.3), 14	7 (6.4), 10	28 (25.0) ,41
	Moderate	1 (0.9), 1	1 (0.9), 1	0	1 (0.9), 1	3 (2.7) ,3
	Severe	0	0	0	0	0

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
Table Generation 14FEB2020 at 11:23 AM by Table 14.3.1.3.sas

Table 14.3.1.3. Treatment-Emergent Adverse Events by Severity Grade, System Organ Class, and Preferred Term, Safety Analysis Set

		Treatment				
System Organ Class Preferred Term [a]	**Severity Grades[b]**	**A (N=107) n (%), E**	**B (N=106) n (%), E**	**C (N=108) n (%), E**	**D (N=109) n (%), E**	**Overall (N=112) n (%), E**
Alanine aminotransferase increased	Mild	2 (1.9), 2	1 (0.9), 1	1 (0.9), 1	0	4 (3.6), 4
	Moderate	0	0	0	0	0
	Severe	0	0	0	0	0
Aspartate aminotransferase increased	Mild	0	1 (0.9), 1	1 (0.9), 1	1 (0.9), 1	3 (2.7), 3
	Moderate	0	0	0	0	0
	Severe	0	0	0	0	0
Blood albumin decreased	Mild	0	1 (0.9), 1	0	0	1 (0.9), 1
	Moderate	0	0	0	0	0
	Severe	0	0	0	0	0
Blood alkaline phosphatase increased	Mild	1 (0.9), 1	0	3 (2.8), 3	1 (0.9), 1	5 (4.5), 5
	Moderate	0	0	0	0	0
	Severe	0	0	0	0	0

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
Table Generation 14FEB2020 at 11:23 AM by Table 14.3.1.3.sas

Table 14.3.1.3. Treatment-Emergent Adverse Events by Severity Grade, System Organ Class, and Preferred Term, Safety Analysis Set

		Treatment				
System Organ Class Preferred Term [a]	**Severity Grades[b]**	**A (N=107) n (%), E**	**B (N=106) n (%), E**	**C (N=108) n (%), E**	**D (N=109) n (%), E**	**Overall (N=112) n (%), E**
Blood glucose increased	Mild	1 (0.9), 1	1 (0.9), 1	1 (0.9), 1	2 (1.8), 2	5 (4.5), 5
	Moderate	0	0	0	0	0
	Severe	0	0	0	0	0
Blood potassium increased	Mild	1 (0.9), 1	1 (0.9), 1	1 (0.9), 1	2 (1.8), 2	5 (4.5), 5
	Moderate	0	0	0	0	0
	Severe	0	0	0	0	0
Eosinophil count increased	Mild	0	0	2 (1.9), 2	0	2 (1.8), 2
	Moderate	0	0	0	0	0
	Severe	0	0	0	0	0
Haemoglobin decreased	Mild	0	0	0	0	0
	Moderate	1 (0.9), 1	1 (0.9), 1	0	0	2 (1.8), 2
	Severe	0	0	0	0	0
Lymphocyte count decreased	Mild	0	0	1 (0.9), 1	0	1 (0.9), 1
	Moderate	0	0	0	0	0

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
Table Generation 14FEB2020 at 11:23 AM by Table 14.3.1.3.sas

Table 14.3.1.3. Treatment-Emergent Adverse Events by Severity Grade, System Organ Class, and Preferred Term, Safety Analysis Set

		Treatment				
System Organ Class Preferred Term [a]	**Severity Grades[b]**	**A (N=107) n (%), E**	**B (N=106) n (%), E**	**C (N=108) n (%), E**	**D (N=109) n (%), E**	**Overall (N=112) n (%), E**
	Severe	0	0	0	0	0
Neutrophil count decreased	Mild	1 (0.9), 1	0	0	1 (0.9), 1	2 (1.8), 2
	Moderate	0	0	0	0	0
	Severe	0	0	0	0	0
Neutrophil count increased	Mild	0	1 (0.9), 1	1 (0.9), 1	0	2 (1.8), 2
	Moderate	0	0	0	0	0
	Severe	0	0	0	0	0
Platelet count decreased	Mild	0	0	1 (0.9), 1	0	1 (0.9), 1
	Moderate	0	0	0	0	0
	Severe	0	0	0	0	0
Urine analysis abnormal	Mild	0	3 (2.8), 3	2 (1.9), 2	3 (2.8), 3	8 (7.1), 8
	Moderate	0	0	0	1 (0.9), 1	1 (0.9), 1
	Severe	0	0	0	0	0
White blood cell count decreased	Mild	1 (0.9), 1	0	0	0	1 (0.9), 1

