| | |
|---|---|
| Official Title: | A Randomized, Single-dose, Open-label, Two-way Crossover Pivotal Study to Assess the Bioequivalence between Albuterol Sulfate inhalation aerosol 108mcg per actuation (MDI, eq. to albuterol 90mcg/puff) and Proair HFA (albuterol sulfate) Inhalation Aerosol 90 mcg per actuation (MDI, eq. to albuterol 90mcg/puff) in Healthy Volunteers under Fasting Conditions |
| NCT Number: | NCT04803734 |
| Document Date: | Protocol Version 2.0: May-02-2021 |

# 1. TITLE PAGE

**A Randomized, Single-dose, Open-label, Two-way Crossover Pivotal Study to Assess the Bioequivalence between Albuterol Sulfate inhalation aerosol 108mcg per actuation (MDI, eq. to albuterol 90mcg/puff) and Proair HFA(albuterol sulfate) Inhalation Aerosol 90 mcg per actuation (MDI, eq. to albuterol 90mcg/puff) in Healthy Volunteers under Fasting Conditions**

Protocol No.: TW20-4502
Protocol Version: 1.0
Protocol Version Date: Jan-08-2021

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## 1.1 PROTOCOL REVISION CONTROL

| Version # (Version Date) | Affected Sections |
|---|---|
| 1.0 (Jan-08-2021) | N/A (New protocol) |
| **2.0 (May-02-2021)** | **9.6** |

## 1.2 AMENDMENT

| **Version # (Version Date)** | **Modifications** |
|---|---|
| **2.0 (May-02-2021)** | **Change the rule of echelons** |

## 1.3 PROTOCOL APPROVAL/SIGNATURE PAGE-SPONSOR

I have read the proceeding protocol:

"A Randomized, Single-dose, Open-label, Two-way Crossover Pivotal Study to Assess the Bioequivalence between Albuterol Sulfate inhalation aerosol 108mcg per actuation (MDI, eq. to albuterol 90mcg/puff) and Proair HFA(albuterol sulfate) Inhalation Aerosol 90 mcg per actuation (MDI, eq. to albuterol 90mcg/puff) in Healthy Volunteers under Fasting Conditions" and agree that it contains all necessary details for conducting the study.

On behalf of Intech Biopharm Ltd., I agree to the terms of this study protocol.

[redacted]

Intech Biopharm Ltd.

Date: May-05-2021
(MMM-DD-YYYY)

## 1.4 PROTOCOL APPROVAL/SIGNATURE PAGE-PRINCIPLE INVESTIGATOR

I have read the proceeding protocol:

"A Randomized, Single-dose, Open-label, Two-way Crossover Pivotal Study to Assess the Bioequivalence between Albuterol Sulfate inhalation aerosol 108mcg per actuation (MDI, eq. to albuterol 90mcg/puff) and Proair HFA(albuterol sulfate) Inhalation Aerosol 90 mcg per actuation (MDI, eq. to albuterol 90mcg/puff) in Healthy Volunteers under Fasting Conditions" and agree that it contains all necessary details for conducting the study.

On behalf of Tamshui Mackay Memorial Hospital, I agree to the terms of this study protocol and will conduct the study in compliance with this protocol.
Signature certifies approval of this clinical protocol.

[redacted] Date: May-07-2021

[redacted] M.D. (MMM-DD-YYYY)

Principal Investigator
Tamshui Mackay Memorial Hospital

# 2. INVESTIGATORS AND FACILITIES

## 2.1 FACILITIES

| | |
|---|---|
| Sponsor | Intech Biopharm Ltd.<br>3F., No.36, Ln. 358, Ruiguang Rd., Neihu Dist., Taipei City 114, Taiwan<br>Phone: +886-2-7721-8877<br>Fax: +886-2-7721-8800 |
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| Clinical Facility | Clinical Pharmacology Unit,Mackay Memorial Hospital<br>No.45, Minsheng Rd., Tamshui District, New Taipei City 25160, Taiwan<br>Phone: +886-2-2809-3000<br>Fax: +886-2-2809-3082 |
| Clinical Laboratory | Tamshui Mackay Memorial Hospital<br>No. 45, Minsheng Rd., Tamshui District, New Taipei City 25160, Taiwan<br>Phone: +886-2-2809-4661<br>Fax: +886-2-2809-4679<br><br>Protech Pharmaservices Corporation<br>11F., No.3, Park St., Nangang District, Taipei City 11503, Taiwan<br>Phone: +886-2-5558-0000<br>Fax: +886-2-5558-0055<br><br>or any other certified lab in case of emergency |
| Bioanalytical Laboratory | Protech Pharmaservices Corporation<br>11F., No.3, Park St., Nangang District, Taipei City 11503, Taiwan<br>Phone: +886-2-5558-0000<br>Fax: +886-2-5558-0055 |
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| Institutional | Mackay Memorial Hospital Institutional Review Board (MMHIRB) |

| | |
|---|---|
| Review Board (IRB) | 8F, No. 92, Sec. 2, Zhongshan N. Rd., Zhongshan District, Taipei City 10449, Taiwan<br>Phone: +886-2-2543-3535<br>Fax: +886-2-2521-9529 |

## 2.2 INVESTIGATORS AND PARTICIPANTS

| Name | Affiliation / Address | Responsibility |
|---|---|---|
| [redacted] M.D. | Tamshui Mackay Memorial Hospital<br>No.45, Minsheng Rd., Tamshui District, New Taipei City 25160, Taiwan | Principal Investigator |
| [redacted] M.D. | Tamshui Mackay Memorial Hospital<br>No.45, Minsheng Rd., Tamshui District, New Taipei City 25160, Taiwan | Sub-Investigator |
| [redacted], M.D. | Tamshui Mackay Memorial Hospital<br>No.45, Minsheng Rd., Tamshui District, New Taipei City 25160, Taiwan | Sub-Investigator |
| [redacted] M.D. | Tamshui Mackay Memorial Hospital<br>No.45, Minsheng Rd., Tamshui District, New Taipei City 25160, Taiwan | Sub-Investigator |
| [redacted] M.S. | Protech Pharmaservices Corporation<br>11F., No.3, Park St., Nangang District, Taipei City 11503, Taiwan | Pharmacokineticist |
| [redacted] Ph.D. | Protech Pharmaservices Corporation<br>11F., No.3, Park St., Nangang District, Taipei City 11503, Taiwan | Pharmacokineticist |

## 3. SYNOPSIS

| | |
|---|---|
| Protocol Title | A Randomized, Single-dose, Open-label, Two-way Crossover Pivotal Study to Assess the Bioequivalence between Albuterol Sulfate inhalation aerosol 108mcg per actuation (MDI, eq. to albuterol 90mcg/puff) and Proair HFA(albuterol sulfate) Inhalation Aerosol 90 mcg per actuation (MDI, eq. to albuterol 90mcg/puff) in Healthy Volunteers under Fasting Conditions. |
| Objective | The objective of this study is to evaluate the bioequivalence between two formulations of MDI, eq. to albuterol 90mcg/puff in healthy volunteers under fasting conditions. |
| Study Design and Study Population | A single-dose, randomized, open-label, two-period, two-sequence, two-treatment, two-way crossover, bioequivalence pivotal study.<br><br>Sixty healthy volunteers, 20-60 years of age, inclusive, with a body mass index (BMI) within 18.0-30.0 $kg/m^2$, inclusive, will be randomized. |
| Test Drug (T) | Albuterol Sulfate inhalation aerosol 108mcg per actuation (equivalent to 90mcg of Albuterol) |
| Reference Drug (R) | Proair HFA(albuterol sulfate) Inhalation Aerosol 90 mcg per actuation |
| Treatment | A single dose of albuterol inhalation aerosol (2 puffs) in each period. |
| Duration of Confinement | For each period, subject will be confined from at least 10.5 hours prior to dosing until at least 24-hours post-dose, for a total of at least 34.5 hours. |
| Washout | At least 14 days between each dosing. |
| Safety Monitoring | ● Vital signs (blood pressure [BP], pulse rate [PR] and body temperature) will be obtained at pre-dose and at 0.5, 16 and 24 hours after dosing in each study period.<br>● The Investigator will be present from approximately 30 minutes prior to dosing until 4 hours after dosing in each study period. The Investigator will remain on-call throughout the duration of the study. |

