Clinical Study Protocol D6572C00001	
Drug Substance	Aclidinium bromide /Formoterol fumarate
Study Code	D6572C00001 M-AS464-01
Version	1.0
Date	24 March 2017

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

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

AstraZeneca

VERSION HISTORY

Version 1.0, 23 March 2017
Initial Creation

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This Clinical Study Protocol has been patient to a peer review according to AstraZeneca Standard procedures. The clinical study protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

PROTOCOL SYNOPSIS

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 (COPD)

Principal Investigator

Study site(s) and number of patients planned

Twenty (20) Chinese male and female patients with stable moderate to severe COPD will be dosed.

Study period		Phase of development
Estimated date of first patient enrolled	Q3-Q4 2017	Phase IIa
Estimated date of last patient completed	Q1-Q2 2018	

Study design

This is a Phase IIa, open-label, repeat-dose trial to investigate the pharmacokinetics (PK), safety and tolerability of single and multiple twice daily doses of inhaled aclidinium bromide/formoterol fumarate 400/12 µg in Chinese male and female patients with stable moderate to severe COPD.

Twenty COPD Chinese patients of at least 40 years of age or older, will participate in the study.

Patients will be admitted to the trial center on Day -1 and will be discharged on Day 7, 48 hours after last IP administration on Day 5 and after the completion of the 48-hour PK sample collection and safety assessment on Day 7. A follow up visit that will be performed within 5 days of the final PK sample collection on Day 7.

Safety measurements and blood samples for PK assessments will be collected at predetermined time points on Days 1 through 7.

Objectives

Primary Objective:	**Outcome Measure:**
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 COPD.	The following pharmacokinetic parameters will be calculated when applicable for aclidinium bromide, its metabolites and formoterol fumarate: Day 1: C_{max}, t_{max}, AUC_{last}, AUC_{τ}, C_{min} Day 5: $C_{ss,max}$, $t_{ss,max}$, λ_z, $t_{½\lambda z}$, $AUC_{ss,\tau}$, CL/F*, V_z/F*, C_{av}, %Fluctuation, $C_{ss,min}$, $R_{ac}(C_{max})$ $R_{ac}(AUC_{\tau})$ and $R_{ac}(C_{min})$. Additional parameters may be determined where appropriate *Only for Aclidinium bromide and formoterol

Secondary Objective:	**Outcome Measure:**
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.	AEs/SAEs Blood pressure Clinical laboratory parameters (haematology, serum biochemistry and urinalysis) 12-lead ECG parameters

Procedures and assessments

After obtaining written informed consent, all patients will be screened within 21 days prior to the first investigational product (IP) dose administration on Day 1 at Visit 2. Eligibility screening will consist of inclusion and exclusion criteria evaluation; complete medical and surgical history/COPD history; prior and concomitant medications; demographics; inhaler training; physical examination, body weight and height; blood pressure; 12-lead electrocardiogram (ECG); spirometry and reversibility test; clinical laboratory tests (haematology, serum biochemistry and urinalysis); serum pregnancy test for women of childbearing potential; serology (anti-hepatitis C virus, hepatitis B surface antigen and anti-human immunodeficiency virus [HIV] type 1); urine drugs of abuse and alcohol screen; and adverse event (AE) monitoring. Relief medication is to be provided to the patient at Visit 1 (Screening visit) as necessary.

Spirometry will be conducted at Visit 1 (Screening) to confirm eligibility criteria and COPD severity stage (post-bronchodilator forced expiratory volume in 1 second [FEV_1] according to the Global Initiative for Chronic Obstructive Lung Disease [GOLD] guidelines 2016).

Upon admission to the trial center on Day -1 of Visit 2 (the day preceding the first day of IP administration [Day 1]), the following procedures are to be performed: review of inclusion and exclusion criteria; prior and concomitant medications; inhaler training; blood pressure; 12-lead ECG; clinical laboratory tests (haematology, serum biochemistry and urinalysis); physical examination; serum pregnancy test for women of childbearing potential; urine drugs of abuse and alcohol screen; and AE monitoring.

Each eligible patient will be dosed on Day 1. On Day 1 through Day 4, patients will receive one inhalation of aclidinium bromide/formoterol 400/12 µg BID (morning and evening) via the Genuair® multidose dry powder inhaler (DPI). On Day 5 patients will receive only the morning dose of one inhalation of aclidinium bromide/formoterol 400/12 µg via the Genuair® multidose DPI. Patients will be discharged on Day 7, 48 hours after last IP administration and completion of the 48-hour PK sample collection and safety assessments. Relief medication is to be provided to the patient during the treatment period as necessary.

From Day 1 through Day 7 at Visit 2, safety measurements (blood pressure, 12-lead ECG and AE monitoring) and blood samples for PK assessments will be collected at predetermined time points.

A follow-up Visit will be performed within 5 days of the final PK sample collection on Day 7. The following procedures are to be performed at the Follow up Visit: recording of concomitant medications; physical examination; blood pressure; clinical laboratory tests, 12-lead ECG; serum pregnancy test for women of childbearing potential and AE monitoring.

Patients who prematurely discontinue from the study (withdrawal) will participate in a Premature Discontinuation Visit that will include physical examination, clinical laboratory test, 12-lead ECG, blood pressure, serum pregnancy test for women of childbearing potential, and assessment of AEs and concomitant medications to ensure patient´s safety.

The total amount of blood to be collected for safety assessments will be 29 mL. For female patients of childbearing potential an additional 9 mL will be collected for serum pregnancy test.

Blood samples for serum pregnancy tests will be sent to the site local laboratory for analysis. Test for drugs of abuse and alcohol screen will also be performed at the site. All other blood and urine specimens will be sent to a central laboratory (Covance) in China for analysis.

AE and recording of concomitant medications will be monitored starting after the time the informed consent is signed through the completion of the follow-up; should any AEs or serious adverse events (SAEs) be ongoing at that time, they will be followed up until resolution, stabilization, or the PI and the Sponsor agree that follow-up is no longer necessary.

Relief medication (salbutamol pMDI 100 µg/puff) will be permitted as needed throughout the study, for all participating patients.

Pharmacokinetic Assessments

Serial blood samples will be collected for PK assessments of aclidinium bromide and its metabolites (LAS34823 and LAS34850) and formoterol in plasma 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 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 h (15 time points)

The total amount of blood to be collected for the PK assessments will be 264 mL (33 time points x 8 mL). All PK plasma specimens will be sent to Covance in China for analysis.

Aclidinium bromide undergoes rapid hydrolysis in human plasma to its acid (LAS34850) and alcohol metabolites (LAS34823). Therefore, blood samples generated in study must be stabilized with 4-(2-aminoethyl) benzene sulfonyl fluoride hydrochloride (AEBSF) and temperature control to guarantee that these samples are not altered between the collection time and the time they are stored frozen (at –70°C). The time from blood draw to freezing of plasma samples should be completed as quickly as possible and should not exceed 30 minutes. Laboratory kits containing additives and AEBSF will be provided by the Covance Central Services.

Target patient population

Twenty (20) Chinese male and female patients who are aged ≥ 40, current or former smokers with a smoking history of ≥ 10 pack-years, and with stable, moderate to severe COPD (GOLD guidelines 2016). Patient must have screening post-bronchodilator test $FEV_1/FVC < 70\%$ and $FEV_1 \geq 30$ and < 80% of the predicted normal value.

Duration of treatment

The total duration of the trial for each patient will be approximately 5 weeks. There will be a run-in period of up to 21 days followed by treatment period of 8 days (including admission Day -1, 5 treatment days, and 2 days for PK sampling after last IP dose), and a follow up visit that will be performed within 5 days of the final PK sample collection on Day 7.

Investigational product, dosage and mode of administration

The IP consists of a fixed-dose combination (FDC) of a long-acting anticholinergic drug, namely aclidinium bromide, combined with the long-acting β_2-agonist formoterol fumarate (aclidinium bromide 400 µg/formoterol fumarate 12 µg inhalation powder)

The aclidinium bromide/formoterol 400/12 µg FDC inhalation powder will be administered via the Genuair® device (dry powder inhaler, DPI) via oral inhalation.

Statistical methods

Analysis will be done using the safety and PK populations. All patients who complete the treatment period (Days 1-5) and have evaluable PK parameters will be defined as the PK population. All patients who receive at least 1 dose of aclidinium bromide/formoterol will be defined as the safety population.

PK Parameters will be summarized descriptively by compound/study day separately using appropriate descriptive statistics including tables, listings and graphs, as appropriate.

Descriptive statistics for demographics and other baseline characteristics will be provided.

Safety Outcomes: The incidence of TEAEs will be presented by system organ class and preferred term; by relationship to investigational product, by severity, seriousness, and action taken with IP. Clinical laboratory parameters, vital signs, and 12-lead ECG will be analysed for both absolute values and change from baseline by means of descriptive statistics. Shift tables will be performed when applicable. An outlier analysis of the appropriate ECG parameters and potentially clinical significant laboratory values will also be presented.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
AE	Adverse Event
ALT	Alanine Aminotransferase
AM	Morning (antemeridian)
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
ATS	American Thoracic Society
AUC	Area Under the Curve
AUC_{ex}	Percentage of AUC obtained by extrapolation, calculated as $[(C_{last}(pred)/\lambda z)/AUC * 100]$
AUC_{last}	Area under the plasma concentration-curve from time zero to the time of last quantifiable concentration
AUC/D	Area under the concentration-time curve from time zero extrapolated to infinity divided by the dose
$AUC_{ss,\tau}/D$	Area under the concentration-time curve zero to 12 h divided by the dose
AUC_{τ}	Area under the plasma concentration-curve from time zero to 12 hours post dose
AUC_{τ}/D	Area under the concentration-time curve zero to 12 h divided by the dose
AUMC	Area Under the First Moment Curve
BLQ	Below the lower limit of quantification
β-hCG	β-human chorionic gonadotropin
BID	Twice daily
BMI	Body Mass Index
BP	Blood Pressure
bpm	Beats per minute
CFDA	China Food and Drug Administration
C_{av}	Average steady state concentration
CI	Confidence Interval
CK	Creatine kinase
CL/F	Apparent clearance for parent drug estimated as dose divided by AUC

Abbreviation or special term	Explanation
C_{max}	Observed maximum concentration
C_{max}/D	Observed maximum concentration divided by dose
C_{min}	Observed minimum concentration within a dosing interval
$C_{ss,av}$	Average plasma concentration during a dosing interval, estimated as AUCss,τ/12
$C_{ss,max}$	Observed maximum concentration, taken directly from the individual concentration-time curve on Day 5
$C_{ss,min}$	Observed minimum concentration, taken directly from the individual concentration-time curve on Day 5
$C_{ss,max}$ /D	Observed maximum concentration divided by dose
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CRO	Clinical Research Organisation
CSA	Clinical Study Agreement
CSR	Clinical Study Report
DAE	Discontinuation of Investigational Product due to Adverse Event
DBP	Diastolic Blood Pressure
DES	Data Entry Site
DILI	Drug-Induced Liver Injury
DMP	Data Management Plan
DPI	Dry Powder Inhaler
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
E-R	Exposure-response
ERS	European Respiratory Society
EU	European Union
FDA	Food and Drug Administration
FDC	Fixed Dose Combination
FEV_1	Forced Expiratory Volume in one second
FVC	Forced Vital Capacity
GCP	Good Clinical Practice

Abbreviation or special term	Explanation
GGT	Gamma-glutamyl transferase
GMP	Good Manufacturing Practice
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HBsAg	hepatitis B surface antigen
HIV	Human immunodeficiency virus
HL	Hy's Law
HR	Heart Rate
IATA	International Airline Transportation Association
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IP	Investigational Product
λ_z	Terminal rate constant
LABA	Long-Acting β2-agonist
LAMA	Long-Acting Muscarinic Antagonist
LLOQ	Lower Limit of Quantification
LS	Least Square
LSLV	Last Subject Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
mmHg	Millimeters of mercury
msec	Milliseconds
MRT	Mean residence time calculated by AUMC/AUC, where AUMC is the area under the first moment-time curve
NA	Not applicable
ND	Not determined
N obs	Number of data points included in the log-linear regression analysis
OTC	Over-the-counter medicine
PD	Pharmacodynamic
PHL	Potential Hy's Law
PI	Principal Investigator
PK	Pharmacokinetics
PM	Evening (Post meridiem)

Abbreviation or special term	Explanation
PP	Per-Protocol
PR(PQ)	Period that extends from the beginning of the P wave (the onset of atrial depolarization) until the beginning of the QRS complex (the onset of ventricular depolarization)
PR interval	Duration in milliseconds from the beginning of wave P to onset of ventricular depolarisation (Q and R)
PT	Preferred Term
QRS	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 formulae ($QT/RR^{1/2}$)
QTcF interval	QT interval corrected, Fredericia formulae ($QT/RR^{1/3}$)
Rac(C_{max})	Accumulation ratio for C_{max} estimated as ratio of $C_{ss,max}$ on Day 5/C_{max} on Day 1
Rac(C_{min})	Accumulation ratio for C_{min} estimated as ratio of $C_{ss,min}$ on Day 5/C_{min} on Day 1
Rac(AUCτ)	Accumulation ratio for AUC_{τ} estimated as ratio of $AUC_{ss,\tau}$ on Day 5/AUC_{τ} on Day 1
RR	Respiratory rate
RSq adj	Adjusted coefficient of determination for calculation of λ_z
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SE	Standard error
SOC	System Organ Class
SOP	Standard Operating Procedure
TBL	Total Bilirubin
TCS	Tata Consultancy Services
TEAE	Treatment-Emergent Adverse Event
TMF	Trial Master File
$t½\lambda z$	Terminal half-life
t_{max}	Time to reach maximum concentration

Abbreviation or special term	Explanation
$T_{ss, max}$	Time to reach maximum concentration, taken directly from the individual concentration-time curve
ULN	Upper Limit of Normal
US	United States
V_z/F	Apparent volume of distribution for parent drug at terminal phase (extravascular administration)
WBDC	Web Based Data Capture
$\%AUC_{ex}$	Percentage of AUC obtained by extrapolation
%Fluctuation	Fluctuation index during a dosing interval estimated as $100*(C_{max}-C_{min})/C_{avg}$ (%)

1. INTRODUCTION

1.1 Background and rationale for conducting this study

Chronic Obstructive Pulmonary Disease (COPD), a common preventable and treatable disease, is characterized by airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lungs to noxious particles or gases. Cigarette smoking is the most common risk factor for COPD. Exacerbation and comorbidities contribute to the overall severity in individual patients. COPD is a major cause of morbidity and mortality worldwide and results in an economic and social burden which is both substantial and increasing.

