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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Statistical Analysis Plan

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TABLE OF CONTENTS

PAGE

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

Abbreviation or special term	Explanation
AE(s)	Adverse event(s)
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Code
AUCextr	Extrapolated area under the curve from tlast to infinity
AUCinf	Area under the plasma concentration-time curve from zero to infinity
AUClast	Area under the plasma concentration-time curve from zero to the last quantifiable concentration
AUCτ	Area under the concentration-time curve in the dose interval
BID	Twice daily
BLQ	Below the lower limit of quantification
BMI	Body Mass Index (kg/m^2)
bpm	Beats per minute
Cavg	Average drug concentration over a dosing interval
CI	Confidence Interval
CK	Creatine kinase
CL/F	Apparent total body clearance from plasma after extravascular administration
Cmax	Maximum observed plasma concentration
Cmin	Minimum observed drug concentration
COVID-19	Corona Virus Disease 2019
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CV%	Geometric coefficient of variation
DILI	Drug-induced liver injury
DPI	Dry Powder Inhaler
DRM	Data review meeting
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOS	End of study
%Fluc	Fluctuation index during a dosing interval
GGT	Gamma-glutamyl transferase

Abbreviation or special term	Explanation
HBcAb	Hepatitis B Core Antibody
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HL	Hy's Law
HR	Heart rate
ICF	Informed Consent Form
IP	Investigational Product
λz	Terminal elimination rate constant
λz lower	Lower (earlier) t used for λz determination
λzN	Number of data points used for λz determination
λz span ratio	Time period over which λz was determined as a ratio of t½λz
λz upper	Upper (later) t used for λz determination
LLN	lower limit of normal
LLOQ	Lower Limit of Quantification
LS	Least Square
MedDRA	Medical Dictionary for Regulatory Activities
MFL	Lower multiplying factor
MFU	Upper multiplying factor
mmHg	Millimeters of mercury
MRAUC(0-12)	Metabolite to parent ratio based on AUC(0-12)
MRCmax	Metabolite to parent ratio based on Cmax
MRT	Mean residence time (h) calculated by AUMC/AUC, where AUMC is the area under the first moment-time curve
MRTinf	Mean residence time of the unchanged drug in the systemic circulation
msec	Milliseconds
NA	Not applicable
ND	Not determined
NR	Nonreportable concentration
PD	Protocol Deviation
PDS	Protocol deviations specifications
PHL	Potential Hy's Law

Abbreviation or special term	Explanation
PI	Principal Investigator
PK	Pharmacokinetics
PKS	Pharmacokinetic analysis set
PM	Evening (Post meridiem)
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 (HR)
QTcB interval	QT interval corrected, Bazett formulae ($QT/RR^{1/2}$)
QTcF interval	QT interval corrected, Fredericia formulae ($QT/RR^{1/3}$)
Rac(AUC)	Accumulation ratio for AUCτ
Rac(Cmax)	Accumulation ratio for Cmax
Rac(Cmin)	Accumulation ratio for Cmin
RR	Duration in milliseconds between two R peaks of two consecutive QRS complexes
Rsq adj	Statistical measure of fit for the regression used for λz determination adjusted for the number of used data points
SAE(s)	Serious Adverse Event(s)
SAF	Safety analysis set
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
std	Standard Deviation
TBL	Total bilirubin
TCP	Temporal change parameter based on AUC
TEAE(s)	Treatment-Emergent Adverse Event(s)
TFL(s)	Table, listing and figure(s)
t½λz	Half-life associated with terminal slope of a semilogarithmic concentration-time curve
tlast	Time of last quantifiable concentration

Abbreviation or special term	Explanation
tmax	Time to reach maximum observed concentration
ULN	Upper Limit of Normal
Vz/F	Volume of distribution (apparent) following extravascular administration based on terminal phase
WHO	World Health Organization

AMENDMENT HISTORY

Date	Brief description of change
24/11/2017	Original document (Final 1.0).
20/06/2019	Updated for additional PK parameters and related changes (Draft 1.1).
28/10/2019	Updated for TFL re-numbering, demographic and baseline characteristics changes, prior/concomitant medication text changes, additional PK parameter inclusions and revision to be consistent with the Duaklir (D6572C00001) study SAP updates (Draft 1.2).
26/01/2020	Updated for final comments from AZ and Covance (Draft 1.3).
06/02/2020	Finalization of document (Final 2.0).
12/05/2021	Updated following Protocol Amendment
27/08/2021	Finalization of document (Final 3.0)

1. STUDY DETAILS

1.1 Study objectives

1.1.1 Primary objective

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.

1.1.2 Secondary objectives

To evaluate the safety, and tolerability of aclidinium bromide 400 µg after single and multiple dose administration (twice-daily [BID]) in healthy Chinese subjects. The variables are given in the Section 3.2.

1.2 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 subjects.

All subjects 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 subjects 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) subjects will receive a single dose of aclidinium bromide in the morning (AM) via the Genuair® Dry Powder Inhaler (DPI), followed by a wash out period of 96 hours (considered enough to avoid a carry-over effect). On Day 5 through Day 8, subjects will receive twice daily (BID) doses of aclidinium bromide (AM and PM) via the Genuair® DPI and on Day 9, subjects will receive only the AM dose of aclidinium bromide via the Genuair® DPI. Subjects will be discharged on Day 11, 48 hours after last administration of the investigational product (IP).

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).

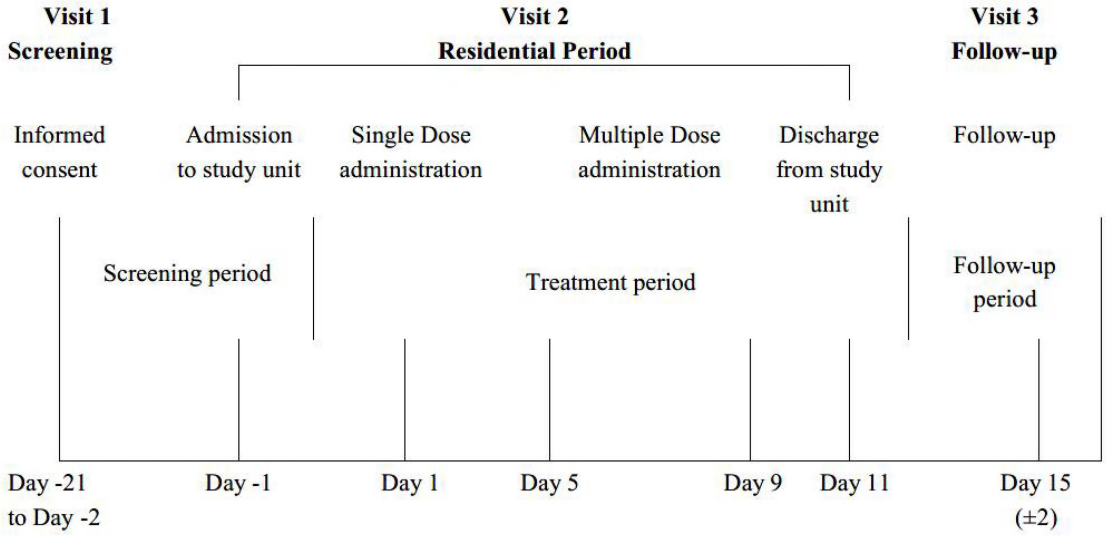
A follow-up visit will take place on Day 15 (±2).