| | |
|---|---|
| Blood Sampling Time-points | Blood samples will be collected at 0-hour (pre-dose), and at 2, 5, 10, 15, 20, 30, 45 minutes, and 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 3, 4, 6, 8, 12, 16 and 24 hours post-dose (a total of 22 sampling points) after dosing in each study period for analysis. |
| Total Blood Volume | Approximately 328 ml of blood, including 20 ml for pre- and post-study procedures and 308 ml for pharmacokinetic analysis. |
| Analyte(s) to be Measured | Plasma samples will be assayed for albuterol using a validated analytical method according to the principles of FDA GLP Title 21 Part 58. |
| Statistical Analysis | For albuterol analysis of variance (ANOVA) for log-transformed $AUC_{0-t}$, $AUC_{0-\infty}$ and $C_{max}$, and untransformed $T_{max}$, $k_{el}$ and $T_{1/2}$. $T_{max}$ will be analyzed using an additional non-parametric test (Wilcoxon test). The 90% confidence intervals (CI) for the Test/Reference ratios of geometric means for $AUC_{0-t}$, $AUC_{0-\infty}$ and $C_{max}$ will be calculated based on the least square means (LSMEANS) and ESTIMATE of the ANOVA. |
| Bioequivalence Criteria | To establish bioequivalence, the calculated 90% CI for the ratio of geometric means for $AUC_{0-t}$, $AUC_{0-\infty}$ and $C_{max}$ for albuterol should fall within 80.00%-125.00%. |

## 4. LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | Adverse Event(s) |
| AMP | Adenosine monophosphate |
| ANOVA | Analysis of variance |
| $AUC_{0-t}$ | Area under the plasma concentration-time curve from zero to last concentration time |
| $AUC_{0-\infty}$ | Area under the plasma concentration-time curve extrapolated to infinity |
| BLQ | Below the lower limit of quantitation |
| BMI | Body Mass Index |
| BP | Blood Pressure |
| bpm | Beats per minute |
| BUN | Blood Urea Nitrogen |
| CI | Confidence Interval |
| $C_{max}$ | Maximum plasma concentrations |
| COPD | Chronic obstructive pulmonary disease |
| CRO | Contract Research Organization |
| CV | Coefficient of variability |
| CYP | Cytochrome P450 |
| ECG | Electrocardiogram |
| eq. | Equivlent to |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| GLP | Good Laboratory Practice |
| γ-GT | Gamma-Glutamyl-Transpeptidase |
| h or hr | Hour(s) |
| HBsAg | Hepatitis B Surface Antigen |
| hCG | Human Chorionic Gonadotropin |
| HCV | Hepatitis C Virus |
| HIV | Human Immunodeficiency Virus |
| ICF | Informed Consent Form(s) |
| ICH | International Council for Harmonisation |
| IRB | Institutional Review Board |
| $k_{el}(\lambda)$ | Plasma elimination rate constant determined by simple linear regression |

| | |
|---|---|
| | based on the terminal phase of plasma concentration |
| Max | Maximum |
| MDI | Metered-Dose Inhaler |
| Mean | Arithmetic mean |
| mg | Milligram(s) |
| Min | Minimum(s) |
| ml | Milliliter(s) |
| mmHg | Millimeters of Mercury |
| MMHIRB | Mackay Memorial Hospital Institutional Review Board |
| MRT | Mean residence time |
| N/A | Not applicable |
| pH | Negative log hydrogen ion concentration |
| PK | Pharmacokinetic(s) |
| PPC | Protech Pharmaservices Corporation |
| PR | Pulse Rate |
| PTE | Pretreatment event |
| R | Reference or Reference drug(s) |
| RBC | Red Blood Cell |
| RLD | Reference Listed Drug |
| SAE | Serious Adverse Event(s) |
| SAS® | Statistical Analysis System |
| SD | Standard deviation |
| SGOT | Serum Glutamic Oxaloacetic Transaminase (same as AST) |
| SGPT | Serum Glutamic Pyruvic Transaminase (same as ALT) |
| SOP | Standard Operating Procedure(s) |
| T | Test or Test drug |
| $T_{1/2}$ | Half-life |
| TFDA | Taiwan Food and Drug Administration |
| TG | Triglycerides |
| $T_{max}$ | Time to reach maximum plasma concentrations |
| WBC | White Blood Cell |

## 5. TABLE OF CONTENT

# 6. BACKGROUND AND PHARMACOKINETICS[1]

## 6.1 INDICATION AND USAGE

**Bronchospasm**

Albuterol is indicated for the treatment or prevention of bronchospasm in patients 4 years of age and older with reversible obstructive airway disease.

**Exercise-Induced Bronchospasm**

Albuterol is indicated for the prevention of exercise-induced bronchospasm in patients 4 years of age and older.

## 6.2 CLINICAL PHARMACOLOGY

Albuterol sulfate is a beta$_2$-adrenergic agonist. The pharmacologic effects of albuterol sulfate are attributable to activation of beta$_2$-adrenergic receptors on airway smooth muscle. Activation of beta$_2$-adrenergic receptors leads to the activation of adenylcyclase and to an increase in the intracellular concentration of cyclic-3′,5′-adenosine monophosphate (cyclic AMP). This increase of cyclic AMP is associated with the activation of protein kinase A, which in turn inhibits the phosphorylation of myosin and lowers intracellular ionic calcium concentrations, resulting in muscle relaxation. Albuterol relaxes the smooth muscle of all airways, from the trachea to the terminal bronchioles. Albuterol acts as a functional antagonist to relax the airway irrespective of the spasmogen involved, thus protecting against all bronchoconstrictor challenges. Increased cyclic AMP concentrations are also associated with the inhibition of release of mediators from mast cells in the airway. While it is recognized that beta2 adrenergic receptors are the predominant receptors on bronchial smooth muscle, data indicate that there are beta-receptors in the human heart, 10% to 50% of which are cardiac beta$_2$-adrenergic receptors. The precise function of these receptors has not been established.

Albuterol has been shown in most controlled clinical trials to have more effect on the respiratory tract, in the form of bronchial smooth muscle relaxation, than isoproterenol at comparable doses while producing fewer cardiovascular effects. However, inhaled albuterol, like other beta-adrenergic agonist drugs, can produce a significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, symptoms, and/or electrocardiographic changes.

## 6.3 PHARMACOKINETICS

The systemic levels of albuterol are low after inhalation of recommended doses. In a crossover study conducted in healthy male and female volunteers, high cumulative doses of PROAIR HFA Inhalation Aerosol (1,080 mcg of albuterol base administered over one hour) yielded mean peak plasma concentrations ($C_{max}$) and systemic exposure ($AUC_{inf}$) of approximately 4,100 pg/mL and 28,426 pg/mL*hr, respectively compared to approximately 3,900 pg/mL and 28,395 pg/mL*hr, respectively following the same dose of an active HFA-134a albuterol inhaler comparator. The terminal plasma half-life of albuterol delivered by PROAIR HFA Inhalation Aerosol was approximately 6 hours. Comparison of the pharmacokinetic parameters demonstrated no differences between the products.

