EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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EMA/CHMP/169578/2012
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Eklira Genuair

International non-proprietary name: **aclidinium bromide**

Procedure No. **EMEA/H/C/002211**

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

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List of abbreviations

ADME	Absorption, distribution, metabolism and excretion
ADR	Adverse Drug Reaction
ANCOVA	Analysis of covariance
AUC	Area-under-the curve
AUC_{0-t}	Area under the concentration-time curve from time zero up to the last measurable concentration
$AUC_{0-\infty}$	Area under the concentration-time curve from time zero to infinity
AUC_{τ}	Area under the concentration-time curve during a dosing interval (τ)
$AUC_{\tau,SS}$	Area under the concentration-time curve during dosing interval (τ) at steady state
AV	Atrioventricular
BChE	Butyrylcholinesterase
BDI	Baseline Dyspnoea Index
BID	Twice daily
BMI	Body mass index
CI	Confidence interval
Cmax	Peak plasma concentration
COPD	Chronic obstructive pulmonary disease
CV	Coefficient of variation
CYP450	Cytochrome P450
DPI	Dry powder inhaler
ECG	Electrocardiogram
EMA	European Medicines Agency
F	Absolute bioavailability expressed in %
fe	Percentage of dose excreted in urine
FEV_1	Forced expiratory volume in 1 second
FRC	Forced residual capacity
FVC	Forced vital capacity
GOLD	Global initiative for Chronic Obstructive Pulmonary Disease
IC	Inspiratory capacity
ICS	Inhaled corticosteroids
IMP	Investigational medicinal product
ITT	Intent-to-treat
iv	Intravenous
IVRS	Interactive Voice Response System
LLOQ	Lower limit of quantification
LS	Least squares
MAA	Marketing Authorisation Application
MACE	Major Adverse Cardiovascular Events
MCID	Minimum clinically important difference
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency

PIF	Peak inspiratory flow
QD	Once daily
QTc	Corrected QT interval
SAE	Serious adverse event
SAP	Statistical analysis plan
SGRQ	St George's Respiratory Questionnaire
SmPC	Summary of Product Characteristics
SMQ	Standard MedDRA Queries
SOC	System organ class
t½	Elimination half-life
TDI	Transition Dyspnoea Index
λ_z	(Terminal) elimination rate constant

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Almirall, S.A. submitted on 28 July 2011 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Eklira Genuair, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 21-24 April 2008.

The applicant applied for the following indication: maintenance bronchodilator treatment to relieve symptoms of patients with chronic obstructive pulmonary disease (COPD).

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/345/2010 for the following condition:

- chronic obstructive pulmonary disease (COPD)

on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

Not applicable.

Market exclusivity

Not applicable.

New active Substance status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that aclidinium bromide is qualified as a new active substance.

Scientific Advice

The applicant received Scientific Advice from a number of European regulatory agencies as well as from the EMA.

Licensing status

A new application was filed in the US (23 June 2011) and Switzerland (9 November 2011) where the product is still not approved.

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur:	**Robert James Hemmings**	Co-Rapporteur:	**Piotr Fiedor**

- The application was received by the EMA on 28 July 2011.
- The procedure started on 17 August 2011.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 07 November 2011. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 04 November 2011.
- During the meeting on 15 December 2011, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 16 December 2011.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 16 February 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 30 March 2012.
- During the CHMP meeting on 19 April 2012, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 25 April 2012.
- The Rapporteurs circulated the Assessment Report on the applicant’s responses to the List of Outstanding Issues to all CHMP members on 3 May 2012.
- During the meeting on 24 May 2012, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Eklira Genuair on 24 May 2012.

2. Scientific discussion

2.1. Introduction

Problem statement

Chronic obstructive pulmonary disease (COPD) is a chronic and progressive disease, characterized by stepwise deterioration of lung function, is a life-limiting illness. Although the causative factors and pathogenesis of COPD are not fully understood, it is commonly accepted, that the exposure (direct and passive) to cigarette smoke, occupational dusts, chemicals and any other pollutants is the most important risk factor for development of this disease. The pathological picture of COPD involves small airway inflammation and remodelling, mucociliary dysfunction, lung architecture damage. The result of the natural course of this disease is a progressive decrease of airflow and deficit in gas exchange in the lungs, resulting in systemic hypoxia with destructive consequences to the whole body, including the cardiovascular system and all internal organs.

A causative therapy of the disease is not available. The strategy of COPD management is symptomatic. The main goals of such therapy are realized by maintenance of best possible airflow with bronchodilators to improve lung function and multidisciplinary supportive care including prevention and/or therapy of exacerbations (respiratory infections), and, anti-inflammatory therapy.

About the product

Aclidinium bromide is classified as an anticholinergic (ATC code R03BB05). It is a long-acting, inhaled anticholinergic agent which has strong affinity and selectivity for all muscarinic receptor subtypes (M1-M5) and kinetic selectivity for the M3 receptor over the M2 receptor. Inhaled aclidinium bromide inhibited acetylcholine-induced bronchoconstriction in anesthetised guinea-pigs, with a duration of action (expressed as the half-life for the bronchodilatory effect) of 29 hours.

Eklira Genuair 322 µg inhalation powder, consists of an adhesive mixture of micronised aclidinium bromide and α lactose monohydrate, contained within a device-metered, dry powder inhaler, Genuair inhaler. Each delivered dose (the dose leaving the mouthpiece) of Eklira Genuair contains 375 µg aclidinium bromide (WHO officially approved INN) equivalent to 322 µg of aclidinium. This corresponds to a metered dose of 400 µg aclidinium bromide equivalent to 343 µg aclidinium.

The claimed and approved indication is the maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD). The proposed delivered dose is 322 µg (metered dose is 343 µg) aclidinium to be used twice daily, corresponding to two oral inhalations per day from the Genuair inhaler.

It should be noted that the data submitted in the application dossier referred to Eklira Genuair 400 µg as the finished medicinal product, which corresponds to the metered dose of the active substance (aclidinium bromide), not the active moiety (aclidinium). This was the basis used during the assessment of this application. However in accordance with the "Guideline on Summary of Product Characteristics (SmPC) and QRD Recommendations on the expression of strength in the name of Centrally Authorised Human Medicinal Products" (as stated in Section 1 of the SmPC and in the name section of the Labelling and Package Leaflet), the CHMP agreed that the strength should refer to the delivered dose of the active moiety (aclidinium) and therefore the name of the medicinal product finally approved by the Committee was expressed as follows: Eklira Genuair 322 µg, in all official approved documents (CHMP opinion/future EC decision and CHMP opinion Annexes I, II and III). The strength is expressed as delivered dose of aclidinium. However, since 400 µg (metered dose of aclidinium bromide) was the strength referred to throughout the non-clinical and clinical development of this

medicinal product and the data submitted in the application, this has been left unchanged in the sections of this assessment report relating to the non-clinical and clinical development. No changes have been made to the dossier or the assessment reports which states the active substance as aclidinium bromide 400 µg metered dose or 375 µg delivered dose.

Type of Application and aspects on development

This application was submitted in accordance with Article 8(3) of Directive 2001/83/EC. It was submitted via the centralised procedure under Article 3(2)(a) of Regulation (EC) No. 726/2004 (optional scope for a new active substance).

National Scientific Advice was given by a number of European regulatory agencies. Two series of clinical Scientific Advice meetings were held, the most recent in 2009 and previously in 2005. Topics discussed in these advice procedures were related to the design of the pivotal studies of aclidinium bromide BID, the adequacy of some clinical pharmacology studies to support registration of aclidinium bromide as well as the design of the pivotal studies of aclidinium bromide QD.

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/345/2010 for chronic obstructive pulmonary disease (COPD) on the granting of a class waiver on the basis that COPD should only be considered in an individual over the age of 40 years with characteristic symptoms of COPD according to GOLD.

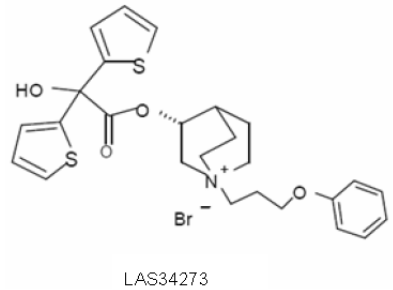
2.2. Quality aspects

2.2.1. Introduction

Eklira Genuair is available as 322 microgram inhalation powder containing aclidinium bromide as the active substance, aclidinium being the active moiety. The product composition is simple, consisting of aclidinium bromide and lactose monohydrate as sole excipient in the device-metered Genuair dry powder inhaler as the primary packaging.

2.2.2. Active Substance

Aclidinium bromide is a selective M3 muscarinic antagonist obtained by chemical synthesis which is chemically designated as (3*R*)-3-[(hydroxy)di(thiophen-2-yl)acetyloxy]-1- (3-phenoxypropyl)-1λ^5-azabicyclo[2.2.2] octan-1-ylium bromide.



LAS34273

Aclidinium bromide is a white to off-white crystalline powder very slightly soluble in water and ethanol, insoluble in tetrahydrofuran and toluene. It exists as a single crystalline form and has one chiral atom. The active form is the R-isomer.

Manufacture

The information on the active substance aclidinium bromide is presented in the form of an Active Substance Master File.

The active substance is manufactured by a synthesis which consists of a number of chemical reaction steps followed by purification by recrystallisation. The particle size characteristics necessary for use by inhalation are ensured by subsequent micronisation.

Starting materials are well characterised. The description of the manufacturing process, characterisation of the drug substance and impurities are in accordance with the EU guideline on Chemistry of new active substances. The manufacturing process is described in detail and critical steps and controls discussed.

Specification

The active substance specification, including parameters, analytical procedures and acceptance criteria is considered suitable for release of batches of active substance.

The specification includes tests for description, melting point, identification by Infrared (IR), bromide identification, loss on drying, sulphated ash, heavy metals, assay by High Performance Liquid Chromatography (HPLC), organic impurities by HPLC, High Performance Capillary electrophoresis (HPCE) and by Solid-Phase Extraction HPLC (SPE-HPLC), residual organic solvents by Gas Chromatography (GC) and particle size by laser diffraction.

The drug substance specification complies with the requirements in Q3A (R), Q3C and Q6A EU/ICH guidelines and with general Ph.Eur. requirements for substances for pharmaceutical use.

The descriptions of the analytical methods are considered acceptable and their validations are performed in accordance with ICH standards and Ph. Eur. requirements.

Batch data from three batches confirm batch to batch consistency and support uniformity of the quality of the active substance.

Stability

Satisfactory stability data on three batches of the micronized active substance stored at ICH long-term conditions (25ºC/60% RH) and at intermediate conditions (30ºC/65%RH) for 60 months and at accelerated conditions (40ºC/75% RH) for 6 months has been provided.

The parameters tested were description, loss on drying, assay (HPLC), organic impurities (HPLC-UV) and particle size distribution.

Supportive stability data for 13 development batches has also been provided.

The specification and the analytical methods used in the stability studies are the same as those for release analysis testing.

The re-test and storage conditions for the unmicronised active substance intermediate is also fully supported by the stability data provided.

Forced degradation studies exposing the active substance to acid, base, aqueous, oxidative and high intensity light conditions have also been performed demonstrating that the active substance is sensitive to basic, acidic and oxidative conditions .

The photo stability study was performed according to ICH Q1B and also demonstrated that aclidinium bromide is photolabile.

The stability data provided support the recommended retest period at the proposed packaging and storage conditions.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

Aclidinium bromide is a selective M3 muscarinic antagonist which has been formulated in finished medicinal product of the active substance and lactose monohydrate as sole excipient in the device-metered Genuair dry powder inhaler as the primary packaging.

The lactose monohydrate is an excipient commonly used in manufacture of dry powder inhalation preparations. Target delivered dose of API (Active Pharmaceutical Ingredient) has been set based on clinical data using the proposed inhalation device and full scale production batches.

The development of the product has been satisfactorily performed and explained and is in accordance with EU guidelines on Development pharmaceutics and EMEA/CHMP/QWP/49313/2005 Corr. on the Pharmaceutical Quality of Inhalation and Nasal Products. Particle size requirements for both API and lactose monohydrate have been justified in terms of their contributions to finished product performance characteristics. Device cleaning issues have been properly addressed and the valid cleaning procedures are reflected in the proposed patient leaflet.

The packaging materials have shown suitability by acceptable product performance characteristics and stability studies.

Adventitious agents

No materials of animal or human origin are used during the manufacture of the active substance.

Lactose monohydrate used in the finished medicinal product is the only material of animal origin used during the manufacture of the drug product. It is certified by the supplier that the lactose monohydrate used in this formulation is produced in compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products" (EMEA/410/01).

Manufacture of the product

Eklira Genuair 322 inhalation powder is manufactured in three stages: blending and sieving, dosing and assembly, labelling and packaging.

The manufacturing formula, flow chart and description of the manufacturing process are presented.

Critical steps are identified and there are no intermediates isolated during the manufacturing process.

The process has been validated to the commercial scale and with the commercial process. The validation of the manufacturing process has been well documented and satisfactory data provided.

Product specification

Satisfactory specification has been presented which is generally compliant with the general requirements of EU/ICH Q6A Guideline on Specifications, Ph.Eur. requirements for Preparations for Inhalation (monograph 671), and EMEA/CHMP/QWP/49313/2005 Corr.

Specification includes tests for description, active substance identification (HPLC-UV and HPLC-Diode Array Detection (HPLC-DAD), lactose identification (IR), physicochemical properties (filling, number of actuations per inhaler), purity by Rapid Resolution Liquid Chromatography (RRLC), water content, assay/content (HPLC), particle size (HPLC) and microbiological control. The proposed test procedures and acceptance criteria comply with the requirements of the Ph. Eur. and current ICH guidelines. Analytical procedures are described and validated.

Batch analysis data on two batches manufactured at the intended site of manufacture, at the intended production scale and packaged in the proposed container and several supportive batches (development, clinical and stability batches) has been provided. Data batches confirm consistency and uniformity of the product indicating that the process is under control.

Stability of the product

Stability data for 24 months at the ICH long term storage condition of 25°C/60% RH, and 6 months at the accelerated storage condition of 40°C/75% RH for two production scale batches has been presented. Supportive stability data has also been provided in support of the claimed shelf-life and storage conditions.

In addition, in-use stability over 90 days has been confirmed for a freshly produced batch, as well as for an aged batch. Supporting in-use stability studies have also been performed on development batches. Stability studies have been performed in accordance with ICH Q1A and Q1B.

The results of the following tests were submitted: appearance, physicochemical properties, identification of the active substance, assay, purity, water content and microbial control.

Analysis of the stability samples has been performed by applying the same analytical methods as per release testing.

Based on the stability results provided, the proposed shelf-life and storage conditions as defined in the Summary of Product Characteristics (SmPC) are acceptable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The new active substance is a selective M3 muscarinic antagonist obtained by chemical synthesis. Information on development, manufacture and control of the active substance and finished medicinal product has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Documentation has been presented to give reassurance on TSE safety.

2.3. Non-clinical aspects

2.3.1. Introduction

A comprehensive nonclinical development has been performed in support of this application.

The pivotal toxicology studies were conducted in accordance with Good Laboratory Practice (GLP). Some, but not all, of the safety pharmacology studies were conducted in compliance with GLP. Those that were conducted in compliance with GLP included the studies on the central nervous system, a study on the respiratory system in guinea pigs and some of the cardiovascular system studies (*in vitro* study in isolated piglet Purkinje fibres and *in vivo* studies on haemodynamic parameters in dogs). The non-GLP studies generally seem to have been conducted in a scientifically appropriate manner.

2.3.2. Pharmacology

Primary pharmacodynamic studies

A series of *in vitro* studies has shown aclidinium bromide to be a competitive inhibitor of muscarinic receptors. It has a similar potency at all five human muscarinic receptors (affinity values of 0.09, 0.1, 0.12, 0.25 and 0.16 nM for M1, M2, M3, M4 and M5 receptors, respectively), but kinetically, shows a preference for the M3 receptor. The *in vitro* test systems used were CHO cells expressing the muscarinic receptors and isolated tissues including guinea pig trachea, guinea pig left atria, human trachea and rabbit iris; carbachol-, acetylcholine- and electrically-induced contractions were used in these studies, and comparisons were made with ipratropium bromide and tiotropium bromide.

Potency was similar for aclidinium, tiotropium and ipratropium bromides in these studies, but offset times/dissociation from the receptors was fastest for ipratropium bromide, and longest for tiotropium bromide. Aclidinium bromide showed offset times/dissociation from the receptors that were longer than for ipratropium bromide, but shorter, although closer to those for tiotropium bromide. For example, half-lives for dissociation from the M3 receptors were 29.2, 0.47 and 62.2 hours for aclidinium bromide, ipratropium bromide and tiotropium bromide, respectively.

In vivo studies showed inhibition of Ach-induced bronchoconstriction in anaesthetised guinea pigs and dogs; potency and onset/duration of action were investigated.

In anaesthetised guinea pigs, the onset of action of aclidinium bromide (30 min) was similar to ipratropium bromide (30 min) but faster than tiotropium bromide (80 min). The duration of action (measured as time needed to decrease the maximal effect by 50%) was also assessed in guinea pigs. The duration of action of aclidinium bromide (t1/2= 29 h) was longer than ipratropium bromide (t1/2= 8h) and shorter than tiotropium bromide (t1/2= 64 h).

Aclidinium bromide and tiotropium bromide showed similar long-lasting effects on acetylcholine-induced bronchospasm in dogs, inhibiting it up to 87% and 99% respectively, when administered by aerosolation in a liquid formulation.

The S-isomer of aclidinium bromide (LAS35040) had little affinity for muscarinic receptors *in vitro* (45.5 nM, 16 nM and 154.8 nM for M1, M2 and M3 respectively, which is 325, 94 and 910 times less potent than aclidinium bromide at these receptors) and limited effect on Ach- induced bronchoconstriction in anaesthetised guinea pigs (maximal effect of 37% inhibition at 1000 µg/mL, when administered by aerosol [EC50 >1000 µg/mL compared with 2.9 µg/mL for aclidinium bromide]).

The main metabolites of aclidinium bromide, LAS34823 and LAS34850, had no affinity for muscarinic receptors *in vitro* and did not show any significant effect on Ach- induced bronchoconstriction in anaesthetised guinea pigs when administered by inhalation.

Secondary pharmacodynamic studies

Possible secondary pharmacology effects of aclidinium bromide and its main metabolites LAS34823 and LAS34850 have been investigated using a range of enzymes and receptors. The metabolites showed no affinity for any of the receptors, enzymes, ion channels and transporters tested. Aclidinium bromide showed only moderate affinity (IC50 was ≥ 1 µM) for α1, H1 (central), NK1, and 5-HT uptake receptors. On the basis of these results, secondary pharmacology effects are considered unlikely at therapeutic exposures.

Safety pharmacology programme

Aclidinium bromide had no remarkable effects on the central nervous system in an Irwin test or study of spontaneous activity in mice following single oral doses up to 300mg/kg.

In a series of cardiovascular studies, aclidinium bromide blocked the hERG channel with an IC50 of 19.7 µM. It had no effect on QTc interval in anaesthetised rats or guinea pigs at iv doses or 3 mg/kg or 1 mg/kg, respectively, and there were no ECG changes in a rat repeated dose SC study following doses of 2.5mg/kg twice daily for 25 days. Slight decreases in heart rate were noted in an escalating dose iv study in anesthetised dogs at doses up to 300 µg/kg, without consistent effect on ECG. Transient effects on haemodynamic parameters were recorded at iv doses up to 1000 µg/kg iv in anaesthetised dogs, whilst in conscious dogs at an iv dose of 100 µg/kg, heart rate increased with minimal effect on QT (and negligible effect on QTc). A brief chronotropic effect was noted in conscious dogs at 100 µg/kg iv, in contrast to tiotropium bromide, which produced a more sustained chronotropic effect at a 10-fold lower dose. Therefore there were some minor cardiovascular effects in some studies, but at concentrations that generally exceeded clinical exposure by at least three orders of magnitude.

Aclidinium bromide had no effect on tracheal mucociliary transport rate in isolated piglet trachea or in anaesthetised guinea pigs following an iv dose, and did not affect respiratory parameters in conscious guinea pigs following inhalation of an aerosol.

Studies on renal function in dogs (intravenous dose of 1 mg/kg) and urinary retention in rats (SC doses up to 1 mg/kg) and guinea pigs (intratracheal doses up to 100µg/kg) showed aclidinium bromide to have no significant effects on these parameters, whereas effects were noted with tiotropium bromide and ipratropium bromide.

In anaesthetised mice and conscious rats, aclidinium bromide was less potent in inducing dry mouth than tiotropium bromide and ipratropium bromide. Colonic motility was not affected by aclidinium bromide in anaesthetised guinea pigs, whereas tiotropium bromide significantly inhibited colonic motility. Aclidinium bromide decreased faecal output in conscious rats with a 16-fold lower potency than tiotropium bromide.

These results suggest that aclidinium bromide is less likely to induce urinary retention, dry mouth and/or constipation than tiotropium bromide or ipratropium bromide.

Pharmacodynamic drug interactions

Aclidinium bromide did not affect either the incidence or the rate of formoterol-induced ventricular tachycardia in conscious dogs when the two drugs were co-administered. In addition to the studies with formoterol, the applicant provided new data from studies on the effects of combining aclidinium bromide with indacaterol and salmeterol on the heart rate of conscious dogs following administration of high intravenous doses. The intravenous route of administration was chosen to ensure high peak and onset of activity of both compounds tested. The C_{max} plasma levels were 2000, 7.3 and 49 fold higher than observed in clinical use for aclidinium bromide, salmeterol and indacaterol, respectively. There

was no indication of a synergistic or additive effect on heart rate when these compounds were co-administered. Although no specific studies were conducted with the combination of aclidinium bromide and short-acting beta agonists (e.g. salbutamol), the applicant suggested that the intravenous administration of high doses of LABA may mimic the rapid onset of activity expected from some of the short-acting beta-agonists. Overall the potential for pharmacodynamics interactions between aclidinium bromide and beta adrenergic agents has been discussed adequately.

