25 September 2014
EMA/CHMP/713778/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Duaklir Genuair

International non-proprietary name: Aclidinium bromide/ Formoterol fumarate dihydrate

Procedure No. EMEA/H/C/003745/0000

Note

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

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Administrative information

Name of the medicinal product:	Duaklir Genuair
Applicant:	Almirall S.A Ronda General Mitre, 151 08022 Barcelona Spain
Active substance:	Aclidinium bromide/Formoterol fumarate dihydrate
International Nonproprietary Name/Common Name:	Aclidinium bromide/Formoterol fumarate dihydrate
Pharmaco-therapeutic group (ATC Code):	Drugs for obstructive airway diseases (R03AL05)
Therapeutic indication:	Duaklir Genuair is indicated as a maintenance bronchodilator treatment for airflow obstruction and relief of symptoms in adult patients with chronic obstructive pulmonary disease (COPD).
Pharmaceutical form:	Inhalation powder
Strengths:	340 µg / 12 µg
Route of administration:	Inhalation use
Packaging:	Inhaler (plastic/stainless steel)
Package sizes:	1 inhaler with 60 actuations and 3 inhalers with 60 actuations

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List of abbreviations

AB	Aclidinium bromide
ADME	Absorption, distribution, metabolism and excretion
ADR	Adverse Drug Reaction
AE	Adverse event
ANCOVA	Analysis of covariance
AUC	Area-under-the curve
AUC0-t	Area under the concentration-time curve from time zero up to the last measurable concentration
AUC0-∞	Area under the concentration-time curve from time zero to infinity
AUCτ	Area under the concentration-time curve during a dosing interval (τ)
AUCτ,SS	Area under the concentration-time curve during dosing interval (τ) at steady state
AUC(0-24)	Area under the concentration-time curve from zero to 24 hours
AUC(0-24)	Area under the concentration-time curve over the once-daily dosing interval
AUC(0-t)	Area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration
AUC(0-t')	Area under the concentration-time curve from zero (pre-dose) to the time of last common measurable time-point, t', within subject across treatments
AV	Atrioventricular
BChE	Butyrylcholinesterase
BDI	Baseline Dyspnoea Index
BID	Twice daily
BLQ	Below limit of quantitation
BMI	Body mass index
bpm	Beats per minute
CHMP	Committee for Medicinal Products for Human Use
Cmax	Maximum plasma concentration
CI	Confidence interval
Cl	Clearance
CNS	Central nervous system

COPD	Chronic obstructive pulmonary disease
CV	Coefficient of variation
CYP450	Cytochrome P450
DEREK	Deductive estimation of risk from existing knowledge
DPI	Dry powder inhaler
ECG	Electrocardiogram
EMA	European Medicines Agency
EPAR	European public assessment report
EU	European Union
EXACT	Exacerbation of Chronic Pulmonary Disease Tool
f	Absolute bioavailability expressed in %
fe	Percentage of dose excreted in urine
FDA	Food and Drug Administration
FRC	Forced residual capacity
FEV1	Forced expiratory volume in one second
FF	Formoterol fumarate
FVC	Forced vital capacity
GCP	Good Clinical Practice
g	Gram(s)
g/mol	Gram(s) per mol
GLP	Good laboratory practice
GINA	Global Initiative for Asthma
GOLD	Global Initiative for Obstructive Lung Disease
h	Hour(s)
HPA	Hypothalamic-pituitary-adrenal
HPLC	High performance liquid chromatography
HRQoL	Health-related quality of life
IC	Inspiratory capacity
ICH	International Conference on Harmonisation
ICS	Inhaled corticosteroid
IMP	Investigational medicinal product
IND	Investigational New Drug
ITT	Intent-to-treat

i.v.	Intravenous
IVRS	Interactive Voice Response System
kg	Kilogram(s)
LC-MS/MS	Liquid chromatography–tandem mass spectrometry
L	Litre
LABA	Long-acting β2-adrenergic receptor agonist
LAMA	Long-acting muscarinic antagonist
LLOC	Lower limit of quantification
LS	Least squares
MAA	Marketing authorisation application
MACE	Major Adverse Cardiovascular Events
MCID	Minimum clinically important difference
mg	Milligram(s)
mL	Millilitre
mM	Millimolar
MRM	Multiple reaction monitoring
MRDD	Maximum recommended daily dose
n	Number
ng	Nanogram(s)
NOAEL	No observed adverse effect level
OD	Once a day
PEG	Polyethylene glycol
PIF	Peak inspiratory flow
PFT	Pulmonary Function Tests
pg	Picogram(s)
Ph. Eur.	European Pharmacopeia
PK	Pharmacokinetics
PMSF	Phenylmethylsulfonyl fluoride
PQ interval	Duration in milliseconds from the beginning of P wave to the end of the Q wave
QD	Once daily
QTc	Corrected QT interval

