**Statistical Analysis Plan**

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# A Phase IIa, Open-Label, Repeat-Dose Clinical Trial to Evaluate the Pharmacokinetics, Safety and Tolerability of Aclidinium Bromide / Formoterol Fumarate Fixed Dose Combination Administered Twice-Daily by Inhalation in Chinese Patients With Moderate to Severe Chronic Obstructive Pulmonary Disease

# A Phase IIa, Open-Label, Repeat-Dose Clinical Trial to Evaluate the Pharmacokinetics, Safety and Tolerability of Aclidinium Bromide / Formoterol Fumarate Fixed Dose Combination Administered Twice-Daily by Inhalation in Chinese Patients With Moderate to Severe Chronic Obstructive Pulmonary Disease

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# LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this Statistical Analysis Plan (SAP).

| Abbreviation or special term | Explanation |
|---|---|
| AB/FF 400/12 | aclidinium bromide/formoterol 400/12 μg |
| AE | Adverse event |
| ALP | Alkaline Phosphatase |
| ALT | Alanine Aminotransferase |
| AM | Morning (antemeridiam) |
| AST | Aspartate Aminotransferase |
| ATC | Anatomical Therapeutic Chemical |
| AUC | Area under curve (pg.h/mL) |
| $AUC_{\tau}$ | Area under the plasma concentration curve (pg.h/mL) during the first dosing interval, τ (first dose) |
| $AUC_{last}$ | Area under the plasma concentration-curve from time zero to the time of last quantifiable analyte concentration (pg.h/mL) |
| $AUC_{ss,\tau}$ | Area under the plasma concentration curve during the dosing interval, τ at steady state (pg.h/mL) |
| BID | Twice daily |
| BLQ | Below the lower limit of quantification |
| BMI | Body Mass Index |
| $C_{av}$ | Average plasma concentration (pg/mL) |
| CK | Creatine kinase |
| CL/F | Apparent plasma clearance for parent drug (L/h) |
| $C_{max}$ | Observed maximum concentration (pg/mL) |
| $C_{min}$ | Observed minimum concentration (pg/mL) |
| COPD | Chronic Obstructive Pulmonary Disease |
| CRF | Case Report Form |
| CSP | Clinical Study Protocol |
| CSR | Clinical Study Report |
| $C_{ss,max}$ | Observed maximum concentration, taken directly from the individual concentration-time curve at steady state (pg/mL) |
| $C_{ss,min}$ | Observed minimum concentration, taken directly from the individual concentration-time curve within a dosing interval (pg/mL) |

| Abbreviation or special term | Explanation |
|---|---|
| CV% | Geometric coefficient of variation |
| DDE | Drug Dictionary Enhanced |
| DPI | Dry Powder Inhaler |
| DRM | Data Review Meeting |
| ECG | Electrocardiogram |
| eCRF | Electronic Case Report Form |
| FEV1 | Forced Expiratory Volume in one second |
| %Fluctuation | Fluctuation index |
| FVC | Forced vital capacity |
| GGT | Gamma-glutamyl transferase |
| GOLD | Global Initiative for Chronic Obstructive Lung Disease |
| Hb | Haemoglobin |
| HBsAg | hepatitis B surface antigen |
| HCV | Hepatitis C virus |
| HIV | Human immunodeficiency virus |
| ICF | Informed Consent Form |
| $\lambda_z$ | Terminal rate constant ($h^{-1}$) |
| LLN | Lower Limit of Normal |
| LLOQ | Lower Limit of Quantification |
| MedDRA | Medical Dictionary for Regulatory Activities |
| $MRC_{max}$ | Metabolite to parent ratio for $C_{max}$ |
| $MRAUC_{\tau}$ | Metabolite to parent ratio for $AUC_{\tau}$ |
| mmHg | Millimeters of mercury |
| msec | Milliseconds |
| n obs | Number of data points included in the log-linear regression analysis |
| NA | Not applicable |
| ND | Not determined |
| NR | Non-reportable |
| PCS | Potentially Clinically Significant |
| PDS | protocol deviations specifications |
| PK | Pharmacokinetics |
| PKS | Pharmacokinetic analysis set |

| Abbreviation or special term | Explanation |
|---|---|
| PM | Evening (Post meridiem) |
| pMDI | pressurised metered-dose inhaler |
| PPS | Per protocol set |
| PR interval | Duration in milliseconds from the beginning of wave P to onset of ventricular depolarization (Q and R) |
| PT | Preferred Term |
| QRS interval | Onset of ventricular depolarization |
| QT interval | Duration in milliseconds from the beginning of Q wave to the end of the T wave |
| QTc interval | QT interval corrected by heart rate |
| QTcB interval | QT interval corrected, Bazett formula |
| QTcF interval | QT interval corrected, Fridericia formula |
| Rac($AUC_\tau$) | Accumulation ratio for $AUC_\tau$ |
| Rac($C_{max}$) | Accumulation ratio for $C_{max}$ |
| Rac($C_{min}$) | Accumulation ratio for $C_{min}$ |
| RR | Respiratory rate |
| RSq adj | Adjusted coefficient of determination for calculation of $\lambda_z$ |
| SAE | Serious Adverse Event |
| SAF | Safety analysis set |
| SAP | Statistical Analysis Plan |
| SD | Standard Deviation |
| SOC | System Organ Class |
| SOP | Standard Operating Procedure |
| $t_{½\lambda z}$ | Terminal half-life (h) |
| TEAE | Treatment-Emergent Adverse Event |
| TESAE | Treatment-Emergent Serious Adverse Event |
| TFLs | Tables, Figures and Listings |
| $t_{max}$ | Time to maximum concentration (h) |
| $t_{ss,max}$ | Time to maximum concentration (h), taken directly from the individual concentration-time curve at steady state |
| ULN | Upper Limit of Normal |
| $V_z/F$ | Apparent volume of distribution for parent drug at terminal phase (L) |
| WHO | World Health Organisation |

# AMENDMENT HISTORY

| Date | Brief description of change |
|---|---|
| 17 October 2017 | Original Document (Final 1.0) |
| 03 July 2018 | Updated for formatting, PK trough concentration figures, concomitant medication definition and Spirometry revisions (Final 2.0) |

# 1. STUDY DETAILS

## 1.1 Study objectives

### 1.1.1 Primary objective

The primary study objective is to evaluate the pharmacokinetics (PK) of aclidinium bromide, its metabolites LAS34850 and LAS34823 and formoterol after administration of aclidinium bromide/formoterol 400/12 µg twice-daily (BID) for 5 days in Chinese patients with stable moderate to severe Chronic Obstructive Pulmonary Disease (COPD). The variables are given in Section 3.1.

### 1.1.2 Safety objectives

Secondary objectives are to evaluate the safety, and tolerability of aclidinium bromide/formoterol 400/12 µg twice-daily (BID) administered for 5 days in Chinese patients with stable moderate to severe COPD. The variables are given in the Section 3.2.

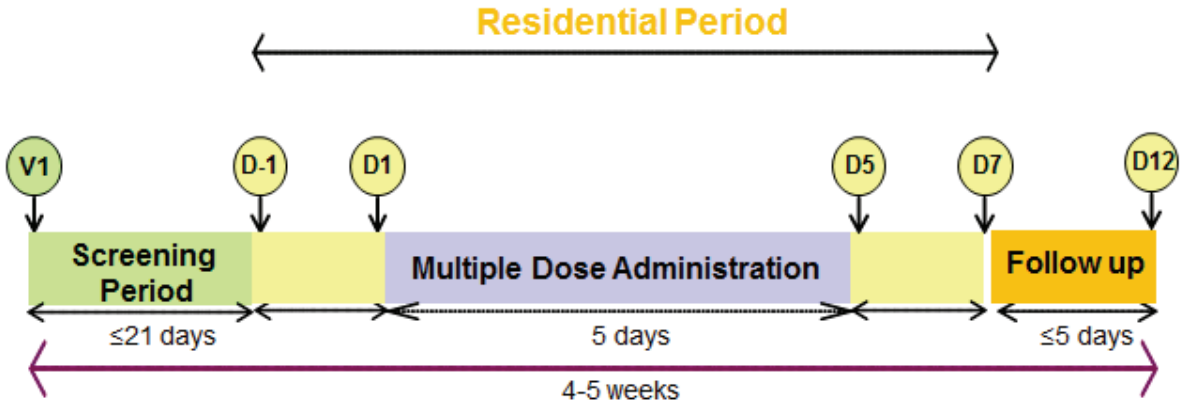
## 1.2 Study design

This is a Phase IIa, single centre, open-label, repeat-dose study to investigate the PK, safety and tolerability of single and multiple twice daily doses of inhaled aclidinium bromide/formoterol 400/12 µg (hereafter referred to as AB/FF 400/12) in Chinese male and female subjects with stable moderate to severe COPD.

