Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Aclidinium bromide

Proprietary Product Name: Bretaris Genuair

Sponsor: A Menarini Australia Pty Ltd

September 2014

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations commonly used in this AusPAR

Abbreviation	Meaning
ADME	Absorption, distribution, metabolism and excretion
ADR	Adverse Drug Reaction
Ae	Amount of unchanged drug excreted into urine
AEs	Adverse events
ALT	alanine aminotransferase
Am	Amount of metabolite excreted into urine
Am1	Amount of LAS34850 excreted into urine
Am2	Amount of LAS34823 excreted into urine
ANCOVA	Analysis of covariance
AST	aspartate aminotransferase
ATS	American Thoracic Society
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
AUCτ	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
BChE	Butyrylcholinesterase
BDI	Baseline Dyspnoea Index
BD	Twice daily
BLQ	Below the lower limit of quantification
BMI	body mass index
BP	blood pressure
bpm	beats per minute

Abbreviation	Meaning
BUN	Blood urea nitrogen
CI	Confidence interval
CL	Total body clearance from plasma
CL/f	Total body clearance from plasma after extravascular administration
CLcr	Creatinine clearance
CLR	Renal clearance
C_{max}	Maximum observed plasma concentration
$C_{max,SS}$	Maximum observed plasma concentration at steady state
C_{min}	Minimum observed plasma concentration
$C_{min,SS}$	Minimum observed plasma concentration at steady state
COPD	Chronic obstructive pulmonary disease
CV	Coefficient of variation
CYP450	Cytochrome P450
DPI	Dry powder inhaler
ECG	Electrocardiogram
EMA	European Medicines Agency
ENR	expanded normal range
E-RS	Exacerbations of COPD Tool – Respiratory Symptoms
EXACT	Exacerbations of Chronic Obstructive Pulmonary Disease Tool
FDC	fixed-dose combination
fe	Percentage of dose excreted in urine
FEV1 $AUC_{0-24/24h}$	Normalised area under the FEV1 versus time curve from 0 to 24 hours post-dose
FEV1	Forced expiratory volume in 1 second
FEV1	Forced expiratory volume in 1 second
FRC	Forced residual capacity

Abbreviation	Meaning
FRC	Functional residual capacity
FVC $AUC_{0-24/24h}$	Normalised area under the FVC versus time curve from 0 to 24 hours post-dose
FVC	Forced vital capacity
FVC	Forced vital capacity
Gaw	Reciprocal airway conductance
GGT	γ-glutamyl transferase
GOLD	Global initiative for Chronic Obstructive Pulmonary Disease
IC	Inspiratory capacity
IC_{50}	Concentration of compound that provides 50% inhibition
ICH	International Conference on Harmonisation
ICS	Inhaled corticosteroids
IMP	Investigational medicinal product
ISS	Integrated Summary of Safety
ITT	Intent-to-treat
Ki	Constant of inhibition
L	Litre(s)
LAS34273	Aclidinium bromide
LAS34850	active metabolite of aclidinium
LAS34823	alcoholo metabolite of aclidinium
LLOQ	Lower limit of quantification
LS	Least squares
MACE	Major Adverse Cardiovascular Events
MCID	Minimum clinically important difference
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency

Abbreviation	Meaning
MIP	maximal inspiratory pressure
MMRM	Mixed-effects model for repeated measures
MTD	Maximum tolerated dose
NADPH	Nicotinamide-adenine-dinucleotide phosphate
OR	Odds ratio
PCS	potentially clinically significant
PD	Pharmacodynamic(s)
PI	Product Information
PIF	Peak inspiratory flow
PK	Pharmacokinetic(s)
pm	*Post-meridiem*
PP	Per-protocol
PT	preferred term
QD	once daily (*quoque die*)
QoL	Quality of life
QT	Time in msec from start of the Q wave to end of the T wave (on ECG)
QTc	Corrected QT interval
QTc	QT interval corrected for heart rate
QTcB or QTcF	QT interval corrected by Bazett formula [QT/RR1/2] or Fridericia formula [QT/RR1/3] where RR interval is time in msec between R peaks of 2 consecutive QRS complexes
QTci	QT interval corrected by subject-specific correction formula
Raw	Airway resistance
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error

Abbreviation	Meaning
SEM	Standard error of the mean
sGAW	Specific airway conductance
SGRQ	St George's Respiratory Questionnaire
SmPC	Summary of Product Characteristics (EU)
SMQ	Standardised MedDRA query
SOC	System organ class
t 1/2	Elimination half-life
TDI	Transition Dyspnoea Index
TEAE	treatment-emergent adverse event
TLC	Total lung capacity
T_{max}	Time to reach C_{max}
Vz	Apparent volume of distribution during the terminal phase
Vz/f	Apparent volume of distribution during the terminal phase after extravascular administration
Wmax	Highest work rate the patient is able to maintain for at least 30 seconds
λZ (Terminal)	elimination rate constant

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Decision:	Approved
Date of decision:	18 March 2014
Active ingredient:	Aclidinium bromide
Product name:	Bretaris Genuair
Sponsor's name and address:	A Menarini Australia Pty Ltd L8, 67 Albert Avenue Chatswood NSW 2067
Dose form:	Powder for inhalation
Strength:	322 µg of aclidinium (as bromide) per actuation (delivered dose)
Container:	Genuair inhaler, delivering either 30 or 60 doses
Pack sizes:	Cartons containing: 1 x 30 unit dose inhaler; 1 x 60 unit dose inhaler and 3 x 60 unit dose inhalers
Approved therapeutic use:	*Bretaris Genuair is indicated as a long term maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).*
Route of administration:	Oral inhalation
Dosage:	One inhalation twice daily
ARTG number:	206071

Product background

This AusPAR describes the application by the sponsor A Menarini Australia Pty Ltd to register the new chemical entity aclidinium bromide for the following indication;

> *Bretaris Genuair is indicated as a long term maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).*

Aclidinium bromide inhalation powder is presented in a device metered dry powder inhaler (DPI) called Genuair. This inhaler is designed to deliver 30 or 60 doses. Treatment involves twice daily oral inhalation delivered by the included inhaler device. Each metered dose contains 400 µg aclidinium bromide; the actual delivered dose contains 375 µg aclidinium bromide.

Aclidinium bromide is a competitive muscarinic receptor antagonist with subnanomolar affinity across all five human muscarinic receptor subtypes. Its dissociation from M3 receptors was more than 4 times slower than its dissociation from M1 and M2 receptors.

There are numerous drug classes available for the treatment of COPD, including β2 agonists, anticholinergic agents, combination of β2 agonists and inhaled corticosteroids and methyl xanthines.

Other anti-muscarinic agents registered in Australia are ipratropium and tiotropium.

The current indication of ipratropium bromide (metered dose aerosol inhaler) is

> *Atrovent metered aerosol is indicated as a bronchodilator for maintenance treatment of bronchospasm associated with asthma and chronic obstructive pulmonary disease (COPD),*

The registered indication for the nebuliser solution Atrovent is

> *Moderate asthmatic attacks; chronic forms of asthma; asthma in patients with diminished cardiac reserve; chronic obstructive bronchitis with bronchospasm; bronchospasm during or after surgery, use during assisted ventilation with a respirator. Administration of Atrovent via a nebuliser is intended for those patients who cannot use a metered dose aerosol*

The registered indication of Spiriva, tiotropium, is

'Spiriva is indicated for the long term maintenance treatment of bronchospasm and dyspnoea associated with chronic obstructive pulmonary disease (COPD). Spiriva is indicated for the prevention of COPD exacerbations.'

Recently, another long-acting anticholinergic bronchodilator, Seebri Breezhaler (glycopyrronium bromide), was approved for once daily use in long term maintenance treatment of COPD. It was recommended for the following indication:

> *For use as a once-daily maintenance bronchodilator treatment to relieve symptoms of patients with chronic obstructive pulmonary disease (COPD).*

Olodaterol, a long acting β agonists (LABA) was recommended for approval for once daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD.

Regulatory status

This is the application for a new chemical entity.

At the time the TGA considered this application, a similar application had been approved in the countries listed in Table 1 below.

Table 1. Overseas regulatory status

Country	Date of approval	Approved indication
United States	23 July 2012	Long-term, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema
European Union (EU)	2 July 2012	Maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD)
Switzerland	25 April 2013	Maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD)

Country	Date of approval	Approved indication
Canada	29 July 2013	Long term maintenance bronchodilator treatment in patients with chronic obstructive pulmonary

Breatris Genuair has also been approved in Mexico (30 September 2013).

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent PI please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

II. Quality findings

Introduction

Each delivered dose (the dose leaving the mouthpiece) contains 322 µg of aclidinium (as the bromide) which is equivalent to a metered dose of 343 µg aclidinium (as the bromide).

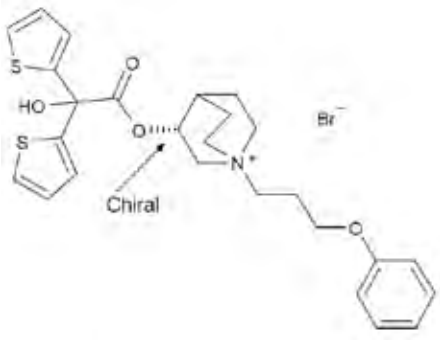
The recommended dose is one inhalation taken twice daily and the product is intended for use as a long term maintenance bronchodilator treatment to relieve symptoms in adult patients with Chronic Obstructive Pulmonary Disease (COPD).

The product has not been considered by the TGA's Pharmaceutical Subcommittee (PSC) and there are no British Pharmacopeia (BP) or US Pharmacopeia (USP) monographs available for the drug substance or drug product.

Drug substance (active ingredient)

The drug substance has the following structure (Figure 1).

Figure 1. Chemical structure of aclidinium bromide



Aclidinium bromide is a white to off white crystalline solid that is very slightly soluble in water and practically insoluble in common organic solvents. It has one chiral centre and exists in one polymorphic form (designated form I).

The drug substance is controlled by a specification that includes appropriate limits for assay impurities, residual solvents and particle size. Appropriate validated analytical methods were described for all of the specification tests.

The levels of four impurities were adequately qualified.

Drug product

The inhalation powder is composed entirely of aclidinium bromide and lactose which serves as a carrier for the drug substance. The powder is filled into a pre-assembled cartridge that measures either 30 or 60 actuations (the strength and fill weight of the inhalation powder in the cartridge are the same, only the counter and lock out systems are changed). The powder is then delivered using a device metered (Almirall) dry powder inhaler.

The product is manufactured using conventional blending, filling and packing methods.

The quality of the drug product is controlled by a specification that includes limits for: the content of aclidinium bromide per cartridge; the levels of degradants and total impurities in the powder; the uniformity of the delivered dose; the mean delivered dose and the fine particle dose. The microbial content of the powder is also adequately controlled.

The analytical methods used were all adequately validated and described.

Stability data were provided to support a shelf life for the product of 36 months when it is stored in the proposed packaging (the dry powder inhaler is contained in a heat sealed aluminium pouch) below 30ºC. Stability testing has also demonstrated that an in use period of 90 days from opening the pouch is justified.

Quality summary and conclusions

Approval is recommended from a chemistry and quality control perspective.

III. Nonclinical findings

Introduction

The general quality of the submitted nonclinical data was high. All pivotal studies examining single-dose toxicity, repeat-dose toxicity, genotoxicity, carcinogenicity and reproductive toxicity were conducted under Good Laboratory Conditions (GLP) conditions. Only some of the safety pharmacology studies were GLP compliant however, although the non GLP studies were nevertheless adequately documented.

Pharmacology

Aclidinium bromide is a muscarinic receptor antagonist. Other members of the class (ipratropium bromide, tiotropium bromide and glycopyrronium bromide) are already approved as inhalational therapies for COPD. Of relevance to therapy in COPD, bronchoconstriction is mainly mediated by activation of postsynaptic M3 receptors and M1 and M3 receptor activation results in mucus secretion.[1] Presynaptic M2 receptors operate to inhibit acetylcholine (ACh) release, so lesser antagonism of this negative feedback mechanism would appear to be desirable (although it may be irrelevant in the context of simultaneous postsynaptic receptor antagonism). M4 and M5 receptor subtypes have not been identified in human lung.[2]

[1] Gosens R., Zaagsma J., Meurs H. and Halayko A.J. (2006) Muscarinic receptor signaling in the pathophysiology of asthma and COPD. Respir. Res. 7: 73
[2] Barnes P.J. (1993) Muscarinic receptor subtypes in airways. Life Sci. 52: 521–527

Primary pharmacology

Aclidinium bromide was shown to have high affinity for all five human muscarinic ACh receptor subtypes (binding affinity, Ki, 0.09–0.25 nM) where it acted as a competitive inhibitor. Aclidinium had comparable affinity compared to tiotropium at M1, M2 and M3 receptors, and was approximately4 to 10 times more potent than ipratropium. The rate of dissociation from M3 receptors observed for aclidinium in vitro (29 h) was in between the short acting ipratropium (0.5 h) and the long acting tiotropium (62 h); the drug's dissociation from M3 receptors was more than 6 times slower than from M2 receptors and more than 4 times slower than from M1 receptors. Aclidinium bromide inhibited contractions induced by cholinergic agonists and electrical field stimulation in isolated preparations of guinea-pig trachea and human bronchus, acting with potency similar to that of tiotropium and ipratropium. In vivo, long lasting antagonism of Ach induced bronchoconstriction by inhaled aclidinium bromide was demonstrated in guinea pigs and dogs and was shown to be equally effective cf. tiotropium and ipratropium. Consistent with the in vitro findings, the duration of action of aclidinium in the guinea pig (half-life 29 h) was in between that of ipratropium (8 h) and tiotropium (64 h).

The active ingredient in Bretaris Genuair is presented as the R-enantiomer only. The S enantiomer of aclidinium was shown to have much lower muscarinic receptor affinity compared to the R enantiomer (approximately300, 100 and 900 times less potent at human M1, M2 and M3 receptor subtypes) and produce much weaker inhibition of Ach induced bronchoconstriction in the guinea pig in vivo. The two major metabolites of aclidinium (alcohol and carboxylic acid metabolites formed by rapid hydrolysis) showed no significant affinity for human muscarinic receptors in binding studies in vitro or relevant anti bronchoconstrictor activity in guinea pigs in vivo.

Secondary pharmacodynamics and safety pharmacology

Aclidinium bromide and its two hydrolysis products were screened for secondary activity against a panel of enzymes, receptors, transporters and/or ion channels. The a1B-adrenoceptor was identified as the highest affinity secondary target, with aclidinium bromide inhibiting radioligand binding by 67% at 1 µM. Given that this concentration is more than 7000 times higher than the peak plasma concentration (C_{max}) in patients at the maximum recommended human dose, the finding is not considered to be of clinical relevance.

Specialised safety pharmacology studies covered the core battery of systems (central nervous system (CNS), cardiovascular and respiratory) as well as the renal and gastrointestinal systems. CNS function was unaffected in mice following oral administration at ≤300 mg/kg. However, signs of central anticholinergic toxicity were observed at higher doses in mice in an acute toxicity study (dyspnoea, abnormal quietness and abnormal gait at ≥500 mg/kg orally (PO); clonic convulsions at 1000 mg/kg PO).

Aclidinium bromide, as well as its alcohol (LAS34823) and carboxylic acid (LAS34850) metabolites, were shown to be able to inhibit hERG potassium (K+) channel current in transfected mammalian cells, but only very weakly. The 50% inhibitory concentration (IC_{50}) values for inhibition by aclidinium bromide and its alcohol metabolite (19.7 and approximately30 µM, respectively) are approximately145000 times higher than the plasma C_{max} in patients at the maximum recommended human dose, while the IC_{50} for the carboxylic acid metabolite (significantly exceeding 30 µM) is more than 3700 times its clinical C_{max}. In isolated pig Purkinje fibres, action potential parameters were unaffected by aclidinium bromide and its alcohol metabolite at concentrations up to 1 µM (>7300 and >4800 times the clinical C_{max}) and by the carboxylic acid metabolite at concentrations up to 3 µM (>370 times the clinical C_{max}). Higher concentrations were seen to reduce the

maximum rate of depolarisation, decrease action potential amplitude and/or alter action potential duration.

Tachycardia was observed after IV administration of 1 mg/kg aclidinium bromide in anaesthetised guinea pigs (plasma levels of aclidinium at 15 min post-dose were >500 times the clinical C_{max}). Tachycardia was not observed in anaesthetised dogs following IV administration at ≤1 mg/kg, nor in anaesthetised pigs at up to the same dose but a approximately2 fold increase in heart rate was seen in conscious dogs at 100 µg/kg IV (animal: human C_{max}, >40). The tachycardia lasted for up to 3 h (compared to more than 6 h with tiotropium at 10 µg/kg IV); there was no increase in heart rate at doses of aclidinium bromide ≤10 µg/kg. With inhalational administration, aclidinium bromide increased heart rate in dogs at 500 µg/kg (19 times the human daily dose on a body surface area basis), with the effect smaller and shorter lasting compared to 25 µg/kg tiotropium. A slight increase in the resistance of the vertebral vascular bed was observed in dogs 2 h after IV administration of 300 µg/kg. Blood pressure and heart rate were unaffected in rats after inhalational administration of aclidinium bromide at 2 mg/kg (approximately23 times the human daily dose on a body surface area basis). Aclidinium bromide did not affect the QTc[3] interval in rats (≤3 mg/kg IV; 2.5 mg/kg twice a day (BD) subcutaneously (SC)), guinea pigs (≤1 mg/kg IV) or dogs (≤100 µg/kg IV).

Aclidinium bromide did not affect specific pulmonary resistance, tidal volume or respiratory rate in guinea pigs following aerosol exposure (1 mg/mL). The mucociliary transport rate of the trachea was not affected by the drug in vitro (≤1000 µM; pig) or in vivo (1 mg/kg IV; guinea pig).

Urine volume and electrolyte excretion were unaffected by aclidinium bromide in rats up to 1 mg/kg SC. Intratracheal administration of the drug did not alter urinary volume or micturition pressure in guinea pigs at up to 100 µg/kg (yielding 130 times the clinical C_{max} for aclidinium). Renal vascular resistance, glomerular filtration rate and urinary sodium and potassium excretion were unaffected in dogs dosed at 1 mg/kg IV. Increased urine volume, with decreased osmolality, was seen in various repeat-dose toxicity studies; this possibly reflects increased water intake to compensate for dry mouth caused by the drug's anticholinergic activity. Aclidinium bromide was shown to induce dry mouth in mice (inhalation; 50% effective dose (EC_{50}) 711 µg/mL by nebuliser) and rats (SC; ED_{50}, 38 µg/kg) [less potent than ipratropium or tiotropium]. Faecal output over 24 h was decreased in rats after SC administration (ED_{50} approximately0.5 mg/kg) and a decrease in colonic motility (without reaching statistical significance) was observed in guinea pigs at 1 mg/kg SC.

Pharmacokinetics

Absorption of aclidinium bromide after inhalation was shown to be rapid in mice, rats and dogs, with peak plasma concentrations typically observed at the first sampling time point (5 to 10 min post-dose). Similarly in COPD patients, the plasma C_{max} was achieved within 15 min following inhalation. Plasma exposure (area under the concentration time curve (AUC)) was less than dose-proportional in mice, while dose-proportionality was highly variable in rats and dogs. Plasma AUC was only increased with repeated administration at the lowest inhalational doses in rats. No consistent sex differences were observed. Bioavailability by the inhalational route in rats was estimated to be 47%; it should be

[3] QT interval is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. A prolonged QT interval is a risk factor for ventricular tachyarrhythmias and sudden death. The QT interval is dependent on the heart rate (the faster the heart rate, the shorter the QT interval). To correct for changes in heart rate and thereby improve the detection of patients at increased risk of ventricular arrhythmia, a heart rate-corrected QT interval ***QTc*** is often calculated.

noted that the accuracy of this estimate is impacted by considerable inter-study variability.

Oral bioavailability was seen to be low in the laboratory animal species, with extensive metabolism evident. In humans, absolute bioavailability following inhalation of a single 200 µg dose was reported to be less than 5% (Clinical Study M/43273/05).

Aclidinium bromide is subject to rapid hydrolysis, giving rise to the major metabolites LAS34823 (alcohol derivative) and LAS34850 (carboxylic acid derivative). Following inhalational administration, plasma C_{max} and AUC values for the alcohol metabolite were generally less than those for aclidinium in mice and rats and modestly higher (typically approximately2 fold) than the parent in dogs. Plasma levels of the carboxylic acid metabolite, in contrast, were very much greater than the parent in the laboratory animal species (roughly 45, 5 and 30 fold higher with respect to C_{max}, and 75, 13 and 145 fold higher with respect to AUC, in mice, rats and dogs, respectively, at the various doses employed in the toxicity studies). A similar pattern was observed in humans: peak plasma concentrations of the alcohol metabolite were slightly less than that of the parent drug whereas peak levels of the carboxylic acid metabolite were approximately25 times higher than the parent, and plasma AUC was approximately3 times higher compared to the parent compound for the alcohol metabolite and approximately100 times higher compared the parent compound for the carboxylic acid metabolite, in patients receiving 400 µg/day (at steady state).

Hydrolysis of aclidinium occurs via both chemical and enzymatic means. In vitro experiments with rat and/or human hepatic, pulmonary, renal and intestinal subcellular fractions revealed chiefly non enzymatic hydrolysis. No relevant differences in the rate of disappearance of aclidinium were seen following incubation with human pulmonary fractions from smokers compared to non-smokers. Hydrolysis mainly occurred in plasma, and butyrylcholinesterase (BChE) was identified as the main esterase catalysing the hydrolysis of aclidinium in human plasma. The in vitro half-life of aclidinium bromide in human plasma (2.4 min) was 40 to 825 times shorter cf. tiotropium, ipratropium and glycopyrronium.

Additional minor pathways of metabolism, observed in experiments with animal and human liver microsomes, involved hydroxylation of the phenyl ring of the parent and of the alcohol metabolite (found to be mediated by CYP2D6), loss of the thiophene ring (chiefly mediated by CYP3A4) with subsequent ester hydrolysis (involving CYP3A4 and 2D6) and reduction of the ketone group, thiophene ring oxidation and reduction of the carboxylic acid metabolite. In vivo metabolism was investigated in mice, rats, rabbits, dogs and humans. Together with the in vitro data, the studies reveal a qualitatively similar pattern of metabolism across species, with no unique human metabolites. All human metabolites were demonstrated to be formed in each of the laboratory animal species (mouse, rat, rabbit and dog) either in vitro or in vivo with only one exception, formation of hydroxyl-2-thienylacetic acid (metabolite m1; LAS101563); a very minor human metabolite which was not observed in dogs. Some covalent binding was observed following incubation of aclidinium bromide and to a lesser extent the carboxylic acid metabolite with human liver microsomes. This was seen to involve formation of reactive metabolites by CYP3A4 and 2D6 and was largely prevented by the addition of glutathione. Covalent binding was also seen in vitro with mouse, rat, dog and human hepatocytes and was qualitatively similar across species. Together, the low level of binding observed, the significant excess of glutathione and glutathione transferases in the liver compared to drug and metabolite concentrations to allow for detoxification and the absence of liver damage in animals at high relative exposure levels (see *Repeat-dose toxicity*) supports a lack of clinical significance for the finding.

In contrast to plasma, levels of unchanged aclidinium bromide present in the lung and bronchial lavage fluid far exceeded those of either hydrolysis product following

inhalational administration in rats. Similar concentrations of aclidinium bromide and the alcohol and carboxylic acid metabolites were seen in rat lungs after one and six months of treatment.

Tissue distribution studies using radiolabelled (^{14}C) aclidinium bromide (labelled at different sites in separate experiments to account for hydrolysis of the parent) in rats revealed rapid and widespread distribution following IV administration, more limited distribution after intratracheal administration and low absorption following oral administration. Highest tissue: plasma C_{max} ratios after IV dosing were found in tissues associated with excretion (bladder and contents, kidney, small intestine and contents), and the pancreas and the thyroid; penetration of the blood-brain barrier was low (brain C_{max}, approximately5 to 8 times lower than the plasma C_{max}). No particular or irreversible binding to melanin was evident. Plasma protein binding by aclidinium bromide itself could not be properly investigated due to hydrolysis. Plasma protein binding attributable to the alcohol metabolite was low (12 to 26% in mouse, rat, rabbit and dog plasma; 15% in human plasma) and moderate for the carboxylic acid metabolite (66–87% in mouse, rat, rabbit and dog plasma; 87% in human plasma). The extent of binding was independent of concentration. Binding to human serum albumin and human a 1 acid glycoprotein was shown.

Excretion of ^{14}C aclidinium bromide derived radioactivity following IV administration was principally via the urine in dogs and humans, while excretion was more evenly divided between urine and faeces in mice, rats and rabbits. Excretion after intratracheal administration was investigated in dogs, with the faecal route dominating when the site of radiolabelling was retained by the alcohol metabolite and the urinary route dominating when the radiolabel was retained by the carboxylic acid metabolite. Excretion was principally in the form of metabolites in all species.

The laboratory animal species display pharmacokinetic profiles for aclidinium bromide sufficiently similar to that in humans to allow them to serve as appropriate models for assessment of the drug's toxicity in humans.

Pharmacokinetic drug interactions

CYP450 isozymes play only a minor role in the clearance of aclidinium bromide. In studies with human liver microsomes investigating the potential of aclidinium bromide and its two main metabolites to inhibit CYPs 1A2, 2A6, 2B6, 2B8, 2C9, 2C19, 2D6, 2E1, 3A4/5 and 4A9/11, aclidinium bromide and its alcohol metabolite were shown to inhibit CYP2D6 with respective Ki values of 0.78 μM and 15.5 μM (>5700 and approximately75000 times higher than the clinical C_{max}); very weak inhibition of CYP3A4 by aclidinium bromide was also shown (IC_{50} approximately90 μM), while all other IC_{50} values were >100 μM. The drug and its hydrolysis products did not induce CYPs 1A2, 2B6, 2C8, 2C9, 2C19 or 3A4/5 in cultured human hepatocytes (tested up to approximately17 to 21 times the clinical C_{max}).

