CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202450Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	202450	*Submission Dates*	0000 (06/24/2011)
Brand Name		TBD	
Generic Name		Aclidinium Bromide Inhalation Powder	
Clinical Pharmacology Reviewer		Ping Ji, Ph.D.	
Pharmacometrics Reviewer		Atul Bhattaram, Ph.D.	
Pharmacometrics Team Leader		Yaning Wang, Ph.D.	
Clinical Pharmacology Team Leader (Acting)		Suresh Doddapaneni, Ph.D.	
OCP Division		Division of Clinical Pharmacology-II	
OND Division		Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)	
Sponsor		Forest Research Institute	
Relevant IND(s)		68, 653	
Submission Type; Code		505 (b) (1)	
Formulation; Strength(s)		Breath actuated multi-dose dry powder inhaler containing 400 mcg of aclidinium bromide per actuation. Each actuation delivers 375mcg from the mouth piece.	
Indication		Long-term maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.	
Proposed Dosing Regimen		400 mcg BID dosing	

Table of Contents

1 Executive Summary

1.1 Recommendations

NDA202450 for Aclidinium Bromide Inhalation Powder submitted by Forest Research Institute is acceptable from a Clinical Pharmacology and Biopharmaceutics perspective.

1.2 Phase IV Commitments

None.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Background

Aclidinium bromide inhalation powder, an adhesive mixture of micronized adclidinium bromide and α-lactose monohydrate administered by a device-metered dry powder inhaler (DPI), is intended for use in patients with chronic obstructive pulmonary disease (COPD). The proposed indication is for the long-term, maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema. The proposed dose is 1 inhalation of 400 µg aclidinium bromide twice daily.

Aclidinium bromide was evaluated in 14 *in vitro* studies in human biomaterials, 11 clinical pharmacology and biopharmaceutics studies. The clinical pharmacology studies were designed to evaluate the pharmacokinetics (PK) in healthy subjects and COPD patients and effect of intrinsic and extrinsic factors on the PK. The commercial inhalation device for aclidinium bromide of Almirall inhaler SD2FL (MC) was evaluated in 1 clinical pharmacology study in healthy subjects (LAS-PK-12) and pivotal clinical trials.

Pharmacokinetics in Healthy Subjects

Absorption

The absolute bioavailability of aclidinium bromide following inhalation of a 200 µg dose from the clinical inhalation device Almirall Inhaler SD2FL (SC) is <5% (Study M/34273/05). Using the commercial inhalation device Almirall Inhaler SD2FL (MC) (Study LAS-PK-12), the time to reach the maximum plasma concentrations of aclidinium bromide (t_{max}) is about 0.08 hour. The Cmax of aclidinium bromide is approximately dose-proportional over the dose range of 200 to 800 µg. Aclidinium bromide exhibited dose-proportional and time-independent PK following the inhaled administration of 200 µg, 400 µg, or 800 µg BID.

Distribution

The *in vivo* pulmonary disposition and distribution of 200 µg aclidinium bromide was evaluated in healthy subjects using the clinical inhalation device Almirall Inhaler MD2 (Study M/34273/03). About 34% of the delivered dose was deposited in the lungs. Following

intravenous administration of aclidinium bromide of 400 µg, the mean apparent volume of distribution is high (~300 L) (Study M/34273/08).

Metabolism and Elimination

In vitro metabolism studies demonstrated that the major route of metabolism of aclidinium bromide is via enzymatic and chemical (nonenzymatic) hydrolysis into its alcohol (LAS34823) and acid (LAS34850) metabolites, which were tested to be pharmacologically inactive. Butyrylcholinesterase is the main human esterase responsible for the hydrolysis. Plasma concentrations of the acid metabolite are approximately 100-fold greater than those of the alcohol metabolite and parent aclidinium bromide. Biotransformation via cytochrome P-450 (CYP-450) isozymes plays a minor role in the total metabolic clearance of aclidinium bromide.

The *in vivo* characterization and identification of the metabolites of aclidinium bromide in plasma and excreta after iv administration of [^{14}C] aclidinium bromide was conducted in study M/34273/04. Approximately 1% of a single intravenous dose of aclidinium bromide is excreted in urine as unchanged drug. The remaining dose is hydrolyzed and excreted as metabolites (up to 65% in urine and 33% in feces). The estimated effective half-life of aclidinium is ~5-8 hours (LAS-PK-12).

Pharmacokinetics in COPD Patients

The PK of aclidinium bromide in COPD patients from clinical inhalation device Almirall Inhaler SD2FL (SC) was assessed in study M/34273/09 and compared to that in healthy subjects with the same device (Studies M/34273/05 and M/34273/08). Cross-study comparison showed that aclidinium bromide appeared to exhibit lower Cmax and higher AUC in COPD patients as compared to healthy subjects. The time to reach Cmax in COPD patients appeared to be delayed as compared to healthy subjects.

Table: Mean (CV%) PK Variables of Aclidinium Bromide from Studies M/34273/05, M/34273/08, and M/34273/09.

Subjects	Dose (µg)	Dosing	Study #	N	Cmax (pg/mL)	AUC (pg•h/mL)	Tmax (h)	CL/F (L/h)
Healthy	200	SD	M/34273/05	12	52.7 (63.8)	76.8 (43.5)	0.09	3051.1 (43.0)
Healthy	400	SD	M/34273/08	6	113.9 (81.5)	147.2 (68.5)	0.08	3651.3 (47.7)
COPD	200 QD	SD	M/34273/09	12	39.0 (46.2)	75.4 (49.0)	0.25	-
		SS	M/34273/09	12	37.8 (44.1)	103.1 (45.4)	0.25	2284.1 (43.8)
	400 QD	SD	M/34273/09	12	82.3 (32.0)	193.5 (51.4)	0.25	-
		SS	M/34273/09	12	86.1 (31.6)	199.6 (36.4)	0.25	2288.6 (39.7)

Pharmacokinetics in Special Populations

Age

The age effect on the PK of aclidinium bromide was evaluated after a single dose and at steady state (3-day dosing) in a broad age range of moderate to severe COPD patients administered by inhalation via the Almirall Inhaler SD2FL (SC) (Study M/34273/09). Age had no impact on the PK properties of aclidinium bromide.

Renal Impairment

The influence of renal impairment on the PK of a single inhaled dose of aclidinium bromide (400 µg) from the clinical inhalation device Almirall Inhaler *SD2FL (SC)* was investigated in study M/34273/08. No clinically significant differences in the comparisons between the normal renal function group and each of the renal insufficiency groups were observed for the plasma PK parameters of aclidinium bromide.

Hepatic Impairment

The effect of hepatic impairment on the exposure of aclidinium bromide and its two main metabolites was not conducted as metabolism is mediated by non-enzymatic hydrolysis and hydrolysis by butyryl cholinesterase (an uniquitous enzyme present in many tissues).

Drug-Drug Interactions

In vitro metabolism studies using human liver microsomes showed that neither aclidinium bromide nor its two main metabolites are likely to inhibit or induce the most important CYP450 enzymes or to inhibit esterases at the therapeutic dose. *In vitro* studies showed that aclidinium bromide and its two main metabolites are not P-gp transporter substrates and inhibitors. As such, no clinical drug-drug interaction studies were conducted.

2 Question-Based Review

2.1 General Attributes

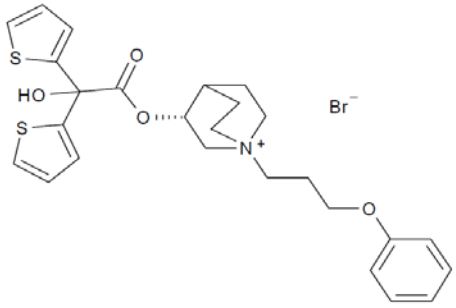
2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology of this drug?

Aclidinium bromide inhalation powder is indicated for the long-term, maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema. Earlier clinical program investigated the administration of aclidinium bromide with doses ranging from 25 to 800 µg QD. In a pre-NDA meeting on 03 Mar 2009 for the QD regimen, Forest Laboratories, Inc., obtained feedback from FDA on the completeness of the application. Based on this feedback, Forest evaluated higher and more frequent dosing regimens and has generated new data focusing on the evaluation of aclidinium bromide at doses ranging from 100 µg to 800 µg BID.

2.1.2 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Drug Substance:
The active ingredient in aclidinium bromide inhalation powder is Aclidinium bromide. Its chemical name is (3R)-3-[(hydroxy)di(thiophen-2-yl)acetyloxy]-1-(3-phenoxypropyl)-1λ^5-azabicyclo[2.2.2]octan-1-ylium bromide.

The chemical structure is:



Molecular Formula: $C_{26}H_{30}NO_4S_2Br$

Relative Molecular Mass: 564.56 (Cation = 484.65)

Chirality: [redacted] (b) (4)

Physical Description: White or off-white powder

Polymorphism: [redacted] (b) (4)

Hygroscopicity: Non-hygroscopic

Specific Optical Rotation: $[\alpha]_D^{20}$ = -25° to -21° (DMF [redacted] (b) (4) w/v)

Particle Size: Aclidinium bromide drug substance is micronized. For additional information pertaining to the particle size distribution of the drug substance.

pH: 5.3 (1% w/w suspension in purified water)

Log P: 1.9 (HPLC analysis)

Melting Point: c.a. 224-229°C

Solubility: Aclidinium bromide is sparingly soluble in methanol, very slightly soluble in water and in ethanol [redacted] (b) (4)

Drug Product: Aclidinium bromide is formulated as an inhalation powder, comprised of a mixture of micronized aclidinium bromide and α-lactose monohydrate, which functions as a carrier. The mixture is delivered by the Almirall inhaler device, a non-refillable, breath-actuated, multi-dose, metered, dry powder inhaler (DPI) device. Each inhaler delivers 60 nominal doses, and each actuation delivers approximately 375 mcg of aclidinium bromide from the mouthpiece (based on in vitro testing at a flow rate of 60 L/min for 2 seconds). The proposed dose is one inhalation of 400 mcg aclidinium bromide, administered twice daily.

2.1.3 What are the proposed mechanism of action and therapeutic indication(s)?

The basis of aclidinium bromide therapeutic activity in COPD patients is its kinetically selective M3 muscarinic antagonist activity leading to block of acetylcholine-induced bronchoconstriction.

Aclidinium bromide 400 µg BID is indicated for the long-term, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.

2.1.4 What are the proposed dosage(s) and route(s) of administration?

The proposed metered dose is 1 inhalation of 400 µg aclidinium bromide, administered BID, with doses preferably 12 hours apart.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

In supportive of the 400 µg aclidinium bromide twice daily submission, sponsor conductred 14 *in vivo* pertinent human biomaterial studies, 11 Phase 1 studies, 2 Phase 2 studies, 3 Phase 3 efficacy and safety studies, and 3 long-term safety studies.

Four trials were conducted to investigate primarily the PK of inhaled aclidinium bromide in healthy subjects (M/34273/01, M/34273/05, M/34273/06 and LAS-PK-12). Two clinical studies investigated the influence of the intrinsic factors of renal impairment and age on PK parameters of aclidinium bromide (M/34273/08 and M/34273/09, respectively). There were two ADME trials investigating lung deposition of aclidinium bromide (M/34273/03) and mass balance following IV administration (M/34273/04), respectively. Two pharmacodynamic (PD) trials were conducted in healthy subjects (M/34273/00) and in COPD patients (M/34273/21). A thorough QT/QTc study (M/34273/11) report was also submitted.

Table 2.2.1-1 Overview of Pertinent Human Biomaterial Studies

Study ID	Study Objective	In Vitro Model
Plasma protein Binding		
(b) (4)/10	Plasma protein binding	Dialysis cell systems using mouse, rat, rabbit, dog & human plasma. Aclidinium bromide: [^{14}C-U-phenyl]- & [^{14}C-U-glycolyl]-labelled.
In Vitro Metabolism		
B.34273.25	*In vitro* metabolism	Human liver microsomes Aclidinium bromide: [^{14}C-U-phenyl]- (for ^{14}C-LAS34823) & [^{14}C-U-glycolyl]-labelled (for ^{14}C-LAS34850).
B.34273.38	*In vitro* metabolism in different species	Liver microsomes from humans, rat, mouse & dog. Aclidinium bromide: [^{14}C-U-phenyl]- & [^{14}C-U-oxalyl] labelled.
(b) (4)/09	*In vitro* metabolism in different species	Liver microsomes from rat, dog, human, mouse & rabbit & pooled human lung microsomes Aclidinium bromide: [^{14}C-U-phenyl]- & [^{14}C-U-glycolyl]-labelled.
B.34273.40	Stability in extrahepatic subcellular fractions	Intestinal, renal & pulmonary microsomes & pulmonary S9 fraction.
B.34273.39	*In vitro* metabolism and covalent binding	Human liver S9 fraction Aclidinium bromide: [^{14}C-U-phenyl]- & [^{14}C-U-oxalyl]-labelled.

B.34273.M	Covalent binding	Human liver microsomes Aclidinium bromide: [^{14}C-U-phenyl]- & [^{14}C-U-glycolyl-
B.34273.S	*In vitro* metabolism and irreversible protein binding	Human hepatocytes. Aclidinium bromide: [^{14}C-U-phenyl]- & [^{14}C-U-glycolyl]-labelled.
Human Esterases Responsible for Enzymatic Hydrolysis of Aclidinium Bromide		
B.34273.22	Esterases responsible for hydrolysis	Human plasma, hepatic & lung microsomes & S9 fractions.
Effect on Human Cytochrome P450 enzymes and Human Esterases		
B.34273.24	Effect on hepatic CYP450 activities	Human liver microsomes.
XT093028	Capacity to induce CYP450 activities	Cultured fresh human hepatocytes
B.34273.N	Effect on esterase activities	Human plasma.
Potential P-glycoprotein substrate and inhibitory activity		
PRD-RPT-EXP-	P-glycoprotein substrate activity	Caco-2 cell monolayers
PRD-RPT-EXP-	P-glycoprotein inhibitory activity	Caco-2 cell monolayers

Table 2.2.1-2. Overview of Clinical Pharmacology Trials Conducted and Submitted in this NDA

Study ID	Study Objective	Study Design	Treatment	Population
M/34273/01	To assess tolerability and to identify MTD of single inhaled doses. To determine PK profile.	Randomized, single ascending dose, placebo controlled single blind. Single centre trial.	Single doses of 600, 1200, 1800, 2400, 3000, 3600, 4200, 4800, 5400 and 6000 µg aclidinium bromide or placebo administered as dry powder inhaled capsules via Cyclohaler®.	16 healthy male subjects (Caucasian) aged 23 to 46 years.
M/34273/05	Part I: To evaluate safety and tolerability of single iv doses and to determine MTD for Part II. Part II: To estimate absolute bioavailability.	Part I: Randomized, single blind, placebo controlled, three-period, cross-over. Part II: Randomized, open, two-period crossover. Single centre trial.	Part I: single doses of aclidinium bromide at doses of 25, 50, 100, 200, 300 or 400 µg, or placebo, administered by iv infusion over 5 minutes. Part II: single dose of 200 µg aclidinium bromide, administered either via Almirall inhaler or iv.	24 healthy male subjects (Caucasian): 12 in Part I and 12 in Part II. Subjects aged 19 to 45 years.
M/34273/06	To assess safety, tolerability and PK following multiple QD inhaled doses.	Randomized, ascending multiple dose, single blind, placebo controlled, four-period crossover. Single centre trial.	Multiple QD doses (5 consecutive days) of aclidinium bromide (at 200, 400 or 800 µg) or placebo, via Almirall inhaler.	16 healthy subjects (Caucasian): 8 female, 8 male. Subjects aged 21 to 38 years.
LAS-PK-12	To assess safety, tolerability and PK following multiple BID inhaled doses.	Randomized, single blind, placebo controlled, parallel group, ascending multiple dose. Single centre trial.	Multiple BID doses (7 consecutive days) of aclidinium bromide (at 200, 400 or 800 µg) or placebo, via Almirall inhaler.	30 healthy subjects aged 20 to 45 years.

PK = pharmacokinetics; iv = intravenous, MTD = maximum tolerated dose; QD = once daily; BID = twice daily

M/34273/08	To evaluate PK, safety and tolerability in subjects with normal renal function and with either mild, moderate or severe stable, chronic renal insufficiency.	Single centre, open-label clinical trial.	Single dose of 400 µg aclidinium bromide (given as two 200 µg doses) administered via Almirall inhaler.	24 subjects, aged 35 to 73 years: 6 with normal renal function and 18 with stable, chronic renal insufficiency categorised as mild (n = 6), moderate, (n = 6) or severe (n = 6). Degree of renal insufficiency determined by creatinine clearance.
M/34273/09	To evaluate PK in COPD patients with a broad age range and to evaluate whether PK behaviour is affected by patient age. To evaluate safety and tolerability.	Multi centre, open-label, two-period clinical trial.	First study period: 3 days of QD dosing with 200 µg aclidinium bromide. Second study period: 3 days of QD dosing with 400 µg aclidinium bromide (400 µg given as two 200 µg doses). Aclidinium bromide administered via Almirall inhaler.	24 subjects with moderate to severe COPD. 12 subjects aged 44-59 years (young) and 12 aged 70-79 years (elderly).

Study ID	Study Objective	Study Design	Treatment	Population
M/34273/03	To investigate *in vivo* pulmonary deposition and distribution of aclidinium bromide from Almirall inhaler at 90 L/min To evaluate tolerability and safety.	Single centre, randomized, open-label clinical trial.	A single 200 µg dose of aclidinium bromide. Radiolabelled formulation with [^{99m}]Tc (with < 10 MBq radioactivity) administered by a multimode dry powder inhaler.	12 healthy male Caucasian subjects aged 18 to 63 years.
M/34273/04	To determine rates and routes of elimination of iv [^{14}C] aclidinium bromide and to characterize and identify metabolites in plasma and excreta. To evaluate safety and tolerability.	Single centre, randomized, open-label mass-balance study. Two treatment groups: one to receive [phenyl-U-^{14}C] aclidinium bromide and the other to receive [glycolyl-U-^{14}C] aclidinium bromide.	A single iv infusion (over 5 minutes) of either 400 µg [phenyl-U-^{14}C] or 400 µg [glycolyl-U-^{14}C] aclidinium bromide, containing approximately 40 chi of radioactivity.	12 healthy male subjects (11 Caucasian, 1 black) aged 20 to 34 years, 6 in treatment group A and 6 in treatment group B.
M/34273/00	To assess pharmacological activity, safety, tolerability and PK.	Single centre, randomized, double blind, placebo controlled, three-period, cross-over study of single ascending doses.	Single doses of aclidinium bromide, administered via Cyclohaler®. Doses of active drug: 50, 300 and 600 µg.	12 healthy male subjects, aged 18 to 43 years
M/34273/21	To assess safety, tolerability, PD and PK.	Two centres; randomized, double blind, placebo-controlled, four-period crossover study of 3 ascending doses.	Single doses of 100, 300 and 900 µg aclidinium bromide, administered via Cyclohaler®.	17 male subjects, aged 48 to 71 years, with moderate to severe COPD and significant ipratropium response.

Study ID	Study Objective	Study Design	Treatment	Population
M/34273/11	To assess effect on QT interval and overall cardiovascular safety. General safety and tolerability. Systemic exposure to aclidinium bromide and metabolites and their relationship with ECG changes.	Single centre, randomized, parallel group, placebo- and positive-controlled clinical trial. Aclidinium/placebo comparison double-blind. Moxifloxacin /placebo comparison open-label.	Multiple doses (3 days QD dosing) of aclidinium bromide (at 200 or 800 µg) or placebo or moxifloxacin (400 mg). Aclidinium and placebo administered via Almirall inhaler. Moxifloxacin administered orally.	272 healthy subjects aged 18 to 45 years.

The clinical program for aclidinium bromide 200 and 400 µg, administered BID was conducted in 3 Phase 3 efficacy studies with 1933 randomized patients (M/34273/34, LAS-MD-33, and LAS-MD-38 [Part A]) and 5 supportive studies, including 2 Phase 2 dose-range finding studies with 109 randomized patients (M/34273/23 and M/34273/29), and 3 long-term safety studies with 1344 randomized patients (LAS-MD-35, LAS-MD-36, and LAS-MD-38 [Part B]).

Table 2.2.1-3. Overview of Phase 3 Efficacy Trials Conducted to Evaluate Aclidinium BID.

Study Number	*Aclidinium Bromide Dose (µg)*	*Study Design*	*Control Group(s)*	*Treatment Duration*	*Number of Patients*[a]	*Endpoint(s)*	
						Primary	*Secondary*
M/34273/34 / Completed	200, 400	r, db, p	pbo	24 wks	828	Trough FEV_1	Peak FEV_1 TDI SGRQ
LAS-MD-33 / Completed	200, 400	r, db, p	pbo	12 wks	561	Trough FEV_1	Peak FEV_1
LAS-MD-38 (Part A) / Completed	200, 400	r, db, p	pbo	12 wks	544	Trough FEV_1	Peak FEV_1

BID = twice daily; db = double blind; FEV_1 = forced expiratory volume in one second; p = parallel group; pbo = placebo (controlled); r = randomized; SGRQ = St. George's Respiratory Questionnaire; TDI = transition dyspnea index;
wks = weeks.

a Number of patients randomized.

Study Number	*Aclidinium Bromide Dose (µg)*	*Study Design*	*Control Groups*	*Treatment Duration*	*Number of Patients*[a]	*Endpoint(s)*	
						Primary	*Secondary*
M/34273/23 Completed	400	r, db, cxo	pbo, TIO	15 days[b]	30	FEV_1 $AUC_{0\text{-}12/12h}$	Spiro[c] Symptoms Rescue medication
M/34273/29 Completed	100, 200, 400	r, db, cxo	pbo, FOR	1 wks[b]	79	FEV_1 $AUC_{0\text{-}12/12h}$	Spiro[c]
LAS-MD-36[d] Completed	200, 400	r, db, p	-	52 wks	291	Trough FEV_1	Peak FEV_1
LAS-MD-35[d,e] Ongoing	200, 400	r, db, p	-	52 wks	605	Trough FEV_1	Peak FEV_1
LAS-MD-38[d,e] (Part B) Ongoing	400	r, ol, p	-	40 wks	448	Trough FEV_1	Peak FEV_1

BID = twice daily; cxo = crossover; db = double blind; FEV_1 = forced expiratory volume in one second; FEV_1 $AUC_{0\text{-}12/12h}$ = normalized area under the FEV_1 versus time curve between 0 and 12 hours postdose; FEV_1 $AUC_{0\text{-}24/24h}$ = normalized area under the FEV_1 versus time curve between 0 and 24 hours postdose; FEV_1 = $AUC_{12\text{-}24/12h}$ = normalized area under the FEV_1 versus time curve between 12 and 24 hours postdose; FOR = formoterol 12 µg BID; ol = open label; p = parallel group; pbo = placebo (controlled); r = randomized; spiro = spirometry; TIO = tiotropium 18 µg once daily; wks = weeks.

a Number of patients randomized.

b Duration of each treatment period within the crossover study.

c Spirometry for M/34273/23: FVC $AUC_{0\text{-}12/12h}$; FEV_1 and FVC $AUC_{0\text{-}24/24h}$; and $AUC_{12\text{-}24/12h}$ trough FEV_1 and FVC, FEV_1 and FVC over time. Spirometry for M/34273/29: FEV_1 $AUC_{0\text{-}24/24h}$; FEV_1 $AUC_{12\text{-}24/12h}$; and trough FEV_1.

d Primary objective of these studies was investigation of long-term safety and tolerability.

e As per the data cut-off of 01 Nov 2010.

Other clinical development programs of aclidinium bromide also included aclidinium bromide 200 µg QD program and the fixed-dose combination program of aclidinium bromide and formoterol.

2.2.2 What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (also called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?

The selection of the primary response endpoints were in line with the recommendations in the draft guidance "Guidance for Industry: Chronic Obstructive Pulmonary Disease: Developing Drugs for Treatment".

The primary and secondary efficacy/pharmacodynamic endpoints and their measurements in the three efficacy and safety clinical studies are listed in the table below.

Table 2.2.2. Efficacy/pharmacodynamic primary and secondary endpoints.

Study	Primary Endpoints	Secondary Endpoints
M/34273/34	Change from baseline in morning pre-dose (trough) FEV1 at Week 24 for the European Union (EU) filing and Week 12 for the United States (US) filing.	• Change from baseline in peak FEV1 at Week 24 for the EU filing and Week 12 for the US filing. • Number (%) of patients achieving a clinically relevant improvement (≥1 unit) in Transition Dyspnoea Index (TDI) focal score at Week 24. • Number (%) of patients achieving a clinically relevant improvement (≥4 units) compared to baseline in the Saint George's Respiratory Questionnaire (SGRQ) total score at Week 24.
LAS-MD-33	Change from baseline in morning predose (trough) FEV1 at Week 12	Change from baseline in peak FEV1 at Week 12
LAS-MD-38	Change from baseline in morning predose (trough) FEV1 at Week 12	Change from baseline in peak FEV1, at Week 12

Please refer to the clinical review by Dr. Jennifer Pippins for final assessment of safety and efficacy findings from these studies.

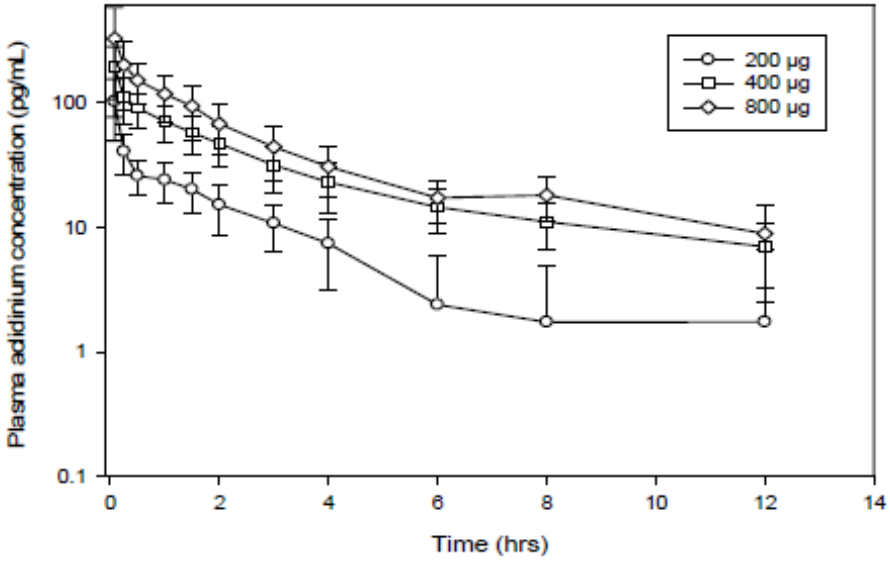
2.2.3 What are the PK characteristics of Aclidinium Bromide and its metabolites?

a) What are the single-dose and multiple-dose PK characteristics?