Subjects 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 subject´s safety. Subjects prematurely discontinued from the study will not be replaced.

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

Figure 1 Study flow chart



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 subjects.

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

Single and Multiple Dose (Twice-Daily) treatment will be as follows:

Investigational product	Dosage form and strength
Aclidinium bromide	Powder for inhalation administered via multidose DPI (Genuair ®) 400µg/inhalation

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 subject 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.

The schedule of assessments is presented in Table 1.

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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	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 subjects needs additional time to washout any prior medications, the ICF must be provided before Visit 1. Subjects 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. Subjects 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. Subjects 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 of the CSP.
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.

1.3 Number of subjects

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

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

2. ANALYSIS SETS

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

2.2 Safety analysis set

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

Unless otherwise stated, the SAF 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 SAF.

2.3 Pharmacokinetic analysis set

The PK analysis set (PKS) will consist of all subjects in the SAF who received at least 1 dose of aclidinium bromide and have at least 1 of the parameters (Cmax, AUCinf, AUClast or AUCτ) 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 subjects 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 subjects excluded from the PKS will be listed only. Concentration data for subjects excluded from the PKS will be presented in the individual figures of concentration versus time plots.

2.4 Protocol deviations

The criteria for the assessment and reporting of protocol deviations will be stipulated in a separate study specific protocol deviation specification (PDS) 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 subjects from the PKS.

Important deviations will be defined before database lock and analysis sets will be assessed at the data review meeting (DRM).

Important deviations will include the following:

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

This list of important protocol violations is not necessarily complete, the final decision will be made at the DRM.

Table 2 shows important protocol deviations and how each deviation will affect the assignment of subjects and/or specific data points to the PKS.

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

Table 2 Important protocol deviations and population classification

Item #	Event description	Excluded from analysis set	
		Safety	PK
1	Subject met the following exclusion criteria: Positive results for drugs of abuse at Visit 1 (Screening).	No	Yes^{+}
2	Subject meet the following exclusion criteria: 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.	No	No^{+}
3	Subject met the following exclusion criteria: Have consumed caffeine or any grapefruit-containing products within 48 hours or alcohol within 72 hours before Day -1.	No	No^{+}
4	Subject met the following exclusion criteria: 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).	No	No
5	Subject met the following exclusion criteria: Have any gastrointestinal, hepatic, or renal condition that might affect the absorption, distribution, biotransformation, or excretion of aclidinium bromide.	No	Yes^{+}
6	Subject has missing date/time for PK blood sampling.	No	Yes^{++}
7	Subject has missing sample for PK blood sampling.	No	Yes^{++}
8	Subject received prohibited concomitant medication.	No	Yes^{+}
9	Subject did not adhere to dietary restrictions prior to or after dosing per protocol specification and/or prior to Day -1 at Visit 2 until discharge from trial centre.	No	No^{+}

Item #	Event description	Excluded from analysis set	
		Safety	PK
10	Subject received incorrect treatment or has missing dosing information (including completely missing record, missing date/time, dose).	No	Yes+
11	Subject developed discontinuation criteria but continued in the study.	Yes+	Yes+
12	Other protocol deviations.	No+	No+

+To be confirmed at the DRM; time-point specific or global PKS exclusion. ++Excluded from the specific time-point only.

3. STUDY VARIABLES

3.1 Pharmacokinetic variables

Serial blood samples will be collected for PK assessments of IP and its metabolites (LAS34823 and LAS34850) in plasma 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).

- Day 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 is 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

Data permitting, the single dose (Day 1) and multiple dose (Day 9) PK parameters listed in Section 4.2.5.1 will be derived for the IP and its metabolites LAS34850 and LAS34823 from plasma concentrations.

3.2 Safety variables

Safety variables will include the following:

- Adverse events (AEs)
- Clinical laboratory parameters (haematology, serum biochemistry and urinalysis)
- Vital Signs (blood pressure)
- 12-Lead ECG parameters

3.3 Adverse events

The definitions of AEs and SAEs are given in 6.1 and 6.2 respectively of the Clinical Study Protocol.

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

3.4 Vital signs and 12-lead electrocardiogram

Blood pressure and safety 12-lead ECG will be collected at:

- Visit 1 (Screening and/or re-screening).
- Visit 2 on Day -1/Day -1 (re-screening), 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 or premature discontinuation visit.
- Both systolic blood pressure and diastolic blood pressure (in mmHg) will be measured after at least 5 minutes resting. Measurements will be carried out with subject in resting position and preferably always on the same arm. Data will be recorded on the eCRF.

Please note: Visit 1 includes Visit 1 (screening)/(re-screening) and Day -1 includes Day -1/Day-1 (re-screening). For screen failure occurring after completing Day -1, the expected visit order for re-screened subjects is: Visit 1 (screening); Day -1; Visit 1 (re-screening); Day -1 (re-screening); Day 1. And for screen failure occurring before Day -1, the expected visit order is: Visit 1 (screening); Visit 1 (re-screening); Day -1; Day 1.

Further, height and weight will be measured along with vital signs at screening/re-screening.

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.

• QTc using Bazett's formula (QTcB): 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.

3.5 Clinical laboratory parameters

The laboratory variables (serum pregnancy test for women of childbearing potential, haematology, serum biochemistry and urinalysis) presented in Table 3 will be measured at Screening Visit 1, Day -1 and Day 11 and at the Follow-up or premature discontinuation Visit. Included is also serology which is only collected at screening.

Please note: Visit 1 includes Visit 1 (screening)/(re-screening) and Day -1 includes Day -1/Day-1 (re-screening). For screen failure occurring after completing Day -1, the expected visit order for re-screened subjects is: Visit 1 (screening); Day -1; Visit 1 (re-screening); Day -1 (re-screening); Day 1. And for screen failure occurring before Day -1, the expected visit order is: Visit 1 (screening); Visit 1 (re-screening); Day -1; Day 1.

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. If the investigator considers that a result is clinically relevant or doubtful, additional blood samples may be collected in unscheduled visits.

Table 3 Laboratory safety variables

Haematology/Haemostasis (whole blood)	Clinical Chemistry (serum or plasma)
B-Haemoglobin (Hb)	S/P-Creatinine
B-Haematocrit	S/P-Bilirubin, total (TBL)
B-Erythrocytes count	S/P-Alkaline phosphatase (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 1 and 2	

HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HIV= human immunodeficiency virus.

3.6 Hy's Law

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

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

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

Potential Hy's Law:

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:

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.

The analysis for Hy's law is presented in Section 4.2.6.4.