Twenty COPD Chinese subjects of 40 years of age or older, will participate in the study. The target population is based on current or former smokers with a smoking history of ≥10 pack-years, aged ≥40, COPD subjects with stable moderate to severe airflow obstruction (post-bronchodilator FEV1 ≥30% and <80% and post-bronchodilator FEV1/FVC <70%). Refer to the clinical study protocol (CSP) for the full list of inclusion and exclusion criteria.

The study will consist of a Screening Visit (to check for eligibility) conducted after signature of the Informed Consent Form (ICF) and maximum 21 days before the first dose of AB/FF 400/12, followed by a residential period from Day -1 to Day 7, of which treatment period is scheduled between Day 1 and Day 5 and a follow up period of 5 days after discharge. The whole study duration for each subject is expected to last approximately 5 weeks. The study flow chart for each treatment sequence is shown in Figure 1 below.

**Figure 1 Study flow chart**




Subjects who meet all criteria at screening will be admitted to the study center on Day -1, the day prior to first AB/FF 400/12 administration. On Day 1 through Day 4, they will receive one inhalation of AB/FF 400/12 µg BID. The morning dose will be administered at approximately 08:00 hours, and the evening dose 12 hours after the morning dose (at approximately 20:00 hours) and the 12-hour PK sample collection.

On Day 5, at approximately 08:00 hours, subjects will receive one inhalation of AB/FF 400/12 µg. There will be no PM dose administered. Subjects will be discharged on Day 7, 48 hours after last AB/FF 400/12 administration on Day 5 and after the completion of the 48-hour PK sample collection and safety assessment on Day 7.

Subjects who prematurely discontinue from the study (withdrawal) will participate in a Premature Discontinuation Visit.

Rescue medication (salbutamol pMDI 100 µg/puff) is to be provided to the subjects at Visit 1 (Screening), and can be re-supplied throughout the study as necessary according to use.

Pharmacokinetic assessments will be conducted at specific time-points in the clinical unit during the residential period (from Day -1 to Day 7). Safety assessments will be performed at Screening, during the treatment period and follow-up or premature discontinuation visits, as presented in Table 1 below.

## Table 1 Schedule of Assessments

| Procedure | Screening Day -21 to Day -2 | Day -1 | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | Follow-Up Visit Days 8-12[c] or Premature Discontinuation[2] |
|---|---|---|---|---|---|---|---|---|---|---|
| Informed consent | X | | | | | | | | | |
| Demographics | X | | | | | | | | | |
| Inclusion/Exclusion criteria | X | X | | | | | | | | |
| Medical/surgical and COPD history | X | | | | | | | | | |
| Prior and Concomitant Medications[3] | X | X | X | X | X | X | X | X | X | X |
| Spirometry[12] | X | | | | | | | | | |
| Inhaler Training | X | X | | | | | | | | |
| Admission to Study Center | | X | | | | | | | | |
| Meals (provided by study center)[13] | | X | X | X | X | X | X | X | X | |
| Discharge from the Study Center[4] | | | | | | | | | X | |
| Outpatient Visit | X | | | | | | | | | X |
| Physical examination[5] | X | X | | | | | | | | X |
| 12-lead ECG and blood pressure [6] | X | X | X | X | X | X | X | | | X |
| Laboratory Tests[7] | X | X | | | | | | | | X |
| Pregnancy Test[8] | X | X | | | | | | | | X |
| Serology[9] | X | | | | | | | | | |
| Drug-of-abuse and Alcohol Screen | X | X | | | | | | | | |
| Dosing of AB/FF 400/12[10] | | | X | X | X | X | X | | | |
| PK Blood samples[11] | | | X | X | X | X | X | X | X | |
| Adverse Event review | X | X | X | X | X | X | X | X | X | X |

AE = adverse event; AM = morning; BMI = body mass index; COPD= Chronic Obstructive Pulmonary Disease; DPI = dry powder inhaler; ECG = electrocardiogram; e
form; HIV = human immunodeficiency virus; ICF = Informed Consent Form; PK = pharmacokinetic; PM = evening

1. If the subject needs additional time to washout any prior medications, the ICF must be provided before Visit 1. Subjects must discontinue medications after informed c
2. The premature discontinuation visit/assessments will be performed as soon as possible after subject discontinuation.
3. Any treatment administered during the 2 weeks before the ICF signature and during the Run-in Period must be recorded into the eCRF to ensure a proper washout of a
From Visit 1 (Screening) onwards, any new treatments taken or any change to the ongoing medications during the participation in the study, apart from AB/FF 400/12, w
eCRF by the investigator or designee.
4. Subjects will be discharged from the study center after the completion of the PK blood sample collection and safety assessments.
5. Height and weight will be measured and BMI will be calculated at Visit 1 (Screening) only.
6. Safety ECGs (including heart rate) and blood pressure will be collected at Visit 1 (Screening), at Visit 2 (from Days -1 on admission to Day 5) and at the Follow-up V
Discontinuation Visit. On Visit 2 (from Day 1 to Day 5) the standard 12-lead ECG will be performed at 0h morning pre-dose and at 2 hours (± 15 min) post morning dos
after the subject has rested quietly in a seated position for at least 5 minutes. If blood sampling, blood pressure assessments, and ECG recordings are scheduled at the san
sequence will be followed: 1) ECG recording; 2) blood pressure assessments; and 3) blood sampling, assuring that PK blood sampling occurs on the time-point. If an EC
time as a meal, the ECG must be obtained first.
7. Includes blood, serum, and urine samples. Subjects are required to fast for at least 8 hours prior to the collection of specimens.
8. For women of childbearing potential, a serum pregnancy test will be done at visit 1 (Screening); on Day -1 (Visit 2), and at the Follow-up visit or Premature Discontin
must be available and reviewed prior to dosing on Day 1 on Visit 2.
9. Serum for anti-hepatitis C virus, hepatitis B surface antigen and anti-HIV type 1. Results must be available and reviewed prior to dosing on Day 1 (Visit 2).
10. On Day 5, only the morning dose of aclidinium bromide/formoterol 400/12 µg will be administered; no evening dose will be administered. At approximately 08:00 h
receive one inhalation of aclidinium bromide/formoterol 400/12 µg via the Genuair® multidose DPI.
11. PK blood samples will be collected on Day 1 of Visit 2 at 0 hour (approximately 15 minutes prior to the morning dose), 5 minutes, 15 minutes, 30 minutes, 1 hour, 1
hours, 6 hours, 8 hours, and 12 hours post the morning dose (the 12-hour sample will be collected 5 minutes before the evening dose).
On Days 2-4 of Visit 2, PK blood samples will be collected at 0 hour (approximately 5 minutes prior to the morning and evening dose).
On Day 5 of Visit 2, PK blood samples will be collected at 0 hour (approximately 5 minutes prior to the morning dose), 5 minutes, 15 minutes, 30 minutes, 1 hour, 1.5 h
hours, 6 hours, 8 hours, 12 hours, 24 hours, 36 hours and 48 hours post morning dose. Time window allowance for all PK time-points are indicated in Section 2.2.
12. Administer inhaled salbutamol (100 µg x 4 puffs) through a spacer device at a minimum of 10 minutes after the previous spirometry test. Ten (10) to 15 minutes afte
perform the 1 set of spirometry forced manoeuvres again.
13. No breakfast will be served on Day 1 and Day 5.

## 1.3 Number of subjects

Due to the exploratory nature of the study the sample size is not based on formal statistical considerations. The sample size is based on experience from previous similar Phase I and Phase II studies with aclidinium bromide and formoterol.

A total of 20 subjects are deemed sufficient to ensure appropriate characterization of the PK of aclidinium bromide, LAS34823, LAS34850 and formoterol.

# 2. ANALYSIS SETS

Subject dispositions will be summarized using All Subjects Screened. Descriptive statistics for demographics and other baseline characteristics as well as safety analyses will be provided using the safety population. PK analysis will be done using the PK population.

## 2.1 Definition of analysis sets

### 2.1.1 All Subjects Screened

All subjects who have signed the Informed Consent form.

### 2.1.2 Safety analysis set (SAF)

All subjects who receive at least one dose of AB/FF 400/12 will be included in the safety population.

### 2.1.3 Pharmacokinetic analysis set (PKS)

All subjects who took at least one dose of AB/FF 400/12 and have at least one of the parameters ($C_{max}$, $C_{ss,max}$, AUC, $AUC_{last}$ or $AUC_{ss,\tau}$) evaluable and are assumed not to be affected by factors such as important protocol deviations. All protocol deviations that occur during the study will be considered for their severity/impact and will be taken into consideration when subjects are assigned to the PK analysis sets.

The exclusion of any subjects from the PK analysis set will be documented by the PK scientist including the reason(s) for exclusion.