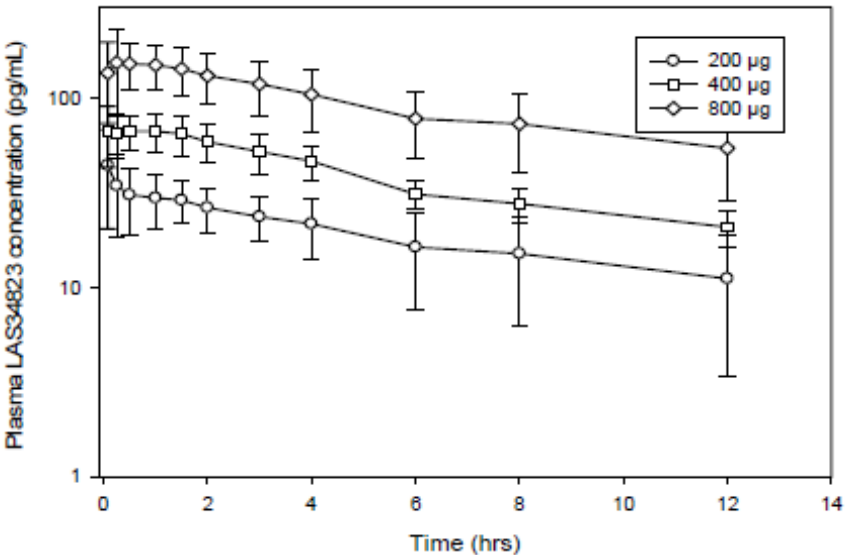
LAS-PK-12 is the only pharmacokinetic study conducted using the final commercial formulation SD2FL(MC). In this study, the pharmacokinetics of aclidinium bromide was assessed after both single dose (first dose) and multiple doses. After the first dose, the Cmax of aclidinium bromide and its two metabolites was approximately dose proportional over the dose range of 200 µg to 800 µg. At the dose of 400 µg, aclidinium reached maximum plasma concentrations at ~0.08 h. LAS34823 and LAS34850, the major inactive metabolites, reached maximum plasma concentration at ~0.61 and 3.63 hours, respectively.

Figure 2.2.3-1: Mean (± SD) Plasma Concentrations Versus Time After the Morning Dose on Day 1 Following Inhalation of 200 µg, 400 µg, and 800 µg Aclidinium Bromide Twice Daily (LAS-PK-12)

A. **Aclidinium**



B. **LAS34823**



C. **LAS34850**

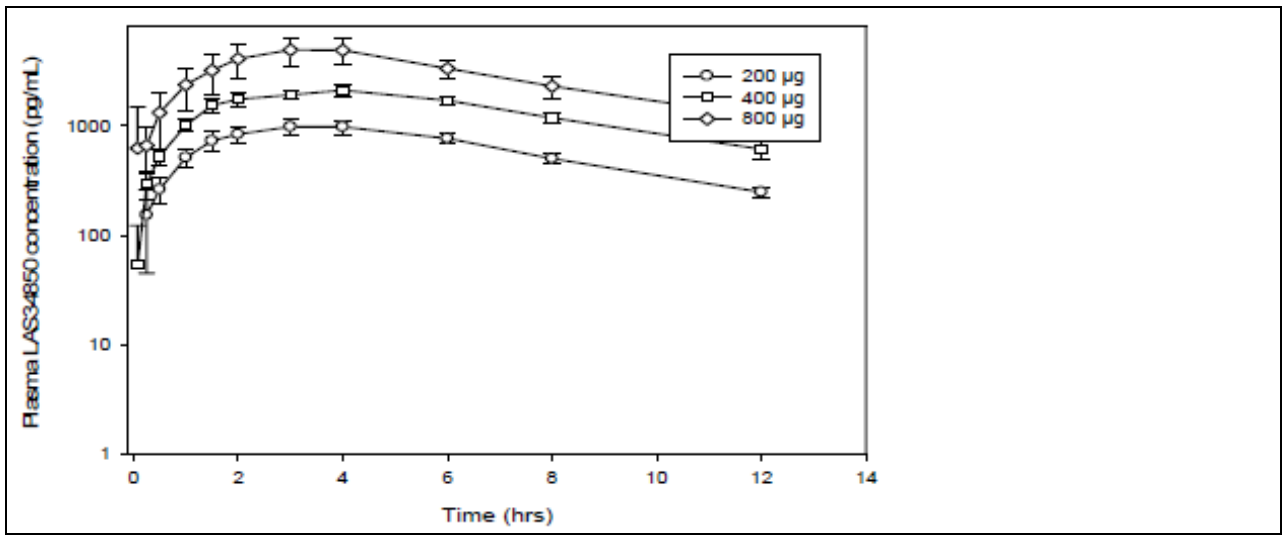

Plasma LAS34850 concentration (pg/mL)
1000
100
10
1
0
2
4
6
8
10
12
14
Time (hrs)
200 µg
400 µg
800 µg

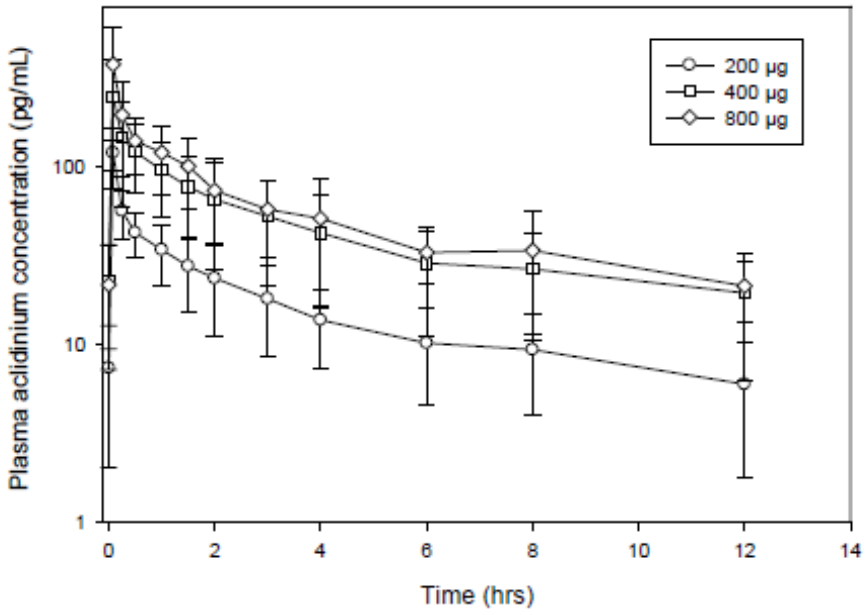
Table 2.2.3-1: Pharmacokinetic parameters (mean, %CV) for Aclidinium, LAS34823, and LAS34850 after Single-Dose Administration of 200, 400, and 800 mcg on Day 1.

Parameter	*Aclidinium*		
	200 µg	*400 µg*	*800 µg*
C_{max}, pg/mL	102.74, 51.40	194.23, 45.21	360.06, 62.01
T_{max}, h	0.08, 0.00	0.08, 0.00	0.10, 56.84
$T_{½}$, h	2.35, 28.42	5.91, 39.80	4.49, 63.01
$AUC_{τ}$, pg • h/mL	97.64, 40.24	324.88, 34.43	494.66, 37.59
$AUC_{0-∞}$, pg • h/mL	109.40, 35.76	386.69, 34.83	566.34, 46.04
Parameter	*LAS34823*		
	200 µg	*400 µg*	*800 µg*
C_{max}, pg/mL	46.66, 43.08	76.30, 25.95	174.85, 35.07
T_{max}, h	0.26, 192.59	0.61, 103.02	0.75, 125.99
$T_{½}$, h	12.44, 98.94	11.25, 66.97	9.37, 38.66
$AUC_{τ}$, pg • h/mL	229.39, 41.40	464.66, 19.80	1106.57, 31.55
$AUC_{0-∞}$, pg • h/mL	475.49, 81.67	809.09, 33.21	1881.72, 44.02
Parameter	*LAS34850*		
	200 µg	*400 µg*	*800 µg*
C_{max}, pg/mL	1011.75, 15.67	2151.90, 13.49	5272.08, 28.68
T_{max}, h	3.38, 15.33	3.63, 20.52	3.63, 32.77
$T_{½}$, h	3.81, 15.17	4.22, 22.19	4.06, 7.61
$AUC_{τ}$, pg • h/mL	7378.83, 8.54	16,153.34, 7.83	34,997.13, 21.16
$AUC_{0-∞}$, pg • h/mL	8746.15, 7.61	20,022.40, 12.38	42,176.87, 21.66

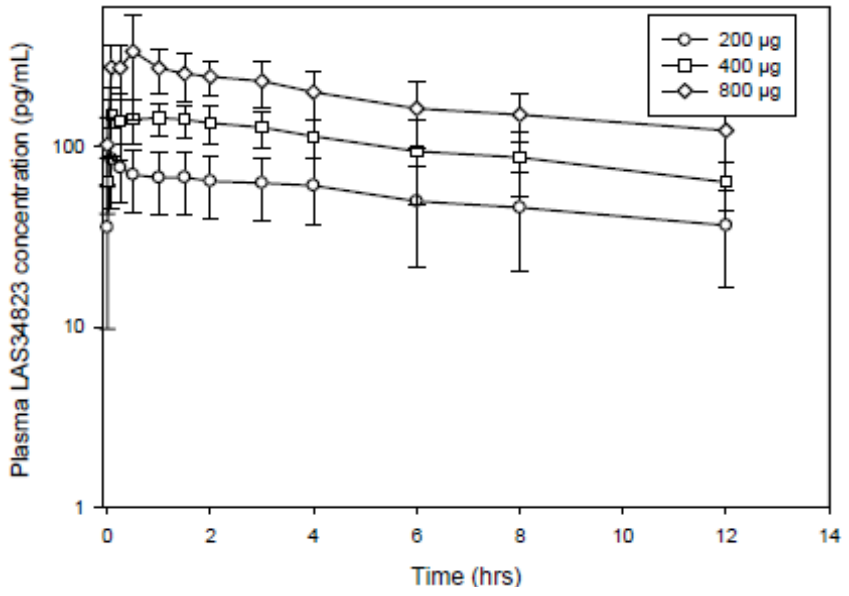
After multiple dosing, the accumulation ratio ws minimal to moderate for 200 µg, 400 µg, and 800 µg BID treatment groups. The estimated effective half-life of aclidinium is ~5-8 hours.

Figure 2.2.3-2: Mean (± SD) Plasma Concentrations Versus Time After the Morning Dose on Day 7 Following Inhalation of 200 µg, 400 µg, and 800 µg Aclidinium Bromide Twice Daily (LAS-PK-12)

A: aclidinium bromide



B: LAS34823



C: LAS34850

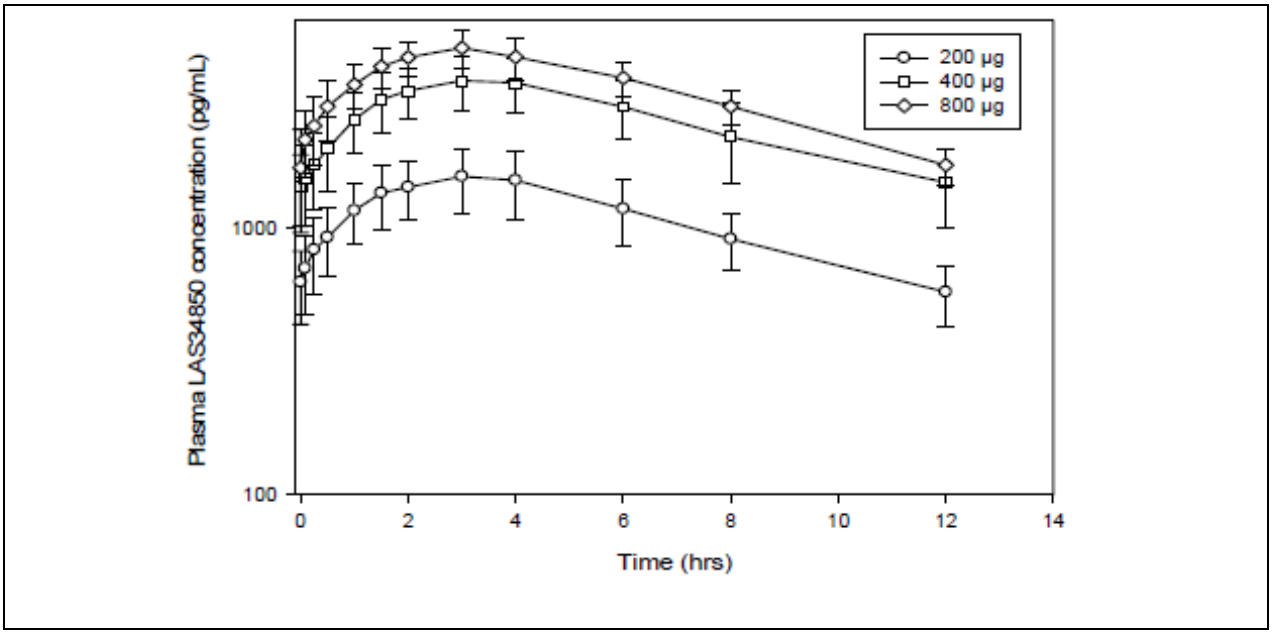
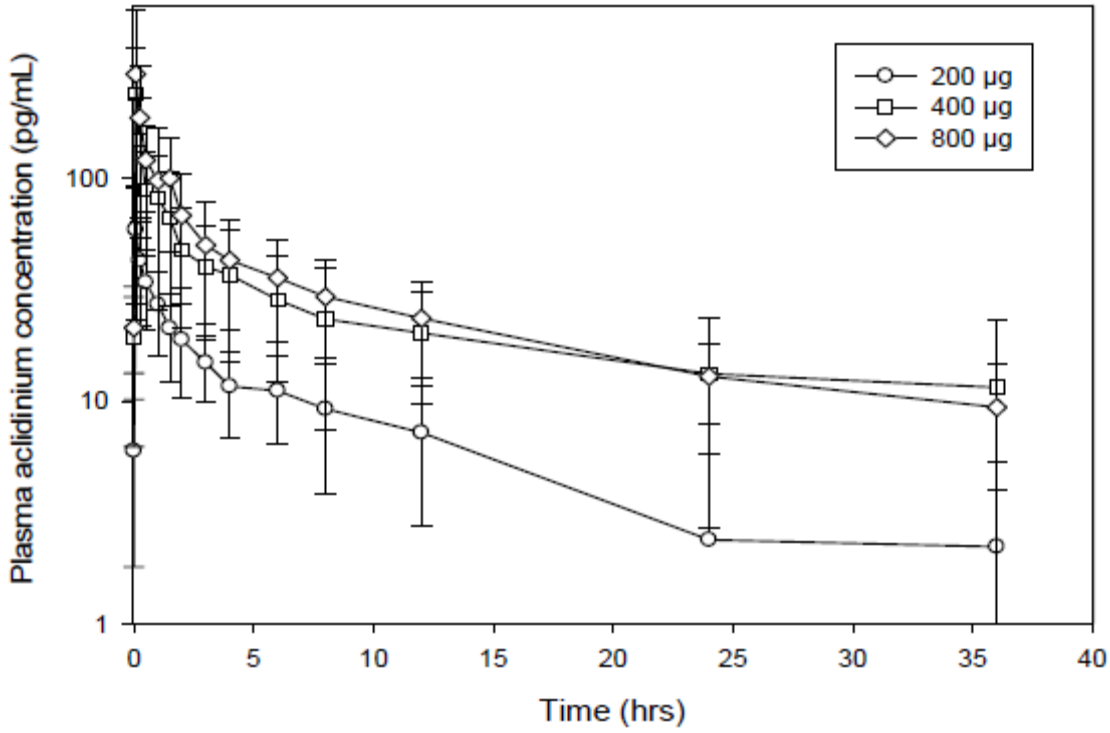
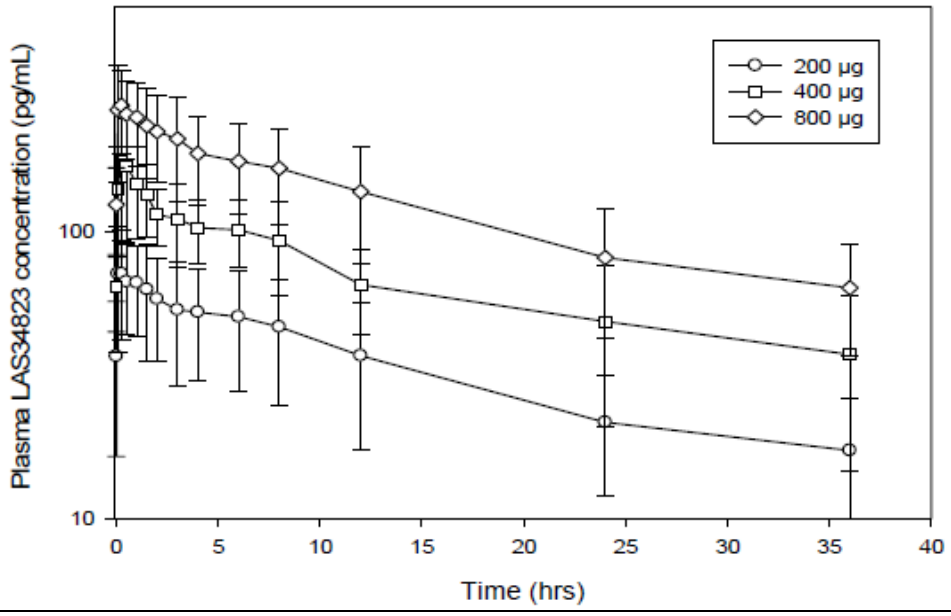

Plasma LAS34850 concentration (pg/mL)
1000
100
0
2
4
6
8
10
12
14
Time (hrs)
200 µg
400 µg
800 µg

Figure 2.2.3-3: Mean (± SD) Plasma Concentrations Versus Time After the Evening Dose on Day 7 Following Inhalation of 200 µg, 400 µg, and 800 µg Aclidinium Bromide Twice Daily

A: Aclidinium



B: LAS34823



C: LAS34850

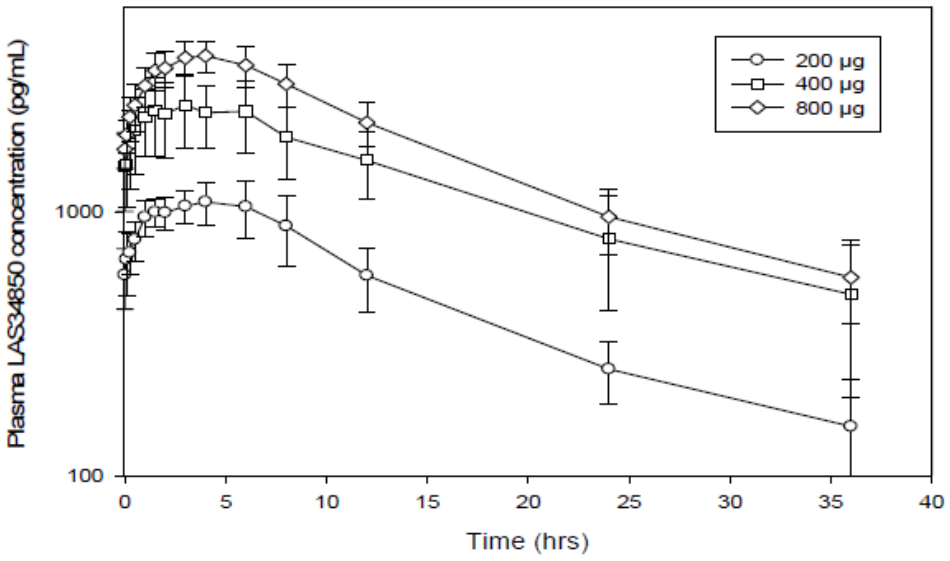


Table 2.2.3-2: Pharmacokinetic parameters (mean, %CV) for Aclidinium after Single-Dose Administration of 200, 400, and 800 mcg on Day 7.

Parameter	*Morning*		
	200 µg	*400 µg*	*800 µg*
$C_{max,ss}$, pg/mL	119.91, 37.09	254.71, 56.97	377.14, 62.65
$C_{min,ss}$, pg/mL	5.98, 69.97	19.51, 68.02	20.88, 36.38
T_{max}, h	0.14, 109.11	0.20, 164.05	0.08, 0.00
$T_{½}$, h	12.41, 103.88	6.77, 32.05	6.41, 24.88
λ_z, 1/h	0.10, 69.67	0.11, 30.92	0.11, 24.37
$AUC_{\tau,ss}$, pg • h/mL	190.66, 42.67	535.76, 51.85	651.14, 43.45

Parameter	*Evening*		
	200 µg	*400 µg*	*800 µg*
$C_{max,ss}$, pg/mL	63.21, 49.86	240.47, 60.57	307.80, 86.51
$C_{min,ss}$, pg/mL	7.22, 61.85	19.52, 55.61	22.07, 54.16
T_{max}, h	0.16, 96.65	0.10, 56.84	0.10, 56.84
$T_{½}$, h	10.93, 61.75	17.03, 40.80	16.30, 26.35

Table 2.2.3-3: Pharmacokinetic parameters (mean, %CV) for LAS34823 after twice daily dose Administration of 200, 400, and 800 mcg on Day 7.

Parameter	*Morning*		
	200 µg	*400 µg*	*800 µg*
$C_{max,ss}$, pg/mL	90.13, 38.87	168.62, 26.44	378.11, 50.41
$C_{min,ss}$, pg/mL	36.64, 55.18	63.72, 29.98	121.28, 33.82
T_{max}, h	0.31, 160.65	1.35, 149.31	1.04, 66.81
$T_{½}$, h	10.72, 18.37	9.38, 28.48	12.53, 73.35

Parameter	*Evening*		
	200 µg	*400 µg*	*800 µg*
$C_{max,ss}$, pg/mL	94.44, 32.78	185.48, 42.39	293.06, 37.42
$C_{min,ss}$, pg/mL	36.84, 52.72	65.04, 32.81	136.94, 43.78
T_{max}, h	0.34, 92.10	0.59, 95.32	0.36, 127.56
$T_{½}$, h	20.90, 21.35	26.00, 51.70	19.90, 23.68

Table 2.2.3-4: Pharmacokinetic parameters (mean, %CV) for LAS34850 after twice daily dose Administration of 200, 400, and 800 mcg on Day 7.

Parameter	*Morning*		
	200 µg	*400 µg*	*800 µg*
$C_{max,ss}$, pg/mL	1581.47, 26.35	3726.27, 22.36	4853.28, 14.94
$C_{min,ss}$, pg/mL	575.94, 25.86	1368.09, 36.05	1652.33, 20.29
T_{max}, h	3.00, 17.82	3.31, 26.68	3.13, 20.51
$T_{½}$, h	6.10, 24.41	6.45, 18.98	5.48, 15.84
Parameter	*Evening*		
	200 µg	*400 µg*	*800 µg*
$C_{max,ss}$, pg/mL	1125.92, 17.39	2644.85, 30.55	3999.88,15.15
$C_{min,ss}$, pg/mL	570.71, 27.07	1385.83, 27.49	1886.50, 11.97
T_{max}, h	4.06, 44.83	3.06, 30.78	3.88, 25.57
$T_{½}$, h	11.84, 28.35	14.77, 46.58	12.37, 27.01

b) How does the PK of the drug in healthy volunteers compare to that in patients?

The pharmacokinetics of aclidinium bromide in COPD patients from clinical inhalation device Almirall Inhaler SD2FL was assessed in study M/34273/09 and compared to that in healthy subjects with the same device (Studies M/34273/05 and M/34273/08). Cross study comparison showed that aclidinium bromide appeared to exhibit lower Cmax and higher AUC in COPD patients as compared to healthy subjects. The time to reach Cmax in COPD patients appeared to be delayed as compared to healthy subjects.

Table 2.2.3-5: Mean (CV%) PK Variables of Aclidinium Bromide from Studies M/34273/05, M/34273/08, and M/34273/09.

Subjects	Dose (µg)	Dosing	Study #	N	Cmax (pg/mL)	AUC (pg•h/mL)	Tmax (h)	CL/F (L/h)
Healthy	200	SD	M/34273/05	12	52.7 (63.8)	76.8 (43.5)	0.09	3051.1 (43.0)
Healthy	400	SD	M/34273/08	6	113.9 (81.5)	147.2 (68.5)	0.08	3651.3 (47.7)
COPD	200 QD	SD	M/34273/09	12	39.0 (46.2)	75.4 (49.0)	0.25	-
		SS	M/34273/09	12	37.8 (44.1)	103.1 (45.4)	0.25	2284.1 (43.8)

	400 QD	SD	M/34273/09	12	82.3 (32.0)	193.5 (51.4)	0.25	-
		SS	M/34273/09	12	86.1 (31.6)	199.6 (36.4)	0.25	2288.6 (39.7)

c) What are the characteristics of drug absorption?

In healthy subjects, the absolute bioavailability of aclidinium bromide following inhalation of a 200 µg dose from the clinical inhalation device Almirall Inhaler SD2FL (SC) is <5% (Study M/34273/05). Using the commercial inhalation device Almirall Inhaler SD2FL (MC) (Study LAS-PK-12), the time to reach the maximum plasma concentrations of aclidinium bromide (t_{max}) is about 0.08 hour. The Cmax of aclidinium bromide is approximately dose-proportional over the dose range of 200 to 800 µg.

In COPD patients, C_{max} is achieved approximately 10 to 15 minutes following inhalation from the clinical inhalation device Almirall Inhaler SD2FL (SC) (M/34273/09).

d) What are the characteristics of drug distribution?

The *in vivo* pulmonary disposition and distribution of 200 µg aclidinium bromide was evaluated in healthy subjects using the clinical inhalation device Almirall Inhaler MD2 (Study M/34273/03). About 34% of the delivered dose was deposited in the lungs. Following intravenous administration of aclidinium bromide of 400 µg, the mean apparent volume of distribution is high (~300 L) (Study M/34273/08).

The plasma protein binding of aclidinium bromide was investigated in vitro ([(b) (4)]/10). The main plasma protein that binds aclidinium bromide in vivo is albumin. Due to the rapid hydrolysis of aclidinium bromide, it is likely that the protein binding that was measured corresponded to the protein binding of the metabolites and not parent compound. Plasma protein binding was 87% for the acid metabolite (LAS34850) and 15% for the alcohol metabolite (LAS34823).

e) Does the mass balance study suggest renal or hepatic as the major route of elimination?

Because aclidinium is an ester, it is quickly hydrolyzed in plasma to an alcohol metabolite (LAS34823) and acid metabolite (LAS34850), and neither renal nor hepatic is the major route of elimination.

In study M/34273/04, twelve healthy male subjects were randomized to receive either a single IV dose of 400 µg of [phenyl-U-14C] aclidinium bromide (n=6) or a single IV dose of 400 µg of [glycolyl-U-14C] aclidinium bromide (n=6). Following IV administration, aclidinium is hydrolyzed rapidly in plasma to two molecules, the alcohol metabolite (LAS34823) and the acid metabolite (LAS34850) because aclidinium is an ester. The hydrolysis of [phenyl-U-14C] aclidinium will produce [14C] LAS34823 (14C-labelled alcohol metabolite) and unlabelled acid metabolite, whereas hydrolysis of [glycolyl-U-14C] aclidinium produces [14C] LAS34850 (14C-labelled acid metabolite) and unlabelled alcohol metabolite. Both [14C] LAS34823 and [14C] LAS34850 were observed at the first sampling time point of 5 min.

Table 2.2.3-6: Pharmacokinetic parameters of LAS34850 and LAS34823 following IV doses of 400 µg aclidinium.

