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The Pharmacokinetics, Safety and Tolerability of Aclidinium Bromide 400 μg Administered by Inhalation as Single and Multiple (Twice Daily) Doses in Healthy Chinese Participants

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Purpose: To date, aclidinium pharmacokinetic (PK) studies have focused on Caucasian populations, and no data are available for Chinese populations. We aimed to characterize the PK and safety profile of aclidinium and its metabolites (LAS34823 and LAS34850) following single and multiple (twice-daily; BID) dosing in healthy Chinese participants, and to compare PK data between Chinese and Caucasian populations.

Materials and methods: In this Phase I, open-label study (NCT03276052), healthy participants from a single site in China received aclidinium bromide 400 μg via a dry powder inhaler. The Day 1 single dose was followed by a washout period of 96 hours. On Days 5 through 8, participants received BID doses.

Results: Twenty healthy Chinese participants, aged 18–45 years, were enrolled. Aclidinium absorption was rapid (median time to maximum concentration [t_{max}] 0.08 hours post-dose following single/multiple doses). LAS34823 had a similar median t_{max} of 0.08 hours, whereas LAS34850 t_{max} occurred later (median 2.50–3.00 hours). Aclidinium, LAS34823, and LAS34850 concentrations declined in a bi-phasic manner; geometric mean half-life was 13.5 hours (single dosing) and 21.4 hours (multiple dosing), while steady state was generally achieved after 5 days' continuous dosing. Area under the concentration–time curve during a dosage interval (AUC_τ) metabolite to parent ratios for LAS34823 were 2.6 (Day 1) and 2.9 (Day 9), while LAS34850 had ratios of 136.0 and 94.8, respectively. Aclidinium accumulation occurred after 5 days of BID dosing (LS mean accumulation ratio for AUC_τ Day 9/Day 1: 214.1% [90% CI, 176.5, 259.6]); LAS34823 accumulation was similar, while LAS34850 accumulation was lower. Between-participant exposure variability was moderate to high for aclidinium and LAS34823, and low for LAS34850.

Conclusion: Single and multiple doses of aclidinium were well tolerated in healthy Chinese participants. The safety profile of and exposure to aclidinium was consistent with previous studies conducted in Caucasian populations.

Keywords: aclidinium bromide, bronchodilator, China, chronic obstructive pulmonary disease, pharmacokinetics, safety

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities[1] and is a leading cause of chronic morbidity and mortality worldwide.[2] In China, the average prevalence of COPD is 5.9% (ranging from 1.2% to 8.9% across different studies) with significantly higher rates among patients aged >35 years, underlining COPD as a major public health problem in this

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country.[3] Studies in China have revealed tobacco exposure and biomass fuel/solid fuel usage as two important risk factors, with male sex, increasing age, low body mass index (BMI), family history, childhood or family history of respiratory disease, occupational dust exposure, and low education level also playing a role.[3]

Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines recommend LAMAs as maintenance therapy for patients with a high risk of exacerbation (≥2 exacerbations or ≥1 exacerbation leading to hospitalization in the previous year, or severe airflow limitation [GOLD Stage III and IV]) and/or a high level of symptoms (GOLD Groups B, C and D).[1] Pivotal clinical studies of the LAMA aclidinium bromide 400 µg administered twice daily (BID) via a multidose breath-actuated device-metered dry powder inhaler (DPI) have demonstrated a clinically and statistically significant bronchodilatory effect[4–6] and aclidinium is approved as a maintenance bronchodilator treatment to relieve symptoms of patients with COPD.[7]

The major metabolic pathways for aclidinium produce two metabolites as a result of non-enzymatic and enzymatic hydrolysis of its carboxylic ester moiety: the inactive alcohol metabolite LAS34823 and the inactive acid derivative LAS34850. Although the genetic locus of butyrylcholinesterase (the enzyme responsible for the hydrolysis of aclidinium) contains polymorphisms,[8,9] variation in pharmacokinetic (PK) variables for other LAMAs has been shown to be low between different ethnicities;[10,11] therefore, ethnicity was not expected to influence the PK of aclidinium.

To date, aclidinium pharmacokinetic studies have been performed in Caucasian participants, and no data are available for Chinese participants. Therefore, this study aimed to characterize the PK and safety profile of aclidinium bromide 400 µg after single and multiple (BID) dose administration by inhalation in healthy Chinese participants, and to compare PK data between Chinese and Caucasian populations.

