A Phase I, Open-Label, Single and Multiple Dose (Twice-Daily), Clinical Trial to Evaluate the Pharmacokinetics, Safety and Tolerability of Aclidinium Bromide 400 µg Administered by Inhalation in Healthy Chinese Participants

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Clinical Study Protocol D6572C00002	
Drug Substance	Aclidinium bromide
Study Code	D6572C00002 M-AS273-01
Version	4.0
Date	05 Feb 2021

A Phase I, Open-Label, Single and Multiple Dose (Twice-Daily), Clinical Trial to Evaluate the Pharmacokinetics, Safety and Tolerability of Aclidinium Bromide 400 µg Administered by Inhalation in Healthy Chinese Participants

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

VERSION HISTORY

Version 4.0, 05 Feb 2021

Changes to the protocol are summarised below:

General changes across all sections in the CSP:

- The reference to doses of 200 µg and 800 µg, randomisation, ascending and incomplete design, treatment periods and sequences have been removed to keep only the single and multiple dose administration of aclidinium bromide 400 µg.
- One additional day is added for the washout period from single to multiple dose administration phase and for the follow-up visit to ensure the drug is cleared from the body (5 times half-life from parent compound and metabolites).
- Twenty participants will be dosed instead of 18 which is still similar to previous Phase I studies with aclidinium bromide and ensures consistency with the initial protocol submitted to the Regulatory Authority.

Protocol synopsis, *Principal Investigator*
This new protocol version may imply a change of the previously selected Principal Investigator. Therefore, those details have been removed. The confirmed Principal Investigator and required additional information will be detailed in the Clinical Study Report.

Protocol synopsis, *Study period*
Section 9.3 *Study timetable and end of study*
The study period has been updated according to the current plan.

Protocol synopsis, *Study Design*
Section 1.4 *Study Design*
Section 3.11.1 *Replacement of participants*
It has been clarified that participants prematurely discontinued from the study will not be replaced with the exception of reasons related to study disruption due to cases of civil crisis, natural disaster, or public health crisis.

Protocol synopsis, *procedures and assessments; pharmacokinetic assessments*
Section 5.2.1 *Collection of samples*
Section 5.6 *Table 3 total blood volume*
Description about blood volume (including entire section 5.6 and table 3) removed from this version per protocol template and to avoid risk of inconsistencies with the submission forms.

Protocol synopsis, *procedures and assessments*
Section 3.2 *Exclusion criteria; exclusion#7*
Section 4, *table 1 Schedule of Assessments; footnote g*
Section 5.1.1 *Laboratory assessments*

Human immunodeficiency virus (HIV) antibody test is updated to include HIV type 2 and align with the common testing at sites which usually includes both HIV types, 1 and 2.

Protocol synopsis, Pharmacokinetic Assessments
The temperature storage range for the PK sample has been clarified to be -70 ±10°C.

Protocol synopsis, *statistical methods*
Due to removal of the 200µg and 800µg treatment arms, frequency counts for qualitative variables and descriptive statistics for quantitative variables will be summarised across all participants and not by treatment (dose level of aclidinium bromide).
The removal of the 200µg and 800µg doses means that dose proportionality of aclidinium bromide and its metabolites will no longer be analysed for PK parameters. Time dependency in PK will still be evaluated for aclidinium bromide 400µg.

Section 1.1 *Background and rationale for conducting this study*
- Dates of marketing authorisations in the European union, Norway and Iceland, and in the United States are clarified to 20 Jul 2012 and 23 Jul 2012 respectively. The number of countries where the product is authorized (92) has also been updated, with Korea added to the list of authorized countries.
- Number of clinical trials and number of patients exposed to aclidinium bromide are updated per the Investigator's Brochure.
- Inclusion of a clinical trial completed recently (D6560C00002) and an ongoing clinical trial (D6570C00002, also known as M-AS464-30 and part of the clinical development in China) with aclidinium bromide 400µg are added to the description to provide the most recent data in terms of safety.

Section 1.4.1 *Study Conduct Mitigation During Study Disruptions Due To Cases Of Civil Crisis, Natural Disaster, Or Public Health Crisis*
Appendix D. *Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis*
The impact of COVID-19 has highlighted the risk to continuity of clinical trials during times of study disruption, whether by civil crisis, natural disaster or public health crisis. This section details the measures that may be implemented if a participant is not able to visit a study site to ensure that the clinical trial can continue, whilst minimizing risk to the participant, maintaining compliance with GCP, and minimizing risks to study integrity. These changes will only be initiated at a time of study disruption.

Therefore, new wording was added, which would give guidance on how the study could continue in the event of a serious disruption with, details of mitigation that could be employed to ensure study continuity.

Section 3.1 *Inclusion criteria*

Inclusion#2 explanatory note clarified that the method of birth control should be a non-hormonal product, which ensure consistency with the medication restrictions (section 3.2 exclusion#8 and section 7.8 Prior and concomitant medication).

Inclusion#3 body mass index (BMI) updated from ≤26 kg/m2 to ≥19 and ≤26 kg/m^2 and body weight removed in order to ensure inclusion of participants with a BMI within the range expected for a healthy population.

Inclusion#4 Resting heart rate updated from 45 to 50 bpm as expected for healthy participants and aligned to the initial protocol submitted to the Regulatory Authority.

Inclusion#6 Added a reference to section 7.4 to highlight the instruction about training on DPI inhaler use is followed and documented properly.

Section 3.2 ***Exclusion criteria***
Exclusion#4 QTcF criteria updated from ≥430 msec for male and ≥450msec for female to 450msec and 460msec for male and female respectively. This change is aligned to AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram.

Exclusion#13 is newly added to exclude participants with a previous history of COVID-19 infection.

Exclusion#19 is newly added to ensure any other condition not considered in the exclusion criteria, but relevant per the investigator's opinion, can be considered exclusionary for the study.

Exclusion#13 and #19 exploratory note is added to clarify that local guidance is to be followed for prevention of spreading and management of COVID-19 infection.

Section 3.2 ***Exclusion criteria, exclusion#8***
Section 7.8 ***Prior and Concomitant medication***
Exclusion #8, washout period for prior medication and restriction for concomitant medication are applicable to any medication, but it has been updated to include vaccines and add clarity on the requirements.

Section 3.7 ***Methods of unblinding***
This section is now considered as "not applicable" as randomisation is removed from this study.

Section 3.8.1 ***Dietary and Fluid Restrictions***
The instruction has been updated to provide some flexibility in relation to the documentation on the amount of food and low fat (<20g) is not a requirement any longer. The site can follow their own SOPs.

Section 3.8.2 ***Other Restrictions***

Requirement on the blood or plasma donation post follow-up visit is removed, as that was required post-study completion, which may be out of the study scope.

Section 3.9.1 ***Procedures for discontinuation of a subject from investigational product and from the study***

Section removed from this CSP version as most of the instruction was covered by section 3.9 and additional information was kept in that section (question about reasons to discontinuation, presence of adverse events, return of study drugs, reference to assessment to be conducted per table 1).

Section 4, ***table 1 Schedule of Assessments***
Footnote b, definition of concomitant medication is updated per the latest version of the statistical analysis plan.
Footnote j, inclusion of the full description for breakfast on treatment days is added to clarify on the requirements.

Section 4.1. ***Enrolment/screening period***
Day-1 is part of the enrolment/screening period therefore all details about Day-1 (Visit 2) are moved from section 4.2 to this section.

Section 4.2.1 ***Treatment Period (Visit 2: Day 1 to Day 11)***
The duration of this period has been clarified in the text (from Day 1 until completion of the 48-hour PK sample collection and safety assessment on Day 11).

Section 5.1.2 ***Physical examination***
Reference to “Medical History/Physical examination eCRF form” is replaced by “Medical History eCRF form” according to the eCRF standard design.

Section 5.2.1 ***Collection of samples***
In order to give more flexibility and improve the logistics at site, the accepted time window for PK pre-dose time point is updated from "±10 min" to "within 30 min prior to IP administration" on Day 1 and Day 9. It is also updated from "±10 min" to "within 10 min prior to IP administration" on Days 6-8.

Section 6.2 ***Definition of serious adverse event***
New instruction on the reporting of and severity for malignant tumours have been added to the CSP in line with the latest CSP template.

Section 6.6.1 ***Maternal exposure***
A clarification on the type of CRF to be used is added: eCRF will be used for pregnancy reporting and paper based form will be used for reporting of pregnancy outcome.

Section 7.1 ***Identity of investigational product(s)***
It has been clarified that the empty Genuair® for training can be used as needed to learn the correct technique for use of the device.

Section 7.2 ***Dose and treatment regimens***
The treatment dose of 400 µg aclidinium bromide will be given as 1 inhalation, so "one inhalation" is added to the single morning dose description to make it clear.

Section 7.3 ***Labelling***
Instruction updated to clarify that Treatment period, Treatment dose and Randomisation number blank fields are not applicable to complete on the label as per current CSP.

Section 7.4 ***Training on DPI inhaler use***
The importance of the proper inhalation technique and training has been highlighted in this section, as well as the requirement on the distribution of the written instructions to the participant and documentation to be provided by PI.

Section 7.8 ***Prior and concomitant medication***
Description is updated to allow that medication for treating adverse event is given to the subjects without requiring further sponsor approval that may delay a timely treatment.

Section 8. ***Statistical analyses***
Due to removal of the 200µg and 800µg treatment arms, frequency counts for qualitative variables and descriptive statistics for quantitative variables will be summarised across all participants and not by treatment (dose level of aclidinium bromide). This affects tables related to participant disposition, demographic and baseline characteristics, prior and concomitant medication, pharmacokinetic data, adverse events, blood pressure, 12-Lead ECG and laboratory assessments. Additionally, for pharmacokinetic data, plots of geometric means (± geometric SD) will be presented based on all participants and not by dose level.

The removal of the 200µg and 800µg doses means that dose proportionality of aclidinium bromide and its metabolites will no longer be analysed for PK parameters. Time dependency in PK will still be evaluated for aclidinium bromide 400µg.

Section 10.3 ***Ethics and regulatory review***
Regulatory Reporting Requirements for SAEs added according to the latest CSP template.

Appendix A ***Additional Safety Information***
Medication error language has been added for consistency with latest CSP template.

Appendix C ***Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law***
This section has been updated to ensure consistency with the latest CSP template.

Some minor changes in the format, typo correction and update to terms such us subject(s) changed to participant(s), randomize replaced by randomise, center replaced by centre,

rush corrected to rash, and Covance changed to Central laboratory have been implemented in this version of the CSP.