Experiments examining the potential of aclidinium bromide and its two major metabolites to inhibit human plasma esterases (acetylcholinesterase, BChEe, paraoxonase, carboxylesterase and arylesterase) revealed no clinically relevant activity. Inhibitory activity was greatest for aclidinium bromide against BChE, with the Ki value (2.7 μM) almost 20000 times greater than the peak plasma concentration of the drug in patients at the recommended dose. In experiments with Caco 2 cell monolayers, aclidinium bromide and its carboxylic acid metabolite were shown not to be substrates for P glycoprotein, while the alcohol metabolite was found to be a weak substrate at most; none of the three compounds act as P glycoprotein inhibitors.

Toxicology

Acute toxicity

Single-dose toxicity studies were conducted by the oral route in mice and by the inhalational, oral and IV routes in rats. All studies involved an observation period of 14 days as recommended in the relevant guideline[4]. No mortality or signs of toxicity were observed in rats after inhalational administration at 3.7 (males) or 3.8 mg/kg (females), doses approximately42 to 43 times the recommended clinical dose on a mg/m^2 body surface area basis, indicating a low order of acute toxicity by the clinical route. There were also no deaths or clinical signs in rats at up to the highest dose tested by the IV route (1.2 mg/kg; tested in males only). Oral administration caused no deaths in rats (≤2000 mg/kg) but deaths occurred in mice at 500 mg/kg (the lowest dose studied) and 1000 mg/kg. Oral administration produced various clinical signs consistent with antimuscarinic activity in both species beginning from the lowest dose level (500 mg/kg; such as mydriasis, dyspnoea and abnormal gait).

Repeat-dose toxicity

Studies by the inhalational route of up to 3 months duration were conducted in mice, 6 months in rats and 9 months in dogs. Other routes were used in studies in rats (oral up to 4 weeks, IV up to 2 weeks and SC up to 6 months) and dogs (oral up to 4 weeks and IV up to 2 weeks). The duration of the pivotal studies, the species used (rats and dogs), group sizes and the use of both sexes were consistent with recommendations in relevant EU guidelines. Inhalational administration was once daily in animals (compared to twice daily dosing proposed in patients) but this is not considered to impact validity. Inhalational dosing involved administration of dry powder formulated as a 10% strength in lactose in the longest studies (approximately 3 times the clinical strength but with the same excipient profile). The shorter inhalational studies used various lower strengths (0.72 to 0.79% in lactose) and/or undiluted powder. Aerosolised particles were of respirable size in all studies. Inhalational administration was by nose only exposure in mice and rats and oronasal exposure in dogs. Control groups received air or vehicle (lactose), with dual control groups used in some studies.

Relative exposure

Exposure ratios have been calculated based on animal: human plasma AUC_{0-24h} for the parent drug (for consideration of systemic toxicity) and animal: human lung deposited dose adjusted for lung weight (for consideration of local toxicity) (Table 2). Lung deposited doses were calculated assuming 8% deposition in rodents (based on data obtained in rats in Studies B.34273.18 and B.34273.19), 25% deposition in dogs[5] and 30.1% deposition in humans (Clinical Study M/34273/03), lung weights of 0.2, 1.45, 80 and 1000 g for mice, rats, dogs and humans, respectively, and body weights of 0.03, 0.25 and 10 kg for mice, rats and dogs, respectively. High local and systemic exposure ratios were obtained in the animal studies. When dose ratios are calculated based on alveolar surface area rather than lung weight, smaller local exposure ratios are obtained (approximately 4 times lower in mice, 3 times lower in rats and 7 times lower in dogs) but the dose multiples are still significant. Adequate exposure to the drug's main metabolites, LAS34823 (alcohol derivative) and LAS34850 (carboxylic acid derivative and the main circulating component) was also achieved in the animal studies; animal: human plasma AUC values for these compounds at the upper doses in the pivotal repeat-dose toxicity

[4] EU 3BS1a Single dose toxicity
[5] Wolff R.K. and Dorato M.A. (1993) Toxicologic testing of inhaled pharmaceutical aerosols. Crit. Rev. Toxicol. 23: 343–369

studies and the carcinogenicity studies are 4 to 29 times higher (LAS34823) and 4.5 to 78 times higher (LAS34850) compared to those in patients.

Table 2. Relative local and systemic exposure achieved in selected inhalational toxicity studies

Species	Study	Achieved dose mg/kg/day	Lung deposited dose µg/g tissue	Plasma AUC_{0-24h} ng·h/mL	Exposure ratio	
					L	S
Mouse (B6C3F1)	RCC 841849 (PK: B.34273.09) [3 months]	0.20	2.4	32.2	10	83
		0.62	7.4	82.8	31	212
		2.55	30.6	103.6	127	266
	RCC 852075 (PK: B.34273.28) [carcinogenicity]	0.30	3.6	19.9	15	51
		0.79	9.5	46.3	39	119
		2.45	29.4	50.5	122	129
Rat (Wistar)	RCC 845323 (PK: B.34273.15) [26 weeks; pivotal]	0.010	0.14	5.26	0.6	13
		0.036	0.50	7.73	2.1	20
		0.083	1.1	9.47	5	24
		0.20	2.8	17.3	11	44
	RCC 810797 (PK: B.34273.04) [26 weeks]	0.10	1.4	9.71	6	25
		0.47	6.5	29.6	27	76
		2.4	33.1	118.0	137	303
	RCC 852076 (PK: B.34273.27) [carcinogenicity]	0.019	0.26	–	1.1	–
		0.069	0.95	16.9	4	43
		0.20	2.8	21.4	11	55
Dog Beagle	RCC 810808 (PK: B.34273.07) [9 months; pivotal]	0.031	0.97	0.352	4	0.9
		0.225	7.0	9.27	29	24
		0.810	25.3	14.4	105	37

Species	Study	Achieved dose mg/kg/day	Lung deposited dose µg/g tissue	Plasma AUC_{0-24h} ng·h/mL	Exposure ratio	
					L	S
Human COPD patients	[steady state]	[800 µg/day]	0.241	0.390#	–	–

Plasma AUC values in animals are from the last day sampled and for males and females combined;
= based on doubling of the AUC_{0-24h} value reported at 400 µg QD in Clinical Study M.34273/09 (0.195 ng·h/mL), to account for BD administration. L=local and S=systemic exposure.

Major toxicities

The major target organs for toxicity identified in the inhalational studies were respiratory tract tissues (nasal cavity, larynx and lung), the Harderian gland and the parotid gland. Changes were also observed in the liver and effects on the eye and heart were also seen. Studies involving inhalational administration are the focus of the assessment, though findings from studies not involving the clinical route are also discussed below where relevant.

No treatment related histopathological lesions were found in mice treated at ≤2.55 mg/kg/day by inhalation for 3 months (local exposure ratio [ERlocal] 127; systemic exposure ratio [ERsystemic] 266]) nor in any of the inhalational studies in dogs (≤0.810 mg/kg/day in the pivotal 9 month study; ERlocal 105; ERsystemic 37).

In rats, nasal cavity goblet cell hyperplasia and inflammation were found with inhalational administration at all doses used in the short term studies (≥0.4 mg/kg/day for 2 weeks; ≥0.16 mg/kg/day for 4 weeks) and there was an increased incidence of nasal cavity goblet cell proliferation with treatment at ≥0.47 mg/kg/day for 6 months. A low incidence of nasal cavity hyaline inclusions (minimal in severity) and epithelial disorganisation (slight) was seen at 0.20 mg/kg/day in rats in the pivotal 6 month study, while there were no nasal cavity lesions at 0.083 mg/kg/day (ERlocal 5). Noting the absence of similar findings in dogs, rats are more sensitive to such changes compared with other species due to the greater relative drug deposition in this region.

Squamous metaplasia was observed in the rat larynx at ≥0.036 mg/kg/day by inhalation in the pivotal study (ERlocal 2.1 [ERlocal at the No Observable Effect Level (NOEL) [0.010 mg/kg/day], 0.6). This was of low incidence, minimal in severity up to the highest dose used in the study (0.20 mg/kg/day; ERlocal 11), is considered an adaptive response[6] and was completely reversible. Findings from the rat carcinogenicity study confirm it is not a pre-neoplastic lesion.

Microscopic findings in the lungs of rats in the pivotal 6 month study comprised increased alveolar macrophages, alveolar haemosiderin deposition and a slight increase in the incidence/severity of haemosiderin deposition in the adventitia of blood vessels, observed at inhalational doses ≥0.08 mg/kg/day; these were fully reversed after a 6 week treatment free period. Alveolar macrophage conglomeration with compression of alveolar walls and perivascular inflammation was seen in another 6 month inhalational rat study (chiefly at ≥0.47 mg/kg/day; ERlocal ≥27) but the finding was not confirmed in further 6 month

[6] Osimitz T.G., Droege W. and Finch J.M. (2007) Toxicologic significance of histologic change in the larynx of the rat following inhalation exposure: a critical review. Toxicol. Appl. Pharmacol. 225: 229–237

studies. The NOEL for effects on the lung is 0.036 mg/kg/day in the rat (ERlocal 2.1) and 0.810 mg/kg/day in the dog (ERlocal 105).

Effects on glands were noted in rats and/or dogs and are considered to reflect reduced secretions (classic antimuscarinic activity). Increased porphyrin deposition (≥0.010 mg/kg/day), acinar hypertrophy (≥0.036 mg/kg/day), acinar hyperplasia (2.0 mg/kg/day) and acinar dilation (3.9 mg/kg/day) were observed in the Harderian gland in inhalational studies in rats; the findings are not relevant to humans, which lack this gland.

The parotid gland showed basophilic acini and acinar hypertrophy at all dose levels in the pivotal rat study (≥0.010 mg/kg/day; ERsystemic ≥13), with acinar atrophy observed at higher doses in other 6 month studies (≥0.47 mg/kg/day; ERsystemic ≥76). Dry oral mucus membranes and dry nose were observed in dogs with IV administration (≥0.06 mg/kg/day). Suppression of body weight gain with decreased food consumption was commonly observed across studies and is probably at least partly due to decreased salivation. A number of deaths in the rat inhalational studies are also seen to be related to decreased salivation, leading to asphyxiation from choking during nightly food consumption. Gasping and coughing or retching episodes were shown to be induced by SC treatment in rats and accompanied by increased intrathoracic pressure. Minor haemorrhages in the lung may have resulted from the gasping/choking episodes, giving rise to the hemosiderin deposition observed in the lungs in the species. Tear production was decreased in dogs at ≥0.225 mg/kg/day by inhalation (ERsystemic ≥24) and conjunctivitis and keratitis were noted in the eyes of dogs treated at 5 or 25 mg/kg/day PO.

Hepatocellular hypertrophy was observed in rats treated at ≥0.083 mg/kg/day by inhalation for 6 months; reversibility was shown. The pivotal studies establish No Adverse Effect Levels (NOAELs) for liver changes of 0.036 mg/kg/day in rats (ERsystemic 20) and 0.810 mg/kg/day in dogs (ERsystemic 37).

Various additional findings of note in the studies relate to the drug's antimuscarinic activity. Heart rate was increased in the pivotal dog study at ≥0.225 mg/kg/day by inhalation; there were no cardiac lesions. Aclidinium bromide induced mydriasis in rats at 2 mg/kg/day by inhalation and also at ≥150 mg/kg/day PO, at ≥0.06 mg/kg/day IV and at 1 mg/kg/day SC. Oral administration was associated with compacted faeces in rats at ≥40 mg/kg/day, attributable to local anticholinergic effects on gastrointestinal smooth muscle. Signs of central anticholinergic activity (somnolence, tremors, recumbency and decreased activity) were observed in dogs at 200 mg/kg/day PO and 0.6 mg/kg/day IV.

Genotoxicity

The potential genotoxicity of aclidinium bromide was investigated in the standard battery of tests (bacterial mutagenicity, mouse lymphoma tk assay and bone marrow micronucleus test) as well as in an assay for unscheduled deoxyribonucleic acid (DNA) synthesis ex vivo in hepatocytes. The conduct of the studies was in accordance with relevant EU guidelines. Concentrations/doses used were appropriate. A suitable set of *Salmonella typhimurium* and *Escherichia coli* (*E. coli*) strains were used in the bacterial mutation assays.

Equivocal results were obtained with the drug in the in vitro assays. When seen, increases in revertants in the bacterial mutagenicity assays were generally small (close to 2 fold), and increases in mutant colony frequency in the mammalian forward mutation assay (observed only in the presence of metabolic activation) were also relatively modest and without concentration dependence. Clear negative results were obtained though in both assays involving treatment in vivo. The highest doses used in the studies yield plasma levels of aclidinium bromide and its main metabolites massively greater than that in patients. In the bone marrow micronucleus test, conducted by the oral route in mice,

animal: human exposure ratios (based on plasma C_{max} and AUC) at the highest dose used (2000 mg/kg) were >2400 times for the unchanged drug, >660 times for the alcohol metabolite and >8200 times for the carboxylic acid metabolite. For the unscheduled DNA synthesis assay, conducted by the SC route in rats, plasma levels measured in animals at the highest dose (20 mg/kg) were >5400 times higher than the clinical C_{max} for aclidinium bromide, and >1200 and >300 times greater for the alcohol and carboxylic acid metabolites. On a weight of evidence basis, aclidinium bromide is not considered to pose a genotoxic hazard to patients. The results of the carcinogenicity studies support that the drug is devoid of relevant genotoxic activity.

Carcinogenicity

The carcinogenic potential of aclidinium bromide by the inhalational route was investigated in 2 year studies in mice and rats. Group sizes were adequate and dose selection was appropriate. The highest dose levels used exceeded the maximum tolerated dose (based on suppression of body weight gain of >10%) but survival was unaffected by treatment. Very high multiples of the clinical AUC were obtained in both studies.

No carcinogenic effect was seen for the drug in either species. The highest dose used in the mouse study (2.45 mg/kg/day) is estimated to yield 122 times the clinical exposure locally in the lung and 129 times the clinical systemic exposure. For the rat study, the highest dose (0.20 mg/kg/day) is associated with animal: human exposure ratios of 11 (local) and 55 (systemic).

Reproductive toxicity

Submitted reproductive toxicity studies covered all stages (fertility, early embryonic development, embryofetal development, and pre and postnatal development) and used the clinical route of administration (inhalation). The oral route was additionally used in an embryofetal development study in rabbits. Numbers of animals and species selection (rats, and additionally rabbits for embryofetal development) were appropriate. Treatment in the pre/postnatal development study was temporarily suspended around the time of parturition, so potential effects on the birthing process have not been examined; the timing/duration of treatment was otherwise appropriate.

Relative exposure

Very high multiples of the clinical plasma AUC for aclidinium bromide were achieved in the studies (Table 3). Exposure to the major metabolites achieved in the animals was also high and adequate.

Table 3. Relative exposure in reproductive toxicity studies

Species	Study	Route	Dose mg/kg/day		AUC_{0-24h} ng·h/mL	Exposure ratio
Rat Wistar	Fertility [RCC A10934]	inhalation	♂	0.74	51.0	131
				1.84	73.2	188
				4.8	120	308
			♀	0.86	62.7	161
				2.0	92.0	236
				4.6	114	292
	Embryofetal development [RCC 826637]	inhalation	0.78		23.7	61
			1.76		35.1	90
			5.02		69.9	179
	Pre-/postnatal development [RCC A35381]	inhalation	0.018		6.7[a]	17
			0.20		17.3[a]	44
			1.9		37.9[b]	97
Rabbit Himalayan	Embryofetal development [RCC 838776]	inhalation	0.40		1.89	5
			1.14		4.66	12
			3.58		10.8	28
	Embryofetal development [RCC A19056]	PO	150		36.5	94
			300		40.4	104
			600		31.8	82
Human COPD patients	[steady state]	inhalation	[800 µg/day]		0.390[#]	–

[a] = estimated based on toxicokinetic data from the pivotal rat 6-month repeat-dose toxicity study;
[b] = estimated based on toxicokinetic data from the rat embryofetal development study;
[#] = based on doubling of the AUC_{0-24h} value reported at 400 µg QD in Clinical Study M.34273/09 (0.195 ng·h/mL) to account for BD administration.

Aclidinium bromide derived radioactivity was shown to cross the placenta after IV administration in rats. Peak fetal concentrations of radioactivity were 0.6 times the maternal plasma in experiments where the site of radiolabelling was retained by the alcohol metabolite and 4.4 times lower than the maternal plasma C_{max} when the radiolabel was retained by the carboxylic acid metabolite. Moderate transfer of aclidinium bromide

derived radioactivity into milk was shown in lactating rats following IV administration; peak concentrations in milk were reached slowly (observed at 6 h postdose).

Fertility was reduced in male rats treated at 4.8 mg/kg/day by inhalation, with pre and postimplantation losses increased in the untreated females with which they were paired. In female rats, fertility was reduced with treatment at ≥2.0 mg/kg/day, accompanied by a statistically significant reduction in the number of corpora lutea (indicating impairment of ovulation). The NOELs for effects on male and female fertility are 1.84 and 0.86 mg/kg/day, respectively (associated with animal: human exposure ratios of 188 and 161).

Aclidinium bromide was not teratogenic in either rats or rabbits. Delayed ossification of fetuses (cranium, vertebrae, sternebrae, digit or toe) was observed at all dose levels tested in the pivotal rat embryofetal development study (≥0.78 mg/kg/day by inhalation; relative exposure, ≥61). Embryofetal development was unaffected in rabbits treated at ≤3.58 mg/kg/day by inhalation (relative exposure, ≤28), while fetal weight was reduced in the species with oral administration at ≥300 mg/kg/day. Effects on embryofetal development in rats and rabbits occurred in the context of maternotoxicity and the findings are not considered to reflect a direct toxic effect of the drug on the embryo/fetus.

Treatment-related effects on pre/postnatal development were limited to decreased preweaning body weight gain, observed in rats at inhalational doses ≥0.20 mg/kg/day (estimated relative exposure ≥44). Some recovery was evident post-weaning, though normal body weight was not fully reached at maturity. The NOEL for pup development was 0.018 mg/kg/day (estimated relative exposure 17).

Pregnancy classification

The sponsor has proposed Pregnancy Category B3. Category B3 is for:

> *'Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.'*

Category B3 is considered appropriate from a nonclinical perspective based on findings of delayed ossification and decreased fetal body weight in laboratory animals.

Local tolerance and antigenicity

Local tolerance tests were adequately conducted and revealed no dermal irritation and no significant ocular irritation with aclidinium bromide in rabbits. In the mouse local lymph node assay, aclidinium bromide was found to act as a slight skin irritant but not as a contact skin sensitiser. Negative results were returned for the drug in the passive cutaneous anaphylaxis test, conducted in rats. Aclidinium bromide did not show and airway sensitising potential in guinea pigs.

Impurities

Two impurities required toxicological qualification.

Significant multiples of the maximum potential human doses of these two impurities exist at the NOAEL established in the pivotal 9 month repeat-dose toxicity study in dogs (on both a local and systemic basis). No structural alerts for genotoxicity were revealed by DEREK (deductive estimate of risk from existing knowledge) analysis. They are therefore considered to be qualified.

Five other impurities in the drug substance were found to contain structural alerts for genotoxicity by DEREK analysis. Proposed limits for these are below the International

Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) qualification threshold and resultant doses are all below the standard threshold of toxicological concern (TTC) value of 1.5 μg/day. The structural alerts were overruled by negative Ames tests for three of these, while two also returned positive results for bacterial mutagenicity. Of these two, one impurity was present in the drug batch used in the rodent carcinogenicity studies at sufficient levels (and resultant doses) to establish a lack of carcinogenic concern. The single remaining genotoxic impurity will be present at ≤200 parts per million (ppm), yielding a maximum human dose of 0.16 μg/day, which is more than 9 times lower than the TTC. As such, none of these impurities are considered to pose a relevant toxicological hazard and the proposed limits are acceptable.

Proposed impurity limits are considered to be acceptable from a toxicological perspective, based on qualification in the pivotal repeat-dose toxicity study in dogs or the rodent carcinogenicity studies, and/or application of the TTC (threshold of toxicological concern) principle.

Paediatric use

Bretaris Genuair is not intended for use in patients under 18 years of age and no specific studies in juvenile animals were submitted.

Nonclinical summary

- The general quality of the nonclinical dossier was high. All pivotal safety related studies were conducted under GLP conditions except for some of the studies on safety pharmacology.
- Aclidinium bromide is a competitive muscarinic receptor antagonist with subnanomolar affinity across all five human muscarinic receptor subtypes. Antagonism of acetylcholine induced contraction of isolated human bronchus and guinea-pig trachea was shown for the drug in vitro and long-lasting inhibition of ACh-induced bronchoconstriction was demonstrated after inhalation in guinea pigs and dogs. The two main metabolites (hydrolysis products) and the drug's other enantiomer (S-enantiomer; not included in the active ingredient) do not possess significant antimuscarinic activity.
- No clinically significant off-target activity was found for aclidinium bromide or its main metabolites in secondary pharmacology studies. Safety pharmacology studies covered the CNS, cardiovascular, respiratory, renal and gastrointestinal systems, with classic anticholinergic effects observed (such as tachycardia, dry mouth and decreased gastrointestinal motility). Inhibition of the hERG K+ channel did not occur at clinically relevant concentrations.
- Rapid absorption of aclidinium bromide after inhalation was shown in laboratory animal species and humans. Hydrolysis (mediated both enzymatically and non-enzymatically) gives rise to the two main metabolites, found in all species. The drug's carboxylic acid metabolite is the major circulating component but unchanged drug is chiefly present in lung. Metabolism by CYPs was minor and there was some associated covalent binding due to the formation of reactive metabolites (largely prevented by glutathione). There were no unique human metabolites. Limited tissue distribution after intratracheal administration was shown in rats and penetration of the blood-brain barrier in the species was low.
- Aclidinium bromide displayed a low order of acute toxicity by the inhalational route in rats.

- Pivotal repeat-dose toxicity studies were conducted in rats (6 months) and dogs (9 months) using the inhalational route; non pivotal studies involved mice, rats and dogs, and administration by inhalation or other routes (oral, IV, SC). The major target organs for toxicity identified with inhalational administration were respiratory tract tissues (nasal cavity, larynx and lung), the Harderian gland and the parotid gland, with changes also observed in the liver; effects on the eye and heart were also seen.
- Aclidinium bromide gave equivocal results in assays for bacterial and mammalian mutagenicity in vitro but returned clear negative results in in vivo genotoxicity studies (the mouse bone marrow micronucleus test and the unscheduled DNA synthesis assay in rat liver) at very high multiples of the clinical exposure. Carcinogenicity studies in mice and rats conducted by the inhalational route revealed no tumourigenicity at very high multiples of the clinical plasma AUC and high or very high multiples of the lung deposited dose.
- Aclidinium bromide and/or its metabolites were shown to cross the placenta and be excreted into milk in rats. Fertility was reduced in male and female rats but only at very high exposure multiples. Adverse effects on embryofetal development comprised delayed ossification in rats and decreased fetal weight in rabbits occurring in the context of maternotoxicity; teratogenicity was not observed in either species. Postnatal bodyweight gain was reduced in the offspring of rats treated with aclidinium bromide during gestation and lactation.
- Local tolerance and antigenicity studies revealed no dermal and no significant ocular irritation in rabbits and no skin (mouse) or airway (guinea pig) sensitising potential.

Conclusions and recommendation

- The nonclinical dossier contained no major deficiencies.
- Primary pharmacology studies showing potent and long-lasting antimuscarinic activity support the drug's use for the proposed indication.
- Secondary pharmacology studies revealed no clinically significant off-target activity. Safety pharmacology studies showed a classic antimuscarinic profile. The findings in the repeat-dose toxicity studies are consistent with minimal to mild local irritation (similar to that observed with other inhaled drugs) and for the most part systemic anticholinergic activity. The likelihood of systemic anticholinergic effects in patients is predicted to be reasonably low, based on the limited systemic exposure to the drug due to rapid hydrolysis to pharmacologically inactive metabolites. The absence of treatment related histopathological lesions in the 9 month repeat dose toxicity study in dogs, involving inhalational administration of doses yielding over 100 times the lung deposited dose and almost 40 times the plasma AUC expected in patients at the recommended human dose, offers particular support for safety in patients.
- Aclidinium bromide is not considered to pose a genotoxic or carcinogenic hazard to patients. The significance of equivocal results observed in in vitro genotoxicity assays can be discounted by convincing negative results in the in vivo genotoxicity assays and the negative results of both rodent carcinogenicity studies.
- Adverse effects on embryofetal development seen in rats and rabbits occurred at very large multiples of the human exposure and are considered most likely to have occurred secondary to maternotoxicity rather than to reflect a direct toxic effect of the drug on the embryo/fetus. Large multiples of the human exposure are also evident at the NOELs established for effects on fertility and postnatal development indicating limited clinical relevance.

- There are no nonclinical objections to the registration of Bretaris Genuair for the proposed indication.
- The evaluator recommended amendments to the draft Product Information but the details of these are beyond the scope of this AusPAR.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

Parasympathetic nerves are the dominant bronchoconstrictor neural pathway in airways, and cholinergic tone is the major reversible component in COPD.[7, 8] Cholinergic mechanisms are also important in the regulation of submucosal gland secretion, which is increased in COPD. Cholinergic nerves exert their bronchoconstrictor and mucus secretory effects via the activation of muscarinic receptors in airway smooth muscle and submucosal glands, respectively. Blockade of these muscarinic receptors with antagonists, such as ipratropium, oxitropium and tiotropium provides clinical benefit in COPD.

Short acting inhaled anticholinergic drugs (for example ipratropium and oxitropium), which require frequent dosing to maintain a bronchodilator effect, have been used to treat patients with symptomatic COPD since the 1970s as first-line agents and are known to be safe and effective bronchodilators.[9] The sponsors state that only one long acting anticholinergic bronchodilator is available (tiotropium).