In a study of the burden of obstructive lung disease (BOLD Study), the crude prevalence of COPD, all stages, among the study populations ranged from 11.4% in Guangzhou, China to 26.1% in Salzburg, Austria (Buist et al 2007). The prevalence of COPD in China is 8.2% in those aged over 40 years old (Zhong et al 2007).

COPD is characterized by structural changes in the airways resulting from repeated injury and repair and by bronchoconstriction, which is an important target for pharmacologic interventions (GOLD 2016). Dyspnoea, chronic cough and sputum production are the most common clinical symptoms. Adrenergic and cholinergic pathways mediate bronchoconstriction in COPD.

Anticholinergic compounds such as ipratropium, oxitropium, tiotropium, aclidinium glycopyrronium or umeclidinium have been shown to provide clinical benefit in the treatment of COPD. These therapeutic agents block the muscarinic acetylcholine receptors in the bronchial smooth muscle and thus decreasing the cholinergic tone (muscarinic antagonism). β_2-adrenergic agonists such as albuterol, formoterol, salmeterol or indacaterol stimulate β_2-receptors in the bronchial smooth muscle resulting in similar effects to those of anticholinergics. Both anticholinergic drugs and β_2-adrenergic agonists decrease bronchoconstriction (increased FEV_1) and thereby reduce dyspnoea and COPD exacerbations, increase exercise tolerance, and improve quality of life.

As a result of their differing mechanisms of action and similar pharmacodynamic effects, β_2-agonists and muscarinic antagonists have been used simultaneously in the same inhalation device for the treatment of COPD.

Several combinations of LABA and LAMAs have been recently approved worldwide for the treatment of COPD, i.e. Ultibro (indacaterol/glycopyrronium) and Anoro (vilanterol/umeclidinium). The clinical studies have shown that the combined use of a LABA and a LAMA results in greater improvement of bronchodilation as well as a better symptoms control compared with monotherapies (Pelaia et al 2014, Maltais et al 2014, Maleki-Yazdi et al 2014).

Duaklir® Genuair® is a combination product of LAMA (aclidinium bromide) and LABA (formoterol fumarate) approved in Europe for the treatment of COPD at a dose of 400/12 μg (delivered as 340/12 μg) twice daily in 2014 (Duaklir® Genuair® SmPC 2015). Since then, aclidinium/formoterol has been approved in more than 35 countries and is marketed in more than 21 countries globally. Additional studies are to be initiated to support the regulatory registration in other territories, including China.

Results from the current trial will characterize the pharmacokinetic (PK) profile of aclidinium/formoterol fumarate in Chinese COPD patients.

The Investigator Brochure (IB) of aclidinium bromide/formoterol fumarate contains relevant preclinical and clinical findings with the product.

1.2 Rationale for study design, doses and control groups

The current trial aims to characterize the pharmacokinetics (PK) and safety profile of aclidinium bromide/formoterol 400/12 μg BID after multiple doses in Chinese patients with stable moderate to severe COPD.

The present agent has been developed as a long-term control drug for COPD treatment. When aclidinium bromide/formoterol was repeatedly administered twice a day for five days in the LAC-PK-01 study, it was confirmed that the drug concentration of plasma aclidinium bromide and its metabolites, and the concentration of plasma formoterol, reached a steady state in five days, and it is considered that the concentration of plasma aclidinium bromide reached a steady state in five days in the KRPAB1102-D202 study in Japan; therefore, five-day repeated administration was set for the present trial. Moreover, we set the dosage (aclidinium bromide/formoterol 400/12μg) and the subjects (COPD patients) taking into account the fact that it will be possible to compare pharmacokinetic data from aclidinium bromide /formoterol administration to Chinese patients.

In addition, the dose strength selected for this study corresponds to the currently registered product.

Twenty (20) patients with stable moderate to severe COPD are to be enrolled in this study and are considered to be a sufficient number to meet the objective of the study.

1.3 Benefit/risk and ethical assessment

Aclidinium bromide /formoterol 400/12 μg is currently approved in Europe as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).

The clinical development programme for aclidinium bromide/formoterol 400 μg/12 μg has shown to provide additional efficacy benefits compared to those associated with aclidinium or formoterol fumarate monotherapies (as assessed by measures of lung function, COPD symptoms and disease-specific health status) and yet the safety and tolerability of aclidinium

400 µg/formoterol fumarate 12µg is generally comparable to that of the component monotherapies (D'Urzo et al. 2014, Singh et al. 2014).

The safety profile for aclidinium bromide /formoterol 400/12 µg is based on the clinical experience after exposure at the recommended therapeutic dose for up to 12 months. The type and severity of adverse reactions associated with aclidinium bromide /formoterol 400/12 µg is comparable to each of the monocomponents.

The most frequently reported adverse reactions with aclidinium bromide/formoterol 400/12 µg were nasopharyngitis (7.9%) and headache (6.8%).

Other commonly reported adverse reactions with aclidinium bromide/formoterol 400/12 µg are urinary tract infection, sinusitis, tooth abscess, insomnia, anxiety, headache, dizziness, tremor, cough, diarrhoea, nausea, dry mouth, myalgia, muscle spasms, oedema peripheral and blood creatine phosphokinase increased.

Hypokalaemia, hyperglycaemia, agitation, dysgeusia, tachycardia, electrocardiogram QTc prolonged, palpitations, rash, pruritus, blurred vision, dysphonia, throat irritation, urinary retention, stomatitis and blood pressure increased are uncommon adverse reactions that could be observed with the aclidinium bromide/formoterol 400/12 µg.

The major metabolic pathways of aclidinium bromide in humans are nonenzymatic and enzymatic hydrolysis of its carboxylester moiety leading to two inactive metabolites, LAS34823 and LAS34850. Although the genetic locus of the enzyme responsible for the hydrolysis (butyrylcholinesterase) contains polymorphisms, the incidence of the variants reported in Asians and Caucasians are low and it is inferred that there is no great difference in the distribution of enzymatic activity between races. Moreover, since aclidinium bromide undergoes non enzymatic hydrolysis (its half-life at physiological pH, 1.2 hours), it is considered that ethnicity differences are unlikely to affect the metabolism of aclidinium bromide.

The pharmacokinetic parameters related to the absorption, distribution and elimination of aclidinium/formoterol, obtained in Japanese COPD patients (Study KRP-AB1102F-D302) were broadly comparable to the pharmacokinetic data obtained for aclidinium/formoterol in Western subjects. In addition, no differences in systemic exposure were seen for aclidinium bromide or formoterol fumarate when administered as a fixed dose combination or as monotherapies in clinical study LAC-PK-02.

Therefore, on the basis of the available pharmacokinetic data in Asian and Caucasian population and the lack of drug-drug interactions between aclidinium and formoterol, similar exposure is expected in Chinese COPD patients than in Japanese or Caucasian patients.

Based on the study drug safety profile, no specific risk is anticipated with the dose and the dose regimen proposed in this trial. Still, investigators will ensure adequate medical care of the trial participants at all times throughout the course of the study.

1.4 Study Design

This is a Phase IIa, single centre, open-label, repeat-dose study to investigate pharmacokinetics (PK), safety and tolerability of aclidinium/formoterol 400/12 µg administered twice-daily by inhalation in Chinese male and female patients with stable moderate to severe COPD.

All patients will sign an ICF before starting any study related procedure.

The study will consist of a Screening Visit (Visit 1) conducted after signature of the ICF and maximum 21 days before the first dose of investigational product (IP) administration on Day 1 at Visit 2. Eligibility screening will consist of inclusion and exclusion criteria evaluation; complete medical and surgical history/COPD history; prior and concomitant medications; demographics; inhaler training; physical examination; blood pressure assessment; 12-lead electrocardiogram (ECG); spirometry and reversibility test; clinical laboratory tests; serum pregnancy test for women of childbearing potential; serology (anti-hepatitis C virus, hepatitis B surface antigen, and anti-human immunodeficiency virus [HIV] type 1); urine drugs of abuse and alcohol screen; and adverse event (AE) monitoring. Relief medication is to be provided to the patient at Visit 1 (Screening).

All patients fulfilling inclusion/exclusion criteria will be admitted to the clinical unit the day preceding the 1st IP dose. On Day 1 through Day 4, patients will receive one inhalation of aclidinium bromide/formoterol 400/12 µg BID (morning and evening) via the Genuair® DPI. On Day 5 patients will receive only the morning dose of one inhalation of aclidinium bromide/formoterol 400/12 µg via the Genuair® DPI. Patients will be discharged on Day 7, 48 hours after last IP administration.

Pharmacokinetics and safety assessments will be conducted at specific time points in the clinical unit during the residential period (from Day -1 to Day 7 at Visit 2).

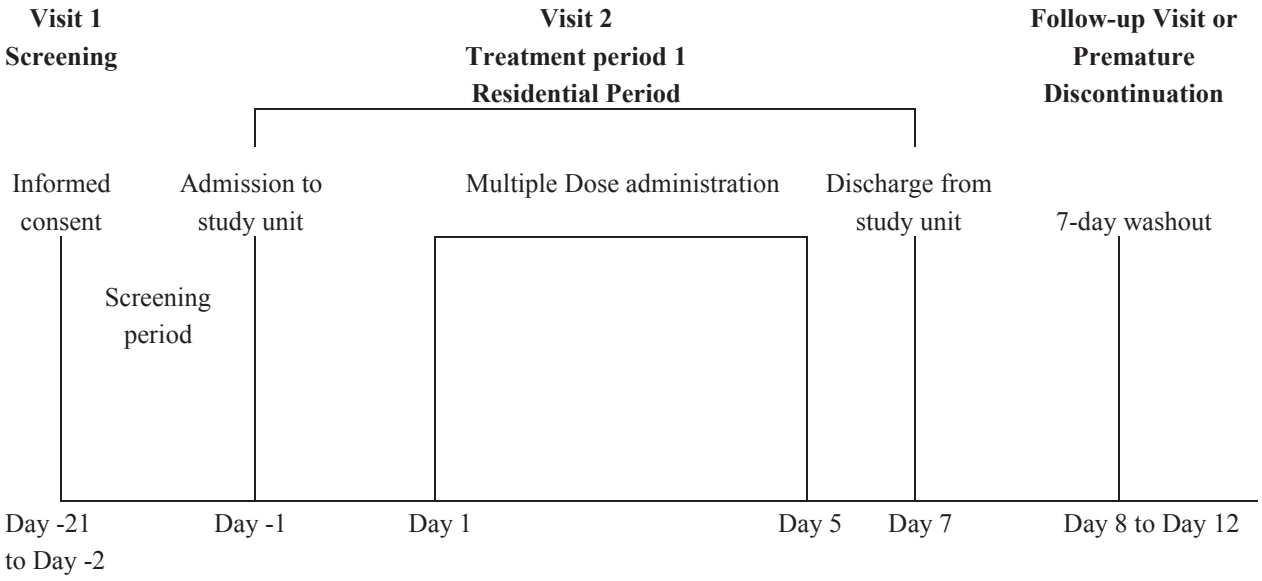
A follow-up visit will be performed within 5 days from patient's discharge after last PK sample collection on Day 7.

Patients who prematurely discontinue from the study (withdrawal) will participate in a Premature Discontinuation Visit that will include physical examination, clinical laboratory test, 12-lead ECG, blood pressure, serum pregnancy test for women of childbearing potential, and assessment of AEs and concomitant medication to ensure patient´s safety.

A complete list of all procedures and assessments is provided in the Schedule of Assessments in Table 1.

The study flow chart for each treatment sequence is shown in Figure 1.