The pharmacokinetic profile of PROAIR HFA Inhalation Aerosol was evaluated in a two-way cross-over study in 11 healthy pediatric volunteers, 4 to 11 years of age. A single dose administration of PROAIR HFA Inhalation Aerosol (180 mcg albuterol base) yielded a least square mean (SE) $C_{max}$ and $AUC_{0-\infty}$ of 1,100 (1.18) pg/mL and 5,120 (1.15) pg/mL*hr, respectively. The least square mean (SE) terminal plasma half-life of albuterol delivered by PROAIR HFA Inhalation Aerosol was 166 (7.8) minutes.

Information available in the published literature suggests that the primary enzyme responsible for the metabolism of albuterol in humans is SULTIA3 (sulfotransferase). When racemic albuterol was administered either intravenously or via inhalation after oral charcoal administration, there was a 3- to 4-fold difference in the area under the concentration-time curves between the (R)- and (S) albuterol enantiomers, with (S)-albuterol concentrations being consistently higher. However, without charcoal pretreatment, after either oral or inhalation administration the differences were 8- to 24-fold, suggesting that the (R)-albuterol is preferentially metabolized in the gastrointestinal tract, presumably by SULTIA3.

The primary route of elimination of albuterol is through renal excretion (80% to 100%) of either the parent compound or the primary metabolite. Less than 20% of the drug is detected in the feces. Following intravenous administration of racemic albuterol, between 25% and 46% of the (R)-albuterol fraction of the dose was excreted as unchanged (R)-albuterol in the urine.

## 6.4 ADVERSE EVENTS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the AE that appear to be related to

drug use and for approximating the incidence. There is a chance that in this clinical trial, new, unexpected adverse events may occur.

Most common adverse reactions (incidence ≥ 3%) are: Asthma: nasopharyngitis, headache, upper respiratory tract infection, pharygolaryngeal pain, sinusitis, influenza, back pain, nasal congestion, stomach discomfort, vomiting, and oral candidiasis. COPD: nasopharyngitis, oral candidiasis, bronchitis, sinusitis, upper respiratory tract infections.

### 6.5 PREGNANCY CATEGORY

Pregnancy Category C

## 7. STUDY OBJECTIVE AND RATIONALE

The objective of this study is to evaluate PK profile of the test product of Albuterol Sulfate inhalation aerosol 108mcg per actuation (equivalent to 90mcg of Albuterol base) and to determine its bioequivalence to the RLD in healthy volunteers under fasting conditions.

### 7.1 PRIMARY OBJECTIVE

This study is designed to assess the bioequivalence of the test product and the reference products under fasting conditions. Test product will be considered bioequivalent to reference product if the T/R ln-transformed $AUC_{0-t}$, $AUC_{0-\infty}$ and $C_{max}$ are within 80.00-125.00% of those of the reference.

### 7.2 SECONDARY OBJECTIVE

The other PK-variables will be assessed for descriptive purposes. As for safety parameters, AE and vital signs (BP, PR and body temperature) will be recorded.

## 8. STUDY DESIGN

### 8.1 DISCUSSION OF STUDY DESIGN

This pivotal study will be conducted by a way of single-dose, randomized, open-label, two-period, two-sequence, two-treatment, single-centre, two-way crossover design to examine the bioequivalence of Albuterol Sulfate inhalation aerosol 108mcg per actuation (equivalent to 90mcg of Albuterol base) (MDI, eq. to albuterol 90mcg/puff) [Test, T] and Proair HFA(albuterol sulfate) Inhalation Aerosol 90 mcg per actuation (MDI, eq. to albuterol 90mcg/puff) [Reference, R]. The investigational drugs will be studied using a crossover design with 60 healthy volunteers being administered a single dose as equivalent to 180 mcg of albuterol under fasting conditions. Each

subject will be drawn at 0-hour (sampling before dosing as baseline), and at 2, 5, 10, 15, 20, 30, 45 minutes, and 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 3, 4, 6, 8, 12, 16 and 24 hours post-dose in each study period. Blood samples will be collected and analyzed for albuterol concentrations by using LC-MS/MS

Subjects who meet the eligibility criteria will be randomly assigned to receive the study drugs according to the two-treatment, two-period, two-sequence randomization scheme (T-R or R-T). The randomization scheme will be generated by using SAS® version 9.2 or higher prior to first dosing period. For example: if subjects are randomized to the T-R sequence, they will receive the test product in Period 1, and then, following at least 14-day washout period, receive the reference product in Period 2.

At least 14-day was estimated to be adequate to avoid carry-over effects of the preceding treatments. The trial will be performed as an open-label study as the PK profile should not be expected to be affected by having the knowledge of which study drug was administered. Blinding of the Investigator/clinical staff and subjects is not considered necessary.

## 8.2 STUDY CONFINEMENT AND WASHOUT

Subjects will be confined to the clinic site from at least 10.5 hours prior to dosing until at least 24-hours post-dose, for a total of at least 34.5 hours for each study period. This study will consist of two study periods with one washout period of at least 14 days between each dosing.

## 8.3 RANDOMIZATION AND BLINDING

In this study, the assignment of treatment groups, known as the randomization scheme will be generated by a computer program, writer and run in SAS® Version 9.2 or higher at PPC to produce a balanced (if possible) random allocation of subjects into treatment sequences. Subjects will be assigned consecutive subject numbers in an ascending order. This number will identify the subject and determine the treatment sequence the subject will undergo. Treatment assignment will be described in the randomization scheme.

Subjects who meet the eligibility criteria will be randomly assigned to receive the study drugs according to the randomization schedule prior to dosing of period 1. Subjects will be assigned consecutive subject numbers in an ascending order. After randomization, any subjects withdrew due to any reason will not be replaced.

This is an open-label study and subjects as well as clinical staff will not be blinded to the

randomization. The analytical laboratory will not have access to the randomization scheme until the bioanalytical analysis is complete. Subjects will be randomized equally into one of the following two sequence groups:

| | Period 1 | Washout | Period 2 |
|---|---|---|---|
| Sequence 1 | T | ≥ 14 days | R |
| Sequence 2 | R | | T |

Each subject is scheduled to receive a total of two treatments by the end of the study.

## 9. SUBJECT SELECTION

### 9.1 PRE-STUDY PROCEDURES

The following screening procedures will be conducted on each potential subject:

- Obtain written informed consent for screening.
- Record medical/medication history and demographic information based on the interview with the potential subject.
- Review of inclusion/exclusion criteria for each potential subject.
- Obtain height and body weight to calculate BMI.
- Obtain vital signs (seated BP, PR as well as temperature).
- Perform electrocardiogram (ECG) and chest X-ray. (The results of ECG and chest X-ray within previous 30 days will be accepted for evaluation.)
- Collect blood and urine samples for hematology, biochemistry, serology, urinalysis, screening for drugs of abuse. Perform breath alcohol test. Pregnancy test will be performed only for female subjects. For a complete listing of all tests to be performed, please refer to Section 9.2 Assessment. (The results of laboratory test within previous 30 days will be accepted for evaluation.)
- Perform a physical examination.
- Principal Investigator's/Sub-Investigator's review of inclusion/exclusion criteria and all screening results/data to assess eligibility of each potential subject.

Screening procedures will be conducted within thirty (30) days prior to dosing in Period 1 (Day -30 to Day -1).

## 9.2 CLINICAL LABORATORY ASSESSMENT

| TYPE OF TEST | COMPONENTS | | |
|---|---|---|---|
| Hematology | • Hemoglobin<br>• Hematocrit | • RBC count<br>• Platelet count | • WBC and differential |
| Biochemistry | • Total protein<br>• γ-GT<br>• SGOT<br>• SGPT<br>• Albumin | • Creatinine<br>• Glucose<br>• BUN<br>• TG | • Uric Acid<br>• Total cholesterol<br>• Alkaline Phosphatase<br>• Total Bilirubin |
| Urinalysis | • Urine Bilirubin<br>• Occult blood<br>• Glucose | • pH<br>• Ketone body<br>• Leukocytes | • Urobilinogen<br>• Protein<br>• Specific gravity<br>• Nitrite |
| Urine Tests for Drugs of Abuse[α] | • Amphetamines<br>• Barbiturates<br>• Benzodiazepines | • Cocaine<br>• Opiates<br>• Phencyclidine | • Tetrahydrocannabinol |
| Other Tests | • Breath alcohol test[α]<br>• Pregnancy test[β] | | |
| Serology[γ] | • Anti-HIV<br>• HBsAg<br>• Anti-HCV | | |

**α** Urine tests for drugs of abuse and breath alcohol tests will be performed at screening and check-in of each period.