Version 3.0, 01 March 2018 Changes to the protocol are summarised below:
Study period updated according to current projection. Page 5. Protocol Synopsis. Safety laboratory assessments will be sent to the site local laboratory for analysis instead of the central laboratory. The sections affected with this change are listed below, Page 8. Section: Protocol synopsis. Page 44. Section: 5.1.1 Laboratory safety assessments. Page 46. Section: 5.1.1.2 Urinalysis. Page 83. Section: Identification of Potential Hy's Law Cases. Text regarding the blood pressure to be determined in sitting position after 5 minutes is deleted as only resting condition is required as per site procedures. The sections affected with this change are listed below, Page 37. Table 1. Scheduled assessments. Footnote e. From page 39 to 42. Section: 4.2.1 Period 1 (Visit 2: Day -1 to Day 10) / Period 2 (Visit 3: Day 14 to Day 24). Page 48. Section: 5.1.4.1 Blood pressure. The sequence for collection of ECG and vital signs is removed so if blood sampling, vital sign assessments, and ECG recordings are scheduled at the same time points, the ECG recording and blood pressure assessment will need to be collected prior to blood sampling instead of 1) ECG and 2)blood pressure, as requested by the site. The sections affected with this change are listed below, Page 37. Table 1. Scheduled assessments. Footnote f. Page 39. Section: 4.2 Treatment period. Changes in the Sponsor's protocol approval implemented in the signature page.

Version 2.0, 23 March 2017 Changes to the protocol are summarised below:
Section 2.1 (Primary Objective) and Abbreviations list- Inclusion of PK parameter $R_{ac}(C_{min})$ Section 3.2 (Exclusion Criteria)- Exclusion criteria 3 modified to delete "supine" as per site standard procedure: Sustained resting systolic blood pressure $\geq$ 140 or $\leq$ 90 mmHg and

resting diastolic blood pressure ≥ 90 or ≤ 50 mmHg at Visit 1 (Screening) or Day -1 at Visit 2.

Exclusion criteria 7 modified to delete HBc antibody IgM from serology as per PI request. Laboratory parameter also deleted from Table 2 in section 5.1.1 (Laboratory Safety Assessments)

Exclusion criteria 11 modified to "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 screening (Visit 1)." as per site request to include blood/plasma donation maximum volume allowed.

Section 3.8.1 (Dietary and Fluid Restrictions)- Inclusion of sentence: "Time window allowance for each meal is ± 1 hour, except on Day 1/8 and Day15/22 where breakfast will not be served.".

Text regarding documentation of the percentage or amount of unconsumed food for each subject has been modified to clarify that the site should at least document this information for Day 1/15 and Day 8/22.

The site is no longer required to provide a copy of the menu with the total nutritional content of each meal to the Sponsor. Relevant sentence has been deleted.

Section 4 (Study Plan and timing of procedures)- Study Plan and footnotes have been updated according to the below changes.

The blood pressure should be determined in sitting position after 5 minutes instead of supine position as per site standard procedures.

Inclusion of reference to section 5.2.1 for PK sample collection time window allowance.

Inclusion of time window allowance for ECG (± 15 min) and blood pressure (± 30 min) measurements post IP administration.

Urinalysis has been added to Day -1 and Day 10 to match the schedule for other safety lab tests as per site request.

Section 5.2.1 (Collection of samples)- Inclusion of recommended time window allowance for PK time points.

Section 5.6 (Total blood volume)- Table 3 footnote has been updated to include serum pregnancy test only to be performed for women of childbearing potential.

Section 6.3.1 (Time period for collection of adverse events)- Inclusion of sentence "In case an SAE is notified to the investigator after last follow up contact as per protocol, this should

be proactively reported to AstraZeneca for recording in the Safety Database, but without further recording in the eCRF." as per site request. Section 8.3.3 (Protocol Deviations)- Deletion of the sentence referencing the Window Allowance Document, as this document is no longer required because the PK time window allowances are included in the protocol. Section 8.4.1.1 (Pharmacokinetics parameters)-Inclusion of C_{min} for Day 1/Day 15; and $C_{ss,min}$ and Rac (C_{min}) for Day 8/Day 22. Section 9.3 (Study Timelines and end of study)- Timelines updated to study start on Q3-Q4 2017 and to end by Q3-Q4, 2017 as per site request.

Version 1.0, 2 November 2016
Initial creation

This submission document contains confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

This Clinical Study Protocol has been subject 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.

AstraZeneca

PROTOCOL SYNOPSIS

A Phase I, Open-Label, Single and Multiple Dose (Twice-Daily), Clinical Trial to Evaluate the Pharmacokinetics, Safety and Tolerability of Aclidinium Bromide 400 µg Administered by Inhalation in Healthy Chinese Participants

Principal Investigator

The name and curriculum vitae of the investigator participating in the trial will be detailed in the Clinical Study Report of the trial.

Study site(s) and number of participants planned

Twenty (20) healthy volunteers are planned to be dosed in one centre in China.

Study period		Phase of development
Estimated date of first subject enrolled	Q2-Q3 2021	Phase I
Estimated date of last subject completed	Q4 2021	

Study design

This is a Phase I, single centre, open-label study to investigate the pharmacokinetics (PK), safety and tolerability of single and multiple twice daily doses of inhaled aclidinium bromide 400 µg in healthy Chinese male and female participants.

Twenty healthy Chinese participants, aged 18 to 45 years, will participate in the study. Site will be instructed to recruit the same number of males and females to try to get a balanced distribution by gender in the study as much as possible.

Participants will be admitted to the trial centre on Day -1 and will be discharged on Day 11, 48 hours after last IP administration on Day 9 and after the completion of the 48-hour PK sample collection and safety assessment on Day 11. A follow-up visit will be performed on Day 15 (±2).

Safety measurements and blood samples for PK assessment will be collected at predetermined time points on Days 1 through 11.

The treatment period will consist of a single dose of aclidinium bromide 400 µg followed by a 96 hours wash out period and then the same treatment will be administered twice-daily for five consecutive days.

Participants prematurely discontinued from the study will not be replaced with the exception of reasons related to study disruption due to cases of civil crisis, natural disaster, or public health crisis.

Objectives

Primary Objective:	**Outcome Measure:**
To investigate the pharmacokinetics (PK) of aclidinium bromide and its metabolites after single and multiple doses (twice-daily [BID]) of aclidinium bromide 400 µg in Chinese Healthy volunteers	The following pharmacokinetic parameters will be determined when possible, for aclidinium bromide and its metabolites after single dose administration: C_{max}, t_{max}, λ_z, $t_{½\lambda z}$, AUC_{last}, AUC_{τ}, $AUC_{(0-\infty)}$, C_{min}, CL/F*, V_z/F* The following PK parameters will be calculated for aclidinium bromide after 5 days of repeated dose administration: $C_{ss,max}$, $t_{ss,max}$, λ_z, $t_{½\lambda z}$, $AUC_{ss,\tau}$, CL/F*, V_z/F*, $C_{ss,av}$, %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

Secondary Objective:	**Outcome Measure:**
To evaluate the safety, and tolerability of aclidinium bromide 400 µg after single and multiple dose administration (twice-daily [BID]) in healthy Chinese participants.	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 participants 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; smoking history; prior medications; demographics; inhaler training; physical examination, body weight and height; blood pressure; 12-lead electrocardiogram (ECG); 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]); urine drugs of abuse and alcohol screen; and adverse event (AE) monitoring.

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

Each eligible participant will enter on treatment period on Day 1. On that same day, participants will receive a single dose of aclidinium bromide in the morning (AM) via the Genuair® DPI, followed by a wash out period of 96 hours. On Day 5 through Day 8, participants will receive twice daily (BID) doses of aclidinium bromide (AM and PM) via the Genuair® DPI and on Day 9, participants will receive only the aclidinium bromide AM dose via the Genuair® DPI. Participants will be discharged on Day 11, 48 hours after last IP administration.

From Day 1 through Day 11 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.

Clinical laboratory tests (haematology, serum biochemistry and urinalysis) and serum pregnancy test for women of childbearing potential will be performed under fasting conditions on Day-1 at Visit 2 and 48 hours after last IP administration on Day 11.

A follow up visit will be performed on Day 15 (±2). The following procedures are to be performed at the Follow-up Visit: recording of concomitant medications; physical examination; blood pressure; 12-lead ECG and AE monitoring.

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

For safety assessments, blood and urine samples tests will be sent to the site local laboratory for analysis. Drugs of abuse and alcohol screen will be performed locally at the site.

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.

Pharmacokinetic Assessments

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

- Day 1: pre-morning dose, 5, 15, 30 min and 1h, 1.5h, 2, 3, 4, 6, 8, 12, 24, 36 and 48 hours. (15 time points)
- Day 6-8: pre-morning and pre-evening dose (6 time points)
- Day 9: pre-morning dose, 5, 15, 30 min and 1h, 1.5h, 2, 3, 4, 6, 8, 12, 24, 36 and 48 hours (15 time points)

All PK plasma specimens will be sent to Central laboratory 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 ±10°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 Central Laboratory Services.

Target population

Twenty (20) healthy Chinese male and non-pregnant, non-lactating female participants, between 18 and 45 years old, will be dosed.

Duration of treatment

The total duration of the trial for each participant will be approximately 5.5 weeks. There will be a run-in period of up to 21 days followed, by a treatment period, which will include a single dose of aclidinium bromide, followed by a 96 hours wash out period and then the same treatment being administered twice daily for four consecutive days, plus morning dose on day 9, and a follow up visit that will be performed on Day 15 (±2).

Investigational product, dosage and mode of administration

Aclidinium bromide 400 µg BID inhalation powder will be administered via the Genuair® device (dry powder inhaler, DPI) via oral inhalation (1 inhalation).

Statistical methods

No formal statistical hypothesis testing will be performed. The analyses of PK, safety and tolerability data will be summarised descriptively including tables, listings and figures, as appropriate.

Pharmacokinetic outcomes:

The time dependency will be evaluated by comparing $AUC_{ss,\tau}$ on Day 9 with $AUC_{(0-\infty)}$ on Day 1. Accumulation will be evaluated by comparing $AUC_{ss,\tau}$ on day 9 with AUC_{τ} on Day 1 and $C_{ss,max}$ on Day 9 with C_{max} on Day 1.

A linear mixed-effect model will be used with the logarithm of the PK parameters as the response variable and day as a fixed effect. Day will be treated as a repeated effect within participant.

From these models, LS means together with 95% CI for Day 1 and Day 9, and LS means together with 90% CI for the difference for Day 9 versus Day 1 will be obtained. The results will be transformed back to the original scale by exponentiation to provide estimates of geometric LS means, geometric LS mean ratios for Day 9/Day 1, and corresponding 90% CI.

Safety Outcomes: The incidence and distribution of TEAEs will be summarized. 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, blood pressure and potentially clinical significant laboratory values will also be presented.

