2. SYNOPSIS

Study centre

The study was conducted at one study centre in China.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

The study objectives and criteria for evaluation are presented in Table S1.

Table S1 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To investigate the PK of aclidinium bromide and its metabolites after single and multiple doses of aclidinium bromide 400 µg BID in healthy Chinese participants.	• The following PK parameters were determined, when possible, for aclidinium bromide and its metabolites after single dose administration: – C_{max}, t_{max}, AUC_{inf}, AUC_{last}, $AUC_{(0-12)}$, $t_{½\lambda z}$, CL/F^a, V_z/F^a, MRT_{inf}^a, C_{min}, MRC_{max}, $MRAUC_{(0-12)}$. • The following PK parameters were calculated for aclidinium bromide and after 5 days of repeated dose administration: – C_{max}, t_{max}, AUC_{τ}, AUC_{last}, $t_{½\lambda z}$, CL/F^a, V_z/F^a, C_{min}, C_{avg}, TCP, $R_{ac}(C_{max})$, $R_{ac}(C_{min})$, $R_{ac}(AUC)$, MRC_{max}, $MRAUC_{(0-12)}$, %Fluc.
Secondary	
• To evaluate the safety, and tolerability of aclidinium bromide 400 µg 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.

[a] Only for aclidinium bromide.

AE = adverse event; AUC = area under the concentration-time curve; $AUC_{(0-12)}$ = AUC from time 0 to 12 hours post-dose; AUC_{inf} = AUC from zero to infinity; AUC_{last} = AUC from zero to the last quantifiable concentration; AUC_{τ} = AUC in the dose interval; BID = twice-daily; C_{avg} = average drug concentration over a dosing interval; CL/F = apparent total body clearance from plasma after extravascular administration; C_{max} = maximum observed plasma concentration; C_{min} = minimum observed drug concentration; ECG = electrocardiogram; $MRAUC_{(0-12)}$ = metabolite to parent ratio based on $AUC_{(0-12)}$; MRC_{max} = metabolite to parent ratio based on C_{max}; MRT_{inf} = mean residence time of the unchanged drug in the systemic circulation; %Fluc = fluctuation index during a dosing interval, estimated as $100*(C_{max} - C_{min})/C_{avg}$ (%); PK = pharmacokinetic; $R_{ac}(AUC)$ = accumulation ratio for AUC_{τ}; $R_{ac}(C_{max})$ = accumulation ratio for C_{max}; $R_{ac}(C_{min})$ = accumulation ratio for C_{min}; SAE = serious adverse event; $t_{½\lambda z}$ = half-life associated with terminal slope of a semi-logarithmic concentration-time curve; TCP = temporal change parameter based on AUC; t_{max} = time to reach maximum observed concentration; V_z/F = volume of distribution (apparent) following extravascular administration based on terminal phase.

Study design

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

Twenty healthy Chinese participants, aged 18 to 45 years, participated in the study, with approximately equal male/female distribution.

The study comprised of a screening visit (Visit 1) conducted after signature of the informed consent form and maximum 21 days prior to Day 1, where medical history, physical examination, blood pressure assessment, laboratory analysis, 12-lead electrocardiogram (ECG) were conducted. All participants fulfilling inclusion/exclusion criteria were admitted to the study centre the day preceding the first dose (Day -1, prior to Visit 2).

On Day 1 (Visit 2) participants received a single dose of 400 µg aclidinium bromide in the morning via one oral inhalation of the Genuair® dry powder inhaler (DPI), followed by a washout period of 96 hours. On Day 5 through Day 8, participants received BID doses of 400 µg aclidinium bromide each (morning and evening) via the Genuair® DPI and on Day 9, participants received only the morning dose of aclidinium bromide via the Genuair® DPI. Participants were discharged on Day 11, 48 hours after last investigational product (IP) administration.

Pharmacokinetics and safety assessments were conducted at specific time points in the study centre during the residential period. A follow-up visit took place on Day 15 (± 2).