**β** For females, serum hCG will be performed only at screening. Urine hCG will be performed at check in of each period and post examination.

**γ** Serology test will only be performed at screening

## 9.3 INCLUSION/EXCLUSION CRITERIA

### 9.3.1 INCLUSION CRITERIA

Potential subjects meeting **all** of the following criteria may be included in the study:

1. Healthy male and female volunteers, aged 20-60, inclusive.
2. BMI of 18.0-30.0 kg/m², inclusiv e. The body weight should be over 50 kg, inclusive. (BMI will be calculated as weight in kilogram [kg]/height in meters$^2$ [m$^2$]).
3. Healthy or Non Clinical Significant, according to the medical history, ECG, chest X-ray and physical examination as determined by the Principal Investigator/Sub-Investigator.
4. Systolic blood pressure between 90-139 mmHg, inclusive, and diastolic blood pressure between 50-90 mmHg, inclusive, and pulse rate between 50-100 bpm, inclusive and temperature between 35.0-37.4℃.
5. Screening laboratory values within reference range or NCS as determined by the Principal Investigator/Sub-Investigator.
6. Ability to comprehend and be informed of the nature of the study, as assessed by clinical staff. Capable of giving written informed consent prior to receiving any study medication. Must be able to communicate effectively with clinical staff.
7. Willing to fast for at least 14 hours and to consume standard meals.
8. Availability to volunteer for the entire study duration and willing to adhere to all protocol requirements.
9. Agree not to have a tattoo, body piercing, or any invasive procedure and blood donation until the end of the study.
10. Never-smokers; or former smokers who have smoked ≥ 100 cigarettes in their lifetime and have not consumed any tobacco or tobacco containing products for at least 12 months prior to screening.
11. Subjects who are non-asthmatic, defined as no clinical history of asthma, allergy or atopy.
12. Able to perform special breathing using nebulizer correctly as per the required standard.
13. Subjects must fulfill at least one of the following:
    - Be surgically sterile for a minimum of 6 months;
    - Post-menopausal for a minimum of 1 year;
    - Agree to avoid pregnancy and use medically acceptable method of contraception from screening day until 30 days after the study ends (last study procedure).

    Medically acceptable methods of contraception include non-hormonal intrauterine device or double barrier method (condom with foam or vaginal spermicidal suppository, diaphragm with spermicide). Complete abstinence alone can be used as a method of contraception.

### 9.3.2 EXCLUSION CRITERIA

Potential subjects meeting any of the following criteria will be excluded:

1. Known history or presence of any clinically significant hepatic (e.g. active liver disease, hepatic impairment), renal/genitourinary (e.g. renal impairment), gastrointestinal, cardiovascular, cerebrovascular, pulmonary, endocrine (e.g. hypothyroidism), immunological, musculoskeletal (e.g. myopathy, rhabdomyolysis), neurological, psychiatric, dermatological, hematological disease, or any other medical conditions, unless determined as not clinically significant by the Principal Investigator/Sub-Investigator.
2. Presence of any clinically significant illness within 30 days prior to first dosing, as determined by the Principal Investigator/Sub-Investigator.
3. Presence of any significant physical or organ abnormality as determined by the Principal Investigator/Sub-Investigator.
4. A positive test result for any of the following: HIV, Hepatitis B surface antigen, Hepatitis C, drugs of abuse (amphetamines, barbiturates, benzodiazepines, cocaine, opiates, phencyclidine, tetrahydrocannabinol), breath alcohol test. Positive pregnancy test for female subjects.
5. Known history or presence of:
   - Alcohol abuse within one year prior to first drug administration;
   - Drug abuse or dependence;
   - Hypersensitivity or idiosyncratic reaction to albuterol, its excipients, and/or related substances;
   - Allergy to standardized meal provided by site and/or presence of any dietary restrictions;
6. Intolerance to and/or difficulty in blood sampling through venipuncture.
7. Abnormal diet patterns (for any reason) during the 4 weeks preceding the study, including fasting, high protein diets etc.
8. Except for screening procedures, blood donation that results in blood loss of not more than 250 ml in the past 2 months prior to first dosing; blood loss of more than 250 ml within 3 months prior to first dosing.
9. Donation of plasma by plasmapheresis within 7 days prior to first drug administration.
10. Individuals who receives an investigational drug from 2 months prior to first drug administration.
11. Consumption of products containing caffeine/methylxanthines, poppy seeds and/or alcohol within 48 hours before dosing and products containing grapefruit and/or pomelo (shown to inhibit cytochrome P450 [CYP] 3A4 activity) within 10 days prior to first drug administration.
12. Use of any medication, including oral multivitamins, herbal and/or dietary supplements within 30 days prior to first drug administration (except topical agents without systemic absorption as

determined by the Principal Investigator/Sub-Investigator).

13. Females taking oral or transdermal hormonal contraceptives within 30 days prior to first drug administration.
14. Females having used implanted, injected, intravaginal, or intrauterine hormonal contraceptive within 6 months prior to first drug administration.
15. Individuals having undergone any major surgery within 6 months prior to the start of the study, unless deemed otherwise by Principal Investigator/Sub-Investigator.
16. Using tobacco products, nicotine products (patches, gum etc.) within 6 months prior to first drug administration.
17. Lactating women.

## 9.4 CONCOMITANT MEDICATIONS

Any concomitant medication (prescription or over-the-counter, except for spermicidal/barrier contraceptive products), any herbal and/or dietary supplements will not be permitted during the study unless deemed otherwise by the Principal Investigator/Sub-Investigator.

Each case where concomitant medication or herbal/dietary supplement is used during the restriction period will be reported as soon as possible to the PPC Pharmacokineticist and/or the Sponsor and will be reviewed on a case by case basis to determine the subject's further participation in the study.

## 9.5 STUDY RESTRICTIONS

If any subject does not comply with these restrictions, at any time prior to or during the study, continued participation will be re-assessed by the Principal Investigator/Sub-Investigator, PPC Pharmacokineticist and/or the Sponsor.

If drug therapy other than those specified in the protocol is required during the study, the decision whether to continue or discontinue the subject's participation in the study will be made by the Principal Investigator/Sub-Investigator, Pharmacokineticist, and/or the Sponsor.