TABLE OF CONTENT

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
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AM	Morning (antemeridiam)
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
$AUC_{(0-\infty)}$	Area under the concentration-time curve from time zero extrapolated to infinity
AUC_{ex}	Percentage of $AUC_{(0-\infty)}$ obtained by extrapolation, calculated as $[(C_{last}(obs)/\lambda z)/AUC_{(0-\infty)} * 100]$
AUC_{last}	Area under the plasma concentration-curve from time zero to the time of last quantifiable concentration
$AUC_{(0-\infty)}/D$	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
bpm	Beats per minute
C_{av}	Average steady state concentration
CI	Confidence Interval
CK	Creatine kinase
CL/F	Apparent clearance for parent drug estimated as dose divided by $AUC_{(0-\infty)}$
C_{max}	Observed maximum concentration
C_{max}/D	Observed maximum concentration divided by dose
C_{min}	Observed minimum concentration within a dosing interval

Abbreviation or special term	Explanation
$C_{ss,av}$	Average plasma concentration during a dosing interval, estimated as $AUC_{ss,\tau}/12$
$C_{ss,max}$	Observed maximum concentration, taken directly from the individual concentration-time curve on Day 9
$C_{ss,min}$	Observed minimum concentration, taken directly from the individual concentration-time curve on Day 9
$C_{ss,max}$ /D	Observed maximum concentration divided by dose
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Corona Virus Disease 2019
CRF	Case Report Form
CRO	Clinical Research Organisation
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CV%	Geometric coefficient of variation
DAE	Discontinuation of Investigational Product due to Adverse Event
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
EU	European Union
FEV_1	Forced Expiratory Volume in one second
GCP	Good Clinical Practice
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
IATA	International Airline Transportation Association
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IP	Investigational Product

Abbreviation or special term	Explanation
λ_z	Terminal rate constant
LLOQ	Lower Limit of Qualification
LS	Least Square
MDI	Metered-dose inhaler
MedDRA	Medical Dictionary for Regulatory Activities
mmHg	Millimeters of mercury
msec	Milliseconds
MRT	Mean residence time calculated by $AUMC/AUC_{(0-\infty)}$, 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	Premature discontinuation
PHL	Potential Hy's Law
PI	Principal Investigator
PK	Pharmacokinetics
PM	Evening (Post meridiem)
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 depolarization (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 ($QT/RR^{1/3}$)
$R_{ac}(C_{max})$	Accumulation ratio for C_{max} estimated as ratio of $C_{ss,max}$ on Day 9/C_{max} on Day 1)
$R_{ac}(AUC_{\tau})$	Accumulation ratio for AUC_{τ} estimated as (ratio of $AUC_{ss,\tau}$ on Day 9/AUC_{τ} on Day 1)
$R_{ac}(C_{min})$	Accumulation ratio for C_{min} estimated as (ratio of $C_{ss,min}$ on Day 9/ C_{min} on Day 1)
RR	Respiratory rate
RSq adj	Adjusted coefficient of determination for calculation of λ_z
SAE	Serious Adverse Event

Abbreviation or special term	Explanation
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SD	Standard Deviation
SOC	System Organ Class
SOP	Standard Operating Procedure
TBL	Total Bilirubin
TCS	Tata Consultancy Services
TEAE	Treatment-Emergent Adverse Event
TMF	Trial Master File
$t_{½\lambda z}$	Terminal half-life
t_{max}	Time to reach maximum concentration
$t_{ss, max}$	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)
$\%AUC_{ex}$	Percentage of $AUC_{(0-\infty)}$ obtained by extrapolation
%Fluctuation	Fluctuation index during a dosing interval estimated as $100*(C_{max}- C_{min})/C_{av}$ (%)

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 2020). Dyspnoea, chronic cough and sputum production are the most common clinical symptoms. Adrenergic and cholinergic pathways mediate bronchoconstriction in COPD.

Bronchodilators are central to the symptomatic management of COPD and may be given on an as-needed basis for acute symptomatic relief, or as a maintenance treatment for prevention or reduction of symptoms. Currently used bronchodilators include β_2-agonists, anticholinergics, theophylline or a combination of these drugs.

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). Anticholinergic drugs decrease bronchoconstriction (increased FEV_1) and thereby reduce dyspnoea and COPD exacerbations, increase exercise tolerance, and improve quality of life.

Aclidinium bromide is a novel long acting muscarinic antagonist that received its first marketing authorisations in the European Union (EU), Norway and Iceland for the treatment of COPD by a Centralised Procedure (Eklira® Genuair® and Bretaris® Genuair®) and in the United States (US; Tudorza™ Pressair™) on 20 Jul 2012 and 23 Jul 2012, respectively. Since then, aclidinium bromide has been authorised in 92 countries worldwide, including the countries of EU, the US, Switzerland, Canada, Australia, Japan and Korea.

Aclidinium bromide is indicated as a twice daily (BID) maintenance bronchodilator treatment to relieve symptoms of patients with COPD. The authorised metered dose is a single inhalation of aclidinium bromide 400 µg BID via a multidose breath-actuated device-metered dry powder inhaler (DPI; described herein as the Genuair® inhaler). Each delivered dose (the

dose leaving the mouthpiece) contains 375 µg of aclidinium bromide equivalent to 322 µg of aclidinium.

The clinical development programme for aclidinium BID comprised 13 Phase I/II studies that investigated the clinical pharmacology/pharmacokinetics of aclidinium bromide and 16 Phase II, Phase III and Phase IV studies that provided evidence of its efficacy and safety. Approximately 9207 participants have received aclidinium bromide 400 µg BID in clinical studies (Investigator's Brochure - IB).

The 3 pivotal clinical studies of aclidinium bromide BID 400 µg have demonstrated a clinically and statistically significant bronchodilatory effect when compared to the placebo throughout the 12 and 24 weeks treatment period; treatment with aclidinium bromide 400 µg BID was associated with an improvement in dyspnoea, disease-related health status (St. George's Respiratory Questionnaire [SGRQ]) and daily and night-time symptoms (Jones et al 2012, Kerwin et al 2012). Furthermore, Phase II Studies M/34273/23 (Fuhr et al 2012) and M/34273/29 (Singh et al 2012) showed the overall bronchodilation of aclidinium bromide 400 µg BID to be broadly comparable to that of commercially available bronchodilators, tiotropium and formoterol. Evidence of the benefits of aclidinium bromide on exercise endurance, lung hyperinflation, exertional dyspnoea and daily physical activity was observed in Study M/34273/40 (Beeh et al 2014).

To support registration of aclidinium bromide for patients with COPD in Japan and Korea, four studies in Asian patients were conducted by AstraZeneca's co-development partners. A pharmacokinetic study (KRP-AB1102-D202), a Phase II study (KRP-AB1102-D201) and a long-term safety study (KRP-AB1102-D301) have been conducted in Japan and a Phase III bridging study, has been conducted in Korea (DW_EKL001). Overall, as in studies in Western patients, aclidinium bromide at a dose of 400 µg BID was more effective than lower doses tested (100 µg BID and 200 µg BID) in Asian patients with COPD. In Japan, aclidinium approval was granted in 2015 and in 2014 in Korea.

Most recently, a Phase IV, randomised, double-blind, placebo-controlled study showed that Aclidinium bromide 400 µg BID does not increase the risk of cardiovascular events, even in a patient population at a higher risk of such events; and demonstrated the favourable effect of aclidinium bromide in reduction of COPD exacerbations. The safety profile of aclidinium bromide 400 µg BID in Study D6560C00002 was similar to that of the pooled safety populations, despite the treatment duration being longer in Study D6560C00002 (up to 3 years, as compared to up to 6 months in the pooled safety populations), and the different characteristics of the patient populations.

One clinical study of aclidinium bromide is currently ongoing. This is a Phase III clinical trial of aclidinium/formoterol in patients with COPD that is being conducted in China and other Asian countries including India, Taiwan, Vietnam and Philippines (D6570C00002, also known as M-AS464-30). As this study includes an aclidinium bromide 400 µg BID comparator arm, safety data from this study will contribute to the safety database for aclidinium bromide. Based on current data compiled from this ongoing trial, no concerns regarding the safety of aclidinium bromide 400 µg have been raised.

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.

Consistently with these arguments, similar systemic exposure parameters were observed in Japanese patients as in Western participants after 7 days of twice daily repeated administration of aclidinium bromide at doses of 200 µg and 400 µg to Japanese patients (KRP-AB1102-D202).

Common adverse events (≥1/100 to <1/10) which may be "expected" with aclidinium bromide treatment include sinusitis, nasopharyngitis, headache, cough, diarrhoea and nausea. Uncommon adverse events (≥1/1,000 to <1/100) are blurred vision, tachycardia, dysphonia, dry mouth, urinary retention, rash, stomatitis and pruritus.

Full pharmacological, toxicological and pharmacokinetic information is described in the IB.

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 400 µg after single and multiple dose administration (BID) from the Genuair® multidose dry powder inhaler in healthy Chinese participants.

Dosing aclidinium bromide twice-daily for 5 consecutive days is considered to be the adequate duration to reach steady state and to characterize the PK profile in Chinese participants. The dose strength of 400 µg BID corresponds to the currently registered product and the dose that is being considered for development and future marketing authorisation in China.

Due to the known terminal elimination half-life of aclidinium bromide (~19h), a 96-hour washout period between single and multiple administration phase is considered enough to avoid a carry-over effect.

Twenty (20) healthy participants are to be enrolled in this study. This is considered to be a sufficient number to meet the objective of the study. Healthy participants are to be enrolled to avoid possible interference of concomitant medication or diseases with the primary objectives' parameters.

1.3 Benefit/risk and ethical assessment

The current trial is a Phase I trial in healthy participants. Participants will not receive any known health benefit from participating in the trial. No known risks are applicable other than

those described in the aclidinium bromide IB. 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 I, single centre, open-label study to investigate the pharmacokinetics (PK), safety and tolerability of single and multiple twice daily doses of inhaled aclidinium bromide 400 µg in healthy Chinese male and female participants.

All participants will sign an ICF before starting any study related procedures.

The study will consist of a Screening Visit (Visit 1) conducted after signature of the ICF and maximum 21 days prior to Day 1, where medical history, physical examination, blood pressure assessment, laboratory analysis, 12-lead ECG will be conducted.

All participants fulfilling inclusion/exclusion criteria will be admitted to the clinical unit the day preceding the 1st dose(Day -1, Visit 2).

On Day 1 (Visit 2) participants will receive a single dose of aclidinium bromide in the morning (AM) via the Genuair® DPI, followed by a wash out period of 96 hours. On Day 5 through Day 8, participants will receive twice daily (BID) doses of aclidinium bromide (AM and PM) via the Genuair® DPI and on Day 9, participants will receive only the AM dose of aclidinium bromide via the Genuair® DPI. Participants will be discharged on Day 11, 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 11).