The available concentration data and PK parameter data for any subjects excluded from the PK analysis set will be listed only, and presented in the individual figures of concentration time plots.

## 2.2 Protocol deviations

The criteria for the assessment and reporting of protocol deviations will be stipulated in a separate study specific protocol deviation specification document.

Important deviations from the protocol may lead to the exclusion of subjects from the PK analysis set. Data may be excluded from summary statistics and inferential analysis of concentrations at a specific time-point without excluding the subject from the PKS.

Important deviations and analysis sets will be defined before database hard lock at the data review meeting.

Important deviations will include the following:

- Violation of inclusion and/or exclusion criteria that may influence PK analysis;
- Administration of prohibited concomitant medications that are expected to influence the measurement of the PK endpoints;
- Missing dose, incomplete or interrupted administration.

Table 2 shows important protocol deviations that affect the assignment of subjects and/or specific data points to analysis sets.

The separate protocol deviations specifications (PDS) document provides details on specific checks and the formatting for reporting deviations.

**Table 2 Important protocol deviations and analysis set classification**

| | Excluded from analysis set | |
|---|---|---|
| **Event description** | **SAF** | **PKS** |
| Subject met this exclusion criterion: Positive results for drugs of abuse at Visit 1 (Screening). | No | Yes$^{+++}$ |
| Subject met this exclusion criterion: Taken any medication within 14 days before the first dose of AB/FF 400/12, or hormonal drug products and traditional Chinese medicines within 30 days before the first dose of AB/FF 400/12, with the exception of allowed medications listed in Section 7.9. | No | Yes$^{+++}$ |
| Subject met this exclusion criterion: Have any clinical condition that might affect the absorption, distribution, biotransformation, or excretion of aclidinium bromide/formoterol fumarate. | No | Yes$^{+}$ |
| Subject met this exclusion criterion: Have consumed any grapefruit-containing products within 48 hours or alcohol within 72 hours before Day -1 at Visit 2. | No | Yes$^{+++}$ |
| Subject has missing date/time for PK blood sampling | No | Yes$^{+++}$ |
| Subject has missing sample for PK blood sampling | No | Yes$^{++}$ |
| Subject received prohibited medication | No | Yes$^{+++}$ |
| Subject did not adhere to dietary restrictions prior to or after dosing per protocol specification | No | Yes$^{+++}$ |
| Subject is missing dosing information (including completely missing record, missing date/time, dose) | No | Yes$^{+++}$ |
| Subject received incorrect treatment. | No | Yes$^{+++}$ |
| Other protocol deviations | Yes$^{++}$ $^{+}$ | Yes$^{+++}$ |

+ Assessed at DRM and transcribed to protocol deviations log if assessed as important. ++Excluded from the specific time-point only.

+++ To be confirmed at the DRM; time-point specific or global PPS/PKS exclusion.

# 3. PRIMARY AND SECONDARY VARIABLES

## 3.1 Pharmacokinetic variables

Serial blood samples for PK assessments of aclidinium bromide, its metabolites (LAS34823 and LAS34850) and formoterol in plasma will be collected at the following time-points:

- Day 1: pre-dose, 5, 15, 30 min and 1h, 1.5h, 2, 3, 4, 6, 8 and 12h (12 time-points)
- Day 2-4: pre-morning and pre-evening dose (6 time-points)
- Day 5: pre-dose, 5, 15, 30 min and 1h, 1.5h, 2, 3, 4, 6, 8, 12, 24, 36 and 48 hours (15 time-points)

The recommended time window allowance for PK blood collection is the following:

Day 1 and Day 5:

- Pre-dose: -30 min for Day 1 and -10 min for Day 5
- 5-30 min: ± 1 min
- 1-6 hours: ± 5 min
- 8-12 hours: ± 10 min
- 24-48 hours: ± 30 min

Days 2 to 4:

- Pre-dose: - 10 min

Where possible, the following PK parameters will be calculated for aclidinium bromide, its metabolites LAS34823 and LAS34850 and formoterol:

<u>Day 1</u>

- $C_{max}$ – Observed maximum concentration (pg/mL), taken directly from the individual concentration-time curve (first dose)
- $t_{max}$ – Time to maximum concentration (h), taken directly from the individual concentration-time curve (first dose)
- $C_{min}$ – Minimum plasma drug concentration (pg/mL) at the end of the dosing interval (first dose)

- $AUC_{last}$ – Area under the plasma concentration-curve from time zero to the time of last quantifiable analyte concentration (pg.h/mL)

- $AUC_{\tau}$ – Area under the plasma concentration curve during the first dosing interval, $\tau$ (first dose) (pg.h/mL)

- $MRC_{max}$ – Metabolite to parent ratio for $C_{max}$, estimated by dividing the metabolites $C_{max}$ by the parent $C_{max}$

- $MRAUC_{\tau}$ – Metabolite to parent ratio for $AUC_{\tau}$, estimated by dividing the metabolites $AUC_{\tau}$ by the parent $AUC_{\tau}$

Day 5

- $C_{ss,max}$ – Observed maximum concentration (pg/mL), taken directly from the individual concentration-time curve at steady state

- $C_{ss,min}$ – Observed minimum concentration (pg/mL), taken directly from the individual concentration-time curve within a dosing interval on Day 5

- $t_{ss,max}$ – Time to maximum concentration (h), taken directly from the individual concentration-time curve at steady state

- $\lambda_z$ – Terminal rate constant ($h^{-1}$), estimated by log-linear least square regression of the terminal part of the concentration-time curve

- $t_{½\lambda z}$ – Terminal half-life (h), estimated as $(\ln 2)/\lambda_z$

- $AUC_{ss,\tau}$ – Area under the plasma concentration curve during the dosing interval, $\tau$ at steady state (pg.h/mL)

- CL/F* – Apparent plasma clearance for parent drug estimated as dose divided by $AUC_{ss,\tau}$ (L/h)

- $V_z$/F* – Apparent volume of distribution for parent drug at terminal phase (L), estimated by dividing the apparent clearance (CL/F) by $\lambda_z$

- $C_{av}$ – Average plasma concentration (pg/mL) during a dosing interval, estimated as $AUC_{ss,\tau}$ /12

- %Fluctuation – Fluctuation index during a dosing interval estimated as $100*(C_{max}-C_{min})/C_{av}$ (%)

- $Rac(C_{max})$ – Accumulation ratio for $C_{max}$ estimated as $C_{ss,max}$ on Day 5/ $C_{max}$ on Day 1

- $Rac(C_{min})$ – Accumulation ratio for $C_{min}$ estimated as $C_{ss,min}$ on Day 5/ $C_{min}$ on Day 1

- Rac($AUC_\tau$) – Accumulation ratio for AUCτ estimated as $AUC_{ss,\tau}$ on Day 5/ $AUC_\tau$ on Day 1

- $MRC_{max}$ – Metabolite to parent ratio for $C_{ss,max}$, estimated by dividing the metabolites $C_{ss,max}$ by the parent $C_{ss,max}$

- $MRAUC_\tau$ – Metabolite to parent ratio for $AUC_{ss,\tau}$, estimated by dividing the metabolites $AUC_{ss,\tau}$ by the parent $AUC_{ss,\tau}$

The following diagnostic parameters of the plasma PK analysis will be listed, but not summarised:

- $\lambda_z$ interval – Lower and upper limit of the time interval (h) of the log-linear regression to determine $\lambda_z$

- Rsq adj – Adjusted coefficient of determination for calculation of $\lambda_z$

- $\lambda_z$,N – Number of data points included in the log-linear regression analysis

Additional parameters may be determined as appropriate.

*Only for Aclidinium bromide and formoterol

## 3.2 Safety variables

Safety and tolerability variables will include the following categories of variables:

- Adverse events (AEs) and Serious adverse events (SAEs)

- 12-lead Electrocardiogram (ECG) parameters

- Blood pressure parameters

- Laboratory parameters

### 3.2.1 Adverse events

The definitions of AEs and SAEs are given in Sections 6.1 and 6.2 respectively of the CSP.

Adverse events will be recorded from the time of informed consent up to the follow-up visit or premature discontinuation visit.

### 3.2.2 12-lead ECG parameters

A 12-lead safety ECG will be obtained at the following time-points:

- Screening

- Day -1
- Day 1 to Day 5; at pre-dose, 2 h post-dose
- Follow-up or Premature Discontinuation visit in case of early termination.

At each time-point above, the Investigator will provide an overall interpretation of the safety ECG as normal, abnormal or borderline, and the result recorded in the CRF. If abnormal, the clinical significance (Yes or No), will also be recorded on the CRF.

The parameters determined will be heart rate, RR interval, PR interval, QRS interval, QT interval, QTc interval (including QTcB and QTcF).