QT interval	Duration in milliseconds from the beginning of Q wave to the end of the T wave
SAE	Serious adverse event
SAP	Statistical analysis plan
SEM	Standard error of the mean
SGRQ	St George's Respiratory Questionnaire
SmPC	Summary of product characteristics
SMQ	Standard MedDRA Queries
SOC	System organ class
SPE	Solid-phase extraction
TEAE	Treatment Emergent Adverse Event
TDI	Transition Dyspnoea Index
□z	(Terminal) elimination rate constant
VT	Ventricular tachycardia
t½	Terminal elimination half-life
µg	Microgram(s)
µL	Microlitre(s)
%	Percentage

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Almirall S.A submitted on 24 October 2013 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Duaklir Genuair, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 21 March 2013.

The applicant applied for the following indication: "Duaklir Genuair is indicated as a maintenance bronchodilator treatment for airflow obstruction and relief of symptoms in adult patients with chronic obstructive pulmonary disease (COPD)."

The legal basis for this application refers to:

Article 10(b) of Directive 2001/83/EC – relating to applications for fixed combination medicinal product.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision C/W/2011 on the granting of a class waiver.

The proposed indication is for the symptomatic treatment of Chronic Obstructive Pulmonary Disease (COPD). This indication is not applicable for the paediatric population. Therefore no studies have been conducted in the paediatric population.

On 30 April 2009, the European Medicines Agency (EMA) confirmed the applicability to aclidinium/formoterol of the EMA decision (P/1/2007) of 3 December 2007 on a class waiver from the European Paediatric Regulation (Regulation [EC] Number 1901/2006) granted for the condition COPD. Aclidinium/formoterol is indicated for adult patients only.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 20 May 2010, 4 October 2010 and 23 June 2011.The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier. At this time, the Phase II dose finding studies were ongoing (LAC-MD-27, M/40464/26) and the Applicant sought advice with regard the proposed overall clinical programme (including the clinical pharmacology and Phase III programmes) and safety database. CHMP clarifications on aspects of the advice received on the

clinical pharmacology programme were given in October 2010.

Once the results from the Phase II dose-finding studies of aclidinium/formoterol (LAC-MD-27, M/40464/26) and from the Phase III studies of aclidinium monotherapy were available, the Applicant revised the proposed clinical development programme in accordance with the CHMP Scientific Advice received in 2010. Follow-up Scientific Advice was provided by the CHMP in June 2011 regarding the dose-selection for the Phase III studies of aclidinium/formoterol, the revised Phase III clinical programme and the clinical data required to support the bridge between the registered formoterol monotherapy (Foradil® Aerolizer®) and formoterol monotherapy via Genuair®.

Licensing status

A new application was filed in the following countries: Canada.

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

1.2. Manufacturers

Manufacturer responsible for batch release

Industrias Farmacéuticas Almirall, S.A.
Ctra. Nacional II, Km 593
08740 Sant Andreu de la Barca, Barcelona
Spain

1.3. Steps taken for the assessment of the product

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

Rapporteur: Robert James Hemmings Co-Rapporteur: Piotr Fiedor

- The application was received by the EMA on 24 October 2013.
- The procedure started on 20 November 2013.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 7 February 2014. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 7 February 2014.
- During the meeting on 6 March 2014 the Pharmacovigilance Risk Assessment Committee (PRAC) adopted the PRAC Advice on the submitted Risk Management Plan.
- During the meeting on 20 March 2014, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 21 March 2014.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 23 May 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 30 June 2014.
- During the CHMP meeting on 24 July 2014, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 15 August 2014.

- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 2 September 2014.
- During the meeting on 11 September 2014 the Pharmacovigilance Risk Assessment Committee (PRAC) adopted the PRAC Advice on the submitted Risk Management Plan.
- During the meeting on 25 September 2014, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Duaklir Genuair.

2. Scientific discussion

2.1. Introduction

Problem statement

COPD is a preventable respiratory disorder characterised by airflow limitation, which is not fully reversible. The airflow limitation is usually progressive and is associated with an abnormal inflammatory response in the lungs to noxious particles or gases, primarily caused by cigarette smoking. COPD is characterized by symptoms of chronic and progressive breathlessness (or dyspnea), cough, and sputum production which can be a major cause of disability and anxiety associated with the disease.