Methods

Study Design

This was a Phase I, open-label, single and multiple dose (BID) study (NCT03276052) performed at a single site in China (West China Hospital of Sichuan University) between October and November 2021 (Figure 1). After providing informed consent, participants were screened for eligibility within 21 days before the first dose administration. During the treatment period, participants remained at the trial center for 11 nights (Day −1 to Day 11). Participants were trained on inhaler use prior to administration (Day −1). On the morning of Day 1, a single dose of aclidinium bromide 400 µg was administered via oral inhalation using a Genuair® DPI, followed by a washout period of 96 hours. On Days 5 through 8, participants received BID doses, morning and evening; on Day 9 they received a morning dose only, with a discharge visit on Day 11 post-treatment completion. A follow-up visit occurred on Day 15 (±2 days).

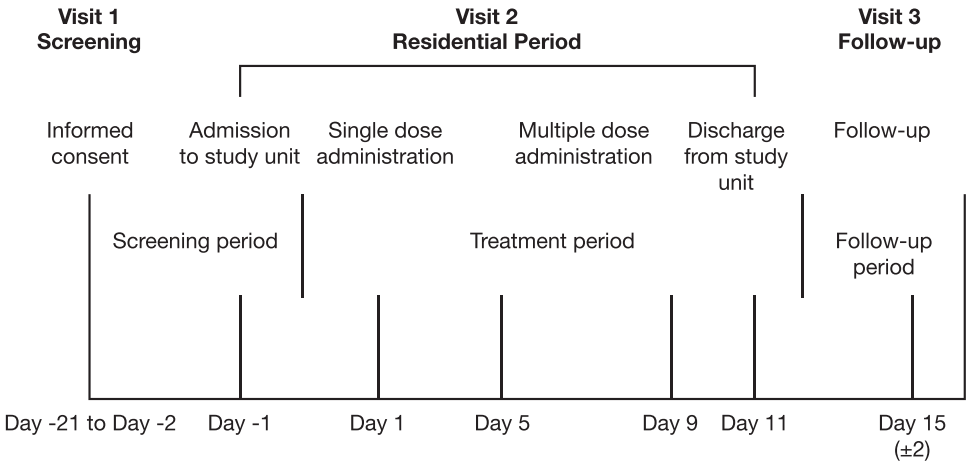

Figure 1 Study Design.

Participants

Healthy Chinese men or non-pregnant, non-lactating women aged 18–45 years with a BMI ≥19 kg/m^2 and ≤26 kg/m^2, a resting heart rate ≥50 beats per minute (bpm) and ≤100 bpm who were non-smokers at the time of the study and demonstrated satisfactory technique in the use of the DPI were included. Exclusion criteria included history of any significant drug allergy or hypersensitivity to aclidinium or other muscarinic antagonists; abnormal and clinically significant results on the physical examination, medical history, serum biochemistry, hematology, or urinalysis at screening and sustained resting systolic blood pressure ≥140 mmHg or ≤90 mmHg and resting diastolic blood pressure ≥90 mmHg or ≤50 mmHg at screening or Day-1.

Pharmacokinetic Evaluation

For the single dose, blood samples were taken at the following time points: Day 1 pre-dose (approximately 15 minutes prior to the morning dose) and at 5 minutes, 15 minutes, 30 minutes, 1 hour, 1.5 hours, 2 hours, 3 hours, 4 hours, 6 hours, 8 hours, 12 hours, 24 hours (ie Day 2), 36 hours (ie Day 2) and 48 hours (ie Day 3) post-morning dose. For multiple dosing, blood samples were taken at the following time points: Days 6–8 pre-dose (approximately 5 minutes prior to the morning and evening doses) and Day 9 at pre-dose (approximately 5 minutes prior to the morning dose) and post-morning dose on Day 9 (at the same time points as for the single post-morning dose).

Aclidinium plasma concentrations and those of the two aclidinium metabolites (LAS34823 and LAS34850) were established using solid-phase extraction and analysis by liquid chromatography with tandem mass spectrometry (Covance Pharmaceutical R&D Co., Ltd.). Validation was performed prior to sample analysis, while reproducibility analyses were performed during the study; aclidinium, LAS34823, and LAS34850 were within the accepted criteria for incurred sample reproducibility. A non-compartmental analysis model, developed using an internally validated software system (Phoenix WinNonLin® v6.4; Certara L.P., Princeton, NJ, USA), was used to analyze PK parameters. Assessments included area under the concentration–time curve during a dosage interval (AUC_τ) at Day 1 and Day 9; AUC from zero to infinity (AUC_{inf}); AUC from zero to the last quantifiable concentration (AUC_{last}); half-life associated with terminal slope of a semi-logarithmic concentration–time curve ($t_{½\lambda z}$); apparent total clearance of the drug from plasma after oral inhalation (CL/F); apparent volume of distribution (Vz/F); maximum concentration (C_{max}); time to reach C_{max} (T_{max}); minimum concentration (C_{min}); metabolite to parent ratio based on C_{max} (MRC_{max}); mean residence time of the unchanged drug in the systemic circulation (MRT_{inf}); and metabolite to parent ratio based on AUC_τ ($MRAUC_\tau$). For PK parameter derivation, pre-dose Day 1 concentrations below the lower limit of quantification (LLOQ) were set to zero; concentrations below the limit of quantification were set to missing for all concentration profiles after this point.