Pharmacokinetic parameter	LAS34850: following 400 µg [phenyl-U-^{14}C] *aclidinium bromide* (N=6)	LAS34823: following 400 µg [glycolyl-U-^{14}C] *aclidinium bromide* (N=6)
AUC_{0-t} (pg.h/mL)	26500 (11.1)	2340.4 (26.9)
$AUC_{0-\infty}$ (pg.h/mL)	27487 (11.2)	2366.8 (26.8)
C_{max} (pg/mL)	14444 (19.4)	11460 (23.5)
t_{max} (h)	0.09 (0.08 - 0.20)	0.08 (0.08 - 0.10)
$t_{1/2}$ (h)	3.41 (13.1)	2.70 (28.2)
λ_z (1/h)	0.21 (12.4)	0.28 (28.9)

Arithmetic mean (CV%) data are presented for all parameters with the exception of t_{max} for which median (min-max) are presented)

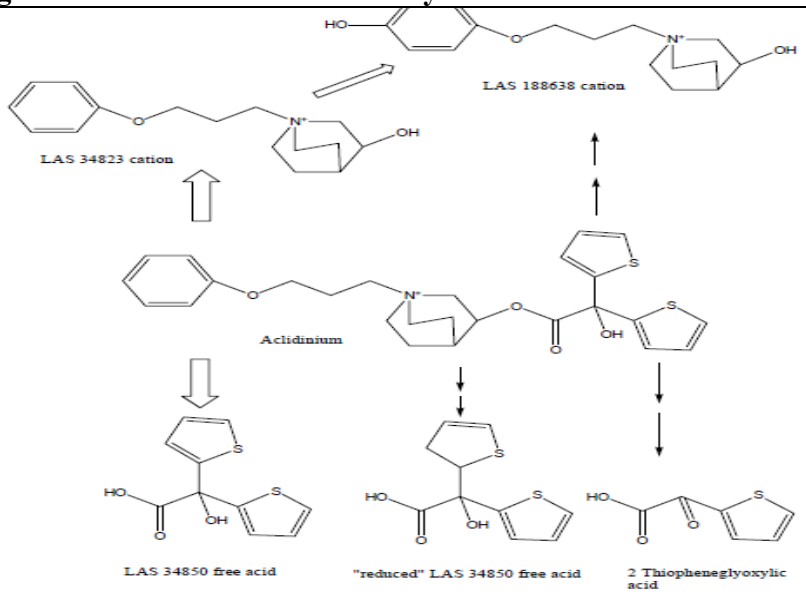
Source: Page4 of clinical study report M/34273/04.

Following IV administration of a 400 µg dose of [14C] aclidinium bromide ([phenyl-U-14C] or [glycolyl-U-14C]), aclidinium was extensively metabolised and approximately 1% of the dose was excreted as unchanged aclidinium.

f) What are the characteristics of drug metabolism?

In vitro studies demonstrated that the major route of metabolism of aclidinium bromide is via enzymatic and chemical (nonenzymatic) hydrolysis into its alcohol (LAS34823) and acid (LAS34850) derivatives. Butyrylcholinesterase is the main human esterase responsible for the hydrolysis, whereas in vitro studies showed significant hydrolysis in the absence of this enzyme (Report No. B.34273.22). The mass balance and metabolic profile of aclidinium bromide in healthy subjects (M/34273/04) showed that the drug is rapidly hydrolyzed in plasma to an alcohol and acid metabolite. Plasma concentrations of the acid metabolite are approximately 100-fold greater than those of the alcohol metabolite and unchanged aclidinium bromide. In vivo (M/34273/04) and in vitro studies (Report No. B.34273.22) showed biotransformation via cytochrome P-450 (CYP-450) isozymes to play a minor role in the total metabolic clearance of aclidinium bromide.

Figure 2.2.3-4: Metabolic Pathway of Aclidinium Bromide in Healthy Subjects



g) What are the characteristics of drug excretion?

Renal clearance has only a minor role in the clearance of aclidinium bromide from plasma. Approximately 1% of a single intravenous dose of aclidinium bromide is excreted in urine as unchanged drug. The remaining dose is hydrolyzed and excreted as metabolites (up to 65% in urine and 33% in feces [M/34273/04]).

Studies M/34273/05, M/34273/08, and M/34273/09 showed the urinary excretion of a single inhaled dose of aclidinium bromide to be very low, with approximately 0.1% of the dose recovered in urine at 48 hours.

Clearance of aclidinium bromide from the plasma is rapid with an estimated effective half-life of aclidinium is ~5-8 hours (LAS-PK-12).

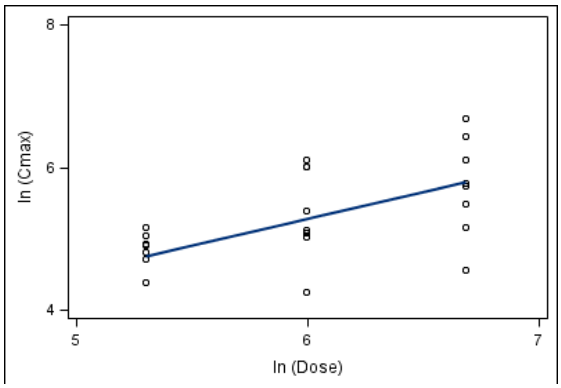
h) Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

Linearity was established over the twice daily inhaled dose range of 200 µg and 800 µg aclidinium bromide.

Aclidinium bromide plasma Cmax and AUC is exhibited linear PK behavior following multiple dose inhaled administration of 200 µg, 400 µg, or 800 µg BID (LAS-PK-12). A power model of *AUC(Cmax)=aDose^b* was used to assess the linearity of exposure of aclidinium at steady state (Day 7). For both Auc and Cmax, *b* is not significantly from 1.

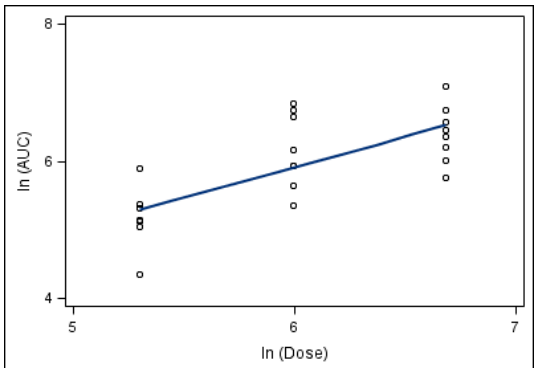
Figure 2.2.3-5: Pharmacokinetic Parameters vs Dose for Aclidinium After Multiple-Dose Administration of 200, 400, and 800 µg Aclidinium Bromide (LAS-PK-12).

Cmax



Slope=0.89, p=0.53 (H0: slope=1)

AUC



Slope=0.75, p=0.28 (H0: slope=1)

i) How do the PK parameters change with time following chronic dosing?

The PK variables of aclidinium bromide were not affected after repeated inhaled doses.

After repeated inhaled doses of aclidinium bromide 200 to 800 µg in healthy volunteers, the accumulation index (AI) based on AUC was about 1.4; the AI based on Cmax was 1.1. The Tmax was comparable after single dosing as compared to chronic dosing for aclidinium (LAS-PK-12).

Table 2.2.3-7: Summary of PK characterististics of aclidinium bromide in healthy subjects following inhaled doses of 200, 400 and 800 µg (geomean, CV%; Tmax: meadian) (LAS-PK-12).

Dose (ug)	Study Day	Cmax (pg/mL)	Tmax (h)	AUC (pgh/mL)
200	1	102.74	0.08	-
	7 (morning)	119.91 (37.09)	0.14	190.66 (42.67)
	7 (evening)	63.21 (49.86)	0.16	
400	1	194.23 (45.21)	0.08	324.88 (34.43)
	7 (morning)	254.71 (56.97)	0.20	535.76 (51.85)
	7 (evening)	240.47 (60.57)	0.10	468.35 (49.54)
800	1	360.06 (62.01)	0.10	

	7 (morning)	377.14 (62.05)	0.08	651.14 (43.45)
	7 (evening)	307.80 (86.51)	0.10	594.37 (51.61)

j) What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

The inter-subject variability was less than 60% and intra-subject variability was less than 45% for aclidinium.

The C_{max} and AUC showed a moderate to high degree of inter-subject variability (CV%) were generally in the range 40%-60%. The intra-subject variability of AUC (CV%) was estimated to be 11%, and of Cmax was estimated to be 43% (LAS-PK-12).

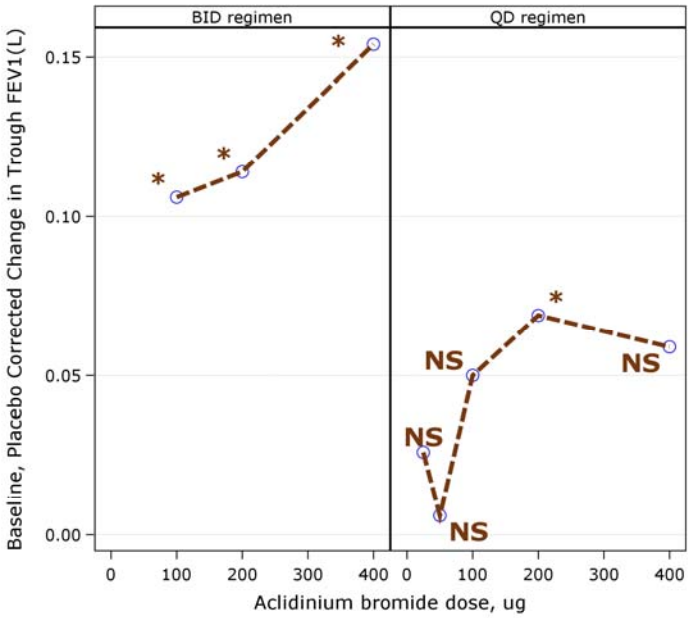
2.2.4 Exposure-response

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

The sponsor has adequately characterized the relationship between dose and changes in trough FEV1.

The following figure shows the relationship between aclidinium bromide dose (once-daily, QD or twice-daily, BID) and changes in trough FEV1 in dose-finding studies.

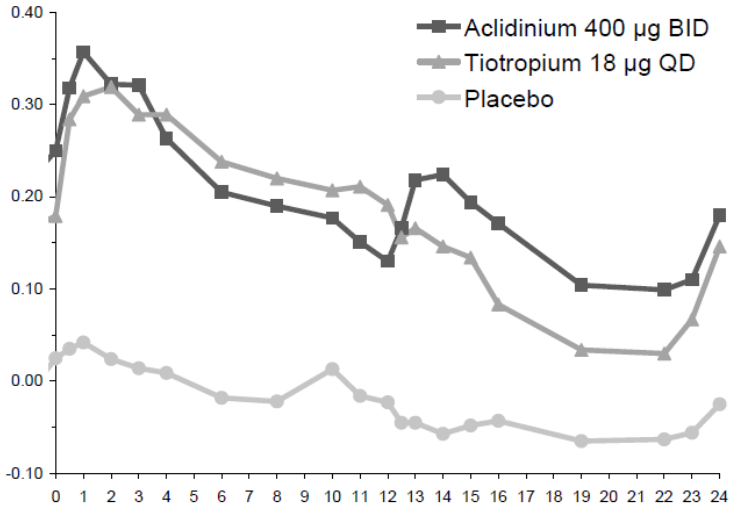
Figure 2.2.3-6. Relationship between aclidinium bromide dose, ug and baseline, placebo corrected change in trough FEV1 on day 7 in study M/34271/39 (BID regimen) and LAS-MD-CL22 (QD regimen) (Phase 2 dose finding studies).



Source: Data from table 2.2.2-1 on page 71 in summary-clin-effectiveness-ise-vol1.pdf and from table 9 on page 59 in las-md-cl22.pdf

Figure shows the time course of bronchodilatory effects (change from baseline FEV1) on day 15, in study M/34271/23, when aclidinium bromide (400 ug) is administered using BID regimen. Also shown is the time course of bronchodilatory effects after QD administration of tiotropium (18 ug).

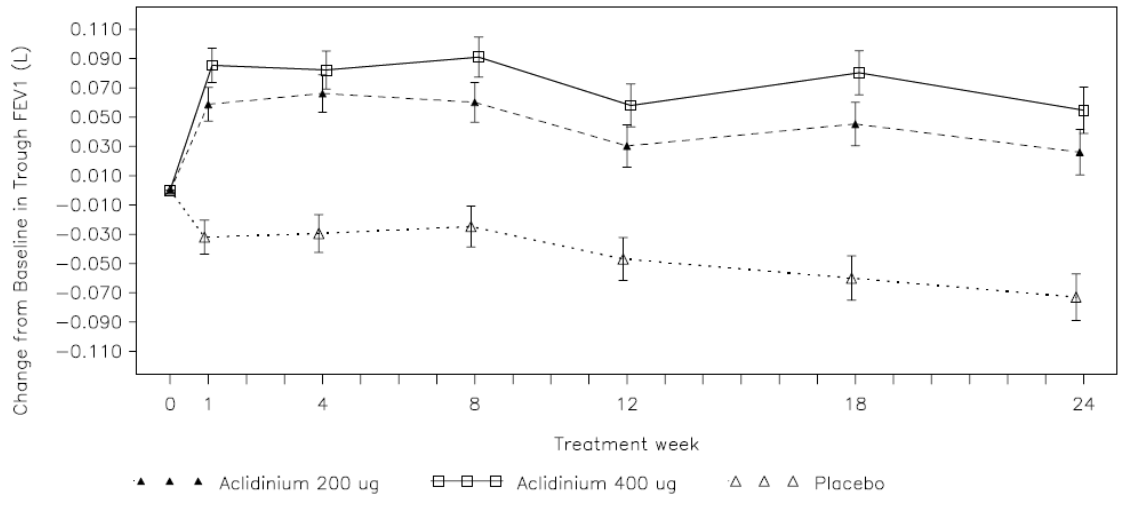
Figure 2.2.3-7. Time course of bronchodilatory effects (change from baseline FEV1) after administration of aclidinium bromide using BID regimen in Study M/34271/23 (Phase 2 dosing regimen finding study).



Source: Figure 2.2.1-1 on page 69 in summary-clin-effectiveness-ise-vol1.pdf

Figure shows the mean changes from baseline, up to week 24, in trough FEV1 in Phase 3 study (M34273/34). The data suggests that treatment effects attained early (Week 1) in the study are maintained till Week 24.

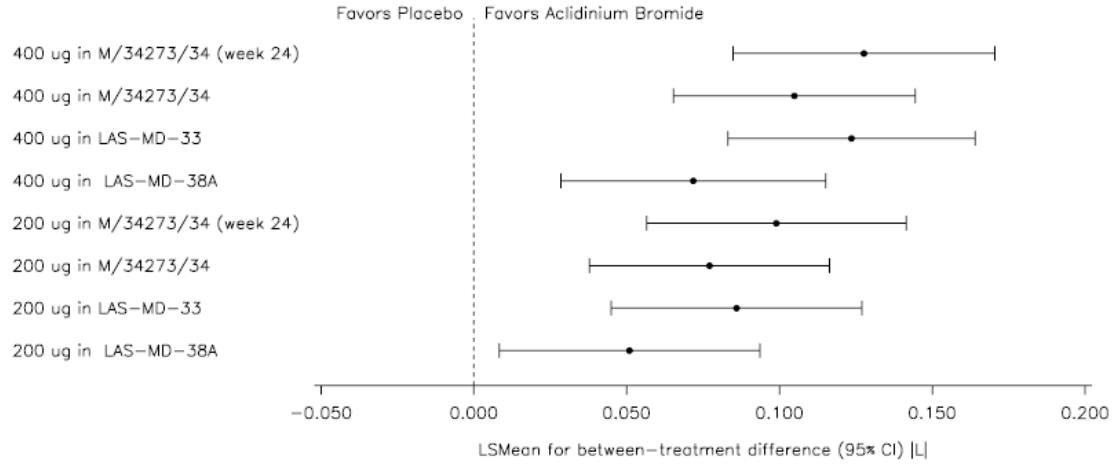
Figure 2.2.3-8. Least Square Mean Changes from Baseline up to Week 24 in Trough FEV1 by Treatment in Study M/34273/34 — ITT Population.



Source: Figure 2.1.1-1 on page 40 in summary-clin-effectiveness-ise-vol1.pdf

Figure shows the baseline, placebo-corrected change in trough FEV1 at Week 12 after 200 and 400 ug dose in Phase 3 studies. Shown also are treatment differences at week 24 in M/34273/34.

Figure 2.2.3-9. Treatment Differences (Aclidinium Bromide 200 µg and 400 µg versus Placebo) in Least Square Means (and 95% CIs) for Changes from Baseline to Week 12 in Trough FEV1 in the Phase 3 Efficacy Studies M/34273/34, LAS-MD-33, and LAS-MD-38 (Part A) — ITT Populations.



CI = confidence interval; FEV_1 = forced expiratory volume in one second; ITT = intent to treat; LS = least square.

Source: Figure 3.2.1.1-1 on page 92 in summary-clin-effectiveness-ise-vol1.pdf

Additional details of the exposure response findings can be seen in the pharmacometrics review in the appendix.

2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

Sponsor did not evaluate the relationship between concentration and safety measures. For detailed safety assessment at different dose levels, please refer to the Clinical review by Dr. Jennifer Pippins.

2.2.4.3 Does this drug prolong the QT or QTc interval?

Aclidinium bromide does not have any significant impact on QTc interval. Please refer to the review by QT-IRT group for further details.

2.3 Intrinsic Factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics?

a) Elderly

The pharmacokinetics of aclidinium bromide administered via inhalation QD for 3 days was investigated in moderate to severe COPD patients aged 40 to 59 years and aged 70 years and over (M/34273/09). For both age groups, aclidinium bromide was rapidly absorbed, with a median time to peak plasma concentrations of 10 to15 minutes, and no difference was observed in systemic exposure. Exposur to the acid and alcohol metabolites was, however, somewhat higher in the elderlye compared to the younger patients. In general, the PK properties of aclidinium bromide are similar in young and elderly patients. The higher exposure to the metabolites observed in elderly patients is not considered clinically relevant, as these metabolites appear devoid of pharmacological activity. Therefore, no dose adjustment is considered necessary for elderly COPD patients.

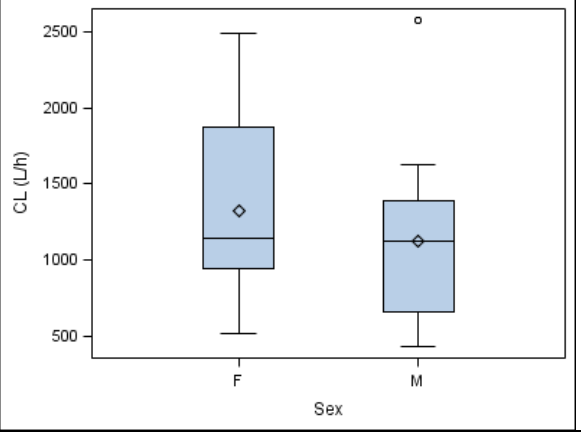
b) Pediatric patients

Since COPD is not a disease seen in pediatric patients, safety and effectiveness of aclidinium bromide in children and adolescents below 18 years of age have not been established. Aclidinium bromide is not recommended in this population.

c) Gender

Women appeared to have comparable exposure on the exposure of aclidinium bromide as compared to men.

Figure 2.3.1: Boxplot of CL versus Sex in Study LAS-PK-12.



d) Race

The race effect on the PK of aclidinium bromide was not evaluated.

e) Renal impairment

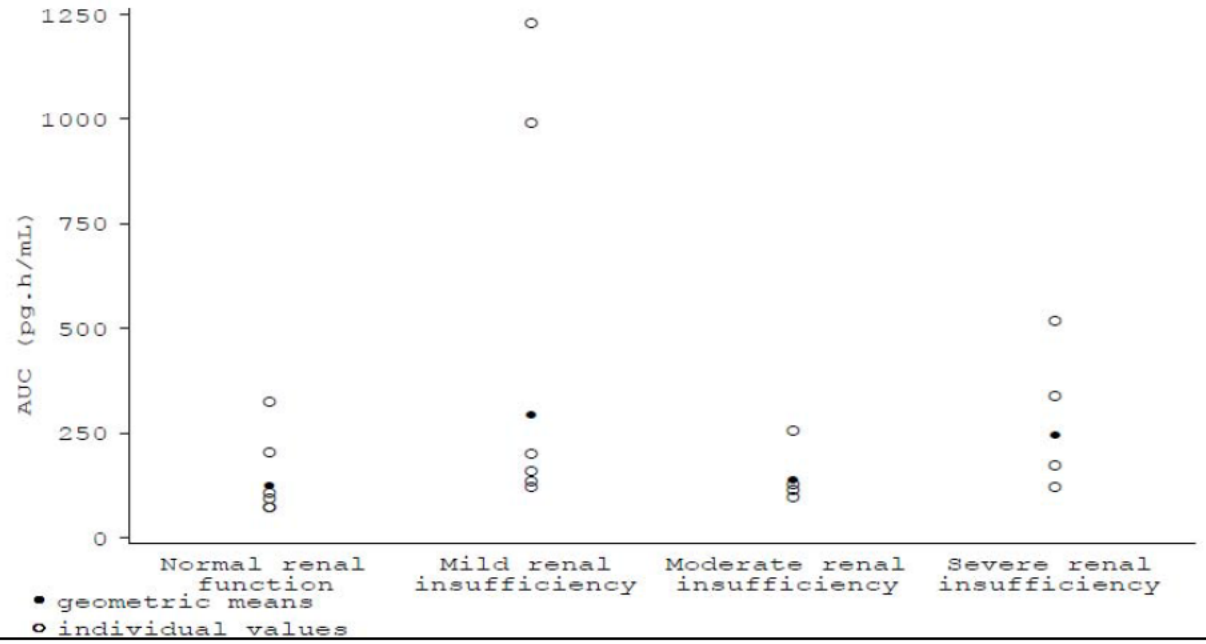
No clinically significant differences in the comparisons between the normal renal function group and each of the renal insufficiency groups were observed for the plasma PK parameters of aclidinium bromide.

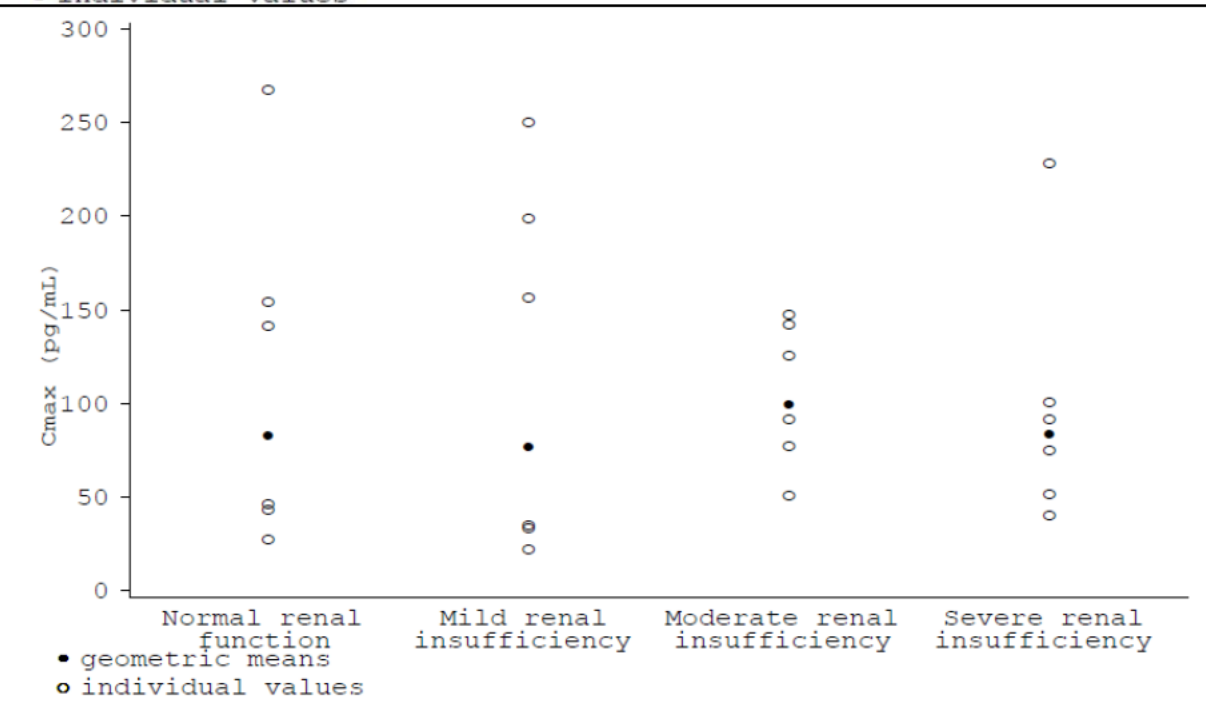
The influence of renal impairment on the PK of a single inhaled dose of aclidinium bromide (400 μg) from the clinical inhalation device Almirall Inhaler *SD2FL (SC)* was investigated in subjects with normal renal function and with mild, moderate and severe renal in study M/34273/08. This was a single dose, open label, clinical study. Twenty-four subjects were randomised; 18 with renal insufficiency (six subjects for each of the three renal insufficiency groups: mild, moderate and severe) and six subjects with normal renal function. Each subject received a single dose of aclidinium bromide (400 μg) from the Almirall Inhaler by inhalation on a single occasion, as two puffs (200 + 200 μg; the second puff administered immediately after the first). The plasma pharmacokinetic parameters of aclidinium bromide are presented in the following table:

Table 2.3.1: The plasma pharmacokinetic parameters of aclidinium bromide.

Parameter	Normal renal function (N=6)	Mild renal insufficiency (N=6)	Moderate renal insufficiency (N=6)	Severe renal insufficiency (N=6)
C_{max} (pg/mL)	113.9 (81.5)	116.5 (84.7)	106.3 (36.5)	98.5 (69.0)
t_{max} (h)	0.08 (0.08 - 0.25)	0.08 (0.08 - 1.00)	0.08 (0.08 - 0.08)	0.08 (0.08 - 0.53)
$t_{1/2}$ (h)	2.33 (51.7)	10.59 (109.9)	2.58 (50.8)	6.23 (84.1)
AUC (pg.h/mL)	147.2 (68.5)	474.2 (105.6)	149.8 (48.5)	288.6 (62.3)

Figure 2.3.2: AUC and Cmax of Aclidinium Bromide in Subjects with Normal Renal Function and Renal Insufficiency (Mild, Moderate, and Severe)





The intersubject variability for Cmax and AUC was big and no clinically significant differences in the comparisons between the normal renal function group and each of the renal insufficiency groups were observed for the plasma pharmacokinetic parameters of aclidinium bromide.

f) hepatic impairment

The effect of hepatic impairment on the exposure of aclidinium bromide and its two main metabolites was not conducted.

Hepatic metabolism plays a very minor role in the clearance of aclidinium bromide, which is metabolized mainly by chemical (nonenzymatic) and enzymatic cleavage. The primary human esterase involved in the enzymatic hydrolysis of aclidinium bromide is butyrylcholinesterase. The influence of hepatic dysfunction on the pharmacokinetics of aclidinium bromide is not likely. Dose adjustments are not considered necessary for patients with hepatic impairment.

g) genetic polymorphism

The impact of genetic polymorphism on the PK of aclidinium bromide was not evaluated.