Figure 1 Study flow chart



2. STUDY OBJECTIVES

2.1 Primary objective

Primary Objective:	Outcome Measure:
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 COPD.	The following pharmacokinetic parameters will be calculated when applicable for aclidinium bromide, its metabolites and formoterol fumarate: Day 1: C_{max}, t_{max}, AUC_{last}, AUC_{τ}, C_{min} Day 5: $C_{ss,max}$, $t_{ss,max}$, λ_z, $t_{½\lambda z}$, $AUC_{ss,\tau}$, CL/F*, V_z/F*, C_{av}, %Fluctuation, $C_{ss,min}$, $R_{ac}(C_{max})$ $R_{ac}(AUC_{\tau})$ and $R_{ac}(C_{min})$. Additional parameters may be determined where appropriate *Only for Aclidinium bromide and formoterol

2.2 Secondary objectives

Secondary Objective:	Outcome Measure:
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.	AEs/SAEs Blood pressure Clinical laboratory parameters (haematology, serum biochemistry and urinalysis) 12-lead ECG parameters

3. PATIENT SELECTION, ENROLMENT, RANDOMISATION, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

3.1 Inclusion criteria

For inclusion in the study patients should fulfil the following criteria:

1. Ability to communicate with medical team and staff, willing to participate in the trial, willing to give written informed consent, and comply with the trial procedures and restrictions.

2. Chinese men or non-pregnant, non-lactating women, aged ≥40 years old at Visit 1 (Screening).

   Explanatory note: A female is considered to be of childbearing potential unless is at least one year post-menopausal or permanently sterilised (e.g. tubal occlusion, hysterectomy, bilateral salpingectomy). Women of childbearing potential are allowed to enter the trial if they have a negative serum pregnancy test at the Visit 1 (Screening) and a negative serum pregnancy test at Day -1 and are using, during the last two months before the Visit 1 (Screening) and during the whole duration of the trial, at least one medically approved and highly effective method of birth control defined as those, alone or in combination, which result in a low failure rate (i.e less than 1% per year) when used consistently and correctly. Male participants are not requested to use contraception methods during their participation on the trial.

3. Patients with a diagnosis of COPD (GOLD guidelines, 2016) for a period of at least 6 months prior to Visit 1 (screening).

4. Current or former smokers with a smoking history of ≥ 10 pack-years.

   Explanatory notes:

   a. Former smoker condition defined as having quit smoking ≥ 6 months before Visit 1 (Screening).

   b. Pack-years is calculated by dividing the number of cigarettes smoked per day by 20 (the number of cigarettes in a pack) and multiplying this figure by the number of years a person has smoked. For example, a person who smokes 40 cigarettes a day and has smoked for 10 years would have a 20 pack-year smoking history (40 cigarettes per day ÷ 20 cigarettes per pack = 2; 2 x 10 years of smoking = 20 pack-year history). In case of intermittent smoking/non-smoking periods, pack-years is calculated by summing all periods pack-years.

   c. Patients smoking other tobacco types will not be allowed, unless they meet the cigarette criterion as well.

5. Patients with moderate to severe stable COPD (Stage II or Stage III, according to GOLD Guidelines 2016) at Visit 1: post-bronchodilator FEV_1 ≥30% and < 80% and post-bronchodilator FEV_1/FVC < 70%.

Explanatory note: "post" means FEV1 and FVC between 10 to 15 minutes after inhalation of 400 μg of salbutamol from acceptable and repeatable pulmonary function testing according to the American Thoracic Society (ATS)/European Respiratory Society (ERS) 2005 criteria. Predicted normal values to be used for calculation purposes are based on European Community for Steel and Coal predicted values (Quanjer et al. 1993).

6. Must be able to perform repeatable pulmonary function testing for FEV_1 according to ATS/ERS 2005 criteria at Visit 1 (Screening).

3.2 Exclusion criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled:

1. Involvement in the planning and/or conduct of the study (applies to AstraZeneca staff and/or site staff) or patients employed by or relatives of the employees of the site or sponsor.

2. Previous enrolment or randomisation in the present study.

3. History or current diagnosis of asthma.

4. Any respiratory tract infection (including the upper respiratory tract) or COPD exacerbation (including the mild COPD exacerbation) within 6 weeks prior to screening or during the run-in period.

5. Patients hospitalized for COPD exacerbation (an emergency room visit for longer than 24 hours will be considered a hospitalization) within 3 months prior to screening and during the run-in period.

6. Use of long-term oxygen therapy ≥ 15 hours per day.

7. Patient with a history of hypersensitivity reaction to inhaled anticholinergics, sympathomimetic amines, inhaled medication, or any component thereof.

8. Patients with known narrow-angle glaucoma, symptomatic bladder neck obstruction, acute urinary retention, or patients with symptomatic nonstable prostatic hypertrophy.

   Explanatory note: Patients with well-controlled, stable, asymptomatic benign prostatic hyperplasia (BPH) may be eligible to participate in the trial.

9. Patients with Type I or uncontrolled Type II diabetes, uncontrolled hypothyroidism or hyperthyroidism, hypokalaemia, hyperadrenergic state, or uncontrolled or untreated hypertension.

10. Clinically significant cardiovascular conditions.

Explanatory note: The following are examples of clinically significant cardiovascular conditions:

- Myocardial infarction within the 6 months prior to Visit 1 (Screening).
- Thoracic surgery within 12 months prior to Visit 1 (Screening)
- Unstable angina or unstable arrhythmia, which has required changes in the pharmacological therapy or other intervention within 12 months prior to Visit 1 (Screening) or newly diagnosed arrhythmia within the previous 3 months prior to Visit 1 (Screening).
- Hospitalization within 12 months prior to Visit 1 (Screening) for heart failure functional class III (marked limitation of activity and only comfortable at rest) and class IV (need of complete rest, confinement to bed or chair, discomfort at any physical activity, and presence of symptoms at rest) as per the New York Heart Association.

11. Patient with resting systolic blood pressure ≥ 160 mmHg, a resting diastolic blood pressure ≥ 100 mmHg, or a resting heart rate ≤ 50 bpm or ≥ 100 bpm at Visit 1 (Screening) or/and at Visit 2 (Day-1 to Day 7).

    Explanatory note: Patient can be with or without pharmacological therapy.

12. Have a body mass index (BMI) ≥ 40 kg/m^2

    Explanatory note: [BMI (kg/m^2) = Body weight (kg)/Height^2 (m^2)]

13. Electrocardiogram (ECG) at Screening or Day -1 showing corrected QT interval (QTc) using Fridericia's correction (QTcF) > 470 msec.

14. Patients with clinically relevant abnormalities in the results of the laboratory tests, ECG parameters (other than QTcF), or in the physical examination at Visit 1, except those related to COPD.

15. Positive results for drugs of abuse in the urine at Visit 1 (Screening).

    Explanatory note: Drugs of abuse include alcohol, benzoylecgonine (cocaine), methadone, barbiturates, amphetamines, benzodiazepines, cannabinoids, opiates, and phencyclidine.

16. Positive test for hepatitis B surface antigen (HBsAg), hepatitis C antibody and/or human immunodeficiency virus (HIV) I antibodies at Visit 1 (Screening).

17. History of malignancy of any organ system (including lung cancer), treated or untreated, within the past 5 years other than basal or squamous cell skin cancer.

Explanatory note: Patients are excluded whether or not there is evidence of local recurrence or metastases.

18. Any other serious or uncontrolled physical or mental condition/disease.

    Explanatory note: As judged by the investigator, the dysfunction could place the patient at a higher risk as a result of his/her participation in the trial, or confound the results of the trial, or would be likely to prevent the patient from complying with the requirements of the trial or completing the trial.

19. Patient with a history (within 2 years prior to Visit 1 [Screening]) of drug and/or alcohol abuse that may prevent trial compliance based on investigator judgment.

20. Taken any medication within 14 days before the first dose of IP, or hormonal drug products and traditional Chinese medicines within 30 days before the first dose of IP, with the exception of allowed medications listed in Section 7.9.

    Explanatory note: Medications include any prescription or over-the-counter medicinal products, health supplements and herbal remedies.

21. Participation in any other clinical investigation using an experimental drug requiring repeated blood or plasma drawn within 60 days of Day 1 at Visit 2.

22. Have participated in a blood/plasma donation or blood loss greater than 400 mL within 90 days or greater than 200 mL within 30 days prior to Visit 1 (Screening).

23. Have any clinical condition that might affect the absorption, distribution, biotransformation, or excretion of aclidinium bromide/formoterol fumarate.

24. Have consumed caffeine or any grapefruit-containing products within 48 hours or alcohol within 72 hours before Day -1 at Visit 2.

    Explanatory note: Examples include coffee, tea, cola, chocolate, diet pills, "energy drinks”.

25. Inability to be venipunctured or tolerate venous access as determined by the investigator or designee.

26. Inability to use a multidose DPI.

27. Subjects unable to give their consent, or subjects of consenting age but under guardianship, or vulnerable subjects.

28. In the opinion of the PI, subjects who are unlikely to comply with the protocol requirements, instructions, and trial-related restrictions.

Explanatory note: Examples include uncooperative attitude, inability to return for follow-up visits, and improbability of completing the clinical trial. This also includes subjects who have problems understanding the protocol requirements; instructions and trial-related restrictions; the nature, scope and possible consequences of the clinical trial.

29. Previously taken aclidinium or previously participated in an investigational study of aclidinium within 6 months of Day 1

Procedures for withdrawal of incorrectly enrolled patients see Section 3.4.

3.3 Patient enrolment

Investigator(s) should keep a record, the patient screening log, of patients who entered pre-study screening.

Patient numbers will be assigned at Visit 1 (Screening) or at informed consent form (ICF) signature, consecutively starting with the lowest number available.

The Investigator(s) will:

1. Obtain signed ICF from the potential subject before any study specific procedures are performed.

2. Assign a unique Patient Identification number. This number will be composed of two parts: the first 4 digits (fixed) representing the site identifier. The next 3 digits (ascending) which will be assigned sequentially within each site, starting with 001. The subject identification number will be used to identify the subject throughout the study and will be recorded in the electronic Case Report Form (eCRF).

3. At Screening and Day -1 (Visit 2), the investigator will determine patient's eligibility. See Sections 3.1and 3.2. Patients not meeting inclusion and/ or meeting exclusion criteria will be marked as "screen failures" and should have the final evaluation eCRFs completed.

If a patient withdraws from participation in the study, then his/her Patient ID code cannot be reused.

3.4 Procedures for handling incorrectly enrolled patients

Patients who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. Patients who are enrolled, but subsequently found not to meet all the eligibility criteria must not be initiated on treatment, and must be withdrawn from the study.

Where a patient does not meet all the eligibility criteria but is enrolled in error, or incorrectly started on treatment, the Investigator should inform the AstraZeneca study physician

immediately, and a discussion should occur between the AstraZeneca study physician and the investigator regarding whether to continue or discontinue the patient from treatment. The AstraZeneca study physician must ensure all decisions are appropriately documented.

3.5 Methods for assigning treatment groups

Not applicable

3.6 Methods for ensuring blinding

This is an open-label trial.

3.7 Methods for unblinding

Not applicable**.**

3.8 Restrictions

3.8.1 Dietary and Fluid Restrictions

On treatment days, breakfast will be served approximately 2 hours prior to IP, lunch at approximately 4.5h after IP, dinner approximately 2 hours prior IP and snack approximately 2h after IP. Time window allowance for each meal is ± 1 hour, except on Day 1 and Day 5 where breakfast will not be served.

Water is allowed as desired except for 1 hour before and 1 hour after IP administration.

Patients will be instructed to consume the entire contents of each meal and snack, if possible. Trial center personnel will document the percentage or the amount of unconsumed food for each subject, at least on Day 1 and Day 5.

Standard low fat (< 20 g) meals and snacks during trial confinement will be provided according to the trial center SOPs and in accordance with this protocol. Meals should not include any xanthine-containing beverages or food (eg, coffee, tea, cola, chocolate, diet pills, "energy drinks"), or caffeine.

On days that serum biochemistry samples will be drawn (Visit 1 [Screening], Day -1 at Visit 2 and Follow Up Visit), a fast of at least 8 hours will be observed.

Patients must abstain from caffeine, and xanthine-containing beverages or food (eg, coffee, tea, cola, chocolate, diet pills, "energy drinks"), grapefruit, grapefruit juice, Seville oranges or other products containing grapefruit or Seville oranges from 48 hours (2 days) prior to entry in the trial center on Day -1 at Visit 2 until discharge from the trial center.

Abstain from alcohol from 72 hours (3 days) prior to entry in the trial center on Day -1 at Visit 2 until discharge from the trial center.

3.8.2 Other Restrictions

All patients will have to comply with the following general requirements:

- Strenuous activity, sunbathing, and contact sports are prohibited within 96 hours (4 days) prior to admission into the trial center on Day -1 at Visit 2, and for the duration of the trial.
- Smoking and exposure to cold air, dust, or polluted air should be avoided for at least 1 hour before Visit 1 (Screening) until the completion of all Screening procedures.
- Blood or plasma donation until 3 months after the Follow-up Visit.

Any event likely to interfere with the objectives of the trial will be communicated to the investigator and reported without delay to AstraZeneca.