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
Table Generation 14FEB2020 at 11:23 AM by Table 14.3.1.3.sas

Table 14.3.1.3. Treatment-Emergent Adverse Events by Severity Grade, System Organ Class, and Preferred Term, Safety Analysis Set

		Treatment				
System Organ Class Preferred Term [a]	**Severity Grades[b]**	**A (N=107) n (%), E**	**B (N=106) n (%), E**	**C (N=108) n (%), E**	**D (N=109) n (%), E**	**Overall (N=112) n (%), E**
	Moderate	0	0	0	0	0
	Severe	0	0	0	0	0
White blood cell count increased	Mild	0	1 (0.9), 1	0	0	1 (0.9), 1
	Moderate	0	0	0	0	0
	Severe	0	0	0	0	0

Listing Reference: 16.2.7.3
Notes: Percentages are based on the number of subjects (N) in each treatment and overall
Each subject will only be counted once per Preferred Term and once per System Organ Class.
n(%)=number and percentage of subjects in the category; E= Number of AEs, TEAE= Treatment-Emergent Adverse Event
[a] All adverse events as described by the investigators (verbatim term) were coded using MedDRA version 22.0
[b] The severity of an AE is graded as Mild, Moderate, or Severe.If any AE occurs more than once, the highest severity is summarized. An AE with a missing severity designation is summarized as a severe AE.

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
Table Generation 14FEB2020 at 11:23 AM by Table 14.3.1.3.sas

Table 14.3.1.4. Treatment-Emergent Adverse Events by Relationship to Study Drug, System Organ Class, and Preferred Term, Safety Analysis Set

		Treatment				
System Organ Class Preferred Term [a]	**Relationship [b]**	**A (N=107) n (%), E**	**B (N=106) n (%), E**	**C (N=108) n (%), E**	**D (N=109) n (%), E**	**Overall (N=112) n (%), E**
Subject with at least 1 TEAE	Related	7 (6.5), 9	2 (1.9), 3	7 (6.5), 12	5 (4.6), 8	21 (18.8), 32
	Not Related	2 (1.9), 2	6 (5.7), 11	6 (5.6), 6	4 (3.7), 4	18 (16.1), 23
CARDIAC DISORDERS	Related	1 (0.9), 1	0	0	1 (0.9), 1	2 (1.8), 2
	Not Related	0	0	1 (0.9), 1	0	1 (0.9), 1
Sinus bradycardia	Related	0	0	0	0	0
	Not Related	0	0	1 (0.9), 1	0	1 (0.9), 1
Sinus tachycardia	Related	0	0	0	1 (0.9), 1	1 (0.9), 1
	Not Related	0	0	0	0	0
Ventricular extrasystoles	Related	1 (0.9), 1	0	0	0	1 (0.9), 1
	Not Related	0	0	0	0	0
GASTROINTESTINAL DISORDERS	Related	0	0	0	0	0
	Not Related	0	0	2 (1.9), 2	0	2 (1.8), 2
Diarrhoea	Related	0	0	0	0	0
	Not Related	0	0	2 (1.9), 2	0	2 (1.8), 2

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
Table Generation 14FEB2020 at 11:27 AM by Table 14.3.1.4.sas

Table 14.3.1.4. Treatment-Emergent Adverse Events by Relationship to Study Drug, System Organ Class, and Preferred Term, Safety Analysis Set

		Treatment				
System Organ Class Preferred Term [a]	**Relationship [b]**	**A (N=107) n (%), E**	**B (N=106) n (%), E**	**C (N=108) n (%), E**	**D (N=109) n (%), E**	**Overall (N=112) n (%), E**
GENERAL DISORDERS AND ADMINISTRATION	Related	1 (0.9), 1	0	0	0	1 (0.9), 1
	Not Related	0	1 (0.9), 1	1 (0.9), 1	0	2 (1.8), 2
Influenza like illness	Related	0	0	0	0	0
	Not Related	0	0	1 (0.9), 1	0	1 (0.9), 1
Pyrexia	Related	1 (0.9), 1	0	0	0	1 (0.9), 1
	Not Related	0	0	0	0	0
Swelling arm	Related	0	1 (0.9), 1	0	0	1 (0.9), 1
	Not Related	0	0	0	0	0
INFECTIONS AND INFESTATIONS	Related	0	1 (0.9), 1	0	0	1 (0.9), 1
	Not Related	1 (0.9), 1	1 (0.9), 1	0	0	2 (1.8), 2
Pharyngitis	Related	0	1 (0.9), 1	0	0	1 (0.9), 1
	Not Related	1 (0.9), 1	0	0	0	1 (0.9), 1
Urinary tract infection	Related	0	0	0	0	0
	Not Related	0	1 (0.9), 1	0	0	1 (0.9), 1