3.7 Other variables

3.7.1.1 Demographic and baseline characteristics

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

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

- History of Tobacco Use (Non-smoker, Former, Current)

3.7.1.2 Prior and concomitant medication

As recorded on the eCRF, prior medication is defined as any medication taken between 14 days prior to the ICF date and the date of 1st IP dose.

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 according to the latest World Health Organization (WHO) drug dictionary and will be listed by subjects.

3.7.1.3 Drug administration

Dosing of IP will occur on the Day 1 and Day 5 through Day 9.

Drug administration, overdose, and drug accountability report will be recorded.

3.7.1.4 Drugs of abuse, serology and meal data

Results for drugs of abuse and serology assessments, as well as meal data will not be reported as part of the clinical study report (CSR).

3.7.1.5 Physical examination

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

4. ANALYSIS METHODS

4.1 General principles

This Statistical Analysis Plan (SAP) describes the statistical analyses of demographics, baseline characteristics, concomitant medication, PK, safety and tolerability data planned in the trial protocol. All data analyses will be performed by PAREXEL, except the derivation of PK parameters for IP, its metabolites LAS34823 and LAS34850 which will be performed by LabCorp Drug Development. SAS®version 9.4 (SAS Institute, Inc., Cary, North Carolina) will be used to create all datasets and all tables, figures and listings (TFLs). Pharmacokinetic parameters will be derived using non-compartmental methods with Phoenix® WinNonlin® Version 8.1, or higher and/or SAS® Version 9.4 or later.

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

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

Categorical variables will be summarized with counts (n) and percentages (%) and will be summarized by all subjects. Descriptive statistics (n, mean, standard deviation [SD], median, minimum and maximum, first and third quartiles) will be calculated for each quantitative variable (unless otherwise stated). As a rule (unless otherwise specified), mean, SD and median, will be reported to one decimal place more than the observed values, minimum and maximum with the same number of decimal places as the observed values. For PK concentrations and parameters please follow rules for standard statistics and significant figures in the CSRHLD Reporting Standards.

4.1.1 Handling of repeated/unscheduled measurements

Unless otherwise indicated, the following rules will apply to any repeated safety

measurements for visit-based summary and analysis purposes:

- If the repeated measurement of a specific parameter occurs prior to IP administration on Day 1 the last obtained value prior to dosing will be used in the descriptive statistics and in the calculation of changes from baseline.

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

- If the repeated measurement of a specific parameter occurs after IP administration on Day 1 and the reason for the repeat is a technical error/device error, then the second value will be used in descriptive statistics and in the calculation of changes from baseline.

- If a whole visit is repeated after IP administration on Day 1 then the repeated visit will be used in the descriptive statistics and in the calculation of changes from baseline.

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

4.2 Analysis and reporting

4.2.1 Subject disposition

The cause of screening failure will be listed for all subjects screened. This will include the inclusion criteria not met and exclusion criteria met along with age, sex, race and ethnic population. If the subject was none-the less entered into treatment, the treatment will be provided along with the protocol version if applicable. Screening failures will be summarized (n and percent) for inclusion criteria not met and exclusion criteria met. Discontinuations from the study will be listed, including date of discontinuation and primary reason for discontinuation.

Informed consent response will be listed including the date of informed consent, the date/time of confirmed eligibility and whether subjects complied with all inclusion/exclusion criteria.

Assignment of subjects to analysis sets and reasons for exclusion from an analysis set will be listed by subjects and summarized by all subjects.

Discontinuations from the study will be listed, including date of discontinuation and primary reason for discontinuation. Subjects disposition will be summarized for all subjects. The tabulation will include the following information: number of subjects screened and re-screened, number and percentage of subjects treated, number and percentage of subjects

completing the study and the number and percentage of subjects who were withdrawn (including reasons for withdrawal). Disposition data will be presented based on all subjects enrolled and the denominator for percentages will be the number of subjects enrolled. Important protocol deviations as defined in the PDS will be listed for each enrolled subject. Furthermore, any protocol deviations (important and non-important) and/or issues associated with COVID-19 pandemic will be listed.

4.2.2 Demographic and baseline characteristics

Demographic variables (including age, sex, race, height, weight and BMI) will be listed and summarised for all subjects in the SAF.

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

Smoking history will be listed by subject including the variables recorded as specified in Section 3.7.1.1 for all subjects in the SAF. The smoking usage status will be summarized (n and percent) by all subjects for the SAF.

4.2.3 Prior and concomitant medication

The number and percentage of subjects 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. Subjects 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.

4.2.4 Drug administration

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

4.2.5 Pharmacokinetics

4.2.5.1 Calculation or derivation of the pharmacokinetic parameters

The PK parameters derived using the concentration data from the IP and its metabolites LAS34850 and LAS34823 will be calculated according to AstraZeneca Pharmacokinetic standards.

PK analysis will, where data allow, be carried out using actual elapsed times determined from the PK sampling and dosing times recorded in the database. If actual elapsed times are missing, nominal times may be used. Nominal sampling times may be used for any agreed interim PK parameter calculations if required.

Data permitting, the following single dose (Day 1) PK parameters will be derived for the IP and its metabolites LAS34850 and LAS34823 from plasma concentrations:

Parameter	Definition
Cmax	Maximum observed plasma concentration
tmax	Time to reach maximum observed concentration
AUCinf	Area under plasma concentration-time curve from zero to infinity
AUClast	Area under the plasma concentration-time curve from zero to the last quantifiable concentration
AUC(0-12)*	Area under the concentration-time curve from time 0 to 12 hours post-dose
$t_{½\lambda z}$	Half-life associated with terminal slope of a semilogarithmic concentration-time curve
CL/F	Apparent total body clearance from plasma after extravascular administration (IP only)
Vz/F	Volume of distribution (apparent) following extravascular administration based on terminal phase (IP only)
MRTinf	Mean residence time of the unchanged drug in the systemic circulation (IP only)
Cmin	Minimum observed drug concentration
MRCmax	Metabolite to parent ratio based on Cmax
MRAUC(0-12)	Metabolite to parent ratio based on AUC(0-12)

* Equivalent to AUC_{τ} for BID dosing

Data permitting, the following multiple dose (Day 9 after 5 days of repeated BID dosing) PK parameters will be derived for the IP and its metabolites LAS34850 and LAS34823 from plasma concentrations:

Parameter	Definition
Cmax	Maximum observed plasma concentration
tmax	Time to reach maximum observed concentration
AUCτ	Area under plasma concentration-time curve in the dose interval
AUClast	Area under the plasma concentration-time curve from zero to the last quantifiable concentration
t½λz	Half-life associated with terminal slope of a semilogarithmic concentration-time curve
CL/F	Apparent total body clearance from plasma after extravascular administration (IP only)
Vz/F	Volume of distribution (apparent) following extravascular administration based on terminal phase (IP only)
Cmin	Minimum observed drug concentration
Cavg	Average drug concentration over a dosing interval
TCP	Temporal change parameter based on AUC
Rac(Cmax)	Accumulation ratio for Cmax
Rac(Cmin)	Accumulation ratio for Cmin
Rac(AUC)	Accumulation ratio for AUCτ
MRCmax	Metabolite to parent ratio based on Cmax
MRAUC(0-12)	Metabolite to parent ratio based on AUC(0-12)
%Fluc	Fluctuation index during a dosing interval, estimated as 100*(Cmax - Cmin)/Cavg (%)

The following PK variables will be calculated for diagnostic purposes where applicable:

Parameter	Definition
λz lower	Lower (earlier) t used for λz determination
λz upper	Upper (later) t used for λz determination
λzN	Number of data points used for λz determination
λz	Terminal elimination rate constant
Rsq adj	Statistical measure of fit for the regression used for λz determination adjusted for the number of used data points
λz span ratio	Time period over which λz was determined as a ratio of t½λz
AUCextr	Extrapolated area under the curve from tlast to infinity, [(Clast)/ λz)/AUCinf* 100, expressed as percentage of AUCinf]
tlast	Time of last quantifiable concentration

Additional PK parameters may be determined if appropriate.