3.9 Discontinuation of investigational product and study withdrawal

If a patient is discontinued from IP, the patient will be withdrawn from further study procedures.

Any patient may withdraw from the trial at any time during the trial at the discretion of the Investigator or at the request of the patient. The main reason for such a premature discontinuation must be documented in the eCRF.

Patients may be prematurely discontinued from the trial by the Investigator for any of the following reasons:

- Adverse Event: if a patient experiences an AE (including COPD exacerbations), their premature discontinuation will be considered at the discretion of either the investigator or the patient regardless of the causal relationship to the IP. AE should be indicated as the reason for discontinuation in the eCRF, and the appropriate AE eCRF form must be completed.
- Protocol deviation: After enrolment, any protocol deviations detected should be corrected when possible and the patient should be allowed to continue. The following will lead to discontinuation of treatment: protocol deviations that could affect patient's safety (eg, illness requiring treatment(s) which in the clinical judgement of the Investigator [or after discussion with the trial monitor] might invalidate the trial by interfering with the IP); deviations due to patient non-compliance with the study protocol.
- Failure to meet randomisation criteria: Violations of inclusion and/or exclusion criteria detected after enrollment. See Section 3.4 for patients not fulfilling inclusion/exclusion criteria but detected after enrollment.

- Lost to follow-up: Non-attendance. In these cases, the Investigator should make every effort to ascertain the whereabouts, reason for lack of attendance, the health of the patient, and to assure patient attendance as soon as possible. Every effort (at least 3 documented attempts in the medical records) should be made to contact the patient. A registered mail letter will be sent to the subject and documented in the medical records.

- Withdrawal by subject: The patient is permitted to stop his/her participation at any time during the trial without incurring any loss in his/her medical care. The Investigator should ensure that such withdrawal is not due to AEs, in which case this reason should be selected.

- Pregnancy: In case of pregnancy, the female patient will be immediately discontinued from the trial.

- "Other": at the Investigator's request, study cancellation or any other reason not described above.

- Patient withdrawal due to death.

All dosed patients who prematurely discontinue from the trial, regardless of cause, will be seen for a premature discontinuation visit. Procedures/assessments for the premature discontinuation are indicated in the Schedule of Assessments (Table 1).

If there is a medical reason for withdrawal, the patient will remain under the supervision of the Investigator until satisfactory health has returned.

Patients prematurely discontinued from the trial will not be replaced. A minimum of 10 COPD patients completed are required in this trial.

3.9.1 Procedures for discontinuation of a patient from investigational product and from the study.

At any time, patients are free to discontinue investigational product or withdraw from the study (i.e., investigational product and assessments – see Section 3.9), without prejudice to further treatment. A patient that decides to discontinue investigational will always be asked about the reason(s) and the presence of any adverse events. If possible, they will be seen and assessed by an Investigator(s). Adverse events will be followed up (See Section 6); and all study drugs should be returned by the patient.

For any patient who withdraws from the IP, the investigator will:

1. Ask the subject to undergo the Premature Discontinuation Visit AS SOON AS POSSIBLE after discontinuation of IP.

The date and the main reason for such a premature discontinuation must be documented in the eCRF.

3.10 Criteria for withdrawal

3.10.1 Screen failures

Screening failures are patients who do not fulfil the eligibility criteria for the study, and therefore must not be randomised. These patients should have the reason for study withdrawal recorded as 'Screen Failure' (ie, patient does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (not randomised patients).

3.11 Premature Discontinuation of the study

The "end of trial" is defined as the date when all patients enrolled in the trial performed the last contact (either Visit 3 Follow-up or Premature Discontinuation Visit) and will be communicated to Regulatory Authorities and Ethics Committees on due time according to local regulations.

The Sponsor reserves the right to prematurely terminate (i.e., suspend) the trial for reasons such as:

- The principal investigator and the sponsor feel that the type, number and /or severity of AEs justify discontinuation of the trial.
- Data not known before become available and raise concern about the safety of the study drug so that continuation would pose potential risks to the patient.
- The Sponsor decides to discontinue the trial.

If the trial is terminated or suspended, the Sponsor will promptly inform the Investigator/trial center and the Regulatory Authorities. The EC should be promptly informed and provided the reason(s) for the termination or suspension by the PI/Sponsor, as specified by the applicable regulatory requirement(s).

The Investigator will inform the patients and will collect and keep all the data up to the date of discontinuation. Samples retrieved up to the date of trial termination will be analyzed as per protocol.

Regardless of the reason for termination, all data available for the subject at the time of discontinuation of follow-up must be recorded in the eCRF. All reasons for discontinuation of treatment must be documented.

If the trial is terminated or suspended, trial results will be reported according to the requirements outlined in this protocol as far as applicable.

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the patients' interests.

4. STUDY PLAN AND TIMING OF PROCEDURES

Table 1 Schedule of Assessments

	Screening period	Treatment period							Follow-up period
	Visit 1[1]	Visit 2							
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 Trial Center		X								
Meals (provided by trial center)[13]		X	X	X	X	X	X	X	X	
Discharge from the Trial 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 IP[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; IP = investigational product; PK = pharmacokinetic; PM = evening

1. If the patient needs additional time to washout any prior medications, the ICF must be provided before Visit 1. Patients must discontinue medications after informed c
2. The premature discontinuation visit/assessments will be performed as soon as possible after patient 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 the IP, will be re investigator or designee.
4. Patients will be discharged from the trial 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 patient 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. Patients 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 5.2.1
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.

4.1 Enrolment/screening period

This period will start with the signature of the Informed Consent Form (ICF), will follow with Visit 1 (Screening) when Chinese male and female COPD patients will be screened for participation in this trial within 21 days before Day 1 dosing, and will end at completion of all tests and procedures on Day -1. Eligible patients will be admitted to the trial center on Day -1.

Prior to ICF signing, investigators will evaluate suitability of patients for entry in the trial by comparing past and current medical status, as documented in the patient's medical records, to the inclusion/exclusion criteria of this study protocol.

Patients' ICF signature must be obtained before performing any procedure related to the trial. ICF must be signed after the patient has received sufficient information about the trial, after he/she has had the opportunity to ask any questions related to the study and considered the options.

Patients who require a washout period from prohibited concomitant treatments after ICF signature, Visit 2 will be scheduled later according to the wash-out length required for the specific medication stopped prior to Day -1 (Visit 2) (see section 7.9). Trial assessments will be performed at Visit 1 and patient will be dispensed one inhaler of relief medication and trained on its use.

At Screening, to verify the eligibility of subjects, the following evaluations will be performed:

- Obtain informed consent.
- Assess inclusion/exclusion criteria.
- Complete medical/surgical history, COPD history, smoking history and demographic (age, sex, race, and BMI).
- Perform a complete physical examination including body weight (in light indoor clothes, without shoes) and height.
- Collect blood pressure.
- Perform the 12-lead ECG.
- Collect blood and urine samples for the safety laboratory tests (including serology, haematology, biochemistry and urinalysis tests).
- Test for drugs of abuse and alcohol screen.
- Collect blood sample for serum β-human chorionic gonadotropin (β-hCG) pregnancy test only for women of childbearing potential.
- Adverse event (AE) monitoring and assessment.

- Record in the eCRF all medications the patient is currently taking and has taken during the previous 14 days before signature of the ICF. Remind the subject to avoid prohibited medications (see Section 7.9for details).
- Train the patient on the Genuair ® DPI user instructions. The investigator/designee will evaluate proper use of the device by the patient and provide additional training if needed. (See section 7.5)
- Provide relief medication to the patient as necessary and train patient on using the pressurized metered-dose inhaler, if necessary.
- Provide a patient diary to record relief medication use and AEs during the screening period until Visit 2.
- Spirometry Forced manoeuvre test (FEV_1 and FVC measurement): Three technically adequate measurements will be performed according to acceptability and repeatability criteria that meet ATS/ERS guidelines.
- Bronchodilator test (Reversibility test): administer inhaled salbutamol (100 µg x 4 puffs) through a spacer device at least 10 minutes after previous spirometry test. Three technically adequate measurements will be performed 10-15 minutes after inhalation of albuterol according to the ATS/ERS acceptability & repeatability criteria. Record each measurement.
- Document participation in the study into the subject's medical records.

Only patients who meet all inclusion/exclusion criteria will be allowed to continue to Visit 2.

4.2 Treatment period (Visit 2: from Day -1 to Day 7)

The sequence of evaluations in each day is recommended, but the specific order will depend on the site logistics provided the time-points referred to the IP administration (pre-dose and post-dose) are respected.

All patients will remain in the trial center from Day -1 at Visit 2 until the completion of the 48-hour PK sample collection and safety assessments on Day 7. Patients will be discharged from the trial center on Day 7 after all safety assessments and PK collections are completed.

If blood sampling, blood pressure assessments, and ECG recordings are scheduled at the same time points, the following 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 ECG is scheduled at the same time as a meal, the ECG must be obtained first.

4.2.1 Day -1

The following procedures will be performed:

- Reassess the inclusion/exclusion criteria to confirm the eligibility of the patient before being dosed on Day 1.
- Review with patient if any AEs occurred or any prior and/or concomitant medication that may have been taken since last visit.
- Assess relief medication use as documented in the patient diary.
- Perform the 12-lead ECG
- Blood pressure assessment. The BP should be determined in sitting position after 5 minutes.
- Blood and urine sample collection for the safety laboratory tests (haematology, biochemistry and urinalysis). Patients should be fasting a minimum of 8 hours prior to safety laboratory test collection.
- Perform a complete physical examination.
- Test for drug of abuse and alcohol screen
- Collect blood sample for serum β-human chorionic gonadotropin (β-hCG) pregnancy test only for women of childbearing potential.
- Train the patient on how to use the Genuair ® DPI device. The investigator/designee will evaluate proper use of the device by the patient and provide additional training if needed.
- Relief medication is to be provided to the patient during the treatment period as necessary.
- Provide meals according to Section 3.8.1
- Have the patient remain in the study center overnight.

4.2.2 Day 1

- Perform 12-lead ECG before morning (AM) IP administration (pre AM dose).
- Blood pressure assessment before IP administration (pre AM dose). The BP should be determined in sitting position after 5 minutes.
- Collect PK blood samples at morning pre-dose (approximately 15 minutes before the IP administration). Time window allowance in section 5.2.1

- Administer the 1st dose of AM IP approximately at 8:00 hours by inhalation from the Genuair ® DPI. The investigator or study personnel should check that the patient has used the inhaler correctly. Window allowance deviation for IP will be ± 1h.
- Collect PK blood samples at 5, 15, 30 min and 1h, 1.5h, 2, 3, 4, 6, 8, 12 h post IP AM administration. Time window allowance in section 5.2.1
- Perform 12-lead ECG at 2 hours (± 15 min) post IP administration. (post AM dose)
- Blood pressure assessment at 2 hours (± 30 min) post IP administration (post AM dose). The BP should be determined in sitting position after 5 minutes.
- Administer the evening (PM) dose of IP at approximately 20:00 hours (12 hours after AM dose) by inhalation from the DPI on Day 1. The investigator or study personnel should check that the subject has used the inhaler correctly. Window allowance deviation for IP will be ±1h in either AM dose or PM dose.
- Review with patient if any AEs occurred
- Assess relief and allowed concomitant medication use.
- Provide meals according to section 3.8.1. No breakfast will be served on Day 1.
- Have the patient remain the study center overnight.

4.2.3 Day 2 to Day 5

- Perform 12-lead ECG before IP administration (pre AM dose).
- Blood pressure assessment before IP administration (pre AM dose). The BP should be determined in sitting position after 5 minutes.
- From Day 2 to Day 4 administer AM IP aprox. at 8:00 hours and IP evening (PM) dose at approximately 20:00 hours (12 hours after AM dose). On Day 5, only the AM dose (aprox. at 8:00 hours) will be administered. No PM dose will be administered. Window allowance deviation for IP will be ±1h in either AM dose or PM dose
- On Days 2, 3 and 4 collect PK blood samples at pre-dose (approximately 5 minutes before the IP AM and PM administration). Time window allowance in section 5.2.1

- On Day 5 collect PK blood samples at pre-dose (approximately 5 minutes before the IP administration) and at 5, 15, 30 min and 1h, 1.5h, 2, 3, 4, 6, 8, 12 h post IP administration. Time window allowance in section 5.2.1
- Perform 12-lead ECG at 2 hours (± 15 min) post IP administration (post AM dose).
- Blood pressure assessment at 2 hours (± 30 min) post IP administration (post AM dose). The BP should be determined in sitting position after 5 minutes.
- Review with subject if any AEs occurred
- Assess relief and allowed concomitant medication use.
- Provide meals according to section 3.8.1. No breakfast will be served on Day 5.
- Have the patient remain in the study center overnight.

4.2.4 Day 6 and Day 7

- Collect PK blood samples at 24h, 36h and 48h post IP administration on Day 5. Time window allowance in section 5.2.1
- Review with subject if any AEs occurred.
- Assess relief and allowed concomitant medication use.
- Have the patient remain in the study center overnight on Day 6.
- Provide meals according to section 3.8.1.
- Discharge the subject on Day 7 after all safety and PK assessments are completed.