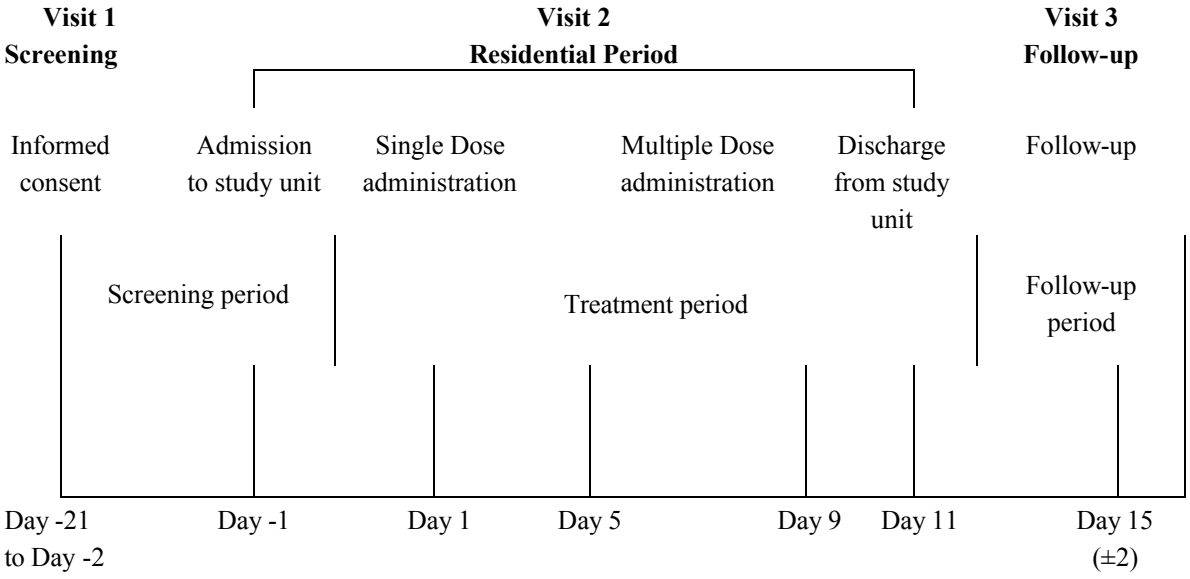
A follow-up visit will take place on Day 15 (±2).

Participants who prematurely discontinue from the study (withdrawal) will participate in a Premature Discontinuation Visit that will include physical examination, clinical laboratory tests, 12-lead ECG, blood pressure, serum pregnancy test for women of childbearing potential, and assessment of AEs and concomitant medication to ensure participant´s safety. Participants prematurely discontinued from the study will not be replaced, with the exception of study disruption reasons as described in Appendix D.

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

A complete list of all procedures and assessments is provided in the Schedule of Assessments in Table 1 (Section 4).

Figure 1 Study flow chart



1.4.1 Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

The guidance given below supersedes instructions provided elsewhere in this CSP and should be implemented only during cases of civil crisis, natural disaster, or public health crisis (e.g., during quarantines and resulting site closures, regional travel restrictions, and considerations if site personnel or study participants become infected with SARS-CoV-2 or similar pandemic infection), which would prevent the conduct of study-related activities at study sites, thereby compromising the study site staff or the participant's ability to conduct the study. The investigator or designee should contact the study Sponsor to discuss whether the mitigation plans below should be implemented.

To ensure continuity of the clinical study during a civil crisis, natural disaster, or public health crisis, changes may be implemented to ensure the safety of study participants, maintain compliance with Good Clinical Practice, and minimize risks to study integrity.

Where allowable by local health authorities, ethics committees, healthcare provider guidelines (e.g., hospital policies) or local government, these changes may include the following options:

- Obtaining consent/reconsent for the mitigation procedures (note, in the case of verbal consent/reconsent, the Informed Consent Form (ICF) should be signed at the participant's next contact with the study site).

- Rescreening: Additional rescreening for screen failure and to confirm eligibility to participate in the clinical study can be performed in previously screened participants. The investigator should confirm this with the designated study physician.

For further details on study conduct during civil crisis, natural disaster, or public health crisis, refer to Appendix D.

2. STUDY OBJECTIVES

2.1 Primary objective

Primary Objective:	Outcome Measure:
To investigate the pharmacokinetics (PK) of aclidinium bromide and its metabolites after single and multiple doses of aclidinium bromide 400 µg twice-daily (BID) in Chinese Healthy volunteers	The following pharmacokinetic parameters will be determined when possible, for aclidinium bromide and its metabolites after single dose administration: C_{max}, t_{max}, λ_z, $t_{½}\lambda_z$, AUC_{last}, AUC_{τ}, $AUC_{(0-\infty)}$, C_{min}, CL/F*, V_z/F* The following PK parameters will be calculated for aclidinium bromide and after 5 days of repeated dose administration: $C_{ss,max}$, $t_{ss,max}$, λ_z, $t_{½}\lambda z$, , $AUC_{ss,\tau}$, CL/F*, V_z/F*, $C_{ss,av}$, %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

2.2 Secondary objectives

Secondary Objective:	Outcome Measure:
To evaluate the safety, and tolerability of aclidinium bromide 400 µg twice-daily (BID) after single and multiple dose administration in healthy Chinese participants.	AEs/SAEs Blood pressure Clinical laboratory parameters (haematology, serum biochemistry and urinalysis) 12-lead ECG parameters

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

Each participant 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, participants 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 restrictions.

2. Healthy participants: Chinese men or non-pregnant, non-lactating women, 18 through 45 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 show to have a negative serum pregnancy test at the Screening Visit (Visit 1) and a negative serum pregnancy test at Day -1 and are using, during the last two months before the Screening Visit and during the whole duration of the trial, at least one medically approved non-hormonal 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. Have a body mass index (BMI) $\geq$19 kg/m^2 and $\leq$ 26 kg/m^2.

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

4. Resting heart rate $\geq$ 50 beats per minute (bpm) and $\leq$ 100 bpm at Visit 1 (Screening) and at admission to the unit on Day -1 at Visit 2.

5. Non-smoker (never smoked or has not smoked within 2 years prior to the first dose of investigational product [IP]).

6. Demonstrate satisfactory technique in the use of the DPI at screening. See section 7.4 training on DPI inhaler use.

3.2 Exclusion criteria

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

1. History of any significant drug allergy or hypersensitivity to aclidinium bromide or other muscarinic antagonists.

Explanatory note: Significant drug allergy includes anaphylaxis or hepatotoxicity; a history of allergy to the test drug, formulation excipients, or any drug chemically similar to the drug under investigation.

2. Have abnormal and clinically significant results on the physical examination, medical history, serum biochemistry, haematology, or urinalysis at Visit 1 (Screening).

3. Sustained resting systolic blood pressure ≥ 140 or ≤ 90 mmHg and resting diastolic blood pressure ≥ 90 or ≤ 50 mmHg at Visit 1 (Screening) or Day -1 at Visit 2.

4. Electrocardiogram (ECG) showing corrected QT interval (QTc) using Fridericia's correction (QTcF) ≥ 450 msec for male participants and ≥460 msec for female participants as indicated in the centralised reading report assessed at Screening (Visit 1).

Explanatory note: In addition, participants with any other risk factors for QT/QTcF prolongation or any abnormality in the ECG that, in the opinion of the PI, increases the risk of participating in the trial will be excluded, such as sick sinus syndrome, second or third-degree atrioventricular block, any type of tachycardia, more than one premature ventricular contraction on a 12-lead ECG, incomplete or complete left bundle-branch block, nonsinus rhythm, or evidence of myocardial ischemia/infarction (either changes suggesting acute ischemia/infarction or changes from previous tracings compatible with an infarction during the preceding 6 months).

5. Have a history of alcohol or substance abuse within the previous 5 years, as reported by the participants.

6. Positive results for drugs of abuse at Visit 1 (Screening).

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

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

8. Use of any medication within 2 weeks or within the equivalent time of 5 half-lives of taking the last dose (whichever is longer) before the first dose of IP, or hormonal drug products and traditional Chinese medicines within 30 days before the first dose of IP.

Explanatory note: Include any medication (prescription or over-the-counter [OTC]), health supplements, herbal/traditional remedies and vaccines.

9. Have consumed caffeine or any grapefruit-containing products within 48 hours or alcohol within 72 hours before Day -1.

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

11. 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 screening (Visit 1).

12 Recent history of a disease or condition that would result in any residual upper respiratory airways/lung inflammatory process or residual limited lung function at the time of Day 1 at Visit 2.

Explanatory note: Upper respiratory infection with residual symptoms, pulmonary infection in the previous 3 months, thoracic surgery within the last 12 months.

13. History of confirmed COVID-19 infection.

Explanatory note: Local guidance on precautions for prevention of spreading and management of COVID-19 infection must be followed.

14. Have any gastrointestinal, hepatic, or renal condition that might affect the absorption, distribution, biotransformation, or excretion of aclidinium bromide.

15. Inability to be venipunctured or tolerate venous access as determined by the PI or designee.

16. Participants unable to give their consent, or participants of consenting age but under guardianship, or vulnerable participants.

17. In the opinion of the PI, participants 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 participants who have problems understanding the protocol requirements; instructions and trial-related restrictions; the nature, scope and possible consequences of the clinical trial.

18. Participant is a relative of the Investigator or any sub-investigator, research assistant, pharmacist, trial coordinator, or other staff or directly involved in the conduct of the clinical trial.

19. Any other conditions that, in the Investigator's opinion, might have indicated the participant to be unsuitable for the study (e.g. confirmed/suspected COVID-19)

Explanatory note: Local guidance on precautions for prevention of spreading and management of COVID-19 infection must be followed.

Procedures for withdrawal of incorrectly enrolled participants see Section 3.4.

3.3 Enrolment and randomisation

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

The Investigator(s) will:

1. Obtain signed informed consent from the potential participant before any study specific procedures are performed.

2. Assign potential participant a unique participant 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, starting with 001. The participant identification number will be used to identify the participant throughout the study and will be recorded in the electronic Case Report Form (eCRF).

3. Determine participant eligibility (see Sections 3.1 and 3.2). Participant not meeting inclusion and exclusion criteria will be marked as "screen failures" and should have the final evaluation eCRF completed.

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

Randomisation is not applicable in this study.

3.4 Procedures for handling incorrectly enrolled or randomised participants

Participants 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. Participants 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 participant does not meet all the eligibility criteria but 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 participant 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 study is open-label.

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 9 where breakfast will not be served.

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

Participants will be instructed to consume the entire contents of each meal and snack, if possible. Trial centre personnel will document the percentage or the amount of food (consumed or unconsumed food according to the trial centre SOPs) for each participant, at least on Day 1 and Day 9.