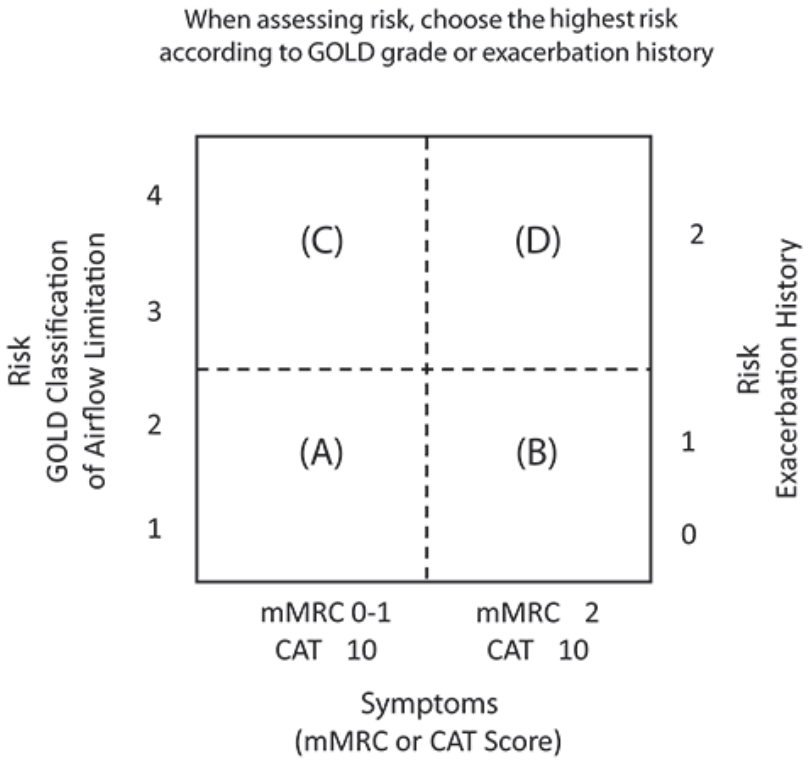
The disease is not limited to the airways and treating physicians are faced with a multi-component disease that is characterised by a range of pathological changes, which include mucous hypersecretion, airway narrowing, loss of alveoli in the lungs, and loss of lean body mass and cardiovascular effects at a systemic level. COPD patients are also heterogeneous in terms of their clinical presentation, disease severity and rate of disease progression. Their degree of airflow limitation, as measured by FEV_1, is also known to be poorly correlated to the severity of their symptoms.

COPD is a major cause of chronic morbidity and mortality throughout the world. It is estimated that approximately eight percent of the population have COPD and approximately ten percent of those over 40 years of age. However the true prevalence of the disease is likely to be higher than this due to under-diagnosis and delayed diagnosis until the disease becomes clinically apparent and is then moderately advanced. COPD is the fourth leading cause of death in Europe and is expected to rise to third by 2020.

The goals of COPD assessment are to determine the severity of the disease, its impact on patient's health status and the risk of future events (such as exacerbations, hospital admissions or death), in order to, eventually guide therapy. The most used classification based on severity of airflow limitation in COPD (based on post-bronchodilatory FEV1) is the Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification. Patients with FEV1/FVC <0.70 are classified into mild, moderate, severe and very severe based on spirometry as below:

GOLD 1	Mild	FEV1 ≥ 80% predicted
GOLD 2	Moderate	50% ≤ FEV1 < 80% predicted
GOLD 3	Severe	30% ≤ FEV1 < 50% predicted
GOLD 4	Very Severe	FEV1 < 30% predicted

Recently, GOLD has recommended an approach of combined COPD assessment based on the impact of COPD on an individual patient which combines symptomatic assessment with the patient's spirometric classification and/or risk of exacerbations. This approach is illustrated below.



Patient Category	Characteristics	Spirometric Classification	Exacerbations Per Year	mMRC	CAT
A	Low Risk, Less Symptoms	GOLD 1-2	1	0-1	<10
B	Low Risk, More Symptoms	GOLD 1-2	1	2	10
C	High Risk, Less Symptoms	GOLD 3-4	2	0-1	<10
D	High Risk, More Symptoms	GOLD 3-4	2	2	10

The most important aspect of management of the condition is educational and social: the avoidance and cessation of tobacco smoking. However, once COPD is established the recommendations for the pharmacological treatment of COPD are based on the severity of the condition. The current GOLD recommendations on the pharmacological therapy for stable COPD are depicted below:

Patient Group	**Recommended first choice**	**Alternative choice**	**Other possible treatments**
A	SA anticholinergics prn or SA beta2-agonist prn	LA anticholinergic or LA beta2- agonist or SA beta2-agonist and SA anticholinergic	Theophylline
B	LA anticholinergic or LA beta2-agonist	LA anticholinergic and LA beta2-agonist	SA beta2-agonist and/or SA anticholinergic

			Theophylline
C	ICS + LA beta2-agonist or LA anticholinergic	LA anticholinergic and LA beta2-agonist or LA anticholinergic and PDE-4 inhibitor or LA beta2-agonist and PDE4 inhibitor	SA beta2-agonist and/or SA anticholinergic Theophylline
D	ICS + LA beta2-agonist and/or LA anticholinergic	ICS + LA beta2-agonist and LA anticholinergic or ICS + LA beta2-agonist and PDE4 inhibitor or LA anticholinergic and LA beta2-agonist or LA anticholinergic and PDE-4 inhibitor	Carbocysteine SA beta2-agonist and/or SA anticholinergic Theophylline

The GOLD recommendation is that the combined use of long-acting beta agonists and anticholinergics may be considered if symptoms are not improved with single agents (Evidence - B which is randomized controlled trials – limited body of data).