The following PK parameters were calculated for aclidinium after 5 days of repeated dose administration (Day 9): C_{max}; t_{max}; AUC_τ; AUC_{last}; $t_{½\lambda z}$; CL/F; Vz/F; C_{min}; average drug concentration over a dosing interval (C_{avg}); temporal change parameter based on AUC (TCP); accumulation ratio for C_{max} ($Rac_{(Cmax)}$); accumulation ratio for C_{min} ($Rac_{(Cmin)}$); accumulation ratio for AUC_τ ($Rac_{(AUC)}$); C_{max} (MRC_{max}); AUC_τ ($MRAUC_\tau$); and fluctuation index during a dosing interval, estimated as $100*(C_{max}-C_{min})/C_{avg}$ (%) (%Fluc).

Safety Evaluations

Treatment-emergent adverse events (AEs), serious AEs (SAEs), blood pressure, clinical laboratory parameters (hematology, serum biochemistry and urinalysis), and 12-lead electrocardiogram (ECG) parameters were included as safety outcome measures. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 24.1.

Statistical Analyses

No formal statistical hypothesis testing was performed; PK, safety and tolerability data were summarized descriptively. The safety analysis set consisted of all participants who received ≥1 dose of aclidinium bromide and had available post-dose safety data. The PK analysis set consisted of all participants in the safety analysis set who had evaluable data for ≥1 of C_{max}, AUC_{inf}, AUC_{last} or AUC_τ, and were assumed not to be affected by important protocol deviations.

Time-dependency was evaluated by comparing AUC_{τ} on Day 9 with AUC_{inf} on Day 1. Accumulation was evaluated by comparing AUC_{τ} on Day 9 with Day 1, and by comparing C_{max} on Day 9 and Day 1. A linear mixed-effect model was used with the natural logarithm of the PK parameters as the response variable and Day as a fixed effect. Day was treated as a repeated effect within each participant. From these models, least squares (LS) means together with 95% confidence intervals (CIs) for Day 1 and Day 9, and LS means together with 90% CI for the difference for Day 9 versus Day 1 were obtained. The results were 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.

Treatment-emergent AEs were summarized as number and percentage of participants or, where applicable, the number of events. Clinical laboratory parameters, vital signs, and 12-lead ECG were analyzed for both absolute values and change from baseline by means of descriptive statistics. Potentially clinically significant abnormalities were identified.

Results

Participants

Twenty participants were enrolled, all of whom completed the study and were included in both PK and safety analysis sets (55% of participants were male, mean age was 27.2 years, and 70% were in the "normal" BMI category; Table 1).

Pharmacokinetics

Mean plasma concentrations of aclidinium and both metabolites were higher on Day 9 after 5 days of BID dosing, compared with Day 1 after one dose (Figure 2 and Supplementary Figure 1). Plasma concentrations fell below the LLOQ in the majority of participants by 36 hours post-dose on Day 1 but were quantifiable in all but one participant (aclidinium only) up to the last sample of 48 hours on Day 9 (Figure 2 and Supplementary Figure 1).

PK of Aclidinium

Median (range) t_{max} occurred at 0.08 (0.08–0.10) hours post-dose on Day 1 and Day 9 (Table 2). Following C_{max}, aclidinium concentrations declined in a bi-phasic manner; mean $t_{½\lambda z}$ was 13.5 hours on Day 1 and 21.4 hours on Day 9 (Table 2). As all $t_{½\lambda z}$ values were calculated over a period less than three times the resultant half-life, the terminal phase may not have been fully characterized. In addition, for five profiles on Day 1 and four profiles on Day 9, adjusted R-squared regression fits were <0.8 (terminal phase).

A time-dependent change in exposure was observed; LS mean ratio (90% CI) for AUC_{τ}/AUC_{inf} was 134.4% (105.3, 171.6). Accumulation of aclidinium was detected in plasma after 5 days of BID dosing (LS mean accumulation ratio [90% CI] for AUC_{τ} Day 9/Day 1: 214.1% [176.5, 259.6]; C_{max}: was 143.1% [112.5, 181.9]). Accumulation in C_{min} was also apparent; LS mean ratio was 355.4%. (Note: Day 1 data were concentration 12 hours post-dose, and Day 9 data were minimum concentration during the 12-hour dosing interval). Of note, the extrapolated areas for AUC_{inf} on Day 1 were >20% in 50% of the participants for aclidinium. Therefore, AUC_{inf}, CL/F, Vz/F and MRT_{inf} from Day 1 and TCP from Day 9 should be considered with caution. Mean CL/F was similar on Day 1 (1503.0 L/h) and Day 9 (1118.0 L/h), as was mean Vz/F on Day 1 (29,280.0 L) and Day 9 (34,550.0 L) (Table 2). Steady state concentrations appeared to be achieved by Day 9, based on pre-dose (trough) concentrations, and were as expected based on the estimated Day 1 mean $t_{½\lambda z}$.