2.3.3. Pharmacokinetics

Absorption

Pharmacokinetic studies confirmed exposure of mice, rats and dogs to aclidinium bromide and its main metabolites LAS34823 (alcohol derivative, quaternized 3-(R)-quinuclidinol) and LAS34850 (acid derivative, dithienylglycolic acid), irrespective of the route of administration.

Generally, exposure to aclidinium bromide and its alcohol metabolite were similar, with the main circulating compound being the acid metabolite.

Aclidinium bromide is poorly absorbed by the oral route, and rapidly hydrolysed non-enzymatically and by esterases distributed throughout the body, therefore its oral systemic bioavailability is negligible.

Exposure to aclidinium bromide and its metabolites in humans following an inhaled 400 µg dose is considerably lower than the values obtained in the animal studies.

Distribution

Aclidinium bromide, labelled as either [phenyl-14C] or [glycolyl-14C], was rapidly and widely distributed following intravenous administration to male and female albino rats and pregnant females. The main organs of distribution were kidney, bladder, pancreas and GI tract tissues. Absorption and distribution were lower after oral dosing, with radioactivity mainly in GI tissues.

A single intratracheal injection to male albino rats showed similar absorption and distribution to that following oral administration, but with higher levels in the lungs.

Distribution did not appear to be different in pigmented compared with albino rats. Radioactivity crosses the placenta in pregnant rats and is found in the milk of lactating rats.

Binding to melanin is limited and reversible.

In vitro plasma protein binding showed that the acid metabolite (LAS34850) of aclidinium bromide was more highly bound than the alcohol metabolite (LAS34823), with binding across species ranging from 66 to 87% and 12 to 26%, respectively. Binding was independent of concentration and in human plasma, binding appears to be mainly to human serum albumin.

Metabolism

In vitro and *in vivo* studies demonstrate that the main metabolic pathway for aclidinium bromide is hydrolysis to its alcohol and acid metabolites, LAS34823 (quaternized 3-(R)-quinuclidinol) and LAS34850 (dithienylglycolic acid), respectively, in all species studied (mouse, rat, rabbit, dog and human). There are no human-specific metabolites.

In human liver microsomes, non-enzymatic hydrolysis was the main route of metabolism of aclidinium bromide. Other minor oxidative metabolic routes were identified for aclidinium bromide and the alcohol

metabolite LAS34823, mainly catalysed by CYP2D6 and CYP3A4. The acid metabolite LAS34850 was not further metabolised enzymatically in human liver microsomes.

There were no qualitative differences in the metabolism of aclidinium bromide when incubated with human and Aroclor 1254-induced rat S9 liver fractions. Covalent protein binding was low in all the conditions assayed and there was no significant difference between the two species, although there was a tendency for the covalent binding to be higher in the Aroclor 1254-induced rat S9 liver fractions.

In vitro irreversible binding in mouse, rat, rabbit, dog and human hepatocytes was <2% in all cases.

In hepatocytes from mouse, rat, rabbit, dog, and human, the main radioactive metabolites of [14C-phenyl]-LAS34273 were LAS34823 (M2, the alcohol metabolite) and its p-hydroxy metabolite (M1). Glucuronide conjugates were also formed. The major radioactive metabolite of [14C-glycolyl]-LAS34273 in hepatocytes was LAS34850 (the acid metabolite). Several minor polar metabolites were also seen.

Aclidinium bromide was less stable than ipratropium bromide, tiotropium bromide and glycopyrrolate bromide in plasma from humans, dogs, rats and guinea pigs.

Investigation of the enzymes involved in hydrolysis of aclidinium bromide showed that the B-esterases and particularly butyrylcholinesterase had a major role. Butyrylcholinesterase is widely distributed in the human body, mainly localised in plasma but butyrylcholinesterase activity has also been observed in human pulmonary and liver subcellular fractions, which means that aclidinium bromide hydrolysis can take place in these organs before entering the systemic circulation after inhalatory and oral administration.

In vivo metabolism studies in rat, dog, mouse and pregnant rabbit reflect the *in vitro* findings.

Excretion

Both urinary and faecal routes of elimination are used. Following intravenous administration of [14C]-glycolyl-aclidinium bromide, most radioactivity (mostly LAS34850) was eliminated in the urine in all species investigated, while intravenous administration of [14C]-phenyl-aclidinium bromide led to most radioactivity (LAS34823, mono-hydroxy-LAS34823 and its glucuronide conjugate) being eliminated mainly in the urine in mice, dogs and humans, mainly in the faeces in rats and equally in urine and faeces in pregnant rabbits. Most of the dose was eliminated within 48 hours in most species, although in man, elimination was generally within 96 or 120 hours.

Pharmacokinetic drug interactions

In vitro studies on the effects of aclidinium bromide and its main metabolites LAS34823 and LAS34850 as substrates, inducers and/or inhibitors of human hepatic cytochrome P450 isozymes, plasma esterases or P-glycoprotein have been conducted.

Aclidinium bromide and its metabolites LAS34823 and LAS34850 did not show any significant induction of cytochrome P450 expression in cultured human hepatocytes.

Aclidinium bromide and LAS34823 competitively inhibited CYP 2D6 (IC50s of 2.4 and 20.6 µM, respectively) and aclidinium bromide showed slight inhibition of CYP 3A4/5 (IC50 of about 90 µM).

Aclidinium bromide competitively inhibited human plasma acetylcholinesterase and butyrylcholinesterase activities with a Ki of 6.3 µM and 2.7 µM, respectively, and showed some inhibition of carboxylesterase activity (IC50 of about 50 µM). LAS34823 slightly inhibited acetylcholinesterase and butyrylcholinesterase with IC50 values of about 100 µM Paraoxonase and

arylesterase were not inhibited by any of the compounds, and LAS34850 (100 μM) had no effect on the activity of any of the esterases studied.

These IC50 values are well in excess of the human plasma Cmax levels of aclidinium bromide (0.077 ng/mL, 0.136 nM) or LAS34823 (0.071 ng/mL, 0.207 nM) following inhalation of therapeutic doses of aclidinium bromide (400μg BID). Therefore clinically relevant doses of aclidinium bromide would not be expected to alter the disposition of drugs metabolised by the human CYP450 enzymes or of acetylcholine or drugs metabolised by the human esterases.

P-glycoprotein is not inhibited by aclidinium bromide or its metabolites, and nor are they substrates for this transporter, therefore the disposition of aclidinium bromide or drugs that are P-gp substrates are unlikely to be altered when co-administered.

2.3.4. Toxicology

Single dose toxicity

Aclidinium bromide showed little or no toxicity in rats following single oral, intravenous or inhalation doses of up to 2000 mg/kg, 1.2 mg/kg or 3.7-3.8 mg/kg, respectively. Deaths in an oral mouse study occurred only in females and at the low and mid doses and not at the high dose of 2000 mg/kg. In a subsequent (micronucleus) study using the same oral doses, there were no deaths. The deaths in the single-dose study remain unexplained.

Repeat dose toxicity

Repeated dose studies have been carried out in mice, rats and dogs using the clinical (inhalation) route as well as intravenous, subcutaneous and oral routes. A number of the studies were conducted to investigate the cause of deaths seen in the rat studies.

In a 13-week inhalational study in the mouse, reduced body weight gains were observed at the top dose (2 mg/kg/day) and liver weights were increased in treated animals. The NOAEL was considered to be 0.61 mg/kg/day.

Effects on the respiratory system were noted in 2-week and 4-week inhalational toxicity studies in the rat. Nasal cavity goblet cell hyperplasia and inflammation were noted in the nasal cavity in the 2-week study, with the inflammation suggestive of minor irritation. In the 4-week study, pathological findings in the Harderian gland were seen. Nasal cavity and nasopharyngeal goblet cell hyperplasia and alveolar macrophages were also noted but there was no accompanying inflammation and the findings were not considered to be of toxicological concern.

In the 6-month inhalational toxicity study in rats at doses from 0.1 to 2 mg/kg/day, a number of deaths without dose-dependence occurred. Remnants of the dry food were found in the larynx and oesophagus, and the presence of food was considered to be related to a reduction in salivation due to the pharmacological action of aclidinium bromide. Hypertrophy of the parotid glands and associated pathological findings were correlated with the proposed pharmacologically mediated reduction in salivation. The main histopathological findings in this 6-month study comprised haemosiderin deposition in the adventitia of blood vessels of the lungs, perivascular inflammation in arterioles and arteries along with BALT and alveolar macrophages at all doses. Alveolar wall hyperplasia/hypertrophy was increased in incidence at the mid- and high-dose. The Harderian gland was again a target organ with porphyrin deposition and hypertrophy noted. A NOAEL was not established in this study.

A second 6-month inhalation study was conducted in rats using lower doses of 0.01, 0.04, 0.08, 0.2 mg/kg/day. There were a similar number of deaths in the treated animals, which were again

considered to be related to the pharmacological action of aclidinium bromide. These animals also had remnants of food in the larynx and oesophagus. The lungs, Harderian glands and parotid glands were again primary target organs. The NOAEL established in this second 6-month rat inhalational toxicity study was 0.04 mg/kg/day. The AUC for aclidinium bromide was about 20-fold that in humans, extrapolated from the AUC in young and old COPD patients following metered doses of 400 µg once daily.

The same pattern of deaths (7/100 treated rats) occurred in a further 6-month inhalational toxicity study at 0 and 2 mg/kg/day. Yellowish or reddish discoloration or discoloured foci in the lungs was seen in some animals at the end of the study, accompanied by pigment-laden alveolar macrophages and/or alveolar macrophage conglomerates. Broncho-alveolar lavage fluid investigations showed no effects on IL-6, TNF-α and histamine levels but there were increased numbers of macrophages in the broncho-alveolar lavage fluid in a few treated animals from 2 months onwards. Histopathology investigations showed haemosiderin deposition in alveolar macrophages after 1 month of exposure, which increased in incidence and severity until the end of the study. Macrophage conglomeration with compression of alveolar walls was not seen in this study, and there was also no inflammatory component of small arteries and arterioles. As seen in the earlier studies, findings in the Harderian gland were observed. Squamous metaplasia was noted in the larynx in some treated animals after 3 months of exposure. This finding had been shown to be reversible in the previous 6-month study. In the parotid gland, diffuse acinar hypertrophy was noted in a few cases at 6 months.

Another 6-month inhalation toxicity study was carried out in rats at 0 or 2 mg/kg/day to compare the toxicity of two different batches of aclidinium bromide. The findings were similar to those in the previous study, with target organs being the lungs, parotid glands and Harderian glands. There was no difference in toxicity profile between the two batches.

In a further study to investigate whether inhibition of salivation and impairment of swallowing due to the anti-muscarinic action of aclidinium bromide was responsible for the deaths noted in inhalation studies, telemetered rats were dosed at 0 or 2.5 mg/kg twice daily via the subcutaneous route for 25 days. Aclidinium bromide induced gasping and coughing episodes, which were more frequent during the dark period i.e. during the period of feeding. Rats appeared to have difficulty swallowing. In a second rat study using the subcutaneous route with treatment over 28 days and with diurnal access to food, the most noteworthy clinical signs observed were difficulty with swallowing the food and repeated choking and gasping episodes. A low incidence and slight severity of pigment-laden alveolar and adventitial macrophages in the lungs was seen.

In a 26-week study via the subcutaneous route, rats were dosed at 1 mg/kg/day and effects due to the pharmacological action of aclidinium bromide were seen. These included two deaths with food remnants in the larynx, reversible mydriasis, and histopathological findings in lungs, parotid glands and Harderian glands.

The studies conducted are considered to provide sufficient evidence that the deaths seen in the repeated-dose rat studies are a result of the antimuscarinic activity of aclidinium bromide resulting in reduced salivation and resultant difficulty in swallowing food. Anti-muscarinic activity affecting oesophageal motility may also have been involved. Choking and gasping episodes and remnants of food in the larynx could explain the pigment-laden alveolar macrophages in the lung and deaths by asphyxiation. A similar explanation for the cause of the unusual mortality has been proposed for tiotropium bromide. Further support for the mechanism is the absence of increases of inflammatory markers in the bronchioalveolar lavage fluid and of inflammatory infiltrates in the lungs in the mechanistic inhalation study, suggesting an absence of hypersensitivity or immunological reaction.

Oral studies were carried out in the rat for 2 and 4 weeks. Findings included mydriasis and compacted faeces in the rectum and colon and were expected antimuscarinic pharmacological effects of aclidinium

bromide. The NOAELs were the high doses of 640 and 450 mg/kg/day, respectively. Mydriasis was again noted in a 14-day repeated intravenous (bolus) dose study in rats at all doses (0.06-0.6 mg/kg/day), with the highest dose being the NOAEL, at which AUC was 130-fold human exposure.

In 2-week and 4-week inhalation studies in dogs, transient increases in heart rate and shortening of P-Q and/or Q-T intervals were seen at doses of 0.125, 1 and 2 mg/kg/day. Food consumption and body weight increased and salivary gland weight increased at 1 and 2 mg/kg/day.

In a 39-week inhalation study in dogs, the high dose of 1.6 mg/kg/day was reduced to 0.8 mg/kg/day following the deaths of some male dogs. Reduced tear production and increased incidence and severity of restlessness (in males) were seen, as well as decreased body weight and food consumption. Transient increases in heart rate and P-wave amplitude and/or shortening of QT interval occurred. The reduced tear production and changes in heart rate were reversible and the NOAEL was considered to be 0.22 mg/kg/day.

A 2-week oral study in dogs at doses of 0, 12.5, 25, 50, 100, 200 mg/kg/day showed decreased food intake and body weight and increased heart rate from 25 mg/kg/day. At 50 mg/kg/day and above, there were signs of effects on the central nervous system, with decreased activity and tremors, and additional signs at the high dose included somnolence, recumbency and abnormal posture. The NOAEL was therefore 25 mg/kg/day.

In a 4-week oral study in dogs, aclidinium bromide at doses of 5, 25, 125 mg/kg/day was generally well tolerated, with effects considered to be related to the pharmacological action such as increased heart rate and reduced tear production. Ophthalmic findings were related to decreased tear production. The NOAEL is considered to be 125 mg/kg/day.

In these two oral studies in dogs, similar doses were used but the NOAELs were quite different. Clinical signs indicative of CNS effects were noted at 50, 100 and 200 mg/kg/day in the 2-week study but not in the 4-week study. The latter study is considered more reliable than the dose range-finding study. The polar nature of aclidinium bromide makes it unlikely to cross the blood brain barrier. The plasma concentrations of both aclidinium bromide and the major acid metabolite LAS34850 were greater in the 4-week than in the 2-week study. The clinical signs in the 2-week study were therefore attributed to secondary effects caused by the pharmacological activity of a high dose of an antimuscarinic drug on the gastrointestinal tract rather than a direct effect on the CNS. The dogs used in the 4-week study came from a different breeder and could have been less sensitive to the local gastrointestinal effects induced by aclidinium bromide than the animals used in the 2-week study.

In a 2-week intravenous study in dogs, there were pharmacological signs (dry oral mucous membranes, dry noses and increased heart rate) at all doses (0.06, 0.2 and 0.6mg/kg/day). These effects were not evident in the recovery animals. The NOAEL was therefore considered to be 0.6 mg/kg/day.

Toxicokinetic data

Toxicokinetic analysis showed animals were exposed to aclidinium bromide and its major alcohol and acid metabolites, LAS34823 and LAS34850, following administration via the inhalation, intravenous, oral and subcutaneous routes. In general, exposures (Cmax and AUC) to aclidinium bromide and the alcohol metabolite LAS34823 were similar, irrespective of administration route, but the main circulating metabolite was LAS34850.

For comparison with the exposures in the pivotal toxicity studies, the AUC value for aclidinium bromide from study M/34273/09 in male COPD patients following a single daily dose of 400 µg for 3 days was extrapolated to represent clinical dosage of 400 µg BID. Higher single inhaled doses (up to 6000 µg)

were given to healthy volunteers, but the only study in which the intended clinical dose of 400 µg twice daily was administered was in LAS-PK-12, in which, in healthy male subjects, the Cmax was 0.248 ng/mL and the AUC was 1.004 ng.h/mL. Consequently if these values are used rather than the extrapolated values from the study (M/34273/09) in young and elderly COPD patients (Cmax 0.077 ng/mL and AUC 0.392 ng.h/mL), the safety margins will be lower. Furthermore, the patient study M/34273/09 was a 3-day study, whereas LAS-PK-12 was a 7-day study, where it is more likely that steady state will have been reached. Nevertheless, the exposure margins would still be acceptable if these higher values were used for the calculations.

Safety margins for metabolites LAS34823 and LAS34850 based on Cmax and AUC for all pivotal toxicity studies in general are very large, except for the 26-week inhalation toxicity study in rats based on AUC, where these are below 1 for both metabolites owing to the low NOAEL value in this species. However, the systemic safety of LAS34823 and LAS34850 was confirmed in oral and intravenous toxicity studies in rats and dogs, where higher NOAEL values were attained. Additionally, neither metabolite is pharmacologically active.

Genotoxicity

In the *in vitro* genotoxicity studies (Ames test and the mouse lymphoma forward mutation assay), results were either negative, equivocal or weakly positive and did not appear to have any relationship to the purity of the batches used. Positive findings only occurred in the presence of S9 fraction from Arochlor-1254 induced rat liver.

In the Ames test, positive findings appeared to be restricted to S. typhimurium strain TA98 at high concentrations of aclidinium bromide, and increases in revertants were around 2-fold, the criterion for a positive response. In the mouse lymphoma forward mutation assays, there was no clear concentration-related response.

Two *in vivo* studies were conducted, using different end-points and tissues. These were a mouse bone marrow micronucleus test and an unscheduled DNA synthesis (UDS) assay in rat liver. In the mouse study, oral doses up to 2000 mg/kg were administered and in the rat study, SC doses of 8 and 20 mg/kg were used; toxicokinetic data demonstrated systemic exposure at these doses. Both *in vivo* studies were negative. At the top dose (2000 mg/kg) in the mouse study, AUC(0-24) was 1776.5 ng.h.mL; this is 4532-fold the AUC of 0.392 ng.h/mL.

The potential formation of reactive metabolites was investigated previously in an *in vitro* metabolism and covalent protein binding study in human liver and Aroclor 1254-induced rat liver S9 fractions (B.34273.39), in which metabolism was similar in the two species and covalent protein binding was low (<0.15%) in all conditions assayed. However, the covalent protein binding was slightly higher for the samples incubated with Aroclor 1254-induced rat S9 liver fraction.

The overall conclusion, based on negative/equivocal/weak positive findings in *in vitro* studies, limited covalent protein binding and negative *in vivo* studies using different end points and exposures that were 3 orders of magnitude greater than human exposure, combined with negative carcinogenicity assay results, is that aclidinium bromide is not genotoxic.

Carcinogenicity

Two-year carcinogenicity studies were conducted in mice and rats using the inhalation route. There were no treatment-related neoplastic findings in either species. Non-neoplastic changes in the mouse were confined to the nasal cavities. In the rat, there were non-neoplastic changes in the lung, respiratory tract and Harderian gland, and some deaths related to the pharmacology of aclidinium bromide, as seen in the chronic inhalation toxicity studies. Toxicokinetic analysis demonstrated that

both species were exposed to aclidinium bromide and its main metabolites and at the high doses in both studies, which were considered to be the NOAELs (2.5 mg/kg/day in mice and 0.2 mg/kg/day in rats), exposure exceeded that in man following a therapeutic dose by at least 25-fold.

Reproduction Toxicity

In an inhalation fertility and early embryonic development study in rats, reductions in fertility parameters (number of corpora lutea and implantation sites) were noted. The AUC at the NOAEL of 0.4 mg/kg twice daily was 160-fold that in humans. Deaths in this study appeared to be related to the same pharmacological mechanism as in the repeated dose toxicity and carcinogenicity studies.

Aclidinium bromide did not show teratogenic or embryotoxic effects in developmental toxicity studies in rats and rabbits by inhalation at doses up to 2.4 and 1.8 mg/kg twice daily, respectively. In the rat study, slight non-dose-related effects on fetal weight and ossification were observed in the treatment groups, so a NOAEL was not established for fetotoxicity. In a rabbit development study via the oral route at doses up to 600 mg/kg/day, aclidinium bromide reduced fetal weights at 300 and 600 mg/kg/day, without any teratogenic effects. The AUC at the NOAEL of 150 mg/kg/day was 93-fold that in man.

Reductions in food consumption in dams and body weight gain in dams and pups were observed in an inhalational pre- and post-natal development study in the rat from 0.2 mg/kg/day. Three developmental indices of the pups showed marginal changes at 2.4 mg/kg/day, corresponding with reduced pup weights. The NOEL for the F0 dams and the F1 offspring was 0.02 mg/kg/day. However, the NOAEL for reproductive capacity of the F1 animals was 2.4 mg/kg/day.

Local Tolerance

Aclidinium bromide was non-irritating to skin or eyes (producing only a reversible reddening of the conjunctivae) in primary irritation studies in rabbits.

Other toxicity studies

Antigenicity

Aclidinium bromide was not a sensitiser in a passive cutaneous anaphylaxis (PCA) test in rats, by inhalation in guinea pigs or in a local lymph node assay in mice following dermal administration.

Impurities

The drug substance specification limits a number of impurities, four of which exceed the qualification threshold. These were qualified by their presence in batches of drug substance used in the chronic toxicity and carcinogenicity studies, and in the case of quaternized 3-(R)-quinuclidinol (LAS34823) and dithienylglycolic acid (LAS34850), because they are the main alcohol and acid metabolites of aclidinium bromide. Additional non-genotoxic impurities are limited at ≤ 0.1% and therefore do not require qualification.

A number of impurities with genotoxic alerts were investigated in bacterial reverse mutation studies. Three of these were negative and are limited in the drug substance specification at ≤ 0.1% (either named or within 'any unspecified impurity'). Two were positive, one of which, 1-bromo-3-phenoxy-propane is limited to ≤ 200ppm and the other, bromo-propoxy-propyl derivative, was not named in the initial drug substance specification and therefore controlled as any unspecified impurity (≤ 0.1%). Although exposure to these compounds would be below the threshold of toxicological concern (TTC) if

they were present at their proposed limits (and therefore the limits are acceptable), given the positive Ames test for the bromo-propoxy-propyl derivative, this has now been added as a specified impurity in the drug substance specification and limited at $\leq$ 0.10%

Bromopropoxyphenylpropyl derivatives (isomers) are not controlled in the drug substance specification but were reportedly present in one batch of aclidinium bromide that was manufactured using 1-bromo-3-phenoxypropane from a supplier different from the one currently used. As these compounds have an alert for genotoxic potential and were present in the batch in which they were detected at 0.4%, which would result in an intake greater than the TTC, the applicant provided a commitment to ensure that the absence of bromopropoxyphenylpropyl derivatives (isomers) will be confirmed if a different supplier of 1-bromo-3-phenoxypropane is used in the future.