If an entire concentration-time profile is not quantifiable, the profile will be excluded from the PK analysis.

The minimum requirement for the calculation of area under the curve (AUC) values will be the inclusion of at least 3 consecutive quantifiable concentrations. Where there are only 3 quantifiable concentrations at least one of these should follow the peak concentration.

Individual concentrations may be excluded from the analysis for legitimate scientific reasons e.g, dosing issues, vomiting after dose administration and prohibited co-medication. Any excluded data, together with the justification for exclusion, will be clearly documented in the CSR.

4.2.5.2 Presentation of pharmacokinetic data

The PK concentrations and the PK parameters will be listed and presented in tabular and graphical form, as appropriate, according to the version of the AstraZeneca Corporate CSRHLD TFL templates and reporting standards as documented in the TFL shells, that include applicable descriptive statistics, defined handling of individual concentrations below the lower limit of quantification (LLOQ) and precision/rounding rules for PK concentration and parameter data.

Exclusion of concentration and/or parameter data from PK summaries may apply, this will be flagged in the listings with the reason(s) for exclusion.

Plasma Concentrations

A listing of concentration versus scheduled time data will be presented by analyte and Visit/PK day for the SAF. A listing of all concentration-time data, ie, PK scheduled times, actual sample collection times, sample actual relative times, as well as derived sampling time deviations will be presented by analyte and Visit/PK day for all enrolled patients.

Plasma concentrations for each scheduled time point will be summarized for each analyte and Visit/PK day using appropriate descriptive statistics, based on the SAF.

Pharmacokinetic Parameters

All reportable plasma PK parameters will be listed for each patient by analyte and Visit/PK day based on the PKS.

All PK parameters will be summarized by analyte and Visit/PK day using appropriate descriptive statistics, based on the PKS.

Graphical Presentation of PK Data

Individual concentration-time data will be graphically presented on linear and semi-logarithmic scales by analyte for the SAF. Each individual's plot will include the

concentration versus actual time profiles from Day 1 and Day 9 overlaid on the same plot, plotted separately for each analyte. Combined individual plasma concentration versus actual times grouped by analyte will be plotted separately for PK Day 1 and Day 9 on both the linear and semi-logarithmic scale for all subjects in the PKS. Combined individual trough concentrations (am and pm predose concentrations on Day 6 to 9) will be plotted over time with all individuals overlaid in the same plot on the linear scale only and presented separately by analyte for the PKS.

Figures for the geometric mean concentration-time data will be presented with PK Day 1 and 9 overlaid on the same figure, plotted separately by analyte on both a linear with (geoSD) error bars and semi-logarithmic scale (no error bars), based on the PKS. Geometric mean trough concentrations (am and pm pre-dose concentrations on Day 6 to 9) will be plotted over time on the linear scale only and presented separately by analyte for the PKS. For consistency, the summary concentrations plotted will reflect what is presented in the concentration summary tables.

4.2.5.3 Analysis of time dependency

The time dependency will be evaluated by comparing AUCτ on Day 9 with AUCinf 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 subject.

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.

The following SAS code will be used for the time dependency analysis, repeated for each analyte and parameter type (as defined above).

CCI [redacted]

CCI [redacted]

[redacted].

Checking of assumptions for Model 1 is detailed in Section 4.4.

4.2.5.4 Analysis of accumulation

Accumulation will be evaluated by comparing AUCτ on Day 9 with AUC(0-12) on Day 1 and Cmax on Day 9 with Cmax on Day 1.

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

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.

The following SAS code will be used for the accumulation analysis, repeated for each analyte and parameter type (as defined above).

CCI [redacted]

[redacted] CCI [redacted]

Checking of assumptions for Model 1 is detailed in Section 4.4.

4.2.6 Analysis of safety data

4.2.6.1 Adverse events

Adverse events (AEs) will be coded using the latest available MedDRA version.

A treatment emergent AE (TEAE) is defined as an AE with start date/time on or after the first dose of IP or within 15 days from the last dose. AEs with missing start date/time will be handled as detailed in Section 4.3.2.

Treatment emergent AEs will be allocated to treatment periods as follows:

Any AE occurring after first IP on Day 1 through 15 days from the last dose will be allocated to the treatment.

Listings will be presented by subjects in chronological order of AE and will include visit and day where relevant for each of the following:

- All AEs, including the AE number, verbatim term, PT and SOC.
- All AEs with onset and resolution, including classification of the AE as pre-treatment or TEAE, the PT and verbatim term, onset date/time, resolution date/time and time from the last dose of IP.
- All AEs by relationship and causality, including the PT and verbatim term, severity, action taken with regards to IP, outcome, causality, whether the AE was serious, and whether the AE resulted in the subject being withdrawn.

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

The following tabulations will be presented for TEAEs only:

- TEAEs in any category
- TEAEs by PT and SOC
- Number and percentage of all subjects with TEAEs by causality and PT
- TEAEs by maximum reported intensity and PT
- TESAEs, by PT and SOC
- TEAEs leading to discontinuation, by PT and SOC
- Non-serious TEAEs occurring in greater than 5% of subjects

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

- Serious AEs: AE as reported, PT, time from start of treatment to onset of AE, time from last dose of IP to onset of AE, time from start of treatment to becoming serious, the outcome, action taken with IP and whether there is a reasonable possibility that the AE was caused by the IP.
- Adverse events leading to discontinuation: AE as reported, PT, time from start of treatment to onset of AE, time from start of treatment to discontinuation, whether the AE is serious, the outcome and whether there is a reasonable possibility that the AE was caused by IP.

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

4.2.6.2 Adverse events of special interest

SOC terms, along with Standard MedDRA Query (SMQs) and PTs used to identify the treatment emergent AEs of special interest (AESI) are included in the Table 4 below.

The number and percentage of subjects with treatment emergent anticholinergic events will be tabulated by SOC and PT based on the SAF.