> Comments: Recently, another long-acting anticholinergic bronchodilator Seebri Breezhaler (glycopyrronium bromide) has been approved for once daily use in long-term maintenance treatment of COPD.

Clinical trials have shown that tiotropium provides clinical benefit in COPD but is also associated with certain anticholinergic events such as urinary retention and dry mouth[10], and as tiotropium is excreted via the kidney there is also the need to closely monitor patients with renal impairment. Aclidinium bromide, like tiotropium, 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.[11] Aclidinium bromide is an ester and is highly unstable in plasma, undergoing rapid and extensive non-enzymatic (chemical) and enzymatic hydrolysis (mainly by BChE)[12] into two pharmacologically-inactive metabolites. As a result, aclidinium bromide undergoes very rapid and complete clearance from the body and its systemic

[7] Postma DS, Keyzer JJ, Koeter GH, et al. Influence of the parasympathetic and sympathetic nervous system on nocturnal bronchial obstruction. Clin Sci 1985; 69: 251-8.
[8] Coulson FR, Fryer AD. Muscarinic acetylcholine receptors and airway diseases. Pharmacol Ther 2003; 98:59-69.
[9] Ferguson GT, Cherniack RM. Management of chronic obstructive pulmonary disease. N Engl J Med 1993; 32:1017-22.
[10] Kesten S, Celli B, Decramer M, et al. Tiotropium Handihaler in the treatment of COPD: a safety review. Int J Chron Obstruct Pulmon Dis 2009; 4:397-409.
[11] Gavalda A, Miralpeix M, Ramos I, et al. Characterization of aclidinium bromide, a novel inhaled muscarinic antagonist, with long duration of action and a favourable pharmacological profile [published online ahead of print August 26, 2009]. J Pharmacol Exp Ther. oi:10.1124/jpet.109.151639.
[12] Albertí J, Martinet A, Sentellas S, et al. Identification of the human enzymes responsible for the enzymatic hydrolysis of aclidinium bromide. Drug Metab Dispos. 2010 Jul;38(7):1202-10.

bioavailability following inhalation is very low (<5%). These characteristics of aclidinium bromide confer the following potential advantages to its use:

1. Sustained bronchodilation over 24 hours with BD dosing[13].
2. A reduced potential for anticholinergic side effects. Nonclinical studies have shown that the propensity of aclidinium bromide to induce pharmacological effects typical of anticholinergic drugs, such as urinary difficulty/urinary retention, dry mouth and constipation, was lower than that of tiotropium and/or ipratropium.[14, 15]
3. A good safety profile: conventional nonclinical studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and reproductive and developmental toxicity revealed no special hazard for humans, and a significant safety margin when aclidinium bromide is administered at the therapeutic dose,
4. A reduced potential for drug interactions: it was considered unlikely that other medicinal products metabolised by human cytochrome P450 (CYP450) enzymes or esterases would be affected by co-administration of aclidinium bromide.
5. No need for dose adjustment in renal/hepatic impairment.
6. Potentially better treatment compliance due to ease of administration through the DPI.

Contents of the clinical dossier

Scope of the clinical dossier

This application for marketing authorisation for aclidinium bromide is supported by data from clinical studies in which 5447 COPD patients worldwide received at least one dose of investigational medicinal product (IMP).

The current dossier includes twice daily (BD) dosing studies (proposed dosing frequency) as well as once daily (QD) dosing and fixed combination dosing studies. The submission contained the following clinical information:

- Eleven clinical pharmacology studies, including eight that provided pharmacokinetic data and 3 that provided pharmacodynamic data. Biopharmaceutics of inhaled aclidinium bromide investigated lung deposition (M/34273/03) and absolute bioavailability (M/34273/05), and also evaluated whether the proposed patient population had sufficient peak inspiratory flow (PIF) to use the inhaler device (M/34273/07). Clinical pharmacology studies provided information on pharmacokinetics (M/34273/01, M/34273/05, M/34273/06 and LAS-PK-12) and the influence of age (M/34273/09) and renal impairment (M/34273/08) on pharmacokinetics, and in addition provided information on the absorption, distribution, metabolism and excretion (ADME; M/34273/03, M/34273/04), on the primary pharmacodynamic effects of aclidinium bromide (M/34273/00, M/34273/21) and on the effects of aclidinium bromide on QTc interval (M/34273/11).
- Population pharmacokinetic analyses: Not applicable.

[13] Inhaled aclidinium bromide inhibited acetylcholine-induced bronchoconstriction in anesthetised guineapigs, with a duration of action (expressed as the half-life for the bronchodilatory effect) of 29 hours; substantially longer than that of ipratropium (8 hours) but shorter than that of tiotropium (64 hours).
[14] Montero JL, Anton F, Viñals M, et al. Effect of aclidinium bromide, a novel long-acting anticholinergic, on salivation, colonic motility and faecal output in different animal models. Poster ERS Berlin 2008
[15] Gras J, Llupia J, Llenas JL, et al. The preclinical urinary and renal safety profile of aclidinium bromide, a novel long-acting anticholinergic drug. Poster ERS Berlin 2008.

- Three pivotal randomised, double-blind placebo-controlled, efficacy/safety studies which aclidinium bromide 400 µg and 200 µg BD; 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) were evaluated.
- Two Phase II dose-finding studies (M/34273/23 and M/34273/29).
- Three long term safety and efficacy studies of aclidinium bromide ; 400 µg and 200 µg BD were investigated in two randomised, double-blind, parallel group studies: a 52 week extension study of LAS-MD-33 (LAS-MD-36) and a further 52 week study (LAS-MD-35). In addition, a 40 week open label extension study of LAS-MD-38 Part A (LAS-MD-38 Part B) which investigated long term safety and efficacy of aclidinium bromide 400 µg was conducted.
- Seven studies with once daily dosing of aclidinium bromide**.** Prior to conduct of the clinical development program of aclidinium bromide BD, a clinical development program of aclidinium bromide administered once daily (QD) had been conducted.
- Clinical development of aclidinium bromide in combination with formoterol is ongoing in a parallel clinical program. Details of this ongoing program are not provided as it is not considered relevant for this application (safety data have been provided as appropriate).
- Three studies of combination of aclidinium bromide and formoterol**.** Efficacy data have not been evaluated in as much detail as it is not relevant to this submission. However, the safety data have been evaluated in detail.
- Pooled analyses, meta-analyses and sponsor's *Integrated Summary of Efficacy and Integrated Summary of Safety*.

Two clinical studies of aclidinium bromide 400 µg BD are ongoing; one study to confirm the bronchodilatory profile over 24 hours compared to that of tiotropium (M/34273/39) and a further study to investigate effects on exercise tolerance (M/34273/40).

> Comments: The studies conducted to date with aclidinium bromide provide an extensive body of information that enables a rigorous evaluation of the benefit-risk profile for aclidinium bromide as a maintenance bronchodilator treatment for patients with moderate to severe COPD.

Paediatric data

The submission did not include paediatric data. On 3 December 2007, the European Medicines Agency (EMA) granted a class waiver (P/1/2007) for the condition COPD from the European Paediatric Regulation (Regulation [EC] Number 1901/2006) requirement for a Paediatric Investigation Plan on the basis that the condition should only be considered in an individual over the age of 40 years with characteristic symptoms of COPD according to GOLD.

Good clinical practice

All clinical trials have been conducted in accordance with the principles and practices of Good Clinical Practice and the Declaration of Helsinki.

Pharmacokinetics

Studies providing pharmacokinetic data

Table 4 (below) shows the studies relating to each pharmacokinetic topic.

Table 4. Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID
PK in healthy adults	General PK - Single dose	M34273/ 05 M34273/ 00 M34273/ 03 M34273/ 04
		M34273/ 01
	- Multi-dose	LAS-PK-12A M34273/ 06
	Bioequivalence† - Single dose	Not applicable
	- Multi-dose	
	Food effect	Not applicable
PK in special populations	Target population §- Single dose -Multiple dose	M34273/ 21 M34273/ 09
	Hepatic impairment	None
	Renal impairment	M34273/08
	Neonates/infants/children/adolescents	None
	Elderly	None
Genetic/gender-related PK	Males versus females	None
PK interactions	Not evaluated	None
Population PK analyses	Healthy subjects	None
	Target population	None
	Other	None

† Bioequivalence of different formulations.
§ Subjects who would be eligible to receive the drug if approved for the proposed indication.

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

Evaluator's conclusions on pharmacokinetics

Absorption

Aclidinium bromide is rapidly absorbed from the lung, achieving maximum plasma concentrations within 5 minutes of inhalation in healthy subjects and normally within the first 15 minutes in COPD patients. The mean C_{max}, attained after inhalation of single doses of 400 µg was approximately 80 pg/mL in COPD patients (Study M/34273/09, n=24 [12 young and 12 elderly]) and higher at 100 pg/mL to 200 pg/mL in healthy volunteers (Studies M/34273/08 [n=6] and LAS-PK-12 [n=8], respectively). Steady-state plasma levels were attained within seven days of twice daily dosing and considering the short half-life; steady-state may be reached soon after the first dose. No accumulation on repeat dosing was observed at steady-state. The fraction of the inhaled dose that reaches the systemic circulation as unchanged aclidinium is very low at less than 5%.

Distribution

Whole lung deposition of inhaled aclidinium bromide via the Genuair inhaler averaged approximately 30% of the metered dose. The plasma protein binding of aclidinium bromide determined in vitro most likely corresponded to the protein binding of the metabolites due to the rapid hydrolysis of aclidinium bromide in plasma; plasma protein binding was 87% for the carboxylic acid metabolite and 15% for the alcohol metabolite. The main plasma protein that binds aclidinium bromide is albumin.

Metabolism

Aclidinium bromide is rapidly and extensively hydrolysed to its pharmacologically inactive alcohol and carboxylic acid derivatives. The hydrolysis occurs both chemically (non-enzymatically) and enzymatically by esterases, BChE being the main human esterase involved in the hydrolysis. Plasma levels of the acid metabolite are approximately 100 fold greater than those of the alcohol metabolite and the unchanged active substance following inhalation. The low absolute bioavailability of inhaled aclidinium bromide (<5%) is because aclidinium bromide undergoes extensive systemic and pre systemic hydrolysis whether deposited in the lung or swallowed. Biotransformation via CYP450 enzymes plays a minor role in the total metabolic clearance of aclidinium bromide.

Elimination

The terminal elimination half-life of aclidinium bromide is approximately 2 to 3 hours. Following intravenous administration of 400 µg radiolabelled aclidinium bromide to healthy subjects approximately 1% of the dose was excreted as unchanged aclidinium bromide in the urine. Up to 65% of the dose was eliminated as metabolites in the urine and up to 33% as metabolites in the faeces. Following inhalation of 200 µg and 400 µg of aclidinium bromide by healthy subjects or COPD patients, the urinary excretion of unchanged aclidinium was very low at about 0.1% of the administered dose indicating that renal clearance plays a minor role in the total aclidinium clearance from plasma.

PKs in special populations

In Study M34273/09, PK profiles of aclidinium bromide in plasma were similar between Days 1 and 3, in COPD patients aged 40 to 59 years and in patient's aged ≥70 years. The plasma exposure at the 400 µg inhaled dose being approximately 2 times higher than that for the 200 µg dose. Thus, it can be concluded that the pharmacokinetic behaviour of aclidinium bromide in elderly patients is not different from that in younger adult patients. Furthermore, the higher exposure of the two main metabolites observed in the elderly patients is considered clinically irrelevant since these metabolites are devoid of activity at a wide array of receptors and enzymes, including muscarinic receptors. As such, a dosage adjustment for elderly COPD patients is not required.

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.

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.

Drug interactions

No human drug interaction studies have been conducted. *In vitro* studies have shown that aclidinium bromide at the therapeutic dose or its metabolites do not inhibit or induce any of the cytochrome P450 (CYP450) enzymes and do not inhibit esterases (carboxylesterase, acetylcholinesterase and BChE). In vitro studies have shown that aclidinium bromide or the metabolites of aclidinium bromide are not substrates or inhibitors of P-glycoprotein.

Pharmacodynamics

Studies providing pharmacodynamic data

Table 5 shows the studies relating to each pharmacodynamic topic and the location of each study summary.

Table 5. Submitted pharmacodynamic studies.

PD Topic	Subtopic	Study ID
Primary pharmacology:	In male COPD patients	M34273/21
	To characterise PIF generated through Novolizer and the Handihaler dry powder inhalers by COPD patients	M/34273/07
Secondary Pharmacology	Effect on QT intervals	M34273/11A
Gender other genetic and Age-Related Differences in PD Response	Effect of gender	None
	Effect of age	None
PD Interactions	Not evaluated	None
Population PD and PK-PD analyses	Healthy subjects	Not applicable
	Target population	None

None of the pharmacodynamic studies had deficiencies that excluded their results from consideration.

Evaluator's conclusions on pharmacodynamics

Aclidinium bromide is a competitive, selective muscarinic receptor antagonist (anticholinergic) with a longer residence time at M3 receptors than M2 receptors. M3

receptors mediate contraction of airway smooth muscle. Inhaled aclidinium bromide acts locally at airway smooth muscle to antagonise M3 receptors and induce bronchodilation. Nonclinical in vitro and in vivo studies showed rapid, dose-dependent and long lasting inhibition by aclidinium bromide of acetylcholine induced bronchoconstriction. Aclidinium bromide is quickly broken down in plasma and the level of systemic anticholinergic side effects is therefore low.

The Phase II, single, ascending dose Study M34273/21 in COPD patients showed statistically significant improvements compared with placebo for FEV1 and FVC at all LAS34273 doses (100 µg, 300 µg and 900 µg) from 15 min to 24 hours after single inhalation. However, the proposed dose of 400 µg BD was not evaluated in this study.

No effects on QT interval (corrected using either the Fridericia or Bazett method or when individually corrected) were observed when aclidinium bromide (200 µg or 800 µg) was administered once daily for 3 days to 272 healthy subjects in a thorough QTc study M34273/11.

The proposed drug is an inhalation powder containing active drug and lactose in a dry powder inhaler (DPI), the Novolizer inhaler. This device presents minor changes with respect to the marketed Novolizer® and meets at least the same standards. The main difference is that the Novolizer® is a refillable device whereas the proposed Almirall Novolizer is a disposable device. Each device has a dose counter display to track the number of doses remaining and features to ensure patient compliance. When the coloured button on the top of the DPI device is pressed a single dose of inhalation powder is loaded into the powder inhalation channel. A window on the front of the device simultaneously changes from red to green to indicate that the dose is ready for breath actuated inhalation. During the breath, patients should hear a click indicating that they have breathed in strongly enough for the device to work. Additionally, a change in the front window from green to red informs the patient that the inhalation has been successfully performed.

As per the EU Guideline CPMP/EWP/4151/00 (*Points to consider on the requirements for clinical documentation for orally inhaled products*), it should be defined which patient groups will normally be able to produce a sufficient Peak Inspiratory Flow (PIF) to use the inhaler and which special groups may have problems. According to the FDA guidance for industry entitled "*Points to consider: clinical development programs for Metered Dose Inhaler (MDI) and DPI products*" to relate the in vitro tests to in vivo performance for DPIs (which are dependent on patient effort for deaggregation and dose delivery) studies should be conducted to determine what flow characteristics are obtained through the device by adult patients with varying degrees of obstructed lung function. The Phase II Study M34273/07 was conducted to assess the PIF generated by moderate and severe COPD patients through the proposed Novolizer DPI[16] containing placebo. Results of this study show that all COPD patients enrolled in the trial were able to produce a higher PIF through the Novolizer inhaler than through the HandiHaler® device. Overall, COPD patients with a moderate to severe disease were able to generate sufficient inspiratory airflow through the Novolizer to reliably inhale the full dose and activate the trigger threshold.

Dosage selection for the pivotal studies

Two Phase II studies with BD dosing (M34273/29 and M34273/23) evaluated the BD dosing regimen of aclidinium bromide and used formoterol and tiotropium for benchmark comparison. Study 29 evaluated a range of doses of aclidinium (100, 200 and 400 µg) and

[16] Sponsor comment: "This study was not conducted with the marketed Novolizer device but with an already modified device; an intermediate version between Novolizer and Genuair."

will be discussed in this section while study 23 used only one dose of aclidinium bromide (400 µg BD) and will be discussed later.

For further details on the design and results from these studies see Attachment 2 Dosage selection for the pivotal studies.

Efficacy

Studies providing efficacy data

The following studies provided efficacy data for this submission:

- Three pivotal randomised, double-blind placebo-controlled, efficacy/safety studies which aclidinium bromide 400 µg and 200 µg BD; 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) were evaluated.
- Three long term safety and efficacy studies of aclidinium bromide ; 400 µg and 200 µg BD were investigated in two randomised, double-blind, parallel group studies: a 52 week extension study of LAS-MD-33 (LAS-MD-36) and a further 52 week study (LAS-MD-35). In addition, a 40 week open label extension study of LAS-MD-38 Part A (LAS-MD-38 Part B) which investigated long term safety and efficacy of aclidinium bromide 400 µg was conducted.
- Seven studies with once daily dosing of aclidinium bromide. Prior to conduct of the clinical development program of aclidinium bromide BD, a clinical development program of aclidinium bromide administered QD had been conducted.

Evaluator's conclusions on efficacy

Long-term maintenance bronchodilator treatment to relieve symptoms in adult patients with Chronic Obstructive Pulmonary Disease (COPD)

Prior to conduct of the clinical efficacy program of aclidinium bromide BD, a clinical program to investigate the efficacy of aclidinium bromide 200 µg QD in patients with COPD was conducted and completed. An overview of the clinical studies designed to provide efficacy information on aclidinium bromide QD is provided in the *Other efficacy studies*, *Long-term efficacy* section above.

Although statistically significant bronchodilatory effects of aclidinium bromide 200 µg QD were demonstrated in two Phase III, double blind, placebo controlled, randomised clinical trials (M/34273/30 and M/34273/31), the trough FEV1 effect size (that is, approximately 60 mL) observed with aclidinium bromide 200 µg QD was lower than the 0.100 L effect size considered of clinical relevance and suggested that a higher daily dose and/or a different dose regimen (such as BD) may be necessary to improve bronchodilator efficacy. Furthermore results of another Phase II crossover Study M/34273/25 which investigated further the bronchodilatory profile of aclidinium bromide 200 µg QD administered in the morning or in the evening showed that night time bronchodilation following morning administration of aclidinium bromide was insufficient to overcome the known increase in nocturnal cholinergic tone. Relevant night time bronchodilation was achieved, however, following evening administration of aclidinium bromide.

The Phase II, placebo controlled, dose-finding Study M/34273/22 evaluated 5 doses of aclidinium bromide administered QD for 4 weeks in 464 COPD patients; this study also included an open-label tiotropium treatment arm. In general, peak bronchodilatory effects (as assessed by FEV1 and FVC) on the first and last days of dosing were higher for

aclidinium bromide 200 µg than for aclidinium bromide 400 µg and comparable for aclidinium bromide 200 µg and tiotropium.

The relatively low bronchodilator efficacy attained with aclidinium bromide 200 µg QD in pivotal QD studies M/34273/30 and M/34273/31 compared to that achieved with aclidinium bromide 200 µg QD in this study provoked a review of per-patient FEV1 data from this study. It was noted that trough FEV1 values reported at Day 28 for one patient in the 200 µg aclidinium bromide group were markedly higher than the trough FEV1 values reported for other patients in the study (absolute change from baseline to Day 28 in trough FEV1 was 4.09 L for the outlier whereas the range of values for all other study patients was between -0.65 and 1.55 L). Hence, results from this study suggest that the bronchodilation achieved with 400 µg QD is a >100 mL clinically relevant improvement. However, the sponsors have not conducted any direct comparison between QD and BD dosing with 400 µg aclidinium bromide.

The clinical efficacy program for aclidinium bromide 200 µg and 400 µg, administered BD, was conducted in North America, Europe and South Africa, and comprises three pivotal studies (M/34273/34, LAS-MD-33 and LAS-MD-38 Part A) and five supportive studies, two Phase II studies (M/34273/23 and M/34273/29) and three Phase III long term safety studies (LAS-MD-35, LAS-MD-36 and LAS-MD-38 Part B).

The primary evidence of the efficacy of aclidinium bromide is from the 6 month pivotal Study M/34273/34. This study showed aclidinium bromide 400 µg BD to be associated with clinically and statistically significant effects with respect to bronchodilation, symptomatic improvements including exacerbation control and improvements in disease-specific health status. The results of pivotal Study LAS-MD-33 were comparable to those of Study M/34273/34. Further evidence of the benefits of aclidinium bromide was to be obtained from pivotal Study LAS-MD-38 Part A but due to an imbalance between treatment groups at baseline in lung function and COPD severity in Study LAS-MD-38 Part A the sponsor considers that although statistically significant results were obtained for its primary and secondary endpoints, the study may not provide a reliable estimate of the true treatment effect due to imbalance in baseline COPD characteristics. Supportive evidence of efficacy is derived from Phase II Studies M/34273/23 and M/34273/29 and long term studies LAS-MD-35 and LAS-MD-36.

Patient population

The pivotal studies included male and females aged > 40 years, current or ex-smokers of more than or equal to 10 pack years with a clinical diagnosis of moderate to severe stable COPD (as per the Global Initiative for Chronic Lung Disease (GOLD) criteria) with postbronchodilator FEV1 <80% predicted and ≥30% of predicted and FEV1/FVC less than 0.7 and an absence of respiratory tract infection or COPD exacerbation in the 6 weeks (3 months if hospitalisation was required) prior to the screening visit. The inclusion and exclusion criteria confirmed that patients included in the studies were representative of the target patient population for aclidinium bromide (namely patients with moderate to severe COPD). In the pivotal studies and long term safety studies, patients were permitted to continue treatment with stable doses of inhaled corticosteroids, oral sustained release theophylline and/or oxygen as required (≤15 hours per day). Stable doses of oral and/or parenteral corticosteroids (≤10 mg/day) were also permitted. Patients were provided with a marketed salbutamol metered dose inhaler to be taken as needed. Thus, the Phase III clinical studies have been performed in the patient population in which therapy with aclidinium bromide would be appropriate.

Efficacy endpoints

FEV1 is a well-established measure of treatment efficacy that is commonly used to evaluate lung function improvement in COPD trials; its use in the diagnosis of COPD is supported by GOLD guidelines (2008). The CPMP *"Points to Consider on Clinical Investigation of Medicinal Products in the Treatment of Patients with Chronic Obstructive Pulmonary Disease"* (CPMP/EWP/562/98) states that for an indication of symptomatic relief of COPD, statistically significant benefit should be demonstrated not only for FEV1 but also for a pre-specified measure of symptomatic benefit. In Study M/34273/34 (the only study with recommended 24 week study duration), the proportion of patients with a clinically significant improvement in the Mahler Transition Dyspnoea Index (TDI) Focal score was pre-specified as the dominant symptomatic endpoint. The proportion of patients with a clinically significant improvement in the St George's Respiratory Questionnaire (SGRQ) Total score was evaluated as a further secondary endpoint. These efficacy measures were assessed as additional efficacy variables in studies LAS-MD-33 and LAS-MD-38 Part A due to the shorter treatment duration (12 weeks). Daily COPD symptoms were additional efficacy variables in Study M/34273/34. Daily symptoms were assessed according to the Exacerbations of Chronic Pulmonary Disease Tool - Respiratory Symptoms (E-RS)[17]. COPD exacerbations by PROs in 12 week studies 33 and 38A; however, investigated by PRO and EXACT criteria in pivotal Study 34. Other supportive endpoints such as use of relief medication were also used in all pivotal studies. Spirometric substudies within each of the 3 pivotal Phase III studies further evaluated detailed bronchodilatory profile of aclidinium bromide 200 and 400 µg BD.

Efficacy results

Bronchodilation

In each of the pivotal studies and in the analysis of the pooled populations, aclidinium bromide 400 µg was associated with greater numerical improvements versus placebo in the change from baseline to Week 12 and/or Week 24 in M/34273/34 in trough FEV1 than the 200 µg dose. The treatment differences between aclidinium bromide 400 µg and placebo were of a magnitude (≥100ml difference from placebo in trough FEV1) considered clinically significant[18] in Studies M/34273/34 and LAS-MD-33 and in both pooled analyses. Clinically significant treatment differences between aclidinium bromide 200 µg and placebo in the change from baseline in trough FEV1 were not observed in any of the pivotal studies or in the pooled analysis. Statistical superiority of the 400 µg dose over the 200 µg dose in the change from baseline in trough FEV1 was observed in the pooled population of M/34273/34 and LAS-MD-33 and in the pooled population of all three pivotal studies but not in the individual pivotal studies (Table 6).

[17] The E-RS is a patient-reported outcome tool developed to evaluate the severity of COPD symptoms (domains of breathlessness, cough and sputum, chest symptoms). An algorithm was used to calculate the E-RS Total Score from the domain scores. The items comprising the E-RS were selected from an existing measure, the Exacerbations of Chronic Obstructive Pulmonary Disease Tool (EXACT)**28,29** that was developed to assess frequency, severity and duration of exacerbations of COPD. The E-RS is designed as a daily diary to be completed nightly before bedtime via an electronic device, for example, a personal digital assistant (PDA).
[18] Cazzola M, MacNee W, Martinez FJ, et al. on behalf of the American Thoracic Society/European Respiratory Society Task Force on outcome of COPD. Outcomes for COPD pharmacological trials: from lung function to biomarkers. Eur Respir J 2008;31:416-68

Table 6. LS Mean Treatment differences between aclidinium bromide 400 µg or 200 µg and placebo in the change from baseline in trough and peak FEV1 in pivotal studies M/34273/34 and LAS-MD-33 and LAS-MD-38 Part A and the pooled population. ITT populations.