2.3.2 Based upon what is known about exposure-response relationships and their variability, and the groups studied (volunteers vs. patients); what dosage regimen adjustments, if any, are recommended for each of these subgroups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

a) Elderly

No dose adjustment is needed for elderly.

b) Gender

No dose adjustment is needed for women or men.

c) Race

The race effect was not evaluated.

d) Renal impairment

No dose adjustment is needed for renal impairment patients.

e) Hepatic impairment

No dose adjustment is needed for renal impairment patients.

f) Genetic polymorphism

Genotype data from subjects in clinical pharmacology studies were not submitted. The need for dose adjustment based on common drug metabolism gene variants cannot be determined.

g) Pregnancy and lactation

Aclidinium bromide should not be used during pregnancy and lactation as not adequate and well-controlled studies have been conducted.

2.4 Extrinsic Factors

2.4.1. What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

NA.

2.4.2. Drug-Drug Interactions

a) Is there an *in vitro* basis to suspect in vivo drug-drug interactions?

In vitro studies showed that aclidinium bromide is not like to have significant in vivo drug-drug interaction potential from a CYP enzymes perspective.

In vitro studies investigating the ability of aclidinium bromide and its major metabolites to inhibit (B.34273.24, 2006) or induce (XT093028, 2009) the most important CYP isozymes or to inhibit esterase activities (B.34273.N, 2008) indicated that neither aclidinium bromide nor its 2 main metabolites are likely to inhibit or induce the most important CYP enzymes or to inhibit esterases at the therapeutic dose.

P-glycoprotein is not expected to play a significant role in the absorption, distribution, metabolism, excretion of aclidinium bromide (PRD-RPT-EXP-00049, 2009). Furthermore, the absorption, distribution, metabolism, excretion of coadministered P-glycoprotein substrate drugs is not expected to be affected by aclidinium bromide or metabolites (PRD-RPT-EXP-00050, 2009).

b) is the drug a substrate of CYP enzymes?

No.

c) Is the drug an inhibitor and/or an inducer of CYP enzymes?

In vitro studies investigating the ability of aclidinium bromide and its major metabolites to inhibit (B.34273.24, 2006) or induce (XT093028, 2009) the most important CYP450 isozymes or to inhibit esterase activities (B.34273.N, 2008) indicated that neither aclidinium bromide nor its two main metabolites are likely to inhibit or induce the most important CYP450 enzymes or to inhibit esterases at the therapeutic dose.

The capacity of LAS 34273, and its hydrolysis products, LAS 34823 (alcohol derivative) and LAS 34850 (acid derivative) to inhibit the most important CYP450 enzymes in human liver microsomes was evaluated in B.34273.24. Both competitive inhibition and mechanism-based inhibition potential were evaluated at different concentrations (0, 0.1, 0.5, 1, 5, 25, 50, 100 μM) in this study.

Table 2.4.2: The in vitro inhibition IC50 for aclidinium, LAS 34823, and LAS 34850 to inhibit the most important CYP450 enzymes in human liver microsomes.

Enzyme	IC_{50} (μM)		
	LAS 34273	LAS 34823	LAS 34850
CYP1A2	> 100	> 100	> 100
CYP2A6	> 100	> 100	> 100
CYP2B6	> 100	> 100	> 100
CYP2C8	> 100	> 100	> 100
CYP2C9	> 100	> 100	> 100
CYP2C19	> 100	> 100	> 100
CYP2D6	2.4 (Ki 0.78)	20.6 (Ki 15.5)	> 100
CYP2E1	> 100	> 100	> 100
CYP3A4/5	88.1 (TST)	> 100	> 100
	91.8 (NIF)	> 100	> 100
CYP4A9/11	> 100	> 100	> 100

Following therapeutic inhalatory doses of LAS 34273 (200 μg/day), the total plasma Cmax values of LAS 34273, LAS 34823 and LAS 34850 are below 0.8 nM, 0.5 nM and 7.1 nM, respectively. Taking in consideration these low plasma concentrations and the results of this study, it can be concluded that clinically relevant doses of LAS 34273 would not be expected to alter the disposition of drugs metabolised by the human CYP450 enzymes examined.

d) is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

P-glycoprotein is not expected to play a significant role in the absorption, distribution, metabolism, excretion of aclidinium bromide (PRD-RPT-EXP-00049, 2009). Furthermore, the absorption, distribution, metabolism, excretion of coadministered P-glycoprotein substrate drugs is not expected to be affected by aclidinium bromide or metabolites (PRD-RPT-EXP-00050, 2009).

e) are there other metabolic/transporter pathways that may be important?

No.

f) does the label specify co-administration of another drug (e.g., combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?

Label did not specify co-administration of another drug in the treatment of COPD.

g) what other co-medications are likely to be administered to the target patient population?

No.

h) are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions or protein binding?

No

k) What issues related to dose, dosing regimens or administrations are unresolved, and represent significant omissions?

No.

2.4.3. Based upon what is known about exposure-response relationships and their variability, what dosage regimen adjustments, if any, do you recommend for each of these factors? If dosage regimen adjustments across factors are not based on the exposure-response relationships, describe the basis for the recommendation.

a) Smoking

No dose adjustment is needed.

b) Drug-drug interaction

No dose adjustment is needed.

2.5 General Biopharmaceutics

2.5.1 Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

Aclidinium bromide has not been classified as specific BCS class compound. Aclidinium bromide is sparingly soluble in methanol, very slightly soluble in water and in ethanol (b) (4)

Partition coefficient between 1-octanol and aqueous phosphate buffer ate pH 7.4 is logP=1.9.

2.5.2. What is the *in vivo* relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation in terms of comparative exposure?

The commercial formulation was used in two phase 2 studies and pivotal phase 3 trials. A bioequivalence study was not conducted between the to-be-marketed formulation and the clinical trial formulations as there was no need for it .

2.5.4. What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

The food effect on the PK was not evaluated as this is an inhalation route of administration.

2.6 Analytical Section

2.6.1 How are the active moieties identified and measured in the plasma and urine in the clinical pharmacology studies?

Aclidinium bromide and its metabolites in human biological samples were identified and quantified via validated analytical methods.

Analytical measurements of of aclidinium bromide and its metabolites in plasma and urine samples were measured with a validated analytical method.

The method from study LAS-PK-12 consisted of mixing the human plasma samples with the internal standards ([2H5] LAS34273, [2H3] LAS34823 and [2H6] LAS34850) and adding acetonitrile containing 5% formic acid to precipitate the plasma proteins in an ice bath. All analytes and their internal standards in the isolated supernatant were extracted using a mixture of methyl-tert-butyl ether and methylene chloride (3:2, v/v). After evaporation of the organic extract, the dry residue was reconstituted in 0.1 M formic acid. The components in the reconstituted sample were separated by a XDB Eclipse C18 column (50 x 4.6 mm, 1.8 µm particle size) and detected by electrospray ionization (ESI) mass spectrometry with MRM of positive (for aclidinium and LAS34823) and negative ion (for LAS34850 free acid).

The analysis of the urine samples generated in the clinical trials M/34273/05, M/34273/08 and M/34273/09 was conducted with a validated method at (b) (4) . The method was validated achieving a LLOQ of 0.02 ng/mL, 0.25 ng/mL and 2 ng/mL for aclidinium bromide, LAS34823 and LAS34850, respectively. In order to avoid the possible chemical hydrolysis of aclidinium bromide, urine samples were collected into tubes containing formic acid (5 µL formic acid per 1 mL of urine) and they were immediately stored deep frozen until analysis. The method consisted of solid phase extraction followed by LC-MS/MS analysis using three deuterated internal standards: one for aclidinium bromide ([2H5] aclidinium bromide, also known as LAS101789 or LAS34273-d5-phenyl); one for the alcohol metabolite LAS34823 ([2H5] LAS34823) and one for the acid metabolite LAS34850 ([2H6] LAS34850, also known as LAS101887 or dithienylglycolic acid-d6).

2.6.2 Which metabolites have been selected for analysis and why?

The alcohol (LAS34823) and the acid derivative (LAS34850) were measured as they are main metabolites. However, this review focused on aclidinium bromide as the two main metatbolites are not active metabolites.

2.6.3 Howe was the assay performed for aclidinium bromide, LAS34823, and LAS34850?

The analytical methods performed for aclidinium bromide, LAS34823, and LAS34850 were validated. Bioanalytical methods were validated for the quantification of total aclidinium bromide (LAS34273) and its two main metabolites, the alcohol (LAS34823) and the acid derivative (LAS34850) in all human matrices analysed. The parameters validated were sensitivity, selectivity, lower limit of quantification, linearity, precision, accuracy, recovery, matrix effects, carry over, dilution effect and stability.

a) what is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

The range of standard curve in various studies is shown in the following table. The linear regression with the weighting factor of 1/x2 was used for the standard curve fitting.

Table 2.6.3. Application of the LC-MS/MS Validated Analysis Methods to Routine Analysis of Aclidinium Bromide and its Metabolites in Plasma Samples of Clinical Studies

PK Study No.	*Bioanalytical Study Report No. (year)*	*Analytical Method Validation ID*	*Aclidinium Bromide*	*LAS34823*	*LAS34850*
			LLOQ / Linearity range QCs: Inter-assay Precision (CV%) and Accuracy (% deviation)	*LLOQ / Linearity range QCs: Inter-assay Precision (CV%) and Accuracy (% deviation)*	*LLOQ / Linearity range QCs: Inter-assay Precision (CV%) and Accuracy (% deviation)*
M/34273/00	(b) (4) 34273/0001 5 (2001)	(b) (4)	0.5 ng/mL / 0.5-100.0 ng/mL >20% / >20%	0.5 ng/mL / 0.5-100.0 ng/mL <14.2% / <15.0%	5.0 ng/mL / 5.0-400.0 ng/mL <15.0% / <4.0%
M/34273/01	B.34273.02 (2002)		0.1 ng/mL / 0.1-10.0 ng/mL <10.0% / <4.6%	0.1 ng/mL / 0.1-10.0 ng/mL <7.8% / <6.2%	1.0 ng/mL / 1.0-20.0 ng/mL <10.8% / <4.2%
M/34273/04	PRD-RPT-BDM-00163 (2008)		5.0 pg/mL / 5.0-200.0 pg/mL <8.0% / <5.2%	5.0 pg/mL / 5.0-200.0 pg/mL <7.1% / <8.6%	100 pg/mL / 100-2000.0 pg/mL <5.1% / <3.5%
M/34273/05	PRD-RPT-BDM-00096 (2008)		5.0 pg/mL / 5.0-200.0 pg/mL <7.4% / <3.7%	5.0 pg/mL / 5.0-200.0 pg/mL <8.7% / <3.4%	100 pg/mL / 100-2000.0 pg/mL <3.7% / <3.6%
M/34273/06	B.34273.17 (2004)		0.05 ng/mL/ 0.05-2.0 ng/mL <10.1% / <3.1%	0.05 ng/mL/ 0.05-2.0 ng/mL <9.7% / <3.6%	0.5 ng/mL / 0.5-15.0 ng/mL <11.0% / <3.2%
M/34273/08	0655/158 (2007)		5.0 pg/mL / 5.0-200.0 pg/mL <8.5% / <5.0%	5.0 pg/mL / 5.0-200.0 pg/mL <13.1% / <2.0%	100 pg/mL / 100-2000.0 pg/mL <5.9% / <3.1%
M/34273/09	PRD-RPT-BDM-00122 (2008)		5.0 pg/mL / 5.0-200.0 pg/mL <6.6% / <4.6%	5.0 pg/mL / 5.0-200.0 pg/mL <10.1% / <6.2%	100 pg/mL / 100-2000.0 pg/mL <4.8% / <7.0%
M/34273/11	B.34273.23 (2004)		0.05 ng/mL/ 0.05-2.0 ng/mL <8.9% / <3.3%	0.05 ng/mL/ 0.05-2.0 ng/mL <8.5% / <1.3%	0.5 ng/mL / 0.5-15.0 ng/mL <9.7% / <4.5%
M/34273/21	B.34273.14 (2002)		0.1 ng/mL / 0.1-10.0 ng/mL <13.5 % / <3.4%	0.1 ng/mL / 0.1-10.0 ng/mL <6.8% / <8.1%	1.0 ng/mL / 1.0-20.0 ng/mL <11.3% / <8.8%
LAS-PK-12	PRD-RPT-BDM-00294 (2009)		5.0 pg/mL / 5.0-200.0 pg/mL <7.5% / <6.2%	5.0 pg/mL / 5.0-200.0 pg/mL <4.3% / <6.5%	100 pg/mL / 100-2000.0 pg/mL <5.3% / <3.6%

PK Study No.	*Bioanalytical Study Report No. (year)*	*Analytical Method Validation ID*	*Aclidinium Bromide*	*LAS34823*	*LAS34850*
			LLOQ / Linearity range QCs: Inter-assay Precision (CV%) and Accuracy (% deviation)	*LLOQ / Linearity range QCs: Inter-assay Precision (CV%) and Accuracy (% deviation)*	*LLOQ / Linearity range QCs: Inter-assay Precision (CV%) and Accuracy (% deviation)*
M/34273/05	0655/179 (2008)	(b) (4) urine	0.02 ng/mL / 0.02-2.00 ng/mL <6.3% / <5.4%	0.25 ng/mL / 0.25-25.0 ng/mL <11.1% / <9.0%	2.00 ng/mL / 2.00-200 ng/mL <5.1% / <4.6%
M/34273/08	0655/159 (2008)	urine	0.02 ng/mL / 0.02-2.00 ng/mL <7.0% / <14.2%	0.25 ng/mL / 0.25-25.0 ng/mL <3.4% / <2.0%	2.00 ng/mL / 2.00-200 ng/mL <3.1% / <4.8%
M/34273/09	0655/157 (2008)	urine	0.02 ng/mL / 0.02-2.00 ng/mL <7.5% / <6.8%	0.25 ng/mL / 0.25-25.0 ng/mL <4.3% / <4.3%	2.00 ng/mL / 2.00-200 ng/mL <4.5% / <1.4%

b) what are the lower and upper limits of quantification (LLOQ/ ULOQ) and what is the accuracy and precision at these limits?

Characteristics of relevant HPLC-MS/MS methods used in clinical studies for the determination of aclidinium bromide, LAS34823, and LAS34850 concentrations are summarized in the following table:

Table 2.6.4. Summary of Intra-Assay Variability and of Inter-Assay Variability Obtained Drugin the Validation of the LC-MS/MS Analytical Methods Used in Pharmacokinetic Studies

Report No. of Analytical Method Validation	*Sample*	*Target Substance/LLOQ*	*Intra-Assay Variability (QCs: Low, Medium, High)*		*Inter-Assay Variability (QCs: Low, Medium, High)*		*PK Study in which Method was used*	*Study Site*
			Precision (%CV)	*Accuracy (% Bias)*	*Precision (%CV)*	*Accuracy (% Bias)*		
(b) (4) /34273/00014 (2001)	Plasma	LAS34273 / 0.5 ng/mL LAS34823 / 0.5 ng/mL LAS34850 / 5 ng/mL	3.0 – 4.8 3.3 – 9.7 2.5 – 6.1	-2.8– 10.8 -5.4 – -4.4 -9.4 – 0.0	3.6 – 11.7 3.6 – 4.4 4.3 – 4.9	-7.9 – -4.8 -10.1 – -7.7 -8.9 – 0.2	M/34273/00	(b) (4)
B.34273.01 (full validation, 2002)	Plasma	LAS34273 / 0.1 ng/mL LAS34823 / 0.1 ng/mL LAS34850 / 1 ng/mL	2.3 – 10.5 1.9 – 13.5 3.8 – 11.5	-13.9 – 4.2 -10.5 – 9.2 -12.1 – 5.3	11.6 – 5.6 7.5 – 11.4 8.6 – 11.0	-4.7 – -0.4 -3.9 – 3.4 -4.5 – 0.0	M/34273/01 M/34273/21	
B.34273.16 (partial validation, 2004)	Plasma	LAS34273 / 0.02[a] ng/mL LAS34823 / 0.02[a] ng/mL LAS34850 / 0.5 ng/mL	2.7 – 5.5 2.7 – 7.1 2.2 – 5.8	-8.7 – 6.6 0.0 – 2.8 -11.2 – -2.6	--	--	M/34273/06 M/34273/11	
0655/149 (full validation, 2007) 0655/176 (partial validation, 2008)	Plasma	LAS34273 / 5 pg/mL LAS34823 / 5 pg/mL LAS34850 / 100 pg/mL	3.8 – 7.3 4.5 – 9.8 3.7 – 7.6	-3.3 – 3.0 -10.9 – 6.0 -1.8 – 5.3	8.6 – 13.0 7.5 – 12.8 3.9 – 12.9	0.7 – 5.0 -2.1 – 4.0 -7.8 – -0.7	M/34273/08	
PRD-RPT-BDM-0087 (full validation, 2008) PRD-RPT-BDM-0088 (full validation, 2008)	Plasma	LAS34273 / 5 pg/mL LAS34823 / 5 pg/mL LAS34850 / 100 pg/mL	1.8 – 4.3 1.7 – 6.9 1.6 – 4.0	-8.5 – 3.3 -7.2 – 9.8 -2.3 – 4.6	2.7 – 5.5 3.6 – 8.6 2.4 – 3.4	-4.2 – 0.5 -1.3 – 1.3 -0.9 – 1.5	M/34273/04 M/34273/05 M/34273/09	
PRD-RPT-BDM-00268 (full validation, 2009)	Plasma	LAS34273 / 5 pg/mL LAS34823 / 5 pg/mL LAS34850 / 100 pg/mL	0.9 – 7.5 1.2 – 8.0 2.0 - 7.2	-3.5 – 5.0 -5.7 – 0.8 -3.2 – 6.3	2.7 – 5.2 2.9 – 4.9 3.7 – 4.6	-1.5 – 2.7 -4.1 – -1.7 0.4 – 6.0	LAS-PK-12	
0655/151 (full validation, 2008)	Urine	LAS34273 / 0.02 ng/mL LAS34823 / 0.25 ng/mL LAS34850 / 2 ng/mL	2.1 – 4.9 1.4 – 3.3 1.5 – 3.6	-5.5 – -1.0 -4.8 – -3.0 -6.2 – -1.9	6.3 – 6.8 2.7 – 3.5 2.5 – 4.7	3.0 – 6.9 -3.6 – -3.0 -1.2 – 0.0	M/34273/05 M/34273/08 M/34273/09	

Source: Page 27 of 43 in 2.7.1 Summary of Biopharmaceutics

c) what is the sample stability under the conditions used in the study? (long-term, freeze-thaw, sample-handling, sample transport, autosampler)

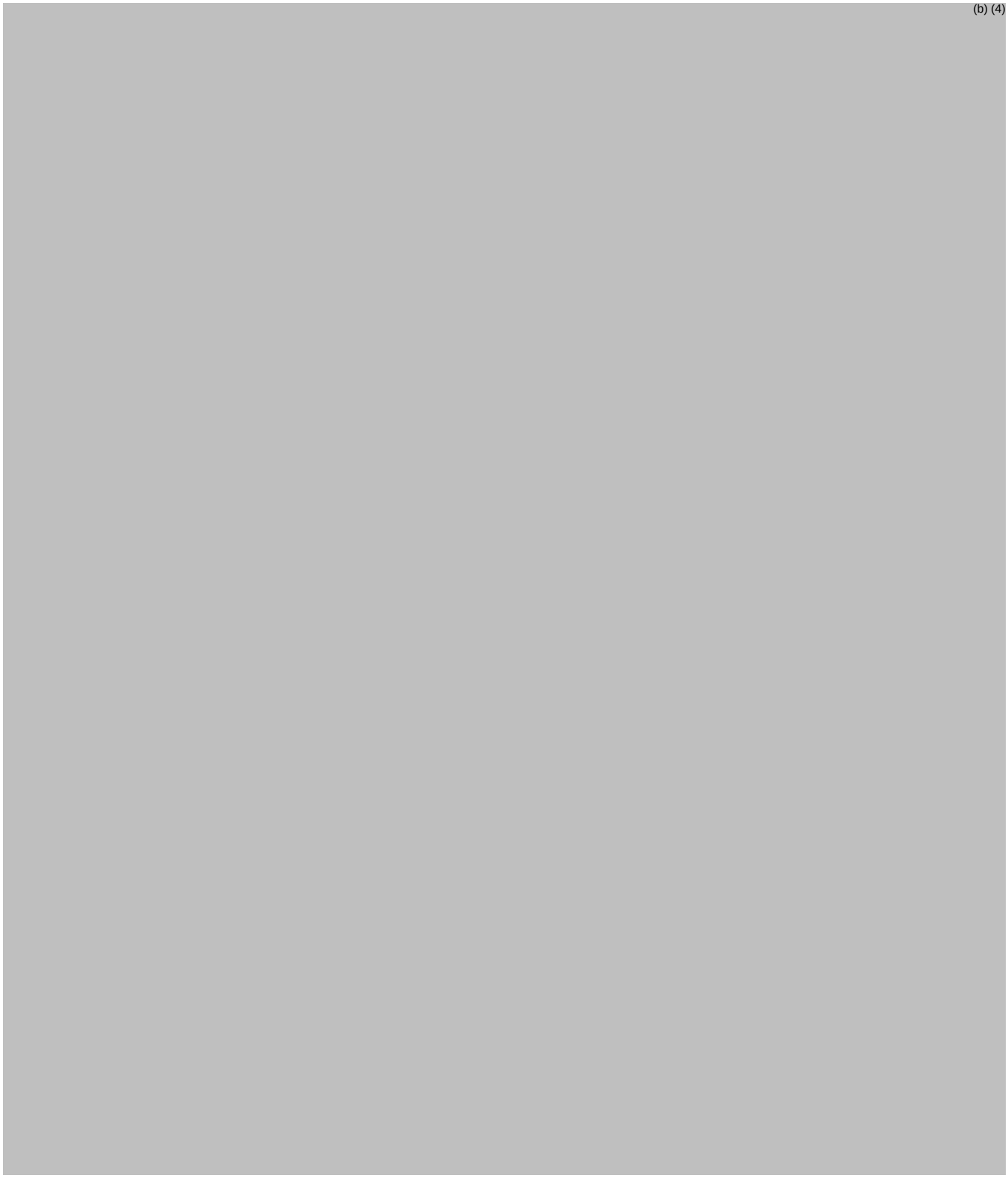
Stability of aclidinium bromide and its two main metabolites under processing and storage conditions was demonstrated in stabilized plasma samples for freeze-thaw stability in at least 3 additional freeze-thaw cycles at -70 °C (sample thaw carried out in an ice bath), short-term bench-top for at least 24 hours at +4°C and for at least 6 hours in an ice-bath. Long-term stabilized plasma freezer stability at -70 °C was established for at least 716 days (PRD-RPT-BDM-00308, 2009). Similar stabilities were also demonstrated for aclidinium bromide and its two main metabolites under processing and storage conditions in stabilized urine samples for freeze-thaw stability in at least 3 additional freeze-thaw cycles (sample thaw carried out at room temperature) and shortterm bench-top for at least 6 hours at room temperature. Long-term stabilized urine freezer stability at -70 °C was established for at least 9 months (Report 06551/151, 2008).

Autosampler stability (extract stability) in support of injection of samples during sample analysis and stability of the stock solutions during experimental use was also demonstrated. All analyses were carried out within established stabilities.

3. Detailed Labeling Recommendations

(b) (4)

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page



4. Appendixes

4.1 Pharmacometric Review

Office of Clinical Pharmacology:
Pharmacometric Review

1 Summary of Findings

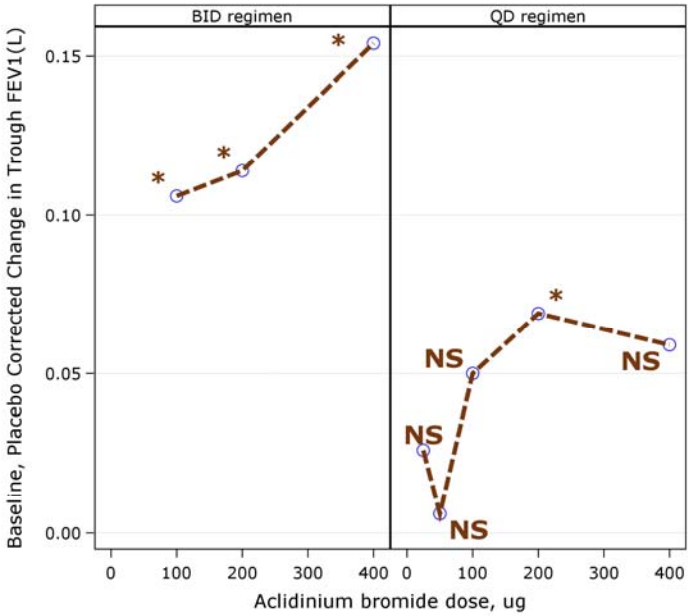
1.1 Key Review Questions

The purpose of this review is to address the following key questions.

1.1.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) with regards to efficacy?

Figure shows the relationship between aclidinium bromide dose (once-daily, QD or twice-daily, BID) and changes in trough FEV1 in dose-finding studies. The BID dosing regimen was studied based on feedback from Agency after completion of Phase 3 program of QD dosing regimen (Refer to 2 Pertinent regulatory background in this review for more details).

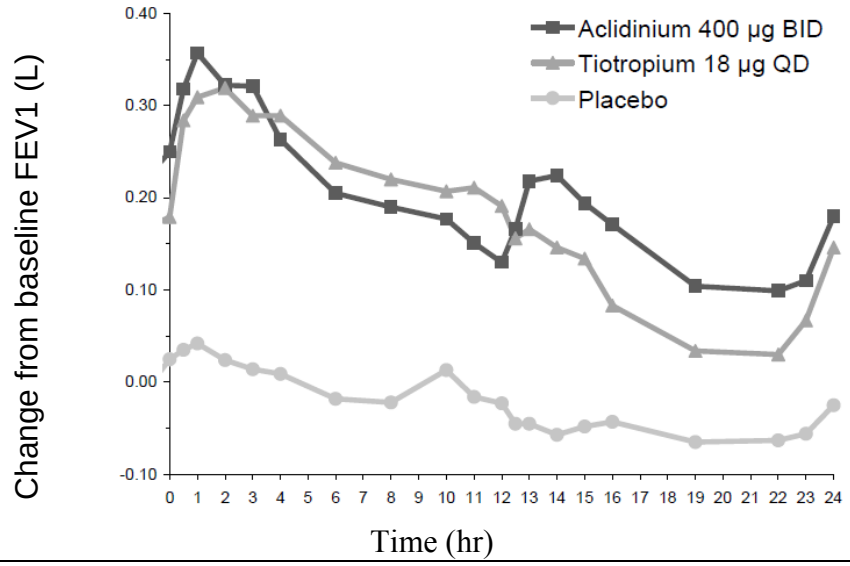
Figure 1. Relationship between aclidinium bromide dose, ug and baseline, placebo corrected change in trough FEV1 on day 7 in study M/34271/39 (BID regimen) and LAS-MD-CL22 (QD regimen) (Phase 2 dose finding studies).



Source: Data from table 2.2.2-1 on page 71 in summary-clin-effectiveness-ise-vol1.pdf and from table 9 on page 59 in las-md-cl22.pdf

Figure shows the time course of bronchodilatory effects (change from baseline FEV1) on day 15, in study M/34271/23, when aclidinium bromide (400 ug) is administered using BID regimen. Also shown is the time course of bronchodilatory effects after QD administration of tiotropium (18 ug).