2.3.5. Ecotoxicity/environmental risk assessment

Ecotoxicity data of aclidinium bromide are presented below.

Substance (INN/Invented Name): Aclidinium bromide			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}		**n.a**	Potential PBT (Y/N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	**1.9**	B/**not B**
	BCF	**n.a**	B/not B
Persistence	DT50 or ready biodegradability	**n.a**	P/not P
Toxicity	NOEC or CMR	**n.a**	T/not T
PBT-statement :	**The compound is not considered as PBT**		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	**0.004; default values of Fpen, WASTEWinhab, DILUTION**	µg/L	> 0.01 threshold (Y/**N**)
Other concerns (e.g. chemical class)	**Aclidinium bromide is not stable under acid and alkaline conditions**		(Y/N)

Aclidinium bromide $PEC_{surfacewater}$ value is below the action limit of 0.01 µg/L and is not a PBT substance as log Kow does not exceed 4.5.

2.3.6. Discussion on non-clinical aspects

In vitro and *in vivo* pharmacology studies have shown aclidinium bromide to be a long acting, reversible M3 muscarinic receptor antagonist with a rapid onset of action.

Secondary pharmacology studies showed little affinity for other receptor types or ion channels.

Safety pharmacology studies showed that aclidinium bromide may have a lower propensity to affect the urinary and gastrointestinal systems than either ipratropium bromide or tiotropium bromide. Minor changes in cardiovascular parameters occurred at concentrations well in excess of expected therapeutic concentrations.

Metabolism is similar across species, with rapid hydrolysis to its main alcohol and acid metabolites, both of which are pharmacologically inactive. The acid metabolite is the major circulating metabolite irrespective of route of administration. There would appear to be little propensity for pharmacokinetic drug-drug interactions.

In toxicity studies, the findings generally reflect the exaggerated pharmacology of aclidinium bromide, such as dry mouth, reduced salivation and tear production. The lungs, Harderian glands and parotid glands were primary target organs. Inhalation studies in rats led to a number of deaths, which were further investigated in repeated inhalation studies and other mechanistic studies. These studies suggest that the deaths were likely due to reduced salivation causing gasping and choking episodes, with difficulty swallowing leading to remnants of food in the larynx and oesophagus.

Toxicokinetic analysis measured aclidinium bromide and its main acid and alcohol metabolites, and exposures at the NOAEL in the toxicology studies generally exceed the human exposure by at least one order of magnitude.

In vitro genotoxicity studies showed some equivocal or weak positive results at high concentrations in the presence of metabolic activation, but two *in vivo* studies were negative and there were no neoplastic findings in 2-year carcinogenicity studies and therefore aclidinium bromide is not considered to be genotoxic or carcinogenic.

Reproductive toxicity studies revealed an effect on female fertility and fetotoxicity, not teratogenic in rats or rabbits.

Aclidinium bromide is not a sensitiser and was non-irritant in local tolerance studies in rabbit eye or skin, although the inhalation studies did show some evidence of irritation in the nasal passages in rats.

A series of studies was conducted to qualify impurities and these are appropriately limited in the drug substance specification.

The environmental risk assessment showed that the use of the product is unlikely to pose a risk to the environment.

2.3.7. Conclusion on the non-clinical aspects

The pharmacodynamics, pharmacokinetic and toxicological properties of aclidinium bromide have been adequately demonstrated. Overall, the non-clinical programme does not highlight any safety concerns for the patient treated twice a day with inhalational therapeutic doses of aclidinium bromide 400 µg.

2.4. Clinical aspects

2.4.1. Introduction

The application is supported by data from clinical studies in which 5447 COPD patients worldwide received at least one dose of investigational medicinal product (IMP).

The efficacy of aclidinium bromide BID was investigated in two Phase II studies (M/34273/23 and M/34273/29) which enabled the bronchodilatory profile of aclidinium bromide at steady-state to be benchmarked against that of tiotropium and formoterol. In addition, study M/34273/29 demonstrated the dose-response of aclidinium bromide. The Phase III clinical development programme comprised three randomised, double-blind placebo-controlled studies which evaluated aclidinium bromide 400 µg and 200 µg BID; one with a 24-week treatment duration (M/34273/34) and the other two with 12-week treatment durations (LAS-MD-33, LAS-MD-38 Part A). The study designs and target populations

of these Phase III studies were similar with the only difference between the studies, other than treatment duration, being the choice of secondary endpoints.

The claimed and final approved indication was the maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).

National Scientific Advice was given by a number of European regulatory agencies related to the clinical development programme (QD as well as BID development).

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 1: Overview of Healthy Subject Pharmacokinetic Studies

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.	Randomised, 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: Randomised, single blind, placebo controlled, three-period, cross-over. Part II: Randomised, 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.	Randomised, 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.	Randomised, 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.

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

Table 2: Overview of Intrinsic Factor Pharmacokinetic Studies

Study ID	Study Objective	Study Design	Treatment	Population
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).

Abbreviations: PK pharmacokinetics; QD once daily; COPD chronic obstructive pulmonary disease.

Table 3: Overview of Pivotal Studies Contributing to the Efficacy Evaluation of Aclidinium Bromide BID

Study Code / Status	Aclidinium Bromide Dose (µg)	Design	Control Group(s)	Treatment Duration	Number of Patients[a]	Variable(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

[a] Number of patients randomised.

Abbreviations: BID=twice daily; db=double-blind; FEV_1=forced expiratory volume in one second; p=parallel group; pbo=placebo (controlled); r=randomised; SGRQ=St. George's Respiratory Questionnaire; TDI=Transition Dyspnoea Index; wks=weeks.

2.4.2. Pharmacokinetics

Four clinical studies were conducted to investigate primarily the PK of inhaled aclidinium bromide in healthy subjects. One of these studies was a single ascending dose study (M/34273/01), two were cross-over designs investigating single ascending doses (M/34273/05) or multiple doses administered once daily (M/34273/06) and one was a parallel group study to investigate multiple doses administered BID (LAS-PK-12).

The PK of multiple QD doses of inhaled aclidinium bromide were investigated in Study M/34273/06, however low plasma levels of aclidinium bromide relative to the LLOQ of the assay hampered meaningful PK analysis in this study.

In addition studies M/34273/03 investigated the distribution of aclidinium bromide into the lungs, M/34273/04 was a mass balance study following an intravenous administration of [14C] aclidinium bromide in healthy volunteers and AML/10 investigated the extent of protein binding of aclidinium bromide and its metabolites.

One study was conducted in patients with COPD, Study M34273/21, a randomised, double blind, placebo-controlled, four period cross over study of 3 ascending doses (100 µg, 300 µg and 900 µg). This was primarily a study to investigate the pharmacodynamic effect of aclidinium bromide – a 'proof-of-concept' study. However, PK/PD relationships were not investigated as plasma levels of aclidinium bromide were below the LLOQ of the bioanalytical assay.

A further study (M/34273/09), which was primarily conducted to investigate the effects of age on the PK of aclidinium bromide, does give some further information on the PK in the target population.

Absorption

Aclidinium bromide is rapidly absorbed following inhalation. In healthy subjects, C_{max} is achieved approximately 5 minutes following inhalation. In COPD patients, C_{max} is achieved approximately 10 to 15 minutes post-dose.

Aclidinium bromide plasma exposure increased with increasing single inhaled doses up to 4200 µg.

Aclidinium bromide has a low absolute bioavailability of <5%.

Distribution

Following iv administration the mean apparent volume of distribution during the terminal phase for aclidinium bromide appeared to increase with ascending dose from 200 to 400 µg from 140 to 302 L, respectively, although individual subject data at all dose levels were highly variable (M/34273/05).

Differences were observed in the volume of distribution with different doses. The applicant concluded that these are more likely related to the highly variable results and the small number of subjects per dose level available rather than changes in this parameter (CV's of 81% [n=6] and 79% [n=4] with the 200 and 400 µg iv doses, respectively). Following inhalation of aclidinium bromide, very high and aberrant physiological values for volume of distribution (Vz/f) were observed, reflecting the very low bioavailability associated with this route of administration.

A scintigraphic analysis of the pulmonary disposition and distribution of [^{99}mTc]-radiolabelled aclidinium bromide demonstrated that 30.11% of the dose is deposited in the lung of which nearly 10% only reaches the central region of the lung.

The inactive metabolites of aclidinium bromide were found to be highly protein bound with the acid metabolite (LAS34850) demonstrating a protein binding of 90% and the alcohol metabolite

(LAS34823) demonstrating a protein binding of 10%. Protein binding of parent aclidinium bromide could not be ascertained owing to the rapidity with which it is metabolised in plasma.

Elimination

The metabolism of aclidinium bromide was investigated following intravenous administration to human subjects. Aclidinium bromide is hydrolysed in plasma to two molecules, the alcohol metabolite (LAS34823) and the acid metabolite (LAS34850) because aclidinium bromide is an ester. *In vitro* studies demonstrated that the metabolites are devoid of significant affinity on any receptors studied, including muscarinic receptors. Aclidinium bromide and its metabolites were inactive when tested against a panel of relevant enzymes (e.g. phosphodiesterase, monoaminoxidase A and B, ATPase and acetylcholinesterase).

The major metabolite is LAS34850 which has a plasma concentration about 100 times that of the parent compound aclidinium bromide. LAS34823 appears in plasma at similar concentrations to aclidinium bromide.

Aclidinium bromide is rapidly metabolised in plasma so that only 0.1% of the dose, administered by inhalation, is excreted unchanged in the urine. The metabolites are then mainly excreted in urine, some unchanged (30-50%) and the rest after further hydroxylation.

Dose proportionality and time dependencies

From the data from two studies (M/34273/05 and LAS-PK-12) the claims that aclidinium bromide exhibits dose proportionality and time independent kinetics were considered not supported. However the lack of adequate characterisation of aclidinium t1/2 is mitigated by the large portion of total AUC represented by the 0-12 h time interval. This was supported by the lack of evidence of accumulation in trough concentrations in Study LAS-PK-12 after twice daily dosing for 7 days, albeit in healthy volunteers.

The applicant presented further discussions that, with a further review of the data in Studies M/34273/05 and LAS-PK-12, were sufficiently reassuring that aclidinium bromide does indeed exhibit dose proportionality and time-independent kinetics. Therefore the CHMP concluded that a multiple dose study in renal patients would not be required.

Special populations

Renal impairment

Renal impairment may affect the excretion of the metabolites and this has been investigated in a single dose, open label, clinical trial to assess the pharmacokinetics of aclidinium bromide 400 µg administered by inhalation in healthy subjects and subjects with various degrees of chronic renal insufficiency (M/34273/08).

The $AUC_{(0\text{-}t)}$ was similar across the groups of patients with mild to severe renal impairment and higher than in the healthy controls. T½ and the elimination rate constant (λ_z) tended to be higher in the renally impaired groups compared to healthy individuals, while the apparent total plasma clearance (Cl/f) tended to be lower.

A similar pattern was seen for the two metabolites but to a greater extent with the increase in T½ and λ_z reaching statistical significance for LAS 34850. However as the metabolites are inactive the increase in exposure in patients with renal impairment is unlikely to be clinically relevant.

This was a single dose study in accordance with Guidance CHMP/EWP/225/02 which states that a single dose study is sufficient when the drug exhibits linear and time independent pharmacokinetics.

It is not possible from these results to assess whether there would be accumulation of aclidinium bromide following multiple dosing but as aclidinium bromide exhibits dose proportionality and time independent kinetics then the proposal not to recommend a dose adjustment for renal impairment is supported.

Hepatic impairment

Aclidinium bromide undergoes very rapid and complete clearance from the body as a consequence of both chemical and enzymatic hydrolytic cleavage primarily by plasma esterases. Hepatic metabolism plays a very minor part in the clearance of aclidinium bromide and, therefore, hepatic dysfunction is very unlikely to alter its PK. Consequently, a study to assess the influence of hepatic dysfunction on PK was considered unnecessary and has not been performed.

Elderly

A multiple dose, open-label, cross over (two period) study (M/34273/09) was conducted to assess the pharmacokinetics of aclidinium bromide at the then proposed therapeutic dose (200 µg QD) and twice this dose administered by inhalation, after single administration and at steady state. One objective of this study was to evaluate whether the pharmacokinetic behaviour of aclidinium bromide is affected by the age of the patients so eligible patients were randomised to two groups according to their age:

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

The overall exposure of the 'old' age group was not increased compared to the 'young' age group at the dose levels investigated.

Exposure to the acid metabolite LAS34850 was generally higher in the elderly compared to the young age group as evidenced by a higher AUC_t and AUC_t^{ss} for both doses and higher C_{max} on Day 3 for the 200 µg dose and Days 1 and 3 for the 400 µg dose. A similar pattern was seen for the PK of the alcohol metabolite LAS34823. Although these differences reached statistical significance they are unlikely to be clinically relevant as the metabolites of aclidinium bromide are inactive.

Gender and race

No specific analyses of pharmacokinetics according to gender and race and no specific studies to explore the effects of gender and race were conducted. In the pivotal efficacy studies there was a higher proportion of males in study M/34273/34 (67%) compared to studies LAS-MD-33 (53%) and LAS-MD-38 Part A (53%) and the majority of patients in the pivotal studies were Caucasian (91% to 95%). There were minor differences in the racial profile between studies due to their conduct in different geographical regions.

Aclidinium bromide is only minimally absorbed into the systemic circulation (probably <5%) so any pharmacokinetic variations according to race and gender are unlikely to give clinically meaningful changes to the pharmacokinetics of the drug.

Pharmacokinetic interaction studies

From the known metabolism of aclidinium bromide and the results of *in vitro* studies it can be concluded that the probability of pharmacokinetic interactions with other drugs is low. The systemic

absorption of aclidinium bromide is very low and aclidinium bromide is rapidly metabolised to its inactive metabolites LAS34823 and LAS34850. As aclidinium bromide is metabolised by esterases in the plasma and any unchanged aclidinium bromide and its metabolites are largely excreted in the urine interaction with drugs metabolised through the CYP450 isoenzyme system is unlikely. This conclusion is supported by *in vitro* data.

2.4.3. Pharmacodynamics

Mechanism of action

Aclidinium bromide is a long-acting, inhaled anticholinergic agent which has strong affinity and selectivity for all muscarinic receptor subtypes (M1-M5) and kinetic selectivity for the M3 receptor over the M2 receptor. Inhaled aclidinium bromide inhibited acetylcholine-induced bronchoconstriction in anesthetised guinea-pigs, with a duration of action (expressed as the half-life for the bronchodilatory effect) of 29 hours.

Primary pharmacology

A study (M/34273/00) was conducted to investigate the bronchodilatory activity, tolerability and pharmacokinetics of single ascending doses 50, 300 and 600 µg of aclidinium bromide in healthy subjects. Measures of pharmacodynamic activity evaluated included specific airway conductance (sGaw), airway resistance (Raw) and the ability of aclidinium bromide to reduce methacholine-induced bronchoconstriction (PC35). The results were consistent across the parameters measured, showing an improvement of all the doses of aclidinium bromide studied compared to placebo. However only the 300 µg and 600 µg doses demonstrated a statistically significant improvement over placebo for all three parameters. There was no statistically significant improvement seen between the 300 µg dose and the 600 µg dose suggesting that the effect plateaus at this dose level.

A further study (M/34273/21) assessed the tolerability, pharmacodynamics and pharmacokinetics of aclidinium bromide administered by inhalation in male patients with Chronic Obstructive Pulmonary Disease (COPD). A total of 17 subjects (16 planned), aged 48 to 71 years, with stable moderate to severe COPD (according to criteria of American Thoracic Society) and a significant response to ipratropium bromide, were randomly allocated to one of four treatment sequences. Each sequence required subjects to receive a single dose of aclidinium bromide (100, 300 and 900 µg), in an ascending manner, and placebo. All three doses of aclidinium bromide improved the normalised FEV1 AUC(0-24) and there was little difference between the doses. However there appeared to be a clear dose relationship to the mean of change from baseline of normalised FEV_1 $AUC_{(0-24)}$ and all three doses demonstrated a clinically meaningful improvement.

From these results the applicant decided that a once daily dose would be effective over the full 24 hours. However in two Phase III studies investigating 200 µg QD it was found that trough FEV1 was lower than the 100ml considered to be clinically relevant. A further study also demonstrated that the effect did not last the full 24 hours so the applicant considered it necessary to investigate a BID dosing regimen. Doses of 200 µg BID and 400 µg BID were carried forward into a second Phase III development programme.

Secondary pharmacology

Aclidinium bromide, as an anticholinergic, would be expected to cause anticholinergic adverse effects such as dry mouth, pharyngitis, blurred vision, GI motility problems such as constipation, urinary retention and tachycardia.

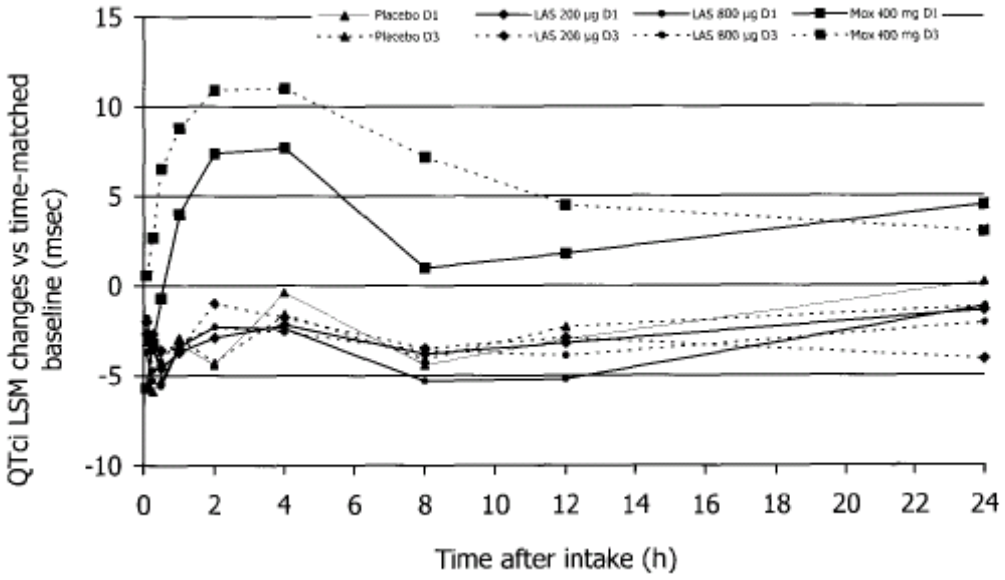
These adverse reactions have been reported in the clinical studies. Also monitoring of vital signs and ECGs was conducted in PK/PD studies and there was no evidence of clinically relevant abnormalities in these parameters.

A thorough QT study was conducted in the early development of aclidinium bromide but investigated only doses of 200 µg and 800 µg QD administered by inhalation over 3 days. Moxifloxacin was administered as control.

On day 1, the greatest (placebo-corrected) positive difference in QTc interval observed were 2.5 msec at 15 mins in subjects treated with aclidinium bromide 200 µg (95% CI, -0.9, 5.8msec) and 2.1 msec at 2 hours in subjects treated with aclidinium bromide 800 µg (95%CI, -1.2, 5.4 msec).

Similarly on Day 3 , the greatest (placebo-corrected) positive difference in QTc interval observed were 3.3 msec in subjects treated with aclidinium bromide 200 µg (95% CI, -0.4, 6.9 msec) and 2.0 msec in subjects treated with aclidinium bromide 800 µg (95%CI, -1.6, 5.6 msec).

Figure 1: Mean change in QTc interval from Time-Matched Baseline to Day 1 and Day 3



Subjects receiving moxifloxacin showed a statistically significant increase in mean time-matched QTc at all time points compared to placebo. These ranged from 4.2 msec (at 23.5 hours) to 15.2 msec (at 2 hours) with the exception of 5 minutes post-dose on Days 1 and 3 (-2.6 and 2.6 msec respectively) and 15 minutes post-dose on Day 1 (2.8 msec).

No significant changes were observed in any other parameters (heart rate, supraventricular and ventricular ectopics, time on atrial fibrillation and number of pauses [RR > 2 msec]) of the 12-lead ECG or the 24-hour Holter monitoring with either dose of aclidinium bromide compared with placebo.

The results were reassuring regarding the potential for aclidinium bromide to prolong the QTc interval, although the doses studied are low compared to the proposed dose of 400 µg BID.

Further monitoring of cardiovascular parameters was conducted in the Phase III studies.

2.4.4. Discussion on clinical pharmacology

The pharmacokinetic data are limited by a high LLOQ in the earlier studies. However the studies performed demonstrated that about 30% of the dose of aclidinium bromide is deposited in the lungs from where it is absorbed into the systemic circulation.

Aclidinium bromide has a low absolute bioavailability of <5% and is rapidly cleared from the systemic circulation by metabolism to two inactive metabolites, an alcohol metabolite LAS43823 and an acid metabolite LAS34850.

Unchanged aclidinium bromide (<1% of the dose) is excreted in the urine as is the major part of the two metabolites, either unchanged or after further metabolism by hydrolysis.

The pharmacokinetics of single doses of aclidinium bromide and its metabolites were investigated in renally impaired patients and no clinically relevant increase in exposure was demonstrated. Therefore it can be concluded that no dose adjustment is required for patients with renal impairment.

As hepatic metabolism plays a very minor part in the metabolism of aclidinium bromide pharmacokinetic data were not generated in patients with hepatic impairment and no dose adjustment was proposed. This was accepted by the CHMP.

The mechanism of action of aclidinium bromide was investigated *in vitro* and it was found to act by inhibiting acetylcholine-induced bronchoconstriction.