4.3 Follow-up period (Visit 3)

Patients are required to return to the trial centre for a Follow-up Visit (performed within 5 days of the final PK sample collection on Day 7 of Visit 2).

The following procedures are to be performed at the Follow-up Visit:

- Assessment of AEs and concomitant medications.
- Perform physical examination.
- Perform 12-lead ECG.

- Blood pressure assessment.
- Clinical laboratory tests (haematology, serum biochemistry and urinalysis).
- Serum pregnancy test for women of childbearing potential.

4.4 Premature discontinuation visit

If the patient is agreeable, the following procedures should be performed at this visit as soon as the subject has been discontinued from the trial:

- Assessment of AEs and concomitant medications.
- Perform physical examination.
- Perform 12-lead ECG.
- Blood pressure assessment.
- Clinical laboratory tests (haematology, serum biochemistry and urinalysis).
- Serum pregnancy test for women of childbearing potential.

5. STUDY ASSESSMENTS

The Electronic Data Capture (EDC) system will be used for data collection and query handling. The investigator will ensure that data are recorded on the electronic Case Report Forms (eCRF) as specified in the study protocol and in accordance with the instructions provided.

The investigator ensures the accuracy, completeness and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The investigator will sign the completed eCRF. A copy of the completed eCRFs will be archived at the study site.

5.1 Safety assessments

5.1.1 Laboratory safety assessments

Blood samples and urine samples for determination of clinical biochemistry, haematology and urinalysis will be taken at the times indicated in the Study Plan (see Section 4).

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. The date, time of collection and results (values, units and reference ranges) will be recorded on the appropriate eCRF page.

The clinical chemistry, haematology, serology and urinalysis will be performed by Covance laboratory services which will provide the report to the site. Covance will provide the trial center with blood sampling kits and shipment supplies. A specific manual will be distributed by Covance. Serum pregnancy test will be performed by the site local laboratory.

Complete routine laboratory assessments will be performed under fasting conditions. Patients are required to fast for at least 8 hours prior to the collection of specimens.

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at centre as source data for laboratory variables.

Throughout the trial, new clinically relevant findings or worsening of a pre-existing finding in the laboratory results must be considered an AE and must be recorded on the AE eCRF form. For information on how AEs based on laboratory tests should be recorded and reported, see Section 6.3

In case of technical problems, or if the Investigator considers a result is clinically relevant or doubtful, additional blood samples may be collected within a reasonable time and will be sent to the central laboratory for analysis (see Sections 5.1.7and 5.1.8 for Repeated and Unscheduled test criteria)

The following laboratory variables will be measured:

Table 2 Laboratory Safety Variables

Haematology/Haemostasis (whole blood)	Clinical Chemistry (serum or plasma)
B-Haemoglobin (Hb)	S/P-Creatinine
B-Hematocrit	S/P-Bilirubin, total
B-Erythrocytes count	S/P-Alkaline phosphatise (ALP)
B-Leukocyte count	S/P-Aspartate transaminase (AST)
B-Leukocyte differential count (absolute count)	S/P-Alanine transaminase (ALT)
B-Platelet (thrombocytes) count	S/P- Gamma-glutamyl transferase (GGT)
	S/P- Lactate dehydrogenase
	S/P-Creatine kinase (CK)
Serology (serum or plasma)	S/P-Albumin
S/P-HBsAg	S/P-Potassium
S/P- anti-HCV	S/P-Calcium, total
S/P- anti-HIV type 1	S/P-Sodium
	S/P- Chloride
	S/P- Inorganic phosphorous
Urinalysis	S/P-Glucose
U-Hb/Erythrocytes/Blood	S/P-Total cholesterol
U-Leukocytes	S/P- Triglycerides
U-Glucose	S/P- Total protein
U-pH	S/P- Uric acid
U-Protein/Albumin	S/P- Urea Nitrogen
U-Bilirubin	
U-Urobilinogen	
U-Ketones	
U-Nitrites	

NB. In case a patient shows an AST **or** ALT ≥3xULN **or** total bilirubin ≥ 2xULN please refer to Appendix C'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions.

During the course of the trial, the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a patient meets potential Hy's Law (PHL) criteria at any point during the trial.

Hy's Law guidance for the Investigator is included in Section 6.3.7and Appendix C.

5.1.1.1 Urinalysis

The urine sample will be sent to Covance central laboratory in China for analysis.

5.1.1.2 Pregnancy Test

For women of childbearing potential only, a serum pregnancy test will be done at Visit 1 (Screening); on Day -1 at Visit 2 and at the Follow up or Premature Discontinuation Visit.

If pregnancy occurs during participation in the trial, the patient must immediately discontinue from the trial. The pregnancy should be reported as described in Section 6.6.

5.1.1.3 Drugs of Abuse Screen

Drugs of abuse and alcohol screen will be performed at Screening (Visit 1) and on Day -1 (Visit 2) at the site.

Urine will be collected for the assessment of the following drugs of abuse: benzoylecgonine (cocaine), methadone, barbiturates, amphetamines, benzodiazepines, cannabinoids, opiates and phencyclidine. Alcohol screen will be performed using a breath test.

5.1.2 Medical History/Physical examination

A medical history of screened patients will be obtained at Visit 1 (Screening) (see Table 2), recording only the relevant demographic and medical data, as required in the Medical History/Physical examination electronic data capture (EDC) form.

A complete physical examination will be performed at Visit 1 (Screening), and at the Follow-Up Visit or Premature Discontinuation Visit (see Table 2). At Visit 1 (Screening), only relevant findings will be recorded in the Medical History/Physical examination eCRF form. On Day -1 or at Follow-up visit or premature discontinuation, new physical examination findings or physical examination findings that have worsened from previously known conditions will be recorded on the AE form. For information on how AEs based on physical examination should be recorded and reported, see Section 6.3

Body weight and height will be measured only at Visit 1 (Screening) (see Table 2), allowing the calculation of BMI. Patients should be in light indoor clothes without shoes.

5.1.3 Spirometry

Spirometry will be conducted at Visit 1 (Screening) to confirm eligibility criteria and COPD severity stage (post-bronchodilator forced expiratory volume in 1 second [FEV1] according to the Global Initiative for Chronic Obstructive Lung Disease [GOLD] guidelines 2016).

All spirometry equipment will be calibrated on the day it is to be used for trial purposes and the calibration will be documented in a log maintained at the trial center. Spirometers will measure the following:

- FVC (maximal volume of air exhaled with maximally forced expiratory effort from a position of maximal inspiration).
- FEV_1 (volume of air expressed in liters exhaled during the first second of performance of the FVC).

European Community for Steel and Coal predicted values (Quanjer et al., 1993) will be used to calculate the percentage predicted for FEV_1/FVC.

The local spirometers that will be used for the pulmonary function tests at the trial center must be in agreement with the standardization stated by the American Thoracic Society (ATS) and European Respiratory Society (ERS) guidelines. Spirometry will be conducted by qualified & experienced personnel. The circumstances of patient's tests should be similar, as much as possible, on all occasions with respect to time of the day, temperature, as well as the technician conducting the test.

5.1.4 ECG

5.1.4.1 Resting 12-lead ECG

Standard 12-lead ECGs will be performed at time points detailed in Table 2 and evaluations will be recorded after approximately 5 minutes resting in a supine position before any blood sampling. Preferably, 12-lead ECGs will always be recorded by the same technician for each patient.

At Visit 1 (Screening), the 12-lead ECG should be recorded at a similar time to the one that will be obtained at pre-dose during the course of the trial. Investigator will assess subject's eligibility according to the centralized reading report (manual reading) of Visit 1. At following visits, 12-lead ECG will be recorded pre morning dose and 2 hours (± 15 min) post morning dose as indicated in Table 2.

ERT, as the responsible company for the centralized electrocardiographic assessments, will provide the site with the 12-lead ECG equipment and supplies, specific training and written instructions.

Following an acquisition of a quality ECG tracing, the investigator or designee will manually read the ECG tracing and will electronically transfer the data to ERT.

Any finding in the ECG tracing will be evaluated by the ERT cardiologist. An overall assessment will be reported by ERT cardiologist as well as the Investigator, both overall assessment evaluations will be reported in the study database. In case of discrepancies, the investigator opinion/judgement will not be questioned and this will be specifically documented in the subject's medical notes.

When any 12-lead ECG result exceeds normal ranges, alert reports will be immediately sent by ERT by e-mail to the investigator.

The investigator will review the "manual reading" reports to assess the clinical relevance of any abnormal finding and/or to decide if the subject is or remains eligible for the study.

However, the responsibility for inclusion or continuation of the subject in the study will lie within the investigator in consultancy with the sponsor.

The 12-lead ECG will be recorded at 25 mm/sec and will consist of a recording of leads I, II, III, aVR, aVL, aVF and V1 to V6 and 10 seconds recording of lead II (rhythm strip). At least 3 complete evaluable complexes per lead will be recorded. The following ECG parameters will be determined:

- Heart rate
- RR interval: Duration in milliseconds between two R peaks of two consecutive QRS complexes.
- PR interval: Duration in milliseconds from the beginning of wave P to onset of ventricular depolarization (Q and R).
- QRS interval: Duration in milliseconds of the QRS complex.
- QT interval: Duration in milliseconds from the beginning of Q wave to the end of the T wave
- QTc interval: QTc by heart rate:
  - QTcB interval: QTcB (QT[msec]/RR[sec]$^{1/2}$).
  - QTc using Fridericia's formula (QTcF): QTcF (QT[msec]/RR[sec]$^{1/3}$).

Any abnormal finding in the ECG tracing will be evaluated by the Investigator and will be specifically documented on the eCRF.

Throughout the trial, new clinically relevant findings or worsening of a pre-existing finding in the ECGs (parameters or abnormal findings in the tracing) must be considered as an AE and must be recorded on the AE eCRF form. For information on how AEs based on ECG results should be recorded and reported, see Section 6.3.

In case of technical problems, if the PI considers any result to be clinically relevant or doubtful, additional 12-lead ECGs may be performed using the same equipment and within a reasonable time (see Sections.5.1.7 and 5.1.8).

For information on how AEs based on ECG results should be recorded and reported, see Section 6.3.

5.1.5 Vital signs

5.1.5.1 Blood pressure

Both systolic blood pressure and diastolic blood pressure (in mmHg) will be measured after at least 5 minutes resting, at time points indicated in Table 2, and also before taking any blood samples. Measurements will be carried out with patient in the sitting position and preferably always on the same arm. Data will be recorded on the eCRF.

If there is any suspicion of an unreliable measurement, blood pressure will be measured again. The value obtained on the second measurement will be considered as definitive and will be the one recorded on the eCRF.

For information on how AEs based on vital signs should be recorded and reported, see Section 6.3

5.1.6 Adverse Events

Adverse events will be recorded throughout the trial, see Table 2. Procedures for recording and assessing AEs are included in Section 6.3.

5.1.7 Repeated Tests (Re-Test)

Any test may be repeated at the investigator's discretion in any of the following situations:

At Visit 1 (screening) and on Day -1 at Visit 2 any individual test(s) might be repeated before dosing e.g., in case of impaired results (e.g., blood sample haemolysed) or results requiring confirmation (to ensure patient eligibility or results inconsistent with patient's known past medical conditions, etc…). Patients who do not meet the eligibility criteria (despite the repeated tests) will be screen failed. Repetition of the entire screening visit (Visit 1) is not allowed.

If any of the specific tests of the Screening Visit needs to be repeated, and more than 28 days has elapsed since first test date, the patient will be screen failed.

As deemed necessary by the investigator, ECGs and laboratory test can be repeated at any time during the study in order to follow-up the progress of any clinically relevant abnormal finding, investigate any potential new adverse event, etc.

Before starting any procedure at Visit 2, research personnel will ask the patient about his/her overall status. The following rules with respect to postponing the visit will be adhered to:

- The intake of any prohibited medication, the visit will be postponed (no assessment performed) according to the wash-out length required for the specific prohibited medication taken as long as delay fits the protocol allowed time window.

- For logistic reasons: Patient or Investigator are not able to perform the visit on the scheduled date due to technical or personal issues by site/patient.

The repeated tests will be called “re-test” and will be identified with the same visit identifier as the first attempt.

5.1.8 Unscheduled Tests

As deemed necessary by the investigator, additional safety test(s) can be performed at any time during the trial in order to follow-up on the progress of any clinically relevant abnormal finding, investigate any potential new AE, etc. These additional test(s) out of the initial trial schedule will be called "Unscheduled test" and will not be associated to any trial visit

5.2 Pharmacokinetics

5.2.1 Collection of samples

Blood samples for determination aclidinium bromide and its metabolites LAS34850 and LAS34823 and formoterol fumarate in plasma will be taken at the following time points:

Day 1: 0 hour (pre-dose; approximately 15 minutes prior to the morning dose), 5 minutes, 15 minutes, 30 minutes, 1 hour, 1.5 hour, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours and 12 hours (12 time points).

Days 2-4: 0 hour (pre-dose; approximately 5 minutes prior to the morning and evening dose) (6 time points).

Day 5: 0 hour (pre-dose; approximately 5 minutes prior to the morning dose), 5 minutes, 15 minutes, 30 minutes, 1 hour, 1.5 hour, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, 12 hours, 24 hours, 36 hours and 48 hours post the morning dose (15 time points).