Table 4 Definition of treatment-emergent adverse events of interest

Events of interest	Standard MedDRA Query Category plus additional High Level Terms or Preferred Term, if applicable
Potential Anticholinergic events	Anticholinergic syndrome (narrow and broad search SMQ), Glaucoma (narrow search SMQ) Additional PTs: sinus tachycardia, supraventricular tachycardia, ventricular tachycardia, heart rate increased, palpitations, pupillary reflex impaired, pupils unequal, visual impairment, constipation, gastrointestinal obstruction, ileus paralytic, urinary tract infection, cystitis, urinary incontinence, incontinence, dysuria, urge incontinence, urine flow decreased, bladder irritation, oropharyngeal pain, dysphonia, laryngitis, pharyngitis, and throat irritation

4.2.6.3 Vital signs and 12-lead electrocardiogram

Vital signs:

The results of the blood pressure measurements will be listed by subject and time point including the date/time of the assessment, changes from baseline and repeat/unscheduled measurements. Abnormal values based on the criteria give in Table 5 will also be flagged in the listings.

The baseline for blood pressure measurements will be the last non-missing result before first IP intake. This will be the pre-dose assessment on Day 1. If missing, then if re-screening has been performed, either Day -1 (Re-screening) or Re-screening V1 should be used; else use Day -1 or screening. Descriptive statistics will be presented in the SAF by time point for both observed values and changes from baseline. The number and percentage of subjects with notable changes from pre-dose (baseline) will be tabulated by time point (and ”Any post-baseline visit”) based on the criteria provided in Table 5. Denominator for percentages will be the number of subjects in the SAF.

Table 5 gives the notable high and low changes from baseline to be flagged in the listing.

Table 5 Notable Changes from Baseline in vital signs

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

mmHg=millimeters of mercury.

12-lead electrocardiogram:

The overall interpretation of the 12-Lead ECG results performed for safety evaluation will be listed for each subject. Numeric parameter values (HR, RR, PR, QRS and all QT intervals) are defined in Section 3.4 and derivations are provided below. Observed values and changes from baseline will be presented by time point. The baseline for the safety ECG parameters will be the last non-missing result before first IP intake. This will be the pre-dose assessment on Day 1. If missing, then if re-screening has been performed, either Day -1 (Re-screening) or Re-screening V1 should be used; else use Day -1 or screening. The number and percentage of subjects with outliers defined in Table 6 with respect to 12-lead ECG parameters will be presented for the following categories at each time point (and "Any post-baseline visit").

Table 6 Definition of potentially clinically significant (PCS) values in 12-lead ECG parameters

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

bpm = beats per minute; ECG = electrocardiogram; QTcF = QT interval corrected for heart rate using the Fridericia formula ($QTcF = QT/(RR)^{1/3}$). ($QTcB = QT/(RR)^{1/2}$)

If either condition a) or condition b) are met, the QTcF or QTcB or heart rate value will be considered potentially clinically significant (PCS).

Descriptive statistics and outlier summary will be based on the SAF. For the outlier summary, denominator for percentages will be the number of subjects in the SAF.

Calculation of the ECG parameters

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

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

QTcB interval will be calculated as: QTcB = $(\mathrm{QT}/\mathrm{RR}^{1/2})$ where the QT interval is in msec and the RR interval is in seconds
HR will be calculated as: $\mathrm{HR} = 60/\mathrm{RR}$ interval, where the RR interval is in seconds

4.2.6.4 Clinical laboratory assessments

Haematology and clinical chemistry values will be listed by subject and time point including changes from baseline and repeat/unscheduled measurements. The baseline for clinical laboratory assessments will be the last non-missing result before first IP intake. This will be Day -1, or Day -1 (re-screening) if re-screening performed. If missing, then the baseline will be Visit 1 (screening), or Visit 1 (re-screening), if re-screening is performed.

Descriptive statistics for haematology and clinical chemistry observed values and changes from baseline will be presented for all parameters by time point for the SAF.

Listings will include a flag for out of range values for both notable abnormalities as well as expanded normal ranges as defined in Table 7.

Each laboratory test value will be identified as:

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

will be provided for post baseline time-points (and ”Any post-baseline visit”), the ENR being calculated by multiplying the LLN and ULN of the laboratory by the factor shown in Table 7.

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

be summarised by means of shift contingency tables comparing the values assessed at post-baseline time-points (and "Any post-baseline visit") to the baseline values. Denominator will be the number of subjects in the SAF.

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

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

A laboratory parameter will be defined as "Worsened" if the baseline lab test value is above the expanded upper limit of the corresponding normal range (xULN) specified in Table 7 and the ratio of endpoint value to baseline value is also greater than the corresponding coefficient (multiplying factor) specified in Table 7, or alternatively if the baseline laboratory test value is below the expanded lower limit of the corresponding normal range (xLLN) specified in the above table and the ratio of endpoint value to baseline value is also lower than the corresponding coefficient specified in Table 7.

The laboratory abnormality will be also classified as a "Notable" abnormality if it satisfies the criteria detailed in Table 7, having a baseline value within the notable abnormality limits.

Table 7 Expanded normal ranges and notable abnormalities for laboratory parameters

Laboratory Parameter	**Expanded Normal Ranges**				**Notable Abnormalities**	
	MFL	*MFU*	*Lower Limit*	*Upper Limit*	*Lower Limit*	*Upper Limit*
Haematology						
Haemoglobin	0.85	1.15	MFL × LLN	MFU × ULN	< 60 g/L	> 230 g/L
Haematocrit	0.85	1.15	MFL × LLN	MFU × ULN	< 0.24	NA
Erythrocytes count	0.85	1.15	MFL × LLN	MFU × ULN	NA	NA
Platelets	0.85	1.15	MFL × LLN	MFU × ULN	$< 100 \times 10^9$/L	NA
Leukocyte count	0.85	1.15	MFL× LLN	MFU × ULN	$< 1 \times 10^9$/L	$> 30 \times 10^9$/L

Laboratory Parameter	**Expanded Normal Ranges**				**Notable Abnormalities**	
	MFL	*MFU*	*Lower Limit*	*Upper Limit*	*Lower Limit*	*Upper Limit*
Neutrophils	0.85	1.15	MFL× LLN	MFU × ULN	$< 0.5 \times 10^9$/L	NA
Eosinophils	NA	1.15	MFL× LLN	MFU × ULN	NA	NA
Basophils	NA	1.15	MFL× LLN	MFU × ULN	NA	NA
Lymphocytes	0.85	1.15	MFL× LLN	MFU × ULN	NA	NA
Monocytes	NA	1.15	MFL× LLN	MFU × ULN	NA	NA
Clinical chemistry						
Aspartate aminotransferase (AST)	NA	1.15	NA	MFU × ULN	NA	> 3 × ULN
Alanine aminotransferase(ALT)	NA	1.15	NA	MFU × ULN	NA	> 3 × ULN
Alkaline phosphatase	NA	1.15	NA	MFU × ULN	NA	> 3 × ULN
Gamma-glutamyl transpeptidase	NA	1.15	NA	MFU × ULN	NA	> 3 × ULN
Total bilirubin (TBL)	NA	1.15	NA	MFU × ULN	NA	> 51.3 µmol/L
Creatine-kinase	NA	1.15	NA	MFU × ULN	NA	> 10 × ULN
Lactate dehydrogenase	NA	1.15	NA	MFU × ULN	NA	> 3 × ULN
Blood urea nitrogen	NA	1.15	NA	MFU × ULN	NA	> 17.9 mmol/L
Creatinine	NA	1.15	NA	MFU × ULN	NA	> 265 µmol/L
Uric acid	NA	1.15	NA	MFU × ULN	NA	> 714 µmol/L
Total cholesterol	NA	1.15	NA	MFU × ULN	NA	NA