The data on pharmacodynamic effects in humans, particularly in the patient population with COPD are limited but a dose response effect was demonstrated over the range of single doses of 100 µg to 900 µg in patients with COPD.

The initial development was for a once daily dose of aclidinium bromide hence most of the pharmacodynamic studies were concerned with single or once daily dosing and there are no data on twice daily dosing. However these preliminary results have been superseded by the Phase III clinical development studies.

2.4.5. Conclusions on clinical pharmacology

An adequate number of studies was conducted to characterise the clinical pharmacology of aclidinium bromide. There are some limitations to the data; pharmacokinetic data were limited by a high LLOQ in the earlier studies but concerns regarding the lack of adequate characterisation of aclidinium $t_{1/2}$ were mitigated by the large portion of total AUC represented by the 0-12 h time interval. This was supported by the lack of evidence of accumulation in trough concentrations in Study LAS-PK-12 after twice daily dosing for 7 days, albeit in healthy volunteers.

Therefore the claim of dose proportionality and time-independent kinetics was accepted and a further study in patients with renal impairment at steady state was not considered to be required.

There were also limited pharmacodynamic data in the target population of patients with moderate to severe COPD but this was superseded by clinical data in Phase III studies.

The very limited data on the safety in different races other than Caucasians was noted by the CHMP. However, this was adequately addressed in the RMP as important missing information.

2.5. Clinical efficacy

2.5.1. Dose response studies

Dose-finding studies

Prior to the conduct of the clinical development programme of aclidinium bromide BID, a clinical development programme of aclidinium bromide administered once daily (QD) was conducted. Following completion of a dose-finding study of aclidinium bromide QD (M/34273/22), the efficacy and safety of aclidinium bromide 200 µg QD was investigated in two pivotal studies (M/34273/30 and M/34273/31), and three efficacy profiling studies (M/34273/24, M/34273/25, LAS-MD-26). Studies M/34273/30, M/34273/31 and M/34273/25 indicated that the 24-hour bronchodilator efficacy of aclidinium bromide 200 µg QD was suboptimal in terms of effect size and duration of effect.

In a dose-finding trial of repeated once daily administration by inhalation of aclidinium bromide, matching placebo, or tiotropium bromide in patients with moderate to severe stable COPD, the primary efficacy variable in this study, trough FEV1 at visit 4, demonstrated a statistically and clinically significant improvement over placebo for the 200 µg and 400 µg doses of aclidinium bromide. The 200 µg dose demonstrated a greater improvement than the 400 µg dose and the improvement was of a similar order to that seen with tiotropium. The applicant concluded that the 400 µg dose conferred no further advantage over the 200 µg dose and therefore that the 200 µg dose would have the optimum benefit/risk balance.

A multiple dose, double-blind, double-dummy, 3 period cross-over, placebo controlled clinical study (M/34273/25) to assess whether the time of dosing (a.m. or p.m.) at steady state influences the bronchodilator response of aclidinium bromide compared with placebo in patients with moderate to severe COPD was also conducted in the early development. Although the trough FEV1 values obtained after 6 days treatment were higher than those seen with placebo they did not reach a clinically relevant difference compared to placebo (46ml for the 200 µg a.m. dose and 37ml for the 200 µg p.m. dose). On the basis of the results of these studies the applicant decided to continue the development of aclidinium bromide with a focus on a twice daily dose regimen and also to evaluation higher doses.

2.5.2. Main studies

Study M/34273/34: Efficacy and safety of aclidinium bromide at two dose levels vs placebo when administered to patients with moderate to severe chronic obstructive pulmonary disease (COPD)

Methods

Study Participants

The main inclusion criteria were

- Patients with a clinical diagnosis of stable moderate to severe COPD, according to the GOLD guidelines and stable airway obstruction. Post-salbutamol FEV1/forced vital capacity (FVC)<70% at Screening Visit (Visit 1).
- Patients whose FEV1 at Screening Visit measured between 10 to 15 minutes post inhalation of 400 µg of salbutamol, was ≥30% and <80% of the predicted normal value.
- Current or former cigarette smokers with a smoking history of at least 10 pack-years.

The main exclusion criteria included history or current diagnosis of asthma, any respiratory tract infection (including the upper respiratory tract) or COPD exacerbation in the 6 weeks before the Screening Visit (Visit 1), and patients who were hospitalised for an acute COPD exacerbation within 3 months prior to the Screening Visit.

Treatments

Following a run-in period of approximately 14 days eligible patients were randomised by IVRS in a 1:1:1 ratio to receive either 200 mcg or 400 mcg of aclidinium bromide or placebo administered twice daily using a multidose dry powder inhaler (Genuair) for 24 weeks. Relief medication (salbutamol pMDI 100 mcg/puff) was provided to all patients for use as needed throughout the study.

Efficacy and safety of aclidinium bromide at two dose levels vs placebo when administered to patients with moderate to severe COPD was realized in a prospective, randomised, parallel group, placebo-controlled, double-blind, multinational and multicentre, clinical study of repeated BID administration of inhaled aclidinium bromide (200 µg or 400 µg) or matching placebo in patients with moderate to severe stable COPD. At Visit 2, patients were randomly assigned to receive one of the following double-blind treatments during a 24-Week treatment period:

- Aclidinium bromide 200 µg BID (once in the morning and once in the evening), administered via the Genuair inhaler
- Aclidinium bromide 400 µg BID (once in the morning and once in the evening), administered via the Genuair inhaler
- Placebo to match aclidinium bromide BID, administered via the Genuair inhaler.

Objectives

Efficacy related study objectives were:

1. to assess the long term bronchodilator efficacy of inhaled aclidinium bromide 200 mcg and 400 mcg both administered twice daily, compared to placebo in COPD patients;
2. to assess the benefits of aclidinium bromide 200 mcg and 400 mcg both administered twice daily, compared to placebo in disease-related health status, COPD symptoms and COPD exacerbations.

Efficacy was assessed by bronchodilation tests, COPD symptoms and exacerbations, health related quality of life (QoL), amount of relief medication required and evaluation of treatment compliance. For a subgroup of 20% of patients at selected sites, 12 hour post-dose serial spirometry (FEV_1 and FVC) was performed; inspiratory capacity (IC) was measured 12 hours post-dose.

The safety related study objective was to evaluate the long term safety and tolerability of inhaled aclidinium bromide 200 µg and 400 µg, both administered BID, compared to placebo in the same target population.

Outcomes/endpoints

The primary efficacy endpoints was change from baseline in morning pre-dose FEV1.

Key secondary endpoints were change from baseline in peak FEV1, TDI focal score, SGRQ total score, and exacerbations.

Sample size

A total of 1,250 patients were planned to be screened to achieve a total number of 810 randomised patients; that is 270 patients to each of three treatment groups. Screened: 1061; randomised: 828; completed study: 736; completed treatment: 737 Evaluated for safety: 819; evaluated for efficacy (Intent-to-Treat [ITT] analysis): 819; evaluated for efficacy (Per Protocol [PP] analysis): 759; evaluated for efficacy (serial spirometry sub-study): 191.

Randomisation

The study was realized as a prospective, randomised, parallel group, placebo-controlled, double-blind.

Blinding (masking)

Study personnel and study patients were blinded as to whether the patient was using aclidinium bromide or placebo. The Genuair inhalers containing aclidinium bromide and those containing placebo were of the same external appearance to ensure the double-blind nature of the study.

Statistical methods

All statistical comparisons were two-sided with the significance level set at 0.05. All confidence intervals (CIs) were two-sided 95%.

In total five analysis populations were defined including the following two populations for analysis of efficacy:

- intent-to-treat (ITT) population: all randomised patients who took at least one dose of study medication with both a baseline and at least one post-baseline FEV_1 assessment;
- per-protocol (PP) population: a subset of the ITT population made up of those patients who:

  a) met all inclusion/exclusion criteria liable to affect the efficacy assessment;

  b) attained a sufficient compliance to the treatment received;

  c) did not present serious deviations of the protocol that might affect efficacy.

Patients were assigned to these populations according to the specified definitions at a blind data review meeting before the randomisation codes were broken. All efficacy analyses were based on the ITT population except for COPD exacerbations which were reported for the ITT population and also the safety population. In addition the primary and three secondary efficacy parameters were analysed for the PP population.

Missing data for spirometric efficacy analysis were addressed using the last observation carried forward (LOCF) approach. In addition linear interpolation was used where one or more planned value(s) were missing between a pair of non-missing values. Data collected on a daily diary were summarised at each visit without any imputation and also using the LOCF approach. For all variables where a baseline value was computed, the LOCF approach was used to impute the baseline value to the first post-baseline value if missing.

The primary efficacy variable was the change from baseline in morning pre-dose FEV_1 at Week 24 for the European filing. This was analysed by means of an analysis of covariance (ANCOVA) model with treatment and sex as factors and baseline and age as covariates.

The primary treatment comparisons were:

aclidinium bromide 200 mcg versus placebo

aclidinium bromide 400 mcg versus placebo.

In addition the following comparison was considered:

aclidinium bromide 200 mcg/aclidinium bromide 400 mcg versus placebo.

Adjustment for multiplicity of testing more than one dose was performed using Hochberg's method.

A sensitivity analysis for the primary efficacy parameter was carried out using a direct likelihood approach on the ITT population to assess the effect of missing data on the results of morning pre-dose FEV_1 in which case no imputation was performed. This analysis was conducted using a mixed model for repeated measures (MMRM) of change from baseline in pre-dose FEV_1 with age and baseline value as covariates, and treatment, sex, week and treatment-by-week interaction as fixed effects. A similar method for adjustment for multiplicity was used.

The following secondary efficacy variables were analysed:

1. change from baseline in peak FEV_1 at Week 24 where peak FEV_1 was the highest FEV_1 value observed in the 3-hour period immediately after morning dosing (using the same model as for the primary efficacy variable);
2. percentage of patients achieving a clinically meaningful improvement ($\geq$ 1 unit) in Transition Dyspnoea Index (TDI) focal score at Week 24;
3. percentage of patients achieving a clinically meaningful improvement ($\geq$ 4 units) compared to baseline in the St George's Respiratory Questionnaire (SGRQ) total score at Week 24.

The second and third variables were analysed using a logistic regression model.

A sequential procedure was used to adjust for multiplicity by testing the primary and three secondary variables in this pre-specified order: the primary variable followed by the secondary variables in numerical order.

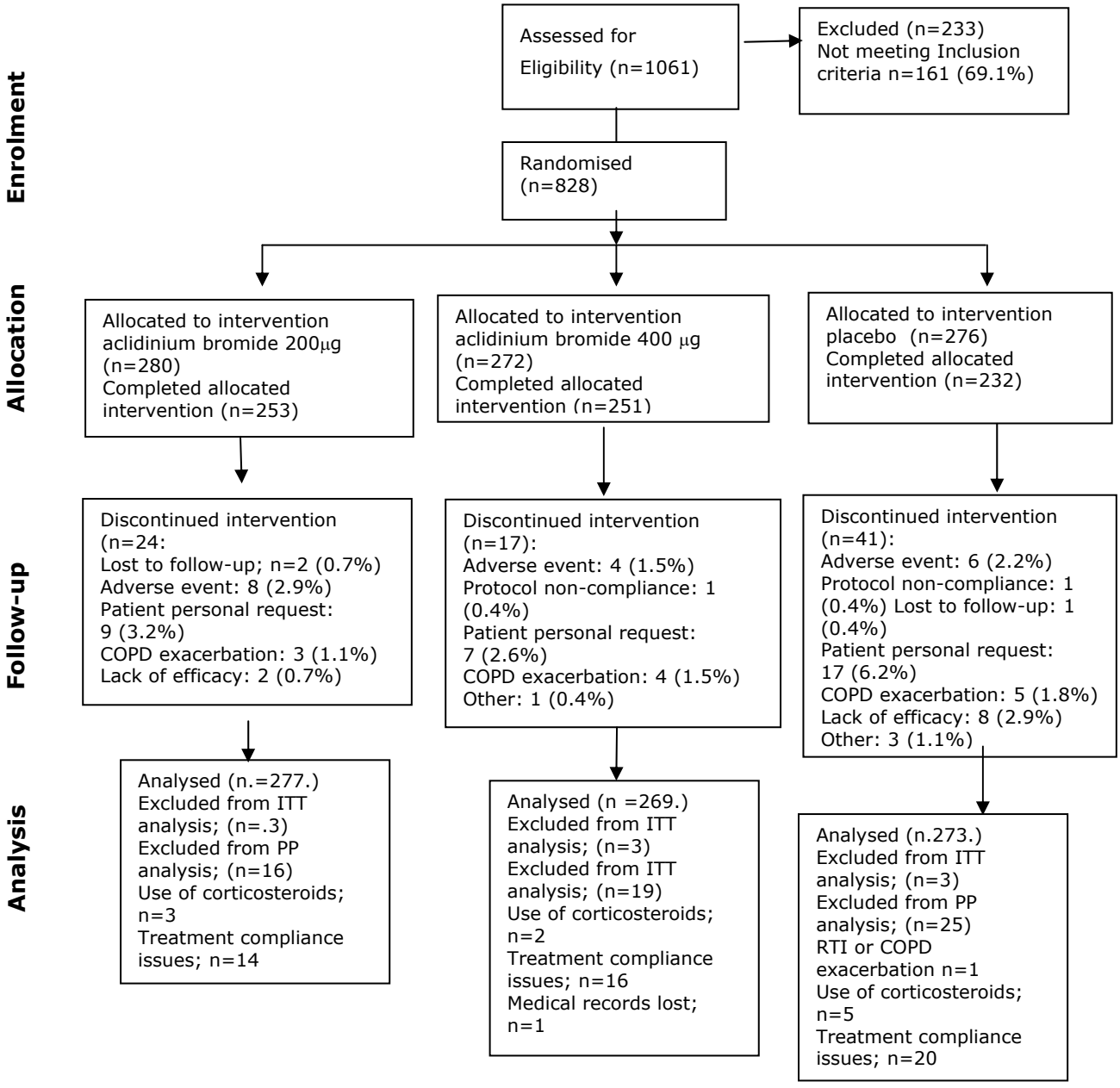
The comparison of the two doses, aclidinium bromide 400 mcg versus aclidinium bromide 200 mcg, was reported although no adjustment for multiple testing was made for this comparison.

The analyses of the primary and all three secondary endpoints at 12 weeks were also conducted to be included in the US submission.

The sample size of 244 evaluable patients was estimated to provide at least 90% power to detect a difference of 90mL in the primary endpoint allowing for adjustment for multiple comparisons at the overall significance level of 0.05.

Results

Participant flow



Baseline data

The treatment groups were comparable with respect to demographic and baseline characteristics. The mean age was 62.0, 62.3, and 62.9 years in the placebo, and aclidinium bromide 200 µg and 400 µg groups, respectively. There were some differences in the age distribution of patients between the three treatment groups. In the aclidinium bromide 400 µg group, a slightly higher percentage of patients

were 70 years and over, and a slightly lower percentage of patients were between 60 and 70 years, compared to the placebo and aclidinium bromide 200 µg groups. In all treatment groups, a higher percentage of male patients compared to female patients were enrolled; 69.2%, 65.3% and 67.7% in the placebo, and aclidinium bromide 200 µg and 400 µg groups, respectively. The majority of patients in all treatment groups were Caucasian (95.0 to 95.5%). The mean BMI was similar among treatment groups and ranged from 26.5 to 27.0 kg/m2.

Smoking history (current and ex-smokers) was evenly distributed across the groups as was the mean duration of smoking in years. However the smoking consumption (pack-years) increased across the groups from placebo to 400mcg BID; [Mean (SD): Placebo; 38.9 (18.3) aclidinium bromide 200mcg BID; 40.0 (19.8) aclidinium bromide 400mcg BID; 41.7 (21.1)].

Numbers analysed

A total of 828 patients were randomised into the study with approximately 10% discontinuing prematurely, 14.9% in the placebo group, and 8.6% and 6.3% for the 200 mcg and 400mcg doses of aclidinium respectively. Although reasons for discontinuation were fairly comparable across treatment groups, a higher percentage discontinued from the placebo group because of lack of efficacy. Full details are provided in the table below.

Table 6 Study patients

	Number (%) of Patients			
	Placebo	AB 200 µg BID	AB 400 µg BID	Total
	N=276	N=280	N=272	N=828
Patient Status	n (%)	n (%)	n (%)	n (%)
Completed study	232 (84.1)	253 (90.4)	251 (92.3)	736 (88.9)
Completed treatment	232 (84.1)	253 (90.4)	252 (92.6)	737 (89.0)
Discontinued	41 (14.9)	24 (8.6)	17 (6.3)	82 (9.9)
Discontinued in the first 12 weeks of the study	34 (12.3)	15 (5.4)	11 (4.0)	60 (7.2)
Reason for discontinuation				
Adverse event	6 (2.2)	8 (2.9)	4 (1.5)	18 (2.2)
Protocol non-compliance	1 (0.4)	0 (0.0)	1 (0.4)	2 (0.2)
Lost to follow-up	1 (0.4)	2 (0.7)	0 (0.0)	3 (0.4)
Patient's personal request	17 (6.2)	9 (3.2)	7 (2.6)	33 (4.0)
COPD exacerbation	5 (1.8)	3 (1.1)	4 (1.5)	12 (1.4)
Lack of efficacy	8 (2.9)	2 (0.7)	0 (0.0)	10 (1.2)
Other	3 (1.1)	0 (0.0)	1 (0.4)	4 (0.5)

AB=aclidinium bromide; BID=twice daily; COPD=chronic obstructive pulmonary disease; N=total number of patients in the randomised population

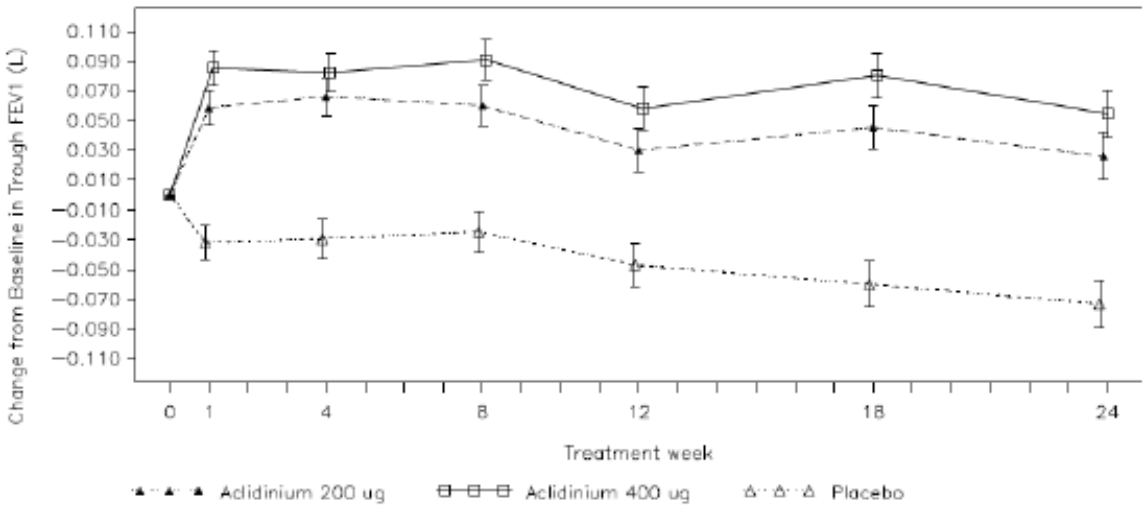
Note: All patients (9 in total) associated with investigator number 1221 were counted as randomised only. The number of patients who completed treatment+the number of patients discontinued, will therefore not add up to the total number of patients randomised (N).

Outcomes and estimation

Primary efficacy endpoint

The primary efficacy endpoint was "change from baseline in morning pre-dose FEV_1 at Week 24 for the ITT population". The following plot of change from baseline in morning pre-dose FEV_1 over 24 weeks shows a greater improvement in this endpoint in both aclidinium bromide dose groups compared to placebo which was consistently higher for the 400 mcg dose than for the 200 mcg dose.

Figure 4 **Change from baseline in morning pre-dose trough FEV_1 (L) by visit over 24 weeks: least squares means (±standard error) (ITT population [LOCF])**



FEV_1=forced expiratory volume in 1 second; ITT=Intent-to-Treat; LOCF=last observation carried forward

The results of the analysis of the primary endpoint, change from baseline in morning pre-dose FEV_1 at Week 24 for the ITT population, are presented in the table below. A statistically significant greater adjusted mean change from baseline at Week 24 was observed for both doses compared to placebo with an estimated difference of 99 mL for aclidinium bromide 200 mcg and 128 mL for 400 mcg. No statistically significant difference between doses was achieved.

Table 18 **Change from baseline in morning pre-dose (trough) FEV_1 (L) at Week 12 and Week 24 (LOCF): primary efficacy analysis (ITT population)**

	Statistic	Placebo (N=273)	AB 200 µg BID (N=277)	AB 400 µg BID (N=269)
Baseline				
	n	273	277	269
	Mean (SD)	1.500 (0.489)	1.514 (0.498)	1.508 (0.525)
Change from Baseline at Week 12				
	n	273	277	269
	LS Mean (SE)	-0.047 (0.015)	0.030 (0.014)	0.058 (0.015)
Between-group comparisons at Week 12				
Comparison versus Placebo	LSMD (95% CI)		0.077 (0.038, 0.116)	0.105 (0.065, 0.144)
	p-value		0.0001	<0.0001
Comparison versus 200 µg BID	LSMD (95% CI)			0.028 (-0.012, 0.067)
	p-value			0.1671
Change from Baseline at Week 24				
	n	273	277	269
	LS Mean (SE)	-0.073 (0.016)	0.026 (0.016)	0.055 (0.016)
Between-group comparisons at Week 24				
Comparison versus Placebo	LSMD (95% CI)		0.099 (0.057, 0.141)	0.128 (0.085, 0.170)
	p-value		<0.0001	<0.0001
Comparison versus 200 µg BID	LSMD (95% CI)			0.029 (-0.014, 0.071)
	p-value			0.1868

AB=aclidinium bromide, ANCOVA=analysis of covariance; BID=twice daily; CI=confidence interval; FEV_1=forced expiratory volume in 1 second; ITT=intent to treat; LOCF=last observation carried forward (with baseline imputation if first post-baseline missing); LS mean=least squares mean; LSMD=least squares mean difference; N=ITT population size; n=number of patients in the analysis; SD=standard deviation; SE=standard error.