Concomitant drug or non-drug treatment administered to subjects as per instructions from physicians for treatment of any AE (as required) will be permitted. Clinical staff will provide the subjects with the treatment (e.g. medication, fluids) and will document all substances given outside of the protocol specified requirements. All cases of concomitant medication or herbal/dietary supplement administration will be reported as soon as possible to the PPC Pharmacokineticist and/or the Sponsor and will be reviewed on a case by case basis to determine the subject's further participation in the study.

| Restriction Period | Item Restricted | Examples |
|---|---|---|
| 6 months prior to first drug administration until the last blood draw in the final study period | Smoke or use tobacco products, nicotine products (patches, gum etc.)<br>Females: implanted, injected, intravaginal, or intrauterine hormonal contraceptive | |
| 30 days prior to first drug administration until the last blood draw in the final study period | Prescription medication, vaccination | Prescription pills, topical systemic creams, inhalants, sprays |
| | Over-the-counter medication, dietary and/or herbal supplements | Acetaminophen, St. John′s Wort, Ricola, oral multivitamins |
| | Oral or transdermal hormonal contraceptives | |
| | Note: Spermicidal/barrier contraceptive products may be permitted. | |
| 10 days prior to first drug administration until the last blood draw in the final study period | Products containing grapefruit and/or pomelo (shown to inhibit cytochrome P450 [CYP] 3A4 activity) | Grapefruit, grapefruit juice, grapefruit candies, pomelo, etc. |
| 48 hours prior to drug administration until after the last blood draw in each study period | Products containing poppy seeds, caffeine/ methylxanthines | Coffee, tea, chocolate, caffeine-containing soft drinks (e.g. Coke, Pepsi, Red Bull) |
| | Alcohol of any kind | Wine, beer, liquor, cocktails |

Subject should avoid driving a car or operating dangerous machinery after dosing until the last blood draw in each study period. The subjects will be advised to use contraceptive methods from at least screening day until 30 days after study has ended (last study procedure). The subjects will be advised to avoid any strenuous exercises within 48 hours before the first administration of the first study period until the final examination. Using tobacco or nicotine products, having a tattoo or body piercing, any invasive procedure, and blood donation will be prohibited during the study.

## 9.6 SAMPLE SIZE

For the pivotal study, a sufficient number of healthy adults will be screened with volunteer's consent and 60 subjects will be randomized under fasting conditions.

When possible, subjects will be enrolled in three echelons for all the planned number of subjects. If the capability/capacity of the clinical study facility is limited during the enrollment, the planned subjects may be split into 3 or more echelons with minimal 18 subjects in each echelon. **If the minimal subject number per echelon fails to meet the requirement, it is acceptable to split more echelons to achieve the designated sample size, as specified in the protocol.** In the circumstance the subjects are enrolled in split groups, statistical analysis will NOT be carried out before all the planned subjects have completed the study. Details for considerations of potential group effects will be stipulated separately in the statistical analysis plan.

## 9.7 DROPOUT AND WITHDRAWAL/TERMINATION

After administration, dropouts should not be replaced for any reason.

The following circumstances may lead to discontinuation of the study by an individual subject who will then be recorded as a drop-out:

- Withdrawal at any time for any reason
- AE necessitating withdrawal from the study
- Circumstances in which the health of the subject would be endangered upon continued participation in the study
- Protocol violation which could jeopardize the conduct of the study as judged by principal investigator
- For female with positive pregnancy test prior dosing
- Incorrect use of investigational product while dosing (e.g. any leak of investigational product from mouth while dosing)

Removal of a subject from the study will only be permitted prior to commencement of bioanalysis. If a subject's participation is terminated prematurely, the cause for the early termination date and time of the termination will be documented on the source documents and in the final study report. Withdrawn and dismissed subjects are not required to adhere to the study specific procedures (e.g. food and fluid restrictions, sample collections). If withdrawn or dismissed after drug administration, these subjects will be asked to adhere to the study restrictions in regards to the safety, prescription medication, over-the-counter medication, dietary and/or herbal supplements for the expected

duration of the restrictions relevant to the study period which the subject withdraws or is dismissed from (that period will be the subject's last study period). Subjects will be asked to adhere to the requirements of not becoming pregnant and using a medically acceptable method of contraception for 30 days after discontinuation in the study (if applicable).

If a subject withdraws or is dismissed from the study, a post-study physical examination and post-study testing will be completed, where possible.

## 10. DRUG PRODUCTS

### 10.1 DRUG INFORMATION

| Treatment Code | T | R |
|---|---|---|
| Drug Name: | Albuterol Sulfate inhalation aerosol 108mcg per actuation (equivalent to 90mcg of Albuterol) | Proair HFA(albuterol sulfate) Inhalation Aerosol 90 mcg per actuation |
| Active ingredient: | Albuterol sulfate | Albuterol sulfate |
| Strength: | eq. to albuterol 90mcg/puff | eq. to albuterol 90mcg/puff |
| Dosage Form: | MDI | MDI |
| Manufactured by: | Intech Biopharm Ltd. | IVAX Pharmaceuticals Ireland Waterford, Ireland |
| Dose: | Single dosing, 180mcg (2 puffs) | Single dosing, 180mcg (2 puffs) |
| Mode of administration: | Inhalation | Inhalation |
| Batch Number | ALMB040 | DAE50A |

### 10.2 LABELING, MAINTENANCE, AND RETENTION OF STUDY DRUGS

The Sponsor will supply a sufficient quantity of the study formulation(s) to allow completion of this study. Records will be made of receipt and dispensing of study drugs supplied and will be maintained by the Pharmacy staff. It is the responsibility of the Sponsor to ensure that all drug supplies provided for the study are manufactured under current Good Manufacturing Practices and

are suitable for human use.

The pharmacist will randomly select the boxes or bottles or containers to be used in the study. An inventory record of the drugs received and dispensed will be maintained by the Pharmacy staff. Each investigational study drug will be tagged with a statement indicating that the drug is an investigational drug to be used only by a Qualified Investigator as well as, Drug Name, Protocol Number, Strength, Sponsor's Name, the recommended storage conditions for the drug, Expiry Date (when available) and Lot/Batch Number. Study drugs will be locked in a temperature controlled room with restricted access. The study drugs will be prepared by pharmacy staff into individual unit-dose containers. Each unit-dose container will contain the Protocol Number, Period Number, Subject Number, Drug Name, Strength and Treatment Code.

## 11. STUDY PROCEDURES

### Efficacy and Safety Measurements and Flow Chart

| **Procedure/Activity** | **Screening** | **Each Period Check-in** | **Period 1 and 2** | **Post study examinations** |
|---|---|---|---|---|
| ICF | X | | | |
| Urine tests for drugs of abuse | X | X | | |
| Breath alcohol test | X | X | | |
| Medical History | X | | | |
| Physical Exam | X | | | X |
| Chest X-ray[α] | X | | | |
| ECG[α] | X | | | |
| BMI | X | | | |
| Vital sign[β] (BP, PR and Temperature) | X | | X | |
| AE Reporting (including PTE)[ε] | X | X | X | X |
| Laboratory tests[γ] | | | | |
| Hematology | X | | | X |
| Biochemistry | X | | | X |
| Urinalysis | X | | | X |
| Serology | X | | | |
| Pregnancy test[δ] | X | X | | X |
| Inclusion/Exclusion Assessment | X | | | |
| Restrictions Compliance Check | | X | X | |
| Drug administration | | | X | |
| PK Sampling | | | X | |
| Meals | | | X | |

**α** The results of ECG and chest X-Ray within previous 30 days will be accepted for evaluation.

**β** Details refer to Section 11. Dosing Procedures and Sampling Time Schedule.

**γ** Details refer to Section 9.2.

**δ** For females subjects, serum hCG will be performed only at screening. Urine hCG will be performed at check in of each period and post examination.

**ε** This study will collect pretreatment event (PTE) and adverse event (AE) after subjects provide written consent in the ICF. Only AE occur after first dosing will be analyzed for safety assessment.

The following section describes the scheduled intervals for this study, whereas the planned time

listed herein is to serve as examples only. The actual time executed for each individual subject will be advanced or postponed for several hours.