### 3.2.3 Blood pressure

Measurements of blood pressure will be performed at the following time-points:

- Screening
- Day -1 to Day 5; at pre-dose, 2 h post-dose
- Follow-up or Premature discontinuation visit in case of early termination.

The following variables will be measured at each time-point:

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)

### 3.2.4 Clinical laboratory variables

Blood and urine samples for determination of clinical chemistry, haematology and urinalysis will be taken at the following time-points:

- Screening
- Day -1
- Follow-up or Premature discontinuation visit in case of early termination.

Serology variables will be assessed at the Screening visit only.

For women of childbearing potential only, a serum pregnancy test will be done at Screening, Day -1, and at the Follow-up/Premature Discontinuation visit.

#### 3.2.4.1 Hy's Law

Hy's law provides an assessment of whether a drug is at high risk of causing a fatal drug-induced liver injury (DILI) when given to a large population.

During the course of the study the investigator remains vigilant for increases in liver biochemistry and is responsible for determining whether a subject meets Potential Hy's Law (PHL) criteria at any point during the study.

A review and assessment of cases to determine whether PHL cases agree with Hy's Law (HL) criteria is performed. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than DILI caused by AB/FF 400/12.

Potential Hy's Law (PHL):

- At least one event of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 3x upper limit of normal (ULN), together with total bilirubin (TBL) ≥ 2xULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

Hy's Law (HL):

- AST or ALT ≥ 3x ULN, together with TBL ≥ 2xULN, where no other reason, other than AB/FF 400/12, can be found to explain the combination of increases, e.g. elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (i.e. on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

## 3.3 Other Variables

Meal consumption data are collected but not included in the CSR.

### 3.3.1 Demographic and baseline characteristics

The following demographic and baseline characteristics variables will be derived at Screening:

- Age group (≤65, 66-75, 76-85, ≥85)

- Body Mass Index (BMI) is derived as continuous variable as weight in Kg divided by height in meter squared (Kg/$m^2$) and categorized (BMI Group) as: Underweight (<18.5), Normal weight (≥ 18.5 and < 25), Pre-obese (≥ 25 and <30) and Obese (≥ 30).

- History of Tobacco Use

Duration of smoking (years) is calculated as follows:

For a former smoker:

$$Duration\ of\ Smoking\ =\ year\ of\ end\ date\ -\ start\ year\ +1$$

For a current smoker:

$$Duration\ of\ Smoking\ =\ screening\ year\ -\ start\ year$$

### 3.3.2 Spirometry data and COPD characteristics at baseline

Spirometry will be performed at screening, from which the following COPD Severity Stage classifications will be derived.

- COPD classification of airflow limitation based on the post-bronchodilator PFT at screening:
  - Stage I (mild): FEV1/FVC <0.70 and FEV1 >=80% predicted
  - Stage II (moderate): FEV1/FVC < 0.70 and 50% ≤ FEV1 < 80% predicted
  - Stage III (severe): FEV1/FVC < 0.70 and 30% ≤ FEV1 < 50% predicted
  - Stage IV (very severe): FEV1/FVC <0.70 and FEV1 <30% predicted

Only subjects with Stage II and Stage III are eligible to be included in the study.

**Derived spirometry parameters:**

At each time point (screening pre- and post-bronchodilation), the maximum FEV1 and FVC value will be flagged from all repetitions obtained during the spirometry tests. From these maximum values the associated derived spirometry parameters will be calculated and are given as follows:

Bronchodilator Reversibility Testing in COPD

- pre-bronchodilator FEV1/ FVC
- post-bronchodilator FEV1/FVC

Absolute bronchial reversibility value:

- $[(\text{post} - \text{bronchodilator FEV1}) - (\text{pre} - \text{bronchodilator FEV1})]$

Percent bronchial reversibility value:

- $$\frac{[(\text{post}-\text{bronchodilator FEV1}) - (\text{pre}-\text{bronchodilator FEV1})]}{(\text{pre}-\text{bronchodilator FEV1})} * 100$$

The maximum post-bronchodilator FEV1 and the derived post-bronchodilator FEV1/ FVC will be used for determining the COPD Severity Stage.

The following baseline COPD characteristics variables will be derived at Screening:

Time since diagnosis (years) is calculated as follows:

$$Time\ Since\ Diagnosis = Year\ of\ Screening - Year\ of\ COPD\ first\ diagnosed\ date + 1$$

### 3.3.3 Prior and concomitant medication

Prior medication is defined as any medication other than AB/FF 400/12 with an end date that shows that the medication ended before the 1st dose of AB/FF 400/12.

Concomitant medication is defined as any medication other than AB/FF 400/12 with a start date indicating that the medication was taken at least once after the first AB/FF 400/12 administration through the last dose day.

Any medication taken after last dose day will be classified as post-treatment medication.

A medication that started before the AB/FF 400/12 administration and continues during treatment is classified as both prior and concomitant medication. It is classified as post-treatment medication if continues after the end of treatment.

All medication will be coded using the latest version of the WHO-Drug Enhanced plus Herbal Dictionary and will be listed by subject.

All medications will be marked as allowed or prohibited (according to Table 5 of the protocol).

### 3.3.4 Drugs of abuse and alcohol

Results for drugs of abuse and alcohol will not be reported as part of the clinical study report (CSR).

### 3.3.5 Physical examination

Any abnormalities in the physical examination will be listed as part of medical history at Screening and as AEs thereafter. No separate listing of physical examination will be presented.

# 4. ANALYSIS METHODS

## 4.1 General principles

This Statistical Analysis Plan (SAP) describes the statistical analyses of demographics, baseline characteristics, concomitant medication, PK, safety and tolerability and exploratory data planned in the study protocol. All data analyses will be performed by PAREXEL, except

the derivation of PK parameters for aclidinium bromide, its metabolites LAS34823 and LAS34850 and formoterol which will be performed by Covance. SAS®version 9.3 (SAS Institute, Inc., Cary, North Carolina) will be used to create all datasets and all tables, figures and listings (TFLs).

Given the exploratory nature, no formal statistical hypothesis testing will be performed in this study. Since no formal testing is planned, and the confidence intervals (CIs) that will be calculated are only for descriptive purposes, no corrections for multiplicity will be used.

All TFLs that will be produced in the study are listed in Appendix 7.1.

Categorical variables will be summarised with counts (n) and percentages (%) and will be tabulated overall. For continuous variables, the number of non-missing observations, mean, standard deviation (SD), standard error of the mean, median, first and third quartiles, minimum and maximum will be tabulated overall. Refer to Section 4.2.7.2 for statistical analysis of the PK data. When applicable, these summaries will be provided by visit and time-point of assessment. As a rule (unless otherwise specified), mean, SD and median, will be reported to one decimal place more than the observed values, minimum and maximum with the same number of decimal places as the observed values. For PK concentrations and parameters please follow rules for standard statistics and significant figures in Section 4.2.7.2.

### 4.1.1 Handling of repeated/unscheduled measurements

Unless otherwise indicated, the following rules will apply to any repeated safety measurements for visit-based summary and analysis purposes:

- If the repeated measurement of a specific parameter occurs prior to AB/FF 400/12 administration on Day 1, then the last obtained value prior to dosing will be used in the descriptive statistics and in the calculation of changes from baseline

- If the repeated measurement of a specific parameter occurs after AB/FF 400/12 administration on Day 1, then then the closest value to the target visit day will be used in descriptive statistics and in the calculation of changes from baseline. If the values are equidistant from the scheduled visit day, the later will be used. For the follow-up or premature discontinuation visit, no target day is defined and the last (non-missing) value will be selected. If the repeated measurement of a specific parameter occurs after AB/FF 400/12 administration on Day 1 and the reason for the repeat is a technical error/device error, then the second value will be used in descriptive statistics and in the calculation of changes from baseline

- If a whole visit is repeated after AB/FF 400/12 administration on Day 1, then the repeated visit will be used in the descriptive statistics and in the calculation of changes from baseline

All measurements, both from scheduled and unscheduled visits, will be presented in the subject data listings, and in case of repeated measurements the value not selected for the analysis will be flagged in the listing.

## 4.2 Analysis and reporting

### 4.2.1 Subject disposition

Discontinuations from the study including screen failures will be listed, including date of informed consent, first and last dose, date of discontinuation and primary reason for discontinuation (inclusion and exclusion criteria not met for screen failures), and duration of treatment in days.

Subjects completing the study will be listed, including the date of informed consent, first and last dose and duration of treatment in days.

Subject disposition will be summarised overall. The tabulation will include the following information: number of subjects screened and screen-failures, number and percentage of subjects dosed, number and percentage of subjects completing the study, completed treatment and the number and percentage of subjects who were withdrawn (including reasons for withdrawal). Additionally, the cause of screening failure will be tabulated for all subjects screened.