P-value, LS mean, and LSMD obtained from an ANCOVA model with change from baseline in trough FEV_1 as response, with treatment group and sex as factors and baseline trough FEV_1 and age as covariates.

Similar findings were observed using the MMRM analysis with estimated treatment differences after 24 weeks of 103mL and 133mL for the lower and higher doses respectively when compared to placebo (p<0.0001 for both). Consistent results were demonstrated by the analysis of the PP population with a difference of 106 mL between aclidinium 200 mcg and placebo and 133 mL between aclidinium 400 mcg and placebo (p<0.0001 for both).

Secondary efficacy endpoints

Change from baseline in peak FEV_1

The results for the analysis of change from baseline in peak FEV_1 at Week 24 for the ITT population are presented in the table below.

Table 19 **Change from baseline in peak FEV_1 (L) at Week 12 and Week 24 (LOCF): secondary efficacy analysis (ITT population)**

	Statistic	Placebo (N=273)	AB 200 µg BID (N=277)	AB 400 µg BID (N=269)
Baseline				
	N	273	277	269
	Mean (SD)	1.500 (0.489)	1.514 (0.498)	1.508 (0.525)
Change from Baseline at Week 12				
	N	273	277	269
	LS Mean (SE)	0.037 (0.016)	0.219 (0.015)	0.227 (0.016)
Between-group comparisons at Week 12				
Comparison versus Placebo	LSMD (95% CI)		0.182 (0.141, 0.224)	0.191 (0.149, 0.233)
	p-value		<0.0001	<0.0001
Comparison versus 200 µg BID	LSMD (95% CI)			0.008 (-0.033, 0.050)
	p-value			0.6956
Change from Baseline at Week 24				
	N	273	277	269
	LS Mean (SE)	0.022 (0.017)	0.206 (0.017)	0.231 (0.017)
Between-group comparisons at Week 24				
Comparison versus Placebo	LSMD (95% CI)		0.185 (0.139, 0.231)	0.209 (0.163, 0.256)
	p-value		<0.0001	<0.0001
Comparison versus 200 µg BID	LSMD (95% CI)			0.025 (-0.021, 0.071)
	p-value			0.2919

AB=aclidinium bromide, ANCOVA=analysis of covariance; BID=twice daily; CI=confidence interval; FEV_1=forced expiratory volume in 1 second; ITT=intent to treat; LOCF=last observation carried forward (with baseline imputation if first post-baseline missing); LS mean=least squares mean; LSMD=least squares mean difference; N=ITT population size; n=number of patients in the analysis; SD=standard deviation; SE=standard error.

P-value, LS mean, and LSMD were obtained from an ANCOVA model for change from baseline in peak FEV_1 as response, with treatment group and sex as factors and baseline FEV_1 and age as covariates.

As for the primary efficacy endpoint both doses were statistically superior to placebo in terms of this endpoint with estimated treatment differences of 185 mL and 209 mL for the 200 mcg and 400 mcg doses respectively compared with placebo (p<0.0001 for both). As before no statistically significant difference was seen between the two doses.

TDI focal score

The results of the analysis of the percentage of patients achieving a clinically relevant improvement (≥1 unit) in TDI at 24 weeks are presented in the table below.

Table 20 **Number and percentage of patients who achieved a clinically relevant difference in TDI (improvement ≥ 1 unit in the focal score) at Weeks 4, 12 and 24 (ITT population [LOCF])**

Visit	Placebo (N=273)	AB 200 µg BID (N=277)	AB 400 µg BID (N=269)
Week 4			
Yes, n (%)	107 (42.0)	131 (49.6)	147 (56.8)
No, n (%)	148 (58.0)	133 (50.4)	112 (43.2)
Comparison versus Placebo			
Odds ratio and 95% CI		1.46 (1.022, 2.077)	1.89 (1.326, 2.699)
p-value		0.0373	0.0004
Week 12			
Yes, n (%)	109 (42.4)	139 (51.5)	156 (59.5)
No, n (%)	148 (57.6)	131 (48.5)	106 (40.5)
Comparison versus Placebo			
Odds ratio and 95% CI		1.53 (1.074, 2.169)	2.06 (1.444, 2.935)
p-value		0.0184	<0.0001
Week 24			
Yes, n (%)	117 (45.5)	144 (53.3)	149 (56.9)
No, n (%)	140 (54.5)	126 (46.7)	113 (43.1)
Comparison versus Placebo			
Odds ratio and 95% CI		1.47 (1.034, 2.091)	1.68 (1.183, 2.399)
p-value		0.0317	0.0038

AB=aclidinium bromide; BDI=Baseline Dyspnoea Index; BID=twice daily; CI=confidence interval; ITT= intent to treat; LOCF=last observation carried forward; N=ITT population size; n=number of patients with ≥ 1 unit of improvement in the focal score and with non-missing BDI; TDI=Transition Dyspnoea Index.

Odds ratio was based on the logistic regression model for the number of patients showing at least 1 point improvement from BDI with treatment group and sex as factors along with age and BDI as covariates.

At Week 24 significantly more patients had clinically relevant improvement in this score in both the aclidinium bromide groups compared to placebo. Statistically significant odds ratios were demonstrated for both doses compared to placebo.

The results of the exploratory analysis of the change from baseline in TDI focal score using the pre-specified ANCOVA model are provided in the following table.

Table 30 TDI Focal Score at Week 4, 12 and Week 24 of treatment. ANCOVA model treatment comparisons (ITT population [LOCF])

	Statistic	Placebo (N=273)	AB 200 µg BID (N=277)	AB 400 µg BID (N=269)
Baseline (BDI)				
	n	265	266	266
	Mean (SD)	6.7 (2.0)	7.0 (2.2)	6.7 (2.1)
TDI at Week 4				
	n	255	264	259
	LS Mean (SE)	0.62 (0.18)	1.27 (0.17)	1.54 (0.17)
Comparison versus Placebo	LSMD (95% CI)		0.65 (0.18, 1.13)	0.92 (0.44, 1.39)
	p-value		0.0073	0.0002
TDI at Week 12				
	n	257	270	262
	LS Mean (SE)	0.86 (0.20)	1.22 (0.19)	1.74 (0.19)
Comparison versus Placebo	LSMD (95% CI)		0.36 (-0.17, 0.90)	0.88 (0.35, 1.41)
	p-value		0.1807	0.0012
TDI at Week 24				
	n	257	270	262
	LS Mean (SE)	0.94 (0.21)	1.54 (0.21)	1.94 (0.21)
Comparison versus Placebo	LSMD (95% CI)		0.60 (0.03, 1.17)	1.00 (0.43, 1.57)
	p-value		0.0387	0.0006

AB=aclidinium bromide; ANCOVA=analysis of covariance; BID=twice daily; CI=confidence interval; ITT= intent to treat; LOCF=last observation carried forward; LSMD=least squares mean difference; TDI=Transition Dyspnoea Index.
P-value and LSMD obtained from an ANCOVA model for change for focal score TDI as response and treatment group and sex as factors and BDI and age as covariates.

At Week 24 compared to placebo the adjusted mean change from baseline in TDI focal score was statistically significantly greater for both doses of aclidinium bromide although the estimated difference was clinically relevant ($\geq$1 unit) only for the 400 mcg dose.

SGRQ total score

The results of the analysis of the percentage of patients achieving a clinically relevant improvement ($\geq$4 units) compared to baseline are presented in the table below.

Table 21 **Number (%) of patients who achieved at least a 4-point reduction from baseline in SGRQ total score at Weeks, 4, 12 and 24 (ITT population [LOCF])**

Visit/Statistic	Placebo (N=273)	AB 200 µg BID (N=277)	AB 400 µg BID (N=269)
Week 4			
Yes, n (%)	106 (39.1)	129 (46.9)	139 (51.7)
No, n (%)	165 (60.9)	146 (53.1)	130 (48.3)
Comparison versus Placebo			
Odds ratio and 95% CI		1.35 (0.944, 1.925)	1.60 (1.117, 2.287)
p-value		0.0999	0.0104
Week 12			
Yes, n (%)	107 (39.5)	143 (52.0)	153 (56.9)
No, n (%)	164 (60.5)	132 (48.0)	116 (43.1)
Comparison versus Placebo			
Odds ratio and 95% CI		1.64 (1.153, 2.331)	1.96 (1.375, 2.802)
p-value		0.0059	0.0002
Week 24			
Yes, n (%)	111 (41.0)	154 (56.0)	154 (57.3)
No, n (%)	160 (59.0)	121 (44.0)	115 (42.8)
Comparison versus Placebo			
Odds ratio and 95% CI		1.83 (1.295, 2.594)	1.87 (1.320, 2.660)
p-value		0.0006	0.0004

AB=aclidinium bromide; BID=twice daily; CI=confidence interval; ITT= intent to treat; LOCF=last observation carried forward (baseline carried forward if first post-baseline is missing); N=Number of patients in ITT; n=number of in the category with non-missing baseline SGRQ score; SGRQ=Saint George's Respiratory Questionnaire.

Odds ratio derived using a logistic regression model for the number of patients showing at least a 4-point reduction from baseline as response with treatment group and sex as factors along with age and baseline SGRQ total scores as covariates.

At Week 24 significantly more patients had a clinically relevant improvement in SGRQ total score for both doses compared to placebo. Statistically significant odds ratios were demonstrated for both doses compared to placebo.

The results of the exploratory analysis of the change from baseline in SGQR total score using the pre-specified ANCOVA model are provided in the following table.

Table 31 SGRQ total score at Week 4, 12 and Week 24 of treatment. ANCOVA model treatment comparisons (ITT population [LOCF])

	Statistic	Placebo (N=273)	AB 200 µg BID (N=277)	AB 400 µg BID (N=269)
Baseline				
	n	271	275	269
	Mean (SD)	44.9 (16.7)	46.2 (17.6)	47.4 (18.4)
Change from Baseline at Week 4				
	n	271	275	269
	LS Mean (SE)	-2.60 (0.63)	-3.35 (0.62)	-5.19 (0.63)
Comparison versus Placebo	LSMD (95% CI)		-0.75 (-2.44, 0.95)	-2.59 (-4.30, -0.89)
	p-value		0.3869	0.0029
Change from Baseline at Week 12				
	N	271	275	269
	LS Mean (SE)	-2.36 (0.72)	-5.52 (0.71)	-6.45 (0.72)
Comparison versus Placebo	LSMD (95% CI)		-3.17 (-5.12, -1.21)	-4.10 (-6.06, -2.13)
	p-value		0.0015	<0.0001
Change from Baseline at Week 24				
	N	271	275	269
	LS Mean (SE)	-2.79 (0.82)	-6.61 (0.80)	-7.41 (0.82)
Comparison versus Placebo	LSMD (95% CI)		-3.82 (-6.01, -1.62)	-4.63 (-6.84, -2.42)
	p-value		0.0007	<0.0001

AB=aclidinium bromide; BID=twice daily; CI=confidence interval; ITT= intent to treat; LOCF=last observation carried forward; LSMD=least squares mean difference; SGRQ=Saint George's Respiratory Questionnaire

P-value and LSMD obtained from an ANCOVA model for change from baseline in the SGRQ (total and three dimension scores) as response and treatment group and sex as factors and baseline SGRQ scores and age as covariates.

At Week 24 compared to placebo the adjusted mean change from baseline in SGRQ total score was statistically significantly greater for both doses of aclidinium bromide although the estimated difference was clinically relevant ($\geq$4 units) only for the 400 mcg dose.

Exacerbations

COPD Exacerbations based on Health Resource Utilisation (eCRF): A numerically smaller percentage of patients experienced at least one COPD exacerbation (mild, moderate, or severe) in the aclidinium bromide 200 µg group (15.9%) and in the aclidinium bromide 400 µg group (14.1%) than in the placebo group (20.5%). Compared to placebo, the percent reduction in odds was 27% (p-value=0.1676) and 36% (p-value=0.0513) for the aclidinium bromide 200 µg and 400 µg doses, respectively.

When assessed as exacerbation rates per patient-year, the percent reduction was approximately 30% (p-value<0.05 for both doses).

A numerically smaller percentage of patients experienced at least one moderate or severe COPD exacerbation in the aclidinium bromide 200 µg group (13.0%) and aclidinium bromide 400 µg group (12.3%) than in the placebo group (16.1%). Compared to placebo, the percent reduction in odds was 22% (p-value=0.3173) and 27% (p-value=0.2063) in the 200 µg and 400 µg dose, respectively.

When assessed as exacerbation rates per patient-year, the percent reduction was 26% (p-value=0.0845) and 28% (p-value=0.0629) for the 200 µg and 400 µg dose, respectively.

Summary of the main study

The following table summarises the efficacy results from the main studiy (M/34273/34) supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 4. Summary of Efficacy for trial M/34273/34

Title: Efficacy and safety of aclidinium bromide at two dose levels vs placebo when administered to patients with moderate to severe chronic obstructive pulmonary disease (COPD)				
Study identifier	M/34273/34			
Design	Randomized, parallel group, placebo-controlled, double-blind study.			
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		24 weeks 2 weeks Not applicable	
Hypothesis	Superiority to placebo			
Treatments groups	AB 200 mcg BID		N= 280; 24 weeks treatment	
	AB 400 mcg BID		N= 272; 24 weeks treatment	
	Placebo		N= 276; 24 weeks treatment	
Endpoints and definitions	Primary endpoint	Pre-dose FEV_1 (L)	Change from baseline in morning pre-dose (trough) FEV_1 at Week 24	
	Secondary endpoint	TDI focal score	Change from baseline in TDI (Transitional Dyspnoea Index) focal score at Week 24	
	Secondary endpoint	SGRQ total score	Change from baseline in SGRQ (St George's Respiratory Questionnaire) total score at Week 24	
Database lock	Not available			
Results and Analysis				
Analysis description	**Primary Endpoint**			
Analysis population and time point description	Intent to treat Week 24 Change from baseline in morning pre-dose (trough) FEV_1			
Descriptive statistics and estimate variability	Treatment group	Placebo	AB 200 mcg BID	AB 400 mcg BID
	Number of subject	273	277	269
	Least squares mean	-0.073	0.026	0.055
	Standard error	0.016	0.016	0.016
Effect estimate per comparison	Least squares mean difference to placebo		0.099	0.128
	95% confidence interval		0.057, 0.141	0.085, 0.170
	p-value		<0.0001	<0.0001
Analysis description	**Secondary Endpoint**			

Analysis population and time point description	Intent to treat Week 24 Change from baseline TDI focal score			
Descriptive statistics and estimate variability	Treatment group	Placebo	AB 200 mcg BID	AB 400 mcg BID
	Number of subject	257	270	262
	Least squares mean	0.94	1.54	1.94
	Standard error	0.21	0.21	0.21
Effect estimate per comparison	Least squares mean difference to placebo		0.60	1.00
	95% confidence interval		0.03, 1.17	0.43, 1.57
	p-value		0.0387	0.0006
Notes	Clinically relevant difference in TDI focal score:1 point			
Analysis description	**Secondary Endpoint**			
Analysis population and time point description	Intent to treat Week 24 Change from baseline SGRQ total score			
Descriptive statistics and estimate variability	Treatment group	Placebo	AB 200 mcg BID	AB 400 mcg BID
	Number of subject	271	275	269
	Least squares mean	-2.63	-6.20	-6.92
	Standard error	0.79	0.77	0.78
Effect estimate per comparison	Least squares mean difference to placebo		-3.57	-4.29
	95% confidence interval		-5.69, -1.46	-6.42, -2.16
	p-value		0.0009	<0.0001
Notes	Clinically relevant difference in SGRQ total score:-4 points			

Analysis performed across trials (pooled analyses and meta-analysis)

As the duration of treatment in the two studies, LAS-MD-33 and LAS-MD-38 Part A, was 12 weeks, they are not considered to be pivotal studies but provide only supportive evidence of efficacy. Therefore study M/34273/34 with 24 weeks duration is considered to be the single pivotal study. In view of the differences in treatment length pooling the studies is not felt to add value statistically especially in the case of the TDI and SGRQ scores where 12 months treatment is probably at the lower limit required for appropriate use of these measures.

Clinical studies in special populations

- Gender

The pharmacokinetics of inhaled aclidinium bromide 200 µg or 400 µg QD for 3 days were investigated in moderate to severe COPD patients aged 40 to 59 years and aged 70 years and over (M/34273/09). Aclidinium bromide was rapidly absorbed in both age groups with a median time to peak plasma concentrations of 10-15 minutes for both age groups. No differences in aclidinium systemic exposure (based on Cmax and AUC) were observed between age groups. Therefore, no dose adjustment was considered necessary for elderly COPD patients.

- Elderly

Study M/34273/09 investigated the effect of age on the pharmacokinetics of multiple QD doses of aclidinium bromide. The Applicant considered that the results of this study support registration of aclidinium bromide 400 µg BID based on the observations that peak plasma concentrations were similar after 7 days dosing with 400 µg BID to those observed after the first dose (study LAS-PK-12) and that the safety margins between human systemic exposure with 400 µg BID and the no observed adverse effect levels in non-clinical toxicity studies were 17- to 187-fold.

No dose adjustments are required for elderly patients or for patients with hepatic or renal impairment. Elderly patients and patients with hepatic or renal impairment can use aclidinium bromide at the recommended dose.

Supportive studies

Supportive Phase III Studies

There were two randomised, parallel group, placebo controlled, double-blind studies (LAS-MD-33 and LAS-MD-38 Part A) of inhaled aclidinium bromide compared to placebo in patients with moderate to severe stable COPD. As the duration of treatment in these studies was 12 weeks, these were not considered to be pivotal studies but to provide only supportive evidence of efficacy.

Following a run-in period of approximately 14 days eligible patients were randomised in a 1:1:1 ratio to receive either 200 mcg or 400 mcg of aclidinium bromide or placebo administered twice daily using a multidose dry powder inhaler for 12 weeks. These studies were essentially the same as Pivotal Study M/34273/34 except in terms of the shorter duration and secondary endpoints. However both SGRQ and TDI scores were included as secondary variables.

Results

The primary endpoint was defined as change from baseline to Week 12 in morning pre-dose FEV_1.

Table 5: Change from baseline in Morning Pre-dose (Trough) FEV1 (L) at Week 12 (LOCF) – ITT Population

Visit	Statistic	Placebo (N = 185)	Aclidinium Bromide 200 µg (N = 184)	Aclidinium Bromide 400 µg (N = 190)
Study LAS-MD-33				
Baseline				
	Mean (SD) SEM Median Min, Max n	1.376 (0.570) 0.0419 1.212 0.548, 3.550 185	1.358 (0.560) 0.0413 1.259 0.470, 2.854 184	1.332 (0.493) 0.0358 1.234 0.562, 2.875 190
Change from Baseline at Week 12				
	LSM (SE)	–0.025 (0.015)	0.062 (0.015)	0.099 (0.015)

Visit	Statistic	Placebo (N = 185)	Aclidinium Bromide 200 µg (N = 184)	Aclidinium Bromide 400 µg (N = 190)
	n	185	184	190
	LSMD [95% CI]	—	0.086 [0.05, 0.13]	0.124 [0.08, 0.16]
	p-value versus placebo	—	< 0.0001	< 0.0001
	p-value versus aclidinium bromide 200 µg	—	—	0.0692
Study LAS-MD-38 Part A				
Baseline				
	Mean (SD) SEM Median Min, Max n	1.459 (0.519) 0.039 1.385 0.534, 2.859 182	1.397 (0.584) 0.043 1.285 0.450, 3.369 182	1.249 (0.519) 0.039 1.166 0.475, 3.056 177
Change from baseline at Week 12				
	LSM (SE)	-0.008 (0.015)	0.043 (0.015)	0.064 (0.016)
	n	182	182	177
	LSMD [95% CI]	-	0.051 (0.01, 0.09)	0.072 (0.03, 0.12)
	p-value versus placebo	-	0.0192	0.0012
	p-value versus aclidinium bromide 200 µg	-	-	0.3415

Note: p-value, LSM, and LSMD were obtained from an ANCOVA model with change from baseline in trough FEV1 with treatment group and sex as factors and baseline FEV1 and age as covariates.
ANCOVA = analysis of covariance; CI = confidence interval; FEV1 = forced expiratory volume in 1 second; ITT = intent to treat; LOCF = last observation carried forward; LSM = least squares mean; LSMD = least squares mean difference; max = maximum; min = minimum; N = ITT population size; n = number of patients at interval.

In Study LAS-MD-33 the estimated treatment difference for the higher dose compared to placebo clearly achieved statistical significance at a clinically relevant level of at least 100 mL. However for the 200 µg dose, although the estimated difference was statistically significant, it was slightly below the size considered to be clinically important. For Study LAS-MD-38 although the estimated difference for both doses was statistically significant, neither reached the clinically relevant level and the estimated differences were considerably smaller than those seen in the other study.

Secondary endpoint

Secondary endpoints in these studies included SGRQ and TDI.

- *SGRQ:* although a statistically significant difference was found for each dose compared with placebo in Study LAS-MD-33, neither difference reached the clinically relevant value of 4 units compared to placebo. In the second study both doses failed to achieve statistical significance in this parameter. However it is possible that the 12-week treatment duration was not sufficient to identify a clinically important difference compared to placebo in terms of this score.

- *TDI:* the results for change from baseline to Week 12 in the TDI score were similar to those for SGRQ, where the statistically significant difference achieved a clinically important level only for the higher dose in both studies.

Study LAS-MD-26

A further multicenter, multinational, randomized, double-blind, placebo controlled, parallel-group study was conducted comparing the repeated once-daily administration of aclidinium bromide 200 µg by inhalation with placebo in patients diagnosed with moderate-to-severe stable COPD. The objective was to investigate the effect of inhaled aclidinium bromide 200 µg on exercise endurance time (ET) after 6 weeks treatment.