**Dosing Procedures and Sampling Time Schedule[α]**

| Day | Time | Events | Corresponding time after dosing | | Number of Sampling[ε] | Vital Signs Measuring[ζ] |
|---|---|---|---|---|---|---|
| | | | Hours | hh:mm | | |
| -1 | ≤21:00 | Subjects Check-in | - | | - | |
| | 21:30 | Start of fasting | - | | - | |
| 1 | 07:00 | | Pre-dose[γ] | | 1 | δ |
| | 07:30 | Dosing[β] | 0 | +00:00 | - | |
| | 07:32 | | 0.033 | +00:02 | 2 | |
| | 07:35 | | 0.083 | +00:05 | 3 | |
| | 07:40 | | 0.167 | +00:10 | 4 | |
| | 07:45 | | 0.25 | +00:15 | 5 | |
| | 08:50 | | 0.333 | +00:20 | 6 | |
| | 08:00 | | 0.5 | +00:30 | 7 | δ |
| | 08:15 | | 0.75 | +00:45 | 8 | |
| | 08:30 | | 1.0 | +01:00 | 9 | |
| | 08:45 | | 1.25 | +01:15 | 10 | |
| | 09:00 | | 1.5 | +01:30 | 11 | |
| | 09:15 | | 1.75 | +01:45 | 12 | |
| | 09:30 | | 2.0 | +02:00 | 13 | |
| | 09:45 | | 2.25 | +02:15 | 14 | |
| | 10:00 | | 2.5 | +02:30 | 15 | |
| | 10:30 | | 3.0 | +03:00 | 16 | |
| | 11:30 | End of fasting and start of lunch | 4.0 | +04:00 | 17 | |
| | 13:30 | | 6.0 | +06:00 | 18 | |
| | 15:30 | | 8.0 | +08:00 | 19 | |
| | 17:30 | Dinner | 10 | +10:00 | - | |
| | 19:30 | | 12.0 | +12:00 | 20 | |
| | 23:30 | | 16.0 | +16:00 | 21 | δ |
| 2 | 07:30 | | 24.0 | +24:00 | 22 | δ |

**α** Time schedule listed herein is to serve as examples. For each individual subject, the execution of subsequent sampling

time will be corresponding to the actual dosing time in relation to the ascending order of random number.

**β** Subjects will be administered an orally inhaled dose of 2 puffs (eq. to albuterol 180 mcg) under fasting conditions. Both start time and end time of inhalation will be recorded.

**γ** Pre-dose sample will be collected within 60 minutes before dosing and shown as 0 hour sample in bioanalytical and statistical analysis report.

**δ** Vital signs: BP, PR and body temperature.

**ε** The suggested time windows for sampling time are listed as follows (Sampling deviation within time window will not apply to protocol deviation):

| Sample No. | No. 2-9 | No. 10-21 | No. 22 |
|---|---|---|---|
| Time window | +2 minutes | +5 minutes | +60 minutes |

**ζ** Pre-dose vital signs will be measured within 2 hours of administration. On dosing day, the acceptable window of vital sign is ± 30 minutes. The non-administration day acceptable window will be measured within ± 60 minutes at a predetermined time. (Measurement of vital sign within time window or vital sign rechecked time exceeding the time window will not be considered as a protocol deviation.)

## 11.1 STUDY PERIOD CHECK-IN PROCEDURES

At check-in for each study period, subjects will be questioned about whether they have complied with the study restrictions.

If drug therapy other than that specified in the protocol is used, a decision to continue or discontinue the subject's participation will be made by the Principal Investigator/Sub-Investigator and/or by the PPC Pharmacokineticist and/or by the Sponsor.

Urine tests for drugs of abuse and a breath alcohol test will be performed on all subjects at each study period check-in. In addition, urine hCG testing will be performed on all female subjects at each study period check-in.

Clinical staff reserves the right to conduct random testing (urine drugs of abuse, urine hCG [females only], or breath alcohol) on any subject at any time during the study to ensure subject compliance and/or safety.

Any subjects with a positive test for urine drugs of abuse, or breathe alcohol or urine hCG (females only) will be withdrawn from the study immediately.

## 11.2 FOOD AND FLUID INTAKE

The day before the study (Day -1), subjects must arrive at clinical facility by 21:00. Subjects will

remain fasted at least 10 hours before dosing and a minimum of 4 hours thereafter. Subjects will be given standardized meals and caffeine/methylxanthine-free beverages at scheduled times. Meals will be served at approximately 4 and 10 hours after dosing on Day 1, and any other food is prohibited. Meals and beverages during confinement will be identical (if feasible) for each study period.

Water will be prohibited 1 hour prior to dosing and restricted until 2 hour after inhalation. No fluids other than water and those served for administration/with meals will be permitted during the confinement.

## 11.3 VITAL SIGNS MEASUREMENTS

In the interest of subject safety, staff will monitor vital signs (BP, PR, and temperature) at pre-dose and at 0.5, 16 and 24 hours post-dose in each study period.

Pre-Dose and Post-Dose:

All subjects with vital signs outside of acceptable range of systolic blood pressure between 90-139 mmHg, inclusive, diastolic blood pressure between 50-90 mmHg, inclusive, and pulse rate between 50-100 bpm, inclusive, will have their vital signs repeated up to two times. If vital signs are still outside of acceptable range Principal Investigator/Sub-Investigator will determine appropriate course of action.

Additional vital signs measurements will be taken if deemed necessary by the Principal Investigator/Sub-Investigator. Blood draws will take precedence over vital signs measurements and other scheduled activities, should a timing conflict arise unless deemed necessary by the Principal Investigator/Sub-Investigator.

## 11.4 CHEST X-RAY AND ECG MONITORING

Chest X-ray and ECG measurements will be performed at screening. For each period, Chest X-ra**y and** ECG measurements are not required unless deemed necessary by the Principal Investigator/Sub-Investigator.

## 11.5 ADDITIONAL TESTING

Additional tests are not required during the study unless deemed necessary by the Principal Investigator/Sub-Investigator.

## 11.6 DOSING

Subjects will take their assigned formulation, designated by the randomization scheme, after at least a 10-hour fasting period at their scheduled time-point.

Two puffs (eq. to albuterol 180 mcg) of test product and reference product will be inhaled per orally. The investigational product will be inhaled with adequate time intervals between subjects to ensure correct blood sampling.

## 11.7 PHYSICAL ACTIVITY

Subjects will stay awake and remain seated in an upright position for the first 4 hours following drug administration, and allowed to rise under supervision only for brief periods of time, in order to comply with study-related activities and to use the washroom. After the first 4 hours they will be allowed to ambulate freely within the clinic. However, if a medical event (i.e. AE) occurs, subjects may be placed in an appropriate position at any time. Subjects will be required to abstain from strenuous activities for the duration of the study period(s).

## 11.8 BLOOD SAMPLING SCHEDULE, SAMPLE COLLECTION, PROCESSING AND STORAGE

Samples will be collected through an indwelling cannula (if possible) placed in a vein. The pre-dose samples will be collected prior to drug dosing. Intravenous indwelling cannula would be kept in place up to 24 hours post-dose by injecting adequate amount but not more than 0.5 ml of normal saline solution during the collection of multiple samples. In such case, the blood sample would be collected after discarding the first 0.5 ml of blood from the tubing. Blood may also be withdrawn by a fresh clean venipuncture either by using sterile syringe and needle or disposable sterilized needle and vacutainer if the cannula is blocked.

If the blood sample collection time coincides with the other study events like vitals, subject well-being questionnaire and meal, the sequence of the events would be followed as: blood sample collection / vitals > subject well-being questionnaire > meal / water.

During the study, blood sample are collected from vein. Subject may suffer the common AE with donating blood, including vasovagal syncope (including temporary weakness, dizzy and nausea) and ecchymoma.

| | |
|---|---|
| Number of Samples | For each subject, the total number of blood draws will be 44 (22 samplings x 2 periods). |
| Total Volume of Blood (for all periods, including approximately 20 ml for pre-, and post-study procedures) | 7 ml of venous blood samples will be collected according to time-point schedule. The total volume of blood withdrawn will be approximately 328 ml, (Up to 10 ml for screening, approximately 308 ml for the two periods and up to 10 ml for post study laboratory test at the end of last period). |
| Blood Sampling Time Points | 0-hour (Pre-dose), and at 2, 5, 10, 15, 20, 30, 45 minutes, and 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 3, 4, 6, 8, 12, 16 and 24 hours post-dose in each study period. |

Type of specimens: plasma

Each blood sample will be collected into a pre-labeled tube containing an applicable anti-coagulant (e.g., heparin sodium or EDTA, depending on the analytic methods to be used). The label includes the trial number, random number, sampling time point, and study period number. The samples collected at each time point will be centrifuged (1900g and 4℃ for 10 minutes or other applicable conditions) to separate the plasma from the whole blood within 30 minutes after drawing the blood samples from the subjects.