About the product

Duaklir Genuair is a fixed dose combination of two known active substances: aclidinium bromide, a long-acting muscarinic antagonist (LAMA) which was granted a marketing authorisation in the European Union (EU) in July 2012, and formoterol fumarate dihydrate, a long-acting β2-adrenergic receptor agonist (LABA) which has been marketed in the EU for more than 15 years. Approved bronchodilators, such as LABAs and LAMAs, have been available for the treatment of COPD patients since 2004 and they can be used alone or together.

Duaklir Genuair 400/12 µg inhalation powder in a device-metered dry powder inhaler (DPI) dry powder for oral inhalation.

Each delivered dose (the dose leaving the mouthpiece) contains 396 mcg of aclidinium bromide (equivalent to 340 mcg of aclidinium) and 12 mcg of formoterol fumarate dihydrate. This corresponds to a metered dose of 400 micrograms of aclidinium bromide (equivalent to 343 mcg of aclidinium) and a metered dose of 12 mcg of formoterol fumarate dihydrate.

The Applicant initially applied for the following indication:

- Duaklir Genuair is indicated as a maintenance bronchodilator treatment for airflow obstruction and relief of symptoms in adult patients with chronic obstructive pulmonary disease (COPD).

The posology requested is one inhalation of Duaklir Genuair 340/12 mcg twice daily.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as inhalation powder containing 400 micrograms of aclidinium bromideand 12 micrograms of formoterol fumarate dihydrate as active substances. Each delivered dose (the dose leaving the mouthpiece) contains 396 micrograms of aclidinium bromide (equivalent to 340 micrograms of aclidinium) and 12 micrograms of formoterol fumarate dihydrate.

Other ingredients are: lactose monohydrate

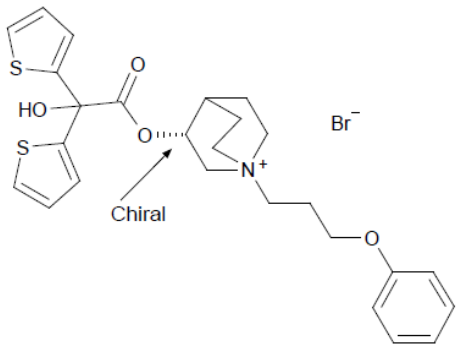
The product is available in an inhaler which is a multicomponent device made of plastic (polycarbonate, acrylonitrile-butadiene-styrene, polyoxymethylene, polyester-butylene-terephthalate, polypropylene, polystyrene) and stainless steel. The mouthpiece is covered with a removable protective cap. The inhaler is supplied sealed in a protective aluminium laminate pouch containing a desiccant sachet.

2.2.2. Active substance

Aclidinium Bromide

General information

The chemical name of aclidinium bromide is (3R)-3-[(hydroxy)di(thiophen-2-yl)acetyloxy]-1-(3-phenoxypropyl)-1λ5-azabicyclo[2.2.2] octan-1-ylium bromide or 1-Azoniabicyclo[2.2.2]octane, 3-[(hydroxydi-2-thienylacetyl)oxy]-1-(3-phenoxypropyl)-, bromide, (3R)-and has the following structure:



The tests used to characterise aclidinium include elemental analysis, UV 1H and 13C NMR, IR, X-ray powder diffraction, chiral centre confirmation and physiochemical characterisation.

Aclidinium bromide is a non-hygroscopic white or off-white crystalline powder sparingly soluble in methanol, very slightly soluble in water and in ethanol, and practically insoluble in acetone, ethyl acetate, tetrahydrofuran and toluene.

Aclidinium bromide exhibits stereoisomerism due to the presence of 1 chiral centre. Aclidinium bromide was shown to exist in a single crystalline form (Form I).. The information on the active substance is provided according to the Active Substance Master File (ASMF) procedure.

Manufacture, characterisation and process controls

At the time of the CHMP opinion, aclidinium bromide information was assessed in Eklira and Bretaris Genuair which were granted a marketing authorisation in the EU in July 2012.

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

Specification

The active substance specification includes tests for description, melting point (Ph Eur), identification (IR, Bromides), loss on drying (Ph Eur), sulphated ash (Ph Eur), heavy metals, assay (HPLC), organic impurities (HPLC), residual organic solvents (Ph Eur), particle size distribution (laser diffraction).

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines.