Disposition data will be presented based on all subjects and the denominator for percentages will be all subjects screened.

Assignment of subjects to analysis sets will be listed by subject and summarised overall for all subjects screened. Reasons for subjects being excluded from the analysis sets will be listed/summarised in the same output.

### 4.2.2 Protocol deviations

All important protocol deviations will be listed for each subject in the SAF. Only important protocol deviations will be listed in the CSR.

### 4.2.3 Demographic and baseline characteristics

Demographic variable (including age, age group, sex, ethnic group, and race) will be listed and summarised for all subjects in the SAF. Subject characteristics (height, weight, BMI, and BMI group) will be listed and summarised for all subjects in the SAF. Percentages for categorical variables (sex, ethnic group, race, age group, BMI group) will have the number of subjects in the SAF as the denominator.

Medical and surgical history data will be listed in the SAF by subject and Medical Dictionary for Regulatory Activities (MedDRA version 20.1 or higher) by System Organ Class (SOC) and MedDRA Preferred Term (PT).

History of tobacco use will be listed by subject including the variables recorded as specified in Section 3.3.1. The number of pack years (cigarettes only), smoking status, and smoking duration will be summarised for all subjects in the SAF. Although collected on the CRF, smoking substance will not be summarised nor listed.

### 4.2.4 Spirometry data and COPD characteristics at baseline

Respiratory Disease History at baseline, including COPD Severity (GOLD categories, as determined by the post-bronchodilation assessment), number of exacerbations in previous 12 months, and time since COPD diagnosis (years) will be listed and summarized in the SAF.

Spirometry results at Screening will be listed for each subject in the SAF. This will include all repetitions of FEV1 and FVC as actual and percent values at each time point as well as the derived parameters (ratio and reversibility) presented in Section 3.3.2. A flag will be included in the listing for the maximum FEV1 and FVC value at each time point to show the values used in the analysis. Derived parameters will be obtained only for the maximum FEV1 and FVC parameters. A summary of all the flagged and derived spirometry parameters will be presented.

### 4.2.5 Prior and concomitant medication

Any medications administered other than AB/FF 400/12 will be classified as prior, concomitant or post-treatment based on the start and end dates of the medication as recorded in the CRF, in accordance with the definition in Section 3.3.3. Partially recorded start and end dates/times will be handled as described in Section 4.3.4.

Prior, concomitant and post-treatment medication will be listed by subject and will include the information as detailed in Section 3.3.3. In addition, the listings will include the preferred term (PT), Anatomical Therapeutic Code (ATC) to a maximum 3$^{rd}$ level and duration of administration.

Duration of medication will be calculated as the time between the start and end dates as:

$$Duration\ of\ Medication\ (days) = end\ date - start\ date + 1$$

For medications with partial or completely missing start date/times and/or end date/times, the duration will not be calculated.

The number and percentage of subjects who used any prior or concomitant medication will be summarised on the SAF, (separately for prior and concomitant medications) by ATC to a maximum of 3$^{rd}$ level and PT. Subjects with multiple drug usage in the same PT will be counted only once.

Percentages will be calculated using the number of subjects in the SAF as the denominator.

Medications taken after last dose will not be included in the summary tables but will be identified in the listing for concomitant medication.

All prohibited medications will be identified in the listing for concomitant medication.

### 4.2.6 Drug administration

Drug administration will be listed for each subject, which will cover everything collected in the CRF.

Drug overdose, drug accountability and rescue medication usage will also be listed.

### 4.2.7 Pharmacokinetics

#### 4.2.7.1 Calculation or Derivation of the Pharmacokinetic parameters

Pharmacokinetic parameters will be derived using non-compartmental methods with Phoenix WinNonlin® Version 6.4, or higher and/or SAS® Version 9.3 or later.

The PK analyses of the plasma concentration data for aclidinium bromide, its metabolites and formoterol will be performed at Covance. PK analysis will, where possible, be carried out using actual elapsed times determined from the PK sampling and dosing times recorded in the database. If actual elapsed times are missing, nominal times may be used at the discretion of the PK Scientist with Sponsor approval.

For Day 1, plasma concentrations that are not quantifiable (NQ) from the time of pre-dose sampling (t=0) up to the time of the first quantifiable concentration will be set to a value of zero. After this time-point, NQ plasma concentrations will be set to missing for all concentration profiles. Where 2 or more consecutive concentrations are NQ at the end of a profile, the profile will be deemed to have terminated and therefore any further quantifiable concentrations will be set to missing for the calculation of the PK parameters unless it is considered to be a true characteristic of the profile of the drug.

If an entire concentration-time profile is NQ, the profile will be excluded from the PK analysis.

$C_{max}$, $C_{min}$, $C_{ss,max}$, $C_{ss,min}$, $t_{max}$ and $t_{ss,max}$ will be determined by inspection of the concentration-time profiles.

Where possible $\lambda_z$ will be calculated by log-linear regression of the terminal portion of the concentration-time profiles where there are sufficient data and $t_{½\lambda z}$ will be calculated as $\ln 2/\lambda_z$. For the determination of $\lambda_z$, the start of the terminal elimination phase for each subject will be defined by visual inspection and will be the first time-point at which there is no systematic deviation from the log-linear decline in plasma concentrations ($\lambda_z$ lower) and the last point ($\lambda_z$ upper) will be the time of the last measurable plasma concentration. The choice of data points used to estimate $\lambda_z$ should follow the general guidelines:

- If there is more than 1 phase, use only observations from the terminal phase.

- In general, the minimum data requirements are 3 measured concentrations spanning 3 half-lives. Where $t_{½\lambda z}$ is estimated over less than three half-lives, the values will be flagged in the data listings.

- Include the last measurable concentration.

- Include only observations after Cmax.

- The adjusted correlation coefficient (Rsq adj) should be ≥0.80. Any $\lambda_z$ with a Rsq adj of <0.8 will be flagged in the data listings along with any parameters derived from $\lambda_z$ (ie. $t_{½\lambda z}$, CL/F, $V_z$/F).

Area under the plasma concentration-curve values will be calculated using trapezoidal methods when concentration is increasing and logarithmic trapezoidal method when concentrations are decreasing.

Three concentrations higher than the lower limit of quantification (LLOQ) are required as a minimum for the AUC parameter to be reported with at least one of these concentrations following $C_{max}$.

For rules pertaining to LLOQ see Section 4.3.1.

#### 4.2.7.2 Pharmacokinetic data

All PK summary statistics will be based on the PKS. All PK listings will be based on the SAF. Data from subjects excluded from the PKS, and also data from subjects in the PKS that have been excluded by the PK scientist during the DRM, i.e. specific time-points/concentrations that won´t be used for the parameter calculation, will be included in the data listings and individual figures, but not in the summary statistics, mean figures or combined individual figures.

A listing of PK blood sample collection times, as well as derived sampling time deviations (the calculated difference between actual sampling time and planned sampling time), will be presented. Any plasma concentration with sampling time that deviates more than 10% from the planned sampling time (20% for the 5-minute timepoint) will be excluded from the descriptive statistics and from the summary plots, but these concentration values will be used for the calculation of the parameters as that will use the actual sampling time. Individual aclidinium bromide, LAS34823 and LAS34850, formoterol plasma concentrations will be listed by subject and time-point. Concentrations that are not used in the summaries will still be included in the listings, with excluded concentrations flagged.

Plasma concentrations for aclidinium bromide, LAS34823, LAS34850 and formoterol will be summarised by Day and nominal time-point using descriptive statistics (geometric mean, geometric mean ± geometric SD, geometric coefficient of variation [CV%], arithmetic mean, SD, minimum, median and maximum). In addition, n and n<LLOQ will also be presented.

If one or more values for a given parameter/time-point/ treatment is zero (or imputed with zero), then no geometric statistics can be calculated for that parameter/time-point/analyte/treatment and the results for geometric statistics will be set to "NA" (not applicable).

Protocol scheduled times will be used for the PK summary tables and geometric mean figures of the plasma concentration-time data.

Descriptive statistics for plasma concentrations that are below the LLOQ will be handled as described in Section 4.3.1.

All plasma PK parameters will be listed for aclidinium bromide, LAS34823, LAS34850 and formoterol. All PK parameters will be summarised, except for the diagnostic parameters (Rsq adj, $\lambda_z$, N and $\lambda_z$ upper/lower intervals) which will be listed only. PK parameters will be summarised by Day based on the PKS, as follows:

- Cmax, Cmin, $C_{ss,max}$, $C_{ss,min}$, $C_{av}$, AUCτ, AUClast and $AUC_{ss,\tau}$ will present n, geometric mean, geometric mean ± geometric SD, geometric CV%, median, arithmetic mean, SD, minimum and maximum.

- t½,λz, CL/F, Vz/F and %Fluctuation will present n, arithmetic mean, SD, median, minimum and maximum.