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

On days that serum biochemistry samples will be drawn (Visit 1 [Screening], Day -1, Day 11, and Follow Up Visit), a fast of at least 8 hours will be observed.

Participants must abstain from caffeine, and xanthine-containing beverages or food (e.g., 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 centre on Day -1 at Visit 2 until discharge from the trial centre.

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

3.8.2 Other Restrictions

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

- Strenuous activity, sunbathing, and contact sports within 96 hours (4 days) prior to admission into the trial centre on Day -1 at Visit 2, and for the duration of the trial.

3.9 Participants discontinuation of investigational product and from the study (withdrawal)

Any participant may withdraw from the trial at any time during the trial at the discretion of the Investigator or at the request of the participant.

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

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

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

1. Adverse Events: If a participant experiences an AE, premature discontinuation will be at the discretion of either the PI or the participant, independent of the relationship to the trial treatment. The appropriate AE eCRF form must be completed.

2. Protocol Deviation: After enrolment into the trial, any protocol violations detected should be corrected when possible and the participant should be allowed to continue. ONLY the following violations should lead to participant discontinuation: those which could affect participant safety (e.g., illness requiring treatment[s] which in the clinical judgment of the Investigator [or after discussion with the trial monitor might invalidate the trial by interfering with the IP) or which are due to participant unwillingness to comply with the trial activities.

3. Failure to meet eligibility criteria: Violations of inclusion and/or exclusion criteria detected after initiating on treatment. See Section 3.4 for participants not fulfilling inclusion/exclusion criteria but detected after initiating on treatment.

4. 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 participant, and to assure participant attendance as soon as possible. Every effort (at least 3 documented attempts in the medical records) should be made to contact the participant. A registered mail letter will be sent to the participant and documented in the medical records.

5. Withdrawal by participant: The participant 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.

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

7. "Other": at the Investigator's request, study cancellation or any other reason not described above.
8. Participant withdrawal due to death.

All dosed participants who prematurely discontinue from the trial, regardless of cause, will be seen for a premature discontinuation visit AS SOON AS POSSIBLE.

A participant that decides to discontinue 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 participant. Procedures/assessments for the premature discontinuation are indicated in the Schedule of Assessments (Table 1).

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

3.10 Criteria for withdrawal

3.10.1 Screen failures

Screening failures are participants who do not fulfil the eligibility criteria for the study, and therefore must not enter on treatment. These participants should have the reason for study withdrawal recorded as 'Screen Failure' (i.e., participant does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (not participant on treatment).

3.11 Premature Discontinuation of the study

The "end of trial" is defined as the date when all participants 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. Certain circumstances may require the premature termination of the trial, such as the following:

- The Investigator and the Sponsor feel that the type, the number and/or severity of AEs justifies discontinuation of the trial.
- The Sponsor decides to discontinue the trial.
- Data not known before become available and raise concerns about the safety of the IP so that continuation would pose potential risks to the participants.

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

The Investigator will inform the participants 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 participant 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 participants' interests.

3.11.1 Replacement of participants

Participants prematurely discontinued from the study will not be replaced, with the exception of study disruption reasons as described in Appendix D.

4. STUDY PLAN AND TIMING OF PROCEDURES

Table 1 Schedule of Assessments

	Screening period	Treatment period							Follow-up period
	Visit 1[a] Screening	Visit 2							Follow up Visit (Visit 3) or PD
Procedure/Study Day	**-21 to -2**	**-1**	**1**	**2-4**	**5**	**6-8**	**9**	**10**	**11**	**15 (±2)**
Sign informed consent	X									
Demographics	X									
Inclusion/Exclusion criteria	X	X								
Smoking history	X									
Medical history	X									
Prior and Concomitant Medications[b]	X	X								X
Inhaler Training	X	X								
Admission to Trial Centre		X								
Meals (provided by trial centre)[j]		X	X	X	X	X	X	X	X	
Discharge from the Trial Centre[c]									X	
Outpatient Visit	X									X
Physical examination, height and weight[d]	X	X								X
12-lead ECG and blood pressure[e]	X	X	X		X	X	X			X
Laboratory Tests (Haematology, Serum Biochemistry)[f]	X	X							X	X[i]
Laboratory Test (Urinalysis)	X	X							X	X[i]
Serum Pregnancy Test	X	X								X[i]
Serology[g]	X									
Urine Drugs of Abuse and Alcohol Screen	X	X								
Dosing of IP			X		X	X	X			

Table 1 Schedule of Assessments

	Screening period	Treatment period							Follow-up period
	Visit 1[a] Screening	Visit 2							Follow up Visit (Visit 3) or PD
Procedure/Study Day	**-21 to -2**	**-1**	**1**	**2-4**	**5**	**6-8**	**9**	**10**	**11**	**15 (±2)**
Blood sampling for pharmacokinetics[h]			X	X		X	X	X	X	
Adverse event review (AEs and SAEs)	X	X	X	X	X	X	X	X	X	X

AE = adverse event; AM = morning; BMI = body mass index; DPI = dry powder inhaler; ECG = electrocardiogram; HIV = human immunodeficiency virus; ICF = Informed Consent Form; IP = investigational product; PI = Principal Investigator; PM = evening; PD= Premature Discontinuation; PK = pharmacokinetic

a. If the participant needs additional time to washout any prior medications, the ICF must be provided before Visit 1. Participants must discontinue medications after informed consent.

b. Prior medication will be defined as any hormonal product or any other medication/herbal remedies taken within 14 days of trial Screening at Visit 1 up to the first dose of aclidinium bromide. Concomitant medication will be defined as any medication taken at least once after the 1st IP administration until the time of the last PK sample on Day 11 (48 hours post-last dose).

c. Participants will be discharged from the trial centre after the completion of the 48-hour PK blood sample collection and safety assessments.

d. Height and weight will be measured and BMI will be calculated at Visit 1 (Screening).

e. Safety ECGs and blood pressure will be collected at Visit 1 (Screening); at Visit 2 on Day -1; and Days 1, Day 5 to 9 at 0 hour (pre AM dose) and at 2 hours post AM dose; and at the Follow-Up Visit or Premature Discontinuation Visit. ECGs and blood pressure measurements will be obtained after the patient has rested quietly for at least 5 minutes. If an ECG is scheduled at the same time as a meal, the ECG must be obtained first.

f. If blood sampling, vital sign assessments, and ECG recordings are scheduled at the same time points, ECG recording and blood pressure assessments will need to be collected prior blood sampling, assuring that PK blood sampling occurs on the time point. Includes blood and serum samples. Participants are required to fast for at least 8 hours prior to the collection of specimens.

g. Serum for hepatitis B surface antigen (HBsAg), hepatitis C antibody and human immunodeficiency virus (HIV) types 1 and 2 antibodies. Results must be available and reviewed prior to dosing on Day 1.

h. PK blood samples will be collected on Day 1 at pre-dose (approximately 15 minutes prior to the AM 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 (i.e. on Day 2), 36 hours (i.e. on Day 2) and 48 hours (i.e. on Day 3) post the AM dose after IP administration.
On Days 6-8, PK blood samples will be collected at pre-dose (approximately 5 minutes prior to the AM and PM dose)
On Day 9, PK blood samples will be collected at pre-dose (approximately 5 minutes prior to the AM 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 (i.e. on Day 10), 36 hours (i.e. on Day 10) and 48 hours (i.e. on Day 11) post the AM dose after IP administration on Day 9.
Time window allowances are indicated in section 5.2.1

i. Laboratory test (haematology, biochemistry and urinalysis) and serum pregnancy test to be performed only at Premature Discontinuation Visit.

j. On treatment days, breakfast will be served approximately 2 hours prior to IP, except on Day 1 and Day 9 where no breakfast will be served.

4.1 Enrolment/screening period

This period will start with the signature of the Informed Consent Form (ICF) at Visit 1 (Screening), when Chinese male and female healthy volunteers 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 participants will be admitted to the trial centre on Day -1. No study specific procedures will be performed prior to signing ICF.

Participants who require a washout period from prohibited concomitant treatments should be seen and sign the ICF prior to Visit 1, to ensure the necessary washout before this visit. No trial assessments will be performed that date, and Visit 1 will be scheduled later according to the wash-out length required for the specific medication stopped.

If no wash-out period is required, Visit 1 assessments will start after signing the ICF to ensure that they meet eligibility criteria. Any participant signing the ICF should be recorded in the eCRF and should be assigned a Participant ID number.

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

Obtain informed consent.

Assess inclusion/exclusion criteria.

Review medical/surgical history, demographic (age, sex and race) and smoking history.

Perform a complete physical examination including body weight (in light indoor clothes, without shoes) and height.

Collect blood pressure.

Perform 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.

Train participants on Genuair® inhaler user instructions. See section 7.4.

Record in the eCRF all medications the participant is currently taking and has taken during the previous 15 days before signature of the ICF. Remind the participant to avoid prohibited medications (see Section 7.8 for details).

Document the participant participation in the study into the participant's medical records.

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

Day -1 (Visit 2)

The following procedures will be performed:

On Day -1, reassess the inclusion/exclusion criteria and review with participant if any AEs occurred.

Perform the 12-lead ECG.

Blood pressure assessment.

Blood and urine sample collection for safety laboratory tests (haematology, biochemistry and urinalysis). Participants should be fasting a minimum of 8 hours prior to safety laboratory test collection.

Perform a complete physical examination.

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.

Train the participant on how to use the DPI device. The investigator/designee will evaluate proper use of the device by the participant and provide additional training if needed. See section 7.4.

Provide meals according to Section 3.8.1.

Have the participant remain in the study centre overnight.

Only participants who meet all inclusion/exclusion criteria will be considered as enrolled in the study and continue to Day 1 at Visit 2.

All participants will remain in the trial centre from Day -1 at Visit 2 until the completion of the 48-hour PK sample collection and safety assessments on Day 11.

4.2 Treatment period

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.

If blood sampling, blood pressure assessments, and ECG recordings are scheduled at the same time points, ECG recording and vital sign assessments will need to be collected prior to 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 Treatment Period (Visit 2: Day 1 to Day 11)

This period will start on Day 1 at Visit 2 until the completion of the 48-hour PK sample collection and safety assessments on Day 11.

Participants will stay overnight at the trial centre for a total of 11 nights (from Day -1 to Day 11).

Day 1

Perform 12-lead ECG before IP administration (pre-dose).

Blood pressure assessment before IP administration (pre-dose).

Collect PK blood samples at pre-dose (approximately 15 minutes before the IP administration). Time window allowance in section 5.2.1

Administer the 1st single dose of AM IP approximately at 8:00 AM by inhalation from the Genuair ® DPI. The investigator or study personnel should check that the participant has used the inhaler correctly. Window allowance deviation for IP will be ±1h.