Target population and sample size

The study was conducted in 20 healthy Chinese men or non-pregnant, non-lactating women, aged 18 to 45 years, with body mass index ≥ 19 kg/m^2 and ≤ 26 kg/m^2 and resting heart rate ≥ 50 beats per minute (bpm) and ≤ 100 bpm at screening and at admission to the study centre. All participants were non-smokers (never smoked or has not smoked within 2 years prior to the first dose of IP).

A total of 43 participants were screened for this study of which 20 participants were enrolled and analysed in the study.

Investigational product: dosage, mode of administration and batch numbers

Table S2 Objectives and Endpoints

Investigational product	Dosage form and strength	Route of administration	Batch number	Manufacturer
Aclidinium bromide	Powder for inhalation administered via multidose (DPI) (Genuair®) 400 µg/inhalation	Inhalation	CCI	Industrias Farmacéuticas Almirall S.A. (IFA). Sant Andreu de la Barca, Barcelona, Spain

DPI = dry powder inhaler.

Duration of treatment

The study comprised of a screening visit of maximum 21 days preceding the first dose. On Day 1, participants received a single dose IP followed by a washout period of 96 hours. On Day 5 through Day 8, participants received BID doses of IP. A follow-up visit took place on Day 15 (± 2).

Statistical methods

Analysis was done using the safety and PK populations. Descriptive statistics for demographics and other baseline characteristics are provided. The number of participants in each analysis set were summarised (except for screening analysis set). The number and percentage of participants who completed the treatment period and of participants who prematurely discontinued are presented. The reasons for premature discontinuation from the treatment period, as recorded on the termination pages of the electronic case report forms, were summarised. Additionally, the cause of screening failure was tabulated for screening analysis set.

The PK analysis set consisted of all participants in the safety analysis set who received at least 1 dose of aclidinium bromide and had at least 1 of the parameters (maximum observed plasma concentration [C_{max}], area under plasma concentration-time curve [AUC] from zero to infinity [AUC_{inf}], AUC from zero to the last quantifiable concentration [AUC_{last}], AUC in the dose interval [AUC_{τ}]) evaluable and were assumed not to be affected by factors such as important protocol deviations (eg, prohibited concomitant medications which were thought to impact on the PK data, or incorrect study medication received).

The safety analysis set included all participants who received at least 1 dose of IP and for whom any safety post-dose data were available. Unless otherwise stated, the safety analysis set was used for the presentation of all demographic and disposition data, as well as all safety analyses. Exposure to IP was also presented using the safety analysis set.

Study population

A total of 43 participants were screened for this study of which 20 participants were enrolled into the study. Of the 23 participants who were not enrolled into the study, 18 participants were screening failures (non-fulfilment of inclusion/exclusion criteria) and 5 participants withdrew consent.

All 20 (100.0%) enrolled participants received and completed treatment and completed the study.

One participant had an important protocol deviation which did not result in excluding the participant from the PK analysis. Eleven participants were reported with visit-related disruptions due to the coronavirus disease 2019 (COVID-19) pandemic; however, these disruptions were considered non-important protocol deviations.

All enrolled participants received treatment and were included in the relevant analysis sets.

Summary of pharmacokinetic results

Absorption of inhaled aclidinium bromide was rapid with a median for time to reach maximum observed concentration (t_{max}) of 0.08 hours post-dose following single and multiple dosing. Concentrations declined in a generally bi-phasic manner over time, with a geometric mean terminal elimination half-life of 13.5 hours from a single dose and 21.4 hours following multiple dosing.

Accumulation of aclidinium bromide with multiple dosing was apparent based on the AUC_{τ} Day 9 to Day 1 least-squares (LS) mean ratio of 214%.