Table 1 Participant Demographics and Characteristics (N = 20)

Parameter	Aclidinium Bromide 400 µg
Age, years (mean [SD])	27.2 (5.2)
Male, n (%)	11 (55.0)
BMI, kg/m^2 (mean [SD])	23.0 (2.3)
Normal weight (≥18.5 and <25 kg/m^2), n (%)	14 (70.0)
Pre-obese (≥25 and <30 kg/m^2), n (%)	6 (30.0)

Abbreviations: BMI, body mass index; SD, standard deviation.

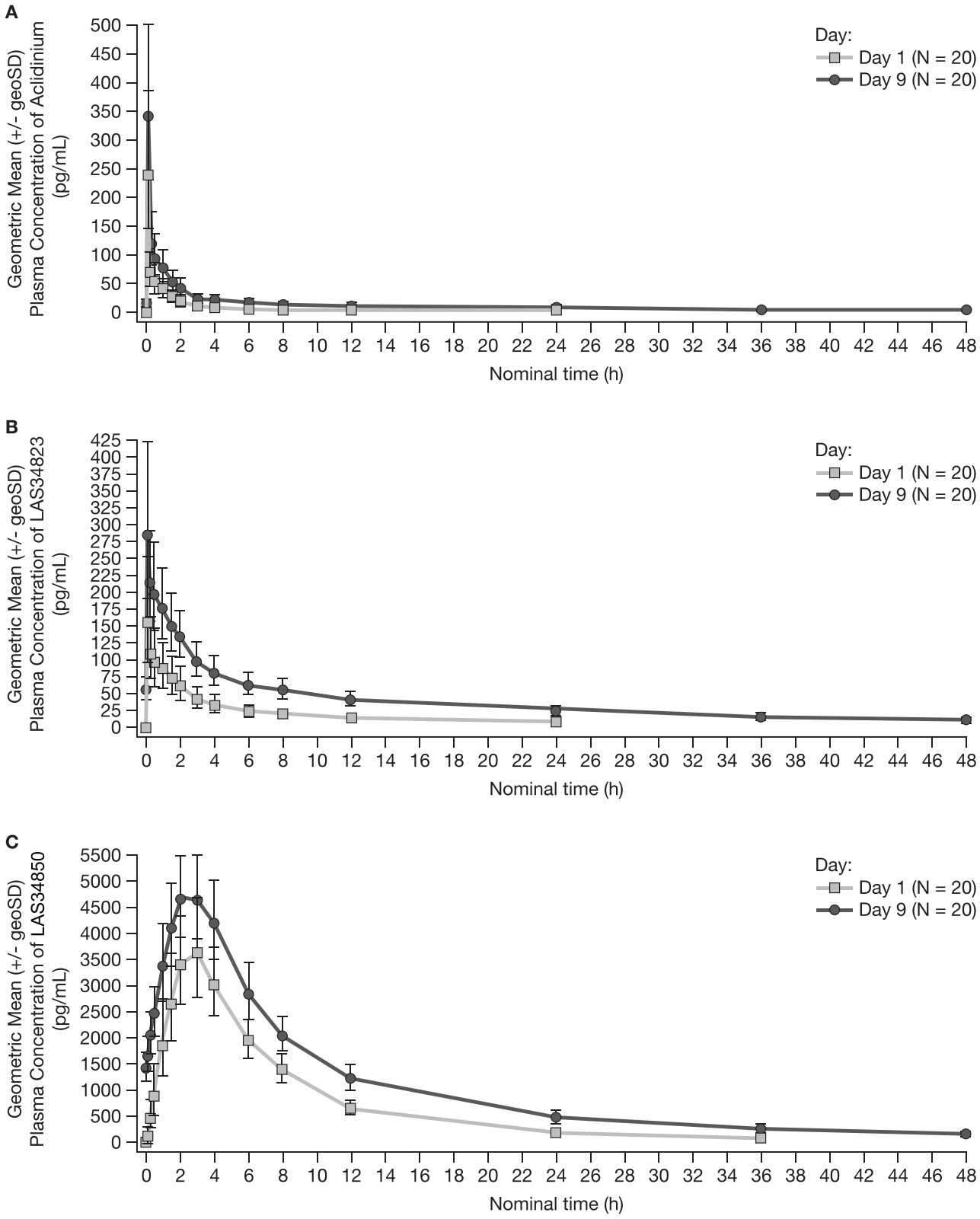

Figure 2 Geometric Mean Plasma Concentration (pg/mL) of (**A**) Aclidinium, (**B**) LAS34823 and (**C**) LAS34850 Versus Time: Day 1 and Day 9.
Notes: Data points are displayed only if ≥3 concentrations are available for each timepoint. Data are plotted on a semi-logarithmic scale on Supplementary Figure 1.
Abbreviation: h, hours.