Batch analysis data (3 validation batches) of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on 3 production batches of active substance from the manufacturer stored in the intended commercial package for 60 months under long term conditions at 25 ºC / 60% RH and 30 ºC / 65% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. Photostability testing following the ICH guideline Q1B was performed. Forced degradation studies exposing the active substance to acid, base, aqueous, oxidative and high intensity light conditions have also been performed demonstrating that the active substance is sensitive to basic, acidic and oxidative conditions . Supporting data was provided to support the proposed requirements for storage and labelling and to demonstrate that standard handling and storage procedures for micronized aclidinium bromide are sufficient to ensure that the quality and the consistency of the active substance are maintained. This includes a risk assessment of the various handling and storage considerations.

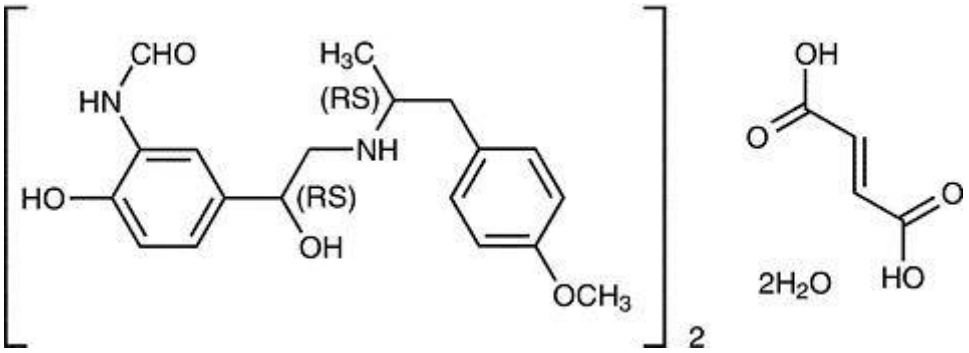
The analytical methods and parameters used were the same as for release and were stability indicating.

The stability results indicate that the drug substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period in the proposed container.

Formoterol

Formoterol fumarate dihydrate is an established active substance described in Ph Eur.

The chemical name of formeterol is (±)-N-[2-hydroxy-5-[(1RS)-1-hydroxy-2-[[(1RS)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl] formamide, (E)-2-butenedioate (2:1 salt) dihydrate and has the following structure:



As there is a monograph of formoterol in the European Pharmacopoeia, the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for formoterol fumarate dihydrate which was provided within the current Marketing Authorisation Application.

Manufacture, characterisation and process controls

The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.

Specification

The control tests were carried out to comply with the specifications and test methods of the Ph. Eur. monograph. In addition to the compendial tests the active substance manufacturer routinely controls identification of crystal form and degree of crystallinity, residue on ignition, heavy metals, palladium, residual solvents, particle size distribution and microbiological purity. The finished product manufacturer carries out additional tests for palladium, residual solvents and particle size distribution. All additional methods were adequately validated and described according to ICH Q2.

Stability

The relevant information was assessed by the EDQM before issuing the Certificate of Suitability.

In addition to the stability testing being carried out by the active substance manufacturer, supportive stability studies to control some specific parameters were carried out during the development program. These specific parameters include those considered as potentially critical for a drug substance to be used in an inhalation product.

Supportive stability studies were performed on the same three micronized batches used as primary ICH stability batches and was completed with 36 months data at 25ºC/60%RH, 12 months data at 30ºC/65%RH and 6 month data at 40ºC/75%RH.

The stability results indicate that the drug substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period in the proposed container.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

Aclidinium bromide and formoterol fumarate dihydrate was formulated as a combination in the finished medicinal product of the active substances and lactose monohydrate as sole excipient in the device metered Genuair dry powder inhaler as the primary packaging.

A fixed combination of aclidinium bromide/formoterol fumarate dihydrate inhalation powder was developed based on the development of the aclidinium monotherapy inhalation powder.

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

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

Inclusion of a lock-out mechanism and overfill in the inhaler means that there is no tail-off in the performance up to the labelled number of actuations when the lock-out of the device occurs beyond the labelled number of actuations. Several studies, including “in-use” studies, investigating delivered dose and fine particle dose of the inhalation powder confirmed the consistent pharmaceutical performance beyond actuation 60.

The inhalation powder is presented in a device-metered dry powder inhaler as the primary packaging, which contains not less than 60 actuations per cartridge. This is overwrapped and heat-sealed in an aluminium pouch with a desiccant sachet. The inhalation powder is permanently situated in a device-metered dry powder inhaler with an integral dose indicator and a removable protective cap. The inhaler is sealed in an aluminium pouch. The material in contact with the inhaler is manufactured in accordance with the EU requirements for direct contact with food and drugs (EU Regulation No. 10/2011, as amended). All tests and specifications together with certificates of analysis from the approved supplier and the finished product manufacturer were provided and all results met specification.