This study lends some supporting evidence to symptomatic improvement in patients with COPD. As dyspnoea often limits COPD patients' every day activities, an improvement in exercise tolerance is desirable. This study, which was conducted with a dose of aclidinium bromide of only 200 µg QD, did show a statistically significant improvement in endurance time. Despite a large SD in the baseline measurements the improvement over placebo in ET was more than 25% of the baseline value and is therefore likely to be perceived as an improvement by the patient.

Phase II Studies

Two Phase II randomised, double-blind, double dummy, cross-over studies (M/34273/23 and M/34273/29) were conducted to investigate the effects of aclidinium bromide compared to placebo and compared to other bronchodilators used in the treatment of COPD.

The first study compared aclidinium bromide 400 µg BID to 18 µg QD of tiotropium and the second study compared two doses of aclidinium bromide, 200 µg BID and 400 µg BID to 12 µg BID of formoterol fumarate.

Results of Study M/34273/23

The primary efficacy endpoint was change from baseline in normalised FEV_1 AUC_{0-12} (L) at Day 15 on treatment, shown in the table below:

Table 11-2. Change from baseline in normalised FEV_1 AUC_{0-12} [L] at Day 15 on treatment. Analysis based on the ANCOVA model: Treatment comparisons. ITT and PP populations.

Treatment (A)	Treatment (B)	LS Mean Difference A–B (SE)	95% CI for the Difference (Lower, Upper)	P-value
ITT population				
Aclidinium bromide	Placebo	0.221 (0.041)	(0.136, 0.306)	<0.0001
Tiotropium	Placebo	0.244 (0.042)	(0.159, 0.330)	<0.0001
Aclidinium bromide	Tiotropium	-0.023 (0.041)	(-0.108, 0.061)	0.5723
PP population				
Aclidinium bromide	Placebo	0.271 (0.031)	(0.207, 0.336)	<0.0001
Tiotropium	Placebo	0.255 (0.031)	(0.191, 0.320)	<0.0001
Aclidinium bromide	Tiotropium	0.016 (0.031)	(-0.047, 0.079)	0.6074

Values are manually rounded.

LSMeans: Least Squares Mean from the ANCOVA model for cross-over designs using the change from baseline in the normalised AUC_{0-12} FEV_1 at Day 15 on treatment as response

P-value obtained from LSMeans statement in PROC MIXED. LOCF approach had been used in this analysis.

The findings of the analysis of the primary efficacy endpoint indicate that, in terms of this lung function parameter, aclidinium bromide 400 mcg twice daily was superior to placebo. Confirmation of the known efficacy of tiotropium compared to placebo endorsed the validity of the study results. However the lack of a statistically significant difference between aclidinium and tiotropium cannot be considered to demonstrate that the effects of the two treatments are the same although the estimated treatment difference between them, 23 mL in favour of tiotropium, would suggest that the effects in this endpoint are similar.

Results of Study M/34273/29

The primary efficacy endpoint was change from baseline in normalised FEV_1 AUC_{0-12} (L) at Day 7 on treatment, as shown in the table below:

Table 11-3. Change from baseline in normalised FEV_1 AUC_{0-12} [L] at Day 7 on treatment. Analysis based on the ANCOVA model: Treatment comparisons – ITT population.

Treatment (A)	Treatment (B)	LS Mean Difference A–B (SE)	95% CI for the difference (Lower, Upper)	p-value
Primary treatment comparisons				
AB 100 µg BID	Placebo	0.154 (0.020)	(0.116, 0.192)	<.0001
AB 200 µg BID	Placebo	0.176 (0.020)	(0.137, 0.215)	<.0001
AB 400 µg BID	Placebo	0.208 (0.020)	(0.170, 0.247)	<.0001
Secondary treatment comparisons				
AB 400 µg BID	AB 100 µg BID	0.054 (0.020)	(0.016, 0.093)	0.0060
AB 400 µg BID	AB 200 µg BID	0.032 (0.020)	(-0.007, 0.071)	0.1065
AB 200 µg BID	AB 100 µg BID	0.022 (0.020)	(-0.017, 0.061)	0.2604
Additional treatment comparisons				
Formoterol 12 µg BID	Placebo	0.210 (0.020)	(0.172, 0.249)	<.0001
AB 100 µg BID	Formoterol 12 µg BID	-0.056 (0.020)	(-0.095, -0.018)	0.0044
AB 200 µg BID	Formoterol 12 µg BID	-0.034 (0.020)	(-0.073, 0.005)	0.0878
AB 400 µg BID	Formoterol 12 µg BID	-0.002 (0.020)	(-0.040, 0.037)	0.9237

LSMeans: Least Squares Mean from the ANCOVA model for cross-over designs; SE: Standard Error.

The findings of the analysis of the primary efficacy endpoint indicate that, in terms of this lung function parameter, all doses of aclidinium bromide were superior to placebo and above the clinically relevant level of 100ml. Confirmation of the known efficacy of formoterol compared to placebo endorsed the validity of the study results. The clear lack of statistical significance between aclidinium 400 mcg and formoterol 12 mcg with an estimated treatment difference of only 2 mL would suggest that the effect on the primary endpoint of these two treatments is similar.

Long-term studies

The following long-term studies were conducted:

Table 6: Long Term Studies in COPD Patients with Twice Daily Dosing

Study	***Treatment Duration***	***Study Status in the Initial SCS***	***Study status in the SCS Addendum***
BID Group 1B: Phase III Long-term studies			
LAS-MD-35	52 weeks	Ongoing	Completed
LAS-MD-33 (12 weeks) plus LAS-MD-36 (52 weeks)	64 weeks	Completed for both studies	Completed for both studies

Long-term safety studies, LAS-MD-35 and LAS-MD-36 were conducted in the US and Canada. The studies were randomised, double-blind, parallel-group studies which were designed primarily to evaluate the safety of aclidinium bromide 400 µg and 200 µg BID, administered for up to 12-months. As there were ethical concerns regarding the inclusion of placebo control groups in long-term COPD clinical trials because of the increased risk of exacerbations in placebo-treated patients, neither study was placebo-controlled. Study LAS-MD-36 was an extension study for patients who participated in pivotal study LAS-MD-33. Patients on aclidinium bromide in the lead-in study continued treatment with aclidinium bromide at the same dose in LAS-MD-36, while only those patients on placebo in the lead-in study were randomised to aclidinium bromide 400 µg or 200 µg. These data were difficult to interpret given the limited sample size and the method of patient enrollment, which was based on patients who

completed study LAS-MD-33 being given the option of continued treatment with aclidinium bromide in study LAS-MD-36.

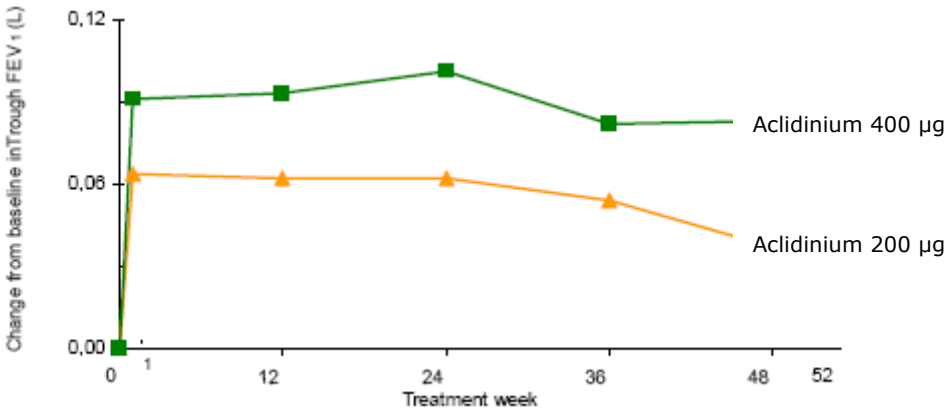
In contrast, in study LAS-MD-35 all patients were randomised to aclidinium bromide 400 µg or 200 µg at study commencement and, therefore, this study represented the more rigorous of the two long-term safety studies for the purposes of efficacy evaluation.

Study LAS-MD-35

Improvements from baseline in bronchodilation were observed with both doses of aclidinium bromide and maintained from Week 1 to Week 52.

Figure 2 below shows the mean change from baseline in morning predose (trough) FEV1 at Weeks 1, 12, 24, 36, 48, and 52. The improvement from baseline to each time point in trough FEV1 was observed for both aclidinium bromide groups. After Week 24, there was a decline in trough FEV1 in both treatment groups, most probably due to the natural decline in FEV1 seen in COPD patients. As early as Week 1, aclidinium bromide 400 µg exhibited an apparent dose separation from aclidinium bromide 200 µg in providing a numerically greater bronchodilator response that was sustained throughout the 52 weeks of the study.

Figure 2: Change from Baseline in Trough FEV1 by Visit (LOCF) Over 52 Weeks: Least Squares (± SE) - ITT Population (Study LAS-MD-35)



Improvements in disease-related health status, as measured by the SGRQ Total score, were observed with both doses of aclidinium bromide. Changes from baseline in SGRQ Total score to all timepoints from Week 12 to Week 52 were consistently greater than the 4-unit improvement threshold considered to be clinically significant.

Table 7: Change from Baseline in SGRQ Total Score at Weeks 12, 24, 36, 48, and 52 (LOCF)—ITT Population

Visit	***AB 200 µg N = 310***	***AB 400 µg N = 290***
	LSMD (SE) 95% CI	*LSMD (SE) 95% CI*
Baseline		
Mean (SD)	48.54 (17.83)	49.83 (18.91)
SEM	1.02	1.12
Median	47.72	49.81
Min, Max	3.73, 89.06	1.44, 96.81
n	305	283

Visit	*AB 200 µg N = 310*	*AB 400 µg N = 290*
Change From Baseline		
Week 12	–6.19 (0.67) –7.52, –4.87	–6.09 (0.70) –7.46, –4.72
Week 24	–6.41 (0.76) –7.89, –4.92	–6.60 (0.78) –8.13, –5.06
Week 36	–5.47 (0.75) –6.939, –3.991	–5.34 (0.78) –6.86, –3.81
Week 48	–5.33 (0.75) –6.79, –3.86	–5.29 (0.77) –6.81, –3.77
Week 52	–5.29 (0.75) –6.77, –3.82	–5.16 (0.78) –6.68, –3.63

Note: SGRQ total score ranged from 0 (best possible health status) to 100 (worst possible health status).

Analyses are based on ANCOVA model for change from baseline in SGRQ total score with treatment group and sex as factors and baseline value and age as covariates.

AB = aclidinium bromide; ANCOVA = analysis of covariance; CI = confidence interval; ITT = intent-to-treat;

LOCF = last observation carried forward; LSM = least squares mean; N = number of patients in the ITT Population; SGRQ = St. George's Respiratory Questionnaire.

Table 8: Number (%) of Patients who Achieved at Least a 4-Point Reduction From Baseline in SGRQ Total Score at Weeks 12, 24, 36, 48, and 52 (LOCF)—ITT Population

Visit	*AB 200 µg N = 310 n/N1 (%)*	*AB 400 µg N = 290 n/N1 (%)*
Week 12	137/305 (44.9)	138/283 (48.8)
Week 24	142/305 (46.6)	139/283 (49.1)
Week 36	138/305 (45.2)	131/283 (46.3)
Week 48	127/305 (41.6)	130/283 (45.9)
Week 52	130/305 (42.6)	128/283 (45.2)

AB = aclidinium bromide; ITT = intent-to-treat; LOCF = last observation carried forward;
N = number of patients in the ITT Population; n = number of patients within a specific category;
N1 = number of patients with available baseline SGRQ total score and at least 1 post-baseline SGRQ total score within a specific category.

Study LAS-MD-36

Treatment with aclidinium bromide was associated with long-term bronchodilation and health-related quality of life benefits that were maintained for the duration of the active treatment period for all treatment groups, although the improvements noted in the treatment group that switched from placebo to aclidinium bromide 200 µg were less robust.

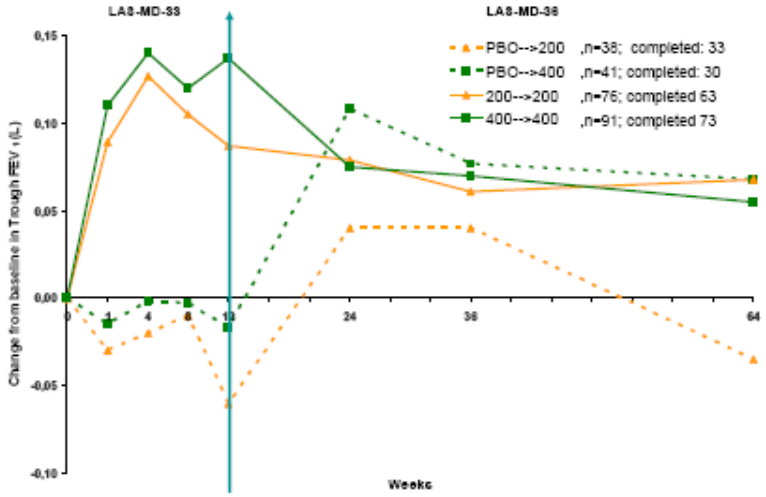
The *primary efficacy endpoint* was the change from baseline in morning pre-dose (trough) FEV1 at Week 64.

The *secondary efficacy endpoint* was the change from baseline in peak FEV1 at Week 64.

Additional efficacy endpoints included:

- Change from baseline in morning pre-dose (trough) FEV1 and peak FEV1 by visit over 64 weeks.
- Change from baseline in SGRQ Total score by visit over 64 weeks.

Figure 3: Change from Baseline in Morning Pre-dose (Trough) FEV1 (L) by Visit Over 64 Weeks: Studies LAS-MD-33 and LAS-MD-36 (ITT Population)



Note: Analyses are based on ANCOVA model for change from baseline in trough FEV_1 with treatment sequence and sex as factors and baseline FEV_1 and age as covariates.
Abbreviations: AB=aclidinium bromide; ANCOVA=analysis of covariance; FEV_1=forced expiratory volume in 1 second; ITT=intent–to-treat.

An improvement from baseline to Week 64 in trough FEV1 was observed in the treatment groups which received aclidinium bromide 200 µg or 400 µg in both the lead-in and extension studies, and in the group which commenced treatment on placebo and switched to aclidinium bromide 400 µg for the extension study. For those patients who were randomised to the placebo-aclidinium bromide 200 µg treatment sequence trough FEV1 was maintained between Week 24 (first timepoint after commencement of active medication) and Week 36 but the effect declined substantially at Week 64.

Table 9: Change from baseline in trough FEV1 at 52 weeks:

Treatment group:	Placebo-Aclidinium bromide 200 µg	Aclidinium bromide 200 µg - Aclidinium bromide 200 µg	Placebo - Aclidinium bromide 400 µg	Aclidinium bromide 400 µg - Aclidinium bromide 400 µg
Trough FEV1 (L); LSM (SE)	-0.035 (0.040)	0.069 (0.028)	0.069 (0.037)	0.056 (0.025)
95% CI	[-0.11, 0.04]	[0.01, 0.12]	[-0.01, 0.14]	[0.01, 0.10]

Similar observations were noted for change from baseline in peak FEV1 by visit over 64 weeks.

Sustained improvements from baseline in SGRQ Total score were observed for the treatment groups that received aclidinium bromide during the lead-in and extension studies and for patients who received placebo in the lead-in study and aclidinium bromide during the extension studies. For all treatment groups, the improvements from baseline in SGRQ Total score were consistently greater than the 4-unit improvement threshold considered to be clinically significant.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

In support of this application the applicant submitted one pivotal Phase III study (M/34273/34) and two supporting Phase III studies (LAS-MD-33 and LAS-MD-38 Part A).

The overall study design of the pivotal study was appropriate with a treatment duration of 6 months as recommended in the current guideline on the clinical investigation of products for the chronic treatment of patients with COPD (CPMP/EWP/562/98). The two supporting studies had a duration of only 12 weeks. The inclusion and exclusion criteria were appropriate in the main clinical studies.

The design of the studies as randomised, parallel group, placebo controlled and double-blind was appropriate and the studies were conducted according to GCP.

Overall the statistical methods were appropriate.

Efficacy data and additional analyses

The findings of the pivotal study, M/34273/34, demonstrated statistically significant improvement for aclidinium bromide 400 mcg twice daily over placebo for the change from baseline in morning pre-dose FEV_1, and for changes from baseline in both the TDI focal score and the SGRQ total score, all after 24 weeks treatment. Although two co-primary endpoints, one investigating lung function and the other symptoms, had not been pre-specified as recommended in the above-mentioned guideline, all three endpoints did demonstrate superiority over placebo at a pre-defined clinically relevant level with appropriate adjustment for multiple testing.

The results of the two further Phase III studies, LAS-MD-33 and LAS-MD-38 Part A, provided limited supportive evidence of efficacy as treatment duration was only 12 weeks rather than 24 weeks as recommended in the guideline. Both studies showed statistically significant improvement for both doses compared to placebo in the lung function parameter and the TDI score although not always reaching clinical relevance. However for the SGRQ total score a significant difference was demonstrated only in the first study and not in the second. It is possible that 12 weeks is not sufficiently long treatment duration to demonstrate an improvement in this score in COPD patients.

Additional confirmation of efficacy in terms of lung function was provided by two Phase II cross-over studies, one comparing aclidinium bromide 400 µg twice daily with tiotropium 18 µg once daily and the other with formoterol 12 µg twice daily. Although neither study was designed to show equivalence or non-inferiority, there was some evidence that the effect of this dose of aclidinium was similar to the approved doses of tiotropium and formoterol. However some caution should be used in the interpretation of the results of these studies as both were considered exploratory and therefore the statistical methodology was not as exhaustive as required for confirmatory Phase III studies with no adjustment for multiple testing and limited investigation of bias introduced by methods used to handle missing data.

Two long-term safety studies were also conducted; LAS-MD-35 and LAS-MD-36. In these two long-term studies it was demonstrated that the treatment effect of aclidinium bromide 400 µg BID seen in the shorter (6 month) pivotal study is maintained for up to 52 weeks with little deterioration. Peak effects were seen at about 24 weeks and the benefits tend to tail off in the second 6 months. It is difficult to draw firm conclusions from these studies as there are no 12-month placebo data but they demonstrated that the benefit of aclidinium bromide on both lung function parameters and quality of life (SGRQ) that was seen in the pivotal trial is maintained over 52 weeks.

The 200 µg BID dose of aclidinium bromide also demonstrated statistically significant improvement in FEV1, TDI and SGRQ in Study M/34273/34 although the results did not always reach a clinically relevant level compared to placebo. In the study with active comparator formoterol fumarate 12 µg BID the 200 µg BID dose of aclidinium bromide demonstrated less efficacy than formoterol fumarate

12 µg BID and aclidinium bromide 400 µg BID but the differences in normalised $FEV1_{(0-12)}$ were not statistically significant. The results seen at 6 months were also maintained through 52 weeks in the long-term safety studies at the dose of aclidinium bromide 200 µg BID.

In one study investigating exercise tolerance a dose of 200 µg QD for 6 weeks demonstrated a statistically and probably clinically significant improvement.

The lower dose of aclidinium bromide (200 µg BID) demonstrated an improvement that was generally statistically significant and often clinically relevant compared to baseline values but just failed to reach a clinically relevant improvement compared to placebo. To address this issue, the applicant provided subgroup analyses for 200µg BID and 400µg BID on FEV1, TDI and SGRQ for patients with less severe disease that helped fully characterise the benefits of aclidinium bromide in various severities of COPD. From the analyses it was seen that the benefit of the 400 µg BID dose is greater even in the patients with less severe COPD although patients with less severe COPD did report a greater improvement in QoL measures than patients with more severe COPD, achieving a clinically meaningful improvement in SGRQ even with a dose of 200 µg BID. However in the placebo-controlled studies lung function parameters showed a greater improvement in the patients with more severe COPD, perhaps because there is more room for improvement in this group.

Overall these results do not suggest that a dose of 200 µg BID of aclidinium bromide would be more beneficial to patients with less severe COPD than a dose of 400 µg BID given similar safety profiles.

In the patients with no exacerbations in the previous year and therefore supposedly less severe COPD a greater improvement in lung function parameters were demonstrated in the pivotal study with similar improvements in SGRQ but a lesser benefit in TDI compared with the overall study population. In the non-placebo controlled studies the change from baseline was similar in the two study populations.

In the group with no exacerbations in the previous year, the patients with less severe COPD (FEV1 ≥65% PN) did show a greater improvement in lung function parameters and a greater improvement in QoL measures. This group achieved a clinically meaningful improvement in trough FEV1, and SGRQ but not in TDI, even with a dose of 200 µg BID aclidinium bromide. The patients with more severe COPD (FEV1 50-65% PN) demonstrated an even greater improvement in lung function at a dose of 200 µg BID but did not achieve a clinically meaningful improvement in SGRQ or TDI.

It was noted that the number of patients other than Caucasians, who constituted 91-95% of the study population, was low. This was satisfactorily addressed in the RMPas important missing information.

2.5.4. Conclusions on the clinical efficacy

The data submitted in the pivotal study (M/34273/34) and the main supporting studies (LAS-MD-33 and LAS-MD-38A) demonstrated that aclidinium bromide 400 µg BID can achieve a clinically relevant improvement in lung function and in symptomatic parameters of patients with moderate to severe COPD compared to placebo.

Overall the improvement seen with a dose of 200 µg BID did not achieve a clinically meaningful level consistently and the applicant's claim that the 400 µg BID dose of aclidinium bromide is the optimal dose given a similar safety profile was endorsed by the CHMP.

2.6. Clinical safety

Throughout the clinical programme of aclidinium bromide BID and QD, the safety and tolerability of aclidinium bromide were evaluated by the monitoring of adverse events, vital signs, physical

examinations, laboratory blood and urine tests and ECG measurements (including Holter monitoring in some studies). The safety population consisted of all subjects/patients who took at least one dose of the investigational medicinal product (IMP).

The primary evidence of safety is based on pooled data from the Safety population of three double-blind, placebo-controlled clinical studies (M/34273/34, LAS-MD-33 and LAS-MD-38 Part A), in which patients with moderate to severe COPD were exposed to BID aclidinium bromide (200 µg or 400 µg) or placebo for up to 12 or 24 weeks (hereafter referred to as "Pivotal Study Population"). This population was chosen for the primary evaluation of safety as the study designs were similar with all three studies being placebo-controlled.