Laboratory Parameter	Expanded Normal Ranges				Notable Abnormalities	
	MFL	*MFU*	*Lower Limit*	*Upper Limit*	*Lower Limit*	*Upper Limit*
Triglycerides	NA	1.15	NA	MFU × ULN	NA	NA
Glucose	0.85	1.15	MFL× LLN	MFU × ULN	< 2.22 mmol/L	> 22.2 mmol/L
Sodium	0.95	1.05	MFL× LLN	MFU × ULN	<115 mmol/L	> 165 mmol/L
Potassium	0.95	1.05	MFL× LLN	MFU × ULN	< 2.6 mmol/L	> 6.9 mmol/L
Calcium, total	0.85	1.15	MFL× LLN	MFU × ULN	< 1.25 mmol/L	> 3.25 mmol/L
Chloride	0.95	1.05	MFL× LLN	MFU × ULN	NA	NA
Inorganic phosphorus	0.85	1.15	MFL× LLN	MFU × ULN	NA	NA
Total Protein	0.85	1.15	MFL× LLN	MFU × ULN	< 20 g/L	> 90 g/L
Albumin	0.85	1.15	MFL× LLN	MFU × ULN	NA	NA

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

For the classification of laboratory values, calculation of changes from baseline and for the purposes of summary statistics, any laboratory parameter value that is given as '<xx.x' or '>xx.x' in the database will be imputed according to rules stated in Section 4.3.1.

Urinalysis and pregnancy test results will be listed.

A separate table of all Hy's Law relevant laboratory parameters ALT, AST and total bilirubin will be provided on the subject basis. Summary statistics will be presented for the maximum post-baseline ALT and AST by TBL.

4.3 Data handling

A subject who withdraws prior to the last planned observation in a study period will be included in the analyses up to the time of discontinuation. In general, missing data will result

in a reduced sample size for the given parameter. No imputation of missing data will be performed except for the below cases. A subjects who withdraws prior to the last planned observation in the study will be included in the analyses up to the time of discontinuation, if no important protocol deviations necessitate the exclusion of collected data from the analysis.

4.3.1 Safety laboratory data with semi-qualitative results

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

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

4.3.2 Missing data for adverse events and medications

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

Missing adverse event causality

- A causality of "related" will be assigned to an AE if the relationship to the IP is missing for an AE and the start date of the AE shows that the AE started on or after the first dose of IP.
- A causality of "not related" will be assigned to an AE if the relationship to the IP is missing for an AE and the start date of the AE shows that the AE started before the first dose of IP.

Missing adverse event intensity and seriousness

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

Missing start date of AEs and medications

Medications with missing or partial start date/time and/or end date/ such that it is not possible to classify as prior or concomitant will be considered as concomitant for the listings and tables.

Adverse events with partially known start dates/times will be handled as follows for the purposes of the tabulations:

- If the start date is completely missing but the end date is known and shows that the AE ended on or after the first dose date, then the start date will be imputed as the first day of dosing; if the end date is known and shows that the AE ended before the first dose date, then the screening date will be used for the start date. If the end date is non-informative

(i.e., is missing or does not contain enough information), the start date will be imputed as the first date of dosing;

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

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

- Missing times will be imputed as 00:00 h or with the time of IP dosing for events starting on a dosing day.

Missing end date of AEs and medications

Missing end date of AEs will not be imputed.

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

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

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

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

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

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

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

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

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

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

4.3.3 Computation of derived variables

4.3.3.1 Definition of Baseline values

The Baseline value for all variables will be the last available value prior to the first IP administration. Scheduled or unscheduled measurements can be used as the Baseline value.

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

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

4.3.3.2 Summary statistics

For the geometric mean, geometric mean ± SD and CV%, the following holds:

$$\text{Geometric mean} = \exp[M_L],$$

where M_L is the arithmetic mean of the natural log-transformed variable.

$$\text{Geometric Mean} \pm \text{SD} = \exp(\text{mean}(\log(\text{PK Conc})) \pm \text{std}(\log(\text{PK Conc})))$$

using the natural logarithm.

$$\text{geometric CV (\%)} = 100 \times [\exp(SD^2) - 1]^{0.5},$$

where the SD/std is the standard deviation of the log-transformed data, using the natural logarithm.

CCI [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

5. INTERIM ANALYSES

NA, no interim analysis will be performed.

6. CHANGES OF ANALYSIS FROM PROTOCOL

Following PK parameters have been added:

- MRCmax - Metabolite to parent ratio for Cmax.
- MRAUC(0-12) - Metabolite to parent ratio for AUC(0-12)

Dose normalized parameters will not be derived as these are not applicable since only 1 dose level will be administered.

Trough concentration plots will be presented in linear scale only as the semi-logorithmic plot would add little value.

"Participants" has been changed to "subjects" in the SAP and TFL Shells to align with AZ CSRHLD standards for TLFs.

7. APPENDIX

7.1 Appendix I – List of tables, figures and listings

7.1.1 TABLES

SUBJECT DISPOSITION

Table 14.1.1.1.1 Subject disposition (All subjects screened)
Table 14.1.1.1.2 Screening failures - Inclusion criteria (All subjects screened)
Table 14.1.1.1.3 Screening failures – Exclusion criteria (All subjects screened)
Table 14.1.2.1.1 Analysis sets (Enrolled subjects)

DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Table 14.1.3.1.1 Demographic characteristics (Safety analysis set)
Table 14.1.3.1.2 Subject characteristics at screening (Safety analysis set)
Table 14.1.3.1.3 History of tobacco use (Safety analysis set)

PRIOR AND CONCOMITANT MEDICATION

Table 14.1.4.1.1 Prior medication (Safety analysis set)
Table 14.1.4.1.2 Concomitant medication (Safety analysis set)