		Comparison					
		400 µg vs Placebo		200 µg vs Placebo		400 µg vs 200 µg	
		LSMD (L)	p-value	LSMD (L)	p-value	LSMD (L)	p-value
Trough FEV_1							
Pivotal studies	M/34273/34 (Week 24)	0.128	<0.0001	0.099	<0.0001	0.029	0.187
	LAS-MD-33 (Week 12)	0.124	<0.0001	0.086	<0.0001	0.038	0.069
	LAS-MD-38A (Week 12)	0.072	0.001	0.051	0.019	0.021	0.342
Pooled Analysis	M/34273/34 & LAS-MD-33 (Week 12)	0.112	<0.0001	0.080	<0.0001	0.032	0.027
	All three pivotal studies[a]	0.100	<0.0001	0.071	<0.0001	0.029	0.017
Peak FEV_1							
Pivotal studies	M/34273/34 (Week 24)	0.209	<0.0001	0.185	<0.0001	0.025	0.292
	LAS-MD-33 (Week 12)	0.192	<0.0001	0.146	<0.0001	0.046	0.041
	LAS-MD-38A (Week 12)	0.125	<0.0001	0.115	<0.0001	0.010	0.692
Pooled Analysis	M/34273/34 & LAS-MD-33 (Week 12)	0.191	<0.0001	0.167	<0.0001	0.024	0.130
	All three pivotal studies[a]	0.172	<0.0001	0.152	<0.0001	0.019	0.144

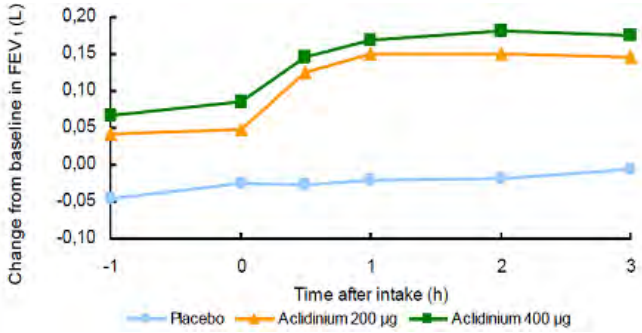
a Studies M/34273/34, LAS-MD-33 and LAS-MD-38 Part A

Analysis is based on ANCOVA model for change from baseline in FEV_1, with treatment group and sex (and study for pooled analyses) as factors, and age and baseline FEV_1 as covariates.

Abbreviations: ANCOVA=analysis of covariance; FEV_1=forced expiratory volume in 1 second; LSMD=LS mean treatment difference.

In the 6 month pivotal Study M/34273/34, clinically significant treatment differences in trough FEV1 were observed between aclidinium bromide 400 µg and placebo at all time-points from Week 1 up to Week 24 but not between aclidinium bromide 200 µg and placebo (Figure 2).

Figure 2. Changes from baseline in FEV1 up to 3 h postdose at Week 12 by treatment in the pooled populations of studies M/34273/34 and LAS-MD-33 ITT population.



Aclidinium bromide 400 µg was associated with greater numerical improvements versus placebo in the change from baseline to Week 24 and/or Week 12 in peak FEV1 than the 200 µg dose in Studies M/34273/34 and LAS-MD-33. Pooled analysis of Studies M/34273/34 and LAS-MD-33 showed that the changes from baseline in peak FEV1 were numerically greater with the 400 µg dose than with the 200 µg dose at Weeks 1 (0.030 L, p=0.022), 4 (0.022 L, p=0.125), 8 (0.034 L, p=0.126) and 12 (0.024 L, p=0.130). Similar observations were made in the pooled analysis of three pivotal studies. In the pooled population of Studies M/34273/34 and LAS-MD-33, the changes from baseline up to 3

hours post-dose were numerically greater with aclidinium bromide 400 µg compared to aclidinium bromide 200 µg at 0.5 hours (0.022 L, p=0.146), 1 hour (0.018 L, 0.250), 2 hours (0.032 L, p=0.042) and 3 hours (0.028 L, p=0.084) postdose. Similar observations were made for the pooled analysis of the three pivotal studies.

Symptomatic improvements

M/34273/34 was the only placebo controlled study conducted with treatment duration of 6 months and was the most important study for evaluation of symptoms. A clinically significant increase in TDI Focal score is at least 1.0 unit and changes from baseline in TDI Focal score with aclidinium bromide 400 µg compared to placebo in Studies M/34273/34, LAS-MD-33 and LAS-MD-38 Part A and in the pooled analyses were either at the minimum clinical important difference (MCID) or very close but this was not observed for the 200 µg dose. At Week 24 in Study M/34273/34, greater numerical increases compared to placebo were observed for aclidinium bromide 400 µg than 200 µg in the likelihood of patients achieving a clinically significant improvement in SGRQ Total score and in the change from baseline to Week 24 in SGRQ Total score. The reduction in SGRQ Total score observed with aclidinium bromide 400 µg in Study M/34273/34 was of a magnitude considered to be clinically significant (that is, at least 4.0 units). This dose response relationship was not seen in Studies LAS-MD-33 or LAS-MD-38 Part A; an observation which may reflect the relatively short duration of these studies for evaluation of this efficacy measure. Greater numerical increases compared to placebo in the changes from baseline in SGRQ Total score with the 400 µg dose than with the 200 µg dose were observed in the pooled analysis of Studies M/34273/34 and LAS-MD-33. Aclidinium bromide 400 µg and 200 µg were associated with statistically significant reductions in exacerbation rate of approximately 30% (exacerbations defined on basis on Health Resource Utilisation or EXACT). COPD exacerbations were categorised by severity and defined as increased COPD symptoms of at least 2 consecutive days requiring one of the following:

1. increased rescue medications and/or inhaled corticosteroid use (mild exacerbation);
2. treatment with antibiotics and/or systemic corticosteroids (moderate exacerbation), or
3. hospitalisation or emergency room treatment (severe exacerbation).

Exacerbation results from the six-month Study 34 suggested a decrease in exacerbations with aclidinium bromide treatment. Results from the 3 month studies were less consistent although this variability may be due in part to a low background rate of exacerbations overall.

Long-term efficacy of proposed dose

The treatment duration of the 3 long term studies (LAS-md 35, LAS-md-36 and LAS-md-38B) were consistent with ICH E1 "*Population Exposure: The Extent of Population Exposure to Assess Clinical Safety*" (CPMP/ICH/375/95). Results of the 6 month pivotal Study M/34273/34 demonstrated consistent improvements with proposed dose of 400 µg BD in terms of bronchodilation (in trough FEV1, peak FEV1) and symptoms (TDI score and SGRQ total score) over the 24 week treatment duration. The results of the pivotal Study M/34273/34 provide no indication of tachyphylaxis with aclidinium bromide when administered over a 6 month treatment duration. Supportive evidence for persistence of efficacy is obtained from long term studies LAS-MD-35, LAS-MD-36 and LAS-MD-38 Part B. Across all three long term studies, increases from baseline in trough FEV1 showed some decline over the treatment period, an observation which is likely to reflect the known decrease in FEV1 that occurs over time in patients with COPD rather than a diminution of the efficacy of aclidinium bromide. Studies LAS-MD-35 LAS-MD-36 and LAS-MD-38 Part B provide evidence for the persistence of efficacy of aclidinium bromide over time and

support the observations from pivotal Study M/34273/34 that there is no loss of efficacy with prolonged administration.

Efficacy in subgroups

Evaluation of the pooled population comprising Studies M/34273/34 and LAS-MD-33 showed no statistically significant differences in the magnitudes of the adjusted mean treatment differences between aclidinium bromide and placebo based on sex (male or female), age group (<60 years, 60 years to 69 years or ≥70 years), BMI group (obese, pre-obese or normal weight/ underweight), COPD severity (mild/moderate or severe/very severe), smoking status (current smokers or ex-smokers), bronchodilator reversibility (reversible or non-reversible) or concomitant use of ICS (using ICS or not using ICS). Similar observations were made with the pooled population comprising studies LAS-MD-33 and LAS-MD-38 Part A with the exception of smoking status (increased treatment effect of the 400 µg dose and reduced treatment effect of the 200 µg dose in current smokers) and bronchodilator reversibility (reduced efficacy in non-reversible patients)

Justification for the proposed 400 µg BD dose

Dose selection and dosing frequency selection for aclidinium bromide were based on previously conducted studies that evaluated a dose of 200 µg once daily and two additional studies, Study 23 and Study 29 that used tiotropium and formoterol for benchmark comparison. Data generated from these studies support a twice daily dosing frequency and the 400 µg twice daily dose demonstrated a greater change in trough FEV1 and time profile serial FEV1 measurement compared to lower doses of 100 µg and 200 µg twice daily (Study M/34273/29). The 400 µg twice daily doses in these studies generally performed better than lower doses and in a similar range to the two active comparators; formoterol 12 µg in Study 29 and tiotropim 18 µg in Study 23. Based on these data and previous experience with the 200 µg once daily dose (200 µg may be suboptimal and that night time bronchodilation achieved with once daily morning dose of aclidinium bromide may be insufficient), the selection of the 400 µg twice daily dose for further evaluation in confirmatory Phase III studies was reasonable.

However, there was no study directly comparing QD and BD dosing of proposed dose of 400 µg aclidinium bromide which is particularly important considering the fact that 400 µg QD showed a clinically relevant improvement in trough FEV1 after 4 weeks treatment in Phase II Study M/34273/22.

In all three pivotal Phase III BD studies, a statistically and clinically significant increase from baseline in morning trough FEV1was observed for aclidinium bromide 400 µg BD compared with placebo. The effect size for the 400 µg twice daily dose ranged from 72 ml to 124 mL across the three studies at Week 12, and the treatment effect appeared to persist when assessed at Week 24 in Study 34. The 200 µg twice daily dose also demonstrated a statistically significant difference from placebo, although the magnitude of the treatment difference was 51 to 86 mL which was smaller than the effect size observed for the 400 µg twice daily dose. Other spirometry based efficacy variables such as peak FEV1 and time profile serial FEV1 curve also support 400 µg twice daily as the appropriate bronchodilator dose for aclidinium bromide. The change from baseline in the SGRQ total symptom score was assessed as another efficacy variable in the three confirmatory studies. Greater decreases in total score were observed for aclidinium bromide compared to placebo and were generally supportive of efficacy but only Study 34 demonstrated a treatment difference between the 400 µg twice daily dose and placebo that exceeded the minimum clinical important difference (MCID) threshold of a 4 unit change.

Limitations of data submitted

There was no study directly comparing QD and BD dosing with proposed dose of 400 µg aclidinium bromide which is particularly important considering the fact that 400 µg QD showed a clinically relevant improvement in trough FEV1 after 4 weeks treatment in Phase II Study M/34273/22.

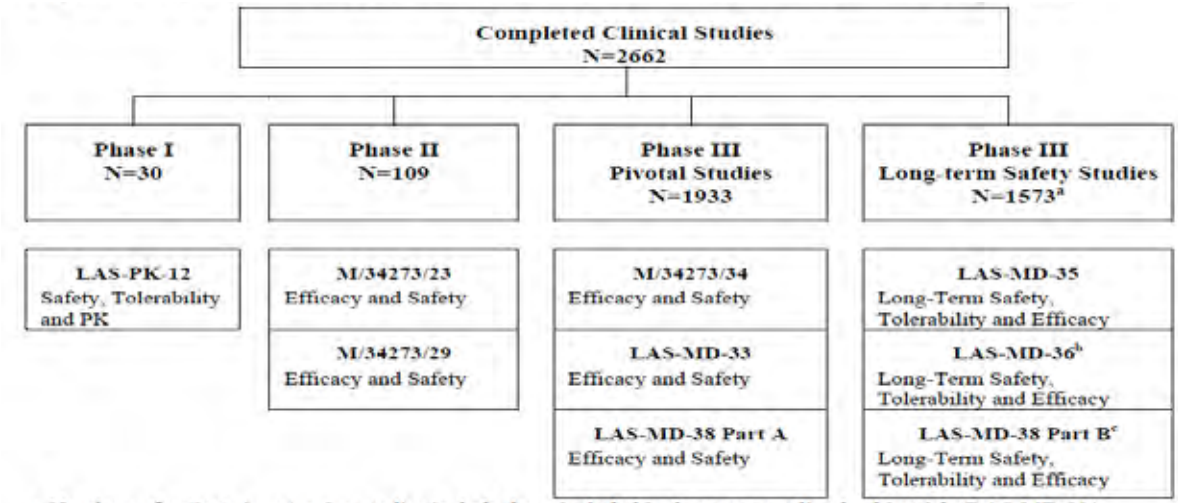
Change in smoking status, tobacco exposure and use of nicotine replacement therapy (as an aid to smoking cessation) were not recorded in the pivotal studies and its potential effect on efficacy outcomes was not evaluated.

Safety

Studies providing safety data

Two separate clinical development programs of aclidinium bromide were conducted between 2000 and 2011, both in patients with moderate to severe COPD. The latter development program investigated the efficacy and safety of aclidinium bromide BD (Figure 3) while the earlier program investigated the efficacy and safety of aclidinium bromide 200 µg QD (Figure 4). Both programs also included Phase I studies in healthy subjects.

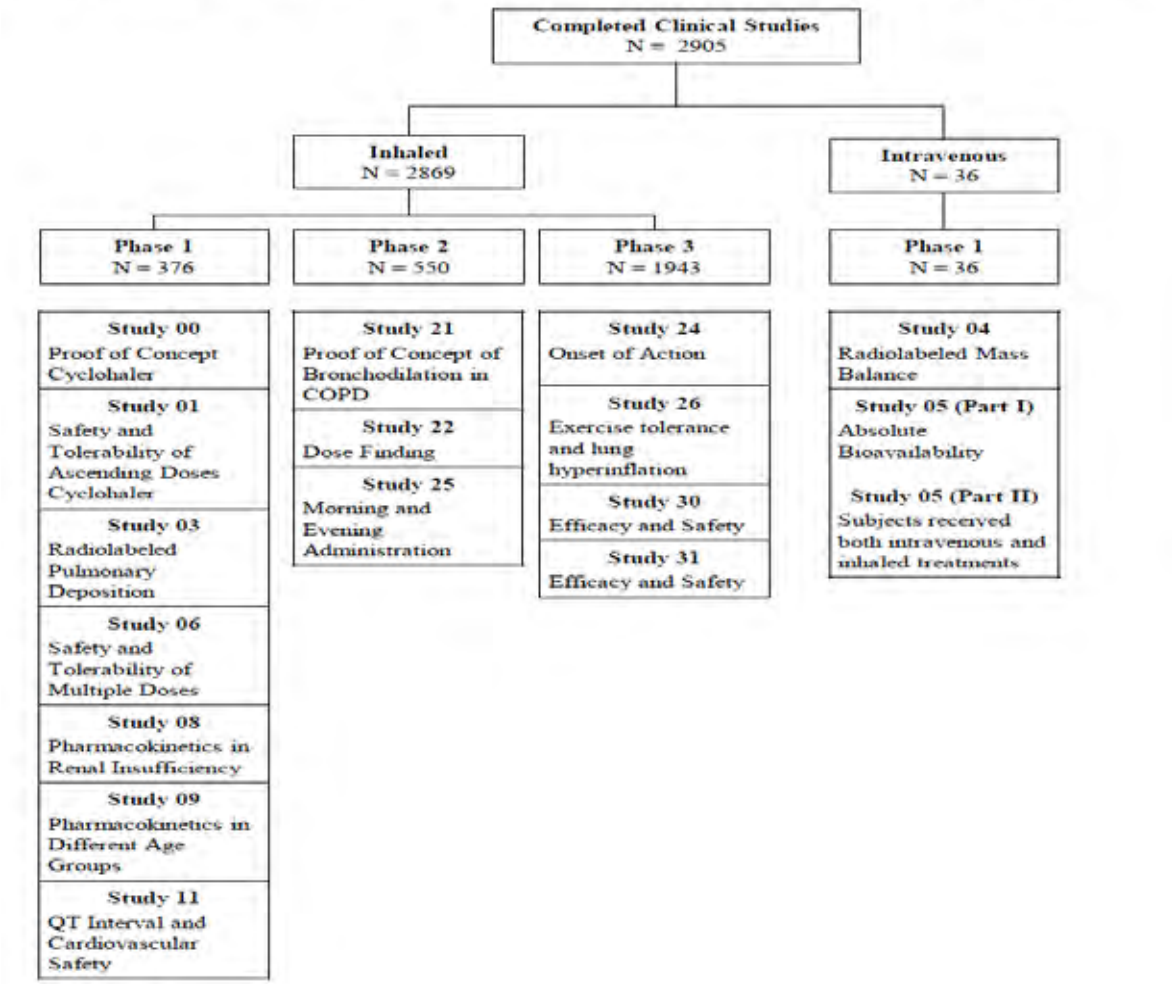
Figure 3. Overview of aclidinium bromide BD clinical program



a Numbers of patients in extension studies include those included in the corresponding lead-in trials (LAS-MD-33/ LAS-MD-36 combined and LAS-MD-38A/ LAS-MD-38B combined).
b LAS-MD-36 was an extension study of pivotal study LAS-MD-33. A total of 561 patients were randomised in Study LAS-MD-33; 291 of the 561 patients subsequently enrolled in the extension study, LAS-MD-36.
c LAS-MD-38 (Part B) was a continuation study of pivotal study LAS-MD-38 (Part A). A total of 544 patients were randomised in Study LAS-MD-38 Part A; 448 of the 544 patients were enrolled in the second part of the study, LAS-MD-38 Part B.

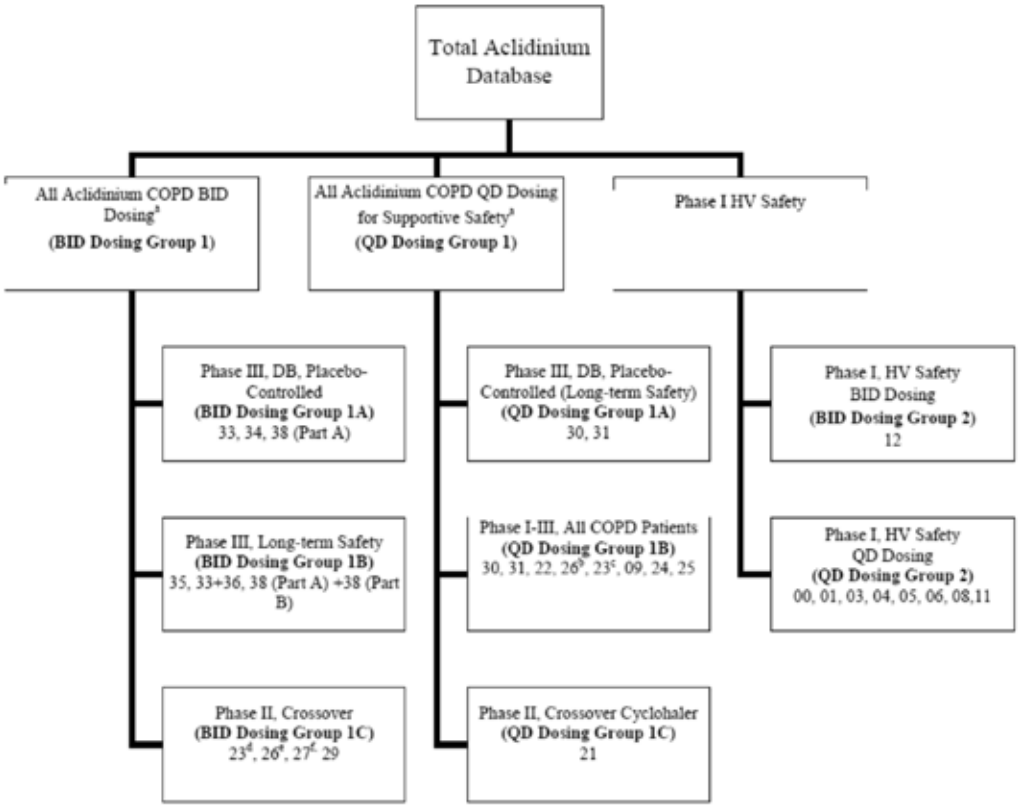
BID = twice daily; N = number of randomised patients/healthy subjects; PK = pharmacokinetics.

Figure 4. Overview of aclidinium bromide QD clinical program



The primary evidence of the safety of aclidinium bromide BD is derived from the pooled analysis of the 3 double blind, placebo controlled, parallel-group Phase III studies, (M/34274/34, LAS-MD-33, and LAS-MD-38 Part A referred to as "Pivotal Study Population" or BD Group 1A) conducted in patients with moderate to severe COPD. 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 the pooled data from the 3 long term safety studies (LAS-MD-33 and LAS-MD-36 combined; LAS-MD-38 Part A and Part B combined, and LAS-MD-35) referred to "Long-term Study Population" of BD Group 1B (Figure 5). Additional supportive data from the BD clinical program is provided by a single completed Phase I, single-blind, placebo controlled, parallel group, dose-escalation, safety, tolerability and PK study (LAS-PK-12) conducted in 30 healthy volunteers. The size of the safety database is adequate.

Figure 5. Study groupings for the Integrated summary of safety



a. Data are integrated for exposure analyses only (BID separate from QD)
b Study listed as 26 in QD Dosing Group 1B is Study LAS-MD-26
c Study listed as 23 in QD Dosing Group 1B is Study M/273FO/23
d Study listed as 23 in BID Dosing Group 1C is Study M/34273/23
e Study listed as 26 in BID Dosing Group 1C is Study M/40464/26
f Study listed as 27 in BID Dosing group 1C is Study LAC-MD-27
BID = twice daily; COPD = chronic obstructive pulmonary disease; DB= double-blind; HV = healthy volunteers; QD = once daily.

Patient exposure

Overall, inhaled aclidinium bromide (at any dose and dose regimen) has been evaluated in 2341 healthy adult subjects and 4344 patients with COPD. A total 2879 COPD patients were treated in clinical trials of aclidinium bromide BD. Of these, 2419 patients received at least one dose of aclidinium bromide BD. Of the 1471 patients treated with proposed dose of aclidinium bromide 400 µg, 970 patients were treated for at least 6 months and 387 patients were treated for at least one year. The extent of exposure at the time of submission meets the minimum of number of patients required for safety evaluation by the relevant by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline.[19] Additionally, a total of 2568 COPD patients were included in studies of aclidinium bromide QD of whom 1925 patients received aclidinium bromide QD for at least one day; 1066 patients received aclidinium bromide 200 µg QD for at least 6 months and 767 patients received aclidinium bromide 200 µg QD for one year (Table 7).

[19]ICH E1: The extent of population exposure to assess clinical safety for drugs intended for long-term treatment of Non-life-threatening conditions.

Table 7. Extent of exposure to aclidinium bromide in patients with COPD. Twice daily and once daily administration.

	Twice Daily Administrationa				Once Daily Administration			
		Aclidinium Bromide				Aclidinium Bromide		
	Placebo N = 940	100 µg N= 73	200 µg N= 1173	400 µg N= 1471	Placebo N =819	<200 µg N= 201	200 µg N= 1657	>200 µg N= 91
Overall Treatment Duration (days)								
N	940	73	1173	1471	819	201	1657	91
Mean (SD)	78.1 (61.3)	7.0 (0.2)	169.8 (138.9)	210.6 (137.0)	159.6 (163.5)	28.3 (4.4)	242.8 (159.6)	21.4 (11.7)
Median	85.0	7.0	166.0	179.0	43	29	364	29
Min, Max	1, 200	7, 8	1, 476	1, 463	1, 407	1, 38	1, 435	3, 31
Treatment Duration, n (%)								
≥ 1 Day	940 (100)	73 (100)	1173 (100)	1471 (100)	819 (100)	201 (100)	1657 (100)	91 (100)
≥1 week	927 (98.6)	73 (100)	1158 (98.7)	1451 (98.6)	697 (85.1)	199 (99.0)	1509 (91.1)	66 (72.5)
≥4 weeks	597 (63.5)	0	939 (80.1)	1214 (82.5)	592 (72.3)	171 (85.1)	1383 (83.5)	56 (61.5)
≥12 weeks	516 (54.9)	0	847 (72.2)	1141 (77.6)	366 (44.7)	0	1130 (68.2)	0
≥24 weeks	196 (20.9)	0	564 (48.1)	970 (65.9)	331 (40.4)	0	1066 (64.3)	0
≥36 weeks	0	0	313 (26.7)	679 (46.2)	313 (38.2)	0	1032 (62.3)	0
≥51 weeks[b]	0	0	282 (24.0)	387 (26.3)	215 (26.25)	0	767 (46.29)	0
Total Patient Years of Exposure	201.0	1.4	545.2	848.3	357.9	15.6	1101.5	5.3

a Includes all BID studies, 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 BID dosing regimen, except LAS-PK-12.

b 52 weeks for Once Daily Adminstration

Patients in the extension studies LAS-MD-36 and LAS-MD-38 Part B or cross-over 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 are counted once in each treatment period.

BID = twice daily; COPD = chronic obstructive pulmonary disease; max = maximum, min = minimum.

These studies provide safety data from substantial cumulative exposure to aclidinium bromide totalling 1394.93 patient-years (PY) in the BD program with exposure ranging from 1 week to ≥357 days (≥51 weeks) in duration, and 1122.45 patient-years in the QD program. A total of 1921 patients were included in the Safety Population of the Pivotal Study Population (BD Group 1A) and 1573 patients were included in the safety population of the Long-Term Study Population (BD Group 1B) from which safety data for long term exposure to aclidinium bromide is derived**.** It should be noted that 500 patients who participated in extension studies LAS-MD-36 and LAS-MD-38 Part B and received aclidinium bromide in lead-in studies LAS-MD-33 and LAS-MD-38 Part A, respectively were included in both the Pivotal Study Population and the Long-Term Study Population. The Phase II Population (BD Group 1C) included 300 patients who received aclidinium bromide of whom 197 received aclidinium bromide 400 µg, 173 received aclidinium bromide 200 µg, 73 received aclidinium bromide 100 µg and 299 received placebo. Duration of exposure for all patients in these short term cross-over studies (BD Group 1C) was up to 2 weeks and 74 patients received at least 3 weeks treatment with aclidinium bromide. In general, extent of exposure by subgroup was balanced across treatment groups with the exception of subgroups of patients with severe/very severe COPD and

patients aged 70 years or older who showed higher exposure to aclidinium bromide, in particular to aclidinium bromide 400 µg, than to placebo.