- Rac ratios, metabolite to parent ratios and $\lambda_z$ will present n, geometric mean, geometric CV%, arithmetic mean, SD, median, minimum and maximum.

- tmax and $t_{ss,max}$ will present only n, median, minimum and maximum.

The statistics:

- geometric mean

- geometric mean ± geometric SD and

- geometric CV%

will be calculated as specified in Section 4.3.4.

Individual plasma concentrations versus actual time will be plotted in linear and semi-logarithmic scale, with separate plots for each subject and concentrations for Day 1 and Day 5 (where applicable) overlaid on the same plot.

Combined individual plasma concentrations will also be plotted in linear and semi-logarithmic scale with separate plots for Day 1 and Day 5, and concentrations for each subject overlaid on the same plot.

Combined individual plasma trough concentration will be plotted over time/day with all individuals overlaid on the same plot, in linear scale only.

Figures for the geometric mean (± geometric SD) concentration-time data will be presented in both a linear and semi-logarithmic scale (SD only on the linear scale), with each Day (Day 1 and Day 5) overlaid on the same plot.

Geometric mean (± SD) plasma trough concentrations versus day profiles (pre-dose on Day 1 to Day 5) will be presented in both linear and semi-logarithmic scale (SD only on the linear scale).

All plots will be produced for aclidinium bromide, LAS34823, LAS34850 and formoterol. All mean and combined individual plots will be based on the PK analysis set. All individual plots will be based on the SAF.

Concentrations that are below the LLOQ will be graphically displayed as described in Section 4.3.4.

### 4.2.8 Analysis of safety data

All safety data (scheduled and unscheduled) will be presented in the data listings. For data summaries analysis visit windowing will be done, as outlined in Section 4.1.1.

#### 4.2.8.1 Adverse events

Adverse events will be coded using MedDRA version 20.1.

A treatment emergent adverse event (TEAE) is defined as an AE that has started after first dose of AB/FF 400/12 or within 15 days from the last dose. AEs with missing start date/time will be handled as detailed in Section 4.3.4.

Listings will be presented for each of the following:

- All AEs, with onset and resolution, including the AE number, including classification of the AE as pre-treatment, post-treatment or TEAE, SOC, PT and verbatim term, onset date/time, resolution date/time and time from the last dose of AB/FF 400/12

- All AEs by relationship and causality, including the PT and verbatim term, severity, action taken with regards to AB/FF 400/12, outcome, causality, whether the AE was serious, and whether the AE resulted in the subject being withdrawn

Adverse events will be summarized based on the SAF, as number and percentage of subjects or where applicable the number of events, with the denominator for percentages being the number of subjects in the SAF

The following tabulations will be presented for TEAEs only:

- AEs in any category

- AEs by SOC class and PT
- Number and percentage of subjects with AEs by causality and PT
- AEs by maximum reported intensity and PT
- SAEs, by PT and SOC
- AEs leading to discontinuation of investigational product, by PT and SOC
- Non-serious AEs occurring in >5% of subjects

Key information (including age and sex) on AEs leading to death, SAEs and AEs leading to discontinuation will be separately presented and contain the following information:

- AEs leading to death: AE as reported, PT, date of death, time from start of treatment with AB/FF 400/12 to onset of AE, time from start of study treatment to death, time from last dose to death, whether there is a reasonable possibility that the AE was caused by AB/FF 400/12, and whether she/he received treatment for AE.
- Serious AEs: AE as reported, PT, time from start of treatment to onset of AE, time from last dose of AB/FF 400/12 to onset of AE, time from start of treatment to becoming serious, the outcome, action taken with AB/FF 400/12 and whether there is a reasonable possibility that the AE was caused by AB/FF 400/12
- Adverse events leading to discontinuation: AE as reported, PT, time from start of treatment to onset of AE, time from start of treatment to discontinuation, whether the AE is serious, the outcome and whether there is a reasonable possibility that the AE was caused by AB/FF 400/12

For AEs with incomplete start or end dates/time, the time to start of treatment will not be calculated.

**Adverse events of special interest**

SOC terms, along with Standard MedDRA Query (SMQs) and PTs used to identify the treatment emergent AEs of special interest (AESI) are included in Table 3.

The number and percentage of subjects with a treatment emergent anticholinergic and $\beta_2$ adrenergic events will be tabulated by SOC and PT.

**Table 3 Definition of Treatment-Emergent Adverse Events of Interest**

| **Events of interest** | **Standard MedDRA Query Category plus additional High Level Terms or Preferred Term, if applicable** | |
|---|---|---|
| Anticholinergic events | Anticholinergic syndrome (narrow and broad search SMQ), Glaucoma (narrow search SMQ)<br>Additional PTs: sinus tachycardia, supraventricular tachycardia, ventricular tachycardia, heart rate increased, palpitations, pupillary reflex impaired, unequal pupils, visual impairment, constipation, gastrointestinal obstruction, ileus paralytic, urinary tract infection, cystitis, urinary incontinence, incontinence, dysuria, urge incontinence, urine flow decreased, bladder irritation, oropharyngeal pain, dysphonia, laryngitis, pharyngitis, and throat irritation | |
| $B_2$ adrenergic events | Hypertension | Hypertension (narrow search SMQ) |
| | Hyperglycaemia | Hyperglycaemia/new onset diabetes mellitus (narrow search SMQ) |
| | Tachyarrhythmias | Tachyarrhythmias (incl supraventricular and ventricular tachyarrhythmias) (SMQ) (narrow and broad search SMQ) plus<br>Additional PTs: tachycardia, heart rate increased, and palpitations |
| | Tremor (excl congenital) | HLT |
| | Additional PTs: Anxiety, Nervousness, Insomnia, Headache, Dizziness, Vision blurred, Mydriasis, Dysgeusia, Throat irritation, Cough, Hypokalemia, Myalgia, Muscle spasms, Urinary retention, Urinary tract infection, Constipation, Oedema peripheral, Electrocardiogram QT interval abnormal, Electrocardiogram QT prolonged. | |

#### 4.2.8.2 Vital signs and 12-lead electrocardiogram

**12-lead electrocardiogram:**

12-Lead ECG results performed for safety evaluation will be listed for each subject and will include the ECG parameters (where applicable) and changes from baseline, overall interpretation assessment by the Investigator (normal/abnormal not clinically significant/abnormal clinically significant) and details of any abnormalities (e.g. flags of the outliers presented in Table 4). ECG parameters will also be summarised by time-point including changes from baseline. The baseline for the safety ECG parameters will be the pre-dose results obtained on Day 1, if missing at Day -1 or screening.

The number and percentage of subjects with outliers with respect to 12-lead ECG parameters will be presented for the following categories in Table 4 at each time-point (and any post-baseline visit):

**Table 4 Definition of potentially clinically significant (PCS) values in 12-lead ECG parameters**

| | Criteria 1 | Criteria 2 |
|---|---|---|
| **QTcF intervals** | | |
| a) Absolute values | > 480 milliseconds (msec) | > 500 msec |
| b) Absolute change from baseline | > 30 msec | > 60 msec |
| **QRS interval** | ≥ 100 msec and an increase of ≥ 25% over baseline value | ≥ 150 msec if baseline is < 150 msec |
| **PR interval** | ≥ 200 msec and an increase of ≥ 25% over baseline value | ≥ 250 msec if baseline is < 250 msec |
| **Heart Rate** | | |
| a) Tachycardia event | ≥ 110 beats per minute (bpm) and an increase of ≥ 15% over baseline value | ≥ 120 bpm if baseline is < 120 bpm |
| b) Bradycardia event | ≤ 50 bpm and a decrease of ≥ 15% over baseline value | ≤ 40 bpm if baseline is > 40 bmp |

bpm = beats per minute; ECG = electrocardiogram; QTcF = QT interval corrected for heart rate using the Fridericia formula (QTcF = QT/(RR)$^{1/3}$).

For QTcF and heart rate, if either condition a) or condition b) are met for one of the two criteria, the value will be considered potentially clinically significant (PCS).

Descriptive statistics and outlier summary, and subject-level data listing will be based on the SAF. For the percentage of subjects, the denominator will be the number of subjects in the SAF.

**Calculation of the ECG parameters**

Derived ECG parameters, i.e. QTcB, QTcF, HR and others as applicable, will be calculated for each time-point, based on values for QT and RR.

QTcB will be calculated as: $\mathrm{QTcB} = \mathrm{QT}/\mathrm{RR}^{1/2}$ where the QT interval is in msec and the RR interval is in seconds

QTcF will be calculated as: $\mathrm{QTcF} = \mathrm{QT}/\mathrm{RR}^{1/3}$ where the QT interval is in msec and the RR interval is in seconds

HR will be calculated as: $\mathrm{HR} = 60/\mathrm{RR}$ interval, where the RR interval is in seconds

**Blood pressure**

The results of the blood pressure measurements will be listed by subject in the SAF and time-point including the changes from baseline. The baseline for blood pressure measurements will be the assessment prior to first dose of study medication on Day 1, if missing Day -1 or screening will be used instead. Subjects with notable changes from baseline will be flagged in the listing as "high" or "low" according to criteria in Table 5.