The desiccant sachet also complies with current EU requirements.

Manufacture of the product and process controls

The manufacturing process consists of 3 main steps: blending and sieving, dosing and assembly, labelling and packaging.

The manufacturing formula, flow chart and description of the manufacturing process were provided.

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

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this pharmaceutical form.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: description, active substance identification (HPLC-UV and Diode Array Detection (DAD), physicochemical properties (filling, number of actuations per inhaler), purity by Rapid Resolution Liquid Chromatography (RRLC), water content, assay (HPLC), particle size (HPLC) and microbiological control.

Batch analysis data on 3 production scale batch and several supportive batches (development, clinical and stability batches) has been provided. Data batches confirm consistency and uniformity of the product indicating that the process is under control.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data of 3 production scale batches of finished product stored under long term conditions for 36 months at 25 ºC / 60% RH, intermediate storage conditions of 30°C/75% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided.

The batches of the medicinal product are to those proposed for marketing and were packed in the primary packaging proposed for marketing.

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

In addition ICH Guideline on Photostability Testing of New Drug Substances and Products was performed.

Samples were tested for: appearance, physicochemical properties, identification of the active substance, assay, purity, water content and microbial control. The analytical procedures used are stability indicating.

Based on available stability data, the shelf-life and storage conditions as stated in the SmPC are acceptable.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.2.6. Recommendation for future quality development

N/A

2.3. Non-clinical aspects

2.3.1. Introduction

The non-clinical studies conducted in support of this application are limited to three non-GLP cardiovascular safety pharmacology studies, a preliminary maximum tolerated dose inhalation study and two GLP inhalation toxicity bridging studies of 4 and 13 weeks duration. The data submitted were assessed with respect to the legal basis of the application, applicable guidelines and other scientific criteria. Limited new non-clinical studies have been submitted. The pivotal repeated-dose inhalation toxicity studies were conducted in accordance with GLP. However, three cardiovascular safety pharmacology studies were not conducted according to GLP. The Applicant argues that the data quality and integrity were to good scientific standards and in line with the Guideline on Safety pharmacology studies for human pharmaceuticals (ICH S7A). This was considered acceptable by the CHMP.

2.3.2. Pharmacology

Primary pharmacodynamic studies and Secondary pharmacodynamic studies

The pharmacological profiles of both aclidinium and formoterol have been extensively characterised and it is accepted that their bronchodilator activity is achieved by different mechanisms of action. Aclidinium is a cholinergic antagonist with a strong and selective affinity for the human M3 muscarinic receptor, whereas formoterol is a long-acting selective β2-adrenergic receptor agonist.

No additional primary or secondary pharmacology studies have been conducted using the combination which is in line with ICH and EU guidance on developing a fixed dose combination product containing two approved compounds. The lack of primary and secondary pharmacology studies is accepted by the CHMP.

Safety pharmacology programme

No safety pharmacology studies apart from cardiovascular safety studies were performed with the combination of aclidinium and formoterol since each individual component has been extensively investigated in various studies on CNS, respiratory, renal/urinary and gastrointestinal safety models, and pharmacological interactions are not expected from the combination of these two agents given their different modes of action.

Two non-GLP cardiovascular safety studies have been conducted in dogs using the i.v. route to further

investigate the ventricular tachycardia finding in the 4-week toxicity bridging study in dogs using the combination via the inhalation route (RCC A25301). The dog was selected for safety evaluation of both aclidinium and formoterol as it is considered a suitable model for the detection of cardiovascular effects.

A third study was performed to assess the effects on heart rate of aclidinium administered concomitantly with formoterol or salmeterol, and tiotropium administered concomitantly with the same β2-adrenergic agonists (FD0601JG).

Study FD0603MV

The cardiovascular safety and of the combination of aclidinium and formoterol in a 17:1 ratio have been evaluated in conscious beagle dogs by i.v. administration (Table 2.4-2).

Table 2.4-2: Arrhythmogenic effects assessed at 24 hours of aclidinium, formoterol and their combination (ratio 17:1) administered intravenously to conscious beagle dogs

Treatment*	Doses (µg/kg)	Number of animals with ventricular tachycardia at 24 h
Formoterol	1	0/4
	3	1/4
	10	4/4
Aclidinium + Formoterol	17+1	0/4
	50+3	2/4
	167+10	3/4
Aclidinium	50	0/4
	167	0/4

* Four dogs received all the treatments

Formoterol dose-dependently induced ventricular tachycardia (VT) in the study. Formoterol 1 µg/kg did not induce VT. In contrast, VT appeared in one and four out of the four formoterol-treated dogs at the doses of 3 and 10 µg/kg respectively. When the combination of aclidinium and formoterol was administered at the lowest dose (17+1 µg/kg), no VT was observed. However, VT appeared in two animals at the dose of 50+3 µg/kg of the combination of aclidinium and formoterol, and in three out of four animals, at the highest dose (167+10 µg/kg).