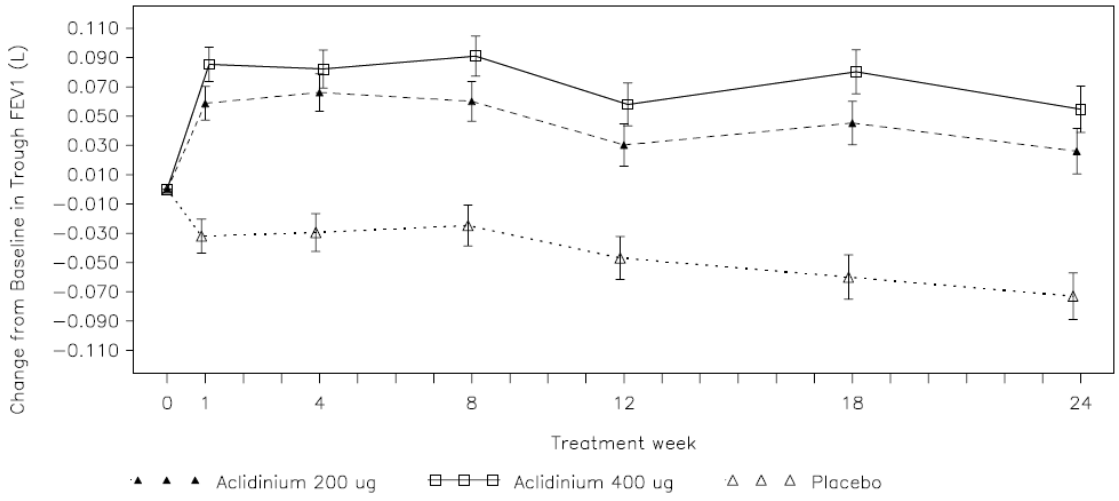
Figure 2. Time course of bronchodilatory effects (change from baseline FEV1) after administration of aclidinium bromide using BID regimen in Study M/34271/23 (Phase 2 dosing regimen finding study).



Source: Figure 2.2.1-1 on page 69 in summary-clin-effectiveness-ise-vol1.pdf

Figure shows the mean changes from baseline, up to week 24, in trough FEV1 in Phase 3 study (M34273/34). The data suggests that treatment effects attained early (Week 1) in the study are maintained till Week 24.

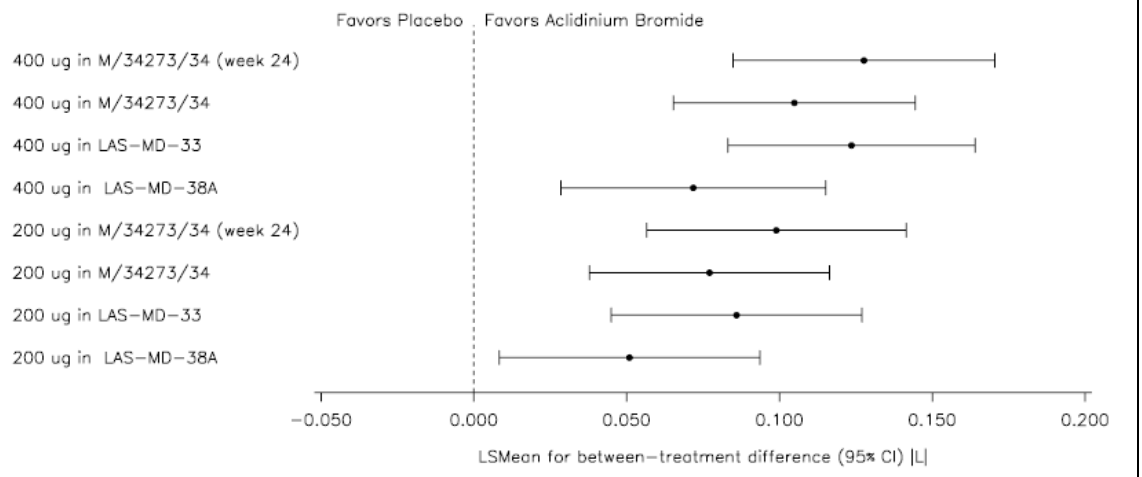
Figure 3. Least Square Mean Changes from Baseline up to Week 24 in Trough FEV1 by Treatment in Study M/34273/34 — ITT Population



Source: Figure 2.1.1-1 on page 40 in summary-clin-effectiveness-ise-vol1.pdf

Figure shows the baseline, placebo-corrected change in trough FEV1 at Week 12 after 200 and 400 µg dose administered BID in Phase 3 studies. Shown also are treatment differences at week 24 in M/34273/34.

Figure 4. Treatment Differences (Aclidinium Bromide 200 µg and 400 µg BID versus Placebo) in Least Square Means (and 95% CIs) for Changes from Baseline to Week 12 in Trough FEV1 in the Phase 3 Efficacy Studies M/34273/34, LAS-MD-33, and LAS-MD-38 (Part A) — ITT Populations.



CI = confidence interval; FEV_1 = forced expiratory volume in one second; ITT = intent to treat; LS = least square.

Source: Figure 3.2.1.1-1 on page 92 in summary-clin-effectiveness-ise-vol1.pdf

Based on the effects of aclidinium bromide in Phase 3 studies, sponsor is seeking the following indication

"The recommended dosage for patients with COPD is one inhalation of (b) (4) 400 mcg twice daily."

Reviewer's Comments: The sponsor has adequately characterized the relationship between dose and changes in trough FEV1. The relationship between concentrations and changes in trough FEV1 have not been characterized. Better bronchodilatory effects are obtained with BID dosing regimen when compared to QD dosing regimen. If there are no safety issues with 400 ug dose administered BID, then the proposed dose and dosing regimen are acceptable.

1.1.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) with regards to safety?

Sponsor did not evaluate the relationship between aclidinium concentration and safety measures. The sponsor did not submit any datasets containing aclidinium serum concentrations.

1.2 Recommendations

NA

1.3 Label Statements

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font.

2 Pertinent regulatory background

Aclidinium bromide is a novel, potent, long-acting antimuscarinic agent under development for the long-term maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema.

The clinical development program was originally focused on development of aclidinium bromide as a QD treatment regimen for patients with COPD. In anticipation of submitting an NDA in 2009 for the QD regimen, Forest Laboratories, Inc., obtained feedback from the Divison (Pulmonary and Allergy Drug Products) on the completeness of the application. At a pre-NDA meeting held on March 3, 2009, the Division responded that while the results of the 2 Phase 3 studies (M/34273/30, M/34273/31) demonstrated statistical significance versus placebo for the primary endpoint of trough FEV1, the treatment difference of 0.061 L was of "uncertain clinical significance," and recommended "exploration of higher doses and more frequent dosing regimens to ensure the selection of the most appropriate and efficacious dose of aclidinium bromide for marketing."

In response to the Division's feedback at the March 3, 2009, pre-NDA meeting, Forest evaluated a higher and more frequent dosing regimen and generated new data for aclidinium bromide at doses ranging from 100 µg to 800 µg BID.

The clinical efficacy program for aclidinium bromide 200 and 400 µg, administered BID was conducted in North America, Europe, Russia, South Africa, and Latin America. The program comprised 3 Phase 3 efficacy studies with 1933 randomized patients (M/34273/34, LAS-MD-33, and LAS-MD-38 [Part A]) and 5 supportive studies, 2 Phase 2 dose-range finding studies with 109 randomized patients (M/34273/23 and M/34273/29), and 3 long-term safety studies with 1344 randomized patients (LAS-MD-35, LAS-MD-36, and LAS-MD-38 [Part B]).

The product is an inhalation powder, an adhesive mixture of micronized aclidinium bromide and α-lactose monohydrate, contained within a device-metered dry-powder inhaler (DPI). The proposed metered dose is 1 inhalation of 400 µg aclidinium bromide twice daily (BID).

3 Results of Sponsor's Analysis

NA

4 Reviewer's Analysis

NA

4.1 Introduction

NA

4.2 Objectives

NA

4.3 Methods

4.3.1 Data Sets

Data sets used are summarized in Table 1.

Table 1. Analysis Data Sets

Study Number	Name	Link to EDR

4.3.2 Software

NA

4.3.3 Models

4.3.4 Results

5 Listing of Analyses Codes and Output Files

File Name	Description	Location in \\cdsnas\pharmacometrics\

4.2 Individual Study Review

Study No.: (b) (4)/10

Study Title: Interspecies comparison of in vitro plasma protein binding of aclidinium bromide.

Objectives:

Methods: Plasma protein binding of [^{14}C]-aclidinium bromide in human, mouse, rat, rabbit and dog was investigated using dialysis cell systems. Two [^{14}C]-radiolabelled forms of aclidinium bromide, labelled in the phenyl and glycolyl moieties, were used. [^{14}C-U-phenyl]-aclidinium bromide had the radiolabel placed in the position shared with the alcohol metabolite and [^{14}C-U-glycolyl]-aclidinium bromide had the radiolabel placed in the position shared with the acid metabolite. Human plasma was tested in duplicate at aclidinium bromide concentrations of 0.05, 0.1, 0.5, 1, 5 and 25 μg/mL. The degree of protein binding of [^{14}C]-aclidinium bromide to human serum albumin (40 g/L) and human α-1 acid glycoprotein (2 g/L) was also determined at 0.1 and 1 μg/mL.

Results: The extent of plasma protein binding was independent of concentration. However, the degree of protein binding differed based on the position of the radiolabel, with the glycolyl moiety being more highly plasma protein bound than the phenyl moiety.

Table 1.2.1.1–1 Protein Binding of [^{14}C–phenyl]–labelled and [^{14}C–glycolyl]–labelled Aclidinium Bromide in Human Plasma, Serum Albumin and α–1 Acid Glycoprotein (Study (b) (4)10)

Radiolabelled form of aclidinium bromide	Statistic	Protein binding (%)		
		Human plasma	Human serum albumin	Human α-1 acid glycoprotein
[^{14}C-glycolyl]-labelled	Mean (SD)	87.3 (2.3)	89.9 (0.5)	83.7 (1.1)
[^{14}C-phenyl]-labelled	Mean (SD)	15.1 (3.0)	9.61 (2.2)	82.8 (1.2)

Conclusions: The main plasma protein binding of aclidinium bromide and its hydrolysis products would be to albumin *in vivo*.

M/34273/05

Study Title: A Phase I, randomized, single-dose, two-part study to evaluate the safety and tolerability of a*clidinium bromide* administered intravenously and to assess the absolute bioavailability of inhaled a*clidinium bromide* in healthy male subjects

Objectives:
Part I
To evaluate the safety and tolerability of single ascending doses of IV *aclidinium bromide* in healthy male subjects based on clinical laboratory tests results, vital sign results, ECG findings, and AEs to determine the MTD of IV *aclidinium bromide*.
Part II
To estimate the absolute bioavailability of *aclidinium bromide* administered by inhalation via the Almirall inhaler.

Study Design: This was a two-part study. Part I was a single-blind, three-period, placebo-controlled study of alternating single-ascending intravenous (IV) doses of *aclidinium bromide*. Following all assessments in Part I, the Investigator and sponsor jointly evaluated all safety and tolerability data of the treatments administered to confirm the maximum tolerated dose (MTD) of *aclidinium bromide*. Additionally, in Part I, pharmacokinetic data were obtained, although these data were not used for determination of the MTD. Part II was an op en-label, single-dose, two-period, crossover study of IV and inhaled doses of *aclidinium bromide*. Pharmacokinetic data were also obtained in Part II.

In Part I, 12 subjects were randomized (1:1) to 1 of 2 treatment groups (Treatment G roup A or B) and participated in 3 treatment periods, with ascending dose levels alternating between groups. Subjects received 2 doses of *aclidinium bromide* and one dose of matching

placebo. Treatment periods were separated by a washout phase of at least 7 days. In addition, Treatment Groups A and B were separated by 7 days. Each subject received a single dose of *aclidinium bromide* or placebo by IV infusion over 5 minutes in each treatment period. Each subject resided at the CRU from the morning of Day -1 (the day before d osing) to the morning of Day 2 (24 hours post-dose) in each treatment period. All subjects participated in a post-study telephone assessment 7 days after the end-of-study evaluation. Dose: 25, 50, 100, 200, 300, 400 mg single dose by IV infusion over 5 minutes.

In Part II, 12 subj ects were randomi zed (1:1) to 1 of 2 treatment groups (Treatment Group C or D) and participated in 2 treatment periods. Su bjects received a single 200 µg dose of *aclidinium brom ide* in each treatment period, by IV infusion over 5 minutes in one treatment period and from the Almirall Inhaler by inhalation of a single puff on one occasion in the alternate treatment period. After each study drug a dministration, the subjects we re followed for a total of 48 hours and left the clinic after the last assessment. Treatment periods were separated by a washout phase of at least 7 days.

Study Population: Healthy male subjects, aged 18 to 45 years.

Data Analysis: Serial blood sampling for PK assessment (*aclidinium bromide*, LAS34850 and LAS34823). Measurements of vital signs, ECG, clinical laboratory and monitoring of AE.

Pharmacokinetic Results: Summary statistics of pharmacokinetic parameters are shown the table below:
Part 1
aclidinium bromide

Parameter	*Aclidinium Bromide*					
	25 µg IV (N=3)	50 µg IV (N=4)	100 µg IV (N=4)	200 µg IV (N=4)	300 µg IV (N=3)	400 µg IV (N=4)
AUC(0-t) (pg.h/mL)	247.5 (37.1)	307.9 (36.0)	857.5 (25.2)	1537.7 (36.8)	2285.8 (21.0)	2365.9 (29.7)
AUC(0-4 h) (pg.h/mL)	249.0 (37.2)	309.5 (36.0)	860.2 (25.3)	1539.6 (36.7)	2288.0 (20.9)	2367.8 (29.7)
AUC(0-6 h) (pg.h/mL)	249.0 (37.2)	309.5 (36.0)	861.5 (25.1)	1541.3 (36.9)	2290.4 (21.0)	2370.5 (29.7)
AUC(0-∞) (pg.h/mL)	NC [a] NC	[b] NC	[b] 154	5.4 (37.0)	2296.1 (21.1)	2539.2 (30.2) [c]
C_{max} (pg/mL)	1536.3 (36.6)	2009.0 (34.7)	5873.3 (26.8)	10605.9 (32.4)	15363.2 (27.4)	17282.4 (30.4)
t_{max} (h)	0.08 (0.08-0.13)	0.10 (0.10-0.17)	0.11 (0.08-0.15)	0.08 (0.08-0.08)	0.10 (0.08-0.10)	0.08 (0.08-0.08)
$t_{1/2}$ (h)	NC [a] NC	[b] NC	[b] 0.83	(80.7)	1.02 (80.6)	1.35 (92.2) [c]
λ_z (1/h)	NC [a] NC	[b] NC	[b] 1.83	(114.7)	0.98 (57.1)	0.81 (60.2) [c]
CL (L/h)	NC [a] NC	[b] NC	[b] 140.4	(28.4)	135.2 (23.9)	169.7 (35.7) [c]
V_z (L)	NC [a] NC	[b] NC	[b] 140.0	(56.0)	185.3 (66.6)	302.4 (79.1) [c]

Arithmetic mean (CV%) data are presented for all parameters with the exception of t_{max} for which median (min-max) are presented

NC = Not calculated

[a] N = 1; [b] N = 2; [c] N = 3

LAS34850

Parameter	*Aclidinium Bromide*					
	25 µg IV (N=3)	50 µg IV (N=4)	100 µg IV (N=4)	200 µg IV (N=4)	300 µg IV (N=3)	400 µg IV (N=4)
AUC(0-t) (pg.h/mL)	819.7 (16.5)	3215.5 (22.2)	6787.0 (7.1)	14180.9 (19.0)	19453.4 (23.2)	27806.7 (22.9)
AUC(0-∞) (pg.h/mL)	1207.0 (11.0)	3798.5 (19.3)	7463.2 (7.5)	15692.5 (18.0)	21766.1 (21.9)	30510.5 (21.1)
C_{max} (pg/mL)	495.9 (12.4)	1432.4 (16.9)	2662.4 (20.5)	6255.7 (8.7)	8801.4 (24.0)	11218.5 (15.3)
t_{max} (h)	0.25 (0.13-0.25)	0.13 (0.10-0.25)	0.13 (0.10-0.27)	0.25 (0.25-0.25)	0.25 (0.10-0.28)	0.25 (0.25-0.25)
$t_{1/2}$ (h)	2.27 (10.2)	3.50 (27.3)	3.62 (7.8)	3.90 (14.4)	4.04 (12.4)	4.22 (17.0)
λ_z (1/h)	0.31 (9.8)	0.21 (26.4)	0.19 (7.8)	0.18 (14.1)	0.17 (11.6)	0.17 (16.8)

Arithmetic mean (CV%) data are presented for all parameters with the exception of t_{max} for which median (min-max) are presented

LAS34823

Parameter	*Aclidinium Bromide*					
	25 µg IV (N=3)	50 µg IV (N=4)	100 µg IV (N=4)	200 µg IV (N=4)	300 µg IV (N=3)	400 µg IV (N=4)
AUC(0-t) (pg.h/mL)	137.5 (39.9)	330.5 (28.7)	656.0 (16.3)	1460.3 (14.7)	2156.8 (21.4)	2646.1 (17.8)
AUC(0-∞) (pg.h/mL)	NC [a]	340.2 (28.3)	711.5 (13.6) [b]	1485.1 (14.5)	2180.7 (20.9)	2675.4 (17.8)
C_{max} (pg/mL)	377.8 (32.4)	1090.4 (20.3)	2178.3 (25.0)	4877.7 (16.7)	7244.5 (47.2)	9737.7 (21.7)
t_{max} (h)	0.08 (0.08-0.13)	0.10 (0.10-0.17)	0.11 (0.08-0.15)	0.08 (0.08-0.08)	0.10 (0.08-0.10)	0.08 (0.08-0.08)
$t_{1/2}$ (h)	NC [a]	1.10 (14.2)	2.17 (24.5) [b]	2.79 (17.7)	2.48 (18.0)	2.76 (12.2)
λ_z (1/h)	NC [a]	0.64 (14.8)	0.33 (23.0) [b]	0.25 (18.6)	0.29 (19.0)	0.25 (12.2)

Arithmetic mean (CV%) data are presented for all parameters with the exception of t_{max} for which median (min-max) are presented

NC = Not calculated

[a] N = 2, [b] N = 3

Part 2
aclidinium bromide

Parameter	*Aclidinium Bromide* 200 µg (Inhaled) (N=12)	200 µg (IV) (N=12)
AUC(0-t) (pg.h/mL)	257.9 (104.9)	1915.3 (38.8)
AUC(0-4 h) (pg.h/mL)	57.2 (48.1)	1727.0 (40.6)
AUC(0-6 h) (pg.h/mL)	71.1 (52.8)	1744.1 (40.4)
AUC(0-∞) (pg.h/mL)	76.8 (43.5) [a] 181	6.3 (53.7) [b]
C_{max} (pg/mL)	52.7 (63.8)	9882.4 (39.4)
t_{max} (h)	0.09 (0.05, 0.35)	0.10 (0.08-0.13)
$t_{1/2}$ (h)	2.64 (43.8) [a] 0.68	(129.3) [b]
λ_z (1/h)	0.30 (40.0) [a] 2.62	(63.4) [b]
CL (L/h)	3051.1 (43.0) [a] 146.2	(59.8) [b]
V_z (L)	10343.3 (30.1) [a] 94.9	(80.9) [b]

Arithmetic mean (CV%) data are presented for all parameters with the exception of t_{max} for which median (min-max) are presented
[a] N = 5; [b] N = 6

A summary of the absolute bioavailability of *aclidinium bromide* for the inhaled formulation, based on the ratio for AUC(0-4 h) and AUC(0-6 h), between the inhaled and IV formulation, is presented in the following table:

	200 µg *Aclidinium Bromide* (Inhaled)	
	F (%) based on AUC(0-4 h)	F (%) based on AUC(0-6 h)
Overall (N=12)	3.48 (38.8) 4.37	(52.1)

Arithmetic mean (CV%) data are presented

The urinary pharmacokinetic parameters of *aclidinium bromide* following inhalation and IV administration are presented in the following table:

Parameter	*Aclidinium Bromide* 200 µg (Inhaled) (N=12)	*Aclidinium Bromide* 200 µg (IV) (N=12)
Ae (ng)	329.5 (33.7) 544	8.0 (19.5)
fe (%)	0.16 (33.7)	2.72 (19.5)
CL_R (mL/min) based on: AUC(0-t) AUC(0-6 h)	 64.4 (84.4) 87.0 (39.4)	 55.5 (48.1) 60.3 (43.7)

Arithmetic mean (CV%) data are presented

The mean pharmacokinetic parameters of LAS34850 following inhaled and IV doses of *aclidinium bromide* are presented in the following table:

Parameter	*Aclidinium Bromide* 200 µg (Inhaled) (N=12)	*Aclidinium Bromide* 200 µg (IV) (N=12)
AUC(0-t) (pg.h/mL)	9616.2 (16.9)	15273.1 (15.1)
AUC(0-∞) (pg.h/mL)	10812.8 (15.4)	16272.8 (14.5)
C_{max} (pg/mL)	1141.8 (24.4)	5506.3 (28.0)
t_{max} (h)	3.00 (2.00, 4.08)	0.12 (0.08-0.28)
$t_{1/2}$ (h)	5.57 (21.8)	4.07 (16.0)
λ_z (1/h)	0.13 (20.5)	0.17 (13.9)

Arithmetic mean (CV%) data are presented for all parameters with the exception of t_{max} for which median (min-max) are presented

The urinary pharmacokinetic parameters of LAS34850 following inhalation and IV administration of *aclidinium bromide* are presented in the following table:

Parameter	*Aclidinium Bromide* 200 µg (Inhaled) (N=12)	200 µg (IV) (N=12)
Am1 (ng)	15506.8 (18.3)	25940.4 (6.5)
fe (%)	15.6 (18.3)	26.2 (6.5)
CL_R (mL/min) based on AUC(0-t)	25.1 (9.8)	27.5 (12.8)

Arithmetic mean (CV%) data are presented

The mean pharmacokinetic parameters of LAS34823 following inhaled and IV doses of *aclidiniumbromide* are presented in the following table:

Parameter	*Aclidinium Bromide* 200 µg (Inhaled) (N=12)	200 µg (IV) (N=12)
AUC(0-t) (pg.h/mL)	235.9 (84.4)	1766.2 (37.1)
AUC(0-∞) (pg.h/mL)	310.7 (76.7) [a] 179	2.2 (37.3)
C_{max} (pg/mL)	43.4 (47.6) 528	9.3 (29.0)
t_{max} (h)	0.50 (0.08-1.50)	0.10 (0.08-0.13)
$t_{1/2}$ (h)	8.23 (53.5) [a] 2.68	(58.3)
λ_z (1/h)	0.10 (41.5) [a] 0.31	(38.6)

Arithmetic mean (CV%) data are presented for all parameters with the exception of t_{max} for which median (min-max) are presented
[a] N = 11

The urinary pharmacokinetic parameters of LAS34823 following inhalation and IV administration of *aclidinium bromide* are presented in the following table:

Parameter	Aclidinium Bromide	
	200 µg (Inhaled) (N=12)	200 µg (IV) (N=12)
Am2 (ng)	8546.0 (53.1) 269	32.1 (45.5)
fe (%)	7.89 (53.1)	24.9 (45.5)
CL_R (mL/min) based on AUC(0-t)	637.6 (21.1)	251.6 (14.0)

Arithmetic mean (CV%) data are presented

Conclusions: The maximum tolerated IV dose of *aclidinium bromide* was not reached in Part I of this study. Single ascending IV doses of 25 to 400 µg, and a 200 µg inhaled dose, of *aclidinium bromide* were well tolerated when administered to healthy male subjects. There was no apparent treatment or dose-related trends in laboratory values, vital signs or 12-lead ECG parameters, or any dose-relationship in the incidence of TEAEs, following IV and inhaled administration of *aclidinium bromide*.

The absolute bioavailability (F) of *aclidinium bromide*, was low following a single inhaled 200 µg dose, with mean values of < 5% (values for individual subjects ranged from approximately 1.6% to 9.1%). Absolute bioavailability calculated using AUC(0-4 h) and AUC(0-6 h) was considered reliable, and clearly reflects the fraction of nominal administered *aclidinium bromide* dose that is systemically available. The use of a truncated AUC for the calculation of F instead of using AUC(0-∞) as stated in the protocol, was a consequence of inconsistent extended pharmacokinetic profiles of *aclidinium bromide* found in Part II of the study for 5 subjects following IV administration and for a further 5 subjects following inhalation.

Following IV administration of 25 to 400 µg *aclidinium bromide* to healthy subjects, maximum plasma concentrations appeared rapidly in plasma, with a mean tmax of 5 to 6 minutes (0.08 to 0.11 hours) after the start of the IV infusion at each dose level. Following Cmax, the plasma levels of *aclidinium bromide* declined rapidly and most of the concentrations measured beyond 45 minutes after the start of the IV infusion were close to the LLOQ of the bioanalytical method. There were no apparent trends in the apparent elimination half-life for *aclidinium bromide* with values, ranging from 0.1 to 2.8 hours, being subject to a high degree of variability (arithmetic CV% > 80%). In general, the rate and extent of exposure were subject to a high degree of variability.

Visual analysis of the single-dose pharmacokinetic parameters of *aclidinium bromide* indicated that exposure, based on mean AUC(0-t), and maximum systemic exposure, based on Cmax, increased in a proportional manner with increasing dose across the 50 to 300 µg dose range. At the 300 µg IV dose level, exposure to *aclidinium bromide* reached a plateau, with AUC(0-t) and Cmax being similar at the 300 and 400 µg doses.

Aclidinium bromide was subject to very rapid clearance from the body, with individual values ranging from 83.7 to 286.1 L/h across the 25 to 400 µg *aclidinium bromide* IV dose range. The mean apparent volume of distribution during the terminal phase for *aclidinium bromide* appeared to increase with ascending dose from 200 to 400 µg *aclidinium bromide* IV, from 140 to 302 L, respectively, although individual subject data at all dose levels were highly variable.

Maximum concentrations of LAS34850 occurred at a median tmax of 8 to 15 minutes after the start of the IV infusion at each dose level. The exposure of LAS34850 was 3 to 12-times higher

than for *aclidinium bromide* across the 25 to 400 µg *aclidinium bromide* IV dose range, and generally increased in a dose-proportional manner. Maximum concentrations of LAS34823 occurred at a median tmax of 5 to 6 minutes after the end of the IV infusion at each dose level. The mean AUC for LAS34823 was generally similar to, or slightly lower than *aclidinium bromide*, and mean Cmax values were lower than the parent drug at all dose levels. Both AUC and Cmax generally increased in a dose-proportional manner with ascending *aclidinium bromide* dose.

Maximum plasma concentrations of LAS34850 appeared at a median tmax of 3 hours post-dose following administration of *aclidinium bromide* via the Almirall Inhaler. Mean systemic exposure of LAS34850, based on AUC(0-t), was 37% lower following inhalation of *aclidinium bromide* compared to that observed following IV administration. Maximum plasma concentrations of LAS34823 appeared approximately 25 minutes later following inhalation of *aclidinium bromide* compared to the IV dose, with individual subject data being more variable.