Collect PK blood samples at 5, 15, 30min 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.

Blood pressure assessment at 2 hours (± 30min) post IP administration.

Review with participant if any AEs occurred.

Provide lunch, dinner and snack according to the time schedule defined in section 3.8.1.

Have the participant remain in the study centre overnight.

Day 2 to Day 4

Collect PK blood samples at 24h, 36h and 48h post IP administration on Day 1. Time window allowance in section 5.2.1

Review with participant if any AEs occurred.

Provide breakfast, lunch, dinner and snack according to the time schedule defined in section 3.8.1.

Have the participant remain in the study centre overnight.

Day 5 to Day 9

Perform 12-lead ECG before morning IP administration (pre-dose).

Blood pressure assessment before morning IP administration (pre-dose).

From Day 5 to Day 8, administer AM IP at approximately 8:00h and IP PM dose at approximately 20:00 hours (12 hours after AM dose). On Day 9, only the AM dose 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 6, 7 and 8, 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 9, 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 morning IP administration.

Blood pressure assessment at 2 hours (± 30 min) post morning IP administration.

Review with participant if any AEs occurred.

Provide breakfast, lunch, dinner and snack according to the time schedule defined in section 3.8.1. No breakfast will be served on Day 9.

Have the participant remain in the study centre overnight.

Day 10 to Day 11

Collect PK blood samples at 24h, 36h and 48h post IP administration on Day 9. Time window allowance in section 5.2.1.

Have the participant remain in the study centre overnight on Day 10.

Blood and urine sample collection for haematology, biochemistry and urinalysis on Day 11. Participants should be fasting a minimum of 8 hours prior to safety laboratory test collection.

Review with participant if any AEs occurred.

Provide a participant's diary for the participant to record any AE and/or concomitant medication used once discharged from the unit.

Provide breakfast, lunch, dinner and snack according to the time schedule defined in section 3.8.1.

On Day 11 collect blood sample for serum β-human chorionic gonadotropin (β-hCG) pregnancy test only for women of childbearing potential.

Discharge the participant on Day 11 after all safety and PK assessments are completed.

4.3 Follow-up period (Visit 3)

Participants are required to return to the trial centre for a Follow-up Visit (performed on Day 15 ±2).

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

- Assessment of AEs and concomitant medications.
- Physical examination.
- Perform 12-lead ECG.
- Blood pressure assessment.

4.4 Premature discontinuation visit

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

- Assessment of AEs and concomitant medications.
- Physical examination.
- Perform 12-lead ECG.
- Blood pressure assessment.
- Collect blood and urine samples for clinical laboratory tests (haematology, serum biochemistry, and urinalysis). Participants should be fasting a minimum of 8 hours prior to safety laboratory test collection.
- Collect blood sample for serum β-human chorionic gonadotropin (β-hCG) pregnancy test only 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 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 the site local laboratory services which will provide the report to the investigator. Site specific procedures will be followed for the sampling analysis.

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

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be 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 EDC 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 that a result is clinically relevant or doubtful, additional blood samples may be collected within a reasonable time and will be sent to the site local laboratory for analysis (see Sections 5.1.6 and 5.1.7 for Unscheduled and Repeated tests 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-Haematocrit	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)
Urinalysis	S/P-Albumin
U-Hb/Erythrocytes/Blood	S/P-Potassium
U-Leukocytes	S/P-Calcium, total
U-Glucose	S/P-Sodium
U-pH	S/P- Chloride
U-Protein/Albumin	S/P- Inorganic phosphorous
U-Bilirubin	S/P-Glucose
U-Urobilinogen	S/P-Total cholesterol
U-Ketones	S/P- Triglycerides
U-Nitrites	S/P- Total protein
	S/P- Uric acid
Serology (serum or plasma)	S/P- Urea Nitrogen
S/P- HBsAg	
S/P-anti-HCV	
S/P- anti-HIV types 1and 2	

NB. In case a participant 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.

As per AstraZeneca standards, during the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a participant meets potential Hy’s Law (PHL) criteria at any point during the trial.

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

5.1.1.1 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 Day 11 at Visit 3, or at Premature Discontinuation Visit.

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

5.1.1.2 Urinalysis

The urine sample will be sent to the site local laboratory in China for urinalysis.

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: cotinine, benzoylecgonine (cocaine), methadone, barbiturates, amphetamines, benzodiazepines, cannabinoids, opiates and phencyclidine. Alcohol screen will be performed using a breath test.

5.1.2 Physical examination

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

A complete physical examination will be performed at the Visit 1 (Screening), on Day -1 at Visit 2; and at the Follow-Up Visit (Table 1). At Visit 1 (Screening), only relevant findings will be recorded in the Medical History eCRF form. From Day -1 to 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.

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

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

5.1.3 ECG

5.1.3.1 Resting 12-lead ECG

Standard 12-lead ECGs will be performed at time points detailed in Table 1 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 participant.

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 participant's eligibility according to the centralized reading report 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 1.

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 and 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 participant'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 participant is or remains eligible for the study.

However, the responsibility for inclusion or continuation of the participant 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 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 Investigator 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 5.1.6 and 5.1.7).

5.1.4 Vital signs

5.1.4.1 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 1. Measurements will be carried out with participant in resting 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.

5.1.5 Adverse Events

Adverse events will be recorded throughout the trial, see Table 1. Procedures for recording and assessing AEs are included in Section 6.3.

5.1.6 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 enrolment e.g., in case of impaired results (e.g., blood sample haemolysed) or results requiring confirmation (to ensure participant eligibility or results inconsistent with participant's known past medical conditions), etc. The full Visit 1 will not be repeated. If any of the specific tests of the Screening Visit need to be repeated, and more than 28 days has elapsed since first test date, the participant 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.

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

5.1.7 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 of aclidinium bromide and its metabolites LAS34850 and LAS34823 in plasma will be taken at the following time points

Day 1: 0 hour (pre-dose; approximately 15 minutes prior to the AM 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 (i.e. Day 2), 36 hours (i.e. Day 2) and 48 hours (i.e. Day 3).

Days 6-8: 0 hour (pre-dose; approximately 5 minutes prior to the AM and PM dose).

Day 9: 0 hour (pre-dose; approximately 5 minutes prior to the AM 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 (i.e. Day 10), 36 hours (i.e. Day 10) and 48 hours (i.e. Day 11) post the AM dose.

The recommended time windows allowance for PK blood collection are the following:

Day 1 and Day 9:

pre-dose: within 30 min prior to IP administration

5 -30 min: ± 1 min

1-6 hours: ± 5 min

8-12 hours: ± 10 min

24-48 hours: ± 30 min

Days 6-8 :

pre-dose: within 10 min prior to IP administration

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 aclidinium bromide and its metabolites, LAS34850 and LAS34823, in plasma will be analysed by Central Laboratory on behalf of AstraZeneca, using a validated bioanalytical method.

Full details of the analytical method used will be described in a separate Bioanalytical Report.

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, if any, 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

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

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 participants.

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 period, 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 participant 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.

Adverse Events (AEs) for **malignant tumours** reported during a study should generally be assessed as **Serious AEs**. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a **non-serious AE**. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfil the attributes for being assessed as serious, although reporting of the progression of the malignant tumour as an AE is valid and should occur. Also, some types of malignant tumours, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as non-serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

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 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 participant'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 participants 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 an 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 an 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).

AE will be collected only once with their 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 participant 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, blood pressure and physical examination will be summarised in the clinical study report.

Medical disorders present at the time of signing the ICF that are part of the participant'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/blood pressure, 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. However, 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, blood pressure, 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 participant 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 SAE 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 (e.g., participant lives too far from the hospital or has no caregiver at home).

An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure or and will notify the IRB/IEC, if appropriate according to local requirements.

6.5 Overdose

As participants 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 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 an SAE, the standard reporting process and 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 participant becomes pregnant during the course of the study, the 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 participant 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 **1 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 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 eCRF is used to report the pregnancy and the paper-based PREGOUT module is used to report the outcome of the pregnancy.

6.6.2 Paternal exposure

Provided that nonclinical data with aclidinium bromide 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 participant'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 and consented, 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	Powder for inhalation administered via multidose DPI (Genuair ®) 400 µg/inhalation	Industrias Farmacéuticas Almirall S.A (IFA). Sant Feliu de Llobregat, Barcelona, Spain

DPI = dry powder inhaler

Single and multiple inhaled doses of aclidinium bromide powder will be administered via the multidose dry powder inhaler (DPI) Genuair®.

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 participant will receive an empty Genuair® DPI that will be used on Visit 1 (Screening) and on Day -1 at Visit 2 . As many practices as needed to learn the correct technique for use of the device will be allowed.

7.2 Dose and treatment regimens

Before taking the first dose of the IP the participant will be instructed by the study personnel on how to use the Genuair® DPI. Participant 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 participants in local language.

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

Each participant will receive a single morning dose (one inhalation) of aclidinium bromide on Day 1.

The multiple dosing phase of the study will start on Day 5. Morning and evening doses of aclidinium bromide will be administered for four days with a final morning dose on Day 9.

The treatment dose of 400 µg aclidinium bromide will be given as 1 inhalation from the 400 µg aclidinium bromide inhaler.

7.3 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 and placed in a box.

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

The medication box, the Aluminium pouch and the Genuair® DPI labels will have blank fields for completion of Treatment period, Treatment dose, Subject ID, Randomisation number and Investigator name. The Subject ID and Investigator name will have to be completed by the investigator before the administration. Blank fields for Treatment period, Treatment dose and Randomisation number will not be applicable to complete according to the current CSP.

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

7.4 Training on DPI inhaler use

Training for the use of the DPI will be done at Screening and on Day -1; the participant will receive an empty Genuair® inhaler device for training. All participants will be trained on the use of the inhaler.

The PK of inhaled products, either from a DPI or a metered-dose inhaler (MDI) is largely dependent upon proper inhalation technique, therefore training on the DPI inhaler use should be conducted carefully. **As many practices as needed to learn the correct technique for use of the device will be allowed.**

Participants will be provided written instructions on the use of the inhaler device.

The Investigator should ensure comprehension of the instructions by the participants and the correct use of the inhaler training devices. This task must be clearly documented and approved by the PI.

7.5 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.

7.6 Compliance

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

Participants will receive all IP doses under the direct supervision of trial centre personnel, which will guarantee compliance. The PI 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 PI.

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

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

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

7.7 Accountability

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

The PI is responsible for the control of the IP under investigation. Adequate records of the receipt (e.g., 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 participant to whom the IP was dispensed.
- Date(s) and quantity of the IP administered to the participant.
- Date(s) and quantity of the IP remaining after dosing completion.