Safety issues with the potential for major regulatory impact

Postmarketing data

Liver toxicity

Although, there was some worsening of abnormal baseline blood chemistry parameters of GGT, glucose and AST at end-of-study, the incidences was low (≤3% for each parameter) and not higher in the aclidinium bromide treatment groups compared to the placebo group. TEAEs of severe intensity were reported for 2 patients in the aclidinium bromide 200 µg dose group (hepatitis C and white blood cell count increased); both events necessitated discontinuation of study drug treatment. There were no cases of 'Hy's Law cases'[20] in any of the clinical studies. Based on data provided, there did not appear to be any safety concerns related to liver toxicity associated with proposed dosing of aclidinium bromide 400 µg BD.

Haematological toxicity

Overall, there was no sign of a higher incidence of new haematology abnormalitites with aclidinium bromide compared to placebo. There was no worsening of baseline haematology abnormalities reported at an incidence above 1% at end-of-study. COPD (exacerbation) was the most frequently reported treatment-emergent adverse event (TEAE) associated with PCS clinical laboratory abnormalities (0.6%, 0.5% and 0.3% with placebo, aclidinium bromide 200 µg and 400 µg, respectively). The PCS clinical laboratory abnormalities associated with COPD (exacerbation) were increases in at least one of neutrophils, lymphocytes and/or white blood cells. Based on data provided, there did not appear to be any safety concerns related to haematological toxicity with proposed dosing of aclidinium bromide 400 µg BD.

Serious skin reactions

None.

Cardiovascular safety

Cardiovascular adverse events are a specific safety event of interest for anticholinergic drugs given the previous findings with tiotropium. To assess cardiovascular safety of aclidinium bromide, an analysis of major adverse cardiac events (MACE) was done. The MACE score is defined as the total number of cardiovascular deaths, nonfatal myocardial infarctions, and nonfatal strokes. The results do not indicate an increased overall MACE score for aclidinium bromide and do not show a definite signal of imbalance for any of the individual categories of events, but the strength of this assessment is limited by the relatively small sample size and a low event rate. Some of the differences seen in the studies were due to only one event, which is not enough to make a definitive conclusion. These data neither confirm nor prove any contribution of aclidinium bromide to cardiovascular risk and interpretation was limited by the limited number of events that

[20] According to the FDA document for Guidance for industry: Drug induced liver injury premarketing clinical evaluation, June 2009, a Hy's law case requires ALL of the following conditions to be satisfied: (1) Drug can cause hepatocellular injury generally shown by a higher incidence of ALT or AST elevations of >3xupper limit of normal (ULN) compared to placebo or a non-hepatotoxic control drug. (2)In a trial subject with such a transaminase elevation, the subject also ahd elevation of total serum bilirubin (TBL) to >2xULN without initial findings of cholestatis (elevated serum alkaline phosphatase) AND (3) No other reason can be found to explain the combination of increased transaminase and TBL, such as viral hepatitis A, B or C, pre-existing acute liver disease or another drug capable of causing the observed injury.

were seen in the program. Furthermore, 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, the proposed PI does state that the safety of these patient groups has not been investigated and aclidinium bromide in these patient groups should be used with caution. Other safety assessments, such as ECGs, Holter monitoring and a thorough QT study, did not show any cardiac safety signals.

Unwanted immunological events

None.

Evaluator's conclusions on safety

Overall, inhaled aclidinium bromide (at any dose and dose regimen) has been evaluated in 2341 healthy adult subjects and 4344 patients with COPD. A total 2879 COPD patients were treated in clinical trials of proposed BD dosing with aclidinium bromide. Of these, 2419 patients received at least one dose of aclidinium bromide BD. Of the 1471 patients treated with aclidinium bromide 400 µg, 970 patients were treated for at least 6 months and 387 patients were treated for at least one year. The extent of exposure at the time of submission meets the minimum of number of patients required for safety evaluation by ICH E1[19]. Additionally, a total of 2568 COPD patients were included in studies of aclidinium bromide QD of whom 1925 patients received aclidinium bromide QD for at least one day; 1066 patients received aclidinium bromide 200 µg QD for at least 6 months and 767 patients received aclidinium bromide 200 µg QD for one year. The size of the safety database is adequate.

Aclidinium bromide 200 µg or 400 µg BD was well tolerated. The overall incidence of AEs was similar in the aclidinium bromide treated groups and the placebo group. Most AEs were mild or moderate in intensity. The incidence of adverse events (AEs) of severe intensity was similar in the aclidinium bromide and placebo groups. The incidence of serious AEs (SAEs) and adverse events leading to premature study discontinuation was similar for aclidinium bromide and placebo treatment groups. The most frequently reported AE (reported in more than 10% of patients) in the Pivotal Study Population and Long-Term Study Population was COPD (exacerbation) which was reported at a lower incidence in the aclidinium bromide treatment groups than in the placebo group in the Pivotal Study Population. Adverse drug reactions observed with aclidinium bromide 400 µg BD are headache, nasopharyngitis, cough, diarrhoea and sinusitis.

The incidence rates per 1000 patient-years (PY) of each of these events in the aclidinium bromide 200 µg and 400 µg groups were lower in the BD Group 1B long term studies than in the BD Group 1A placebo controlled studies suggesting that their frequency does not increase with increasing duration of exposure. Of the treatment-emergent AEs (TEAEs) that were reported with an incidence ≥ 2% in either treatment group, TEAEs of upper respiratory tract infection, diarrhoea, back pain, hypertension and oropharyngeal pain exhibited numerically higher incidences and incidence rates in the aclidinium bromide 400 µg group compared with the aclidinium bromide 200 µg group. Of the common AEs of headache, nasopharyngitis, cough and diarrhoea only diarrhoea was reported with an increased incidence rate in the 400 µg group compared to the 200 µg group in BD Group 1B.

The percentages of patients in BD Group 1B with at least 1 TEAE of severe intensity was slightly higher in the aclidinium bromide 400 µg group compared to 200 µg (200 versus 400 µg: 11.4% versus 12.8%) and COPD (exacerbation) was the most frequently reported severe TEAE (2.5% versus 3.5%). The incidences of individual TEAEs of severe intensity were comparable for the aclidinium bromide 200 µg and 400 µg BD dose groups with the exception of cardiac failure congestive (0% versus 0.5%) and headache (0% versus 0.4%).

The percentage of patients with at least 1 TEAE judged by the investigator to be related to study treatment was higher in the aclidinium bromide 400 µg group compared with the aclidinium bromide 200 µg group; 13.4% versus 10.0%, respectively. TEAEs related to investigational product with an incidence ≥ 1% in either treatment group were dry mouth (200 versus 400 µg: 1.1% versus 1.5%), headache (0.2% versus 1.6%) and cough (0.5% versus 1.1%). The incidence of cardiac failure congestive was low but slightly higher in the aclidinium bromide 400 µg group compared with the 200 µg group (0.4% versus 0.0%).

Cardiovascular adverse events are a specific safety event of interest for anticholinergic drugs given the previous findings with tiotropium. To assess cardiovascular safety of aclidinium bromide, an analysis of major adverse cardiac events (MACE) was done. The MACE score is defined as the total number of cardiovascular deaths, nonfatal myocardial infarctions and nonfatal strokes and results of this analysis have been summarised in Tables 8 and 9.

Table 8. Incidence of patients with MACE: Double-blind, placebo controlled studies of aclidinium bromide administered twice daily to patients with COPD BD Group 1A

Event	Placebo BID N=641 190.6 PY		Aclidinium Bromide 200 µg BID N=644 199.4 PY		Aclidinium Bromide 400 µg BID N=636 198.4 PY	
	n (%)	IR*	n (%)	IR*	n (%)	IR*
MACE Score	4 (0.6)	21.0	2 (0.3)	10.0	2 (0.3)	10.1
CV Death	0	0	1 (0.2)	10.0	1 (0.2)	10.1
Non-fatal myocardial infarction	1 (0.2)	5.2	0	0	0	0
Non-fatal stroke	3 (0.5)	15.7	1 (0.2)	5.0	1 (0.2)	5.0

* IR = incidence of numbers of patients with events per 1000 patient-years
CV = cardiovascular; BID = twice daily; IR = incidence rate; MACE = major adverse cardiovascular events
Studies LAS-MD-33, LAS-MD-38 Part A, and M/34273/34

Table 9. Incidence of patients with MACE in studies LAS-MD-35, LAS-MD-36 and LAS-MD-38 Part B: aclidinium bromide administered twice daily to patients with COPD BD Group 1A

Event	LAS-MD-35				LAS-MD-36				LAS-MD-38 Part B	
	AB 200 µg BID N=311 231.0 PY		AB 400 µg BID N=291 221.1 PY		AB 200 µg BID N=136 109.6 PY		AB 400 µg BID N=153 121.0 PY		AB 400 µg BID N=448 302.2 PY	
	n (%)	IR*	n (%)	IR*	n (%)	IR*	n (%)	IR*	n (%)	IR*
MACE Score	6 (1.9)	26.0	5 (1.7)	18.0	2 (1.5)	15.3	2 (1.3)	13.7	11 (2.5)	36.4
CV Death	0	0	1 (0.3)	4.5	0	0	0	0	2 (0.4)	6.6
Non-fatal MI	4 (1.3)	17.3	2 (0.7)	9.0	1 (0.7)	9.1	1 (0.7)	8.3	5 (1.1)	16.5
Non-fatal stroke	2 (0.6)	8.7	2 (0.7)	9.0	1 (0.7)	9.1	1 (0.7)	8.3	5 (1.1)	16.5

* IR = incidence of numbers of patients with events per 1000 patient-years
CV = cardiovascular; BID = twice daily; COPD = chronic obstructive pulmonary disease; IR = incidence rate; MACE = major adverse cardiovascular events; MI = myocardial infarction.
Studies LAS-MD-35, LAS-MD-36, and LAS-MD-38 Part B

These results do not indicate an increased overall MACE score for aclidinium bromide and do not show a definite signal of imbalance for any of the individual categories of events but the strength of this assessment is limited by the relatively small sample size and a low event rate. Some of the differences seen in the studies were due to only one event which is not enough to make a definitive conclusion. These data neither confirm nor prove any contribution of aclidinium bromide to cardiovascular risk and interpretation was limited by the limited number of events that were seen in the program. Furthermore, 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[21] were excluded from the clinical trials, the proposed PI does state that the safety of these patient groups has not been investigated and aclidinium bromide in these patient groups should be used with caution.

The risk of patients with COPD developing pneumonias, bronchitis or respiratory failure was not increased with aclidinium bromide administration. The incidence of potential anticholinergic adverse events was low with no individual potential anticholinergic adverse event reported in more than 1.7% of patients in any treatment group of the Pivotal Study Population and no individual potential anticholinergic AE was reported in more than 1.1% of patients in the aclidinium bromide 400 µg treatment group. Potential anticholinergic AEs to be reported as adverse drug reactions (ADRs) include dry mouth, dysphonia and tachycardia, although it should be noted that the difference in the incidence of these events between each aclidinium bromide dose group and placebo in the Pivotal Study Population did not exceed 3 patients and therefore the clinical relevance of the observation remains to be determined.

A total of 14 on-treatment deaths were reported in BD Group 1 studies (all studies of aclidinium bromide BD in COPD patients). Of these 14 deaths, 6 were reported in placebo controlled BD Group 1A studies and 8 were reported in the long term safety studies. No deaths were reported in the short term BD Group 1C studies. No dose relationships were observed in the incidence of deaths. The incidence of death (all causes; per 1000 patient-years) in aclidinium bromide clinical trials was consistent with that observed in clinical trials of other medications used in the treatment of COPD. The most common causes of death (by Preferred term (PT)) were in the Cardiac Disorders System organ Class (SOC) (6 of 14 deaths but only 4 of these were adjudicated [by the independent adjudication committee] as cardiovascular deaths according to MACE followed by lung cancer (2 of 14 deaths). The causes of death varied. Some cases appeared unlikely to be related to aclidinium (including lung cancer and sepsis occurring a month after discontinuation) but in other cases causality could neither be confirmed nor ruled out.

The overall percentage of patients reporting at least one TEAE during the first 3 months of treatment in the long term, double blind, placebo controlled studies with aclidinium bromide QD (QD Group 1A studies) was 42.7% for aclidinium bromide 200 µg QD and 45.0% for placebo which was comparable to that observed for the same analysis of the double blind placebo controlled BD Group 1A studies with aclidinium bromide BD (aclidinium bromide 200 µg BD: 45.2%; aclidinium bromide 400 µg BD: 44.8%; placebo: 47.1%).

There was no increase in the overall TEAE incidence with the change from QD to BD dosing and results suggest a lack of a dose response. Comparison of the most commonly reported SOCs and individual preferred terms in these QD and BD analyses also did not reveal a dose response effect.

[21] Heart Failure Functional Classes III and IV as per the New York Heart Association:

Class	Functional Capacity: How a patient with cardiac disease feels during physical activity
I	Patients with cardiac disease but resulting in no limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or anginal pain
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea or anginal pain.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort increases.

The safety data submitted as part of this submission demonstrate that aclidinium bromide 400 µg BD is not associated with significant safety concerns. The pattern of AEs does not differ from that observed for other products of this class.

First round benefit-risk assessment

First round assessment of benefits

The benefits of aclidinium bromide 400 µg BD in the proposed usage are:

Low systemic exposure as inhaled aclidinium bromide has <5% bioavailability resulting from both pulmonary and intestinal absorption.

Low potential for drug-drug interactions: In vitro drug-drug interaction studies indicate that inhaled aclidinium bromide is unlikely to alter the disposition of drugs metabolised by CYP450 enzymes or human esterases or to affect the disposition of co-administered P-glycoprotein substrate drugs. As a consequence of the serious nature of COPD coupled with the likely presence in the COPD population of co-morbid conditions, polypharmacy is common and the availability of additional therapeutic options without potential for drug-drug interactions would be a useful addition to the physicians' armamentarium.

No requirement for dosage adjustment in the elderly or in renally or hepatically impaired populations: No differences in systemic exposure to aclidinium bromide or in the adverse event profile were observed in elderly patients compared to young patients and in patients with renal impairment compared to patients without renal impairment (in Studies M/34273/09 and M/34273/08, respectively). As aclidinium bromide is metabolised by chemical and enzymatic cleavage in plasma, hepatic dysfunction is very unlikely to alter its systemic exposure. There are no special dosage instructions therefore for elderly and patients with renal or hepatic impairment.

The primary evidence of the efficacy of aclidinium bromide is from the 6 month pivotal Study M/34273/34. This study showed aclidinium bromide 400 µg BD to be associated with clinically and statistically significant effects with respect to bronchodilation, symptomatic improvements including exacerbation control and improvements in disease-specific health status. The results of pivotal study LAS-MD-33 were comparable to those of Study M/34273/34. Further evidence of the benefits of aclidinium bromide was to be obtained from pivotal study LAS-MD-38 Part A but due to an imbalance between treatment groups at baseline in lung function and COPD severity in study LAS-MD-38 Part A the sponsor considers that although statistically significant results were obtained for its primary and secondary endpoints, the study may not provide a reliable estimate of the true treatment effect. Supportive evidence of efficacy is derived from Phase II Studies M/34273/23 and M/34273/29 and long term studies LAS-MD-35 and LAS-MD-36.

Principal benefits of aclidinium bromide include:

Bronchodilation: Aclidinium bromide 400 µg BD is associated with clinically significant bronchodilatory effects in the 12 hours following morning and evening administration, which are observed within 30 minutes of the first dose. Peak bronchodilation compared to baseline is achieved within 1 hour to 3 hours following dosing and is maintained for the duration of the study treatment period. Furthermore, Phase II Studies M/34273/23 and M/34273/29 showed the overall bronchodilation of aclidinium bromide 400 µg BD to be broadly comparable to that of commercially available bronchodilators, tiotropium and formoterol.

Dyspnoea (Transitional Dyspnoea Index (TDI[22]) Focal score): A statistically significantly greater percentage of patients treated with aclidinium bromide 400 µg BD compared to placebo had a clinically significant improvement in their breathlessness as assessed by the TDI Focal score (OR 1.7). In addition, the mean increase from baseline to Week 24 in TDI Focal score was of a clinically-significant magnitude.

Disease-specific health status (St. George's Respiratory Questionnaire (SGRQ) Total score[23]): A statistically significantly higher percentage of patients treated with aclidinium bromide 400 µg BD compared to placebo had a clinically significant improvement in disease-specific health status as assessed by the SGRQ Total score (Odds Ratio (OR) 1.9 fold). Treatment with aclidinium bromide 400 µg BD also resulted in a clinically significant improvement from baseline to the end of treatment in SGRQ Total score, compared to placebo.

Maintenance of effect: The bronchodilatory effects of aclidinium bromide 400 µg BD were maintained from Week 1 for the duration of the 24 week study treatment period. The effects on dyspnoea and disease-specific health status were maintained from Week 4 for the duration of the 24 week study treatment period. Supportive evidence for the persistence of efficacy (FEV1 and SGRQ) when aclidinium bromide is administered over a one year treatment period is obtained from long term Studies LAS-MD-35, LAS-MD-36 and LAS-MD-38 Part B.

Daily symptoms and night time and early morning symptoms: Aclidinium bromide 400 µg BD resulted in statistically significant improvements compared to placebo in daily symptoms of breathlessness, chest symptoms and cough and sputum, in night time sputum production and in night time and morning symptoms of breathlessness and cough.

Rescue medication use: Statistically significant reductions with aclidinium bromide 400 µg BD compared to placebo were observed in daily use of rescue medication; an observation which reflects the improvement in symptoms following treatment with aclidinium bromide 400 µg BD.

Exacerbation control: A statistically significant reduction in exacerbation rate of approximately 30% was observed with aclidinium bromide 400 µg BD compared to placebo whether exacerbations were defined according to the validated EXACT daily diary or on the basis of health resource utilisation.

Inhalation device: Aclidinium bromide is administered via the Almirall inhaler, a multidose, device metered, dry powder inhaler whose ease of use was reported by 85% or more of patients in Studies M/34273/30, M/34273/31, M/34273/23 and M/34273/29. The ease of use of the Almirall inhaler may represent an advantage over other devices used for long term bronchodilators. Indeed in Study M/34273/23, 50% preferred the Almirall inhaler to the tiotropium Handihaler®, while 10% preferred the Handihaler® to the Almirall inhaler. In Study M/34273/29, 76% preferred the Almirall inhaler to the formoterol Aerolizer® while 10% preferred the Aerolizer® to the Almirall inhaler.

Good safety profile: Tolerability of medication is a particular challenge in COPD because patients commonly have comorbidities and often receive a number of concomitant medications. There was no increase in the overall TEAE incidence with the change from QD to BD dosing and results suggest a lack of a dose response. Comparison of the most commonly reported SOCs and individual preferred terms in these QD and BD analyses also did not reveal a dose response effect. The safety data submitted as part of this submission

[22] Measures changes in dyspnea severity from the baseline. Rated by seven grades ranging from -3 (major deterioration) to +3 (major improvement). Total score ranging - 9 to + 9. The lower the score, the more deterioration in severity of dyspnea.

[23] Disease-specific instrument designed to measure impact on overall health, daily life, and perceived well-being in patients with obstructive airways disease. Scores range from 0 to 100, with higher scores indicating more limitations.

demonstrate that aclidinium bromide 400 µg BD is not associated with significant safety concerns. The pattern of AEs does not differ from that observed for other products of this class.

First round assessment of risks

The risks of aclidinium bromide 400 µg BD in the proposed usage are:

Lack of a study directly comparing efficacy and safety of QD and BD dosing with 400 µg aclidinium bromide in COPD patients.

Change in smoking status, tobacco exposure and use of nicotine replacement therapy (as an aid to smoking cessation) were not recorded in the pivotal studies and its potential effect on efficacy outcomes was not evaluated.

The cardiac and cerebrovascular safety of other anticholinergic agents has required regulatory discussions in the past. A detailed review of the cardiovascular and cerebrovascular risk associated with aclidinium bromide 400 µg BD has been performed and showed no apparent evidence of an increased cardiovascular or cerebrovascular risk with aclidinium bromide. As 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 have not been included in clinical trials, the EU Summary of Product Characteristics (SmPC) will state that the safety of these patient groups has not been investigated and aclidinium bromide in these patient groups should be used with caution.

Anticholinergic adverse effects: The low bioavailability of inhaled aclidinium bromide suggests a low potential for systemic anticholinergic activity. A thorough review of potential anticholinergic adverse effects in the Pivotal Study Population showed the frequency of individual potential anticholinergic adverse events to be low (≤1.1% with aclidinium bromide 400 µg) and in the range of, or lower than, that reported for other anticholinergic drugs. Few potential anticholinergic adverse events are considered to be ADRs. Furthermore, as patients with symptomatic prostatic hyperplasia, bladder-neck obstruction or narrow-angle glaucoma have not been included in clinical trials the SmPC will state that consistent with the anticholinergic activity of aclidinium bromide it should be used with caution in these patient groups. The co-administration of aclidinium bromide with other anticholinergic drugs has not been studied and is not recommended.

First round assessment of benefit-risk balance

The benefit-risk balance of aclidinium bromide (Bretaris Genuair), given the proposed usage, is favourable.

Overall the benefit-risk profile is considered favourable for aclidinium bromide 400 µg BD given the clinically and statistically significant treatment benefits (as assessed by measures of lung function, symptoms including exacerbations, disease specific health status and exercise tolerance) compared to the identified safety profile. Aclidinium bromide will provide physicians and COPD patients with an effective and safe alternative treatment option for a disease which has limited therapeutic options. Given the serious nature of COPD, the necessity of polypharmacy due to the presence of co-morbid conditions and the highly variable response of patients to treatment, the development of additional pharmacological options, especially those with a good efficacy and safety profile and reduced potential for drug interactions, is necessary.

First round recommendation regarding authorisation

It is recommended that Bretaris Genuair (aclidinium bromide 400 µg twice daily by inhalation) be approved for the long term maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD. However, the approval is subject to incorporation of suggested changes to the proposed PI and satisfactory response to the clinical questions raised in this report (see below).

Clinical questions

Pharmacokinetics

None.

Pharmacodynamics

None.

Efficacy

1. There was no study directly comparing QD and BD dosing with proposed dose of 400 µg aclidinium bromide which is particularly important considering the fact that 400 µg QD showed a clinically relevant improvement in trough FEV1 after 4 weeks treatment in Phase II Study M/34273/22. Why would someone prescribe or use a BD product like aclidinium when a once daily product (tiotropium) and now even Seebri (glycopyrronium bromide) is available, efficacious and generally safe? The sponsors seem to claim that aclidinium reaches therapeutic levels within 2 days, compared to more than a week for tiotropium, and aclidinium resulted in higher night time FEV1s and also lower COPD symptom scores compared to tiotropium. However, the sponsors have not evaluated if a once daily dose of 400 µg would achieve the same effect as there is no direct comparison between twice daily and once daily dosing with 400 µg dose of aclidinium bromide. Could the sponsors please justify lack of such a direct comparison?
2. In the Phase II study M34273/25, the limited bronchodilatory effect during the night following once daily dosing with 200 µg (am) coupled with the known increase in nocturnal cholinergic tone may affect patients' night time/early morning symptom control. Nevertheless, the sponsor considered it unlikely that an increase in aclidinium bromide dose to 400 µg QD would provide clinically relevant night time bronchodilation, given the negligible night time bronchodilation known to be associated with the 200 µg dose QD, and the relatively small increase in predose (trough) FEV1 (approximately 40 mL) between the 200 and 400 µg doses observed in the post hoc analysis of Study M/34273/22. Indeed, it was considered likely that the increase in QD aclidinium bromide dose required to achieve night time bronchodilation could be of a magnitude to compromise the safety profile and that a BD dosing regimen may be the better option.

   The above statement does not seem justified considering the fact that the sponsors have not conducted any study to compare QD versus BD dosing with the 2 doses of aclidinium bromide (200 µg and 400 µg). It would seem that a dose of 400 µg QD be likely to have less safety concerns than BD dosing of the same dose? Could the sponsors please clarify what they mean by the above statement in the Company Study Report (CSR)?

3. Change in smoking status, tobacco exposure and use of nicotine replacement therapy (as an aid to smoking cessation) were not recorded in the pivotal studies and its potential effect on efficacy outcomes was not evaluated. Could the sponsors please provide information on this, especially if any analysis was done to evaluate effect of any change in these parameters on the efficacy outcomes?
4. Two clinical studies of aclidinium bromide 400 µg BD are ongoing; one study to confirm the bronchodilatory profile over 24 hours compared to that of tiotropium (M/34273/39) and a further study to investigate effects on exercise tolerance (M/34273/40). Are any results available from these studies and if they are could the sponsors provide the same for evaluation?

Safety

5. Cardiovascular adverse events are a specific safety event of interest for anticholinergic drugs given the previous findings with tiotropium. To assess cardiovascular safety of aclidinium bromide, an analysis of major adverse cardiac events (MACE) was done. The MACE score is defined as the total number of cardiovascular deaths, nonfatal myocardial infarctions, and nonfatal strokes and results of this analysis have been summarised in Tables 8 and 9). These results do not indicate an increased overall MACE score for aclidinium bromide and do not show a definite signal of imbalance for any of the individual categories of events but the strength of this assessment is limited by the relatively small sample size and a low event rate. Some of the differences seen in the studies were due to only one event, which is not enough to make a definitive conclusion. These data neither confirm nor prove any contribution of aclidinium bromide to cardiovascular risk and interpretation was limited by the limited number of events that were seen in the program. Does the sponsor plan to conduct any postmarketing study to assess the cardiovascular safety of aclidinium bromide?

Second round evaluation of clinical data submitted in response to questions

Details of the sponsor's responses are included in Attachment 2 of this AusPAR. The following is the evaluator's comments on the sponsor's responses.