PHARMACOKINETICS

Table 14.2.1.1.1 Summary of plasma concentrations (pg/mL) for aclidinium bromide (Pharmacokinetic analysis set)
Table 14.2.1.1.2 Summary of plasma concentrations (pg/mL) for LAS34823 (Pharmacokinetic analysis set)
Table 14.2.1.1.3 Summary of plasma concentrations (pg/mL) for LAS34850 (Pharmacokinetic analysis set)
Table 14.2.7.1.1 Summary of plasma pharmacokinetic parameters for aclidinium bromide - single dose (Pharmacokinetic analysis set)
Table 14.2.7.1.2 Summary of plasma pharmacokinetic parameters for aclidinium bromide - multiple dose (Pharmacokinetic analysis set)
Table 14.2.7.2.1 Summary of plasma pharmacokinetic parameters for LAS34823 - single dose (Pharmacokinetic analysis set)
Table 14.2.7.2.2 Summary of plasma pharmacokinetic parameters for LAS34823 - multiple dose (Pharmacokinetic analysis set)
Table 14.2.7.3.1 Summary of plasma pharmacokinetic parameters for LAS34850 - single dose (Pharmacokinetic analysis set)
Table 14.2.7.3.2 Summary of plasma pharmacokinetic parameters for LAS34850 - multiple dose (Pharmacokinetic analysis set)
Table 14.2.7.4.1 Summary of lambda_z related parameters for aclidinium bromide - single dose (Pharmacokinetic analysis set)
Table 14.2.7.4.2 Summary of lambda_z related parameters for aclidinium bromide – multiple dose (Pharmacokinetic analysis set)
Table 14.2.7.5.1 Summary of lambda_z related parameters for LAS34823 - single dose (Pharmacokinetic analysis set)

Table 14.2.7.5.2 Summary of lambda_z related parameters for for LAS34823 - multiple dose (Pharmacokinetic analysis set)
Table 14.2.7.6.1 Summary of lambda_z related parameters for LAS34850 - single dose (Pharmacokinetic analysis set)
Table 14.2.7.6.2 Summary of lambda_z related parameters for for LAS34850 - multiple dose (Pharmacokinetic analysis set)
Table 14.2.8.1.1 Assessment of time-dependency in aclidinium bromide (Pharmacokinetic analysis set)
Table 14.2.8.1.2 Assessment of time-dependency in LAS34823 (Pharmacokinetic analysis set)
Table 14.2.8.1.3 Assessment of time-dependency in LAS34850 (Pharmacokinetic analysis set)
Appendix 16.1.9.1.1 Supporting output for Table 14.2.8.1.1 Assessment of time-dependency in aclidinium bromide (Pharmacokinetic analysis set)
Appendix 16.1.9.1.2 Supporting output for Table 14.2.8.1.2 Assessment of time-dependency in LAS34823 (Pharmacokinetic analysis set)
Appendix 16.1.9.1.3 Supporting output for Table 14.2.8.1.3 Assessment of time-dependency in LAS34850 (Pharmacokinetic analysis set)
Table 14.2.8.2.1 Assessment of accumulation in aclidinium bromide (Pharmacokinetic analysis set)
Table 14.2.8.2.2 Assessment of accumulation in LAS34823 (Pharmacokinetic analysis set)
Table 14.2.8.2.3 Assessment of accumulation in LAS34850 (Pharmacokinetic analysis set)
Appendix 16.1.9.2.1 Supporting output for Table 14.2.8.2.1 Assessment of accumulation in aclidinium bromide (Pharmacokinetic analysis set)
Appendix 16.1.9.2.2 Supporting output for Table 14.2.8.2.2 Assessment of accumulation in LAS34823 (Pharmacokinetic analysis set)
Appendix 16.1.9.2.3 Supporting output for Table 14.2.8.2.3 Assessment of accumulation in LAS34850 (Pharmacokinetic analysis set)

ALL ADVERSE EVENTS
Table 14.3.2.1.1 Adverse events in any category (Safety analysis set)
Table 14.3.2.1.2 Adverse events, by system organ class and preferred term (Safety analysis set)
Table 14.3.2.1.3 Adverse events, by preferred term and maximum reported intensity (Safety analysis set)
Table 14.3.2.1.4 Adverse events, by preferred term and investigator's causality assessment (Safety analysis set)

SERIOUS ADVERSE EVENTS
Table 14.3.4.1.1 Serious adverse events, by system organ class and preferred term (Safety analysis set)
Table 14.3.4.1.2 Serious adverse events - key subject information (Safety analysis set)

ADVERSE EVENTS LEADING TO DISCONTINUATION OF INVESTIGATIONAL PRODUCT

Table 14.3.5.1.1 Adverse events leading to discontinuation of investigational product, by system organ class and preferred term (Safety analysis set)
Table 14.3.5.1.2 Adverse events leading to discontinuation of investigational product – key subject information (Safety analysis set)

OTHER SIGNIFICANT ADVERSE EVENTS
Table 14.3.6.1.1 Non-serious adverse events occurring in greater than 5% of subjects (Safety analysis set)
Table 14.3.6.2.1 Anticholinergic adverse events, by system organ class, and preferred term (Safety analysis set)

LABORATORY VARIABLES
Table 14.3.7.1.1 Haematology laboratory variables over time (Safety analysis set)
Table 14.3.7.1.2 Haematology variables, shift table of treatment-emergent potentially clinically significant values (Safety analysis set)
Table 14.3.7.1.3 Clinical chemistry laboratory variables over time (Safety analysis set)
Table 14.3.7.1.4 Clinical chemistry variables, shift table of treatment-emergent potentially clinically significant values (Safety analysis set)
Table 14.3.7.1.5 Maximum post-baseline ALT and AST by maximum total bilirubin for assessing Hy's Law criteria (Safety analysis set)
Table 14.3.7.2.1 Subjects with potential Hy's Law combined ALT or AST, and TBL elevations for aclidinum bromide - individual subject data (Safety analysis set)

VITAL SIGNS & ECG
Table 14.3.8.1.1 Vital signs variables over time (Safety analysis set)
Table 14.3.8.1.2 Number (%) of subjects with blood pressure notable changes from baseline (Safety analysis set)
Table 14.3.8.2.1 ECG variables, over time (Safety analysis set)
Table 14.3.8.2.2 ECG variables, treatment-emergent potentially clinically significant values (Safety analysis set)

7.1.2 FIGURES
Figure 14.2.3.1.1 Geometric mean (± geoSD) plasma concentration (pg/mL) of aclidinium bromide versus time – Day 1 and 9 (Linear scale) (Pharmacokinetic analysis set)
Figure 14.2.3.1.2 Geometric mean plasma concentration (pg/mL) of aclidinium bromide versus time - Day 1 and 9 (Semi-logarithmic scale) (Pharmacokinetic analysis set)
Figure 14.2.3.2.1 Geometric mean (± geoSD) plasma concentration (pg/mL) of LAS34823 versus time - Day 1 and 9 (Linear scale) (Pharmacokinetic analysis set)
Figure 14.2.3.2.2 Geometric mean plasma concentration (pg/mL) of LAS34823 versus time- - Day 1 and 9 (Semi-logarithmic scale) (Pharmacokinetic analysis set)
Figure 14.2.3.3.1 Geometric mean (± geoSD) plasma concentration (pg/mL) of LAS34850 versus time - Day 1 and 9 (Linear scale) (Pharmacokinetic analysis set)
Figure 14.2.3.3.2 Geometric mean plasma concentration (pg/mL) of LAS34850 versus time - Day 1 and 9 (Semi-logarithmic scale) (Pharmacokinetic analysis set)
Figure 14.2.4.1.1 Geometric mean (± geoSD) plasma trough concentration (pg/mL) of aclidinium bromide from study day 6 to day 9 (Linear scale) (Pharmacokinetic analysis set)