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

Study site personnel, if applicable, or the CRO 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 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).

7.8 Prior and concomitant medication

No concomitant medications are permitted during the study. Participants will be instructed not to take any drugs for at least 14 days before the first day of dosing and during the course of the study. Participants will be specifically reminded that this includes over-the-counter medications such as aspirin, supplements, herbal remedies, tobacco products, illegal drugs, as well as medicines requiring a prescription and vaccines. No hormonal drug products or traditional Chinese medicines will be allowed 30 days before Day 1 and throughout the study. The Investigator or Sponsor reserves the right to exclude a participant from participation in the study if a medication taken 14 or more days before the study start may potentially interfere with the study outcome (e.g., a drug with prolonged half-life). The Sponsor may be contacted if there are questions about any possibly excluded substances.

Participants who take concomitant medication during the study other than the study drug may be withdrawn after discussion with the sponsor, unless for treatment of an adverse event. In the event medication is used, it will be recorded in the appropriate section of the eCRF and in the source documents.

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 Central Laboratory.

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

8.2 Sample size estimate

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

It is planned for 20 participants to enter on treatment in the study.

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 of participants in each analysis set will be summarized (except for Screening analysis set). The number and percentage of participants who complete the treatment period

and of participants who prematurely discontinue will be presented. The reasons for premature discontinuation from the treatment period, as recorded on the termination pages of the eCRFs, will be summarized. Additionally, the cause of screening failure should be tabulated for Screening analysis set.

8.3.1 Safety analysis set

The safety analysis set will include all participants who received at least 1 dose of IP and for whom any safety post-dose data are available.

Unless otherwise stated, the safety analysis set will be used for the presentation of all demographic and disposition data, as well as all safety analyses. Exposure to IP will also be presented using the safety analysis set.

8.3.2 PK analysis set

The PK analysis set will consist of all participants in the safety analysis set who received at least 1 dose of aclidinium bromide and have at least 1 of the parameters (C_{max}, $C_{ss,max}$, $AUC_{(0-\infty)}$ AUC_{last} or $AUC_{ss,\tau}$) evaluable and are assumed not to be affected by factors such as protocol deviations (e.g., prohibited concomitant medications which are thought to impact on the PK data, or incorrect study medication received).

The exclusion of any participants 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 participants excluded from the PK analysis set will be listed only. Concentration data for participants excluded from the PK analysis set will be presented in the individual figures of concentration versus 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 windows allowance 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 participants 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 participants for all participants who entered on treatment. Further details will be described in the statistical analysis plan (SAP).

8.4 Outcome measures for analyses

8.4.1 Pharmacokinetics Outcomes

8.4.1.1 Pharmacokinetics parameters

The following PK parameters will be assessed for aclidinium bromide and its metabolites LAS34850 and LAS34823 on plasma concentrations:

Day 1:

C_{max} - Observed maximum concentration, taken directly from the individual concentration-time curve

C_{min} – Observed minimum concentration, taken directly from the individual concentration-time curve within a dosing interval

t_{max} - Time to reach maximum concentration, taken directly from the individual concentration-time curve

λ_z - Terminal rate constant, estimated by log-linear least squares (LS) regression of the terminal part of the concentration-time curve

$t_{½\lambda z}$ - Terminal half-life, estimated as (ln2)/ λ_z

AUC_{last} - Area under the plasma concentration-curve from time zero to the time of last quantifiable concentration

$AUC\tau$ - Area under the plasma concentration-curve from time zero to 12 hours post-dose

$AUC_{(0-\infty)}$ - Area under the concentration-time curve from time zero extrapolated to infinity. $AUC_{(0-\infty)}$ is estimated by $AUC_{last} + C_{last}/\lambda z$ where C_{last} is the last observed quantifiable concentration

CL/F - Apparent clearance for **parent drug** estimated as dose divided by $AUC_{(0-\infty)}$

V_z/F - Apparent volume of distribution for **parent drug** at terminal phase (extravascular administration), estimated by dividing the apparent clearance (CL/F) by λ_z

MRT – mean residence time calculated by AUMC/$AUC_{(0-\infty)}$, where AUMC is the area under the first moment-time curve

C_{max}/D - Observed maximum concentration divided by dose

AUC_τ/D - Area under the concentration-time curve zero to 12 h divided by the dose

$AUC_{(0-\infty)}$ /D - Area under the concentration-time curve from time zero extrapolated to infinity divided by the dose

Day 9:

$C_{ss,max}$ - Observed maximum concentration, taken directly from the individual concentration-time curve on Day 9

$C_{ss,min}$ – Observed minimum concentration, taken directly from the individual concentration-time curve within a dosing interval on Day 9

$T_{ss,max}$ - Time to reach maximum concentration, taken directly from the individual concentration-time curve

λ_z - Terminal rate constant, estimated by log-linear LS regression of the terminal part of the concentration-time curve

$t_{½\lambda z}$ - Terminal half-life, estimated as (ln2)/ λ_z

$AUC_{ss,\tau}$ - Area under the plasma concentration-curve from time zero to 12 hours post-dose

CL/F - Apparent clearance for drug estimated as dose divided by $AUC_{ss,\tau}$

V_z/F - Apparent volume of distribution for **parent drug** at terminal phase (extravascular administration), estimated by dividing the apparent clearance (CL/F) by λ_z

$C_{ss,max}$ /D - Observed maximum concentration divided by dose

$AUC_{ss,\tau}$/D - Area under the concentration-time curve zero to 12 h divided by the dose

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

%Fluctuation - Fluctuation index during a dosing interval estimated as $100*(C_{max}- C_{min})/C_{av}$ (%), where C_{min} is the minimum concentration at the end of the dosing interval

Rac (C_{max}) - Accumulation ratio for C_{max} estimated as (ratio of $C_{ss,max}$ on Day 9/C_{max} on Day 1)

Rac ($AUC\tau$) - Accumulation ratio for AUC_{τ} estimated as (ratio of $AUC_{ss,\tau}$ on Day 9/AUC_{τ} on Day 1)

Rac (C_{min}) - Accumulation ratio for C_{min} estimated as (ratio of $C_{ss,min}$ on Day 9/ C_{min} on Day 1)

Time - dependency - estimated as ratio of $AUC_{ss,\tau}$ on Day 9/$AUC_{(0-\infty)}$ on Day 1

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

λ_z interval - Lower and upper limit of the time interval (h) of the log-linear regression to determine λ_z

Rsq adj - Adjusted coefficient of determination for calculation of λ_z

n obs - Number of data points included in the log-linear regression analysis

AUCex - Percentage of $AUC_{(0-\infty)}$ obtained by extrapolation, calculated as $[(C_{last}(obs)/\lambda_z)/AUC_{(0-\infty)} * 100]$

Additional PK parameters may be determined where appropriate.

8.4.1.2 Calculation or derivation of the pharmacokinetic parameters

The PK analyses of the plasma concentration data for aclidinium bromide and its metabolites, will be performed at Central Laboratory, on behalf of AstraZeneca. The actual sampling times will be used in the plasma PK parameter calculations.

PK parameters will be derived using non-compartmental methods with Phoenix® WinNonlin® Version 6.3, or higher and/or SAS® Version 9.3 or later. 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 BLQ 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.

8.4.2 Safety and Tolerability Outcomes

AEs

Clinical laboratory parameters (haematology, serum biochemistry, urinalysis)

Vital Signs (blood pressure)

12-lead ECG parameters

8.5 Methods for statistical analyses

8.5.1 General principles

Given the exploratory nature, no formal statistical hypothesis testing will be performed in this study. Since no formal testing is planned, and the confidence intervals (CIs) that will be calculated are only for descriptive purposes, no corrections for multiplicity will be used. All analyses in the sections below will be described in further detail in a study specific SAP.

All original and derived parameters, as well as demographic and disposition data, will be listed and described using summary statistics. Demographic and baseline data, pharmacokinetic data and safety and tolerability data will be summarised for all participants in the appropriate analysis set. All safety data (scheduled and unscheduled) will be presented in the data listings.

Frequency counts (number of participants[n] and percentages) will be made for each qualitative variable. Descriptive statistics (n, mean, standard deviation [SD], median, minimum and maximum) will be calculated for each quantitative variable (unless otherwise stated). All statistical analyses and production of tables, figures and listings will be performed using SAS® Version 9.3 or later.

8.5.2 Missing data

Since the statistical analyses will be predominantly presentations in tables and individual data listings, no specific action will be taken to handle missing data.

A participant who withdraws prior to the last planned observation in a study period will be included in the analyses up to the time of discontinuation. The handling of any missing dates/times in the AE or concomitant medication data will be described in the SAP.

8.5.3 Participant disposition

The assignment of participants to each of the analysis sets will be listed and summarised. Additional listings will be presented for participant discontinuations and informed consent.

8.5.4 Demographic and baseline characteristics

Demographic variables (including age, sex, race, height, weight and BMI) will be listed and summarised for all participants in the safety analysis set.

Medical history data will be listed by participant including description of the disease/procedure, Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and MedDRA Preferred Term (PT).

8.5.5 Prior and concomitant medication

Prior medication is defined as any medication taken up to the 1st dose of IP.

Concomitant medication is defined as any medication taken at least once after the 1st IP administration until the time of the last PK sample on Day 11 (48 hours post-last dose on Day 9).

A medication that is started before the IP administration and continues afterwards is classified as both prior and concomitant medication.

Prior and concomitant medication will be coded using the WHO-Drug Enhanced plus Herbal Dictionary and will be listed by participant.

The number and percentage of participants who used any prior and concomitant medication will be summarised separately by Anatomical Therapeutic Code (ATC) to a maximum of 3rd level, and preferred name. Participants with multiple drug usage in the same preferred name will be counted only once. Any medications taken before the first IP administration and continuing afterwards, will be included in tabulations for both prior and concomitant medications.

8.5.6 Drug administration

Drug administration dates and times will be listed for each participant.

8.5.7 Statistical analysis of the Pharmacokinetic data

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

Plasma concentrations will be summarised using descriptive statistics (n, geometric mean, geometric mean+/-geometric SD, geometric coefficient of variation [CV%], arithmetic mean, arithmetic SD, minimum, median and maximum) based on the PK analysis set.

For descriptive statistics for plasma concentrations that are below the LLOQ will be handled as follows:

- Where there is non-reportable concentration (NR), these will be set to missing.

- At a time point where less than or equal to 50% of the values are BLQ, all BLQ values will be set to the LLOQ, and all descriptive statistics will be calculated accordingly.

- At a time point where more than half (but not all) of the values are BLQ, the arithmetic mean, arithmetic SD, 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 median will be set to BLQ.

- If all values are BLQ at a time point, no descriptive statistics will be 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 fields for arithmetic mean, geometric mean, minimum, median, and maximum.