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
Table Generation 14FEB2020 at 11:27 AM by Table 14.3.1.4.sas

Table 14.3.1.4. Treatment-Emergent Adverse Events by Relationship to Study Drug, System Organ Class, and Preferred Term, Safety Analysis Set

		Treatment				
System Organ Class Preferred Term [a]	**Relationship [b]**	**A (N=107) n (%), E**	**B (N=106) n (%), E**	**C (N=108) n (%), E**	**D (N=109) n (%), E**	**Overall (N=112) n (%), E**
INVESTIGATIONS	Related	6 (5.6), 7	1 (0.9), 2	7 (6.5), 12	5 (4.6), 7	19 (17.0), 28
	Not Related	1 (0.9), 1	5 (4.7), 9	2 (1.9), 2	4 (3.7), 4	12 (10.7), 16
Alanine aminotransferase increased	Related	2 (1.9), 2	0	1 (0.9), 1	0	3 (2.7), 3
	Not Related	0	1 (0.9), 1	0	0	1 (0.9), 1
Aspartate aminotransferase increased	Related	0	0	1 (0.9), 1	1 (0.9), 1	2 (1.8), 2
	Not Related	0	1 (0.9), 1	0	0	1 (0.9), 1
Blood albumin decreased	Related	0	0	0	0	0
	Not Related	0	1 (0.9), 1	0	0	1 (0.9), 1
Blood alkaline phosphatase increased	Related	1 (0.9), 1	0	3 (2.8), 3	1 (0.9), 1	5 (4.5), 5
	Not Related	0	0	0	0	0
Blood glucose increased	Related	1 (0.9), 1	0	1 (0.9), 1	2 (1.8), 2	4 (3.6), 4
	Not Related	0	1 (0.9), 1	0	0	1 (0.9), 1

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
Table Generation 14FEB2020 at 11:27 AM by Table 14.3.1.4.sas

Table 14.3.1.4. Treatment-Emergent Adverse Events by Relationship to Study Drug, System Organ Class, and Preferred Term, Safety Analysis Set

		Treatment				
System Organ Class Preferred Term [a]	**Relationship [b]**	**A (N=107) n (%), E**	**B (N=106) n (%), E**	**C (N=108) n (%), E**	**D (N=109) n (%), E**	**Overall (N=112) n (%), E**
Blood potassium increased	Related	1 (0.9), 1	0	1 (0.9), 1	2 (1.8), 2	4 (3.6), 4
	Not Related	0	1 (0.9), 1	0	0	1 (0.9), 1
Eosinophil count increased	Related	0	0	2 (1.9), 2	0	2 (1.8), 2
	Not Related	0	0	0	0	0
Haemoglobin decreased	Related	0	0	0	0	0
	Not Related	1 (0.9), 1	1 (0.9), 1	0	0	2 (1.8), 2
Lymphocyte count decreased	Related	0	0	1 (0.9), 1	0	1 (0.9), 1
	Not Related	0	0	0	0	0
Neutrophil count decreased	Related	1 (0.9), 1	0	0	1 (0.9), 1	2 (1.8), 2
	Not Related	0	0	0	0	0
Neutrophil count increased	Related	0	1 (0.9), 1	1 (0.9), 1	0	2 (1.8), 2
	Not Related	0	0	0	0	0
Platelet count decreased	Related	0	0	1 (0.9), 1	0	1 (0.9), 1

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
Table Generation 14FEB2020 at 11:27 AM by Table 14.3.1.4.sas

Table 14.3.1.4. Treatment-Emergent Adverse Events by Relationship to Study Drug, System Organ Class, and Preferred Term, Safety Analysis Set

		Treatment				
System Organ Class Preferred Term [a]	**Relationship [b]**	**A (N=107) n (%), E**	**B (N=106) n (%), E**	**C (N=108) n (%), E**	**D (N=109) n (%), E**	**Overall (N=112) n (%), E**
	Not Related	0	0	0	0	0
Urine analysis abnormal	Related	0	0	0	0	0
	Not Related	0	3 (2.8), 3	2 (1.9), 2	4 (3.7), 4	9 (8.0), 9
White blood cell count decreased	Related	1 (0.9), 1	0	0	0	1 (0.9), 1
	Not Related	0	0	0	0	0
White blood cell count increased	Related	0	1 (0.9), 1	0	0	1 (0.9), 1
	Not Related	0	0	0	0	0