Table 2 Pharmacokinetic Parameters of Aclidinium Bromide and Its Metabolites LAS34823 and LAS34850, Following a Single Dose (Day 1) and Following Multiple Dosing (Day 9 After 5 Days of Repeated BID Dosing) of Aclidinium Bromide 400 μg (N = 20)

Parameter		Aclidinium Bromide PK Parameters		LAS34823 PK Parameters		LAS34850 PK Parameters	
		Single Dose (Day 1)	Multiple Dose (Day 9)	Single Dose (Day 1)	Multiple Dose (Day 9)	Single Dose (Day 1)	Multiple Dose (Day 9)
C_{max}, pg/mL	Gmean (gCV%)	238.6 (51.7)	341.3 (40.2)	164.0 (45.1)	294.1 (39.9)	3831 (25.0)	4891 (16.5)
	Min, max	86.9, 544.0	136.0, 645.0	76.6, 368.0	152.0, 650.0	2530.0, 5490.0	3150.0, 6110.0
t_{max}, h	Median	0.08	0.08	0.08	0.08	3.00	2.50
	Min, max	0.08, 0.10	0.08, 0.10	0.08, 0.50	0.08, 0.50	2.00, 3.00	1.50, 3.00
AUC_{inf} (h·pg/mL)	Gmean (gCV%)	266.1 (59.2)	—	684.4 (48.0)	—	29,970.0 (17.6)	—
	Min, max	64.0, 556.0	—	305.0, 1590.0	—	21,000.0, 40,400.0	—
AUC_{τ} (h·pg/mL)	Gmean (gCV%)	167.1 (40.2)	357.8 (32.3)	438.1 (37.3)	1031.0 (25.6)	22,730.0 (18.6)	33,910.0 (15.3)
	Min, max	60.7, 276.0	217.0, 720.0	228.0, 799.0	640.0, 1600.0	15,600.0, 29,000.0	23,600.0, 45,400.0
AUC_{last} (h·pg/mL)	Gmean (gCV%)	208.9 (57.2)	609.4 (36.5)	550.4 (54.1)	1849.0 (25.5)	29,010.0 (18.0)	50,370.0 (16.8)
	Min, max	52.2, 414.0	270.0, 1290.0	228.0, 1310.0	1270.0, 3090.0	20,500.0, 38,500.0	34,600.0, 73,100.0
$t_{1/2\lambda z}$ (h)	Gmean (gCV%)	13.5 (91.6)	21.4 (25.6)	10.0 (43.0)	17.7 (12.4)	8.3 (26.8)	12.7 (19.0)
	Min, max	3.1, 43.4	10.6, 35.7	5.1, 22.6	14.6, 22.2	5.0, 12.3	10.1, 21.5
CL/F (L/h)	Gmean (gCV%)	1503.0 (59.2)	1118.0 (32.3)	—	—	—	—
	Min, max	720.0, 6250.0	555.0, 1850.0	—	—	—	—
Vz/F (L)	Gmean (gCV%)	29,280.0 (45.5)	34,550.0 (40.9)	—	—	—	—
	Min, max	14,900.0, 62,100.0	14,800.0, 66,700.0	—	—	—	—
MRT_{inf} (h)	Gmean (gCV%)	13.5 (95.2)	—	—	—	—	—
	Min, max	3.2, 42.7	—	—	—	—	—
C_{min} (pg/mL)	Gmean (gCV%)	3.3 (56.3)	11.6 (41.2)	14.8 (31.5)	43.0 (28.6)	647.8 (20.8)	1223.0 (19.3)
	Min, max	0.6, 6.6	5.8, 27.5	8.4, 21.7	28.0, 74.4	454.0, 954.0	882.0, 1900.0
MRC_{max}	Gmean (gCV%)	—	—	0.69 (29.14)	0.86 (20.29)	16.05 (48.71)	14.33 (43.98)
	Min, max	—	—	0.37, 1.12	0.62, 1.50	7.71, 45.50	8.31, 37.70
$MRAUC_{\tau}$	Gmean (gCV%)	—	—	2.6 (26.6)	2.9 (23.0)	136.0 (39.6)	94.8 (32.6)
	Min, max	—	—	1.6, 4.2	2.1, 4.6	78.8, 362.0	54.1, 168.0
C_{avg} (pg/mL)	Gmean (gCV%)	—	29.8 (32.3)	—	86.0 (25.6)	—	2826.0 (15.3)
	Min, max	—	18.1, 60.0	—	53.3, 134.0	—	1970.0, 3780.0
TCP	Gmean (gCV%)	—	1.34 (52.38)	—	1.51 (46.61)	—	1.13 (16.83)
	Min, max	—	0.60, 4.11	—	0.64, 3.15	—	0.87, 1.59

(*Continued*)

Table 2 (Continued).