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

Day 1 and Day 5:

- Pre-dose: ± 10 min
- 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

At each time-point, approximately 4 mL of blood will be drawn for the determination of aclidinium bromide and its metabolites and 4 mL for the determination of formoterol fumarate.

The total amount of blood to be collected for the PK assessments will be 264 mL (33 time points x 8 mL).

Samples will be collected, labelled, handled, stored and shipped as detailed in the Laboratory Manual.

5.2.2 Determination of drug concentration

Samples for determination of drug concentration in plasma will be analysed by Covance Laboratories on behalf of AstraZeneca, using validated bioanalytical methods.

Full details of the analytical method used will be described in a separate Bioanalytical report. Results will be only reported for samples shipped within a timeframe for which the stability of aclidinium bromide or formoterol in the samples has been validated and shown to be acceptable.

5.2.3 Storage and destruction of pharmacokinetic samples

Pharmacokinetic (PK) samples will be disposed of after the Bioanalytical Report finalization or six months after issuance of the draft Bioanalytical Report (whichever is earlier), unless requested for future analyses.

Pharmacokinetic samples may be disposed of or destroyed and anonymised by pooling. Additional analyses may be conducted on the anonymised, pooled pharmacokinetic samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.

Incurred sample reproducibility analysis, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the Clinical Study Report but separately in a Bioanalytical Report.

5.3 Pharmacodynamics

5.3.1 Collection of samples

Pharmacodynamic samples will not be taken during the study.

5.4 Pharmacogenetics

Pharmacogenetic samples will not be taken during the study

5.5 Biomarker analysis

Biological samples for biomarker analysis will not be taken during the study

5.6 Total Blood Volume

Table 3 presents the number and volume of blood samples and the total volume of blood that will be collected per patient in the trial.

Table 3 Number and Volume of Blood Samples and Total Blood Volume Collected per Patient

Test	Visit 1	Visit 2			Follow-up Visit or Premature Discontinuation	Number of Samples	Approximate mL/sample	Total mL of Blood
	Screening	Day -1	Day 1	Day 2 to 4	Day 5 to 7	Day 8 – Day 12			
Hematology	1	1				1	3	3	9
Fasting Serum Biochemistry	1	1				1	3	5	15
Serology	1						1	5	5
Serum Pregnancy Test	1	1				1	3	3	9
PK Collections			12	6	15		33	8	264
							Approximate total per subject[a]		**302**

PK= Pharmacokinetic

a This total does not include any additional tests that might be required because of AEs or retesting because of abnormal results or unschedule

b Only for women of childbearing potential.

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

The Investigator will closely monitor any AE and will adopt the necessary clinical measures to ensure the safety of the patients.

6.1 Definition of adverse events

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.

6.2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above.

For further guidance on the definition of a SAE, see Appendix A to the Clinical Study Protocol.

6.3 Recording of adverse events

6.3.1 Time period for collection of adverse events

Adverse Events will be collected from time of signature of informed consent throughout the treatment period and including the follow-up period (i.e. follow-up visit or premature discontinuation visit).

In case an SAE is notified to the investigator after last follow up contact as per protocol, this SAE should be proactively reported to AstraZeneca for recording in the Safety Database, but without further recording in the eCRF.

6.3.2 Follow-up of unresolved adverse events

Any AEs that are unresolved at the patient's last AE assessment in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

6.3.3 Variables

The following variables will be collect for each AE;

- AE (verbatim)
- The date and time when the AE started and stopped
- Maximum intensity
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product (yes or no)
- Action taken with regards to investigational product
- Outcome.

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalisation

- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Description of AE.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Section 6.2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Section 6.2.

For grading the intensity of an AE the following 3 categories will be considered:

- Mild: means awareness of symptoms or signs, but easily tolerated (acceptable).
- Moderate: means enough discomfort to interfere with usual activity (disturbing).
- Severe: means incapacity to work or to perform usual activities (unacceptable).

AEs will be collected only once with its maximum intensity.

6.3.4 Causality collection

The Investigator will assess causal relationship between Investigational Product and each Adverse Event, and answer ‘yes’ or ‘no’ to the question ‘Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?’

For SAEs causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as ‘yes’.

A guide to the interpretation of the causality question is found in Appendix A to the Clinical Study Protocol.

6.3.5 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study personnel: *'Have you/the child had any health problems since the previous visit/you were last asked?*', or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

6.3.6 Adverse events based on examinations and tests

The results from protocol mandated laboratory tests, ECGs, physical examination and vital signs will be summarised in the clinical study report (CSR).

Medical disorders present at the time of signing the ICF that are part of the patient's medical history will only be considered AEs if they worsen after this time.

Relevant abnormalities detected before IP administration in physical exam, laboratory value/vital sign, ECGs will not be considered AEs **if already known** as part of the medical history or **in relation to prior medical conditions**, and will be recorded on the eCRF Medical History/physical examination form/page.

Abnormalities detected in screening/run-in/baseline tests, thought to be due to a study procedure, will be considered AEs.

During the trial, abnormalities (newly occurring or worsening of previously known abnormalities) detected in laboratory values, vital signs, ECGs and physical examination which are considered clinically relevant by the investigator or which require an intervention or a diagnosis test, or may result in the IP discontinuation, should be reported as AEs.

In addition, when an AE meets the criteria of seriousness (SAE), it must also be recorded on the SAE form and reported following the defined timelines (section 6.4).

6.3.7 Hy's Law

Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3xULN together with total bilirubin ≥ 2xULN may need to be reported as SAEs. Please refer to Appendix C for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

6.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate AstraZeneca representatives within one day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the EDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the EDC system is not available, then the Investigator or other study site personnel reports a SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the Investigator/study site personnel how to proceed.

SAEs not considered to be reported to AstraZeneca will be:

- Hospitalisation for a treatment/surgical procedure which was elective or pre-planned for a pre-existing condition that did not worsen during the participation in the study

- Hospitalisation or prolongation of an existing hospitalisation for respite care (eg, patient lives too far from the hospital or has no caregiver at home)

A regulatory report of the SAE (depending on the local requirements) will be produced by AstraZeneca and submitted to the Regulatory Authorities, EC and/or Investigators when applicable according to local regulations.

6.5 Overdose

As patients are admitted to the site unit during the treatment phase, it is very unlikely overdose may occur, however in the accidental case of an overdose please refer to the IB.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the CRF and on the Overdose CRF module.

- An overdose without associated symptoms is only reported on the Overdose CRF module.

If an overdose with associated AE on an AstraZeneca study drug occurs in the course of the study, then the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 6.4.

6.6 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca.

6.6.1 Maternal exposure

If a patient becomes pregnant during the course of the study investigational product should be discontinued immediately.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 6.4) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the CRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy.

6.6.2 Paternal exposure

Provided that nonclinical data with aclidinium and formoterol fumarate based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential and toxicity to reproduction and development do not reveal special hazard for humans, male participants are not requested to use contraception methods during their participation on the trial.

In case of pregnancy of the patient's partners, the participant will not be necessarily discontinued from the trial but the partner's pregnancy should be reported on the Pregnancy form following the same timeframe and routing as described for any participant's pregnancy. These pregnancies will be also followed up, and the outcome of the pregnancy (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should if possible be obtained and documented.

6.7 Management of IP related toxicities

There will be no dose reductions in this study.

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational product(s)

Investigational product	Dosage form and strength	Manufacturer
Aclidinium bromide/formoterol fumarate	Inhalation powder in a multidose DPI (Genuair ®). Every puff of the inhaler administers 400 µg of aclidinium bromide and 12 µg of formoterol (metered dose), via oral inhalation.	Industrias Farmacéuticas Almirall, S.A. (IFA) Sant Feliu de Llobregat, Barcelona, Spain

The IP (Aclidinium Bromide 400 µg/Formoterol Fumarate 12 µg inhalation powder) consists of a fixed dose combination of long-acting anticholinergic drug, namely aclidinium bromide, combined with the long-acting β_2-agonist formoterol fumarate.

The drug product is an inhalation powder comprising of micronized aclidinium bromide and micronized Formoterol fumarate with α-lactose monohydrate as the carrier.

IP manufacturing, labelling, packaging and release will be conducted following Good Manufacturing Practice (GMP). Each Genuair® DPI will be packed in an Alu-Pouch.

Batch numbers will be indicated in the CSR.

For training purposes, each subject will receive an empty Genuair® DPI that will be used on Visit 1 (Screening) and on Day -1 at Visit 2.

7.2 Additional Drug

Relief medication Salbutamol pMDI (100 µg/puff) is considered as additional study drug and the accepted standard brand available in the country will be sourced.

Relief medication is to be provided by the investigator to the patient at the Visit 1 (screening) and re-supplied throughout the study as necessary according to use. When administered for the reversibility test at the study center (screening visit), salbutamol should be given through a spacer device to be certain it has been inhaled properly. During the study, the use of spacers for the salbutamol administration will be permitted, provided they were used routinely by the patient prior to study entry.

Marketed salbutamol pMDI (100 mcg per puff) provided by the Sponsor will ONLY be permitted as relief medication during the participation in the trial to be used on an as-needed basis but it is mandatory that the patient does not intake salbutamol at least 6 hours prior to performing the first spirometry maneuver at Screening. If salbutamol is taken within 6 hours of the scheduled spirometry measurement at Screening, the visit should be rescheduled for the next day.

7.3 Dose and treatment regimens

Before taking the first dose the IP the patient will be instructed by the study personnel on how to use the Genuair® DPI. Subject will practice inhalation technique with empty training devices provided for this purpose. Instructions on how to use the Genuair® DPI will be provided to the subjects in local language.

Further information regarding IP preparation at site will be provided in the investigator drug manual.

From Day 1 to Day 4, at approximately 08:00 hours, patients will receive one inhalation of aclidinium bromide/ formoterol 400/12 µg via the Genuair® multidose DPI. The PM dose (12 hours after the AM dose, at approximately 20:00 hours) will be administered after the 12-hour PK sample collection; patients will receive one inhalation of aclidinium bromide/formoterol 400/12 µg via the Genuair® multidose DPI.

On Day 5, at approximately 08:00 hours, patients will receive one inhalation of aclidinium bromide/ formoterol 400/12 µg via the Genuair® multidose DPI. There will be no PM dose administered.

7.4 Labelling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language.

IP will be supplied in the form of medication kits (medication box). Every medication kit will contain one Genuair® inhaler, inserted in an aluminium pouch along with a desiccant and placed in a box.

In order to allow drug reconciliation and dispensation control, research personnel will record the Patient ID number on the labels of every kit dispensed, as well as on the bags label and inhalers labels.

Training DPI will be provided with the appropriate labelling but the patient number information will be completed by the investigator. All Genuair® DPIs for training will be clearly identified as TRAINING.

7.5 Training on DPI inhaler use

Training for the use of the DPI will be done at Visit 1 (Screening) and on Day -1 at Visit 2; the patient will receive an empty Genuair® inhaler device for training. All patients will be trained on the use of the inhaler. As many practices as needed to learn the correct technique for use of the device will be allowed. The Investigator should ensure the comprehension of the instructions by the patient and the correct use of the inhaler training devices. Patients will be provided written instructions on the use of the inhaler device.

7.6 Storage

All study drugs should be kept in a secure place under appropriate storage conditions. The investigational product label on the pack specifies the appropriate storage.

The person responsible for the IP at the drug distribution centre and hospital pharmacy (or any facility at the research site) will inventory and acknowledge receipt of all IP supplies received as well as its dispensation.

Further information regarding IP storage at site will be provided in the investigator drug manual.

7.7 Compliance

The administration of all study drugs (including investigational products) should be recorded in the appropriate sections of the eCRF.

Patients will receive all IP doses under the direct supervision of trial center personnel which will guarantee compliance. The Investigator is responsible for ensuring that dosing is administered in compliance with the protocol. Delegation of this task must be clearly documented and approved by the Investigator.

Investigational product compliance will be assumed to be 100% when dosing has been recorded in the eCRF.

The trial center will keep an accurate drug disposition record that specifies the amount of IP administered to each patient and the date of administration.

No IP will be administered out of the unit, therefore no extra compliance method will be needed.

7.8 Accountability

The study drug provided for this study will be used only as directed in the study protocol.

The Investigator is responsible for the control of the IP (aclidinium bromide/formoterol 400/12 µg) under investigation. Adequate records of the receipt (eg, Drug Receipt Record) and disposition (e.g. Drug Dispensing Log) of the IP must be maintained. The Drug Dispensing Log must be kept current and should contain the following information:

- Identification of the patient to whom the IP was dispensed
- Date(s) and quantity of the IP administered to the patient.

The study personnel will account for all study drugs dispensed to the patient.

Study site personnel, if applicable, or the AstraZeneca monitor will account for all study drugs received at the site, unused study drugs and for appropriate destruction. Certificates of delivery, destruction and return should be signed.

All records and drug supplies must be available for inspection by the site monitor at every monitoring visit. At the end of the trial, after final IP accountability is performed, all unused IP and relief medication will be destroyed according to appropriate SOPs. If unused IP will be disposed, the disposal will be conducted according to appropriate SOPs after final accountability is performed by the site monitor. The completed Drug Dispensing Log and Drug Return Record(s) will be sent to the trial master file (TMF).