Figure 14.2.4.2.1 Geometric mean (± geoSD) plasma trough concentration (pg/mL) of LAS34823 from study day 6 to day 9 (Linear scale) (Pharmacokinetic analysis set)
Figure 14.2.4.3.1 Geometric mean (± geoSD) plasma trough concentration (pg/mL) of LAS34850 from study day 6 to day 9 (Linear scale) (Pharmacokinetic analysis set)
Figure 14.2.5.1.1 Individual plasma concentrations (pg/mL) of aclidinium bromide versus time (Linear scale) (Safety analysis set)
Figure 14.2.5.1.2 Individual plasma concentrations (pg/mL) of aclidinium bromide versus time (Semi-logarithmic scale) (Safety analysis set)
Figure 14.2.5.2.1 Individual plasma concentrations (pg/mL) of LAS34823 versus time (Linear scale) (Safety analysis set)
Figure 14.2.5.2.2 Individual plasma concentrations (pg/mL) of LAS34823 versus time (Semi-logarithmic scale) (Safety analysis set)
Figure 14.2.5.3.1 Individual plasma concentrations (pg/mL) of LAS34850 versus time (Linear scale) (Safety analysis set)
Figure 14.2.5.3.2 Individual plasma concentrations (pg/mL) of LAS34850 versus time (Semi-logarithmic scale) (Safety analysis set)
Figure 14.2.6.1.1 Combined individual plasma concentrations (pg/mL) of aclidinium bromide versus time - Day 1 and 9 (Linear scale) (Pharmacokinetic analysis set)
Figure 14.2.6.1.2 Combined individual plasma concentrations (pg/mL) of aclidinium bromide versus time - Day 1 and 9 (Semi- logarithmic scale) (Pharmacokinetic analysis set)
Figure 14.2.6.2.1 Combined individual plasma concentrations (pg/mL) of LAS34823 versus time - Day 1 and 9 (Linear scale) (Pharmacokinetic analysis set)
Figure 14.2.6.2.2 Combined individual plasma concentrations (pg/mL) of LAS34823 versus time - Day 1 and 9 (Semi-logarithmic scale) (Pharmacokinetic analysis set)
Figure 14.2.6.3.1 Combined individual plasma concentrations (pg/mL) of LAS34850 versus time - Day 1 and 9 (Linear scale) (Pharmacokinetic analysis set)
Figure 14.2.6.3.2 Combined individual plasma concentrations (pg/mL) of LAS34850 versus time - Day 1 and 9 (Semi-logarithmic scale) (Pharmacokinetic analysis set)
Figure 14.2.6.4.1 Combined individual trough plasma concentrations (pg/mL) of aclidinium bromide versus time (Linear scale) (Pharmacokinetic analysis set)
Figure 14.2.6.5.1 Combined individual trough plasma concentrations (pg/mL) of LAS34823 (Linear scale) (Pharmacokinetic analysis set)
Figure 14.2.6.6.1 Combined individual trough plasma concentrations (pg/mL) of LAS34850 (Linear scale) (Pharmacokinetic analysis set)

7.1.3 LISTINGS

SUBJECT DISPOSITION
Appendix 16.2.1.1.1 Discontinued subjects (All subjects screened)
Appendix 16.2.1.1.2 Subjects completing the study (All subjects screened)
Appendix 16.2.1.1.3 Subjects with reported issues in the Clinical Trial Management System due to COVID-19 pandemic (All subjects screened)

Appendix 16.2.2.1.1 Subjects with important protocol deviations (Safety analysis set)
Appendix 16.2.3.1.1 Subjects excluded from analysis sets (All subjects screened)

DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Appendix 16.2.4.1.1 Demographic and baseline subject characteristics (Safety analysis set)
Appendix 16.2.4.2.1 Medical and surgical history (Safety analysis set)
Appendix 16.2.4.3.1 History of tobacco use (Safety analysis set)
Appendix 16.2.4.4.1 Prior medication (Safety analysis set)
Appendix 16.2.4.4.2 Concomitant medication (Safety analysis set)

DRUG ADMINISTRATION

Appendix 16.2.5.1.1 Administration of investigational product (Safety analysis set)
Appendix 16.2.5.2.1 Overdose of investigational product (Safety analysis set)
Appendix 16.2.5.3.1 Drug accountability (Safety analysis set)

PHARMACOKINETIC DATA

Appendix 16.2.6.1.1 Individual pharmacokinetic sample collection times and deviations (Safety analysis set)
Appendix 16.2.6.2.1 Individual plasma aclidinium bromide concentrations (pg/mL) (Safety analysis set)
Appendix 16.2.6.3.1 Individual plasma LAS34823 concentrations (pg/mL) (Safety analysis set)
Appendix 16.2.6.4.1 Individual plasma LAS34850 concentrations (pg/mL) (Safety analysis set)
Appendix 16.2.6.6.1 Individual plasma aclidinium bromide pharmacokinetic parameters - single dose (Safety analysis set)
Appendix 16.2.6.6.2 Individual plasma aclidinium bromide pharmacokinetic parameters - multiple dose (Safety analysis set)
Appendix 16.2.6.7.1 Individual plasma LAS34823 pharmacokinetic parameters - single dose (Safety analysis set)
Appendix 16.2.6.7.2 Individual plasma LAS34823 pharmacokinetic parameters - multiple dose (Safety analysis set)
Appendix 16.2.6.8.1 Individual plasma LAS34850 pharmacokinetic parameters - single dose (Safety analysis set)
Appendix 16.2.6.8.2 Individual plasma LAS34850 pharmacokinetic parameters - multiple dose (Safety analysis set)
Appendix 16.2.6.9.1 Individual plasma aclidinium bromide lambda z related parameters (Safety analysis set)
Appendix 16.2.6.9.2 Individual plasma LAS34823 lambda z related parameters (Safety analysis set)
Appendix 16.2.6.9.3 Individual plasma LAS34850 lambda z related parameters (Safety analysis set)

ADVERSE EVENT LISTINGS

Appendix 16.2.7.1.1 All adverse events– onset and resolution (Safety analysis set)
Appendix 16.2.7.2.1 All adverse events– relationship and causality (Safety analysis set)

LABORATORY LISTINGS

Appendix 16.2.8.1.1 Individual laboratory data – haematology (Safety analysis set)
Appendix 16.2.8.2.1 Individual laboratory data – clinical chemistry (Safety analysis set)
Appendix 16.2.8.3.1 Individual laboratory data – urinalysis (Safety analysis set)
Appendix 16.2.8.4.1 Individual laboratory data – serum pregnancy test (Safety analysis set)

VITAL SIGNS AND ELECTROCARDIOGRAM LISTINGS

Appendix 16.2.9.1.1 Individual vital signs data (Safety analysis set)
Appendix 16.2.10.1.1 Individual 12-lead electrocardiogram data (Safety analysis set)
Appendix 16.2.10.2 12-lead electrocardiogram overall evaluation (Safety analysis set)

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