Study BIOL0835

A second cardiovascular safety study was performed in dogs to assess the effects of the combination of formoterol and aclidinium on VT at the 33:1 ratio used in the aclidinium/formoterol intended therapeutic dose (400/12 µg BID) for the treatment of patients with COPD.

Table 2.4-3: Arrhythmogenic effects assessed at 24 hours of formoterol and the combination of aclidinium and formoterol (ratio 33:1) administered intravenously to conscious beagle dogs

Treatment*	Doses (µg/kg)	Number of animals with ventricular tachycardia at 24 h
Formoterol	3	1/4
Aclidinium + Formoterol	33+1	0/4
	100+3	4/4

*Four dogs received all 3 treatments

Formoterol 3 µg/kg caused ventricular tachycardia in one out of four dogs, consistent with the formoterol results reported previously. Concerning the effects of the combination of aclidinium and formoterol at the dose of 33+1 µg/kg, no animals showed arrhythmias. At the dose of 100+3 µg/kg, VT was observed in four out of four animals. However, the incidence on VT was less than 1% of cardiac beats in the 90-minute observation period in two dogs. Therefore, the effects on VT are not considered different between formoterol at 3 mg/kg dose and aclidinium/formoterol combination at 100+3 mg/kg dose in this study. The dose of 100+3 µg/kg produced very high systemic exposure in the test animals compared to human dose based on C_{max} (1,471 times for aclidinium and 297 times for formoterol).

The dose of the combination that did not result in VT in this study (33+1 µg/kg) produced a systemic exposure that is 286 times higher for aclidinium and 71 times higher for formoterol based on C_{max}, compared with the systemic exposure at the MRDD of aclidinium/formoterol 400/12 µg BID for the treatment of patients with COPD (C_{max}: 0.128 ng/mL for aclidinium, and 0.0167 ng/mL for formoterol; LAC-PK-01).

Study FD0601JG

In addition, a third study was performed to assess the effects on heart rate of aclidinium administered concomitantly with formoterol or salmeterol, and tiotropium administered concomitantly with the same β2-adrenergic agonists.

In this study, aclidinium 10 µg/kg administered intravenously in combination with formoterol 0.3 µg/kg produced a numerically smaller increase in heart rate than tiotropium 10 µg/kg administered in combination with formoterol 0.3 µg/kg or salmeterol 3 µg/kg; however, the changes were not statistically significantly different from those observed for tiotropium 10 µg/kg in combination with the same β2-adrenergic agonists. The duration of the chronotropic effect measured as time to decrease the effect by 50% (t½) was statistically significantly shorter for aclidinium plus formoterol or salmeterol compared with tiotropium plus formoterol or salmeterol.

Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies have been conducted. Based on the well-established, distinct mechanisms of action for both active substances no drug-interactions are expected. The arguments for not performing pharmacodynamic drug interaction studies were regarded as acceptable by the CHMP.

2.3.3. Pharmacokinetics

The pharmacokinetics of aclidinium and formoterol monotherapies have been adequately characterised in animals together with their enzyme induction and inhibition profiles.

The pharmacokinetic properties of aclidinium after inhalation include: absorption from the lung; a low oral bioavailability of the swallowed fraction of the administered dose; tissue distribution (mainly in the bladder, pancreas, kidneys and tissues of the gastrointestinal tract) and, as a principal characteristic, rapid and complete clearance from the body as a consequence of its non-enzymatic (chemical) and enzymatic ester hydrolysis.

The major metabolite circulating in plasma is the acid derivative, LAS34850 (human plasma half-life 9.4 h), whereas the plasma levels of the alcohol metabolite, LAS34823, are normally similar to those for the unchanged drug. Both metabolites are devoid of pharmacological activity. Because of the low plasma levels achieved at clinically relevant doses, aclidinium and its two metabolites are not expected to alter the disposition of medicinal products metabolised by the human cytochrome P450 (CYP) enzymes and esterase activities.

Formoterol is rapidly absorbed into plasma after inhalation, reaching a maximum plasma concentration within 5 minutes after dosing. A fraction of inhaled formoterol is deposited in the mouth and is most likely absorbed in the gastrointestinal tract. The most prominent metabolic pathway involves direct conjugation at the phenolic hydroxyl group. Secondary metabolic pathways include deformylation and sulfate conjugation. CYP2D6, CYP2C19, CYP2C9 and CYP2A6 have been identified as being primarily responsible for O-demethylation.

As the pharmacokinetic profiles of both active substances have previously been characterised, no additional studies with individual active substances are required. In addition, given the different metabolic profiles and apparent lack of interaction from TK and clinical exposure data, no further pharmacokinetic studies with the combination are considered necessary by the CHMP.