7.9 Prior and Concomitant medications

Any medication taken by the patient within 14 days prior to signature of Informed Consent will be collected in the electronic case report form (eCRF).

The use of the following medications is not allowed during the trial: anticholinesterases, anticholinergics (long and short acting), inhaled ß2 agonists (long and short acting agents, except salbutamol used as relief medication), methylxanthines, continuous oral corticosteroids used at a dose in excess of the equivalent of 10 mg prednisone per day or 20 mg every other day, mast-cell stabilizers, leukotriene modifiers, and nonselective ß1- blocking agents. See Table 4 for a list of concomitant medications that are allowed and not allowed during the trial.

Relief medication (salbutamol pMDI 100 µg/puff) is permitted as needed throughout the trial duration for all patients. In addition, several background medications for the treatment of COPD (inhaled corticosteroids; oral corticosteroids up to a maximum of 10 mg of prednisone/day or 20 mg every other day are permitted if the dose is stable for at least 4 weeks prior to Visit 1 (Screening)). Relief and background therapies will be allowed to help minimize the risk of COPD exacerbations. Use of relief medication will be recorded on a separate medication log by site staff during inpatient stay and recorded on a patient diary during the wash-out period. All relief medication use will be recorded on a specific eCRF page.

No hormonal drug products or traditional Chinese medicines will be allowed 30 days before Day 1 at Visit 2 and throughout the study, except for hormonal IUDs.

No new concomitant medications will be allowed during the trial unless they are approved by the Sponsor or prescribed in response to an AEs. In the event medication is used, it will be recorded in the appropriate section of the eCRF and in the source documents.

Table 4 Allowed Concomitant Medications

Allowed Medication/Class of drug:	**Restrictions**	**Stabilization period**
Inhaled corticosteroids*	Patients who were following a stable regimen of a LABA/ICS combination for at least 4 weeks can be switched to the same inhaled corticosteroid (at the same dose and dose regimen) as monotherapy. In this case no stabilisation period is needed. If treatment is switched to a different inhaled corticosteroid as monotherapy at an equivalent therapeutic dose to the one used for the fixed inhaled combination, a stabilisation period of at least 14 days or longer, until patient is considered stabilised, should occur before Screening (Visit 1). The patient will be considered stabilised if, according to the Investigator's judgement, during the second week of observation there are no changes in symptoms beyond the day to day variation, or symptoms experienced remain at a similar level of those existing before medication change	4 weeks
Continuous oral or parenteral corticosteroids*	Dose equivalent of 10 mg of prednisone per day or 20 mg every other day or lower than this.	4 weeks
Selective β-blocking agents (eg. Atenolol, metoprolol, nebivolol)	-	2 weeks
Oxygen therapy*	< 15 hours a day	4 weeks
Oral sustained-release theophyllines *	Theophylline should be avoided the morning of study visits and begin after visit completion.	4 weeks

*Change in daily dose, dosing schedule, formulation or treatment is unlikely during the course of the trial (the exception being the treatment of a COPD exacerbation).

Table 5 Prohibited Medications

Prohibited Medication/Class of drug:	**Wash-out before Day -1 (Visit 2) and during the trial**
Oral, intra-nasal or parenteral anticholinergic agents such as atropine, glycopyrrolate or biperiden	14 days
Twice daily long-acting inhaled anticholinergics, LAMAs (e.g. aclidinium bromide)	14 days
Once daily long-acting inhaled anticholinergics, LAMAs (e.g. umeclidinium, tiotropium bromide, glycopyrrolate)	14 days
Short-acting inhaled anticholinergics, SAMAs	12h
Inhaled and short acting β2-agonists, SABAs (eg, fenoterol or albuterol, except for albuterol/salbutamol)	6h
Oral* and twice-daily long acting β2-agonists, LABAs (eg, terbutaline*, formoterol or salmeterol)	14h
Once daily long-acting β2- agonists (LABAs) (eg, indacaterol, oladaterol) and once daily combination of LABAs+ICS (eg vilanterol/fluticasone)	14 days
Twice daily LABAs (eg, formoterol, salmeterol) and twice daily combination of LABAs+ICS (eg fluticasone/salmeterol, budesonide/formoterol) Note: Patients can be switched to the same or a different inhaled corticosteroid as monotherapy (see restricted medication section for stabilization period)	14 days
Combination of SABAs+SAMA (eg ipratropium/salbutamol)	12h
Combination of LABA+LAMA (eg indacaterol/glycopyrronium, umeclidinium/vilanterol, tiotropium/olodaterol)	14 days
Methyl-xanthines (eg. Theophylline, theobromine tablets)	14 days
Leukotriene modifiers (eg montellukast)	14 days
PDE IV inhibitors (eg, roflumilast)	14 days
Continuous oral or parenteral corticosteroids used at a dose in excess of the equivalent of 10 mg of prednisone per day or 20 mg every other day Note: can be switched to dose equivalent of 10 mg of prednisone per day or 20 mg every other day as long as they are at stable dose for at least 4 weeks prior to V1	14 days
Non-selective β-blocking agents (eg. Carvedilol, alprenolol, nadolol, propranolol, sotalol, timolol) Note: can be switched to selective β1-blocking agents, as long as they are at stable dose for at least 2 weeks prior to V1	14 days
Herbal/Traditional Chinese Medicine	30 days

Table 6 Relief Medication

Relief/Wash-out and Run-in Medication/Class of drug:	Usage:
Salbutamol pMDI (100 μg/puff) Note: marketed salbutamol available in the participating countries will be supplied in their original box and with its original instructions leaflet (local languages). Where needed according to local regulations, salbutamol boxes will be provided labelled for the purposes of this trial.	Administration should be on "as needed" basis, as per the investigator's instructions from the ICF signature until the end of the trial 6h of wash-out is needed before spirometry test at Visit 1.

Cytochrome P450 (CYP) isozymes 2C9, 2C19, and 2D6, are involved in the metabolism of formoterol fumarate. Patients need to be washed out for a minimum of 14 days prior to dosing and throughout the clinical conduct of this trial of the following medications:

Table 7 CYP P450 Inhibitors

2C9	2C19	2D6	
Fluconazole	Proton Pump Inhibitors:	Bupropion	Doxepin
Amiodarone	Lansoprazole	Fluoxetine	Doxorubicin
Fenofibrate	Omeprazole	Paroxetine	Escitalopram
Fluvastatin	Pantoprazole	Quinidine	Halofantrine
Fluvoxamine	Rabeprazole	Duloxetine	Hydroxyzine
Isoniazid		Terbinafine	Levomepromazine
Lovastatin	Chloramphenicol	Amiodarone	Methadone
Phenylbutazone	Cimetidine	Cimetidine	Metoclopramide
Probenicid	Felbamate	Sertraline	Mibefradil
Sertraline	Fluoxetine	Celecoxib	Midodrine
Sulfamethoxazole	Fluvoxamine	Chlorpheniramine	Moclobemide
Sulfaphenazole	Indomethacin	Chlorpromazine	Perphenazine
Teniposide	Ketoconazole	Citalopram	Ranitidine
Voriconazole	Modafinil	Clemastine	Red-Haloperidol
Zafirlukast	Oxcarbazepine	Clomipramine	Ritonavir
	Probenicid	Cocaine	Ticlopidine
	Ticlopidine	Diphenhydramine	Tripelennamine
	Topiramate		

Table 8 CYP P450 Inducers

2C9	2C19	2D6
Rifampin	Carbamazepine	Dexamethasone
Secobarbital	Norethindrone	Rifampin
	NOT Pentobarbital	
	Prednisone	
	Rifampin	

7.9.1 Other concomitant treatment

Medications other than that described above, which is considered necessary for the subject's safety and well-being, may be given at the discretion of the Investigator and recorded in the appropriate sections of the Case Report Form.

8. STATISTICAL ANALYSES

8.1 Statistical considerations

All data analyses will be performed by Parexel except the derivation of the PK parameters, which will be performed by Covance.

A comprehensive Statistical Analysis Plan (SAP) will be prepared by Parexel prior to first subject rendomised and any subsequent amendments will be documented, with final amendments completed prior to the database lock.

All results will be presented by treatment with descriptive statistics appropriate to the nature of the variables. Demographic and baseline characteristics will be presented. For continuous variables, the number of non-missing observations, mean, standard deviation, standard error of the mean, 95% CI of the mean (except safety data), median, first and third quartiles, minimum and maximum will be presented. For categorical variables: counts (n) and percentages (%) will be presented. These summaries will be provided by time-point of assessment as appropriate.

The SAS® version 9.3 or later will be used for the data analysis. A complete set of raw data listings will be appended to the final CSR.

In general, there will be no imputation of missing data for the safety analyses. Additional details will be provided in the SAP.

8.2 Sample size estimate

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

8.3 Definitions of analysis sets

Analysis will be done using the safety and PK populations. Descriptive statistics for demographics and other baseline characteristics will be provided.

The number and percentage of patients enrolled, patients who complete the treatment period, and those patients included in the PK and Safety populations will be tabulated. Patients who prematurely discontinue along with the reasons as recorded on the termination pages of the eCRFs will be summarized using the Safety population. Additionally, the cause of screening failure should be tabulated for Screening population.

8.3.1 Safety analysis set

All patients who receive at least 1 dose of aclidinium bromide/formoterol will be included in the safety population.

8.3.2 PK analysis set

The PK analysis set is defined as all patients who took at least one dose of IP 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 protocol deviations (e.g., disallowed medication, or incorrect study medication received). All protocol deviations that occur during the study will be considered for their severity/impact and will be taken into consideration when patients are assigned to the PK analysis sets.

The exclusion of any patients or time points from the calculation of the PK parameters will be documented by the PK scientist including the reason(s) for exclusion. The available concentration data and PK parameter data for any patients excluded from the PK analysis set will be listed only, and presented in the individual figures of concentration time plots.

8.3.3 Protocol deviations.

The criteria for the assessment and reporting of protocol deviations will be stipulated in a separate study specific protocol deviation specification document. Safety measurements and PK sample collections performed within the time window allowances recommended in this protocol will not be considered as protocol deviations and will not be reported.

Deviations from the protocol will be assessed as “important” in conjunction with the sponsor. Important deviations from the protocol may lead to the exclusion of subjects from the PK analysis set.

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;
- Time window deviations for PK and safety assessments;
- Administration of prohibited concomitant medications that are expected to influence the measurement of the PK endpoints;
- Missing IP administration.

All protocol deviations will be listed by subject for all randomised subjects. Further details will be described in the statistical analysis plan (SAP).

8.4 Outcome measures for analyses

8.4.1 Pharmacokinetics Variables

Where possible, the following PK parameters will be assessed for aclidinium bromide, its metabolites (LAS34850 and LAS34823) and formoterol on plasma concentrations:

Day 1

C_{max}	Observed maximum concentration, 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 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
$AUC\tau$	area under the plasma concentration curve during the first dosing interval, τ (first dose)

Day 5

$C_{ss,max}$	Observed maximum concentration, taken directly from the individual concentration-time curve at steady state
$C_{ss,min}$	Observed minimum concentration, 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
λz	Terminal rate constant, 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 (ln2)/λz.
$AUC_{ss,\tau}$	area under the plasma concentration curve during the dosing interval,τ at steady state
CL/F	Apparent plasma clearance for parent drug estimated as dose divided by $AUC_{ss,\tau}$
V_z/F	Apparent volume of distribution for parent drug at terminal phase, estimated by dividing the apparent clearance (CL/F) by λz
C_{av}	Average plasma concentration during a dosing interval, estimated as $AUC_{ss,\tau}/12$
%Fluctuation	Fluctuation index during a dosing interval estimated as $100*(C_{max}-C_{min})/Cav$ (%)
$R_{ac}\,(C_{max})$	Accumulation ratio for C_{max} estimated as $C_{ss,max}$ on Day 5/ C_{max} on Day 1
$R_{ac}\,(C_{min})$	Accumulation ratio for C_{min} estimated as $C_{ss,min}$ on Day 5/ C_{min} on Day 1
$R_{ac}\,(AUC_{\tau})$	Accumulation ratio for AUC_{τ} estimated as $AUC_{ss,\tau}$ on Day 5/AUC_{τ} on Day 1

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

λz interval	Lower and upper limit of the time interval (h) of the log-linear regression to determine λz
Rsq adj	Adjusted coefficient of determination for calculation of λz
n	Number of data points included in the log-linear regression analysis
$\%AUC_{ex}$	Percentage of AUC obtained by extrapolation, calculated as $[(C_{last}(obs)/\lambda z)/AUC * 100]$

Additional parameters may be determined as appropriate.