The urinary excretion of *aclidinium bromide* was very low, with a mean of 0.16% and 2.72% being eliminated up to 48 hours post-dose following a 200 µg inhaled and IV dose, respectively. The fraction of the *aclidinium bromide* dose excreted as LAS34850 in the urine was markedly higher than that of *aclidinium bromide* for both formulations, with mean values of 16% and 26% being eliminated up to 48 hours post-dose following the inhaled and IV dose, respectively. The fraction of the dose excreted as LAS34823 in the urine following IV administration of *aclidinium bromide* was similar to LAS34850, with 25% being eliminated up to 48 hours post-dose suggesting that equimolar amounts of these metabolites are formed after the hydrolysis of the parent drug. Following administration of *aclidinium bromide* via the Almirall Inhaler, the fraction of the dose excreted as LAS34823 in the urine was approximately 3-times lower than that following IV infusion.

Renal clearance of LAS34850 was approximately 2-times higher than that of *aclidinium bromide*, with little apparent difference between the inhaled and IV formulations. Renal clearance of LAS34823 was markedly higher than for *aclidinium bromide* and LAS34850. Following 200 µg *aclidinium bromide* IV, renal clearance of LAS34823 was approximately 4- to 5-times higher than *aclidinium bromide*, and 8- to 9-times higher than for LAS34850. Following administration of *aclidinium bromide* via the Almirall Inhaler, renal clearance of LAS34823 was approximately 10-times higher than *aclidinium bromide*, and 22- to 23-times higher than for LAS34850. The main fraction of the dose administered by inhalation or by IV infusion over 5 minutes was recovered in urine as parent drug and metabolites within the first 12 hours post-dose.

LAS-PK-12

Study Title: A randomized multiple dose, placebo controlled, single blind clinical trial to assess the safety, tolerability, and pharmacokinetics of aclidinium bromide administered twice daily by inhalation in healthy volunteers

Objectives:

The objective of this study was to assess the safety, tolerability, and pharmacokinetics of aclidinium bromide following twice-daily, multiple-dose administration from the (b) (4) multidose dry-powder inhaler.

Study Design: Randomized, single-blind, placebo-controlled multiple-dose clinical trial. Thirty healthy male and female subjects received doses of aclidinium bromide or placebo twice a day (BID) for 7 consecutive days. The Sponsor and the Principal Investigator evaluated safety assessments and confirmed tolerability before the next scheduled higher dose strength of aclidinium bromide was administered.
Cohort A: 200 μg aclidinium bromide (or placebo) BID for 7 days
Cohort B: 400 μg aclidinium bromide (or placebo) BID for 7 days
Cohort C: 800 μg aclidinium bromide (or placebo) BID for 7 days

Study Population: 30 healthy male and female subjects (8 active/2 placebo per cohort).

Data Analysis: Serial blood sampling for PK assessment (*aclidinium bromide*, LAS34850 and LAS34823). Measurements of vital signs, ECG, clinical laboratory and monitoring of AE.

Pharmacokinetic Results: Summary statistics of pharmacokinetic parameters are shown in the table below:
aclidinium bromide

Pharmacokinetic Parameters (Mean, %CV) for Aclidinium, LAS34823, and LAS34850 After Single-Dose Administration of 200, 400, and 800 µg Aclidinium Bromide on Day 1			
Parameter	***Aclidinium***		
	200 µg	***400 µg***	***800 µg***
C_{max}, pg/mL	102.74, 51.40	194.23, 45.21	360.06, 62.01
T_{max}, h	0.08, 0.00	0.08, 0.00	0.10, 56.84
$T_{½}$, h	2.35, 28.42	5.91, 39.80	4.49, 63.01
AUC_{τ}, pg • h/mL	97.64, 40.24	324.88, 34.43	494.66, 37.59
$AUC_{0-\infty}$, pg • h/mL	109.40, 35.76	386.69, 34.83	566.34, 46.04
Parameter	***LAS34823***		
	200 µg	***400 µg***	***800 µg***
C_{max}, pg/mL	46.66, 43.08	76.30, 25.95	174.85, 35.07
T_{max}, h	0.26, 192.59	0.61, 103.02	0.75, 125.99
$T_{½}$, h	12.44, 98.94	11.25, 66.97	9.37, 38.66
AUC_{τ}, pg • h/mL	229.39, 41.40	464.66, 19.80	1106.57, 31.55
$AUC_{0-\infty}$, pg • h/mL	475.49, 81.67	809.09, 33.21	1881.72, 44.02
Parameter	***LAS34850***		
	200 µg	***400 µg***	***800 µg***
C_{max}, pg/mL	1011.75, 15.67	2151.90, 13.49	5272.08, 28.68
T_{max}, h	3.38, 15.33	3.63, 20.52	3.63, 32.77
$T_{½}$, h	3.81, 15.17	4.22, 22.19	4.06, 7.61
AUC_{τ}, pg • h/mL	7378.83, 8.54	16,153.34, 7.83	34,997.13, 21.16
$AUC_{0-\infty}$, pg • h/mL	8746.15, 7.61	20,022.40, 12.38	42,176.87, 21.66
A summary of the PK parameters of aclidinium after the morning and evening doses on Day 7 following BID dosing of 200 µg, 400 µg, and 800 µg aclidinium bromide for 7 days is presented below:			
Pharmacokinetic Parameters (Mean, %CV) for Aclidinium After the Day 7 Morning and Evening Doses Following Twice-Daily Administration of 200, 400, and 800 µg Aclidinium Bromide for 7 Days			
Parameter	***Morning***		
	200 µg	***400 µg***	***800 µg***
$C_{max,ss}$, pg/mL	119.91, 37.09	254.71, 56.97	377.14, 62.65
$C_{min,ss}$, pg/mL	5.98, 69.97	19.51, 68.02	20.88, 36.38
T_{max}, h	0.14, 109.11	0.20, 164.05	0.08, 0.00
$T_{½}$, h	12.41, 103.88	6.77, 32.05	6.41, 24.88
λ_z, 1/h	0.10, 69.67	0.11, 30.92	0.11, 24.37
$AUC_{\tau,ss}$, pg • h/mL	190.66, 42.67	535.76, 51.85	651.14, 43.45

$C_{av,ss}$, pg/mL	16.70, 34.81	44.65, 51.85	54.26, 43.35
PTF%	725.57, 47.86	570.42, 55.50	636.37, 50.70
CL/F, L/h	1233.08, 47.99	959.58, 52.99	1431.15, 41.02
$V_{z/F}$, L	19,451.35, 92.88	9796.50, 70.45	13,186.31, 45.31
Parameter	***Evening***		
	200 µg	***400 µg***	***800 µg***
$C_{max,ss}$, pg/mL	63.21, 49.86	240.47, 60.57	307.80, 86.51
$C_{min,ss}$, pg/mL	7.22, 61.85	19.52, 55.61	22.07, 54.16
T_{max}, h	0.16, 96.65	0.10, 56.84	0.10, 56.84
$T_{½}$, h	10.93, 61.75	17.03, 40.80	16.30, 26.35
λ_z, 1/h	0.08, 61.22	0.05, 40.41	0.05, 37.51
$AUC_{\tau,ss}$, pg • h/mL	164.44, 42.65	468.35, 49.54	594.37, 51.61
$C_{av,ss}$, pg/mL	14.04, 38.14	39.03, 49.54	49.53, 51.61
PTF%	413.80, 55.33	611.43, 51.85	520.93, 34.54
CL/F, L/h	1466.00, 52.14	1106.00, 60.48	1608.64, 40.10
$V_{z/F}$, L	18,570.19, 38.01	24,998.78, 54.78	36,686.18, 46.29

A summary of the PK parameters of LAS34823 on Day 7 following the morning and evening doses of 200 µg, 400 µg, and 800 µg aclidinium bromide BID for 7 days is presented below:

Pharmacokinetic Parameters (Mean, %CV) for LAS34823 After the Day 7 Morning and Evening Doses Following Twice-Daily Administration of 200, 400, and 800 µg Aclidinium Bromide for 7 Days

Parameter	***Morning***		
	200 µg	***400 µg***	***800 µg***
$C_{max,ss}$, pg/mL	90.13, 38.87	168.62, 26.44	378.11, 50.41
$C_{min,ss}$, pg/mL	36.64, 55.18	63.72, 29.98	121.28, 33.82
T_{max}, h	0.31, 160.65	1.35, 149.31	1.04, 66.81
$T_{½}$, h	10.72, 18.37	9.38, 28.48	12.53, 73.35
λ_z, 1/h	0.07, 18.95	0.08, 33.04	0.07, 38.80
$AUC_{\tau,ss}$, pg • h/mL	636.56, 47.10	1229.42, 29.77	2238.11, 27.06
$C_{av,ss}$, pg/mL	53.05, 47.10	102.45, 29.77	186.51, 27.06
PTF%	107.28, 25.83	106.17, 33.00	146.68, 89.92
CL/F, L/h	358.96, 32.84	351.76, 30.31	384.69, 31.79
$V_{z/F}$, L	5378.18, 28.09	4736.84, 34.85	6992.00, 84.56

Parameter	*Evening*		
	200 µg	***400 µg***	***800 µg***
$C_{max,ss}$, pg/mL	94.44, 32.78	185.48, 42.39	293.06, 37.42
$C_{min,ss}$, pg/mL	36.84, 52.72	65.04, 32.81	136.94, 43.78
T_{max}, h	0.34, 92.10	0.59, 95.32	0.36, 127.56
$T_{½}$, h	20.90, 21.35	26.00, 51.70	19.90, 23.68
λ_z, 1/h	0.03, 18.77	0.03, 43.34	0.04, 22.02
$AUC_{\tau,ss}$, pg • h/mL	602.86, 44.07	1218.76, 28.35	2203.69, 34.11
$C_{av,ss}$, pg/mL	50.24, 44.07	101.56, 28.35	183.64, 34.11
PTF%	132.41, 61.43	116.21, 42.49	90.60, 54.56
CL/F, L/h	378.28, 34.37	359.58, 36.71	407.36, 38.09
$V_{z/F}$, L	11,617.34, 45.47	12,188.40, 34.39	11,274.91, 31.72
A summary of the PK parameters of LAS34850 after the morning and evening doses on Day 7 following BID dosing of 200 µg, 400 µg, and 800 µg aclidinium bromide for 7 days is presented below:			
Pharmacokinetic Parameters (Mean, %CV) for LAS34850 After the Day 7 Morning and Evening Doses Following Twice-Daily Administration of 200, 400, and 800 µg Aclidinium Bromide for 7 Days			
Parameter	*Morning*		
	200 µg	***400 µg***	***800 µg***
$C_{max,ss}$, pg/mL	1581.47, 26.35	3726.27, 22.36	4853.28, 14.94
$C_{min,ss}$, pg/mL	575.94, 25.86	1368.09, 36.05	1652.33, 20.29
T_{max}, h	3.00, 17.82	3.31, 26.68	3.13, 20.51
$T_{½}$, h	6.10, 24.41	6.45, 18.98	5.48, 15.84
λ_z, 1/h	0.12, 19.60	0.11, 22.88	0.13, 17.81
$AUC_{\tau,ss}$, pg • h/mL	13,045.17, 25.56	30,721.93, 25.42	39,629.97, 12.80
$C_{av,ss}$, pg/mL	1087.10, 25.56	2560.16, 25.42	3302.50, 12.80
PTF%	92.79, 14.62	94.40, 17.91	96.81, 11.35
CL/F, L/h	16.34, 27.88	13.86, 28.53	20.46, 12.32
$V_{z/F}$, L	145.95, 46.75	124.91, 20.37	161.99, 20.25
A summary of the PK parameters of LAS34850 after the morning and evening doses on Day 7 following BID dosing of 200 µg, 400 µg, and 800 µg aclidinium bromide for 7 days is presented below:			

Pharmacokinetic Parameters (Mean, %CV) for LAS34850 After the Day 7 Morning and Evening Doses Following Twice-Daily Administration of 200, 400, and 800 µg Aclidinium Bromide for 7 Days

Parameter	*Evening*		
	200 µg	***400 µg***	***800 µg***
$C_{max,ss}$, pg/mL	1125.92, 17.39	2644.85, 30.55	3999.88,15.15
$C_{min,ss}$, pg/mL	570.71, 27.07	1385.83, 27.49	1886.50, 11.97
T_{max}, h	4.06, 44.83	3.06, 30.78	3.88, 25.57
$T_{½}$, h	11.84, 28.35	14.77, 46.58	12.37, 27.01
λ_z, 1/h	0.06, 22.93	0.05, 28.67	0.06, 22.47
$AUC_{\tau,ss}$, pg • h/mL	10,840.67, 21.37	25,289.52, 28.08	37,975.44, 14.49
$C_{av,ss}$, pg/mL	903.39, 21.37	2107.46, 28.08	3164.62, 14.49
PTF%	63.52, 22.74	59.60, 26.63	66.14, 16.40
CL/F, L/h	19.26, 23.63	17.48, 41.39	21.48, 15.07
$V_{z/F}$, L	332.74, 40.97	345.71, 36.30	380.61, 28.29

Pharmacokinetic Results

Aclidinium

Mean aclidinium Day 1 C_{max} values were 102.74, 194.23, and 360.06 pg/mL for the 200 µg, 400 µg, and 800 µg BID treatment groups, respectively, while Day 1 AUC_τ values were 97.64, 324.88, and 494.66 pg • h/mL. Mean Day 1 $T_{½}$ estimates ranged from 2.4 to 5.9 hours. PK parameters obtained on Day 7 following BID aclidinium bromide administration demonstrated that steady state was achieved, as comparable C_{max}, minimum plasma drug concentration (C_{min}), and AUC_τ were observed after morning and evening administration of aclidinium bromide. Nevertheless, considering the short $T_{½}$ of aclidinium, the steady state was probably reached soon after the first dose. The mean steady-state morning C_{max} values were 119.91, 254.71, and 377.14 pg/mL, and the mean steady-state evening C_{max} values were 63.21, 240.47, and 307.80 pg/mL for the 200 µg, 400 µg, and 800 µg BID treatment groups, respectively. The mean steady-state morning AUC_τ values were 190.66, 535.76, and 651.14 pg • h/mL, and the mean steady-state evening AUC_τ values were 164.44, 468.35 and 594.37 pg • h/mL for the 200 µg, 400 µg, and 800 µg BID treatment groups, respectively. No significant differences were observed between the maximum plasma concentrations achieved after the first dose and those at steady state. The $T_{½}$ estimates were larger on Day 7 than Day 1. This difference may be related to the availability of more non-zero values for the terminal slope on Day 7 as compared with Day 1.

LAS34823

Mean Day 1 C_{max} values were 46.66, 76.30, and 174.85 pg/mL for the 200 µg, 400 µg, and 800 µg BID treatment groups, respectively; the Day 1 AUC_τ values were 229.29, 464.66, and 1106.57 pg • h/mL. The mean T_{max} ranged from 0.26 to 0.75 hours, and the mean Day 1 $T_{½}$ ranged from 9.4 to 12.4 hours.

PK parameters obtained on Day 7 following BID aclidinium bromide administration demonstrated that the steady state was reached. The mean steady-state morning C_{max} values were 90.13, 168.62, and 378.11 pg/mL, and the mean steady-state evening C_{max} values were 94.44, 185.48, and 293.06 pg/mL for the 200 µg, 400 µg, and 800 µg BID treatment groups, respectively. The mean steady-state morning AUC_τ values were 636.56, 1229.42, and 2238.11 pg • h/mL, and the mean steady-state evening AUC_τ values were 602.86, 1218.76, and 2203.69 pg • h/mL for the 200 µg, 400 µg, and 800 µg BID treatment groups, respectively. The $T_{½}$ estimates were larger on Day 7 than Day 1. This difference may be related to the availability of more non-zero values for the terminal slope on Day 7 as compared with Day 1.

LAS34850 The mean Day 1 C_{max} values were 1011.75, 2151.90, and 5272.08 pg/mL for the 200 µg, 400 µg, and 800 µg BID treatment groups, respectively. The Day 1 AUC_{τ} values were 7378.83, 16,153.34, and 34,997.13 pg • h/mL. The mean T_{max} ranged from 3.4 to 3.6 hours, and the mean Day 1 $T_{½}$ estimates ranged from 3.8 to 4.2 hours. PK parameters obtained on Day 7 following BID aclidinium bromide administration demonstrated that the steady state was reached. The mean steady-state morning C_{max} values were 1581.47, 3726.27, and 4853.28 pg/mL, and the mean steady-state evening C_{max} values were 1125.92, 2644.85, and 3999.88 pg/mL for the 200 µg, 400 µg, and 800 µg BID treatment groups, respectively. The mean steady-state morning AUC_{τ} values were 13,045.17, 30,721.93, and 39,629.97 pg • h/mL, and the mean steady-state evening AUC_{τ} values were 10,840.67, 25,289.52, and 37,975.44 pg • h/mL for the 200 µg, 400 µg, and 800 µg BID treatment groups, respectively. The $T_{½}$ estimates were larger on Day 7 than Day 1. This difference may be related to the availability of more non-zero values for the terminal slope on Day 7 as compared with Day 1.
Safety/Tolerability: No deaths, serious adverse events or premature discontinuations were reported in this study. No TEAEs were reported in the twice daily aclidinium bromide 200 µg dose cohort. Eight TEAEs were reported by 6 subjects in the aclidinium group (3 subjects in the 400 µg dose and 3 subjects in the 800 µg dose) and 1 TEAE was reported by 1 patient in the placebo group. The only TEAE reported by more than 1 subject was dry mouth (1 subject in the aclidinium bromide 800 µg group and 1 subject in placebo). All other TEAEs were reported by one subject each. One patient in the aclidinium 800 µg dose group reported 3 TEAEs. Overall, there were no clinically meaningful changes in any laboratory parameter or vital sign measurement. During the PK profiling periods, relative to predose on the day of ECG collection, there were no clinically relevant ECG abnormalities. Conclusions: All doses of aclidinium bromide were generally safe and well tolerated. PK steady state was achieved for all analytes following administration of aclidinium bromide BID for 7 days. Aclidinium bromide exhibited time-independent pharmacokinetics following dosing to steady state, indicating that similar concentration versus time profiles will occur after repeated administration at the same dose and frequency. Exposures for all moieties increased with increasing dose but in a less than dose-proportional manner.

M/34273/04 (LAS-PK-04)

Study Title: A randomized, open-label, single-dose study to assess the metabolism and excretion of a*clidinium bromide* following an intravenous administration of [14C] *aclidinium bromide* in healthy individuals.

Objectives:
To determine the rates and routes of elimination of radioactivity after IV administration of [14C] *aclidinium bromide* in healthy subjects, and to characterise and identify the metabolites of *aclidinium bromide* in plasma and excreta.
To assess the safety and tolerability of a single IV dose of [14C] *aclidinium bromide* based on clinical laboratory parameters, physical examination, electrocardiograms (ECGs), vital sign assessments and adverse events (AEs).

Study Design: This was a single-dose, open-label, single-centre study. Twelve subjects were randomised, 6 received Treatment A: a single IV dose of 400 µg of [phenyl-U-^{14}C] *aclidinium bromide* and 6 subjects received Treatment B: a single IV dose of 400 µg of [glycolyl-U-^{14}C] *aclidinium bromide*. Each dose contained a approximately 40 µCi of radioactivity and was administered as a 5-minute infusion. Subjects were required to remain awake in the semi-recumbent position for 4 hours after drug administration.

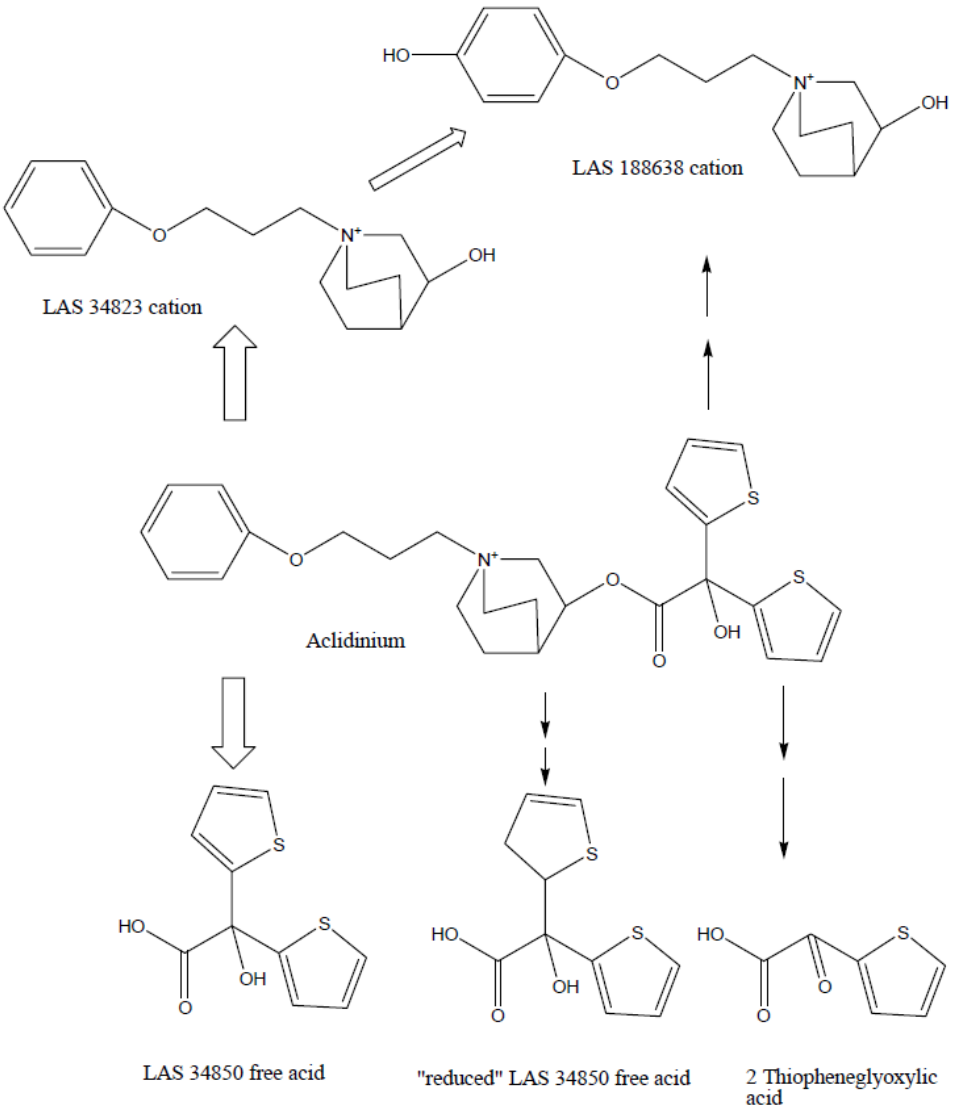
Each subject resided at the CRU for at least 9 days (from Day -1 until the last sample collection on Day 8) and until two consecutive urine and faecal samples contained a radioactivity level less than 3-times the background level or the cumulative radioactivity in the excreta for 1 day was less than 1% of the radioactivity in the administered dose. A follow-up visit was performed within 7 days of study completion or within 7 days.

Study Population: 12 healthy males, aged 18-45 years.

Data Analysis: The PK parameters were calculated, for plasma and whole blood total radioactivity, and *aclidinium bromide* and its two main metabolites (LAS34850 and LAS34823) in plasma. Mass balance in the excretion for radioactivity measured in urine and feces over the collection interval.

Pharmacokinetic Results:

The proposed metabolic pathway of *aclidiium* in healthy male subjects is as follows:



The pharmacokinetic parameters of LAS34850 and LAS34823 following IV doses of 400 µg *aclidinium bromide* are presented in the following table:

Pharmacokinetic parameter	LAS34850: following 400 µg [phenyl-U-^{14}C] *aclidinium bromide* (N=6)	LAS34823: following 400 µg [glycolyl-U-^{14}C] *aclidinium bromide* (N=6)
AUC_{0-t} (pg.h/mL)	26500 (11.1)	2340.4 (26.9)
$AUC_{0-\infty}$ (pg.h/mL)	27487 (11.2)	2366.8 (26.8)
C_{max} (pg/mL)	14444 (19.4)	11460 (23.5)
t_{max} (h)	0.09 (0.08 - 0.20)	0.08 (0.08 - 0.10)
$t_{1/2}$ (h)	3.41 (13.1)	2.70 (28.2)
λ_z (1/h)	0.21 (12.4)	0.28 (28.9)

Arithmetic mean (CV%) data are presented for all parameters with the exception of t_{max} for which median (min-max) are presented)

Total Radioactivity in Plasma and Whole Blood

The pharmacokinetic parameters of total radioactivity in plasma are presented in the following table:

Pharmacokinetic Parameter of Total Radioactivity in Plasma	400 µg [phenyl-U-^{14}C] *aclidinium bromide* (N=6)	400 µg [glycolyl-U-^{14}C] *aclidinium bromide* (N=6)
AUC_{0-t} (ng eq.h/mL)	12.8 (20.3)	105.0 (10.3)
$AUC_{0-\infty}$ (ng eq.h/mL)	18.5 (22.2)	111.6 (9.72)
C_{max} (ng eq/mL)	24.5 (48.6)	42.2 (18.5)
t_{max} (h)	0.09 (0.08 - 0.20)	0.08 (0.08 - 0.10)
$t_{1/2}$ (h)	8.63 (28.5)	13.3 (22.2)
λ_z (1/h)	0.09 (24.3)	0.05 (25.9)

Arithmetic mean (CV%) data are presented for all parameters with the exception of t_{max} for which median (min-max) are presented

The pharmacokinetic parameters of total radioactivity in whole blood are presented in the following table:

Pharmacokinetic Parameter of Total Radioactivity in Whole Blood	400 µg [phenyl-U-^{14}C] *aclidinium bromide* (N=6)	400 µg [glycolyl-U-^{14}C] *aclidinium bromide* (N=6)
AUC_{0-t} (ng eq.h/mL)	2.31 (26.9)	46.9 (14.4)
$AUC_{0-\infty}$ (ng eq.h/mL)	3.35 (21.1)	52.2 (13.0)
C_{max} (ng eq/mL)	10.8 (53.5)	21.4 (15.1)
t_{max} (h)	0.09 (0.08 - 0.20)	0.08 (0.08 - 0.10)
$t_{1/2}$ (h)	1.19 (82.4)	5.53 (13.3)
λ_z (1/h)	0.95 (59.0)	0.13 (14.2)

Arithmetic mean (CV%) data are presented for all parameters with the exception of t_{max} for which median (min-max) are presented

Maximum mean concentrations of total radioactivity in plasma and whole blood were observed at the end of the 5-minute infusion, following both the [phenyl-U-^{14}C] and

[glycolyl-U-^{14}C] aclidinium bromide treatments. Following the IV administration of [glycolyl-U-^{14}C] aclidinium bromide, the AUC0-t (8.2-fold) and C_{max} (1.7-fold) of plasma radioactivity were higher than those following the IV administration of [phenyl-U-^{14}C] aclidinium bromide. Similarly, following the intravenous administration of [glycolyl-U-^{14}C] aclidinium bromide, the AUC_{0-t} (20.3-fold) and C_{max} (2.0-fold) of blood radioactivity were higher than those following the IV administration of [phenyl-U-^{14}C] aclidinium bromide. Because aclidinium is rapidly hydrolyzed to its alcohol (LAS34823 cation) and acid (LAS34850 free acid) metabolites, the difference in radioactivity concentration probably indicates that the clearance of the acid metabolite is slower than the clearance of the alcohol metabolite and/or its metabolite(s).

The mean apparent $t_{1/2}$ of total plasma and whole blood radioactivity was 8.6 and 1.2 hours, respectively for the [phenyl-U-^{14}C] aclidinium bromide treatment and longer, at 13.3 and 5.5 hours, respectively, for the [glycolyl-U-^{14}C] aclidinium bromide treatment.