Listing Reference: 16.2.7.3
Notes: Percentages are based on the number of subjects (N) in each treatment and overall
Each subject will only be counted once per Preferred Term and once per System Organ Class.
n(%)=number and percentage of subjects in the category; E= Number of AEs, TEAE= Treatment-Emergent Adverse Event
[a] All adverse events as described by the investigators (verbatim term) were coded using MedDRA version 22.0
[b]Study medication related adverse events include those adverse events with relationship classified as 'Certainly related', 'Probably related', 'Possibly related', 'Conditionally related', or Unclassifiable, else considered as 'not related'. If any AE occurs more than once, the highest relationship to study medication is used for summary tabulation. Missing relationship for an AE is considered 'related' to study medication.

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
Table Generation 14FEB2020 at 11:27 AM by Table 14.3.1.4.sas

14.3.2. Listings of Deaths, Other Serious and Significant Adverse Events

No deaths or other serious adverse events occurred in the study. Narratives for subjects who discontinued study due to TEAEs are included in Section 14.3.3.

This section contains the following tables:

Number	Title
14.3.2.1	Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term, Safety Analysis Set
14.3.2.2	Serious Study Drug Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term, Safety Analysis Set
14.3.2.3	Treatment-Emergent Adverse Events Leading to Death by System Organ Class and Preferred Term, Safety Analysis Set
14.3.2.4	Drug Related Treatment-Emergent Adverse Events Leading to Death by System Organ Class and Preferred Term, Safety Analysis Set
14.3.2.5	Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation by System Organ Class and Preferred Term, Safety Analysis Set
14.3.2.6	Drug Related Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation by System Organ Class and Preferred Term, Safety Analysis Set
14.3.2.7	Treatment-Emergent Events Leading to Study Discontinuation by System Organ Class and Preferred Term, Safety Analysis Set
14.3.2.8	Drug Related Treatment-Emergent Events Leading to Study Discontinuation by System Organ Class and Preferred Term, Safety Analysis Set
14.3.3.1	Serious Adverse Events, Safety Analysis Set
14.3.3.2	Fatal Adverse Events, Safety Analysis Set

Table 14.3.2.1 Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term, Safety Analysis Set

No subjects reported SAEs in the study

Table 14.3.2.2 Serious Study Drug Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term, Safety Analysis Set

No subjects reported SAEs in the study

Table 14.3.2.3 Treatment-Emergent Adverse Events Leading to Death by System Organ Class and Preferred Term, Safety Analysis Set

No AEs led to death in the study.

Table 14.3.2.4 Drug Related Treatment-Emergent Adverse Events Leading to Death by System Organ Class and Preferred Term, Safety Analysis Set

No AEs led to death in the study.

Table 14.3.2.5 Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation by System Organ Class and Preferred Term, Safety Analysis Set

No AEs led to drug discontinuation in the study.

Table 14.3.2.6 Drug Related Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation by System Organ Class and Preferred Term, Safety Analysis Set

No AEs led to drug discontinuation in the study.

Table 14.3.2.7. Treatment-Emergent Events Leading to Study Discontinuation by System Organ Class and Preferred Term, Safety Analysis Set

	Treatment				
System Organ Class Preferred Term [a]	**A (N=107) n (%), E**	**B (N=106) n (%), E**	**C (N=108) n (%), E**	**D (N=109) n (%), E**	**Overall (N=112) n (%), E**
Subject with at least 1 TEAE	1 (0.9), 1	1 (0.9), 1	1 (0.9), 1	0	3 (2.7), 3
GENERAL DISORDERS AND ADMINISTRATION	1 (0.9), 1	0	1 (0.9), 1	0	2 (1.8), 2
Influenza like illness	0	0	1 (0.9), 1	0	1 (0.9), 1
Pyrexia	1 (0.9), 1	0	0	0	1 (0.9), 1
INFECTIONS AND INFESTATIONS	0	1 (0.9), 1	0	0	1 (0.9), 1
Urinary tract infection	0	1 (0.9), 1	0	0	1 (0.9), 1