8.4.2 Safety and Tolerability Outcomes

- AEs
- Clinical laboratory parameters (hematology, serum biochemistry and urinalysis)
- Blood pressure

- 12-lead ECG parameters

8.5 Methods for statistical analyses

8.5.1 Analysis of the Pharmacokinetic variables

8.5.1.1 Calculation or derivation of the pharmacokinetic parameters

The PK analyses will be performed by Covance on behalf of AstraZeneca. The actual sampling times (calculated based on the start time of dosing) will be used in the PK parameter calculations. PK parameters will be determined using standard non-compartmental methods with Phoenix® Winnonlin® (Version 6.2 or higher). Graphics may be prepared with SAS® Version 9.3 or higher). Pharmacokinetic analyses will be conducted according to AstraZeneca SOPs for PK analyses, if not otherwise indicated.

Plasma concentrations below the lower limit of quantification (BLQ) 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 0. After this point, BLQ plasma concentrations will be set to missing for all concentration profiles. Also, if 2 or more consecutive below the lower limit of quantification concentrations are followed by quantifiable concentrations in the terminal portion of the concentration curve, the profile will be deemed to have terminated and therefore these quantifiable values will be set to missing for the calculation of the PK parameters unless there is a scientific rationale not to do so, this is documented in the PK analysis notes.

If an entire concentration-time profile is BLQ, the profile is excluded from the PK analysis.

The choice of data points used to estimate λz 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 $t_{½}$ is estimated over less than three half-lives, the values will be flagged in the data listings.
- Should include the last measurable concentration.
- Include only observations after $C_{max.}$
- The adjusted correlation coefficient (Rsq adj) should be ≥ 0.80.

Area under the plasma concentration-curve 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 summarised.

8.5.1.2 Statistical analysis of the Pharmacokinetic Parameters

All analyses of the PK parameters will be performed on the PK population. The available concentration data and PK parameter data for any patients excluded from the PK population will be listed only and presented in the individual figures of concentration, but not included in the descriptive statistics or in the inferential statistics.

A listing of PK blood sample collection times as well as derived sampling time deviations will be provided.

Plasma concentrations for aclidinium bromide, LAS34823 and LAS34850 and formoterol will be summarised per day using appropriate descriptive statistics (n, geometric mean, geometric coefficient of variation, arithmetic mean, arithmetic standard deviation [SD], minimum and maximum). For $t_{max,}$ only n, median, minimum, and maximum will be reported.

For descriptive statistics, plasma concentrations below the LLOQ will be handled as follows:

- At a time point where less than or equal to 50% of the values are BLQ, all BLQ values will be set to LLOQ, and all descriptive statistics will be calculated accordingly.
- At a time point where more than 50% (but not all) of the values are BLQ, the arithmetic mean, geometric mean and CV% will be set to not determined (ND) The maximum value will be reported from the individual data and the minimum and maximum are set to BLQ.
- If all values are below LLOQ at a time point, no descriptive statistics are calculated for that time point. Not applicable (NA) will be written in the field for arithmetic SD and geometric CV% and BLQ will be written in mean, minimum, median and maximum in the table.
- The number of observations above the LLOQ (n>LLOQ) will be reported in the Table for each time-point.

Graphical presentations will include: individual/combined individual and mean plasma concentration vs time curves on both linear and semi-logarithmic scale.

Additional graphical presentations of PK data may be added at the discretion of the PK scientist. More details will be provided in the SAP.

8.5.2 Analysis of safety data

All analyses of safety data will be performed on the safety analysis set.

8.5.2.1 Adverse events

All AEs will be coded using MedDRA vocabulary, and will be listed for each subject. A treatment-emergent adverse event (TEAE) is defined as an AE with onset (start date/time) after the 1st dose of IP.

Adverse events will be summarised including tabulations by causality and severity (mild, moderate and severe). All tabulations will be presented by SOC and PT. Furthermore, separate listings of SAEs, AEs that led to discontinuation (DAEs) and AEs that led to death will be presented. The AEs that occur before 1st dosing (i.e., not treatment-emergent) will be excluded from the summary tables.

All tabulations will include the number and percentage of subjects and the number of events where applicable.

Finally, an overview of all AEs will be presented including categories for any AE, AEs with outcome of death, SAEs and AEs leading to discontinuation of study drug.

8.5.2.2 Blood Pressure

The results of the blood pressure measurements will be listed by subject and time point including the date/time of the assessment, changes from baseline and repeat/unscheduled measurements. The baseline for blood pressure measurements will be the pre-dose assessment on Day 1. Descriptive statistics will be presented by time point for both observed values and changes from baseline.

The number and percentage of subjects with notable changes from pre-dose (baseline) will be tabulated by treatment and time point based on the criteria provided in the table below:

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

Abnormal values (based on the criteria above) will also be flagged in the listings.

8.5.2.3 Resting (safety) 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, assessment by the Investigator (normal/abnormal not clinically significant/abnormal clinically significant) and details of any abnormalities. ECG parameters will be summarised by treatment and time point including changes from baseline. The baseline for the safety ECG parameters will be the results obtained on Day -1.

8.5.2.4 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.

8.5.2.5 Laboratory assessments

Haematology and clinical chemistry values will be listed by subject and time point including changes from baseline (Day -1) and repeat/unscheduled measurements.

Summary tabulations will be presented by time point for the safety analysis set.

Laboratory variables will be categorized as low, normal and high based on the reference ranges provided by the safety laboratory. Shift tables will also be presented, showing the number and percentage of subjects with shifts from baseline in each of these categories.

Urinalysis results will be listed.

9. STUDY AND DATA MANAGEMENT

9.1 Training of study site personnel

Before the first patient is entered into the study, an AstraZeneca representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study specific procedures and EDC system(s) utilised.

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff).

9.2 Monitoring of the study

During the study, an AstraZeneca representative will have regular contacts with the study site, including visits to:

- Provide information and support to the Investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed.
- Perform source data verification (a comparison of the data in the CRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (e.g., clinic charts).
- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient.

The AstraZeneca representative will be available between visits if the Investigator(s) or other staff at the centre needs information and advice about the study conduct.

9.2.1 Source data

Refer to the Clinical Study Agreement for location of source data.

9.2.2 Study agreements

The Principal Investigator at each/the centre should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the Clinical Study Agreement shall prevail.

Agreements between AstraZeneca and the Principal Investigator should be in place before any study-related procedures can take place, or patients are enrolled.

9.2.3 Archiving of study documents

The Investigator follows the principles outlined in the Clinical Study Agreement (CSA).

9.3 Study timetable and end of study

The "end of trial" is defined as the date when all patients enrolled in the trial performed the last contact (either Visit 3 Follow-up or Premature Discontinuation Visit).

The study is expected to start in Quarter 3-4 2017 and to end by Quarter 1-2 2018.

The study may be terminated at individual centres if the study procedures are not being performed according to GCP, or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with aclidinium bromide.

9.4 Data management

Data Management (DM) of the study will be performed by Parexel and supervised by DM at AstraZeneca according upon agreed Standard Operating Procedures.

Main DM activities and procedures will be accurately described in the Data Management Plan (DMP), created by Parexel and meeting the sponsor requirements.

An EDC system will be used to collect and manage clinical data in electronic format (eCRF or electronic forms). Parexel will be responsible for EDC and database creation (including all data sources) according to the Sponsor structure specifications.

Consistency and structural checks to be run in the data and listings for Parexel data cleaning and review will be defined in a Data Validation Plan which will be created by Parexel to meet sponsor requirements and standards.

Interactive checks on the EDC will provide a first level of filters. Checks will run when data has been inserted, informing the research personnel through a flag when data must be verified.

The need of additional queries may also be identified during the study as per the listings review by the Parexel DM staff, data coding, SAEs reconciliation process, etc.

Database, checks, programmes for data visualisation, listings programming (for data review and data visualisation) and any programming implying data conversions will be appropriately validated by Parexel.

Reconciliation of SAEs between the clinical database and Drug Safety database will be performed by Parexel DM on ongoing basis and before database soft lock. Procedures to follow will be detailed in the DMP.

Adverse events and medical/surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to WHO DRUG Enhanced extended with Herbal. All coding will be performed by medical coding team at the CRO. MedDRA and WHO DRUG Enhanced extended with Herbal will be used, version number of each dictionary will be documented in the DMP.

Data will be collected during the study execution and transferred to the study data repository at the CRO, where data will be mapped into SDTM datasets on an ongoing basis.

Transfers of SDTM datasets from the study data repository will be periodically received at AstraZeneca during the study and after Database lock. Frequency of these transfers will be agreed between AstraZeneca and the CRO.

All the processes will be carried out according to the specific pre-established processes and timelines documented in the DMP.

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

When all data have been coded, validated, locked and signed, clinical database lock will be declared. Any treatment revealing data (random, PK data, etc) may thereafter be added and after clinical database will has been locked.

An audit trail of all databases will be maintained in order to protect the authenticity and integrity of the clinical data.

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

10.2 Patient data protection

The Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

10.3 Ethics and regulatory review

An Ethics Committee should approve the final study protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the patients. The Investigator will ensure the distribution of these documents to the applicable Ethics Committee, and to the study site staff.

The opinion of the Ethics Committee should be given in writing. The Investigator should submit the written approval to AstraZeneca before enrolment of any patient into the study.

The Ethics Committee should approve all advertising used to recruit patients for the study.

AstraZeneca should approve any modifications to the Informed Consent Form that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the Ethics Committee annually.

Before enrolment of any patient into the study, the final study protocol, including the final version of the Informed Consent Form, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca will provide Regulatory Authorities, Ethics Committees and Principal Investigators with safety updates/reports according to local requirements.

10.4 Informed consent

The Principal Investigator(s) at each centre will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each patient is notified that they are free to discontinue from the study at any time
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed Informed Consent Form(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed Informed Consent Form is given to the patient
- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the informed consent form that is approved by an Ethics Committee.

10.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the Principal Investigator and AstraZeneca.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol (Revised Clinical Study Protocol).

The amendment is to be approved by the relevant Ethics Committee and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to the Principal Investigator. For distribution to Ethics Committee see Section 10.3.

If a protocol amendment requires a change to a centre's Informed Consent Form, AstraZeneca and the centre's Ethics Committee are to approve the revised Informed Consent Form before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each Ethics Committee.

10.6 Audits and inspections

Authorised representatives of AstraZeneca, a regulatory authority, or an Ethics Committee may perform audits or inspections at the centre, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements. The Investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the centre.

11. LIST OF REFERENCES

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Appendix A Additional Safety Information

Further Guidance on the Definition of a Serious Adverse Event (SAE)

Life threatening

'Life-threatening' means that the patient was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the patient's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the patient or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation

Development of drug dependency or drug abuse

A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the patient actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?

- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.

- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?

- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Appendix B International Airline Transportation Association (IATA) 6.2 Guidance Document

Labelling and shipment of biohazard samples

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories. For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are eg, Ebola, Lassa fever virus:

- are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B

- are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations

- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging

- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content

- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable

- Samples routinely transported by road or rail are patient to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

Appendix C Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

Introduction

This Appendix describes the process to be followed in order to identify and appropriately report cases of Hy's Law. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a patient meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Adverse Events (AE) and Serious Adverse Events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

Definitions

Potential Hy's Law (PHL)

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 the IMP, can be found to explain the combination of increases, eg, 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.

Identification of Potential Hy's Law Cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any patient who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3xULN

- AST ≥ 3xULN
- TBL ≥ 2xULN

When a patient meets any of the identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the Investigator (also sent to AstraZeneca representative).

The Investigator will also remain vigilant for any local laboratory reports where the identification criteria are met, where this is the case the Investigator will:

- Notify the AstraZeneca representative
- Request a repeat of the test (new blood draw) by the central laboratory
- Complete the appropriate unscheduled laboratory CRF module(s) with the original local laboratory test result

When the identification criteria are met from central or local laboratory results the Investigator will without delay:

- Determine whether the patient meets PHL criteria (see Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

Follow-up

Potential Hy's Law Criteria not met

If the patient does not meet PHL criteria the Investigator will:

- Inform the AstraZeneca representative that the patient has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team

The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study patients' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated

- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician. This includes deciding which the tests available in the Hy's law lab kit should be used.

- Complete the three Liver CRF Modules as information becomes available

- If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures

Review and Assessment of Potential Hy's Law Cases

The instructions in this Section should be followed for all cases where PHL criteria are met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IP. The AstraZeneca Medical Science Director and Global Safety Physician will also be involved in this review together with other patient matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF

- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the AZ standard processes

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IP:

- Report an SAE (report term 'Hy's Law') according to AstraZeneca standard processes.

  - The 'Medically Important' serious criterion should be used if no other serious criteria apply

  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above

- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review.

References

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Document Name:	d6572c00001-pk-csp-v1
Document Title:	D6572C00001 PK Cliniical Study Protocol version 1
Document ID:	CCI [redacted]
Version Label:	2.0 Approved CURRENT LATEST

Server Date (dd-MMM-yyyy HH:mm 'GMT'Z)	**Signed By**	**Meaning of Signature**
27-Mar-2017 10:41 GMT+0100	PPD [redacted]	Clinical Operations Approval
27-Mar-2017 13:39 GMT+0100	PPD [redacted]	Clinical Development Approval
28-Mar-2017 14:29 GMT+0100	PPD [redacted]	Biostatistics Approval
29-Mar-2017 17:37 GMT+0100	PPD [redacted]	Clinical Approval

Notes: (1) Document details as stored in ANGEL, an AstraZeneca document management system.