The excretion of total radioactivitv in urine and faeces is summarised in the following table:

Matrix	Excretion of Total Radioactivity (%) up to 192 Hours Post-dose	
	400 µg [phenyl-U-^{14}C] *aclidinium bromide* (N=6)	400 µg [glycolyl-U-^{14}C] *aclidinium bromide* (N=6)
Urine	64.7 (3.3)	54.1 (4.2)
Faeces	32.5 (3.4)	19.9 (3.0)
Urine and Faeces	97.3 (0.6)	74.0 (1.4)

Arithmetic mean (± SD) data are presented
N = number of subjects

For the [phenyl-U-^{14}C] and [glycolyl-U-^{14}C] treatments, the predominant route of excretion was renal. For the [phenyl-U-^{14}C] treatment, approximately 65% of the dose (total radioactivity) was excreted in urine and 33% was excreted in faeces through to the last collection interval, with most of the administered radioactivity being recovered in the first 96 hours post-dose (93%). For the [glycoyl-U-^{14}C] treatment, approximately 54% of the dose (total radioactivity) was excreted in urine and 20% was excreted in faeces through to the last collection interval, with most of the administered radioactivity following the [glycoyl-U-^{14}C] treatment being recovered in the first 120 hours post-dose (72%).

- Maximum concentrations of total radioactivity in plasma and whole blood, *aclidinium bromide*, LAS34850 free acid and LAS34823, were observed at the end of the 5-minute infusion, following both the [phenyl-U-^{14}C] and [glycolyl-U-^{14}C] *aclidinium bromide* treatments.

- For the [phenyl-U-^{14}C] and [glycolyl-U-^{14}C] treatments, the predominant route of excretion was renal. For the [phenyl-U-^{14}C] treatment, approximately 65% of the dose (total radioactivity) was excreted in urine and 33% was excreted in faeces through to the last collection interval, with most of the administered radioactivity being recovered in the first 96 hours post-dose (93%). For the [glycoyl-U-^{14}C] treatment, approximately 54% of the dose (total radioactivity) was excreted in urine and 20% was excreted in faeces through to the last collection interval, with most of the administered radioactivity following the [glycoyl-U-^{14}C] treatment being recovered in the first 120 hours post-dose (72%).
- Following the [phenyl-U-^{14}C] *aclidinium bromide* dose, *aclidinium* was eliminated as LAS34823 cation and LAS188638 (*p*-hydroxy LAS34823) metabolites based on the radioactivity measurement in the HPLC analysis (metabolite profile). No additional radioactive metabolite in significant quantity was observed in the metabolite profile following the [phenyl-U-^{14}C] *aclidinium bromide* dose. Following the [glycolyl-U-^{14}C] *aclidinium bromide* dose, *aclidinium* was eliminated as LAS34850 free acid, 2-thiopheneglyoxylic acid, and "reduced" LAS 34850 free acid metabolites based on the metabolite profile. Similarly, no additional radioactive metabolite in significant quantity was observed in the metabolite profile following the [glycolyl-U-^{14}C] *aclidinium bromide* dose. Therefore, it appeared that the *aclidinium bromide* dose was eliminated as LAS34823, *p*-hydroxy LAS34823, LAS34850 free acid, 2-thionpheneglyoxylic acid and "reduced" LAS 34850 free acid metabolites.
- All metabolites of *aclidinium bromide* appeared to be produced by hydrolysis directly (hydrolysis alone) or indirectly (hydrolysis plus additional metabolic transformation or *vice versa*). As no additional metabolite in significant quantity was observed, it may be concluded that almost the entire dose of *aclidinium bromide* was eliminated by hydrolysis to its alcohol (LAS34823 cation) and acid (LAS34850 free acid) metabolites. Following the hydrolysis of the *aclidinium bromide*, approximately 50% of the alcohol metabolite (LAS34823 cation) from hydrolysis was eliminated as *p*-hydroxy LAS34823, and the remaining LAS34823 cation metabolite was excreted as unchanged LAS34823 cation. In addition, approximately 30% of the acid metabolite (LAS34850 free acid) from hydrolysis was eliminated as 2-thiopheneglyoxylic acid and the "reduced" LAS34850 free acid metabolites, and the remaining LAS34850 free acid metabolite was excreted as unchanged LAS34850 free acid metabolite. It is highly possible that LAS34273 was metabolised first and then hydrolysed to these three polar metabolites of the acid metabolite because the acid metabolite was not metabolised by human hepatocytes in an *in vitro* study.
- IV doses of *aclidinium bromide* at a dose level of 400 µg are considered safe and well tolerated when administered to healthy male subjects.

M/34273/01

Study Title: A randomized, single ascending dose, alternating placebo controlled, single blind clinical trial, to assess the tolerability and pharmacokinetics of LAS34273 administered by inhalation in healthy male volunteers.

Objectives: 1. to assess the tolerability and maximum tolerated dose of single doses of LAS34273. 2. to determine the PK profile of LAS34273 at single doses.

Study Design: This is a phase 1, single center, single ascending dose, randomized, single blind, alternating placebo-controlled group clinical trial.

Study Population: 16 subjects (healthy male volunteers aged from 18 to 45 years old) received either a single dose of LAS34273 or placebo

Data Analysis: PK variables in plasma and urine.

Pharmacokinetic Results: Over the dose range up to 6000 ug, dose proportionality could not be demonstrated for LAS34273, and two metabolites.

M/34273/06

Study Title: A randomized, multiple-dose, placebo controlled, crossover, single blind clinical study to assess the safety, tolerability, and PK *of LAS34273* administered by inhalation in healthy individuals.

Objectives: To assess the safety, tolerability, and pK of LAS-34273 after multiple doses by a multiple dose dry powder inhaler.

Study Design: A randomized, multiple-dose, placebo controlled, crossover, single blind clinical trial. Subject received increasing doses of 200 ug, 400 ug, 800 ug LAS34273 or placebo.

Study Population: Healthy males, and female caucasian volunteers.

Data Analysis: PK variables were analyzed descriptively.

Pharmacokinetic Results:

Some PK evaluation was only possible after the highest dose. C_{max} $AUC_{(0-t)}$ and T_{max} were estimated for all subjects with at least one quantifiable plasma concentration. A summary of the data is shown below.

Table: Mean (median) pharmacokinetic parameters obtained for LAS 34273 on day 1 and day 5 after administration of 800 µg

$AUC_{(0-t)}$ (ng h/ml) Mean (SD)		C_{max} (ng/ml) Mean (SD)		T_{max} (h) Median (range)	
Day 1 (N=16)	Day 5 (N=15)	Day 1 (N=16)	Day 5 (N=15)	Day 1 (N=15)	Day 5 (N=11)
0 057 (0 054)	0 078 (0 081)	0 086 (0 048)	0 116 (0 120)	0 250 (0 250-8 000)	0 250 (0 25-1 000)

LAS 34823 (metabolite)

Owing to the same sparse data situation, the evaluation for LAS 34823 after the highest dose was conducted as for parent compound.. A summary of the data is shown below:

Table. Summary of main pharmacokinetic parameters for LAS 34823 on day 1 and on day 5 after an 800 µg inhalative dose of LAS 34273

Parameter		Day 1	Day 5
AUC_{0-t} (ng h/ml)	Mean (SD)	0 148 (0 122) N=16	0 396 (0 536) N=15
C_{max} (ng/ml)	Mean (SD)	0 089 (0 050) N=16	0 135 (0 117) N=15
T_{max} (h)	Median (range)	0 500 (0 250-2 000) N=14	0 500 (0 250-1 000) N=11

LAS 34850

Higher plasma concentrations were generally found for this metabolite enabling some pharmacokinetic evaluation at both the 400 and 800 µg doses. The corresponding summary tables are shown below:

Table: Summary of main pharmacokinetic parameters for LAS 34850 on day 1 and on day 5 after a 400 µg inhalative dose of LAS 34273

Parameter		Day 1	Day 5
$AUC_{(0-t)}$ (ng h/ml)	Mean (SD)	2 199 (3 221) N=16	4 288 (5 589) N=16
C_{max} (ng/ml)	Mean (SD)	0 515 (0 714) N=16	0 948 (1 089) N=16
T_{max} (h)	Median (range)	3 000 (2 000-4 000) N=6	3 000 (1 500-4 000) N=9
$T_{1/2}$ (h)	Mean (SD)	n r	4 643 (2 571) N=6

n r.- no result owing to insufficient data

Table: Summary of main pharmacokinetic parameters for LAS 34850 on day 1 and on day 5 after an 800 µg inhalative dose of LAS 34273

Parameter		Day 1	Day 5
$AUC_{(0-t)}$ (ng h/ml)	Mean (SD)	9 374 (6 527) N=16	13 473 (8 291) N=16
C_{max} (ng/ml)	Mean (SD)	1 742 (1 018) N=16	2 257 (0 949) N=16
T_{max} (h)	Median (range)	3 500 (1 500-4 000) N=14	2 000 (1 000-4 000) N=15
$T_{1/2}$ (h)	Mean (SD)	4 352 (1 588) N=9	5 179 (2 347) N=10

M/34273/08

Study Title: A single dose, open label, clinical trial to assess the pharmacokinetics of a*clidinium bromide* 400 µg administered by inhalation in healthy subjects and subjects with various degrees of chronic renal insufficiency

Objectives: To evaluate the pharmacokinetics of *aclidinium brom ide* and its two main metabolites (LAS34850 and LAS34823) after a single dose in subjects with normal renal function and with various degrees of stable, chronic renal insufficiency, administered by inhalation via the Almirall Inhaler.

To evaluate the safety and tolerability of a single dose of *aclidinium brom ide* in the same study population based on clinical evaluation of safety, laboratory, vital signs, physical examination and electrocardiogram (ECG) tests, as well as adverse events (AEs).

Study Design: This was a single dose, open label, clinical study. Twenty-four subjects were randomised; 18 with renal insufficiency (six subjects for each of the three renal insufficiency groups: mild, moderate and severe) and six subjects with normal renal function.

Each subject received a single dose of *aclidinium brom ide* (400 µg) from the Almirall Inhaler by inhalation on a single occasion, as two puffs (200 + 200 µg; the second puff administered immediately after the first).

Each subject resided at the clinical research unit from the evening of Day -1 (the day before dosing) to the morning of Day 3 (48 hours post dose). Subjects participated in a post-study telephone assessment within 7 days after their final dose.

Study Population: Adult male subjects and non-pregnant female subjects aged between 18 and 79 years old, assigned to the following groups (six subjects per group)

Data Analysis: PK variables were analyzed descriptively.

Pharmacokinetic Results:

The plasma pharmacokinetic parameters of *aclidinium bromide* are presented in the following table:

Parameter	Normal renal function (N=6)	Mild renal insufficiency (N=6)	Moderate renal insufficiency (N=6)	Severe renal insufficiency (N=6)
AUC(0-t) (pg.h/mL)	124.2 (75.4)	388.3 (107.4)	414.5 (126.0)	388.7 (69.0)
AUC (pg.h/mL)	147.2 (68.5)	474.2 (105.6)	149.8 (48.5) [a]	288.6 (62.3) [a]
C_{max} (pg/mL)	113.9 (81.5)	116.5 (84.7)	106.3 (36.5)	98.5 (69.0)
t_{max} (h)	0.08 (0.08 - 0.25)	0.08 (0.08 - 1.00)	0.08 (0.08 - 0.08)	0.08 (0.08 - 0.53)
$t_{1/2}$ (h)	2.33 (51.7)	10.59 (109.9)	2.58 (50.8) [a]	6.23 (84.1) [a]
λ_z (1/h)	0.36 (47.4)	0.14 (64.4)	0.31 (37.1) [a]	0.16 (48.8) [a]
CL/f (L/h)	3651.3 (47.7)	1905.5 (66.8)	3054.6 (35.2) [a]	1887.2 (60.5) [a]
V_z/f (L)	10352 (36.8)	13513 (26.7)	9946 (15.2) [a]	12323 (32.1) [a]

Arithmetic mean (CV%) data are presented for all parameters with the exception of t_{max} for which median (min-max) are presented

[a] N = 4

The urinary pharmacokinetic parameters of *aclidinium bromide* are presented in the following table:

Parameter	Normal renal function (N=6)	Mild renal insufficiency (N=6)	Moderate renal insufficiency (N=6)	Severe renal insufficiency (N=6)
Ae (ng)	360.5 (49.9)	387.3 (70.1)	246.7 (71.1)	92.6 (137.6)
fe (%)	0.09 (49.9)	0.10 (70.1)	0.06 (71.1)	0.02 (137.7)
CL_R (mL/min)	58.6 (89.2)	26.3 (101.7)	13.5 (34.0)	3.5 (126.3)

Arithmetic mean (CV%) data are presented

The urinary pharmacokinetic parameters of LAS34850 are presented in the following table:

Parameter	Normal renal function (N=6)	Mild renal insufficiency (N=6)	Moderate renal insufficiency (N=6)	Severe renal insufficiency (N=6)
A_{m1} (ng)	34445 (19.4)	24479 (43.4)	14799 (38.2)	7769 (90.7)
fe (%)	17.37 (19.4)	12.34 (43.4)	7.46 (38.2)	3.92 (90.7)
CL_R (mL/min)	24.84 (15.2)	17.64 (39.0)	7.63 (26.8)	3.09 (62.4)

Arithmetic mean (CV%) data are presented

Statistical comparisons of the urinary pharmacokinetic parameters of LAS34850 showed significantly lower excretion and renal clearance of LAS34850 for subjects in the moderate and severe renal insufficiency groups compared to the subjects with normal renal function. There were no statistically significant findings for the subjects with mild renal insufficiency compared to those with normal renal function.

The plasma pharmacokinetic parameters of LAS34823 are presented in the following table:

Parameter	Normal renal function (N=6)	Mild renal insufficiency (N=6)	Moderate renal insufficiency (N=6)	Severe renal insufficiency (N=6)
AUC(0-t) (pg.h/mL)	507.2 (38.3)	518.9 (55.4)	590.5 (61.6)	696.5 (120.2)
AUC (pg.h/mL)	641.1 (36.7)	646.0 (50.7)	749.4 (59.3)	654.9 (123.7) [a]
C_{max} (pg/mL)	79.3 (67.0)	67.4 (70.8)	64.1 (44.8)	49.0 (108.4)
t_{max} (h)	0.75 (0.08, 2.00)	1.25 (0.08, 2.00)	1.00 (0.25, 2.00)	1.25 (0.08, 16.00)
$t_{1/2}$ (h)	14.5 (59.6)	13.6 (36.8)	17.0 (79.0)	9.45 (50.0) [a]
λ_z (1/h)	0.06 (61.3)	0.06 (38.6)	0.07 (70.2)	0.09 (46.5) [a]

Arithmetic mean (CV%) data are presented for all parameters with the exception of t_{max} for which median (min-max) are presented
[a] N = 4

The urinary pharmacokinetic parameters of LAS34823 are presented in the following table:

Parameter	Normal renal function (N=6)	Mild renal insufficiency (N=6)	Moderate renal insufficiency (N=6)	Severe renal insufficiency (N=6)
A_{m2}(ng)	14753 (34.9)	9780 (51.4)	5757 (46.2)	5394 (96.7)
fe (%)	6.81 (34.9)	4.52 (51.4)	2.66 (46.2)	2.49 (96.7)
CL_R (mL/min)	442.1 (25.6)	286.3 (26.0)	188.2 (50.6)	195.7 (71.9)

Arithmetic mean (CV%) data are presented

M/34273/09

Study Title: A multiple dose, open-label, two period, clinical trial to assess the pharmacokinetics of a*clidinium brom ide* at therapeutic dose and twice this dose administered by inhalation, after single administration and at steady state, in a broad age range of patients with moderate to severe chronic obstructive pulmonary disease (COPD)

Objectives: To evaluate the pharmacokinetics of aclidinium bromide and its two main metabolites at the therapeutic dose and twice this dose, after a single dose and at steady state (3-day dosing), in a broad age range of moderate to severe COPD patients, administered by inhalation via the Almirall Inhaler.

To evaluate whether the pharmacokinetic behaviour of aclidinium bromide is affected by the age of the patients.

To evaluate the safety and tolerability of aclidinium bromide based on laboratory, physical examination, vital signs and ECG tests, as well as adverse events.

Study Design:
This was a multiple dose, open-label, two-period, multicentre clinical study. Twenty-four patients were randomised; 12 young patients aged 40 to 59 years and 12 elderly patients aged ≥70 years. Male and female patients with a diagnosis of stable, moderate to severe COPD were included in the study.

Aclidinium brom ide was administered by inhalation once daily in the morning as 1 puff (200 µg) on 3 consecutive days in Treatment Period 1, and as 2 puffs (200 + 200 µg) on three consecutive days in Treatment Period 2.

Each patient participated in two 3-day treatment periods, separated by a wash-out period of 7 days. A follow up visit was performed within 7 days after the last treatment day.
follow up visit was performed within 7 days after the last treatment day.

Study Population: Adult male patients and non-pregnant, non-lactating female patients, with a clinical diagnosis of stable moderate to severe COPD, based on age:

Young patients aged 40 to 59 years
Elderly patients aged ≥70 years

Data Analysis: PK variables were analyzed descriptively.

Pharmacokinetic Results:

Aclidinium bromide

The plasma pharmacokinetic parameters of *aclidinium brom ide* for young and elderly patients are presented in the following table:

Parameter	*Aclidinium Bromide* Dose	Young Patients (N=12)		Elderly Patients (N=12)	
		Day 1	Day 3	Day 1	Day 3
AUC(0-t) (pg.h/mL)	200 µg	59.9 (58.7)	81.6 (59.1)	75.5 (83.9)	73.6 (49.8)
	400 µg	175.5 (54.7)	177.6 (40.3)	152.0 (59.3)	164.6 (55.0)
AUC (Day 1) (pg.h/mL)	200 µg	79.9 (48.6)	NA	97.3 (67.4)	NA
	400 µg	193.9 (51.7)	NA	192.6 (48.0)	NA
AUC_{τ} (Day 1) $AUC_{\tau,ss}$ (Day 3) (pg.h/mL)	200 µg	75.4 (49.0)	103.1 (45.4)	92.0 (69.5)	94.7 (37.5)
	400 µg	193.5 (51.4)	199.6 (36.4)	171.3 (56.7)	191.1 (47.4)
C_{max} (Day 1) $C_{max,ss}$ (Day 3) (pg/mL)	200 µg	39.0 (46.2)	37.8 (44.1)	38.3 (62.4)	40.1 (56.0)
	400 µg	82.3 (32.0)	86.1 (31.6)	71.1 (58.2)	67.8 (44.7)
C_{min} /(Day 2) $C_{min,ss}$ (Day 3) (pg/mL)	200 µg	<5.00 (0.00)	<5.00 (0.00)	<5.00 (0.00)	<5.00 (0.00)
	400 µg	<5.00 (0.00)	<5.00 (0.00)	<5.00 (0.00)	<5.00 (29.86)
$C_{av,ss}$ (Day 3) (pg/mL)	200 µg	NA	4.30 (45.40)	NA	3.94 (37.45)
	400 µg	NA	8.32 (36.40)	NA	7.96 (47.38)
t_{max} (h)	200 µg	0.17 (0.08-0.50)	0.19 (0.08-1.00)	0.25 (0.10-2.00)	0.25 (0.08-0.50)
	400 µg	0.17 (0.08-1.00)	0.25 (0.08-1.03)	0.25 (0.08-1.50)	0.25 (0.08-0.50)
$t_{1/2}$ (h)	200 µg	1.71 (37.12)	2.20 (20.18)	1.73 (39.16)	2.26 (29.92)
	400 µg	1.92 (29.03)	2.31 (32.20)	1.97 (29.00)	3.16 (34.38)
λ_z (1/h)	200 µg	0.46 (36.47)	0.33 (21.01)	0.47 (45.74)	0.34 (40.52)
	400 µg	0.39 (32.77)	0.34 (37.70)	0.38 (31.49)	0.24 (33.63)
CL/f (L/h)	200 µg	3025.1 (44.5)	2284.1 (43.8)	2850.5 (58.2)	2328.9 (29.3)
	400 µg	2419.8 (34.8)	2288.6 (39.7)	2784.5 (72.7)	2452.2 (38.2)
V_z/f (L)	200 µg	7066.2 (47.0)	NC	6284.3 (46.4)	NC
	400 µg	6351.0 (36.4)	NC	7024.5 (47.1)	NC

Arithmetic mean (CV%) data are presented for all parameters with the exception of t_{max} for which median (min-max) are presented
NA = Not applicable
NC = Not calculated
C_{min} (Day 2) is at Day 2 pre-dose
$C_{min,ss}$ (Day 3) is at Day 3 pre-dose

The urinary pharmacokinetic parameters of *aclidinium brom ide* for young and elderly patients are presented in the following table:

Parameter	*Aclidinium Bromide* Dose	Young Patients (N=12) Day 1 (24 h)	Young Patients (N=12) Day 3 (24 h)	Young Patients (N=12) Day 3 (48 h)	Elderly Patients (N=12) Day 1 (24 h)	Elderly Patients (N=12) Day 3 (24 h)	Elderly Patients (N=12) Day 3 (48 h)
Ae (0-24 h) (ng)	200 µg	208.9 (46.3)	270.6 (58.5)	296.1 (58.9)	137.8 (50.0)	185.4 (54.7)	204.2 (57.7)
	400 µg	499.0 (50.4)	532.3 (47.5)	607.3 (50.0)	331.7 (41.0)	366.8[a] (39.3)	410.0[a] (41.3)
fe (0-24 h) (%)	200 µg	0.10 (46.25)	0.14 (58.47)	NC	0.07 (50.01)	0.09 (54.71)	NC
	400 µg	0.12 (50.37)	0.13 (47.47)	NC	0.08 (40.95)	0.09 (39.24)	NC
CL_R (mL/min)	200 µg	50.4 (43.2)	50.6[a] (56.3)	NC	37.2[b] (68.5)	37.2[a] (45.5)	NC
	400 µg	47.1 (48.9)	50.2 (56.6)	NC	38.9 (47.9)	34.9[a] (43.9)	NC

Arithmetic mean (CV%) data are presented
NC = Not calculated
[a] N = 11, [b] N = 10

The urinary excretion of *aclidinium bromide* was very low at 0.07% to 0.14% of the dose across all age groups, dose levels and days. The mean renal clearance of *aclidinium brom ide* ranged from 47 to 51 mL/min in young patients compared to 35 to 39 mL/min in elderly patients, for each dose level and day.

LAS34850

The plasma pharmacokinetic parameters of LAS34850 for young and elderly patients are presented in the following table:

Parameter	*Aclidinium Bromide* Dose	Young Patients (N=12)		Elderly Patients (N=12)	
		Day 1	Day 3	Day 1	Day 3
AUC(0-t) (pg.h/mL)	200 µg	6795.5 (41.0)	8151.6 (58.1)	7874.5 (42.4)	11571 (44.2)
	400 µg	15070 (43.6)	20246 (39.8)	20271 (30.7)	25629 (24.3)
AUC (Day 1) (pg.h/mL)	200 µg	7819.8 (34.4)	NA	9123.8 (38.8)	NA
	400 µg	16530 (40.6)	NA	21734 (29.9)	NA
AUC_{τ} (Day 1) $AUC_{\tau,}^{ss}$ (Day 3) (pg.h/mL)	200 µg	7369.8 (35.0)	8569.5 (52.6)	8479.9 (38.2)	11382 (40.8)
	400 µg	15359 (41.6)	18196 (40.0)	20317 (30.2)	22458 (22.0)
C_{max} (Day 1) $C_{max,}^{ss}$ (Day 3) (pg/mL)	200 µg	805.9 (36.2)	844.0 (57.4)	829.2 (30.4)	1029.5 (41.1)
	400 µg	1669.8 (44.7)	1812.0 (48.5)	1942.6 (31.0)	2058.7 (26.3)
C_{min} (Day 2) $C_{min,}^{ss}$ (Day 3) (pg/mL)	200 µg	<100.00 (33.61)	<100.00 (55.75)	<100.00 (58.73)	100.18 (48.56)
	400 µg	128.20 (58.33)	170.43 (43.50)	176.31 (35.79)	233.67 (32.66)
$C_{av,}^{ss}$ (Day 3) (pg/mL)	200 µg	NA	357.06 (52.63)	NA	474.24 (40.75)
	400 µg	NA	758.15 (40.03)	NA	935.74 (21.98)
t_{max} (h)	200 µg	4.00 (1.50-4.02)	4.00 (1.50-6.00)	4.00 (1.50-6.00)	4.00 (2.00-6.00)
	400 µg	4.00 (1.50-4.00)	4.00 (1.50-6.00)	4.00 (2.00-8.00)	4.00 (2.00-6.00)
$t_{1/2}$ (h)	200 µg	5.35 (28.51)	6.41 (37.78)	5.42 (32.50)	8.69 (54.64)
	400 µg	5.86 (30.45)	10.21 (44.22)	5.43 (17.36)	11.58 (39.81)
λ_z (1/h)	200 µg	0.14 (30.82)	0.12 (39.35)	0.14 (27.60)	0.10 (38.70)
	400 µg	0.13 (31.37)	0.08 (41.05)	0.13 (16.87)	0.07 (45.39)

Arithmetic mean (CV%) data are presented for all parameters with the exception of t_{max} for which median (min-max) are presented
NA = Not applicable
C_{min} (Day 2) is at Day 2 pre-dose
$C_{min,}^{ss}$ (Day 3) is at Day 3 pre-dose

Maximum concentrations of LAS34850 occurred at a median tmax of 4 hours post-dose for young and elderly patients at each dose level and day. The t1/2 values for LAS34850 were longer on Day 3 than Day 1 across age groups, and dose levels. These differences are most likely related to the availability of more pharmacokinetic sampling timepoints on Day 3 in comparison to Day 1 for the characterisation of the terminal elimination phase. A change in the elimination rate constant of this metabolite due to the multiple dose administration of *aclidinium bromide* is unlikely since there were no statistically significant differences in t1/2 between the young and elderly, for each dose level and day. The systemic exposure of LAS34850 was very high compared to *aclidinium bromide* for all patients (range 86 to 114-times for young and 104 to 157-times for elderly). LAS34850 AUC(0-t) and AUCτ and Cmax was generally greater in the elderly than the young for each dose and day, and also on Day 3 compared to Day 1, for each age group and dose level. This increase is considered clinically irrelevant since this metabolite is devoid of activity at a wide array of receptors and enzymes, including muscarinic receptors. AUC(0-t) and Cmax for LAS34850 appeared to increase in a dose-proportional manner on both days in the young and elderly. There appeared to be a slight accumulation of LAS34850 from

single dose to steady state for all groups. The comparison between AUC on Day 1 versus AUCτ on Day 3 by age group and dose showed no significant differences, indicating pharmacokinetic linearity and that steady state was achieved by Day 3.