Parameter		Aclidinium Bromide PK Parameters		LAS34823 PK Parameters		LAS34850 PK Parameters	
		Single Dose (Day 1)	Multiple Dose (Day 9)	Single Dose (Day 1)	Multiple Dose (Day 9)	Single Dose (Day 1)	Multiple Dose (Day 9)
$Rac_{(Cmax)}$	Gmean (gCV%)	—	1.43 (44.18)	—	1.79 (45.61)	—	1.28 (20.40)
	Min, max	—	0.69, 3.24	—	0.71, 4.16	—	0.91, 1.76
$Rac_{(Cmin)}$	Gmean (gCV%)	—	3.55 (50.32)	—	2.90 (37.70)	—	1.89 (22.90)
	Min, max	—	2.05, 14.20	—	1.81, 5.24	—	1.16, 2.63
$Rac_{(AUC)}$	Gmean (gCV%)	—	2.14 (37.64)	—	2.35 (40.94)	—	1.49 (16.84)
	Min, max	—	1.13, 4.34	—	1.23, 4.77	—	1.18, 2.15
%Fluc	Gmean (gCV%)	—	1102.0 (34.7)	—	289.2 (35.3)	—	128.9 (14.9)
	Min, max	—	579.0, 2370.0	—	171.0, 713.0	—	101.0, 166.0

Notes: Data are expressed as geometric means, calculated using log transformed data.

Abbreviations: AUC_{inf}, area under the plasma concentration–time curve from zero to infinity; AUC_{last}, area under the plasma concentration–time curve from zero to the last quantifiable concentration; AUC_{τ}, area under the concentration–time curve during a dosage interval; BID, twice daily; C_{avg}, average drug concentration over a dosing interval; CI, confidence interval; CL/F, apparent total body clearance from plasma after extravascular administration; C_{min}, minimum observed drug concentration; C_{max}, maximum concentration; gCV, geometric coefficient of variation; Gmean, geometric mean; h, hours; $MRAUC_{\tau}$, metabolite to parent ratio based on AUC_{τ}; MRC_{max}, metabolite to parent ratio based on C_{max}; MRT_{inf}, mean residence time of the unchanged drug in the systemic circulation; $Rac_{(AUC)}$, accumulation ratio for AUC_{τ}; $Rac_{(Cmax)}$, accumulation ratio for C_{max}; $Rac_{(Cmin)}$, accumulation ratio for C_{min}; $t_{1/2\lambda z}$, 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 C_{max}; Vz/F, volume of distribution (apparent) following extravascular administration based on terminal phase; %Fluc, fluctuation index during a dosing interval.

PK of LAS34823

Median (range) t_{max} occurred at 0.08 (0.08–0.50) hours post-dose on Day 1 and Day 9 (Table 2). Following C_{max}, concentrations declined in a bi-phasic manner; mean $t_{½\lambda z}$ was 10.0 hours on Day 1 and 17.7 hours on Day 9 (Table 2). As all $t_{½\lambda z}$ estimates – with the exception of one value – were calculated over a period of less than three times the resultant half-life, the terminal phase may not have been fully characterized. A time-dependent change in exposure was observed; LS mean accumulation ratio (90% CI) for AUC_{τ}/AUC_{inf} was 150.7% (123.2, 184.3). Accumulation of aclidinium was detected in plasma after 5 days of BID dosing. The LS mean accumulation ratio (90% CI) for AUC_{τ} Day 9/Day 1 was 235.4% (198.6, 279.1); C_{max} was 179.4% (143.5, 224.2). Accumulation in C_{min} was also apparent; LS mean ratio was 290.3%. Of note, the extrapolated areas for AUC_{inf} on Day 1 were >20% in 40% of the participants. Therefore, AUC_{inf} from Day 1 and TCP from Day 9 should be considered with caution. Steady state concentrations appeared to be achieved by Day 9, based on pre-dose (trough) concentrations, and were as expected based on the estimated Day 1 mean $t_{½\lambda z}$. Fluctuations in trough concentrations were observed, with a marginally higher mean pre-dose concentration on the morning of Day 9, likely due to the higher variability observed at this time point. Metabolite to parent ratios for C_{max} were 0.7 (Day 1) and 0.9 (Day 9); AUC_{τ} was 2.6 and 2.9, respectively.