Evaluator's comments on sponsor's response

Question 1.

The sponsors have stated that twice daily dosing with an 'easy to use' inhaler would provide better 24 hour bronchodilation especially to counter the increase in cholinergic tone at nigh time and this has been confirmed in the new study submitted by the sponsors (M34273/39). Overall, the sponsor's response is acceptable.

Question 2.

The sponsor's response is acceptable.

Question 3.

The CHMP guidelines for '*Clinical investigation of medicinal products in treatment of patients with COPD*' states that formal stratification of patients according to their smoking status (current smokers, ex-smokers) should be performed prior to randomisation. This was not done in any of the pivotal clinical studies for aclidinium bromide. Furthermore, tobacco exposure was not monitored during the study and any change in smoking status did not appear to be documented or reported.

Use of nicotine replacement therapy or other smoking cessation aids such as varenicline was also not documented. The reason provided by the sponsors is not acceptable and this issue remains a limitation of this submission.

Question 4.

These 2 studies have been evaluated. In Study M34273/39, 24 hour bronchodilation with aclidinium bromide 400 µg BD was similar to that of tiotropium OD although there was a trend for better night time bronchodilation with aclidinium bromide and numerically greater improvement in COPD symptoms as well as a greater preference for the Almirall inhaler compared to the Handihaler used for tiotropium.

The aim of 3 week, double-blind, crossover Study M34273/40 was to evaluate the effect of aclidinium bromide 400 µg BD compared with placebo on exercise endurance, hyperinflation (as determined by inspiratory capacity [IC] and body plethysmography parameters. Results from this study showing improvements in exercise endurance, lung hyperinflation and daily physical activity over 3 weeks of treatment with aclidinium bromide 400 µg BD compared with placebo. However, interpretation was limited by crossover nature of the study.

Results of these two studies help to confirm the positive benefit-risk profile of aclidinium bromide and the inclusion of the above statement regarding effects of aclidinium bromide on exercise tolerance in proposed PI also seems justified.

Question 5.

Review of the study protocols of the proposed ASCENT and the PASS study indicate that these 2 postmarketing studies should enable adequate assessment of cardiovascular safety of aclidinium bromide.

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of the response to clinical questions, the benefits of aclidinium bromide 400 µg BD in the proposed usage are unchanged from those identified in the First Round Assessment.

Second round assessment of risks

After consideration of the response to clinical questions, the risks of aclidinium bromide 400 µg BD in the proposed usage are:

- The CHMP guidelines for '*Clinical investigation of medicinal products in treatment of patients with COPD*' states that formal stratification of patients according to their smoking status (current smokers, ex-smokers) should be performed prior to randomisation. This was not done in any of the pivotal clinical studies for aclidinium bromide. Furthermore, change in smoking status, tobacco exposure and use of nicotine replacement therapy (as an aid to smoking cessation) were not recorded in the pivotal studies and their potential effect on efficacy outcomes was not evaluated.
- The cardiac and cerebrovascular safety of other anticholinergic agents has required regulatory discussions in the past. A detailed review of the cardiovascular and cerebrovascular risk associated with aclidinium bromide 400 µg BD has been performed and showed no apparent evidence of an increased cardiovascular or cerebrovascular risk with aclidinium bromide. As 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 have not been included in clinical trials, the SmPC will state that the safety of these patient groups has not been investigated and aclidinium bromide in these patient groups should be used with caution.

- Anticholinergic adverse effects: The low bioavailability of inhaled aclidinium bromide suggests a low potential for systemic anticholinergic activity. A thorough review of potential anticholinergic adverse effects in the Pivotal Study Population showed the frequency of individual potential anticholinergic adverse events to be low (≤1.1% with aclidinium bromide 400 µg) and in the range of or lower than that reported for other anticholinergic drugs. Few potential anticholinergic adverse events are considered to be ADRs. Furthermore, as patients with symptomatic prostatic hyperplasia, bladder-neck obstruction or narrow-angle glaucoma have not been included in clinical trials the SmPC will state that consistent with the anticholinergic activity of aclidinium bromide, it should be used with caution in these patient groups. The co-administration of aclidinium bromide with other anticholinergic drugs has not been studied and is not recommended.

Second round assessment of benefit-risk balance

After consideration of the response to clinical questions, the benefit-risk balance of aclidinium bromide 400 µg BD in the proposed usage is unchanged from that identified in First Round Assessment.

Second round recommendation regarding authorisation

It is recommended that Bretaris Genuair (aclidinium bromide 400 µg twice daily by inhalation) be approved for the long term maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD. However, the approval is subject to incorporation of suggested changes to the proposed PI.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan EU RMP Version 2.3 (dated 24 May 2012, Data Lock Point 1 September 2011) and Australian Specific Annex (dated February 2013) which was reviewed by the TGA's Office of Product Review (OPR).

Contents of the submission

A summary of the Ongoing Safety Concerns as specified by the sponsor is shown in the table below (Table 10):

Table 10. Important identified and potential risks and missing information.

Important identified risks	None
Important potential risks	Cardiac disorders (cardiac failure, MI) Cerebrovascular events (stroke, TIA) Mortality Class effects: anticholinergic, paradoxical bronchospasm from inhaled therapies Paediatric (off-label) use Off-label use in pregnancy and lactation
Important identified and potential interactions with other medicinal products, food and other substances	None
Important Missing Information	Renal and hepatic impairment Non-Caucasian patients (including pharmacodynamic data) Patients with the following concomitant illnesses: • Symptomatic benign prostatic hypertrophy (BPH), bladder neck obstruction, urinary retention or narrow-angle glaucoma. • Newly diagnosed or unstable arrhythmias, recent myocardial infarction, unstable angina or heart failure. Concomitant use of other anticholinergics Patients who have experienced a recent exacerbation Off-label use in adults (including asthma [misdiagnoses, coexisting]) Medication/use of device errors

The sponsor proposes routine and additional pharmacovigilance activities for important identified and potential risks and missing information.

The sponsor proposes routine pharmacovigilance activities for important identified and potential risks and missing information (as stated above). Furthermore, additional activities are planned for some of the risks. These activities are summarised in Table 11.

Table 11. Activities additional to routine planned by the sponsor regarding certain safety concerns.

Additional activity	Assigned safety concern	Actions/outcome proposed	Planned submission of final data
PASS	Cardiac disorders Cerebrovascular events Mortality	To establish a cohort of patients diagnosed with COPD initiating treatment with aclidinium bromide to evaluate the cardiovascular safety concerns and all-cause mortality described in the RMP, through sequential nested case-control studies for each endpoint of interest.	Study protocols to be submitted by September 2012. PASS will start when there are 2,000 prescriptions of aclidinium bromide in the defined database.
DUS	Paediatric (off-label use)	To describe the characteristics of new users of aclidinium	Study protocols: by September

Additional activity	Assigned safety concern	Actions/outcome proposed	Planned submission of final data
	Off-label use in pregnancy and lactation Renal and hepatic impairment Other patient populations excluded from the clinical programme Interaction with other medicinal products Patients who have experienced a recent exacerbation Off-label use in adults	bromide and of other selected COPD treatments, including agents in the same class, regarding age, sex, history of chronic disease including cardiovascular diseases, COPD severity, and prior use of COPD medications and other medications. To describe the patterns of use of aclidinium bromide and other selected COPD treatments, among new users, regarding duration of treatment, dose, switching patterns, and use of concomitant medications To evaluate the potential off-label use of aclidinium bromide in adults and children To identify and describe users of aclidinium bromide in patient subgroups for which there is missing information in the RMP To establish the core of a cohort of new users of aclidinium bromide for the future evaluation of safety concerns described in the RMP	2012. Phase I analysis: second half of 2013 or first half of 2014 (time period will be adjusted based on use in the target countries) Phase II analysis: 1 year after the phase 1 analysis
Clinical development in Japanese and Korean patients	Non-Caucasian patients (including pharmacodynamic data)		

The sponsor proposes routine risk minimisation activities for identified risks, important potential risks and missing information.

The presentation of the sponsor's written submission was considered acceptable.

Reconciliation of issues outlined in the RMP report

It is considered that the sponsor's response to the TGA's request for further information has only partially addressed the issues identified in the RMP evaluation report. The RMP evaluator also recommended PI changes but the details of these are beyond the scope of this AusPAR. The outstanding issues are specified below. Additional issues have been raised by the nonclinical evaluator.

Table 12 summarises the OPR's first round evaluation of the RMP, the sponsor's responses to issues raised by the OPR and the OPR's evaluation of the sponsor's responses.

Table 12. Reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	OPR evaluator's comment
Long term safety (more than 12 months) should be added as Important Missing Information.	*The aclidinium bromide Phase III clinical development program consisted of 3 key long term safety studies as follows:* *LAS-35 [NCT01044459] which consisted of a randomised, double blind, multicentre study of 52 weeks duration* *LAS-8B [NCT01045161] which consisted of an open-label treatment continuation of the 12-week ACCORD COPD II study and ran for 52 weeks* *LAS-36 [NCT00970268] which consisted of an open-label extension of the 12-week ACCORD COPDI study and ran for 64 weeks* *In addition, a double blind, randomized, placebo controlled, parallel group, phase IV study to evaluate the effect of aclidinium bromide on long term cardiovascular safety and COPD exacerbations in patients with moderate to very severe COPD (ASCENT COPD) is being conducted in US to assess the safety of aclidinium bromide on major adverse cardiovascular events (MACE), the overall safety of aclidinium bromide and whether aclidinium bromide reduces moderate or severe chronic obstructive pulmonary disease (COPD) exacerbations. A total of 4000 COPD patients will be included*	It is noted that the sponsor refers to ASCENT COPD (NCT01966107) which is not conducted by A Menarini. If A Menarini were able to access all data generated by this trial, were able to report regularly on results through PSURs or otherwise, provide a final study report, and use the data to inform updates to RMPs, this would be considered acceptable.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	OPR evaluator's comment
	in this clinical trial and they will be treated to a maximum of 36 months. The first patient included in this trial was on 16th October 2013. *Besides, the overall pharmacovigilance plan includes a drug utilisation study (DUS) that will cover aspects related to drug utilisation, off-label use, and identification of patient groups with missing information in the RMP.* *As more patients increase the size of the cohort of patients with diagnosed COPD a post authorisation safety study (PASS) will be conducted in the EU to assess the potential cardiovascular safety concerns described in the risk management plan (RMP) for aclidinium bromide. The cohort will include patients initiating treatment with aclidinium bromide, tiotropium, glycopyrronium bromide, fixed-dose combinations of LABA+ICS or LABAs. The sponsor will evaluate whether the use of aclidinium bromide is associated with increased risk of all-cause mortality and cardiovascular events such as congestive heart failure (CHF); acute myocardial infarction, including out-of-hospital coronary heart disease (CHD) death ("AMI"); and stroke. Four sequential nested case-control studies will be conducted to compare the risk of each study endpoint in new users of aclidinium bromide, tiotropium, glycopyrronium bromide, and LABA+ICS with the risk in users of LABAs and between users of aclidinium bromide and users of each of the other study medications.*	

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	OPR evaluator's comment
The study protocol synopses submitted are considered acceptable in regard to the assigned safety concerns for RMP purposes. However, the sponsor is advised to submit the expected dates of availability of the final reports.	*The sponsor submitted the expected dates of availability of data from the PASS and DUS studies.*	This is considered acceptable.
Given the target population is likely to suffer from some form of cardiovascular disease as a co-morbidity, given that cardiac events and cerebrovascular events are classified Important Potential Risks and given that aclinidium will likely to be widely used, it is necessary to conduct a clinical trial to investigate these safety concerns further.	*'Routine Pharmacovigilance monitoring and additional post-authorisation studies (ASCENT clinical trial and EU PASS) are designed to monitor this safety concern. (see above question 2)'*	This is considered acceptable, if the ASCENT COPD trial becomes part of the pharmacovigilance plan, and if 'cardiac events' and 'cerebrovascular events' are both assigned to the ASCENT COPD trial in the pharmacovigilance plan, and if the RMP is updated accordingly.
The sponsor should conduct an additional pharmacovigilance activity, or assign an existing activity, that assesses the safety of aclidinium beyond 12 months.	*'Routine post marketing PV will be conducted alongside the PASS and DUS in the EU, and the ASCENT clinical trial in US to monitor any treatment emergent concerns should they arise. (see above question 2)'*	This is considered acceptable, if the ASCENT COPD trial becomes part of the pharmacovigilance plan.

The sponsor was advised to incorporate the PI changes recommended by the nonclinical evaluator.

In regard to the proposed routine risk minimisation activities, the OPR evaluator also recommended to the Delegate that the draft product information document be revised. The details of these recommendations are however beyond the scope of this AusPAR.

Summary of recommendations

ASCENT COPD trial

The ASCENT COPD trial should become part of the pharmacovigilance plan. 'Cardiac events' and 'cerebrovascular events' should both be assigned to the ASCENT COPD trial in the pharmacovigilance plan. The sponsor should report on data generated by this trial

through PSURs or otherwise, provide a final study report, and use the data to inform updates to RMPs.

However, if the sponsor does not have access to all the data generated by the ASCENT COPD trial (as it is conducted by a different sponsor), other relevant pharmacovigilance activities as outlined in the RMP Evaluation Report should be conducted.

Suggested wording for conditions of registration

RMP

Implement EU-RMP Version 2.3 (dated 24 May 2012, Data Lock Point 01 September 2011) and Australian Specific Annex (dated February 2013) and any future updates (where approved) as a condition of registration.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

Aclidinium bromide is formulated as an inhalation powder and is comprised of a mixture of micronised aclidinium bromide and a-lactose monohydrate; the latter functions as a carrier. The mixture is delivered by the Genuair inhaler device, a non-refillable, breath actuated, multi dose, metered, DPI device.

Each metered dose contains 343 µg of aclidinium (as the bromide), which is equivalent to a metered dose of 400 µg aclidinium bromide (based on in vitro testing at a flow rate of 60 mL/min for 2 s). Each delivered dose (the dose leaving the mouthpiece) contains 322 µg of aclidinium equivalent to 375 µg of aclidinium bromide; (approximately 20 µg is lost in the device under standard testing conditions). The recommended dose of aclidinium is one inhalation of 322 µg aclidinium twice daily.

The powder for inhalation is isolated within the inhaler in a cartridge reservoir. The inhaler is white coloured with an integral dose indicator and a green dosage button. The mouthpiece is covered with a removable green protective cap. The inhaler is supplied sealed in a protective aluminium laminate pouch, placed in a cardboard carton.

The Genuair inhaler is a propellant free metered dose inhalation device. The Genuair inhaler does not appear to have been previously approved by the TGA for any other drug products.

The evaluator mentions the following: *'The quality of the drug product is controlled by a specification that includes limits for: the content of aclidinium bromide per cartridge; the levels of degradants and total impurities in the powder; the uniformity of the delivered dose; the mean delivered dose and the fine particle dose. The microbial content of the powder is also adequately controlled'*.

Device robustness was assessed for functionality and found to be acceptable.

Stability data were provided to support a shelf life for the product of 36 months when it is stored in the proposed packaging (the dry powder inhaler is contained in a heat sealed aluminium pouch) below 30ºC. Stability testing has also demonstrated that an in use period of 90 days from opening the pouch is justified.

This submission has not been considered by Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM).

Overall, the evaluator recommends approval from a chemistry and quality control perspective.

Nonclinical

Primary pharmacology

Aclidinium bromide is a competitive muscarinic receptor antagonist with subnanomolar affinity across all five human muscarinic receptor subtypes and this was seen in a series of in vitro studies. The two main metabolites (hydrolysis products) and the drug's other enantiomer (S-enantiomer; not included in the active ingredient) do not possess significant antimuscarinic activity. 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.

In vivo, long lasting antagonism of acetylcholine induced bronchoconstriction by inhaled aclidinium bromide was demonstrated in guinea pigs and dogs and was shown to be equally effective compared to tiotropium and ipratropium.

The evaluator mentions that, *'no clinically significant off-target activity was found for aclidinium bromide or its main metabolites in secondary pharmacology studies. Safety pharmacology studies covered the CNS, cardiovascular, respiratory, renal and gastrointestinal systems, with classic anticholinergic effects observed (for example, tachycardia, dry mouth and decreased GI motility). Inhibition of the hERG K+ channel did not occur at clinically relevant concentrations'*. These studies also included ipratropium and tiotropium. The results suggest that aclidinium bromide is less likely to induce urinary retention, dry mouth and/or constipation than tiotropium bromide or ipratropium bromide.

Pharmacokinetics

Rapid absorption of aclidinium bromide after inhalation was shown in laboratory animal species and humans. Hydrolysis (mediated both enzymatically and non-enzymatically) gives rise to the two main metabolites, found in all species. The drug's carboxylic acid metabolite is the major circulating component but unchanged drug is chiefly present in lung. Metabolism by CYPs was minor. There were no unique human metabolites. Limited tissue distribution after intratracheal administration was shown in rats and penetration of the blood-brain barrier in the species was low. Mass-balance studies using ^{14}C aclidinium bromide were conducted in mice, rats, pregnant rabbits, dogs and humans. The major route of excretion was generally the urine after intravenous administration. With PO and intratracheal administration, the main route of excretion was faeces, with the exception of dogs given intratracheal [glycolyl-U-^{14}C]-aclidinium bromide where elimination of radioactivity was predominantly via the urine.

Acute toxicity

Aclidinium bromide had a 'low order' of acute toxicity via the inhalational route in rats.

Repeat dose toxicity

Pivotal repeat-dose toxicity studies were conducted in rats (6 months) and dogs (9 months) using the inhalational route; the major target organs for toxicity identified with inhalational administration were respiratory tract tissues (nasal cavity, larynx and lung), the Harderian gland (no analogous human gland) and the parotid gland with changes also observed in the liver. Effects on the eye and heart were also seen. The effects in the lung

tissue were considered to be exaggerated pharmacological effects. There were also supporting studies using other routes of administration involving mice, rats and dogs. Safety margins for the proposed clinical dose, (maximum tolerated dose) identified from these studies were deemed to be adequate.

Genotoxicity

In vitro genotoxicity studies showed negative, equivocal or weakly positive results. However, in vivo studies were negative for genotoxicity. Carcinogenicity studies in mice and rats, conducted by the inhalational route revealed no tumourigenicity at very high multiples of the clinical plasma AUC and high or very high multiples of the lung deposited dose.

Reproductive toxicity

Aclidinium bromide and or its metabolites crossed the placenta and were excreted in rats. Fertility was reduced in males and female rats with high doses. There was delayed ossification seen in rats and reduced foetal weight in rabbits. Teratogenicity was not observed in either species. Postnatal bodyweight gain was reduced in the offspring of rats treated with aclidinium bromide during gestation and lactation.

Local tolerance and antigenicity

Local tolerance and antigenicity studies were negative in rabbits, mice and guinea pigs.

Nonclinical recommendation

The evaluator recommends approval from a nonclinical point of view. Some PI amendments were recommended.

Clinical

Pharmacokinetics

There are 4 single dose studies and 2 multidose studies on healthy volunteers as well as 3 studies on patients.

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 postdose. Aclidinium bromide plasma exposure increased with increasing single inhaled doses up to 4200 µg; and exhibited linear and time independent pharmacokinetic behaviour following multiple dose inhaled administration of 200 µg or 400 µg once day (QD) or 200 µg, 400 µg or 800 µg twice a day (BD). Aclidinium bromide has a low absolute bioavailability.

Bioequivalence

The formulation of the DPI was unchanged during the development process. However, the inhalation device varied. Early studies were conducted using a CyclohalerR capsule based inhalation device. All subsequent trials used the Almirall inhaler which was developed as an improved version of the marketed Novolizer DPI (the latter is marketed for use in delivery of salbutamol, budesonide and formoterol in Europe). The proposed Almirall device (to be marketed as Genuair) used for delivery of aclidinium is a modification of this marketed Novolizer device.

No clinical trials were performed with the marketed Novolizer. Therapeutic equivalence between the CyclohalerR device and the Almirall inhaler was not demonstrated as the CyclohalerR was used as the delivery device for early exploratory studies only. The

evaluator mentions that several modifications were made to the Almirall inhaler during the course of development. However, it is stated that, '*in vitro data demonstrate that the iterative development of the Almirall inhaler during the full development process of aclidinium bromide did not affect its aerodynamic performance*'. The evaluator opines that '*the clinical efficacy results obtained with the different Almirall inhaler prototypes can be compared across trials*'. These studies also showed that the aerodynamic behaviour of aclidinium bromide DPI within the Almirall inhaler device was independent of flow rate over the range likely to be generated by the patients using the device.

Distribution

Following intravenous administration of 25 µg to 400 µg aclidinium bromide in study M34273/05, the mean apparent volume of distribution increased (with ascending dose from 200 µg to 400 µg) from 140 to 302 L. The results were highly variable and the evaluator attributes the differences to, '*the small number of subjects per dose level rather than to changes in this parameter (Coefficient of variation of 81% and 79% with the 200 µg and 400 µg intravenous doses, respectively)*'.

Protein binding

The inactive metabolites of aclidinium bromide were highly protein bound with the acid metabolite (LAS34850) demonstrating a protein binding of 87% and the alcohol metabolite (LAS34823) demonstrating a protein binding of 15%. Protein binding of the parent aclidinium bromide could not be ascertained owing to the rapid metabolism in plasma.

Tissue distribution was examined in one Phase I study (M34273/03) in 12 healthy males where the mean whole lung deposition was 30%. The mean peak inhaled flow rate generated in this clinical study was 79 L/min rather than the targeted value of 90 L/min.

The evaluator mentions that, '*in the breath actuated DPI, drug delivery is likely to be dependent on the peak inhaled flow rate achieved by the subject. Maximum inspiratory effort and high peak inhaled flow (PIF) rate may be required to ensure that de-aggregation of drug particles and the separation of drug particles from carrier particles is as efficient as possible which allows lung deposition to be optimal. The PI and CMI should give adequate instructions so that there is adequate PIF*'.

Metabolism

The mass balance study (M/34273/04) confirmed that aclidinium bromide was rapidly hydrolysed in plasma to an alcohol (LAS34823) and acid metabolite (LAS34850). The evaluator mentions that in vitro studies confirmed minimum activity of CYP450 isozymes in the clearance of aclidinium bromide. As no additional metabolite in significant quantity was observed, it may be concluded that almost the entire dose of aclidinium bromide was eliminated by hydrolysis to its alcohol (LAS34823 cation) and acid (LAS34850 free acid) metabolites. Aclidinium bromide is rapidly metabolised in plasma so that only 0.1% of the dose, administered by inhalation, is excreted in the urine. The metabolites are mainly excreted in the urine, some unchanged (30-50%) and the rest after further hydroxylation. Approximately 30% of the metabolites are excreted in the faeces.

Dose proportionality

The evaluator discussed 2 single dose studies (M/34273/01 and M/34273/05) and a multidose study (M/3427/06). Dose proportionality was not seen in relation to aclidinium bromide or its metabolites in relation to C_{max} or AUC in doses up to 4800 µg (M/34273/01). In Study M/34273/05 dose proportionality was seen at 50 to 300 µg (where it reached a plateau). In the multidose study there was an increase observed although it was less than dose proportional. There was no accumulation seen in this study after twice daily dosing for 7 days.

Pharmacokinetics in COPD

This was studied in M/34273/09 where 200 µg or 400 µg QD was administered over 3 days. Based on C_{max}, $AUC_{(0-t)}$, AUC and AUC_{τ} there were no differences in the rate and extent of exposure between age group, dose level or day. $AUC_{(0-t)}$ and C_{max} for aclidinium bromide appeared to increase in a dose-proportional manner on both days in the young and elderly. The evaluator states that the pharmacokinetics following the dose proposed for marketing has not been studied in this submission.

Renal impairment

This was investigated in M34273/08 where single inhaled doses of aclidinium bromide 400 µg in subjects with normal renal function and with mild, moderate and severe renal impairment was administered. The $AUC_{(0-t)}$ was similar across the groups of patients with mild to severe renal impairment and higher than in the healthy controls. The half-life ($t_{1/2}$) and the elimination rate constant were higher in the renally impaired groups compared with the healthy subjects; the apparent total plasma clearance (Cl/f) tended to be lower. The pattern was similar with the metabolites.

The evaluator mentions that, *'considering the wide therapeutic index of aclidinium bromide (inhaled doses up to 6000µg [30-fold the expected therapeutic dose] have been safely administered to healthy subjects), and the safety, tolerability and PK results found in the present study, it can be concluded that the PK behaviour of aclidinium bromide and its two main inactive metabolites is not altered to a clinically significant extent in subjects with impaired renal function. As such, a dosage adjustment in patients with mild, moderate or severe renal impairment is not needed'*.

It was considered that a single dose study was sufficient and was in accordance with the relevant EU Guideline[24] that states that this is sufficient when the drug exhibits linear and time independent pharmacokinetics.

Hepatic impairment

No study was conducted. Since hepatic metabolism plays an insignificant role in the clearance of aclidinium bromide, the lack of such a study is considered acceptable.

Pharmacokinetics according to age

This was investigated in M/34273/09 where doses of 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. The overall exposure of the elderly group was not increased compared to the young at the dose levels investigated. Whilst the acid and alcohol metabolites showed a higher exposure in the elderly, they are unlikely to be clinically relevant as the metabolites are inactive.

Pharmacokinetic interaction studies

None were submitted. The evaluator states that based on the metabolism of aclidinium bromide and the results of in vitro studies it could be concluded that the potential to interact is low. In addition, the systemic absorption is low and it is very rapidly metabolised. Metabolisms via CYP450 and P glycoprotein have limited impact on the pharmacokinetics of aclidinium bromide; drugs that are substrates or metabolised via these pathways are unlikely to affect aclidinium bromide.

Pharmacodynamics

Three studies (M/34723/00, M34273/21 and M34273/11A) were discussed.

[24]CHMP/EWP/ 225/02. Note for Guidance on the evaluation of the pharmacokinetics of medicinal products in patients with impaired renal function.