Systemic exposure to aclidinium bromide was low relative to the inactive metabolites. For LAS34850, geometric mean AUC from time 0 to 12 hours post-dose ($AUC_{[0-12]}$) metabolite to parent ratios of 136 on Day 1 and 94.8 on Day 9 were observed, whereas for LAS34823, the geometric mean $AUC_{(0-12)}$ metabolite to parent ratios were 2.62 on Day 1 and 2.88 on Day 9.

The geometric mean apparent plasma clearance of aclidinium bromide following single and multiple dosing were 1503 L/h and 1118 L/h, respectively.

Appearance of LAS34823 in the plasma was rapid (median t_{max} of 0.08 hour), similar to that observed for aclidinium bromide, whereas LAS34850 peak plasma exposure occurred later (median t_{max} of 2.50 to 3.00 hours).

Concentrations of LAS34850 and LAS34823 declined in a generally bi-phasic manner over time, with terminal elimination half-lives of 9.96 hours and 17.7 hours on Day 1 and 9, respectively, for LAS34823 and 8.32 hours and 12.7 hours on Day 1 and 9, respectively, for LAS34850.

Overall accumulation of LAS34823 based on $AUC_{(0-12)}$ was consistent with that observed for the aclidinium bromide (LS mean ratio of 235%). Accumulation of LAS34850 appeared lower based on $AUC_{(0-12)}$ LS mean ratio of 149%.

Time-dependent changes in exposure to aclidinium bromide, LAS34823 and LAS34850 based on AUC ratios were 134%, 151% and 113%, respectively. These estimates should be considered with caution, as the extrapolated areas for AUC_{inf} were higher than 20% in 50% and 40% of the participants for aclidinium bromide and LAS34823, respectively.

Moderate to high between-participant variability in exposure was observed for aclidinium bromide and LAS34823 and low between-participant variability for LAS34850.

Steady state was generally achieved by 5 days BID continuous IP dosing for aclidinium bromide and the metabolites.

Summary of safety results

All 20 participants that were enrolled in the study, received treatment and completed the study. There were no treatment-emergent adverse events with outcome of death, SAEs or AEs leading to premature discontinuation of the IP. One AE of special interest (throat irritation) was reported. All TEAEs were mild in intensity. Treatment-emergent AEs (atrial escape rhythm and throat irritation) reported for 2 participants were considered by the investigator to be related to the IP, while TEAEs reported for 4 participants were considered by the investigator to be not related to the IP. No clinically relevant change in mean values over time were observed for any of the laboratory parameters, vital signs, or ECG variables. Some ECG abnormalities were reported and one of them was considered as clinically significant and reported as a TEAE.

Overall conclusions

- The primary objective of the study, the determination of PK parameters for aclidinium bromide and its metabolites LAS34850 and LAS34823 in Chinese healthy participants, was met.
- Absorption of inhaled aclidinium bromide was rapid with a median t_{max} of 0.08 hours post-dose and concentrations declined over time with a geometric mean half-life of 13.5 and 21.4 hours following single and multiple dosing, respectively, which is consistent with the observed steady state concentrations achieved within 5 days of BID dosing. Moderate to high between-participant variability in exposure was observed for aclidinium bromide and LAS34823, with low variability for LAS34850.
- Overall systemic exposure to aclidinium bromide was lower than the inactive metabolites: LAS34850 $AUC_{(0-12)}$ metabolite to parent ratios were 136 on Day 1 and 94.8 on Day 9; LAS34823 $AUC_{(0-12)}$ metabolite to parent ratios were 2.62 on Day 1 and 2.88 on Day 9.

- Accumulation in exposure with multiple dosing was apparent for aclidinium bromide, LAS34823 and LAS34850, based on Day 9 to Day 1 $AUC_{(0-12)}$ ratios of 214%, 235% and 149%, respectively.
- The reported TEAEs and other safety results did not raise any new safety concerns.
- Single and multiple doses of aclidinium bromide 400 µg in Chinese normal controls were well tolerated and consistent with the known safety profile of aclidinium bromide 400 µg.