The urinary pharmacokinetic parameters of LAS34850 for young and elderly patients are presented in the following table:

Parameter	*Aclidinium Bromide* Dose	Young Patients (N=12)			Elderly Patients (N=12)		
		Day 1 (24 h)	Day 3 (24 h)	Day 3 (48 h)	Day 1 (24 h)	Day 3 (24 h)	Day 3 (48 h)
A_{m1} (0-24 h) (ng)	200 µg	9901.6 (41.9)	11904 (60.9)	12963 (60.9)	9211.1 (48.3)	12563 (43.1)	13617 (44.8)
	400 µg	22766.8 (43.2)	25482 (43.6)	28450 (44.2)	22203.3 (37.9)	26096[a] (38.2)	29588[a] (39.7)
fe (0-24 h) (%)	200 µg	9.99 (41.86)	12.01 (60.92)	NC	9.29 (48.27)	12.67 (43.08)	NC
	400 µg	11.48 (43.19)	12.85 (43.55)	NC	11.20 (37.94)	13.16[a] (38.16)	NC
CL_R (mL/min)	200 µg	23.0 (42.9)	22.5 (39.6)	NC	18.2 (29.6)	20.6 (44.1)	NC
	400 µg	25.6 (34.1)	23.9 (30.9)	NC	18.1 (25.0)	19.5 (30.3)	NC

Arithmetic mean (CV%) data are presented
NC = Not calculated
[a] N = 11

The urinary excretion of LAS34850 up to 24 hours after dosing was markedly higher than that of *aclidinium bromide*, at 9.3% to 13.2% of the dose, across all age groups, dose levels and days.

LAS34823

The plasma pharmacokinetic parameters of LAS34823 for young and elderly patients are presented in the following table:

Parameter	*Aclidinium Bromide* Dose	Young Patients (N=12)		Elderly Patients (N=12)	
		Day 1	Day 3	Day 1	Day 3
AUC(0-t) (pg.h/mL)	200 µg	135.6[a] (61.01)	183.9[a] (62.97)	289.8[a] (78.52)	362.8[a] (76.79)
	400 µg	342.9 (68.71)	430.7 (45.97)	607.5 (56.94)	845.6 (76.03)
AUC (Day 1) (pg.h/mL)	200 µg	209.1[c] (64.80)	NA	372.4[a] (79.88)	NA
	400 µg	380.5[a] (63.41)	NA	733.8 (61.72)	NA
AUC_τ (Day 1) AUC_τ^{ss} (Day 3) (pg.h/mL)	200 µg	165.6[a] (59.68)	216.8[a] (56.73)	327.5[a] (65.22)	366.4[a] (57.08)
	400 µg	382.8 (57.18)	443.0 (41.32)	628.7 (52.30)	742.6 (59.44)
C_{max} (Day 1) C_{max}^{ss} (Day 3) (pg/mL)	200 µg	34.0 (58.93)	34.1[a] (41.54)	37.6 (46.25)	41.0 (59.85)
	400 µg	66.2 (43.32)	61.4 (35.15)	79.2 (51.81)	80.5 (39.28)
C_{min} (Day 2) C_{min}^{ss} (Day 3) (pg/mL)	200 µg	<5.00[b] (0.00)	<5.00[a] (0.00)	<5.00 (107.53)	<5.00 (86.21)
	400 µg	<5.00[a] (56.09)	<5.00 (46.55)	7.40 (108.72)	10.70 (105.92)
C_{av}^{ss} (Day 3) (pg/mL)	200 µg	NA	9.03[a] (56.73)	NA	15.27[a] (57.08)
	400 µg	NA	18.46 (41.32)	NA	30.94 (59.44)
t_{max} (h)	200 µg	1.00 (0.25-4.00)	0.50[a] (0.25-2.00)	0.50[a] (0.25-6.00)	1.25 (0.25-8.00)
	400 µg	0.25 (0.25-2.00)	0.25 (0.25-4.00)	1.25 (0.25-8.00)	1.50 (0.25-6.00)
$t_{1/2}$ (h)	200 µg	4.51[c] (79.53)	4.53[b] (42.24)	5.83[a] (41.99)	7.18[a] (46.35)
	400 µg	4.66[a] (44.41)	8.16[a] (50.62)	7.77 (35.00)	11.66 (33.13)
λ_z (1/h)	200 µg	0.21[c] (44.18)	0.17[b] (34.07)	0.13[a] (31.64)	0.12[a] (42.33)
	400 µg	0.18[a] (46.29)	0.09[a] (41.74)	0.10 (39.04)	0.07 (36.83)

Arithmetic mean (CV%) data are presented for all parameters with the exception of t_{max} for which median (min-max) are presented
NA = Not applicable
[a] N = 11, [b] N = 10, [c] N = 9
C_{min} (Day 2) is at Day 2 pre-dose
C_{min}^{ss} (Day 3) is at Day 3 pre-dose

Maximum concentrations of LAS34823 generally occurred later than that of *aclidinium brom ide*, but earlier than that of LAS34850, with median t_{max} between 0.25 and 1.5 hours post-dose for both age groups, dose levels and days. The $t_{1/2}$ values for LAS34823 were slightly longer on Day 3 than Day 1 across age groups, and dose levels, and longer in the elderly compared to the young at each dose level and day. The systemic exposure of LAS34823 was greater than that of *aclidinium brom ide*, by 1.9 to 2.4-times and 3.8 to 5.1-times for young and elderly, respectively. For LAS34823, AUC(0-t), AUC_τ and C_{max} were generally greater in the elderly than young for each dose and day, and also on Day 3 compared to Day 1, for each age group and dose level. This increase is considered clinically irrelevant since this metabolite is devoid of activity at a wide array of receptors and enzymes, including muscarinic receptors. AUC(0-t) and C_{max} for LAS34823 appeared to increase in a dose-proportional manner on both days in the young and elderly. There appeared to be a slight accumulation of LAS34823 from single dose to steady state. The comparison between AUC on Day 1 versus AUC_τ on Day 3 by age

group and dose, showed no significant differences, indicating pharmacokinetic linearity and that steady state was achieved by Day 3.

The urinary pharmacokinetic parameters of LAS34823 for young and elderly patients are presented in the following table:

Parameter	*Aclidinium Bromide* Dose	Young Patients (N=12)			Elderly Patients (N=12)		
		Day 1 (24 h)	Day 3 (24 h)	Day 3 (48 h)	Day 1 (24 h)	Day 3 (24 h)	Day 3 (48 h)
A_{m2} (0-24 h) (ng)	200 µg	4019.7 (31.5)	5446.2 (52.7)	6427.4 (53.1)	4494.1 (57.0)	5971.8 (58.6)	7207.0 (63.3)
	400 µg	9471.5 (55.1)	10784 (39.2)	12902 (41.1)	10159 (52.8)	13192 (71.6)	16375 (85.8)
fe (0-24 h) (%)	200 µg	3.71 (31.48)	5.03 (52.68)	NC	4.15 (57.04)	5.52 (58.55)	NC
	400 µg	4.37 (55.06)	4.98 (39.23)	NC	4.69 (52.84)	6.09 (71.61)	NC
CL_R (mL/min)	200 µg	499.00 (46.17)	558.91 (57.93)	NC	279.57 (39.63)	319.42 (41.55)	NC
	400 µg	448.93 (42.03)	454.06 (48.47)	NC	285.36 (30.78)	307.97 (34.18)	NC

Arithmetic mean (CV%) data are presented
NC = Not calculated
[a] N = 11

The urinary excretion of LAS34823 up to 24 hours after dosing was markedly higher than that of *aclidinium brom ide*, but lower than that of LAS34850, at 3.7% to 6.1% of the dose across all age groups, dose levels and days.

LAS-PK-CL03

Study Title: A single dose, open label clinical trial to assess the in vivo pulmonary desposition of LAS34273 administered to healthy volunteers by inhalation

Objectives: To evaluate the in vivo pulmonary desposition and istribution of LAS34273 from a multiple dry powder inhaler at 90L/min
To assess the tolerability and safety of LAS34273

Study design: This was a single dose, open-label clinical trial. The study consisted of one study period. Scintigraphic images wee acquired immediately after dosing. Dose of 200 ug of LAS34273 radiolabelled with ^{99m}Tc administered by a dry powder inhaler.

Study Population: Twelve healthy male subjects aged 18 to 65 years were completed the study.

Data Analysis: scintigraphic data were analyzed descriptively.

Results:

The mean ± SD values for the percentage of dose deposited at various sites are presented below:

Table S1. Mean ± SD percentage distribution of metered dose

Whole lung	Oropharynx / oesophagus / stomach	Mouthpiece / Inhalation channel	Exhaled air filter
30 11 ± 7.302	54 74 ± 7.192	11.48 ± 4.191	3.66 ± 1.981

The percentage of dose deposited was highest in the oropharynx A mean of 54.74% of the metered dose was deposited in the oropharynx. Lung deposition averaged 30 11% of the metered dose

The highest deposition within the lungs occurred in the most central lung region.

M/34273/00 (LAS-PK-CL00)

Study Title: A double-blind, crossover, single ascending doses, placebo-controlled, pilot clinical trial to assess the activity, tolerability and PK of LAS34273 in male healthy subjects.

Objectives: To assess the pharmacological activity, tolerability and pharmacokinetics of LAS-34273 in male subjects

Study design: This was a double-blind, crossover, single ascending doses, placebo controlled clinical trial. Doses administered include: 50 ug, 300 ug, and 600 ug in single ascending doses. Medication was administered by dry powder inhalation in capsules through a rechargeable device. A minium of 6 days was required between administrations.

Study Population: Twelve healthy male subjects aged 18 to 45 years were completed the study.

Data Analysis: PK data were analyzed descriptively.

PK results: The parent compound and its known metabolites could not be detected in any of the samples taken.

M/34273/11

Study Title: A randomized, parallel, placebo and positive controlled clinical trial to assess the effect on QT interval as well as overall cardiovascular safety of LAS34273 by inhalation in healthy subjects.

Note: the study details were reviewed by QT/IRT.

M/34273/21

Study Title: A double-blind, randomized, single dose, placebo controlled, crossover clinical trial to assess the tolerability, pharmacodynamics, and pharmacokinetics of LAS-34273 administered by inhalation in male chronic obstructive pulmonary disease patients.

Objectives: To assess the tolerability, pharmacodynamics and pharmacokinetics of LAS-34273 at single doses.

Study design: This was a single dose placebo controlled clinical trial. Doses administered include: placebo, 100 ug, 300 ug, and 900 ug once by inhalation.

Study Population: Seventeen COPD subjects aged 40 to 80 years were completed the study.

Data Analysis: PK data were analyzed descriptively.

PK results: The parent compound and its known metabolites could not be detected in any of the samples taken.

PHARMACODYNAMICS

This study has been designed to ascertain whether a bronchodilator effect of LAS 34273 exists, after a single administration of this drug to COPD patients. The trial has been performed in COPD patients, i.e. males with moderate to severe obstruction and with a significant response to ipratropium bromide. The reason of this inclusion criterion was to avoid negative results at this moment with non responding subjects to anticholinergic drugs.

The lung function variables used were FEV1, FVC, PEFR and FEF25-75, measured according to the ATS recommendations.

FEV1

FEV1 is one of the two main criteria for bronchial responsiveness testing according to ATS and European Respiratory Society (ERS) guidelines, and reflects the degree of bronchial obstruction. This criteria is also considered as the main variable by the European Regulatory Authorities and F.D.A.

FEV1 increases in a statistically significant way after LAS 34273 administration with all the doses. The 300 µg and 900µg doses do not show greater efficacy over a 24 h period than the 100µg dose. AUC (0-24)/24 is statistically significantly higher after LAS 34273 administration than after placebo, but no statistically significant differences exist between the three treatment doses. However, 300 µg and 900µg doses tend to provoke greater peak effects. The time of maximal effect occurs earlier than with the 100µg dose. Variations in FEV1 were no more statistically significant after a 24h period for the 100 µg and 900µg doses.

FVC

A rise of FVC after bronchodilators reflects a decrease in hyperinflation, and is not systematically associated with an improvement in FEV1. This variable has also been recognized as a main criteria by the ATS and ERS.

In this study, a 100µg dose of LAS 34273 induces a statistically significant increase in FVC over a 24 h period. Higher doses (300 and 900µg) do not induce further increases. AUC (0-24)/24 is statistically significantly higher after LAS 34273 administration than after placebo, but no statistically significant differences between the three treatment doses. Times of maximal effects occur earlier with the 300 µg and 900 µg doses than the100 µg doses. No significant change of FVC is detected after a 24 h period.

PEFR

Since the reproducibility of PEFR is low in COPD patients, this variable is not accepted as a main criterion by the ATS. Nevertheless, PEFR is a widely used variable.

In this study, statistically significant increases in PEFR are observed over a 24 h period using a 900µg dose of LAS 34273. Less consistent results are obtained with lower doses: only short periods of improvement of PEFR over 24 h are obtained after administration of 100µg and 300µg doses.

FEF25-75

Spontaneous variations in FEF25-75 are high, even in healthy subjects, making changes in this variable difficult to interpret. However, this parameter is an interesting one since it is thought to reflect small airway obstruction. Nevertheless, using this variable, the comparison between the isovolume FEF25-75 obtained before and after bronchodilator is needed, measurements which are usually not calculated by most lung function testing devices.

In this study, FEF25-75 statistically significantly increases over a 24 h period after inhalation of the 300 µg and over a 12 h period for the 100µg or 900 µg doses.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PING JI
03/13/2012

VENKATESH A BHATTARAM
03/13/2012

YANING WANG
03/13/2012

SURESH DODDAPANENI
03/14/2012

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 202450

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**202450**	**Brand Name**	**ND**
OCP Division (I, II, III, IV, V)	**II**	**Generic Name**	**Aclidinium Bromide**
Medical Division	**DPARP (OND-570)**	**Drug Class**	**Long-acting antimuscarinic agent (LAMA)**
OCP Reviewer	**Partha Roy**	**Indication(s)**	**COPD**
OCP Team Leader (Acting)	**Suresh Doddapaneni**	**Dosage Form**	**Inhalation powder**
Pharmacometrics / Pharmacogenomics Reviewer	**Not Applicable**	**Dosing Regimen**	**Twice daily (BID), preferably q12h**
Date of Submission	**6/23/2011**	**Route of Administration**	**Oral Inhalation**
Estimated Due Date of OCP Review	**3/30/2012**	**Sponsor**	**Forest Labs**
Medical Division Due Date	**4/20/2012**	**Priority Classification**	**S**
PDUFA Due Date			

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**x**			
Tabular Listing of All Human Studies	**x**			
HPK Summary	**x**			
Labeling	**x**			
Reference Bioanalytical and Analytical Methods	**x**	**10**		**Includes method validation and trial-specific bioanalytical reports**
I. Clinical Pharmacology				
Mass balance:	**x**	**1**		
Isozyme characterization:	**x**	**7**		
Blood/plasma ratio:				
Plasma protein binding:	**x**	**1**		
Pharmacokinetics (e.g., Phase I) -	**x**			
Healthy Volunteers-	**x**			
single dose:	**x**	**2**		
multiple dose:	**x**	**2**		
Patients-				
single dose:	**x**			
multiple dose:	**x**	**1**		
Dose proportionality -				
fasting / non-fasting single dose:	**x**			
fasting / non-fasting multiple dose:	**x**	**1**		
Drug-drug interaction studies -				**No in vivo DDI trials done**
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 202450

Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:	**x**	**1**		
renal impairment:	**x**	**1**		
hepatic impairment:				
PD -				
Phase 2:	**x**			
Phase 3:	**x**			
PK/PD -				
Phase 1 and/or 2, proof of concept:	**x**	**1**		
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability	**x**	**1**		
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan	**NA**			**Developed only for COPD (not a pediatric indication)**
Literature References	**x**			
Total Number of Studies		**29**		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			x	
2	Has the applicant provided metabolism and drug-drug interaction information?	x			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	x			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?	x			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA	x			

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 202450

	legible so that a substantive review can begin?				
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	x			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			x	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			x	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
____Yes____

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.
None

Partha Roy, Ph.D. — Aug 26, 2011
Reviewing Clinical Pharmacologist — Date

Suresh Doddapaneni, Ph.D. — Aug 26, 2011
Team Leader/Supervisor — Date

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 202450

Background

This is a new drug application submitted by Forest Laboratories for aclidinium bromide inhalation powder administered by a device-metered dry powder inhaler (Almirall inhaler) intended for use in patients with chronic obstructive pulmonary disease (COPD). Aclidinium bromide, a new molecular entity, is a long-acting antimuscarinic agent acting as a bronchodilator under development for the long-term maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema. The proposed dose is 400 mcg twice daily. One other long-acting antimuscarinic agent currently available in the market for this indication is tiotropium bromide inhalation powder (Spiriva® Handihaler®).

Aclidinium bromide was developed initially as a once daily (QD) treatment for COPD and consequently the design of several of the clinical pharmacology studies was based on a QD dose regimen. Subsequent to the conduct of the majority of clinical pharmacology studies, it was decided to pursue a twice daily (BID) dose regimen following which LAS-PK-12 trial was conducted to assess PK and tolerability following multiple BID inhaled doses using the to-be-marketed formulation and device.

The efficacy and safety of aclidinium bromide 400 μg BID is based on the results of 3 Phase 3 randomized, double-blind, placebo-controlled studies (M/34273/34, LAS-MD-33, and LAS-MD-38 [Part A]) and 3 long term safety studies (LAS-MD-38 [Part B], LAS-MD-35, and LAS-MD-36) of up to 52 weeks' duration in adult subjects with moderate to severe COPD.

Overview of Clinical Pharmacology submission and data

A total of 11 clinical pharmacology trials were conducted (Table 1 below).

Four trials were conducted to investigate primarily the PK of inhaled aclidinium bromide in healthy subjects (M/34273/01, M/34273/05, M/34273/06 and LAS-PK-12). Two clinical studies investigated the influence of the intrinsic factors of renal impairment and age, on PK parameters of aclidinium bromide (M/34273/08 and M/34273/09, respectively). There were two ADME trials investigating lung deposition of aclidinium bromide (M/34273/03) and mass balance following IV administration (M/34273/04), respectively. Two pharmacodynamic (PD) trials were conducted in healthy subjects (M/34273/00) and in COPD patients (M/34273/21). A thorough QT/QTc study (M/34273/11) report was also submitted.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 202450

Table 1. Overview of Clinical Pharmacology Trials conducted and submitted in this NDA

Study ID	Study Objective	Study Design	Treatment	Population
M/34273/01	To assess tolerability and to identify MTD of single inhaled doses. To determine PK profile.	Randomized, single ascending dose, placebo controlled single blind. Single centre trial.	Single doses of 600, 1200, 1800, 2400, 3000, 3600, 4200, 4800, 5400 and 6000 µg aclidinium bromide or placebo administered as dry powder inhaled capsules via Cyclohaler®.	16 healthy male subjects (Caucasian) aged 23 to 46 years.
M/34273/05	Part I: To evaluate safety and tolerability of single iv doses and to determine MTD for Part II. Part II: To estimate absolute bioavailability.	Part I: Randomized, single blind, placebo controlled, three-period, cross-over. Part II: Randomized, open, two-period crossover. Single centre trial.	Part I: single doses of aclidinium bromide at doses of 25, 50, 100, 200, 300 or 400 µg, or placebo, administered by iv infusion over 5 minutes. Part II: single dose of 200 µg aclidinium bromide, administered either via Almirall inhaler or iv.	24 healthy male subjects (Caucasian): 12 in Part I and 12 in Part II. Subjects aged 19 to 45 years.
M/34273/06	To assess safety, tolerability and PK following multiple QD inhaled doses.	Randomized, ascending multiple dose, single blind, placebo controlled, four-period crossover. Single centre trial.	Multiple QD doses (5 consecutive days) of aclidinium bromide (at 200, 400 or 800 µg) or placebo, via Almirall inhaler.	16 healthy subjects (Caucasian): 8 female, 8 male. Subjects aged 21 to 38 years.
LAS-PK-12	To assess safety, tolerability and PK following multiple BID inhaled doses.	Randomized, single blind, placebo controlled, parallel group, ascending multiple dose. Single centre trial.	Multiple BID doses (7 consecutive days) of aclidinium bromide (at 200, 400 or 800 µg) or placebo, via Almirall inhaler.	30 healthy subjects aged 20 to 45 years.
M/34273/08	To evaluate PK, safety and tolerability in subjects with normal renal function and with either mild, moderate or severe stable, chronic renal insufficiency.	Single centre, open-label clinical trial.	Single dose of 400 µg aclidinium bromide (given as two 200 µg doses) administered via Almirall inhaler.	24 subjects, aged 35 to 73 years: 6 with normal renal function and 18 with stable, chronic renal insufficiency categorised as mild (n = 6), moderate, (n = 6) or severe (n = 6). Degree of renal insufficiency determined by creatinine clearance.
M/34273/09	To evaluate PK in COPD patients with a broad age range and to evaluate whether PK behaviour is affected by patient age. To evaluate safety and tolerability.	Multi centre, open-label, two-period clinical trial.	First study period: 3 days of QD dosing with 200 µg aclidinium bromide. Second study period: 3 days of QD dosing with 400 µg aclidinium bromide (400 µg given as two 200 µg doses). Aclidinium bromide administered via Almirall inhaler.	24 subjects with moderate to severe COPD. 12 subjects aged 44-59 years (young) and 12 aged 70-79 years (elderly).

Table 1 *continued*

Study ID	Study Objective	Study Design	Treatment	Population
M/34273/03	To investigate *in vivo* pulmonary deposition and distribution of aclidinium bromide from Almirall inhaler at 90 L/min To evaluate tolerability and safety.	Single centre, randomized, open-label clinical trial.	A single 200 µg dose of aclidinium bromide. Radiolabelled formulation with [^{99m}]Tc (with < 10 MBq radioactivity) administered by a multimode dry powder inhaler.	12 healthy male Caucasian subjects aged 18 to 63 years.
M/34273/04	To determine rates and routes of elimination of iv [^{14}C] aclidinium bromide and to characterize and identify metabolites in plasma and excreta. To evaluate safety and tolerability.	Single centre, randomized, open-label mass-balance study. Two treatment groups: one to receive [phenyl-U-^{14}C] aclidinium bromide and the other to receive [glycolyl-U-^{14}C] aclidinium bromide.	A single iv infusion (over 5 minutes) of either 400 µg [phenyl-U-^{14}C] or 400 µg [glycolyl-U-^{14}C] aclidinium bromide, containing approximately 40 chi of radioactivity.	12 healthy male subjects (11 Caucasian, 1 black) aged 20 to 34 years, 6 in treatment group A and 6 in treatment group B.
M/34273/00	To assess pharmacological activity, safety, tolerability and PK.	Single centre, randomized, double blind, placebo controlled, three-period, cross-over study of single ascending doses.	Single doses of aclidinium bromide, administered via Cyclohaler®. Doses of active drug: 50, 300 and 600 µg.	12 healthy male subjects, aged 18 to 43 years
M/34273/21	To assess safety, tolerability, PD and PK.	Two centres; randomized, double blind, placebo-controlled, four-period crossover study of 3 ascending doses.	Single doses of 100, 300 and 900 µg aclidinium bromide, administered via Cyclohaler®.	17 male subjects, aged 48 to 71 years, with moderate to severe COPD and significant ipratropium response.
M/34273/11	To assess effect on QT interval and overall cardiovascular safety. General safety and tolerability. Systemic exposure to aclidinium bromide and metabolites and their relationship with ECG changes.	Single centre, randomized, parallel group, placebo- and positive-controlled clinical trial. Aclidinium/placebo comparison double-blind. Moxifloxacin /placebo comparison open-label.	Multiple doses (3 days QD dosing) of aclidinium bromide (at 200 or 800 µg) or placebo or moxifloxacin (400 mg). Aclidinium and placebo administered via Almirall inhaler. Moxifloxacin administered orally.	272 healthy subjects aged 18 to 45 years.

Several bioanalytical methods have been developed in the course of this drug development in an ongoing effort to improve sensitivity for the determination of plasma concentrations of aclidinium bromide, and its primary metabolites, LAS34850 and LAS34823. As a result, the LLOQ of aclidinium bromide achieved in later studies was 100-fold lower than that in early

studies. In addition, all three analytes were also monitored in urine. All bioanalytical reports including validation reports were properly submitted for review.

Early clinical trials were performed using a Cyclohaler capsule-based inhalation device. In parallel with the clinical development program, subsequent trials were performed using the Almirall inhaler (b) (4)

The mean absolute bioavailability of a single inhaled 200 µg dose of aclidinium bromide was <5%. Data from the lung deposition study revealed that about 30% of the aclidinium bromide metered dose is deposited in the whole lung, with the highest deposition occurring in the central lung region. Considering that aclidinium bromide, like other quaternary ammonium salts, is poorly absorbed by the oral route, the low absolute bioavailability observed by inhalation suggests that part of the fraction reaching the lung is likely locally hydrolyzed. Following inhalation, aclidinium bromide is rapidly absorbed with Cmax of ~10-15 minutes in COPD patients following inhalation. Aclidinium bromide exhibited dose-proportional and time-independent PK following multiple dose inhaled administration of 200 µg, 400 µg, or 800 µg QD or BID. The main plasma protein that binds aclidinium bromide in vivo is albumin. In vitro studies revealed that plasma protein binding was 87% for the acid metabolite and 15% for the alcohol metabolite. Following i.v. administration of 400 mcg aclidinium bromide, the mean apparent volume of distribution is high (~300 L).

In vitro studies demonstrated that the major route of metabolism of aclidinium bromide is via enzymatic and chemical (nonenzymatic) hydrolysis into its alcohol (LAS34823) and acid (LAS34850) metabolites, which were tested to be pharmacologically inactive. Butyrylcholinesterase is the main human esterase responsible for the hydrolysis. Plasma concentrations of the acid metabolite are approximately 100-fold greater than those of the alcohol metabolite and parent aclidinium bromide. Biotransformation via cytochrome P-450 (CYP-450) isozymes plays a minor role in the total metabolic clearance of aclidinium bromide.

Both renal and hepatic elimination play only a minor role in the clearance of aclidinium bromide from plasma. Approximately 1% of a single intravenous dose of aclidinium bromide is excreted in urine as unchanged drug. The remaining dose is hydrolyzed and excreted as metabolites (up to 65% in urine and 33% in feces. Clearance of aclidinium bromide from the plasma is rapid with an elimination half-life of 2-3 hours. Clearance of the metabolites was slower than that of the parent compound, the elimination half-life being approximately 5-6 hours for LAS34850 and ranging between 4 and 14 hours for LAS34823. Half-life seems to slightly increase following multiple dosing resulting in slight accumulation (≤40%). Age had no impact on the PK properties of aclidinium bromide. No formal drug-drug interaction studies were conducted based on a series of in vitro studies that showed lack of any effect (inhibition or induction) on important P450s and P-glycoprotein. No dose adjustment is proposed with respect to any intrinsic factors (age, renal function, etc.) and extrinsic factors (drug-drug interaction).

A 'thorough' QT study was conducted that showed that aclidinium bromide did not prolong the QTc interval following the first dose or under steady-state conditions. Due to the relatively short elimination half-life, aclidinium bromide did not appreciably accumulate upon BID dosing.

Therefore, the sponsor claimed that supratherapeutic QD 800 μg dose provides Cmax ~2-fold higher than the 400 μg BID dosing regimen.

Conclusions

The filing meeting took place on August 12, 2011. The NDA is considered fileable from the clinical pharmacology perspective. It is noticed that no PK data is available in COPD patients from the commercial formulation; however, PK data from the commercial formulation is only available in healthy subjects. No DSI inspection is needed. All PK study reports including Bioanalytical assay and validation reports are available. All PK datasets were submitted electronically. It appears that there is no pharmacometric and/or pharmacogenomics involvement in this NDA. However, since this is a new molecular entity, the respective groups have been contacted. Preliminary review of the proposed label did not reveal any major issue at this time.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PARTHA ROY
08/30/2011

SURESH DODDAPANENI
08/30/2011