PK of LAS34850

Median (range) t_{max} occurred at 3.00 (2.00–3.00) hours post-dose on Day 1 and 2.50 (1.50–3.00) hours post-dose on Day 9 (Table 2). Following C_{max}, concentrations declined in a bi-phasic manner; mean $t_{½\lambda z}$ was 8.3 hours on Day 1 and 12.7 hours on Day 9 (Table 2). As some of the $t_{½\lambda z}$ values (6 for Day 1 and 9 for Day 9) were calculated over a period of less than three times the resultant half-life, the terminal phase may not be adequately characterized in these profiles. A time-dependent change in exposure was observed; LS mean ratio (90% CI) for AUC_{τ} Day 9/Day 1 was 113.1% (103.4, 123.8). Accumulation of aclidinium was detected in plasma after 5 days of BID dosing. The LS mean accumulation ratio (90% CI) for AUC_{τ} Day 9/Day 1 was 149.2% (136.0, 163.6) and for C_{max} was 127.7% (113.9, 143.2). Accumulation in C_{min} was

also apparent; LS mean ratio was 188.8%. Steady state concentrations appeared to be achieved by Day 9, based on pre-dose (trough) concentrations, and were as expected based on the estimated Day 1 mean $t_{½\lambda z}$. Metabolite to parent ratios for C_{max} were 16.1 (Day 1) and 14.3 (Day 9); ratios for AUC_{τ} were 136.0 and 94.8, respectively.

Between-Participant Variability

Between-participant variability in systemic exposure to aclidinium was moderate to high (Table 2): C_{max} coefficient of variation (CV) values were 51.7% for Day 1 and 40.2% for Day 9; AUC_{τ} CV values were 40.2% and 32.3%, respectively. Between-participant variability in systemic exposure to LAS34823 was moderate to high (Table 2). C_{max} CV values were 45.1% for Day 1 and 39.9% for Day 9; AUC_{τ} CV values were 37.3% and 25.6%, respectively. Between-participant variability in systemic exposure to LAS34850 was low (Table 2). C_{max} CV values were 25.0% for Day 1 and 16.5% for Day 9; AUC_{τ} CV values were 18.6% and 15.3%, respectively.

Safety

In total, five participants (25%) experienced a total of seven mild, treatment-emergent AEs (syncope, atrial escape rhythm, orthostatic hypotension, throat irritation, mouth ulceration, alanine aminotransferase [ALT] increased, and aspartate aminotransferase [AST] increased). Throat irritation was considered an "AE of special interest". The majority of events were considered unrelated to treatment by the investigator, with the exception of atrial escape rhythm and throat irritation. There were no deaths, SAEs, or AEs leading to discontinuation.

There were no clinically significant changes from baseline in mean hematological laboratory parameters (Supplementary Table S1). One participant had increased ALT and AST levels which were reported as treatment-emergent AEs; these were not accompanied by elevations in total bilirubin. There were no other clinically significant changes from baseline in mean clinical chemistry parameters (Supplementary Table S1).

One participant had atrial escape rhythm which was reported as a treatment-emergent AE; there were no other clinically significant changes in vital signs or ECG parameters.

Discussion

This study characterized the PK, safety, and tolerability of aclidinium bromide 400 µg in 20 healthy participants from China. Absorption of inhaled aclidinium was rapid, with a median t_{max} of 0.08 hours post-dose following both single and multiple dosing. Appearance of LAS34823 in the plasma was also rapid and similar to that observed for aclidinium (median t_{max} of 0.08 hours), whereas LAS34850 peak exposure occurred later (median t_{max} ranging from 2.50 to 3.00 hours). Concentrations of aclidinium, LAS34823, and LAS34850 declined in a bi-phasic manner over time, with a geometric mean half-life of 13.5 hours (single dosing) and 21.4 hours (multiple dosing). Steady state for aclidinium, LAS34823, and LAS34850 was generally achieved after 5 days of continuous, BID dosing. Systemic exposure to aclidinium was similar to LAS34823 (AUC_{τ} metabolite to parent ratios were 2.6 on Day 1 and 2.9 on Day 9) and low relative to LAS34850 (136.0 on Day 1 and 94.8 on Day 9). Accumulation of aclidinium following multiple dosing was observed; accumulation of LAS34823 was similar to that observed for aclidinium, but accumulation of LAS34850 appeared lower. Time-dependent changes in exposure to aclidinium, LAS34823, and LAS34850 based on AUC ratios were 134.1%, 150.7% and 113.1%, respectively. However, these estimates should be considered with caution, as the extrapolated areas for AUC_{inf} were >20% in 50% and 40% of the participants for aclidinium and LAS34823, respectively and 17.6% for LAS34850. Moderate to high between-participant variability in exposure was observed for aclidinium and LAS34823 (commonly seen with inhalation dosing) and low between-participant variability was observed for LAS34850.