Supportive evidence of safety is based on pooled data from the Safety population of three long-term studies (LAS-MD-35, LAS-MD-36 and LAS-MD-38 Part B) in patients with moderate or severe COPD (hereafter referred to as "Long-Term Study Population"). Studies LAS-MD-36 and LAS-MD-38 Part B were extension studies for patients who completed pivotal studies LAS-MD-33 and LAS-MD-38 Part A; this safety evaluation also includes data obtained in those patients who were treated with aclidinium bromide during the lead-in studies. In studies LAS-MD-36 and LAS-MD-35, patients were exposed to aclidinium bromide 200 µg or 400 µg BID, in a double-blind fashion, for up to 52 weeks. In study LAS-MD-38 Part B, patients were exposed to aclidinium bromide 400 µg for up to 40 weeks in an open-label fashion.

Further supportive evidence of safety is from pooled data from the Safety population of placebo-controlled Phase II studies of aclidinium bromide BID (M/34273/23, M/34273/29, LAC-MD-27 and M/40464/26) in patients with moderate or severe COPD (hereafter referred to as "Phase II Study Population"). Safety data from these placebo-controlled studies were not pooled with data from the double-blind, placebo-controlled pivotal studies because of study design differences between the two groups of studies; the Phase II studies were of cross-over design with short treatment durations (1 to 2 weeks per treatment period).

Patient exposure

The extent of exposure in clinical studies of aclidinium bromide BID in Patients with COPD is shown in the table below:

Table 10: Extent of Exposure in Clinical Studies of Aclidinium Bromide BID in Patients with COPD (Safety Population)

	Initial SCS [a]				***SCS Addendum*** [b]			
	Placebo N=940	**AB 100 µg N=73**	**AB 200 µg N=1173**	**AB 400 µg N=1471**	**Placebo N=940**	**AB 100 µg N=73**	**AB 200 µg N=1173**	**AB 400 µg N=1471**
Mean, days (SD)	78.1 (61.3)	7.0 (0.2)	148.5 (115.5)	153.2 (109.3)	78.1 (61.3)	7.0 (0.2)	169.8 (138.9)	210.6 (137.0)
Median	85.0	7.0	167.0	167.0	85.0	7.0	166.0	179.0
Min, Max	1, 200	7,8	1, 476	1, 463	1, 200	7,8	1, 476	1, 463
≥ 1 day	940 (100)	73 (100)	1173 (100)	1471 (100)	940 (100)	73 (100)	1173 (100.0)	1471 (100.0)
≥ 1 week	927 (98.6)	73 (100)	1158 (98.7)	1449 (98.5)	927 (98.6)	73 (100)	1158 (98.7)	1451 (98.6)
≥ 4 weeks	597 (63.5)	0	942 (80.3)	1214 (82.5)	597 (63.5)	0	939 (80.1)	1214 (82.5)
≥ 12 weeks	516 (54.9)	0	850 (72.5)	1077 (73.2)	516 (54.9)	0	847 (72.2)	1141 (77.6)
≥ 24 weeks	196 (20.9)	0	567 (48.3)	714 (48.5)	196 (20.9)	0	564 (48.1)	970 (65.9)

	Initial SCS[a]				*SCS Addendum*[b]			
	Placebo N=940	**AB 100 µg N=73**	**AB 200 µg N=1173**	**AB 400 µg N=1471**	**Placebo N=940**	**AB 100 µg N=73**	**AB 200 µg N=1173**	**AB 400 µg N=1471**
≥ 36 weeks	0	0	167 (14.2)	202 (13.7)	0	0	313 (26.7)	679 (46.2)
≥ 51 weeks	0	0	100 (8.5)	107 (7.3)-	0	0	282 (24.0)	387 (26.3)
Total Patient Years of Exposure	201.0	1.4	476.9	616.8	201.0	1.4	545.2	848.3

Note: in the summary of clinical safety (SCS) Addendum there are fewer patients in the aclidinium bromide 200 µg group at Weeks 4, 12 and 24 compared with the initial SCS reported data. This is due to changes in study drug start and stop dates made after the 01 Nov 2010 cut-off date for the initial SCS.

a For the initial SCS, studies were: LAC-MD-27, LAS-MD-33, LAS-MD-35, LAS-MD-36, LAS-MD-38 Part A, LAS-MD-38 Part B, M/34273/23, M/34273/29, M/34273/34, and M/40464/26 in COPD patients with twice daily dosing regimen. Please note that ongoing studies (LAS-MD-38 Part B and LAS-MD-35) used a data cut-off date of 01 November 2010 in the initial SCS, completed studies were LAS-MD-38 Part A, LAS-MD-33, and LAS-MD-36 in the initial SCS. Patients in the extension studies LAS-MD-36 and LAS-MD-38 Part B or crossover studies LAC-MD-27, M/34273/23, M/34273/29, and M/40464/26 who had different treatment from the lead-in study or other treatment period were counted multiple times, once in each treatment period.

b Includes data from all completed studies (BID Group 1 - all studies in COPD patients with twice daily dosing regimen).

AB = aclidinium bromide; max = maximum, min = minimum.

With the addition of the two long-term safety studies LAS-MD-35 and LAS-MD-38 Part B, further patients with COPD were exposed to aclidinium bromide for at least 1 year (387) at the proposed dose of 400 µg BID. This was sufficient to make a better assessment of the long-term safety of aclidinium bromide. In addition 282 patients were exposed to aclidinium bromide 200 µg BID for at least 1 year.

Adverse events

The most frequently reported adverse reactions with Eklira Genuair were headache (6.6%) and nasopharyngitis (5.5%).

Adverse Events by Preferred Term with an Incidence of ≥2% in Any Treatment Group in the Pivotal Study Population: Studies M/34273/34, LAS-MD-33 and LAS-MD-38 Part A (Safety Populations)

Preferred Term	***Placebo N=641 n (%)***	***Aclidinium Bromide 200 µg N=644 n (%)***	***Aclidinium Bromide 400 µg N=636 n (%)***
COPD (exacerbation)	100 (15.6)	77 (12.0)	75 (11.8)
Headache	32 (5.0)	43 (6.7)	42 (6.6)
Nasopharyngitis	25 (3.9)	40 (6.2)	35 (5.5)
Cough	14 (2.2)	17 (2.6)	19 (3.0)
Diarrhoea	9 (1.4)	12 (1.9)	17 (2.7)
Hypertension	16 (2.5)	8 (1.2)	10 (1.6)
Back pain	12 (1.9)	18 (2.8)	8 (1.3)
Bronchitis	13 (2.0)	5 (0.8)	7 (1.1)

In the Pivotal Study Population, aclidinium bromide 200 µg or 400 µg did not increase the percentage of patients with at least one adverse event, with any adverse event leading to discontinuation, with any SAEs or who died compared to placebo.

Table 11: Number and Percentage of Patients with Adverse Events in the Pivotal Study Population: Studies M/34273/34, LAS-MD-33 and LAS-MD-38 Part A (Safety Populations)

Category	Placebo N=641 n (%)	Aclidinium Bromide 200 µg N=644 n (%)	Aclidinium Bromide 400 µg N=636 n (%)
At least 1 AE	344 (53.7)	321 (49.8)	319 (50.2)
Any AE Leading to Study Discontinuation	33 (5.1)	27 (4.2)	29 (4.6)
Any SAE	31 (4.8)	31 (4.8)	28 (4.4)
Any Deaths	2 (0.3)	1 (0.2)	3 (0.5)

Abbreviations: AE=adverse event; SAE=serious adverse event.

No dose-related trend in the percentage of patients with adverse events was observed in the Pivotal Study Population or the Long-Term Study Population. In the Phase II Study Population, small increases in the percentage of patients with at least one adverse event and with adverse events of mild intensity were observed with aclidinium bromide 400 µg compared to the placebo, but no differences in the percentages of patients with deaths, SAEs, adverse events leading to discontinuation or adverse events of moderate or severe intensity were observed.

Table 12: Overview of Adverse Events: Long-term Safety Studies of Aclidinium Bromide

Category Number (%) of patients	***Initial SCS***[a]		***SCS Addendum***[b]	
	AB 200 µg BID N = 568 313.5 PY n (%)	**AB 400 µg BID N = 1005 526.2 PY n (%)**	**AB 200 µg BID N = 568 381.8 PY n (%)**	**AB 400 µg BID N = 1005 758.0 PY n (%)**
At least 1 TEAE	335 (59.0)	564 (56.1)	372 (65.5)	694 (69.1)
Any mild TEAE	224 (39.4)	353 (35.1)	251 (44.2)	458 (45.6)
Any moderate TEAE	204 (35.9)	337 (33.5)	232 (40.8)	453 (45.1)
Any severe TEAE	52 (9.2)	94 (9.4)	65 (11.4)	129 (12.8)
Any AE leading to study discontinuation	58 (10.2)	75 (7.4)	66 (11.6)	97 (9.7)
Any SAE	51 (9.0)	81 (8.1)	62 (10.9)	114 (11.3)
Any death	1 (0.2)	5 (0.5)[c]	3 (0.5)	7 (0.7)[c]

AB = aclidinium bromide; AE = adverse event; BID = twice daily; PY= patient-years; SAE = serious adverse event; TEAE = treatment-emergent adverse event

a Includes data from ongoing and completed studies: ongoing studies (LAS-MD-38 Part B and LAS-MD-35) used a data cut-off date of 01 November 2010 in the initial SCS, completed studies were LAS-MD-38 Part A, LAS-MD-33, and LAS-MD-36 in the initial SCS.

b Includes data from all completed studies: LAS-MD-38 Part A and Part B combined, LAS-MD-33 and LAS-MD-36 combined, and LAS-MD-35

c Two of the deaths in the aclidinium bromide 400 µg group occurred in the lead-in studies (Study LAS-MD-33, Patient 114233015; Study LAS-MD-38 Part A, Patient 135438005)

In the aclidinium bromide 400 µg BID group comparing the percentage of patients experiencing TEAEs in the summary of clinical safety (SCS) Addendum with that of the initial SCS demonstrated that there is an increase (56.1% vs 69.1%) but this increase is mainly in mild to moderate TEAEs. Increases in the percentage of patients discontinuing due to TEAEs (7.4% vs 9.7%), SAEs (8.1% vs 11.3%) and deaths (0.5% vs 0.7%) are modest and not unexpected in this patient population. In the absence of a

placebo arm in the long-term safety studies comparison between the doses gave some impression of whether the safety of aclidinium bromide may decrease with time and this appeared not to be so.

Serious adverse event/deaths

Serious adverse events

In the Pivotal Study Population, SAEs were reported by 4.8% of patients treated with placebo, 4.8% of patients treated with aclidinium bromide 200 µg and 4.4% of patients treated with aclidinium bromide 400 µg. The most frequently reported SAE was COPD (exacerbation) which was reported at a lower incidence in the aclidinium bromide treatment groups compared to the placebo group (placebo 2.7%, aclidinium bromide 200 µg 1.4%, aclidinium bromide 400 µg 1.6%).

In the Long-term Study Population the most frequently reported SAE was COPD (exacerbation) and the incidence was numerically higher in the aclidinium bromide 400 µg group compared with the aclidinium bromide 200 µg group (3.6% [47.5 per 1000 PY] vs 2.5% [36.7 per 1000 PY], respectively).

Other than COPD (exacerbation), pneumonia was the only additional SAE reported in at least 1% of the patients, but the incidence was not higher with aclidinium bromide 400 µg compared to aclidinium bromide 200 µg (0.6% vs 1.1%, respectively). Even when combining all SAE terms of pneumonia (including PTs of pneumonia bacterial, pneumonia, lobar pneumonia and pneumonia pneumococcal), the lower incidence in the 400 µg group compared to the 200 µg group was maintained (1.0% vs 1.4%, respectively).

There was a higher incidence of acute renal failure in the aclidinium bromide 400 µg group (0.5%; 6.6 per 1000 PY) compared with the 200 µg group (0%). This incidence included 1 additional patient (153038002, Study LAS-MD-38 Part B) as compared to the incidence reported for acute renal failure in the aclidinium bromide 400 µg group in the initial SCS (0.4%; 7.6 per 1000 PY). Although there was a higher incidence of acute renal failure in the long-term safety population there was a lower number of patients per 1000 PY reflecting the increased exposure.

However in acute renal failure, COPD exacerbations and cardiac failure there is an increased incidence in the aclidinium bromide 400 µg group compared to the aclidinium bromide 200 µg group suggesting a possible dose response in these adverse events and reinforcing the need to ensure the optimal dosing regimen is characterised. However, the numbers are very small and a causal relationship with aclidinium bromide cannot be established. Therefore it was not considered needed to include these adverse events in the SmPC at this stage. The PASS study should give more information on AEs and SAEs in general.

Deaths

A total of 14 on-treatment deaths were reported in the aclidinium bromide BID studies (all studies in COPD patients) of which 9 (2 aclidinium bromide 200 µg, 5 aclidinium bromide 400 µg and 2 placebo) were reported in the initial application, (based on a data cut-off date of 01 Nov 2010). Only one of these deaths was thought to be related to study medication:

Patient 142135024 (aclidinium bromide 400 µg) was a 73-year-old Caucasian female, an ex-smoker with a smoking history of 44 pack-years, whose medical history included COPD since 2007, anxiety in 1996, gastroesophageal reflux disease since 2005, hyperlipidemia since 2007, hypertension since January 2008, acute myocardial infarction in December 2008, and coronary artery disease since December 2008. The patient experienced a COPD exacerbation 103 days after starting treatment with aclidinium bromide 400 µg BID. The patient died on the same day as she was hospitalised.

Since the cut-off date of 1 November 2010 and up until 13 May 2011 there were four deaths in the ongoing long-term studies. Five additional deaths (2 aclidinium bromide 200 µg and 3 aclidinium bromide 400 µg) were reported after 1 November 2012, one of which was reported as a SAE in the initial application but the patient subsequently died.

Other than the one case above, deaths reported in the studies were in patients with concomitant disease that explains the death or death was due to a new diagnosis not related to their COPD or study medication.

Of the total of 14 deaths there were four cardiovascular-related deaths in patients taking aclidinium bromide but these patients had a previous history of ischaemic heart disease or, in one case, the cardio-respiratory arrest occurred 27 days after stopping study medication. In the long-term safety studies two deaths occurred due to "cardiac arrest". These were both in patients known to have a history of drug abuse (one with narcotic abuse) and the patients collapsed suddenly and did not respond to cardiopulmonary resuscitation. Neither death was considered to be related to study medication.

Laboratory findings

Haematological data obtained during the 3 double-blind, placebo-controlled studies did not disclose any clinically relevant change from baseline to end-of-study for any parameter and were not dose dependent. Mean change from baseline values for the chemistry determinations also showed no relevant changes or dose dependence in any treatment arm at end-of-study except for an apparent dose-associated increase in uric acid levels.

There were also some minor increases in liver enzymes ALT and AST but there was no consistent dose response. A similar pattern was seen in the data from the long-term safety studies but there was no evidence of worsening over time. Aclidinium bromide has a very low systemic bioavailability and is almost immediately metabolised, mainly in the plasma, and excreted in the urine with hepatic metabolism playing a very minor role in the clearance of aclidinium bromide. Therefore there is little biological plausibility for aclidinium bromide causing hepatic toxicity.

Table 13: Number (%) of Patients with Potentially Clinically Significant Shifts from Baseline to the End of Study in Clinical Laboratory Values that are either "New" or "Worsening" and Observed in at Least 1% of Patients in Either Treatment Arm: Aclidinium Bromide Administered Twice Daily to Patients with COPD in Long-term Safety Studies (BID Group 1B)

Laboratory Parameter		Initial SCS[a]		SCS Addendum[b]	
		AB 200 µg BID N = 568 313.5 PY	AB 400 µg BID N = 1005 526.2 PY	AB 200 µg BID N = 568 381.8 PY	AB 400 µg BID N = 1005 758.0 PY
Haematology					
Eosinophils	New	2/507 (0.4)	7/818 (0.9)	1/510 (0.2)	9/930 (1.0)
Lymphocytes	New	12/507 (2.4)	13/818 (1.6)	10/510 (2.0)	18/930 (1.9)
Monocytes	New	5/507 (1.0)	11/818 (1.3)	4/510 (0.8)	11/930 (1.2)
Neutrophils	New	21/507 (4.1)	22/818 (2.7)	24/510 (4.7)	40/930 (4.3)
Platelets	New	5/488 (1.0)	7/788 (0.9)	7/492 (1.4)	7/905 (0.8)
White blood	New	9/507 (1.8)	16/818 (2.0)	14/510 (2.7)	31/930 (3.3)

cells					
Blood Chemistry					
Creatine kinase	New	11/509 (2.2)	35/810 (4.3)	20/512 (3.9)	44/925 (4.8)
	Worsened	4/509 (0.8)	10/810 (1.2)	8/512 (1.6)	7/925 (0.8)
Creatinine	New	2/511 (0.4)	7/814 (0.9)	7/514 (1.4)	11/929 (1.2)
	Worsened	5/511 (1.0)	1/814 (0.1)	4/514 (0.8)	3/929 (0.3)
GGT	New	6/511 (1.2)	28/814 (3.4)	12/514 (2.3)	28/929 (3.0)
	Worsened	10/511 (2.0)	28/814 (3.4)	8/514 (1.6)	30/929 (3.2)
Glucose	New	57/507 (11.2)	80/807 (9.9)	65/510 (12.7)	85/923 (9.2)
	Worsened	8/507 (1.6)	15/807 (1.9)	8/510 (1.6)	12/923 (1.3)
LDH	New	5/496 (1.0)	10/786 (1.3)	7/499 (1.4)	12/905 (1.3)
Potassium	New	6/505 (1.2)	15/808 (1.9)	8/508 (1.6)	13/924 (1.4)
SGOT/AST	New	9/500 (1.8)	17/802 (2.1)	8/504 (1.6)	23/917 (2.5)
	Worsened	3/428 (0.7)	7/791 (0.9)	3/504 (0.6)	10/917 (1.1)
SGPT/ALT	New	8/508 (1.6)	16/809 (2.0)	8/511 (1.6)	25/924 (2.7)
Triglycerides	New	15/511 (2.9)	32/813 (3.9)	16/514 (3.1)	38/928 (4.1)
	Worsened	4/511 (0.8)	12/813 (1.5)	5/514 (1.0)	11/928 (1.2)
Urea (BUN)	New	8/511 (1.6)	11/814 (1.4)	11/514 (2.1)	17/929 (1.8)
Uric acid	New	5/511 (1.0)	13/814 (1.6)	4/514 (0.8)	18/514 (1.9)

a Includes data from ongoing and completed studies: ongoing studies (LAS-MD-38 Part B and LAS-MD-35) used a data cut-off date of 01 November 2010 in the initial SCS. Completed studies were LAS-MD-38 Part A, LAS-MD-33, and LAS-MD-36 in the initial SCS.

b Includes data from all completed studies: LAS-MD-38 Part A and Part B combined, LAS-MD-33 and LAS-MD-36 combined, and LAS-MD-35

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BID = twice daily; BUN = blood urea nitrogen; GGT = γ-glutamyl transferase; LDH = lactate dehydrogenase; LLN = lower limit of normal range; SGOT= serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; ULN = upper limit of normal range.

Safety in special populations

Detailed analyses of the impact of age, sex, race, body mass index, COPD severity and the concomitant use of inhaled corticosteroids (ICS) on the frequency of adverse events in the Pivotal Study Population were performed.

There were no consistent patterns of TEAEs to suggest that there is an association between age, sex, body mass index, COPD severity or concomitant ICS and an increased risk of experiencing a TEAE. As would be expected, overall the older age group experienced more TEAEs than the younger age group but still less than placebo within that age group.

There was no evidence that dose adjustment would be necessary on safety grounds on the basis of age, sex, body mass index or COPD severity.

The very limited data on the safety in different races other than Caucasians was noted by the CHMP. However, this was adequately addressed in the RMP as important missing information.

Immunological events

There were no cases of hypersensitivity to aclidinium bromide reported in the clinical programme. As with all inhaled medication paradoxical bronchospasm may occur with aclidinium bromide but from the clinical programme it would seem that it is no more likely with aclidinium bromide than with any other inhaled product. Nevertheless a warning regarding the possibility has been included in section 4.4 of the SmPC.

Safety related to drug-drug interactions and other interactions

No formal studies to investigate drug-drug interactions were conducted. In an overview of TEAE incidence stratified by use of allowed concomitant medications for BID Pivotal studies (including sympathomimetic bronchodilators, methylxanthines, and oral and inhaled steroids) there were no major differences found in the frequencies of TEAEs in patients who used or did not use concomitant medications in the aclidinium bromide treatment groups when compared with placebo.

With the majority of categories of concomitant medications those patients who used the concomitant medications tended to experience more TEAEs than those who did not. However the percentage of patients experiencing TEAEs tended to be lower in the aclidinium groups than in the placebo group.

Discontinuation due to adverse events

AEs leading to permanent treatment discontinuation are also referred to as adverse events leading to dropout (ADOs).

Overall, the incidences of ADOs by SOC were similar among the placebo, aclidinium bromide 200 µg and aclidinium bromide 400 µg treatment arms, and most of the ADOs were from the Respiratory, Thoracic and Mediastinal Disorders SOC, mainly due to COPD exacerbation and to a lesser extent dyspnoea.

Table 14: Patients with adverse events leading to dropout

		Aclidinium Bromide		
	Placebo (N=641) n (%) [Related]	**200µg (N=644) n (%) [Related]**	**400µg (N=636) n (%) [Related]**	**Overall (N=1280) n (%) [Related]**
Pivotal Studies Population				
Patients with at least one ADO	33 (5.1) [6]	27 (4.2) [6]	29 (4.6) [5]	56 (4.4) [11]
Long-term Studies Population				
Patients with at least one ADO	N/A	58 (10.2) [12]	75 (7.5) [23]	133 (8.5) [35]
Phase II Cross-over studies				
Patients with at least one ADO	7 (2.3) [3]	3 (1.7) [0]	4 (2.0) [0]	7 (2.3) [0]

Overall (including the long-term safety studies) 11.6% of patients in the aclidinium bromide 200 µg group and 9.7% of patients in the aclidinium bromide 400 µg group permanently withdrew due to a TEAE. This compares to reported rates of 10.2% for aclidinium bromide 200 µg and 7.5% for aclidinium bromide 400 µg in the table above.