Study M/34723/00 which was a pilot study showed that aclidinium bromide is effective in improving specific airway conductance and reducing bronchial hyper-responsiveness.

In relation to M34273/21**,** a Phase II, single ascending dose, placebo controlled, crossover study in 17 COPD male patients, there was statistically significant improvement in the 4 spirometric parameters measured (forced expiratory volume in 1 second (FEV1), Forced expiratory ratio (FVC), peak expiratory flow rate (PEFR), forced expiratory flow, mid expiratory phase (FEF_{25-75})) following single inhalation of aclidinium bromide (100 µg, 300 µg and 900 µg). Compared to placebo, all three aclidinium bromide doses showed statistically significant improvement in FEV1 and FVC to suggest the bronchodilatory effect; however, there was no significant difference between the 3 doses although the time to maximal efficacy was faster with 300 µg and 900 µg doses (2 hours) compared to the 100 µg dose (2 hours). The onset of action is fast (15 mins).

Based on these results the sponsor conducted 2 Phase III studies investigating 200 µg QD; in these studies the trough FEV1 was lower than the 100 mL considered to be clinically relevant. Thus, doses of 200 µg and 400 µg BD were carried forward in the second, Phase III development program.

QT prolongation

The Phase I, prospective, multiple dose, randomised, parallel group, placebo and positive controlled study in 272 male and female healthy volunteers (M34273/11) showed that LAS34273 at therapeutic dose (200 µg) or supra therapeutic doses (800 µg) did not produce any clinically relevant effect on individual based corrected QT interval[25] (QTci)/ Fridericia's formula QT correction (QTcF), Bazett QT correction (QTcB)/ QT. The assay sensitivity of the study was confirmed as moxafloxacin 400 µg (positive control) produced significant increase in QT intervals compared with placebo. No evidence of a clinically relevant effect on QTc interval was demonstrated in this study.

Time course for pharmacodynamic effects

In the Phase II study (M34273/21), statistically significant improvements compared with placebo for FEV1 and FVC were observed for all aclidinium bromide single ascending doses (100 µg, 300 µg and 900 µg) from 15 min to 24 hours after single inhalation. The results showed highest degree of reversibility with the dose of 300 µg. The onset of action is fast (15 mins) and efficacy is maintained until 24 to 32 hours postdose for the 300 µg and 900 µg doses supporting a once daily administration dosing regimen. However, this (OD) was shelved as the change in FEV1 was less than clinically relevant.

Comparison of drug delivery devices

The evaluator discusses the findings of a Phase II open-label, cross-over, randomised, placebo dose, medical device trial that evaluated the Peak inspiratory flow (PIF) generated through the Novolizer and HandiHaler dry powder inhalers by 48 patients with moderate and severe COPD (M34273/07). There was a marked higher mean PIF generated through the Novolizer (92.0 L/min) compared to the HandiHaler (46.1 L/min), confirming the lower resistance of the Novolizer. The evaluator states that COPD patients with a wide range of disease (moderate and severe) are able to generate sufficient inspiratory airflow through the Novolizer to reliably inhale the full dose and activate the trigger threshold. For both the moderate and severe COPD groups, the highest and mean inhalation volumes were similar for the Novolizer and HandiHaler (A) and were slightly greater than HandiHaler (B). Based on the study findings, the evaluator opines that, '*COPD patients with*

[25] QT interval: a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. A prolonged QT interval is a risk factor for ventricular tachyarrhythmias and sudden death. The QT interval is dependent on the heart rate (the faster the heart rate, the shorter the QT interval). To correct for changes in heart rate and thereby improve the detection of patients at increased risk of ventricular arrhythmia, a heart rate-corrected QT interval *QTc* is often calculated.

a wide range of disease (moderate and severe) are able to generate sufficient inspiratory airflow through the Novolizer to reliably inhale the full dose and activate the trigger threshold'.

Dose ranging studies

Two Phase II studies were discussed (M/34273/29 and M/34273/23). Study M/34273/29 used a range of doses (100, 200 and 400 µg) and Study M/34273/23 used 400 µg BD only.

They were randomised, double blind, placebo and active controlled crossover studies. The design of the two studies was similar overall but there were also notable differences (see Table 13 below).

Table 13. Design differences in Studies M/34273/29 and M/34273/23

	M34273/23	M/34273/29
Active comparator	Tiotropium 18 µg BD	Formoterol 12 µg BD
Aclinidium dose	400 µg BD	400 µg BD 200 µg BD 100 µg BD
Duration of run in period	5 to 9 days	14 ± 3 days
Duration of treatment period	15 days	7 days
Washout interval	9 days	5 days

The primary efficacy variable was Change from baseline in normalised FEV1 area under the curve (AUC) over the 12 hour (h) period immediately after morning study drug administration (AUC_{0-12}) at Day 7 on treatment. The results are shown in Table 14 and Figure 6 below.

Table 14. Results from Study M/34273/23

Trial M/34273/23 (Day 15)	LS Mean	p-value
A 400 µg versus P	0.221	<0.0001
Tio versus P	0.244	<0.0001
A 400 µg versus Tio	0.023	0.572
Trial M/34273/29 (Day 7)		
A 400 µg versus P	0.208	<0.0001
A 200 µg versus P	0.176	<0.0001
A 100 µg versus P	0.154	<0.0001

Trial M/34273/23 (Day 15)	LS Mean	p-value
F versus P	0.210	<0.0001

A=aclidinium; F=formoterol 12 µg BD, p=placebo; tio=tiotropium; p-values from ANCOVA analysis.

Figure 6. Data from Study M/34273/23 Trial M/34273/23 (Day 15)

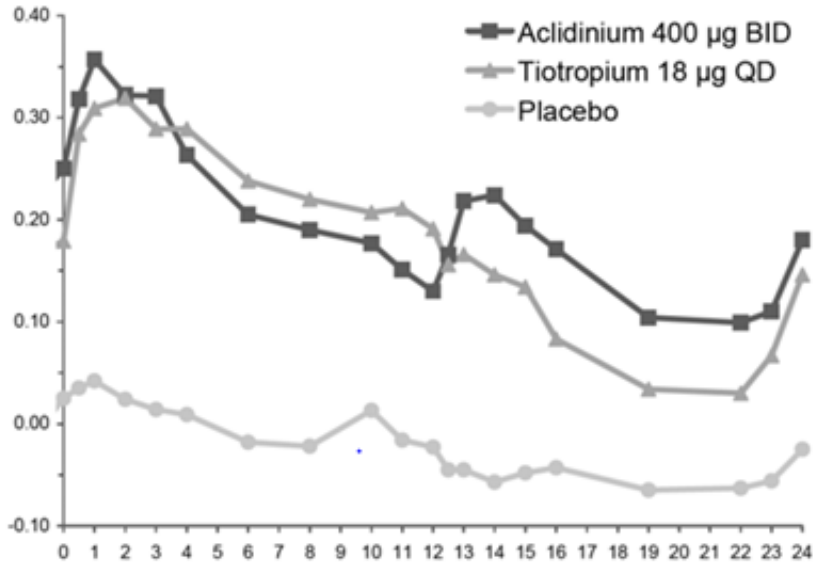
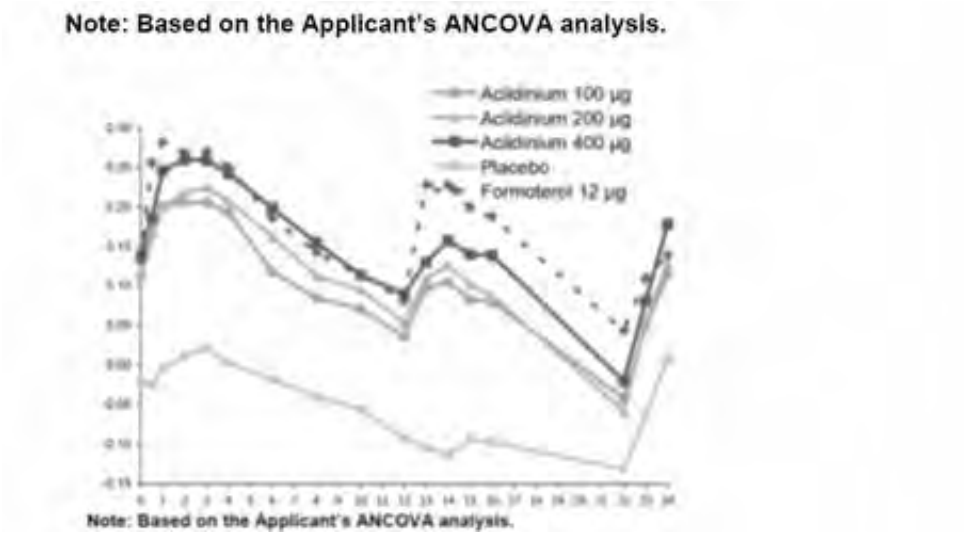


Figure 6 continued. Data from Study M/34273/23 Trial M/34273/23 (Day 15)



These data support the proposed dose of 400 µg BD for the Phase III studies.

Efficacy studies

There were 3 efficacy studies that will be considered which used the proposed dosing regimen and is considered ahead of the other studies. (The evaluator considers them pivotal however only one study (M/34273/34) is of the recommended duration (6

months) for the chronic treatment of patients with COPD[26]. The basic design is given in Table 15 below.

The design of these studies was similar with the main difference relating to the duration.

Table 15. A comparison of the design used in the three studies

Study	Dose µg BD	Design	Control	Treatment duration	N	Variables	
						1^o	2^{o*}
M/34273/34:	200,400	r, db,p	pbo	24 weeks	828	Trough FEV1	Peak FEV1, TDI, SGRQ
LAS-MD-33:	200,400	r, db,p	pbo	12 weeks	561	Trough FEV1	Peak FEV1
LAS-MD-38:	200,400	r, db,p	pbo	12 weeks	544	Trough FEV1	Peak FEV1

BD-twice daily: db-double blind; FEV1-forced expiratory volume in one second; p-parallel; pbo-placebo. 1^o=primary, 2^o=secondary.

Transition Dyspnoea Index (TDI) and St. George's Respiratory Questionnaire (SGRQ)[27] were adjusted for multiplicity in Study M/34273/34.

The objectives were broadly to assess the efficacy and safety of aclidinium bromide 200 µg or 400 µg BD compared with placebo as a long term bronchodilator in patients with moderate to severe COPD. The studies were randomised double blind placebo controlled in design.

The treatment arms consisted of aclidinium bromide 200 µg BD, aclidinium bromide 400 µg BD or placebo BD. Treatment was to be delivered via the device proposed for marketing.

The main inclusion criteria were: adult male or female patients aged 40 years or older with stable moderate to severe COPD (as defined by Global Initiative for Chronic Obstructive Lung Disease [GOLD] guidelines), current or ex-smokers of ≥10 pack years, post salbutamol FEV1 ≥30% and <80% of predicted normal value and FEV1/forced vital capacity (FVC) <70%. The main exclusion criteria were: 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; patients who developed a respiratory tract infection or exacerbation during the run-in period were discontinued from the study before randomisation; hospitalised for an acute COPD exacerbation within 3 months prior to the screening visit. Clinically significant cardiovascular disease was a significant exclusion criterion. These included myocardial infarction during the prior 6 months, newly diagnosed arrhythmias during the past 3 months, unstable angina, unstable

[26] CPMP/EWP/562/98 Points to consider on clinical investigation of medicinal products in the chronic treatment of patients with chronic obstructive pulmonary disease (COPD).
[27] The St George's Respiratory Questionnaire (SGRQ) is an index designed to measure and quantify health related health status in patients with chronic airflow limitation including symptoms, activities that cause breathlessness and impacts (e.g. influence on employment, side effects of prescribed therapies).

arrhythmia and/or NYHA Functional Classification III or IV[28] heart failure requiring hospitalisation in the prior 12 months.

The primary efficacy endpoint: change from baseline in morning pre dose (trough) FEV1 at Week 24 for the European Union (EU) submission and Week 12 for the United States (US) submission. Trough FEV1 was defined as the mean of the 2 largest FEV1 measurements at approximately 11 and 12 hours after the evening dose.

The *main secondary efficacy endpoints* are listed in the table above. There have been additional endpoints also discussed under the individual study evaluation.

Sample size calculations

Study M/34273/34 A sample size of 244 evaluable patients per treatment group provided at least a 90% power to detect as significant a difference of 90 mL between any of the doses of aclidinium bromide and placebo in change from baseline in morning predose (trough) FEV1 after 24 weeks of treatment for EU submission or 12 weeks of treatment for US submission; assuming a common standard deviation of 240 mL using two-sided tests and adjusting for multiple treatment comparisons at the overall significance level of 0.05. The sample size also provided sufficient power to detect treatment differences in the secondary endpoints that were adjusted for multiplicity using a sequential approach to hypothesis testing.

The evaluator mentions that the justification for the difference of 90 mL is not submitted especially as other long acting anticholinergics have used a margin of 100 mL or 120 mL.

Study LAS-MD-33 Calculations factored in a difference of 0.100 mL for the primary efficacy endpoint and were considered acceptable to the evaluator.

Study LAS-MD-38 A **w**as similar to the previous study.

Results

Demographics

The demographics of patients in the three studies are summarised in Table 16 below.

Table 16. Demographics

Study	M/34273/34	LAS-MD-33:	LAS-MD-38A
No Patients randomised	828	561	544
Mean age	62.4	64.3	62.8
Males (%)	67.4	53	53.1
Caucasians (%)	95.2	93.8	90.6

[28] The table below describes the most commonly used classification system for heart failure, the New York Heart Association (NYHA) Functional Classification. It places patients in one of four categories based on how much they are limited during physical activity.

Class	Functional Capacity: How a patient with cardiac disease feels during physical activity
I	Patients with cardiac disease but resulting in no limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or anginal pain
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea or anginal pain.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort increases.

Study	M/34273/34	LAS-MD-33:	LAS-MD-38A
COPD duration (years)	6.8	8.6	8.0
Moderate severity (%)	68.1	58.4	53.0
Severe severity (%)	31.9	39.5	45.8
Current Smokers (%)	52.8	44.8	53.3
Ex-smokers (%)	47.3	55.2	46.7
% predicted FEV1	51.8	47.21	46.15

Primary efficacy endpoint

The primary efficacy endpoint (extracted from FDA website) is shown in Table 17 below.

Table 17. Change from baseline in morning predose (trough) FEV1 (L) at Week 12 or Week 24, Intent-to-Treat population.

Treatment Arm	N	Baseline	Change from baseline	Treatment difference from placebo		
		Mean (SE)	LS Mean (SE)	LS Mean (SE)	95% CI	P-value
LAS-MD-33						
Aclidinium 400 mcg	190	1.328 (0.032)	0.099 (0.014)	0.124 (0.021)	0.08, 0.16	<0.001
Aclidinium 200 mcg	184	1.308 (0.033)	0.061 (0.015)	0.086 (0.021)	0.04, 0.13	<0.001
Placebo	185	1.383 (0.033)	-0.025 (0.015)	--	--	--
M/34273/34						
Week 12						
Aclidinium 400 mcg	269	1.447 (0.029)	0.058 (0.015)	0.105 (0.020)	0.07, 0.14	<0.001
Aclidinium 200 mcg	277	1.453 (0.028)	0.030 (0.014)	0.077 (0.020)	0.04, 0.12	<0.001
Placebo	273	1.419 (0.028)	-0.047 (0.015)	--	--	--
Week 24						
Aclidinium 400 mcg	269	1.447 (0.029)	0.055 (0.016)	0.128 (0.022)	0.08, 0.17	<0.001
Aclidinium 200 mcg	277	1.453 (0.028)	0.026 (0.016)	0.099 (0.022)	0.06, 0.14	<0.001
Placebo	273	1.419 (0.028)	-0.073 (0.016)	--	--	--
LAS-MD-38 Part A						
Aclidinium 400 mcg	177	1.255 (0.036)	0.064 (0.016)	0.072 (0.022)	0.03, 0.12	0.001
Aclidinium 200 mcg	182	1.387 (0.035)	0.043 (0.015)	0.051 (0.022)	0.01, 0.09	0.019
Placebo	182	1.418 (0.035)	-0.008 (0.015)	--	--	--

Source: Agency's Statistical Review.
Note: P-value, LS mean, and LSMD obtained from an ANCOVA model with change from baseline in trough FEV1 as response, with treatment group and sex as factors and baseline trough FEV1 and age as covariates.

The primary efficacy results showed a consistent statistically significant superiority of 400 µg versus placebo. The effect size in LAS-MD-38 Part A is smaller (72 mL) compared to Studies LAS-MD-33 (124 mL) and M/34273/34 (105 mL).This may have been attributed to the imbalance in the severe COPD in the 400 µg groups in Study LAS-MD-33 (35%); in Study M/34273/34 (31%) and in Study LAS-MD-38 Part A (54%). There was also a superiority seen with the 200 µg dose however the effect size was smaller than that observed with 400 µg and thus suggested a dose response.

Secondary efficacy endpoints

The following table (Table 18) shows results for the secondary end points.

Table 18. Mean change from baseline in peak FEV1 (c/w placebo)

Study	200 µg aclidinium bromide	400 µg aclidinium bromide
M/34273/34		
12 weeks	0.182 L p<0.0001	0.191 L p<0.0001
24 weeks	0.185 L p<0.0001	0.209 L p<0.0001
LAS- MD-33		
12 weeks	0.146 L p<0.0001	0.192 L p<0.0001
LAS-MD-38		
12 weeks	0.115 L p<0.0001	0.125 L p<0.0001

The difference between doses was statistically significant in Study LAS-MD-33 only.

Study M/34273/34 also assessed the TDI scores. The following (Table 19) is extracted from the clinical report:

Table 19. TDI Focal score at Week 4, 12 and Week 24 of treatment. ANCOVA model treatment comparison. (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

The evaluator mentions that, *'the percentage of patients with clinically relevant improvement in TDI focal score in the aclidinium bromide 400 µg group was always numerically larger than in the aclidinium bromide 200 µg group'.*

SGRQ scores in Study M34273/34

Results for SGRQ scores in Study M34273/34 are shown below in Table 20.

Table 20. Number (%) of patients who achieved at least 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 with placebo. Whilst these endpoints were assessed in the other two studies, multiplicity adjustments were not factored in and thus are only considered supportive.

A 24 hour PFT substudy was also conducted in approximately 40% of M34273/31 and approximately 30% of the LAS–MD-33 and LAS-MD-38A subjects. These analyses are considered supportive to the primary endpoint and are of limited statistical validity. They are only briefly considered in this report: 1) change in baseline FEV1 and FVC over 12 hours were supportive of the primary endpoints. 2) COPD exacerbations defined as 'an increase in COPD symptoms during at least 2 consecutive days' showed that 2 of the 3 studies (M/34273/34 and LAS –MD-33) showed statistically significant reduction. However, only TDI and SGRQ scores were considered valid secondary efficacy end points where multiplicity adjustments were taken into considerations (M/34273/34 only). There is a statement in the draft PI, '*pooled efficacy analysis of the 6 month and 3 month placebo controlled studies demonstrated a statistically significant reduction in the rate of moderate to severe exacerbations (requiring treatment with antibiotics or corticosteroids or resulting in hospitalisations) with aclidinium 322 mcg twice daily compared to placebo (rate per patient per year:0.31 vs 0.44 respectively; p=0.0149*)'. This should be removed as this is not based on valid statistical principles.

Other efficacy studies

M/34273/23 is a Phase IIa randomised, double blind, double-dummy, placebo and active comparator controlled (tiotropium), 3-period cross-over study was the first clinical study which investigated the 24 hour bronchodilatory profile of multiple doses of inhaled aclidinium bromide 400 µg BD administered to 30 patients with stable moderate to severe COPD and other characteristics similar to that included in the pivotal studies of BD administration. The primary efficacy endpoint was the change from baseline to Day 15 in the normalised area under the FEV1 versus time curve for the 12 hour period following the morning dose (FEV1 $AUC_{0\text{-}12/12h}$). Aclidinium bromide 400 µg BD and tiotropium 18 µg

QD were statistically significantly superior to placebo. There was no statistically significant difference between the two active agents.

Study M/34273/29 has been discussed under dose response.

Long term efficacy studies

The evaluator discusses 3 studies (LAS-MD-35, LAS-MD-36 and LAS-MD-38 Part B). The evaluator states that they were designed primarily to assess long term safety of aclidinium bromide, some efficacy variables were also evaluated to add information on the long term COPD status of patients treated with aclidinium bromide. The primary efficacy endpoint was trough FEV1 and the secondary efficacy endpoint was peak FEV1. Additional efficacy measures evaluated were spirometric measures, SGRQ and use of rescue medication.

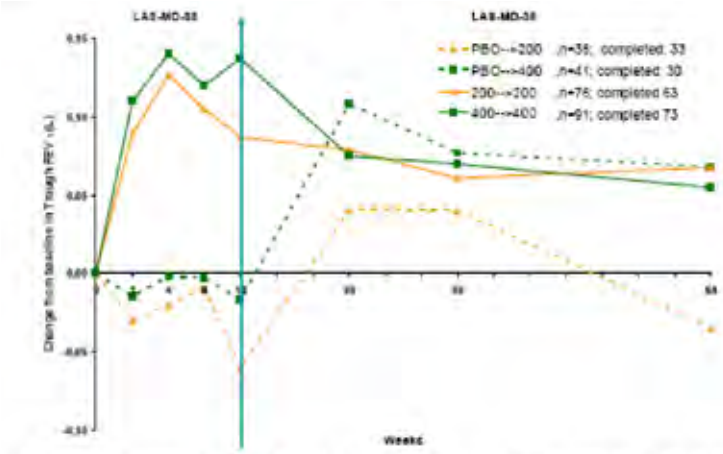
Study LAS-MD-36

This was a long-term, double-blind extension study to evaluate efficacy and safety of aclidinium bromide 200 µg and 400 µg BD in patients who had completed the 12 week pivotal Study LAS-MD-33. Patients who received aclidinium bromide 200 µg or 400 µg BD in LAS-MD-33 continued to receive aclidinium bromide in this study at the same dose BD for a further 52 weeks. Patients who received placebo in LAS-MD-33 were randomised in a 1:1 ratio to receive in this study either aclidinium bromide 200 µg or 400 µg BD for up to 52 weeks. The primary efficacy endpoint was the change from baseline in morning predose (trough) FEV1 at Week 64. The secondary efficacy endpoint was the change from baseline in peak FEV1 at Week 64.

Some 114 subjects were randomised to the 200 µg and 132 subjects to the 400 µg BD aclidinium bromide groups. The evaluator mentions that baseline characteristics were 'generally balanced'; 93.4% were Caucasians; mean duration of COPD 7.9 (5.9) years. 61% had moderate COPD and 36.3 had severe COPD. 44% were current smokers; and 56% were ex-smokers.

The following figure (Figure 7) is extracted from the European Public Assessment Report (EPAR).

Figure 7. Change from baseline in morning predose (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.

The evaluator also mentions that, *'improvement relative to baseline in mean morning pre-dose (trough) FEV1 at Week 64 was observed for patients who remained on active treatment in the extension study and for patients who were randomized to the placebo – aclidinium bromide 400µg treatment sequence. For those patients who were randomized to the placebo*

– aclidinium bromide 200µg treatment sequence, predose trough FEV1 was maintained over time but the effect declined substantially at Week 64. (Similar results were observed for the change from baseline in peak FEV1)'.

Study LAS-MD-35

This was a long-term, randomized, double blind, multicentre, parallel group study. Inhaled aclidinium bromide 200 µg or 400 µg was administered twice a day (BD), once in the morning and once in the evening, via a multidose dry-powder inhaler in 605 patients with moderate to severe, stable COPD for 52 weeks. The main inclusion and exclusion criteria were similar to those described in the pivotal Phase III studies above. The primary efficacy variable was change from baseline in morning predose (trough) FEV1 at Week 52. The secondary endpoint was change from baseline in peak FEV1 at Week 52. There were additional efficacy endpoints as per the previous studies.

Of the 605 randomised patients, 600 (99.2%) had at least 1 post-baseline FEV1 assessment and qualified for the Intention-to-treat (ITT) Population (aclidinium 200 µg=310 and 400 µg=290). At the end of 52 weeks of treatment, the adjusted mean change from baseline in morning predose (trough) FEV1 was 0.034 L and 0.072 L in the aclidinium bromide 200 µg and 400 µg groups, respectively with slightly greater numerical improvement in bronchodilation in the 400 µg groups. Secondary endpoint of peak FEV1 from baseline and aclidinium bromide 400 µg showed a numerically greater response than the 0.185 L in the aclidinium bromide 200 µg group (0.185L and 0.214 L in in the aclidinium bromide 200 µg and 400 µg groups, respectively). In terms of the SGRQ total score, this was greater at all the time points with aclidinium bromide (and above the 4 unit threshold considered clinically significant).

Study LAS-MD-38B

This was a multi center, open-label 40 week continuation of treatment in patients enrolled in Part A of Study LAS-MD-38. The primary efficacy variable was change from baseline in morning predose (trough) FEV1 at Week 52. The secondary endpoint was change from baseline in peak FEV1 at Week 52. A total of 344 patients (76.8%) completed Part B of the study. At the end of 52 weeks of treatment, the adjusted mean change from baseline (Visit 2 in Part A) in morning predose (trough) FEV1 (LOCF) was 0.045 L, 0.030 L and 0.048 L for the placebo versus aclidinium bromide 400 µg, 200 µg versus 400 µg and the 400 µg 400 µg treatment sequences, respectively. Numerical improvement relative to baseline at Week 52 was observed in all treatment sequences. Similar results were observed for the secondary endpoint of change from baseline in peak FEV1 (0.185L, 0.176 L and 0.172 L, respectively).

Studies with once daily dosing

These are of limited relevance to this submission and will not be discussed further.