**Table 5 Blood pressure notable changes from baseline**

| Parameter | Flag | Criteria |
|---|---|---|
| Systolic blood pressure (mmHg) | High | observed value ≥ 180 and increase over baseline of ≥ 20<br>or<br>observed value ≥ 200 and baseline observed value < 200 |
| | Low | observed value ≤ 90 and decrease from baseline ≥ 20<br>or<br>observed value ≤ 75 and baseline observed value > 75 |
| Diastolic blood pressure (mmHg) | High | observed value ≥ 105 and increase over baseline of ≥ 15<br>or<br>observed value ≥ 115 and baseline < 115 |
| | Low | observed value ≤ 60 and decrease from baseline of ≥ 15<br>or<br>observed value ≤ 40 and baseline > 40 |

Descriptive statistics will be presented by time-point for both observed values and changes from baseline, based on the SAF.

The number and percentage of subjects with notable changes from baseline as defined in Table 5 will be tabulated by time-point (and any post-baseline visit) based on the criteria provided, based on the SAF with the denominator for percentages equal to the number of subjects in the SAF.

#### 4.2.8.3 Clinical laboratory assessments

Haematology and clinical chemistry values will be listed by subject and time-point including changes from baseline (Day -1, if missing Screening) measurements.

Listings will include a flag for out of range values for both notable abnormalities as well as expanded normal ranges as defined in Table 6.

Each laboratory test value will be identified as:

- Low: lower than the lower limit of the expanded normal range (ENR),
- Normal: within the ENR limits, and
- High: larger than the upper limit of the ENR

with the ENR being calculated by multiplying the LLN and ULN of the laboratory by the factor shown in Table 6.

Moreover, treatment-emergent abnormalities including the Follow-up Period, defined as newly occurring or worsening, as well as notable abnormalities in laboratory parameters will be identified.

Newly occurring or worsening laboratory abnormalities in laboratory parameters will be identified using the ENR. A laboratory result lying outside the ENR will be considered abnormal.

A laboratory parameter will be defined as showing a "New" abnormality if the observed lab test value is within the ENR at baseline but not at post-baseline time-points, or it is outside the ENR at baseline and outside the ENR at endpoint at different extreme limits (from expanded lower limit to expanded upper limit, or vice versa).

A laboratory parameter will be defined as "Worsened" if the baseline lab test value is above the expanded upper limit of the corresponding normal range (xULN) specified in Table 6 and the ratio of endpoint value to baseline value is also greater than the corresponding coefficient (multiplying factor) specified in Table 6, or alternatively if the baseline laboratory test value is below the expanded lower limit of the corresponding normal range (xLLN) specified in the above table and the ratio of endpoint value to baseline value is also lower than the corresponding coefficient specified in Table 6.

The laboratory abnormality will be also classified as a "Notable" abnormality if it satisfies the criteria detailed in Table 6, having a baseline value within the notable abnormality limits.

## Table 6 Expanded normal ranges and notable abnormalities for laboratory parameters

| Laboratory Parameter | Expanded Normal Ranges | | | | Notable Abnormalities | |
|---|---|---|---|---|---|---|
| | *MFL* | *MFU* | *Lower Limit* | *Upper Limit* | *Lower Limit* | *Upper Limit* |
| **Haematology** | | | | | | |
| Haemoglobin | 0.85 | 1.15 | MFL × LLN | MFU × ULN | < 60 g/L | > 230 g/L |
| Haematocrit | 0.85 | 1.15 | MFL × LLN | MFU × ULN | < 0.24 | NA |
| Erythrocytes count | 0.85 | 1.15 | MFL × LLN | MFU × ULN | NA | NA |
| Platelets | 0.85 | 1.15 | MFL × LLN | MFU × ULN | $< 100 \times 10^9$/L | NA |
| Leukocyte count | 0.85 | 1.15 | MFL× LLN | MFU × ULN | $< 1 \times 10^9$/L | $> 30 \times 10^9$/L |
| Neutrophils | 0.85 | 1.15 | MFL× LLN | MFU × ULN | $< 0.5 \times 10^9$/L | NA |
| Eosinophils | NA | 1.15 | MFL× LLN | MFU × ULN | NA | NA |
| Basophils | NA | 1.15 | MFL× LLN | MFU × ULN | NA | NA |
| Lymphocytes | 0.85 | 1.15 | MFL× LLN | MFU × ULN | NA | NA |
| Monocytes | NA | 1.15 | MFL× LLN | MFU × ULN | NA | NA |
| **Clinical chemistry** | | | | | | |
| Aspartate aminotransferase (AST) | NA | 1.15 | NA | MFU × ULN | NA | > 3 × ULN |
| Alanine aminotransferase(ALT) | NA | 1.15 | NA | MFU × ULN | NA | > 3 × ULN |
| Alkaline phosphatase | NA | 1.15 | NA | MFU × ULN | NA | > 3 × ULN |
| Gamma-glutamyl transpeptidase | NA | 1.15 | NA | MFU × ULN | NA | > 3 × ULN |
| Total bilirubin (TBL) | NA | 1.15 | NA | MFU × ULN | NA | > 51.3 µmol/L |
| Creatine-kinase | NA | 1.15 | NA | MFU × ULN | NA | > 10 × ULN |
| Lactate dehydrogenase | NA | 1.15 | NA | MFU × ULN | NA | > 3 × ULN |
| Blood urea nitrogen? | NA | 1.15 | NA | MFU × ULN | NA | > 17.9 mmol/L |
| Creatinine | NA | 1.15 | NA | MFU × ULN | NA | > 265 µmol/L |
| Uric acid | NA | 1.15 | NA | MFU × ULN | NA | > 714 µmol/L |
| Total cholesterol | NA | 1.15 | NA | MFU × ULN | NA | NA |
| Triglycerides | NA | 1.15 | NA | MFU × ULN | NA | NA |
| Glucose | 0.85 | 1.15 | MFL× LLN | MFU × ULN | < 2.22 mmol/L | > 22.2 mmol/L |

| Laboratory Parameter | Expanded Normal Ranges | | | | Notable Abnormalities | |
|---|---|---|---|---|---|---|
| | *MFL* | *MFU* | *Lower Limit* | *Upper Limit* | *Lower Limit* | *Upper Limit* |
| Sodium | 0.95 | 1.05 | MFL× LLN | MFU × ULN | <115 mmol/L | > 165 mmol/L |
| Potassium | 0.95 | 1.05 | MFL× LLN | MFU × ULN | < 2.6 mmol/L | > 6.9 mmol/L |
| Calcium, total | 0.85 | 1.15 | MFL× LLN | MFU × ULN | < 1.25 mmol/L | > 3.25 mmol/L |
| Chloride | 0.95 | 1.05 | MFL× LLN | MFU × ULN | NA | NA |
| Inorganic phosphorus | 0.85 | 1.15 | MFL× LLN | MFU × ULN | NA | NA |
| Total Protein | 0.85 | 1.15 | MFL× LLN | MFU × ULN | < 20 g/L | > 90 g/L |
| Albumin | 0.85 | 1.15 | MFL× LLN | MFU × ULN | NA | NA |

LLN: lower limit of normal as provided by the safety laboratory; MFL: lower multiplying factor; MFU: upper multiplying factor; ULN: upper limit of normal as provided by the safety laboratory.

For the classification of laboratory values, calculation of changes from baseline and for the purposes of summary statistics, any laboratory parameter value that is given as '<xx.x' or '>xx.x' in the database will be imputed according to rules stated in Section 4.3.2.

Urinalysis results will be listed.

Descriptive statistics for haematology and clinical chemistry will be presented separately by time-point for both observed values and changes from baseline.

The number and percentage of subjects with potentially clinically significant values will be presented by time-point (and at any post-baseline visit), and by type of shift from baseline, separately for haematology and clinical chemistry measurements. Shift is defined as the change in category (low, normal or high as above) at baseline to a post-baseline time-point. The denominator for percentages will be the number of subjects in the SAF. The following shift categories will be shown:

- New (Low/High/Total)
- Worsening (Low/High/Total)
- Notable (Low/High/Total)

Cases of potential Hy's Law, (including PHL and/or HL) where a subject has occurrences of AST or ALT ≥ 3xULN together with total bilirubin ≥ 2xULN will be listed for each subject, along with their demographic characteristics, day and time-point of treatment discontinuation. Summary statistics by treatment group will be presented for the maximum post-baseline ALT and AST by TBL.