- The number of BLQ values (n above LLOQ) will be reported for each time point.

All plasma PK parameters will also be listed and summarised using similar descriptive statistics. For tmax only n, median, minimum and maximum will be reported.

Data from participants excluded from the PK analysis set will be included in the data listings, but not in the summaries or in the inferential statistics.

Individual plasma concentrations versus actual time will be plotted in linear and semi-logarithmic scale, with separate plots for each participant and concentrations for Day 1 and

Day 9 overlaid on the same plot. Combined individual plasma concentration will also be presented in linear and semi-logarithmic scale with separate plots for each day (Day 1 and Day 9).

Figures for the geometric mean (± geometric SD) concentration-time data will be presented in both a linear and semi-logarithmic scale (SD only on the linear scale).

Geometric mean (± SD) plasma trough concentrations versus day profiles (pre-dose on Day 6 to Day 9) will be presented in both linear and semi-logarithmic scale.

All plots will be repeated for aclidinium bromide metabolites.

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

8.5.7.1 Analysis of time dependency in PK and accumulation

The time dependency will be evaluated by comparing $AUC_{ss,\tau}$ on Day 9 with $AUC_{(0-\infty)}$ on Day 1. Accumulation will be evaluated by comparing $AUC_{ss,\tau}$ on day 9 with AUC_{τ} on Day 1 and $C_{ss,max}$ on Day 9 with C_{max} on Day 1.

A linear mixed-effect model will be used with the logarithm of the PK parameters as the response variable and day as a fixed effect. Day will be treated as a repeated effect within participant.

From these models, LS means together with 95% CI for Day 1 and Day 9, and LS means together with 90% CI for the difference for Day 9 versus Day 1 will be obtained. The results will be transformed back to the original scale by exponentiation to provide estimates of geometric LS means, geometric LS mean ratios for Day 9/Day 1, and corresponding 90% CI.

8.5.8 Analysis of safety data

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

8.5.8.1 Adverse events

All AEs will be coded using MedDRA dictionary, and will be listed for each participant. 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 participants 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.

8.5.8.2 Blood Pressure

The results of the blood pressure measurements will be listed by participant 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 participants with notable changes from pre-dose (baseline) will be tabulated by 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.

8.5.8.3 Resting 12-lead electrocardiogram

12-Lead ECG results performed for safety evaluation will be listed for each participant 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 time point including changes from baseline. The baseline for the safety ECG parameters will be the results obtained on Day -1.

8.5.8.4 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.

8.5.8.5 Laboratory assessments

Haematology and clinical chemistry values will be listed by participant 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 participants with shifts from baseline in each of these categories.

Urinalysis results will be listed.

9. STUDY AND DATA MANAGEMENT BY ASTRAZENECA

9.1 Training of study site personnel

Before the first participant 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 eCRFs with the participant's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating participants. This will require direct access to all original records for each participant (e.g., clinic charts).
- Ensure withdrawal of informed consent to the use of the participant's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the participant.

The AstraZeneca representative will be available between visits if the Investigator(s) or other staff at the centre need 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 participants and in all other respects, not relating to study conduct or treatment of participants, 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 participants 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 the study is defined as the date when all participants who entered on treatment in the trial performed the last contact (either Visit 3 Follow-up or premature discontinuation visit).

The study is expected to start in Quarter 2 – 3, 2021 and to end by Quarter 4, 2021.

The study may be terminated at the centre 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 have 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.

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 Participant 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 participants. 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 participant into the study.

The Ethics Committee should approve all advertising used to recruit participants 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 participant 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.

Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

- For all studies except those utilizing medical devices, investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

- European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the [Investigator's Brochure or state other documents] and will notify the IRB/IEC, if appropriate according to local requirements.

10.4 Informed consent

The Investigator(s) at the centre will:

- Ensure each participant is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study.

- Ensure each participant is notified that they are free to discontinue from the study at any time.

- Ensure that each participant is given the opportunity to ask questions and allowed time to consider the information provided.

- Ensure each participant 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 participant.

- Ensure that any incentives for participants who participate in the study, as well as any provisions for participants 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 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

1. Buist AS, McBurnie MA, Vollmer WM, et al. International variation in the prevalenceof COPD (the BOLD Study): a population-based prevalence study. Lancet. 2007; 370:741-50.
2. Zhong N, Wang C, Yao W, et al. Prevalence of chronic obstructive pulmonary disease in China a large, population-based survey. Am J Respir Crit Care Med. 2007; 176: 753-60.
3. Jones PW, Singh D, Bateman ED, et al. Efficacy and safety of twice- daily aclidinium bromide in COPD patients: the ATTAIN study. Eur Respir J 2012; 40: 830-836.

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5. Fuhr R, Magnussen H, Sarem K et al. Efficacy of Aclidinium Bromide 400 µg Twice Daily Compared With Placebo and Tiotropium in Patients With Moderate to Severe COPD. Chest 2012; 141(3):745–752.
6. Singh D, Magnussen H, Kirsten AM et al. A randomised, placebo- and active-controlled dose-finding study of aclidinium bromide administered twice a day in COPD patients. Pulmonary Pharmacology & Therapeutics 25 (2012) 248-253.
7. Beeh K, Watz H, Puente-Maestu L et al. Aclidinium improves exercise endurance, dyspnea, lung hyperinflation, and physical activity in patients with COPD: a randomized, placebo-controlled, crossover trial. BMC Pulmonary Medicine 2014, 14:209.
8. Investigator's Brochure Aclidinium Bromide edition number 18, 10Sep2019.
9. WMA Declaration of Helsinki (18th WMA General Assembly 1964), revised at 59th World Medical Association General Assembly Seoul, October 2008.
10. Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.

Appendix A Additional Safety Information

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

Life threatening

'Life-threatening' means that the participant 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 participant's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (e.g., 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 (e.g., 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 participant 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 participant 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 (e.g., 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 participant 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.

Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study intervention that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error.

- Occurred
- Was identified and intercepted before the participant received the drug
- Did not occur, but circumstances were recognised that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error e.g., medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated e.g., tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed e.g., kept in the fridge when it should be at room temperature
- Wrong participant received the medication (excluding IRT/RTSM errors)
- Wrong drug administered to participant (excluding IRT/RTSM errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IRT/RTSM - including those which lead to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s) e.g., forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AstraZeneca product

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 e.g., 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 e.g., 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 subject 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 Potential Hy's Law (PHL) cases and Hy's Law (HL) cases. 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 participant meets potential Hy's Law (PHL) criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated ALT from a central laboratory **and/or** elevated TBL from a local laboratory.

The investigator will also review Adverse Event data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

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 Product (IMP).

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 IP, can be found to explain the combination of increases, e.g., elevated ALP indicating cholestasis, viral hepatitis, another drug.

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

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 participant who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3xULN
- AST ≥ 3xULN
- TBL ≥ 2xULN

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative
- Determine whether the participant meets PHL criteria by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory eCRF

Follow-up

Potential Hy's Law Criteria not met

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

- Inform the AstraZeneca representative that the participant 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 participant does meet PHL criteria the Investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team
- Within 1 day of PHL criteria being met, the investigator will report the case as an SAE of Potential Hy's Law; serious criteria 'Important medical event' and causality assessment 'yes/related' according to CSP process for SAE reporting.

• The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study participants' follow-up (including any further laboratory testing) and the continuous review of data.

• Subsequent to this contact the Investigator will:

- Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.

- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician.

- Complete the three Liver CRF Modules as information becomes available.

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.

As soon as possible 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 IMP, to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria was met. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

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

Where 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 eCRF.

- If the alternative explanation is an AE/SAE, update the previously submitted Potential Hy's Law SAE and AE CRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following 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 IMP:

- Send updated 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 15 calendar days 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:

- Provides any further update to the previously submitted SAE of Potential Hy's Law, (report term now 'Hy's Law case') ensuring causality assessment is related to IMP and seriousness criteria is medically important, according to CSP process for SAE reporting.

- 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 still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

References

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':
http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Appendix D Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

Note: Changes below should be implemented only during study disruptions due to any of or a combination of civil crisis, natural disaster, or public health crisis (e.g., during quarantines and resulting site closures, regional travel restrictions and considerations if site personnel or study participants become infected with SARS-CoV-2 or similar pandemic infection) during which participants may not wish to or may be unable to visit the study site for study visits. These changes should only be implemented if allowable by local/regional guidelines and following notification from the Sponsor and instructions on how to perform these procedures will be provided at the time of implementation.

D 1 Reconsent of Study Participants During Study Interruptions

During study interruptions, it may not be possible for the participants to complete study visits and assessments on site and alternative means for carrying out the visits and assessments may be necessary, e.g., remote visits. Reconsent should be obtained for the alternative means of carrying out visits and assessments and should be obtained prior to performing the procedures described in Sections D 2 to D 4. Local and regional regulations and/or guidelines regarding reconsent of study participants should be checked and followed. Reconsent may be verbal if allowed by local and regional guidelines (note, in the case of verbal reconsent the ICF should be signed at the participant's next contact with the study site). Visiting the study sites for the sole purpose of obtaining reconsent should be avoided.

D 2 Rescreening of Participants To Reconfirm Study Eligibility

Additional rescreening for screen failure due to study disruption can be performed in previously screened participants. The investigator should confirm this with the designated study physician.

In addition, during study disruption there may be a delay between confirming eligibility of a participant and either enrolment into the study or commencing of dosing with IP. If this delay is outside the screening window specified in section 4.1 the participant will need to be rescreened to reconfirm eligibility before commencing study procedures. This will provide another opportunity to re-screen a participant. The procedures detailed in section 4.1 must be undertaken to confirm eligibility using the same participant ID number.

D 3 Telemedicine follow-up Visit to Replace On-site follow-up Visit (where applicable)

In this appendix, the term telemedicine visit refers to remote contact with the participants using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

During a civil crisis, natural disaster, or public health crisis, the on-site follow-up visits may be replaced by a telemedicine visit if allowed by local/regional guidelines. Having a

telemedicine contact with the participants will allow adverse events, concomitant medication, add other information where relevant to be collected according to study requirements to be reported and documented. Participants will be instructed to return to the trial centre to complete the on-site follow-up assessments (12-lead ECG and blood pressure assessment) as soon as possible.

D 4 Data Capture During Telemedicine follow-up Visit

Data collected during telemedicine follow-up visit will be captured by the qualified HCP from the study site in the medical notes and recorded in the eCRF.

D 5 Replacement of participants

Participants who are withdrawn from the study due to study disruption will not be replaced unless fewer than 10 participants complete treatment. Participants will be replaced only if the sponsor's responsible physician and the Investigator agree it is safe to do so.

Screening failure participants will be replaced until the number of participants on treatment is reached.

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