The separated plasma will be aliquoted into two batches (if feasible), transferred to appropriately labeled tubes, and then stored in a freezer with a temperature of -20℃ or lower at the clinical facility. After the collection and centrifugation procedures, the samples will be maintained in an ice-bath container until stored in the freezer at the clinical facility.

The time between the blood centrifugation and the freezer storage should, in general, not exceed 1 hour. However, exception can be made to allow the above processing time up to 2 hours if the prolonged time period will not interfere with the stability of the analyte(s).

The first of the plasma samples will be packaged with dry ice and delivered from the clinical facility to bioanalytical lab with temperature recording. This first batch will be stored in a freezer with a temperature of -20℃ or lower at the bioanalytical lab until further analysis; the other batch as

back-up will be stored in the freezer of clinical facility and will be delivered separately thereafter if required.

### 11.9 HEALTHY STATUS MONITORING

Health monitoring will be conducted throughout the study or as needed. AE will be reported and monitored after the first dose of the study drug.

### 11.10 POST-STUDY TESTS

An exit physical examination will be conducted upon completion of the study or after withdrawal/dismissal of a subject from the study, where possible.

Within 7 days after completion of the clinical part, a clinical laboratory tests (hematology, biochemistry and urinalysis), as per section 9.2 Clinical Laboratory Assessment, will be performed in order to determine possible changes in the subject's state of health. Study personnel should contact those subjects who do not come back for the post study examinations within a week, and then a 3-day grace period will be given. The subjects will be considered as lost to follow-up after the grace period, and all communication should be recorded. In addition, urine hCG testing will be performed on all female subjects at post-study.

### 11.11 SAMPLE SHIPMENT

The samples from all subjects will be delivered to the analytical facility packed on dry ice. All shipments will be accompanied by an inventory list and delivered to the analytical laboratory. Clinical personnel will notify the analytical laboratory prior to shipment by phone, fax or e-mail.

## 12. ADVERSE EVENT

PPC has established SOP in conformity with regulatory requirements to ensure the timely, accurate, and complete reporting of safety information. This study will collect PTE and AE after subjects provide written consent in the ICF. Only AE occur after first dosing will be analyzed for safety assessment.

### 12.1 ADVERSE EVENT RECORDING AND FOLLOW-UP

Subjects will be instructed to inform clinical personnel of any untoward medical symptoms and/or events that may arise during the course of the study.

Prior to the subsequent study period, subjects will be questioned concerning symptoms that may have occurred after the previous administration of the study drug(s). The incidence, severity and duration of all AE will be recorded according to the following scale:

| | |
|---|---|
| Mild | AE resulting in discomfort, but not sufficient to cause interference in normal daily activities. |
| Moderate | AE resulting in discomfort that is sufficient to cause interference in daily activities. |
| Severe | AE resulting in discomfort causing an inability to carry out normal daily activities. |

AE monitoring and reporting will be followed up until resolution or stabilization at an acceptable level and thereafter the Principal Investigator or Sub-investigator will decide the course of action.

## 12.2 ASSESSING RELATIONSHIP TO STUDY DRUG

The Principal Investigator/Sub-Investigator will assess the relationship of all adverse reactions to the drug, using the following scale:

| | |
|---|---|
| Certain: | A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemical. The response to withdrawal of the drug (de-challenge) should be clinically plausible. The event must be definitive pharmacological or phenomenological, using a satisfactory re-challenge procedure if necessary. |
| Probable/ likely: | A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows an clinically reasonable response to an withdrawal (de-challenge). Re-challenge information is not required to fulfill this definition |
| Possible: | A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear. |
| Unlikely: | A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provides plausible explanation. |
| Unrelated: | A report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified. |

## 12.3 PROCEDURES FOR REPORTING ADVERSE EVENTS

Subjects will be instructed to inform clinic personnel of AE that may arise during the course of the study. Treatment of any AE will be administered under the direction of a physician at Tamshui Mackay Memorial Hospital.

All symptoms will be recorded by clinical staff and will be reviewed by the Principal Investigator/Sub-Investigator prior to any subsequent dosing.

When appropriate, medical tests and examinations will be performed to document resolution of the event(s).

All SAE, whether or not the event is deemed drug-related, will be reported to the Sponsor by telephone within twenty-four hours of PPC's being aware of SAE, followed by a written report within seven days. PPC will be responsible for notifying the IRB and regulatory agencies, if applicable.

The following Sponsor personnel are to be contacted at the occurrence of a SAE:

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General Manager, [redacted] / Intech Biopharm Ltd.
3F., No.36, Ln. 358, Ruiguang Rd., Neihu Dist., Taipei City 114, Taiwan
ROC
Phone: +(02)7721-8877
Fax: +(02)7721-8800

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## 12.4 PREGNANCY REPORTING

If the female subject or the partner of a male subject becomes pregnant while receiving the investigational drugs or within 30 days after the completion of the last dose of study drug, a pregnancy report form should be completed and expeditiously submitted to the sponsor to facilitate the outcome follow-up. Information on the status of the mother and child will be forwarded to the sponsor. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE and will be followed as described in Section 12.

An abortion, whether accidental, therapeutic, or spontaneous, should be always reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a patient exposed to the study drug should be recorded and reported as an SAE.

## 13. BIOANALYTICAL ANALYSIS

Bioanalytical procedures will be performed according to PPC SOP.

## 13.1 ANALYTICAL PROCEDURES

Data management, quality review and reporting of study data pertaining to laboratory analysis of study data will be the responsibility of PPC.

### 13.1.1 SAMPLES TO BE ASSAYED

In general, single batch of each sample will be all analyzed for drug concentration. Samples from subjects being analyzed will be defined prior to sample analysis

### 13.1.2 ANALYTE(S) IN BIOLOGICAL MATRIX

Plasma samples will be assayed and reported at the actual sampling time points (or scheduled sampling time points) for albuterol using a validated analytical method according to the principles of FDA GLP Title 21 Part 58.

## 14. PHARMACOKINETIC AND STATISTICAL ANALYSIS

## 14.1 PHARMACOKINETIC ANALYSIS DATA SET

The data from the following subjects will be included in the final PK and statistical analysis:

1. Subjects who complete all study periods without major/suspect protocol deviation.
2. Subjects who have missed samples that have been determined prior to the start of bioanalytical analysis as not significantly impacting the overall outcome of the study.

Data from subjects who are dismissed or withdraw due to AE will not be included in the final PK and statistical analysis. The data for these subjects will be presented separately.

Any decision to exclude data from the final data set will be provided with a detailed explanation and will be properly recorded and dated.

The final data set will be defined prior to sample analysis.

## 14.2 ANALYSIS OF DATA

PK and statistical analysis will be performed on all data from all subjects in the final data set.