Serum pregnancy test results will be listed but not summarised.

## 4.3 Data handling

Since the statistical analyses will be predominantly presentations in tables and individual data listings, no specific action will be taken to handle missing data. A subject who withdraws prior to the last planned observation in a study period will be included in the analyses up to the time of discontinuation. In general, missing data will result in a reduced sample size for the given parameter. No imputation of missing data will be performed except for the below cases. A subject who withdraws prior to the last planned observation in the study will be included in the analyses up to the time of discontinuation, if no important protocol deviations necessitate the exclusion of collected data from the analysis.

### 4.3.1 Pharmacokinetic data below the lower limit of quantification (BLQ) or non-reportable (NR)

The LLOQs are the following:

- Aclidinium bromide (LAS34273): 2 pg/mL
- LAS34823: 5 pg/mL
- LAS34850: 50 pg/mL
- formoterol: 0.5 pg/mL

Plasma concentrations that are BLQ will be reported as not quantifiable (NQ) for all listings.

For descriptive statistics of Plasma concentration summaries:

- Where there is a NR, these will be set to missing.
- At a time-point where less than or equal to 50% of the values are NQ, all NQ values will be set to the lower limit of quantification (LLOQ), and all descriptive statistics will be calculated accordingly.
- If more than 50%, but not all, of the concentrations are NQ, the geometric mean, geometric mean ± geometric SD and geometric CV% will be reported as not calculable (NC). The maximum value is reported from the individual data, and the minimum and median are set as NQ.
- If all concentrations are NQ at a time-point, the geometric mean, minimum, median and maximum are reported as NQ and the geometric CV% and geometric mean ± geometric SD as NC.
- The number of values below the LLOQ (n<LLOQ) are reported for each time-point along with the total number of collected values (n).

Three observations >LLOQ are required as a minimum for a plasma concentration or PK parameter to be summarised. Two values are presented as a minimum and maximum with the other summary statistics as NC.

For display in figures:

- For mean plots: BLQ values will be handled as described for the descriptive statistics. If this handling results in a geometric mean of "NA", "ND" or "NQ", then the value at that time-point will not be plotted (made missing)

- For individual plots and combined individual plots: BLQ values will be set to zero on Day 1 pre-dose; at all other time-points, BLQ values will be set to missing.

### 4.3.2 Precision and rounding rules for pharmacokinetic data

For PK concentration data, the listings will be presented to the same number of significant figures as the data received from the bioanalytical laboratory; for PK parameters, the listings will be presented according to the following rules:

- $C_{max}$, $C_{min}$, $C_{ss,max}$, $C_{ss,min}$ – will be presented to the same number of significant figures as received from the bioanalytical laboratory.

- $t_{max}$, $t_{ss,max}$, $\lambda_z$ lower and upper time limit – will be presented as received in the data, usually to 2 decimal places

- AUC$\tau$, $AUC_{ss,\tau}$, $AUC_{last}$, $t_{1/2,\lambda z}$, CL/F, $V_z$/F, $C_{av}$, Rac ratios, metabolite to parent ratios, %Fluctuation and Rsq adj – will be presented to 3 significant figures

- $\lambda_z$ – will be presented to 4 significant figures

- $\lambda_z$, N – will be presented as an integer (no decimals)

For PK concentration data all descriptive statistics will be presented to 4 significant figures with the exception of the minimum and maximum which will be presented to 3 significant figures.

For PK parameter data the descriptive statistics will be presented according to the following rules:

- $C_{max}$, $C_{min}$, $C_{ss,max}$, $C_{ss,min}$, AUC$\tau$, $AUC_{ss,\tau}$, $AUC_{last}$, $t_{1/2\lambda z}$, CL/F, $V_z$/F, $C_{av}$, Rac ratios, metabolite to parent ratios and %Fluctuation descriptive statistics will be presented to 4 significant figures with the exception of the minimum and maximum which will be presented to 3 significant figures

- $t_{max}$, $t_{ss,max}$ – all descriptive statistics will be presented as received in the data, usually to 2 decimal places

- $\lambda_z$ – all descriptive statistics will be presented to 5 significant figures with the exception of the minimum and maximum which will be presented to 3 significant figures

Source data shall be used in all derived PK parameter calculations without prior rounding.

### 4.3.3 Safety laboratory data with semi-qualitative results

For the purposes of calculating changes from baseline and summary statistics:

- Laboratory values reported as "<xx.x" will be imputed with half of the given xx.x

- Laboratory values reported as ">xx.x" will be imputed with 1.5 times the given xx.x value

### 4.3.4 Missing data for adverse events and medications

All adverse events and prior/concomitant medication data will be listed as recorded on the CRF, unless stated otherwise. For the purposes of tabulations, the following rules will be followed.

**Missing adverse event causality**

- A causality of "related" will be assigned to an AE if the relationship to AB/FF 400/12 is missing for an AE and the start date of the AE shows that the AE started on or after the first dose of AB/FF 400/12

- A causality of "not related" will be assigned to an AE if the relationship to AB/FF 400/12 is missing for an AE and the start date of the AE shows that the AE started before the first dose of AB/FF 400/12

**Missing adverse event intensity and seriousness**

- An intensity of "severe" and seriousness of "serious" will be assigned to an AE if missing

**Missing start date of AEs and medications**

Adverse events and medications with incomplete (partially known or missing) start dates/times will be handled as follows for the purposes of the tabulations:

- If the start date is completely missing but the known end date is on or after the first dose date, then the start date will be imputed as the first day of dosing; if the known end date is before the first dose date, then the screening date will be used for the start date. If the end date is non-informative (i.e. is missing or does not contain enough information), the start date will be imputed as the first date of dosing;

- If only the start day is missing the day will be imputed as the first day on which a dose was given in that month unless the known end date is before a dose was given in that month; in which case, the date will be imputed as 01. If the end date is non-informative (i.e. is missing or does not contain enough information), the start date will be imputed as the first date of dosing in the known month. If the month is not a dosing month the date will be imputed as 01;

- If the start day and month are missing the date will be imputed as the first day of dosing in the known year unless the known end date is before a dose was given in that year; in which case, the start day and month will be imputed as 01Jan or with the date of screening if this is later. If the end date is non-informative (i.e., is missing or does not contain enough information), the start date will be imputed as the first date of dosing in the known year. If the year is not a year of dosing then the date will be imputed as 01Jan or with the date of screening if this is later;

- Missing times will be imputed as 00:00 h or with the time of AB/FF 400/12 dosing for events starting on a dosing day.

**Missing end date of AEs and medications**

Missing end date of AEs will not be imputed.

For medication, when the start date and the end date are both incomplete, first impute the start date following the steps in the section above "Missing start date of AEs and medications", and then impute the end date, with the following steps:

- If the end date is completely missing or only the year is missing, it will be imputed with last visit date/year or the medication start date/year, whichever occurs later.

- If the end year is not missing but the month is missing, then the following will be imputed:

    - if the end year is prior to the year of last dose, then December 31 will be used

    - if the end year is equal to the year of last dose then the month and day of last dose will be assigned,

    - otherwise, January 1 will be assigned to the missing fields

- If only the end day is missing, then the following will be imputed:

    - if the month and year are the same as the last dose, then the day of last dose will be assigned.

    - if the year is prior to the last dose or the years are the same but the month is prior to last dose, then last day of the month will be used.

- If the year is after the last dose date or the years are the same but the month is after last dose, then first day of the month will be used.

### 4.3.5 Computation of derived variables

#### 4.3.5.1 Definition of Baseline values

The Baseline value for all variables will be the last available value prior to the first AB/FF 400/12 administration. Scheduled or unscheduled measurements can be used as the Baseline value.

Where available, change from Baseline will be listed and summarised for all numeric variables, and is calculated as:-

$$Change\ from\ Baseline = Value - Baseline\ Value$$

#### 4.3.5.2 Summary statistics

For the geometric mean, geometric mean +/- SD and geometric CV%, the following holds:

- SDL is the arithmetic standard deviation of the natural log-transformed variable
- ML is the arithmetic mean of the natural log-transformed variable
- exp denotes the power function based on the natural base e

Geometric mean is calculated as exp[ML].

Geometric mean +/- geometric SD is calculated as exp[ML +/- SDL].

Geometric CV% is calculated as 100 x sqrt[exp($SDL^2$) – 1].

## 5. INTERIM ANALYSES

No interim analysis will be performed.

## 6. CHANGES OF ANALYSIS FROM PROTOCOL

None.

# 7. APPENDIX

## 7.1 Appendix I – List of Tables, figures and listings

### 7.1.1 TABLES

**11. SUMMARY TABLES AND FIGURES, LISTINGS, AND NARRATIVES**

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### 7.1.3 LISTINGS

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