2.6.1. Discussion on clinical safety

Adequate numbers were exposed to aclidinium bromide during the clinical development programme to allow assessment of clinical safety of a dose of 400 µg BID. As per ICH E1 more than the minimum number of patients were exposed for at least 1 year (387 at the proposed dose of 400 µg BID) to provide sufficient safety information for long-term treatment.

In the development programme data on adverse events, serious adverse events and deaths were collected and analysed for the following safety population: Pivotal Study Population, Long-term Study Population and Phase II Study Population.

Throughout the clinical programme of aclidinium bromide BID and QD, the safety and tolerability of aclidinium bromide were evaluated by the monitoring of adverse events, vital signs, physical examinations, laboratory blood and urine tests and ECG measurements (including Holter monitoring in some studies). The safety population consisted of all subjects/patients who took at least one dose of aclidinium bromide.

The following adverse events were reported in a greater percentage of patients taking aclidinium bromide than taking placebo and were included in section 4.8 of the SmPC: headache, nasopharyngitis, cough, diarrhoea and sinusitis. Anticholinergic adverse effects reported during the clinical programme (dry mouth, tachycardia, blurred vision and urinary retention) were also included in the table of adverse events in the SmPC. Furthermore, relevant safety information based on the anticholinergic activity (like caution in patients with symptomatic prostatic hyperplasia or bladder-neck obstruction or with narrow-angle glaucoma) has been included in section 4.4 of the SmPC.

The effects of aclidinium bromide on adverse events of special interest were also explored in the categories of cardiovascular effects, anticholinergic effects and pneumonia/COPD exacerbations.

A thorough QT study (Study M/34273/11) was conducted but as the proposed dose at that time was 200 µg QD the highest dose investigated was 800 µg QD. No evidence of a clinically relevant effect on QTc interval was demonstrated in this study.

In Phase I studies inhalation of single doses up to 6 mg of aclidinium bromide and multiple doses up to 800 µg BID for 7 days were investigated with one episode of tachycardia being reported by one subject taking 800 µg BID.

In the pivotal Phase III studies Holter monitoring was conducted in a subgroup of patients. Although the overall rate of ECG abnormalities was similar across the two aclidinium bromide groups, the rate of reporting of conduction abnormalities, particularly AV block did appear to increase over time. There was also a larger number of patients with QTc prolongation in the aclidinium bromide 400 µg group compared with the aclidinium bromide 200 µg group.

From the long-term safety data there appeared to be an effect of aclidinium bromide on AV-nodal conduction and the applicant was asked to discuss possible mechanisms of action that may explain this. Further to this request, the applicant presented data on the reporting of AV Node conduction defects as a treatment-emergent adverse event (TEAE) and on prolongation of PR interval from centrally assessed ECG recordings. Although there is no consistent dose response association with conduction defects or clinically meaningful increases in PR interval, in the placebo-controlled studies there were no reports of a TEAE of AV block in the placebo group. In the placebo-controlled studies there was a trend towards a greater percentage of patients with a shift to increased PR interval across the doses (2.6% placebo, 3.0% aclidinium bromide 200 µg BID and 3.3% aclidinium bromide 400 µg BID). However, the numbers (and percentages) were small and the trend could be chance.

The applicant explained that the data did not demonstrate a definite association between aclidinium bromide and AV Node block or PR interval prolongation to suggest a causal relationship and there was no known biological mechanism by which aclidinium bromide should cause heart block. There was no evidence of an increased risk of cardiac failure or cerebrovascular adverse effects with aclidinium bromide 400 μg BID. Also there was no evidence of an increased risk of pneumonia when patients with COPD were taking aclidinium bromide.

Taking the above into account, the CHMP requested the applicant to specifically monitor cardiovascular adverse events in the RMP and reports of conduction abnormalities post-authorisation. Additionally, the applicant was requested to commit to Post-Authorisation Safety (PAS) Cohort Study of Inhaled Aclidinium Bromide and the Risk of Selected Cardiovascular Endpoints. (described in the RMP) where cardiovascular adverse events will be particularly monitored. The objectives of this study will be tocompare the risk of heart failure and acute myocardial infarction in patients with COPD on aclidinium bromide with the risk in patients with COPD on other drugs commonly used in COPD.

Since patients with pre-existing cardiovascular abnormalities and, in particular patients with cardiac failure (NYHA stage III-IV) were excluded from the studies, cardiovascular adverse events need to be monitored further by the applicant in the RMP and in the above-mentioned Post-Authorisation Safety Study. Given the lack of data in this patient group, the SmPC in section 4.4 advises that the product should be used with caution.

Additionally, the first step in the above-mentioned post-authorisation safety study (PASS) will be to perform a drug utilisation study (DUS) to cover aspects related to drug utilisation, off-label use, and identification of patient groups with missing information in the RMP. A cohort study will be conducted in new users of aclidinium bromide and new users of other inhaled medications frequently used by patients with COPD. The patients in this DUS will also become the core of a larger patient cohort in which many of the safety concerns outlined in the RMP will be evaluated in a later stage.

2.6.2. Conclusions on the clinical safety

There were no particular safety issues highlighted during the studies submitted with this application. In particular, from the safety data presented, there is no evidence that aclidinium bromide increases the risk of fatal events, cardiovascular disorders or pneumonia in the COPD patient population.

The data on the effects of aclidinium bromide on the QTc interval are limited and an effect of aclidinium bromide on AV-nodal conduction cannot be ruled out. Cardiovascular adverse events need to be monitored further by the applicant in the RMP and in the proposed Post-Authorisation Safety Study (PASS). Cardiovascular adverse events should also be discussed separately in future PSURs.

The CHMP considers the following measures necessary to address issues related to safety:

- Post-Authorisation Safety (PAS) Cohort Study of Inhaled Aclidinium Bromide and the Risk of Selected Cardiovascular Endpoints.

- Drug utilisation study (DUS) to cover aspects related to drug utilisation, off-label use, and identification of patient groups with missing information in the RMP.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

In addition, the CHMP considered that the applicant should take the following minor point into consideration when an update of the Pharmacovigilance system is submitted:

The applicant should have a procedure in place for dealing with responses to requests for information from regulatory authorities, not necessarily in relation to variations, in relation to any aspect of pharmacovigilance.

At the time of this opinion, the applicant was developing an SOP AR/PA015 "Response to Requests for Information from Competent Authorities" and committed to finalise it and have the key personnel duly trained before the Commission Decision.

Risk Management Plan

The applicant submitted a risk management plan.

Table 15. Summary of the risk management plan

Safety Concern	**Proposed Pharmacovigilance Activities (Routine and Additional)**	**Proposed Risk Minimisation Activities (Routine and Additional)**
Identified Risk	Not applicable; none identified.	Not applicable.
Potential Risk		
Cardiac disorders	– Routine pharmacovigilance including follow-up of spontaneous reporting through cardiac and cardiovascular events data capture aid – PASS	SmPC Section 4.8, Undesirable Effects. Tachycardia included as uncommon in table of adverse reactions.
Cerebrovascular events	– Routine pharmacovigilance including follow-up of spontaneous reporting through cerebrovascular events data capture aid – PASS	Currently not applicable
Mortality: cardiovascular, respiratory, overall	– Routine pharmacovigilance including follow-up of spontaneous reporting through death data capture aid – PASS	Currently not applicable
Class Effects: Anticholinergic effects	– Routine pharmacovigilance	SmPC Section 4.8, Undesirable Effects *Pharmacological class undesirable effects:* Dry mouth, tachycardia, dysphonia, blurred vision and urinary retention listed as ADRs. SmPC Section 4.9, Overdose High doses of aclidinium bromide may lead to anticholinergic signs and symptoms.

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
Class Effects: Paradoxical bronchospasm	– Routine pharmacovigilance	SmPC Section 4.4, Special Warnings and Precautions for Use. As with other inhalation therapies, administration of Eklira Genuair may cause paradoxical bronchospasm. If this occurs, treatment with Eklira Genuair should be stopped and other treatments considered.
Paediatric (off-label use)	– Routine pharmacovigilance – DUS	SmPC Section 4.1 Therapeutic Indications Eklira Genuair is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD). SmPC Section 4.2, Posology and Method of Administration. *Paediatric Population* There is no relevant use of Eklira Genuair in children (under 18 years of age) in the indication of COPD. SmPC Section 5.1, Pharmacological Properties The European Medicines Agency has waived the obligation to submit the results of studies with Eklira Genuair in all subsets of the paediatric population in COPD.
Off-label use in pregnancy and lactation	– Routine pharmacovigilance – Focused follow-up of spontaneous reporting through the pregnancy form – DUS (pregnancy only)	SmPC Section 4.6, Fertility, Pregnancy, and Lactation. *Pregnancy* There are no data available on the use of aclidinium bromide in pregnant women. Studies in animals have shown fetotoxicity only at dose levels much higher than the maximum human exposure to aclidinium bromide (see SmPC Section 5.3, Preclinical Safety Data). Eklira Genuair should only be used during pregnancy if the expected benefits outweigh the potential risks. *Breast-feeding* It is unknown whether aclidinium bromide and/or its metabolites are excreted in human milk. As animal studies have shown excretion of small amounts of aclidinium bromide and/or metabolites into milk, a decision must be made whether to discontinue breast-feeding or to discontinue therapy with Eklira Genuair taking into account the benefit of breast-feeding for the child and the benefit of long-term aclidinium bromide therapy to the woman.

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
Missing Information		
Renal and hepatic impairment	– Routine pharmacovigilance – DUS	SmPC Section 4.2, Posology and Method of Administration *Renal Impairment* No dose adjustments are required for patients with renal impairment. *Hepatic Impairment* No dose adjustments are required for patients with hepatic impairment. SmPC Section 5.2, Pharmacokinetic Properties, Special Populations *Hepatically-impaired Patients* No studies have been performed on hepatically impaired patients. As aclidinium bromide is metabolised mainly by chemical and enzymatic cleavage in the plasma, hepatic dysfunction is very unlikely to alter its systemic exposure. No dose adjustment is required for hepatically-impaired COPD patients. *Renally-impaired patients* No significant pharmacokinetic differences were observed between subjects with normal renal function and subjects with renal impairment. Therefore, no dose adjustment and no additional monitoring are required for renally-impaired COPD patients.
Non-Caucasian patients (including pharmacodynamic data)	– Routine pharmacovigilance – Clinical development in Japanese and Korean patients	Currently not applicable

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
Other patient populations excluded from the clinical programme (symptomatic BPH, bladder neck obstruction, urinary retention, narrow-angle glaucoma, newly diagnosed or unstable arrhythmias, recent MI, unstable angina, heart failure, concomitant treatment with other anticholinergics	– Routine pharmacovigilance – DUS (for some conditions, diagnoses might not be reliable or completeness might be a limitation; urinary retention most likely not feasible)	SmPC Section 4.4, Special Warnings and Precautions for Use Patients with a myocardial infarction during the previous 6 months, unstable angina, newly diagnosed arrhythmia within the previous 3 months, or hospitalisation within the previous 12 months for heart failure functional classes III and IV as per the "New York Heart Association" were excluded from the clinical trials and the safety of these patient groups has not been investigated. Eklira Genuair should be used with caution in these patient groups. Consistent with its anticholinergic activity, aclidinium bromide should be used with caution in patients with symptomatic prostatic hyperplasia or bladder-neck obstruction or with narrow-angle glaucoma (even though direct contact of the product with the eyes is very unlikely). SmPC Section 4.5, Interaction with Other Medicinal Products and other Forms of Interaction. Co-administration of aclidinium bromide with other anticholinergic-containing medicinal products has not been studied and is not recommended.
Interaction with other medicinal products	– Routine pharmacovigilance – DUS (concomitant use with other medications including anticholinergics and LABAs)	SmPC Section 4.5, Interaction With Other Medicinal Products and Other Forms of Interaction. Co-administration of aclidinium bromide with other anticholinergic-containing medicinal products has not been studied and is not recommended. Although no formal *in vivo* drug interaction studies have been performed, inhaled aclidinium bromide has been used concomitantly with other COPD medicinal products including sympathomimetic bronchodilators, methylxanthines, and oral and inhaled steroids without clinical evidence of drug interactions. *In vitro* studies have shown that aclidinium bromide or the metabolites of aclidinium bromide at the therapeutic dose are not expected to cause interactions with P-gp substrate drugs or drugs metabolised by cytochrome P450 (CYP450) enzymes and esterases (see section 5.2).
Patients who have experienced a recent exacerbation	– Routine pharmacovigilance – DUS	Currently not applicable

Safety Concern	Proposed Pharmacovigilance Activities (Routine and Additional)	Proposed Risk Minimisation Activities (Routine and Additional)
Off-label use in adults (including adults with asthma [misdiagnoses, coexisting])	– Routine pharmacovigilance – DUS	SmPC Section 4.1, Therapeutic Indications. Aclidinium bromide is indicated as a maintenance bronchodilator treatment to relieve symptoms of patients with chronic obstructive pulmonary disease (COPD). SmPC Section 4.4, Special Warnings and Precautions for Use. Asthma: Eklira Genuair should not be used in asthma; clinical trials of aclidinium bromide in asthma have not been conducted. Deterioration of disease: Eklira Genuair is a maintenance bronchodilator and should not be used for the relief of acute episodes of bronchospasm, i.e. as a rescue therapy. In the event of a change in COPD intensity while the patient is being treated with Eklira Genuair so that the patient considers additional rescue medication is required, a re-evaluation of the patient and the patients' treatment regimen should be conducted.
Medication/use of device errors	– Routine pharmacovigilance	SmPC Section 4.2, Posology and Method of Administration, and the Patient Information Leaflet provide detailed instructions for use. Also refer to Section 3.2.2.

The CHMP, having considered the data submitted, was of the opinion that the below pharmacovigilance activities in addition to the use of routine pharmacovigilance are needed to investigate further some of the safety concerns:

Description	Due date
Post-Authorisation Safety (PAS) Cohort Study of Inhaled Aclidinium Bromide and the Risk of Selected Cardiovascular Endpoints. Full study protocols should be submitted before the study start for CHMP review prior to the product launch.	Study protocols to be submitted by September 2012. PASS will start when there are 2000 prescriptions in the defined database.
Drug utilisation study (DUS) to cover aspects related to drug utilisation, off-label use, and identification of patient groups with missing information in the RMP. Full study protocols should be submitted before the study start for CHMP review prior to the product launch.	Study protocols to be submitted by September 2012. Phase 1 analysis: second half of 2013 or first half of 2014 (time period will be adjusted based on use in the target countries) Phase 2 analysis: 1 year after the phase 1 analysis

No additional risk minimisation activities were required beyond those included in the product information.

2.8. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

COPD treatments may provide symptomatic relief through improvement of airway obstruction, modify or prevent exacerbations, modify the course of the disease or modify disease progression. Demonstration of beneficial effects depends on the treatment objective of the individual drug. Aclidinium bromide is a long acting anticholinergic bronchodilator. The improvement of the symptoms experienced by the patients in terms of lung function and quality of life (QoL) has been investigated. The latter can be measured by the validated St George's Respiratory Questionnaire (SGRQ) and by measurement of dyspnoea (TDI). In lung function an improvement of at least 100 ml in trough FEV1 is considered to be clinically relevant; an improvement in the SGRQ of (-) 4 units and improvement in TDI of 1 unit is also considered to be clinically relevant.

The results of the pivotal study (M/34273/34) support the efficacy of aclidinium bromide 400 µg BID in patients with moderate to severe COPD. This is evidenced by a clinically relevant improvement in the point estimates of the primary endpoint, morning pre-bronchodilator FEV1 at 24 weeks and a clinically relevant improvement in symptomatic parameters (TDI and SGRQ) compared with placebo. Therefore aclidinium bromide has demonstrated a benefit in lung function and symptomatic benefits in patients with moderate to severe COPD.

The results of the pivotal study are supported by the results of two placebo-controlled supportive studies of 12 weeks duration and two active comparator Phase II studies in which the effects of two drugs already licensed for the symptomatic treatment of COPD were compared with those of aclidinium bromide.

Long-term safety studies have also demonstrated that efficacy is maintained up to 52 weeks.

Uncertainty in the knowledge about the beneficial effects

The very limited data in different races other than Caucasians was noted by the CHMP. However, this was adequately addressed in the RMP as important missing information.

There are limited efficacy data beyond 6 months. However the two, primarily safety, studies of 12 months duration demonstrated that the benefit of aclidinium bromide seen in the pivotal study is maintained up to 52 weeks.

Risks

Unfavourable effects

Aclidinium bromide is a long-acting, inhaled anticholinergic agent that inhibits anticholinergic-induced bronchoconstriction. Therefore the risks of aclidinium bromide treatment are those of enhanced therapeutic effect, i.e anticholinergic adverse effects.

The following adverse events were reported in a greater percentage of patients taking aclidinium bromide than taking placebo and were included in section 4.8 of the SmPC: headache, nasopharyngitis, cough, diarrhoea and sinusitis.

Adverse events typically associated with anticholinergic treatments including dry throat, tachycardia, blurred vision and urinary retention were also included in the SmPC.

Uncertainty in the knowledge about the unfavourable effects

Potential cardiovascular effects, which were discussed for this class of drugs, these were investigated in a thorough QT study (Study M/34273/11) and by Holter monitoring of a sub-group of patients in the Phase III studies. No evidence of a clinically relevant effect on QTc interval was demonstrated in this study. In the pivotal Phase III studies and long term safety studies there appeared to be an effect of aclidinium bromide on AV-nodal conduction and the applicant was asked to discuss possible mechanisms of action that may explain this. However there is no known pharmacological rationale for an increase in PR interval with aclidinium bromide and the applicant again presented the data regarding AV node block and prolongation of the PR interval from the clinical studies. There is no consistent dose response association with conduction defects or clinically meaningful increases in PR interval during the studies. The CHMP concluded that there is a need to specifically monitor cardiovascular adverse events in the RMP and Post-Authorisation Safety Study (PASS).

Benefit-risk balance

Importance of favourable and unfavourable effects

The point estimates for the effect of 400 µg BID of aclidinium bromide on trough FEV1 after 24 weeks treatment and on quality of life measures – SGRQ and TDI were consistently above the level of clinical relevance compared to the effects of placebo. These effects are considered important in patients with COPD.

As there are currently no treatments for COPD that affect the inevitable decline in pulmonary function, symptomatic treatment is important to improve the patients' quality of life. This generally takes the form of bronchodilator medication.

In order to obtain the optimum treatment in an individual patient it is frequently necessary to employ polypharmacy and therefore an increase in the available bronchodilators gives the prescriber more choice to tailor the medication to his patient.

Aclidinium bromide acts by inhibiting acetylcholine-induced bronchoconstriction and is not the first in class. Therefore the adverse effects are well known and generally acceptable. The results from the studies submitted in this application do not suggest that aclidinium bromide demonstrates any safety issues that are unrelated to its anticholinergic effects.

Benefit-risk balance

The favourable effects of aclidinium bromide were consistently demonstrated across the pivotal study, supporting Phase III studies and Phase II studies so it is considered that there is certainty that aclidinium bromide has a clinically relevant benefit on the symptoms of moderate to severe COPD.

The adverse effects of aclidinium bromide are well known, not serious and can be reversed on discontinuing the medication. There is no evidence that these adverse effects become more severe with continued use of aclidinium bromide.

Regarding the potential cardiovascular effects in this class of drugs, there is no evidence of a clinically relevant effect on QTc interval. In the pivotal Phase III studies and long term safety studies there appeared to be an effect of aclidinium bromide on AV-nodal conduction. However there is no known pharmacological rationale for an increase in PR interval with aclidinium bromide and there is no consistent dose response association with conduction defects or clinically meaningful increases in PR interval during the studies. The applicant will specifically monitor cardiovascular adverse events in the RMP and Post-Authorisation Safety Study (PASS).

In conclusion, the favourable effects demonstrated with aclidinium bromide in patients with moderate to severe COPD clearly outweigh the identified or potential risks leading to a positive benefit-risk balance.

Discussion on the benefit-risk balance

The ability of aclidinium bromide to relieve the symptoms experienced by patients with moderate to severe COPD in terms of lung function and quality of life (QoL) has been demonstrated. The most common side effects are headache and nasopharyngitis .

The favourable effects on the quality of life of the above-mentioned population are greater than the mild adverse effects that are known for anticholinergic products and that have been demonstrated in the clinical studies.

Therefore, on the basis of quality, safety and efficacy data submitted, the CHMP considers that there is a favourable benefit-to-risk balance for aclidinium bromide.

4. Recommendations

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Eklira Genuair in the maintenance bronchodilator treatment to relieve symptoms of chronic obstructive pulmonary disease (COPD) is favourable and therefore recommends the granting of marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the Marketing Authorisation

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the Marketing Authorisation, is in place and functioning before and whilst the product is on the market.

Risk Management Plan (RMP)

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the RMP presented in Module 1.8.2 of the marketing authorisation and any subsequent updates of the RMP agreed by the Committee for Medicinal Products for Human Use (CHMP).

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- at the request of the European Medicines Agency.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Not applicable

Obligation to conduct post-authorisation measures

The MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
Post-Authorisation Safety (PAS) Cohort Study of Inhaled Aclidinium Bromide and the Risk of Selected Cardiovascular Endpoints. Full study protocols should be submitted before the study start for CHMP review prior to the product launch.	Study protocols to be submitted by September 2012. PASS will start when there are 2000 prescriptions in the defined database

New Active Substance Status

Based on the CHMP review of data on the quality, non-clinical and clinical properties of the active substance, the CHMP considers that aclidinium bromide is to be qualified as a new active substance.

Aclidinium bromide is a New Chemical Entity, which has not previously been authorised in the Community, and this Marketing Authorisation Application (MAA) is therefore eligible for the Centralised Procedure as a New Active Substance, in accordance with Article 3(2)a of Regulation (EC) No. 726/2004 regarding the Scope of the Centralised Procedure, as confirmed by the European Medicines Agency (EMA) on 25th April 2008 (ref. EMEA/CHMP/221778/2008).