### 14.2.1 PHARMACOKINETIC ANALYSIS

The following PK parameters shall be estimated (where possible and appropriate) included in the PK and statistical analyses for the subjects in the final data set:

| | |
|---|---|
| $C_{max}$: | The maximal observed plasma concentration. |
| $T_{max}$: | Time when the maximal plasma concentration is observed. |
| $AUC_{0-t}$: | Area under the concentration-time curve from time zero until the last measurable concentration or last sampling time t, whichever occurs first. $AUC_{0-t}$ is estimated using the trapezoidal method. |
| $AUC_{0-\infty}$: | Area under the concentration-time curve from time zero to infinity, calculated as $AUC_{0-t} + C_{last}/\lambda$, where $C_{last}$ is the last measurable concentration. |
| $k_{el}(\lambda)$: | Terminal elimination rate constant, estimated by linear regression analysis of the terminal portion of the ln-concentration vs. time plot. |
| $T_{1/2}$: | Terminal elimination half-life, estimated as $\ln(2)/\lambda$. |
| MRT: | Mean residence time |

If a subject's pre-dose concentration is less than or equal to 5% of the $C_{max}$ value for that subject in the given period, then the subject's data without any adjustments can be included in all PK measurements and calculations. If the pre-dose value is greater than 5% of the $C_{max}$, data from that subject will be dropped from the PK and statistical analysis. Data for subjects dropped due to higher than 5% of $C_{max}$ pre-dose concentrations will be included in a separate appendix in the final study report.

During PK and statistical analyses, drug concentrations below the lower limit of quantitation (BLQ) of an assay will be considered as zero except when they occur between two non-BLQ concentrations.

Missed samples and non-reportable concentrations (e.g. quantity not sufficient) from the analytical laboratory will be treated in the PK analysis as if they had not been scheduled for collection.

The $k_{el}$, $T_{1/2}$, and $AUC_{0-\infty}$ parameters will not be estimated for plasma concentration-time profiles where the terminal linear phase is not clearly defined.

For subjects with missing or non-reportable concentrations for three or more of the last samples, only the $AUC_{0-t}$, $C_{max}$ and $T_{max}$ will be presented and included in the statistical analysis (if applicable).

### 14.2.2 STATISTICAL ANALYSIS

PK and statistical analyses will be performed using SAS® Version 9.2 or higher by PPC.

Descriptive statistics of all PK parameters (min, max, median, mean, SD and CV) will be provided for the test and reference products.

ANOVA including sequence, subjects nested within sequence, period and treatment will be performed on the log-transformed data for $AUC_{0-t}$, $AUC_{0-\infty}$ and $C_{max}$ and on the raw data for $T_{max}$, $k_{el}$ and $T_{1/2}$. $T_{max}$ will be analyzed using an additional non-parametric test (Wilcoxon test).

For albuterol, the 90% CI of the Test/Reference ratios of geometric means for $AUC_{0-t}$, $AUC_{0-\infty}$ and $C_{max}$ will be calculated based on the LSMEANS and ESTIMATE of the ANOVA.

Additional statistical and alternate tests will be performed if necessary.

### 14.2.3 MISSING DATA

During PK and statistical analyses, treatment of missing data will follow PPC's SOP.

## 14.3 BIOEQUIVALENCE CRITERIA

Bioequivalence will be demonstrated under fasting conditions if the 90% CI for the Test/Reference ratios of geometric means for $AUC_{0-t}$, $AUC_{0-\infty}$ and $C_{max}$ are completely contained within the FDA defined acceptance range of 80.00%-125.00%.

# 15. ETHICAL CONSIDERATIONS

## 15.1 BASIC PRINCIPLES

This research will be carried out in accordance with GCP as set out by the ICH, the basic principles defined in the U.S. Code of Federal Regulations (21 CFR Part 320), Guideline for GCP and the principles enunciated in the most recent version of the World Medical Association Declaration of Helsinki.

## 15.2 INSTITUTIONAL REVIEW BOARD

This Protocol and the ICF will be reviewed and approved by the IRB prior to the initiation of the study. The board is constituted and operates in accordance with ICH Harmonized Tripartite Guideline (GCP Consolidated Guideline).

## 15.3 INFORMED CONSENT FORM

The ICF will be approved by the IRB and a copy will be included in the final report. The ICF will be signed by each subject prior to the study procedure. Each subject will be provided with verbal and written information, in non-technical terms, which will describe the nature and duration of the study. Prior to signing the ICF, subjects will be allowed adequate time to consider the potential benefits and risks associated with their participation in the study. Signed and dated ICFs will be retained with the study records. Subjects/Volunteers will be provided a copy of their signed and dated ICF.

## 15.4 REVISIONS AND/OR AMENDMENTS TO THE PROTOCOL

Revisions and/or amendments to the protocol must be documented and approved by the Principal Investigator and Sponsor. If the revision/amendment will affect subject safety and/or study design, then the amendment will be re-submitted to the IRB for approval. Administrative changes (i.e., change of analytical facility, typographical errors, discrepancies, clarifications) will also be submitted to the IRB. A copy of the IRB's approval documents will be included in the final report.

For revisions or amendments to the protocol that substantially alter the study design after initiation of the study, the Principal Investigator and Sponsor will decide whether a revised ICF will be needed for continued participation.

It is the Sponsor's responsibility to submit, or to assign responsibility to submit, all revisions and amendments to the appropriate regulatory authorities when necessary.

If an amended or revised version of the ICF is introduced during the study, each subject's further consent should be obtained.

## 15.5 INVESTIGATOR RESPONSIBILITIES

The Principal Investigator is responsible for ensuring that the clinical study is performed in accordance with the protocol, the current revision of the Declaration of Helsinki, ICH GCP guidelines and applicable regulatory requirements.

## 15.6 STUDY COMPLETION/TERMINATION

PPC and/or the Sponsor reserve the right to terminate the study at any time, and for any reason.

## 15.7 SPONSOR VISITS

The Sponsor is encouraged to visit PPC and clinical facility, if desired, and at their convenience. The Principal Investigator and staff will provide, if requested, all source documents and/or other study-related documents. The Principal Investigator will maintain regular written and telephone communication with the Sponsor.

## 15.8 CONFIDENTIALITY

The information in this study protocol is confidential. This document contains trade secrets and commercial information that is confidential and may not be disclosed to third parties (except to the IRB, TFDA, FDA, and/or relevant regulatory agencies). These restrictions will apply as well to all future communications if deemed privileged or confidential.

Sponsor, study monitors, auditors, the IRB and applicable regulatory authorities will be granted direct access to the subject's original medical records for verification of clinical trial procedure and/or data, without violating the confidentiality of the subject, to the extent permitted by applicable laws and regulations and that, by signing a written ICF, the subject or the subjects legally acceptable representative authorizes such access.

All documentation collected by the Sponsor or by PPC and clinical facility personnel will be kept confidential. The name and identity of the subjects will remain confidential. If documents containing the subjects' names are photocopied, the name will be redacted from the photocopied version.

# 16. DATA MANAGEMENT/RECORD KEEPING

## 16.1 SOURCE DATA

All data will be recorded in accordance with GCP, to ensure accuracy, completeness, legibility, and timeliness of the data reported. All data will be recorded directly on the source documents and will be considered source data. PPC standard CRF will be supplied. All the evaluations conducted in this study for each subject will be recorded in the CRF. A hardcopy of each CRF prepared using a data management system with an audit trail, signed by the investigator, will be regarded as the original**.** All raw data generated in connection with this study, together with the original copy of the final report, will be retained.

Electronic data capture software TrialOne will be available in this study. Partial data will be entered directly onto the CRF to be considered to be source data (e.g. tracking of biosample/data collection, vital signs, investigational drugs administration, meals/fluids uptake status, etc.)

## 16.2 QUALITY OF DATA

All source documents and laboratory reports will be Quality Control reviewed to ensure accuracy and completeness. AE will be reviewed and assessed for severity and causality by the Principal Investigator/Sub-Investigator. Specific processes of the study, its source documentation and any reports (if applicable) will be audited by the Quality Assurance unit of PPC.

## 16.3 RETENTION OF DOCUMENTS

All records and documents pertaining to the study will be retained by PPC for at least 2 years after the date of approval of the application or at least 5 years after the date of study termination, and will be available for inspection by the Sponsor and/or Regulatory Agencies.

# 17. REFERENCES

1. US FDA label of PROAIR HFA (albuterol sulfate) inhalation aerosol (02/2019)