Pooled analysis

The pooled analysis of Studies M/34723/34, LAS-MD033 and LAS-MD-38 Part A are discussed. They provide supportive information as only one study (M/34723/34) was of 24 weeks duration. The evaluator mentions that '*the pooled analysis summary results also show results from individual studies allowing valid interpretation of results across studies*'.

Study on exercise tolerance LAS-MD-CL6

This was a Phase III, randomised, double blind, placebo controlled, parallel group study to examine the effect of inhaled aclidinium bromide 200 µg QD on exercise endurance and on reducing resting and dynamic lung hyperinflation and to evaluate safety and tolerability in 181 patients with stable moderate/severe COPD. The primary efficacy endpoint of this study was the change from baseline to Week 6 in Endurance Time (ET). A total of 181 patients were randomised to aclidinium bromide 200 µg (n=86) and placebo (n=95). The

primary efficacy endpoint of this study was the change from baseline to Week 6 in Endurance Time (ET). The mean ETs at baseline were 414.1 seconds and 425.8 seconds in the aclidinium bromide and placebo treatment groups, respectively.

Overall conclusions on efficacy

The findings of the pivotal Study M/34273/34 showed statistically significant improvement of aclidinium bromide 400 µg BD over placebo in relation to morning pre-dose FEV1, TDI and SGRQ after 24 weeks. The results of LAS-MD-33 and LAS-MD038 Part A provided limited evidence of efficacy (12 weeks). The evaluator mentions that the inclusion and exclusion criteria confirmed that patients included in the studies were representative of the target patient population for aclidinium bromide (namely patients with moderate to severe COPD). Supportive evidence for persistence of efficacy is obtained from long term studies LAS-MD-35, LAS-MD-36 and LAS-MD-38 Part B.

Subgroup analyses (sex, age, body mass index (BMI), COPD severity, bronchodilator reversibility and concomitant inhaled corticosteroids (ICS) use) did not show any significant effect.

Long term studies LAS-MD-35 and 36 demonstrated that the treatment effect of aclidinium bromide 400 µg BD seen in the shorter pivotal study is maintained for up to 52 weeks with little deterioration; no firm conclusions can be drawn as these data are not placebo controlled.

The evaluator also mentions that there are dose selection studies (Studies M/34273/29 and M/34273/23) that supported the 400 µg BD dose. However the evaluator stated that there was no direct comparison of once daily versus twice daily dosing.

Safety

The evaluator states that primary evidence of the safety of aclidinium bromide BD is derived from the pooled analysis of the 3 double blind, placebo controlled, parallel group Phase III studies, (M/34274/34, LAS-MD-33, and LAS-MD-38 Part A) conducted in patients with moderate to severe COPD. Supportive evidence of safety is based on the pooled data from the 3 long term safety studies (LAS-MD-33 and LAS-MD-36 combined; LAS-MD-38 Part A and Part B combined, and LAS-MD-35).

The secondary safety data is drawn from the QD development program and consists of 8 clinical studies conducted in a similar moderate to severe COPD population to that of the BD program.

Overall, the evaluator states that inhaled aclidinium bromide (at any dose and dose regimen) has been evaluated in 2341 healthy adult subjects and 4344 patients with COPD. A total 2879 COPD patients were treated in clinical trials of aclidinium bromide BD. A total of 2568 COPD patients were included in studies of aclidinium bromide QD.

The adverse events from the pivotal studies are included in Table 21 below. (This has been extracted from the European Public Assessment Report for Bretaris Genuair(EPAR)[29]).

[29] <http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002706/WC500132734.pdf>

Table 21. Adverse events by preferred term with an incidence of ≥2% in any treatment group in the pivotal study population: Studies M/34273, LAS-MD-33 and LAS-MD-38 Part A (Safety population)

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 AE, AE that led to discontinuation, serious adverse events (SAEs) or deaths compared with placebo (Table 22).

Table 22. Number and percentage of [patients with adverse events in pivotal study population. Studies M34273/34, LAS-MD-33 and LAS-MD-38 Part A (Safety Population).

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)

No dose related trend in percentages of patients with adverse events was observed in the pivotal studies or in the long term study population. There appeared to be no impression that the adverse event incidence decreased with time; the overview of the adverse events from the long term studies is given in Table 23 below.

Table 23. 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)

Serious adverse events

In the pivotal studies, the following were reported: placebo 4.8%, aclidinium bromide 200 µg 4.8% and aclidinium bromide 400 µg 4.4%. The most frequently reported event was COPD exacerbation. This was lower in the aclidinium bromide 400 µg group (1.6%) compared with the placebo (2.7%). Pneumonia was the only additional SAE reported in at least 1% of the patients- this was 0.6% in the 400 µg aclidinium bromide group and 1.1 % in the 200 µg aclidinium bromide groups.

Deaths

A total of 16 are reported. Of these, 9 were reported in the once daily studies (2 in the 200 µg aclidinium bromide group; 5 in the 400 µg aclidinium bromide group and 2 in the placebo group). Five deaths were considered 'by the adjudication committees to be cardiovascular'. Of the 5 cardiovascular deaths, 2 were sudden cardiac deaths reported as cardiac arrest while the remaining deaths were due to: possible myocardial infarction, acute cardiac failure and subarachnoid haemorrhage. All 5 patients had extensive cardiovascular medical histories.

The evaluator does not attribute causality to the active treatment (in the BD studies).

Laboratory investigations

There were no trends observed and no significant changes seen.

ECG changes

The individual events were low and balanced between groups. In the long term BD studies there were 3 instances of Supraventricular Tachycardia (SVT) reported as treatment emergent adverse events (TEAEs) for the 400 µg group (c/w 200 µg). In the placebo controlled studies there was a trend towards a greater percentage of patients with a shift to increased PR interval across doses (2.6% placebo, aclinidium bromide 200 µg BD 3.0% and 3.3 % aclinidium bromide 400 BD). These were small and difficult to interpret.

Holter monitoring was conducted in a subset of patients (LAS-MD-33 and 38A). Individual events were infrequent and balanced. Exceptions were Premature ventricular contractions (PVCs) and non-sustained SVT (common with aclidinium bromide than placebo). There were no ventricular fibrillations (VF) or torsade de pointes.

Vital signs

Potentially clinically significant changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP) were infrequent and balanced. Overall TEAEs relating to these events were low.

Cardiovascular events

The evaluator discusses 2 analyses (major adverse cardiovascular events (MACE) and events based on standardised MedRA[30] queries, SMQ[31]). *MACE*: cardiovascular deaths were in line with placebo groups of studies conducted with similar agents. MACE- acute myocardial infarction (AMI) did not reveal any significant findings.

Cardiovascular SMQs: In the BD placebo controlled studies these events were generally balanced between groups. The notable imbalance was brady-arrhythmia/conduction defects/sinus node disorder which was 1.6% aclidinium bromide 400 µg, 0.9% for

[30] MedDRA (Medical Dictionary for Regulatory Activities) is a clinically-validated international medical terminology used by regulatory authorities and the regulated biopharmaceutical industry. The terminology is used through the entire regulatory process, from pre-marketing to post-marketing, and for data entry, retrieval, evaluation, and presentation

[31] Standardised MedDRA Queries (SMQs) are groupings of MedDRA terms, ordinarily at the Preferred Term (PT) level that relate to a defined medical condition or area of interest. SMQs are intended to aid in the identification and retrieval of potentially relevant individual case safety reports.

aclidinium bromide 200 µg and 0.8% in the placebo arm. Also, cardiac failure was 0.8% in the aclidinium bromide 400 µg group, 0.2% in the aclidinium bromide 200 µg group and 0.3% in the placebo group respectively.

Strokes:

The numbers were low making it difficult to draw conclusions.

Pneumonia:

The incidence rate was low (10.1%) with aclidinium bromide 400 µg BD versus placebo (26.2%). The long term studies did not reveal any dose response. The risk of patients with COPD developing pneumonia, bronchitis or respiratory failure was not increased with aclidinium bromide administration.

Anticholinergic events:

There were no significant trends observed and the incidence was low.

Safety results from once daily dosing and the Phase I studies are also discussed in Extract from the CER Attachment 2. This is considered supportive only.

Safety in special populations:

Impact of age, sex, race, BMI, COPD severity and the concomitant use of ICS on adverse events were analysed. There were no significant findings.

Overall safety conclusion

The evaluator states that aclidinium bromide 200 µg or 400 µg BD was well tolerated. The overall incidence of AEs was similar in the aclidinium bromide treated groups to that in the placebo group. Cardiovascular adverse events are a specific safety event of interest for anticholinergic drugs given the previous findings with tiotropium. The results do not indicate an increased overall MACE score for aclidinium bromide and do not show a definite signal of imbalance for any of the individual categories of events but the strength of this assessment is limited by the relatively small sample size and a low event rate. The risk of patients with COPD developing pneumonia, bronchitis or respiratory failure was not increased with aclidinium bromide administration. A total of 14 on-treatment deaths were reported in BD Group 1 studies (all studies of aclidinium bromide BD in COPD patients). There was no obvious causality to aclidinium use.

Response to clinical evaluators questions to the sponsor

The evaluator had requested answers to some questions. Most of the questions were answered to the satisfaction of the evaluator. The exception was the question on the smoking status: *Change in smoking status, tobacco exposure and use of nicotine replacement therapy (as an aid to smoking cessation) was not recorded in the pivotal studies and its potential effect on efficacy outcomes was not evaluated.* The sponsor states that '*the change in smoking status of the patients during these studies would be negligible and therefore for efficacy analyses the smoking status at the start of the study would be used*'. The evaluator states that this remains unanswered and is a significant limitation.

Overall benefits

The evaluator lists low bioavailability, the low potential to cause drug interactions, the fact that there is no requirement to change the dosing in the elderly, renally impaired and hepatic impairment as benefits. In terms of efficacy, the clinical studies showed that aclidinium bromide 400 µg BD provide statistically significant findings in relation to bronchodilation endpoints in those with COPD with replicate findings. TDI and SGRQ scores also showed significant change in the pivotal study. There was maintenance of efficacy in the long term studies.

Overall risks

The main risk identified is the lack of efficacy data on smoking status (that is, the subjects were not stratified according the smoking), and thus the impact of this on efficacy is not determined. The lack of data on those with significant cardiovascular history is also a significant finding.

Overall risk benefit assessment

This was deemed favourable, provided the sponsor incorporated the PI changes recommended.

Sponsor's response

The sponsor's response to the TGA clinical evaluation: It mainly addressed some minor errors in the CER.

Clinical evaluator's recommendation

The clinical evaluator recommended that Bretaris Genuair (aclidinium bromide 400µg twice daily by inhalation) be approved for the long-term maintenance bronchodilator treatment to relieve symptoms in adult patients with Chronic Obstructive Pulmonary Disease (COPD). However, the recommended approval was subject to incorporation of suggested changes to the draft PI.

Risk management plan

The evaluator mentions that routine pharmacovigilance and risk minimisation activities are proposed. Of note, a long term Phase IV study is proposed. This study is to evaluate the effect of aclidinium bromide on long term cardiovascular safety and COPD exacerbations in patients with moderate to very severe COPD and is being conducted in the USA. This is being conducted by a different sponsor. The evaluator recommends all generated data should be reported regularly via Periodic Safety Update Reports (PSURs) or as the final study reports.

Risk-benefit analysis

Delegate's considerations

Device

There are no outstanding issues relating to the proposed device. The proposed device was found to be acceptable from a functionality point of view. The devices used in the clinical studies have been shown to be sufficiently similar to that proposed for marketing. COPD patients with moderate to severe disease were found to be able to generate sufficient inspiratory flow to reliably inhale the full dose and activate the trigger threshold. Instructions for use of the device are included in the Consumer Medicine Information (CMI) and are satisfactory.

Efficacy

Efficacy of the proposed dose was studied in one pivotal study only. The findings are supported by other short term studies. The primary efficacy endpoint was trough FEV1 and is considered satisfactory. However no symptomatic endpoint was used as a co-primary endpoint and this is a deficiency. It is noted however that the pivotal study used TDI and SGRQ scores as secondary endpoints where multiplicity issues were factored in and therefore yielded statistically robust evidence of efficacy. However, in relation to

COPD exacerbations, there was no robust evidence of efficacy and statements to this effect should be removed from the draft PI.

Efficacy appears to be maintained over a 12 month period as evidenced in the long term studies.

There are no pivotal active comparator studies, especially with other anti-muscarinic agents.

Safety

This submission has not been considered by the TGA's Advisory Committee on the Safety of Medicines (ACSOM).

An issue of concern is the potential for cardiovascular events with LAMA.

A meta-analysis of 17 clinical trials with tiotropium showed such a signal, however a large 4 year placebo controlled trial (n=5992) with tiotropium (UPLIFT) did not show a safety signal. Recently, the FDA concluded that the available data (including results from the UPLIFT trial) that SPIRIVA HandiHaler (tiotropium) do not support the increased risk of stroke, heart attack or death from a cardiovascular cause. The relevant publication is: Michele TM, Pinheiro S, Iyasu S. The safety of tiotropium-the FDA's conclusions. NEJM 2010; 363 (12):1097-9.

Cardiovascular events (MACE and SMQs) did not reveal any significant trends. However, the numbers are small and the populations are defined; those with significant cardiovascular disease were excluded and thus the study population may not reflect those who would be using this product in a real world setting. In addition, those exposed for one year (with the proposed dose) was 387 patients. This is a limited number of patients and does not allay the concerns regarding cardiovascular safety.

The proposed long term study to assess cardiovascular safety discussed in the RMP should address this issue. This study is a double blind, randomised, placebo controlled Phase IV study that is currently being conducted in USA to assess long term cardiovascular safety in patients with moderate to very severe COPD. A total of 4000 COPD patients will be included and treated for a maximum of 36 months. The final study report should be submitted to the TGA on completion; this should be a condition of registration.

Summary of issues

Efficacy of the proposed dose is studies in one pivotal study only. The primary efficacy endpoint was trough FEV1; no symptomatic endpoint was used as a co-primary endpoint and this is a deficiency.

In relation to COPD exacerbations, there was no robust evidence of efficacy and statements to this effect should be removed from the draft PI.

An issue of concern is the potential for cardiovascular events with LAMA. Safety findings did not raise any serious concerns. Cardiovascular events (MACE and SMQs) did not reveal any significant trends. However, the numbers are small and the populations are defined; those with significant cardiovascular disease were excluded in the pivotal studies and thus the study population may not reflect those who would be using this product in a real world setting.

Proposed action

The Delegate had no reason to say, at this time, that the application should not be approved for registration.

A condition of registration is the submission of the completed study report of the Phase IV study that is currently being conducted to assess cardiovascular safety.

The ACPM's advice was sought.

Request for ACPM advice

The following questions were asked of the committee:

1. There is one pivotal efficacy study that has one primary efficacy endpoint relating to bronchodilation. The TGA adopted EU Guideline, CPMP/EWP/562/98[26], recommends FEV1 as a measure of lung function and also a measure of symptomatic benefit as a primary endpoint. There are no primary endpoints that deal with symptomatic benefit in the pivotal study (or in any other clinical efficacy studies). Does the committee consider that the efficacy data are adequate to approve aclidinium bromide for long term maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD)?
2. Does the committee agree with the Delegate regarding the deletion of the statement in the draft PI, on claimed benefits in COPD exacerbation?
3. Does the committee agree that there are adequate evidence for safety considering the size of the safety data base and overall duration of the studies?
4. Does the committee agree that the RMP and the long term studies proposed are adequate to monitor for potential cardiac adverse events post registration?
5. Does the committee agree that the risk benefit profile is acceptable to warrant registration?

Response from Sponsor

Overall recommendation

The sponsor agrees with the proposed recommendation by the Delegate to approve the registration of Bretaris Genuair for the following indication:

> *Bretaris Genuair is indicated as a long term maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD.*

Symptomatic endpoint

Issue raised:

Efficacy of proposed dose is based on studies in one pivotal study only. The primary efficacy endpoint was trough FEV1; no symptomatic endpoint was used as a co-primary endpoint and this is a deficiency.

Sponsor comment:

The CPMP '*Points to Consider on Clinical Investigation of Medicinal Products in the Chronic Treatment of Patients with COPD*' (CPMP/EWP/562/98) states that for an indication of symptomatic relief of COPD, statistically significant benefit should be demonstrated for co-primary endpoints of FEV1, as a measure of lung function and also for a measure of symptomatic benefit. The approach adopted for Study M/34273/34 was that FEV1 was selected as the primary efficacy measure and that a pre-specified measure of symptomatic benefit was included as a 'main' secondary endpoint rather than as a co-primary endpoint. This study had a 6 month treatment duration allowing the assessment of symptomatic features while the other two pivotal trials were of 12 weeks duration and considered not long enough for characterising symptoms. These two symptomatic variables were treated as confirmatory claim variables as agreed in the national scientific meetings with

European regulatory agencies. Therefore multiplicity correction was pre planned in the statistical approach (Hochberg method and hierarchical testing methods applied). This approach is in line with the clinical developments of other long acting anti-muscarinic agents approved in Australia for the treatment of COPD such as tiotropium bromide[32] or glycopyrronium bromide[33] and was agreed for aclidinium bromide at national Scientific Advice meetings, as was the choice of primary and secondary variables. Extracts of the minutes with the question where this approach was discussed were submitted to the TGA.

COPD exacerbations

Issue raised:

In relation to COPD exacerbations, there was no robust evidence of efficacy and statements to this effect should be removed from the draft PI.

Sponsor comment:

The sponsor disagrees with the recommendation to remove the evidence of efficacy and statements to COPD exacerbations from the PI. The treatment effect of aclidinium bromide 400 µg BD on the number of COPD exacerbations observed across pivotal trials and different exacerbation definitions is robust, indicating that aclidinium bromide reduces the rate of COPD exacerbations.

The magnitude of the effect is around 30% decrease in the number of patients suffering an exacerbation with respect to placebo-treated patients (see Table 24). The treatment effect is above the cut-off recently suggested as of meaningful clinically important difference for this endpoint (20%).[34] This observed effect is in line to that seen in other approved products.[35] The results from the different exacerbation endpoints go in the same direction of aclidinium bromide decreasing the number of exacerbations (see Table 24).

Table 24 . Effect of Aclidinium Bromide 400µg BD compared to Placebo on exacerbation endpoints across trials

Study	Number of moderate/severe COPD exacerbations RR (95%CI)	Time to first moderate/severe COPD exacerbation HR (95%CI)	Number of patients with at least one moderate/severe COPD exacerbation OR (95%CI)
M/34273/34	0.72 (0.51, 1.02)	0.71 (0.45, 1.12)	0.73 (0.45,1.19)
LAS-MD-33	0.66 (0.41, 1.07)	0.67 (0.31, 1.45)	0.51* (0.24,1.07)
Pooling M/34273/34 & LAS-MD-33	0.71 (0.54, 0.94)	0.70 (0.47,1.03)	NA
LAS-MD-38A	0.82 (0.52,1.29)	0.79 (0.40, 1.57)	0.95 * (0.48, 1.88)
Pooling M/34273/34,	0.74 (0.58, 0.93)	0.72 (0.52, 1.01)	NA

[32] Netherlands Spiriva Handihaler assessment report <http://db.cbg-meb.nl/mri/par/nlh-0718-001.pdf>
[33] Seebri Breezehaler AusPAR <http://www.tga.gov.au/pdf/auspar/auspar-glycopyrronium-130710.pdf>
[34] Jones PW, Beeh KM, Chapman KR, Decramer M, Mahler DA and Wedzicha JA. Minimal clinically important differences in pharmacological trials. AJRCCM. Posted on line 2 January 2014
[35]Wedzicha J, Decramer M and Seemungal TA. The role of bronchodilator treatment in the prevention of exacerbations of COPD. Eur Respir J 2012; 40: 1545–1554

Study	Number of moderate/severe COPD exacerbations RR (95%CI)	Time to first moderate/severe COPD exacerbation HR (95%CI)	Number of patients with at least one moderate/severe COPD exacerbation OR (95%CI)
LAS-MD-33, LAS-MD-38A			

Note: RR: rate ratio; CI: confidence interval; HR: hazard ratio; OR: odds ratio; The rate of COPD exacerbations per patient-year is analysed by means of a Poisson regression for rates and with treatment, sex, and baseline COPD severity as factors and age as covariate, adjusting for the log of the corresponding total exposure time in years for a patient (as an offset variable in the model); Hazard Ratio is derived from a Cox-Proportional Hazards model with time to first moderate or severe COPD exacerbation as response and treatment group, and sex as factors; Odds ratio is based on the logistic regression model for the number of patients with at least 1 COPD exacerbation as response with treatment group as factor along with COPD severity at baseline as covariate; NA: not available in the pre-specified pooled analysis.

Two different tools to assess exacerbations were included in the Study M/34273/34. Both EXACT, a patient reported outcome[36,37] and the Health Care Utilisation tools yielded consistent estimates of the effect of aclidinium bromide (around 30% reduction).

The design of the pivotal trials is not the optimum for assessing exacerbations because it did not include enriched population and was for a treatment duration less than one year. However, trials with a duration inferior a 1 year treatment has been suggested to be a good predictor of trials of more than 1 year duration when assessing exacerbations[38] On the other hand, the use of not enriched population leads to a less sensitive population, even though an effect on exacerbations was observed.

The results of the placebo controlled pivotal studies, irrespectively of the endpoint and COPD exacerbation assessment tool, indicate that aclidinium bromide has an effect on decreasing the number of COPD exacerbations.[39] Data on the rate of exacerbations of the placebo controlled pivotal studies was re-submitted to the TGA.

Cardiovascular safety

Question raised (3):

Is there adequate evidence for safety considering the size of the safety database and overall duration of studies?

Question raised (4):

Is the RMP and the long term studies proposed are adequate to monitor for potential cardiac adverse events post registration?

Sponsor comment:

The sponsor agrees with the Delegate that the size of the safety database and duration of studies is adequate and that RMP and long term studies are appropriate to monitor for potential cardiovascular events post registration.

[36]Leidy NK, Wilcox TK, Jones PW, Roberts L, Powers JH, Sethi S, and the EXACT-PRO Study Group . Standardizing Measurement of Chronic Obstructive Pulmonary Disease Exacerbations. Reliability and Validity of a Patient-reported Diary. Am J Respir Crit Care Med 2011; 183: 323–329 ;

[37] Leidy NK and Murray LT. Patient-reported Outcome (PRO) Measures for Clinical Trials of COPD: The EXACT and E-RS. COPD, 10:393–398, 2013

[38]Karner C, Chong J, Poole P. Tiotropium versus placebo for chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews 2012, Issue 7. Art. No.: CD009285. DOI: 10.1002/14651858.CD009285.pub2.

[39]Jones PW, Singh D, Kerwin E, Lamarca R, Caracta C, Garcia E. Reduced COPD exacerbations associated with aclidinium bromide versus placebo: a pooled analysis of Phase III data. Thorax 2012; 67(Suppl 2): A146

The sponsor commits to submit to the TGA the final reports of the two on-going studies to assess the cardiovascular safety of aclidinium bromide (ASCENT and PASS) as soon as they are completed.

Additional comments

The sponsor also commented on the PI changes that the evaluators recommended to the Delegate. The details of these comments are however beyond the scope of this AusPAR.

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The submission seeks to register a new chemical entity.

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Bretaris Genuair Powder for inhalation containing 400 µg per actuation of aclidinium bromide to have an overall positive benefit–risk profile for the indication;

> *Bretaris Genuair is indicated as a long term maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).*

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration and specifically advised on the inclusion of the following:

- The submission as soon as practicable of the cardiovascular safety study currently underway.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACPM agreed with the Delegate to the proposed amendments to the PI and CMI.

Specific advice

1. *There is one pivotal efficacy study that has one primary efficacy endpoint relating to bronchodilation. The TGA adopted EU Guideline, CPMP/EWP/562/98, recommends FEV1 as a measure of lung function; it also recommends a measure of symptomatic benefit as a primary endpoint, be included in the efficacy studies. There are no primary endpoints that deal with symptomatic benefit in the pivotal study (or in any other clinical efficacy studies). Does the committee consider that the efficacy data are adequate to approve aclidinium bromide for long term maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD)?*

The ACPM advised there is evidence submitted of clinically meaningful improvements in lung function and QOL measures to support the indication proposed.

2. *Does the committee agree with the Delegate regarding the deletion of the statement in the draft PI, on claimed benefits in COPD exacerbation?*

The ACPM agreed with the Delegate that that the statement in the PI the reduction in the rate of exacerbations in COPD was not supported by effective evidence and the definition of exacerbations was non-standard.

3. *Does the committee agree that there are adequate evidence for safety considering the size of the safety data base and overall duration of the studies?*

The ACPM were concerned that there was only 1 6 month randomised, placebo controlled trial. However, the 12 month studies are supportive and there were no clear safety signals of concern. There were an adequate number of subjects exposed to active medication. The ACPM was of the view that these are likely to be sufficient data.

4. *Does the committee agree that the RMP and the long term studies proposed are adequate to monitor for potential cardiac adverse events post registration?*

The ACPM advised that the RMP was adequate in this regard.

5. *Does the committee agree that the risk benefit profile is acceptable to warrant registration?*

The ACPM was of the view that the risk-benefit profile is acceptable.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Bretaris Genuair powder formulation delivering 322 µg aclidinium (as bromide) per actuation inhaler dry powder, indicated for:

> *Bretaris Genuair is indicated as a long term maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).*

Specific conditions of registration applying to these goods

1. The Bretaris Genuair (aclidinium bromide) EU Risk Management Plan (RMP, version 2.3 dated 24 May 2012 (data lock point 1 September 2011) with Australian Specific Annex dated February 2013, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

   An obligatory component of Risk Management Plans is Routine Pharmacovigilance. Routine Pharmacovigilance includes the submission of Periodic Safety Update Reports (PSURs). Reports are to be provided annually until the period covered by such reports is not less than three years from the date of this approval letter No fewer than three annual reports are required.

Attachment 1. Product Information

The Product Information approved for main Bretaris Genuair at the time this AusPAR was published is at Attachment 1. For the most recent PI please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
http://www.tga.gov.au