Single and multiple (5 days of BID) doses were well-tolerated and consistent with the known safety profile of aclidinium; the observed treatment-emergent AEs and other safety results did not raise any new safety concerns.

A number of PK studies examining aclidinium 400 µg have been conducted in Caucasian populations. A Phase 1, randomized, single-dose, crossover study in 30 healthy volunteers (the majority of whom were White) analyzed PK for both aclidinium/formoterol fumarate 400 µg/12 µg combination therapy and the individual monotherapies.[12] For aclidinium alone, compared with our study, C_{max} was similar (215 pg/mL), $AUC_{0\text{-}t}$ was slightly higher (222 pg·h/mL), and t_{max} was the same (0.08 hours). In a Phase 1, open-label, single-dose study, White adults with normal versus

impaired renal function received aclidinium 400 µg. Among the six individuals without impairment, compared with our study, C_{max} was lower (113.9 pg/mL), $AUC_{0\text{-}t}$ was slightly lower (124.2 pg·h/mL), and t_{max} was similar (6.6 minutes).[13]

Multiple-dose studies have also been conducted. In a Phase I, multiple-dose study of 30 healthy US volunteers receiving aclidinium 400 µg, C_{max} was slightly lower (194.2 pg/mL) and AUC_{0-t} was higher (324.9 h·pg/mL) than in this study at Day 1, and both were slightly lower on the evening of Day 7, compared with Day 9 in this study (240.5 pg/mL and 468.4 h·pg/mL, respectively); however, t_{max} was the same (0.08 hours).[14] In another multiple-dose study of 16 White, healthy volunteers receiving aclidinium (200, 400 or 800 µg) or placebo, aclidinium and LAS34823 plasma levels were below the LLOQ in most participants following the 400 µg dose (first blood samples were taken at 15 minutes post-dose),[15] though data were available for the acid metabolite LAS34850. Compared with our study, at Day 1, LAS34850 C_{max} and AUC_{0-t} were substantially lower (520 pg/mL and 2200 h·pg/mL, respectively) but t_{max} was the same (3 hours). Comparing Day 5 data with those on Day 9 in our study, C_{max} and AUC_{0-t} were also substantially lower (950 pg/mL and 4290 h·pg/mL, respectively) and t_{max} was slightly longer (3 hours).

In general, data obtained from a predominantly Caucasian population are not necessarily applicable to Asian patients due to lower average body weight and potentially different metabolic and elimination profiles.[16] However, results reported here confirm that exposure (AUC_{τ} at Day 9) to aclidinium 400 µg in Chinese healthy participants was broadly consistent with previous studies conducted in Caucasian populations.

Limitations of this study include the low number of participants; however, the number included is typical of a PK study of this nature.

Conclusion

In conclusion, in this Phase I, open-label study in healthy participants from a single site in China, absorption of inhaled aclidinium bromide 400 µg was rapid following single and multiple (BID) doses, and accumulation following multiple dosing was observed. Exposure to aclidinium in Chinese healthy participants was consistent with previous studies conducted in Caucasian populations.[12–15] Single and multiple doses were well-tolerated, and the safety profile was consistent with the known safety profile of aclidinium.

Data Sharing Statement

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

Data for studies directly listed on Vivli can be requested through Vivli at www.vivli.org. Data for studies not listed on Vivli could be requested through Vivli at https://vivli.org/members/enquiries-about-studies-not-listed-on-the-vivli-platform/. AstraZeneca Vivli member page is also available outlining further details: https://vivli.org/ourmember/astrazeneca/.

Ethics Approval

The study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Council for Harmonisation Good Clinical Practice Guidelines and conformed with local regulatory requirements. The site Ethics Committee (Ethics Committees on Clinical Trial, West China Hospital of Sichuan University; No. 37 Guoxue Xiang Wu Hou District Chengdu 610041) reviewed and approved the final protocol, any amendments, and the informed consent documentation.

Consent to Participate

Informed consent was obtained from all individual participants included in the study.

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Disclosure

Weimin Li does not have any competing interests to declare in this work. Sami Daoud, Roopa Trivedi, Pradeep Lukka, Eulalia Jimenez and Eduard Molins are employees of AstraZeneca and may hold stock. Catherine Stewart is an employee of Plus Project Partnership and was an employee of Phastar at the time of this study. Pranob Bharali is an employee of AstraZeneca who does not hold stock. Esther Garcia-Gil is a former employee of AstraZeneca. The authors report no other conflicts of interest in this work.

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