Listing Reference: 16.2.7.3
Notes: Percentages are based on the number of subjects (N) in each treatment and overall
Each subject will only be counted once per Preferred Term and once per System Organ Class.
n(%)=number and percentage of subjects in the category; E = Number of AEs, TEAE= Treatment-Emergent Adverse Event
[a] All adverse events as described by the investigators (verbatim term) were coded using MedDRA version 22.0

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
Table Generation 14FEB2020 at 2:18 PM by Table 14.3.1.2.sas

Table 14.3.2.8. Drug Related Treatment-Emergent Events Leading to Study Discontinuation by System Organ Class and Preferred Term, Safety Analysis Set

		Treatment				
System Organ Class Preferred Term [a]	**Relationship [b]**	**A (N=107) n (%), E**	**B (N=106) n (%), E**	**C (N=108) n (%), E**	**D (N=109) n (%), E**	**Overall (N=112) n (%), E**
Subject with at least 1 TEAE	Related	1 (0.9), 1	0	0	0	1 (0.9), 1
	Not Related	0	0	0	0	0
GENERAL DISORDERS AND ADMINISTRATION	Related	1 (0.9), 1	0	0	0	1 (0.9), 1
	Not Related	0	0	0	0	0
Pyrexia	Related	1 (0.9), 1	0	0	0	1 (0.9), 1
	Not Related	0	0	0	0	0

Listing Reference: 16.2.7.3
Notes: Percentages are based on the number of subjects (N) in each treatment and overall
Each subject will only be counted once per Preferred Term and once per System Organ Class.
n(%)=number and percentage of subjects in the category; E = Number of AEs, TEAE= Treatment-Emergent Adverse Event
[a] All adverse events as described by the investigators (verbatim term) were coded using MedDRA version 22.0
[b]Study medication related adverse events include those adverse events with relationship classified as 'Certainly related', 'Probably related', 'Possibly related', 'Conditionally related', or Unclassifiable, else considered as 'not related'. If any AE occurs more than once, the highest relationship to study medication is used for summary tabulation. Missing relationship for an AE is considered 'related' to study medication.

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
Table Generation 14FEB2020 at 2:33 PM by Table 14.3.1.2.sas

Table 14.3.3.1 Serious Adverse Events, Safety Analysis Set

No subjects reported SAEs in the study

Table 14.3.3.2 Fatal Adverse Events, Safety Analysis Set

There were no fatal events during the study.

14.3.3. Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events

No deaths, or other serious adverse events occurred in the study. The following subjects discontinued study due to TEAEs:

Subject [redacted]

Subject [redacted] with no reported medical history, was randomised to treatment sequence CDBA. During treatment period 3, the subject received the reference product FOSTAIR 200/6 mcg (Treatment B) on 24 June 2019. On 07 July 2019 (during the washout after treatment period 3), the subject experienced urinary tract infection for which she was given dexamethasone, tramadol, paracetamol, norfloxacin lactic acid bacillus, ranitidine, and diclofenac. The event was graded by the Investigator as moderate in severity, and assessed as unlikely to be related to study treatment. As a result of this TEAE, the subject was withdrawn from study (on 13 July 2019) prior to receiving treatment period 4 study treatment, thereby not receiving Lupin BDP/FF 200/6 mcg (Treatment A), and the TEAE was still ongoing.

Subject [redacted]

Subject [redacted] with no reported medical history, was randomised to treatment sequence DACB. During treatment period 3, the subject received the test product Lupin BDP/FF 200/6 mcg with oral charcoal (Treatment C) on 02 July 2019. On 23 July 2019 (Day 0 of treatment period 4), the subject experienced influenza like illness for which he was given paracetamol (intravenous and oral), and paracetamol + chlorpheniramine maleate + phenylephrine. The event was graded by the Investigator as moderate in severity, and assessed as unlikely to be related to study treatment. As a result of this TEAE, the subject was withdrawn from study the same day prior to receiving treatment period 4 study treatment, thereby not receiving FOSTAIR 200/6 mcg (Treatment B), and the TEAE resolved the next day.

Subject [redacted]

Subject [redacted] with no reported medical history, was randomised to treatment sequence CDBA. During treatment period 4, the subject received the test product Lupin BDP/FF 200/6 mcg (Treatment A) on 27 July 2019. On 28 July 2019 (Day 1 of treatment period 4), the subject experienced pyrexia for which he was given paracetamol. The event was graded by the Investigator as moderate in severity, and assessed as possibly related to study treatment. As a result of this TEAE, the subject was withdrawn from study the same day (on 28 July 2019), and the TEAE resolved 11 days later on 08 August 2019.