Methods of analysis

Aclidinium and its metabolites LAS34823 and LAS34850

Aclidinium bromide, a quaternary ammonium ester salt, in plasma in vivo is rapidly hydrolysed to its alcohol (LAS34823) and carboxylic acid (LAS34850) metabolites. A liquid chromatography–tandem mass spectrometry (LC-MS/MS) bioanalytical method was developed using PMSF to stabilise the preclinical samples. The assay was validated under strictly controlled conditions of time and temperature during the freeze/thaw process of samples and was successfully validated without stability issues. The approach of stabilization of the blood samples with esterase inhibitor immediately upon blood collection was successfully applied to analysis of dog plasma samples with concentration ranges of 0.1-30 ng/mL for aclidinium bromide and LAS34823, and 5-200 ng/mL for LAS34850.

Formoterol

Two LC-MS/MS bioanalytical methods were developed for the determination of formoterol in dog plasma.

1) Method used in MTD (B.273FO.A) and 4-week inhalation study in dogs (B.273FO.02).

The determination of formoterol in dog plasma (0.1 mL) was carried out by LC/MS/MS (positive ionisation) using MRM ion detection. The analyte was extracted from plasma by an automated protein precipitation extraction procedure using the compound LAS39017 as internal standard. The ionization of the analyte was performed in a TurboIonSpray source, which makes use of a heated auxiliary gas flow. The results obtained in terms of selectivity, linearity, quantitation limit, intra- and inter-batch precision and accuracy, recovery, stability, dilution effect and matrix effect demonstrated the suitability of this method for the quantitative measurements of formoterol in dog plasma (0.1 mL) within the validated concentration range of 0.1-10 ng/mL.

2) Method used in the 13-week inhalation toxicity study in dogs (B.273FO.04).

A new bioanalytical method was developed and validated for the determination of formoterol in dog plasma (0.1 mL) within the concentration range of 10-2000 pg/mL. The determination of formoterol was carried out by LC/MS/MS (positive ionisation) using MRM ion detection. The analyte was extracted from plasma by an automated protein precipitation extraction procedure using deuterated formoterol (formoterol-D6) as internal standard. The ionisation of the analyte was performed in a TurboIonSpray source, which makes use of a heated auxiliary gas flow. The results obtained in terms of selectivity, linearity, quantification limit, intra- and inter-batch precision and accuracy, recovery, stability, dilution effect and matrix effect demonstrated the suitability of this validated concentration range of 10-2000 pg/mL. Appropriate, validated methods of analysis have been used to detect and quantify both active substances in samples taken in the combination toxicity studies.

Absorption

The absorption of aclidinium and formoterol has been assessed in the toxicokinetics conducted during the 4-week and 13-week inhalation toxicity studies in dogs.

In the 13-week inhalation toxicity study in dogs (B.273FO.04), the main aclidinium metabolite circulating in plasma was the acid derivative, LAS34850, achieving AUC_{0-24} values up to 98-fold higher than those of the unchanged compound. By contrast, the plasma levels of the alcohol metabolite, LAS34823, were somewhat similar or slightly higher than those of aclidinium. This pharmacokinetic behaviour is in agreement with the results found in the previous 4-week inhalation toxicity study of aclidinium/formoterol in dogs (B.273FO.02).

There was a trend of increasing exposure parameters of aclidinium and formoterol in relation to the administered dose. Nevertheless, since the plasma levels were subject to a high degree of variability no clear C_{max}/dose or AUC/dose relationships were observed. The comparison between sexes for both aclidinium and formoterol administered alone or in combination showed also a high degree of variability with no significant differences. The comparison between days of treatment for aclidinium showed variable results with no clear differences, whereas for formoterol the exposure found in Week 13 (C_{max} and AUC_{0-24}) was in general lower than that found on Day 1 of treatment, which is consistent with the results obtained in the previous 4-week inhalation toxicity study in dogs (B.273FO.02).

The plasma levels measured after administration of aclidinium 300 µg/kg/day or formoterol 18 µg/kg/day administered alone were higher than those obtained when the active substances were administered in combination (aclidinium/formoterol 300/18 µg/kg/day). This tendency was more clearly observed for formoterol than for aclidinium. However, the mean estimated achieved dose of aclidinium after administration of the combination was about 10-20% below the target dose for aclidinium in the combination, due to a slight increase in the proportion of formoterol (which was targeted in the calculations) in the blend during aerosol generation. On the other hand, there was a higher variability (CV up to 50%) in the plasma levels of formoterol in the animals treated with formoterol alone.

Distribution

No distribution studies have been conducted with aclidinium/formoterol since both individual active substances have been comprehensively investigated.

Metabolism

No metabolism studies have been conducted with aclidinium/formoterol since both individual active substances have been comprehensively investigated and have shown different metabolic pathways.

Excretion

No excretion studies have been conducted with aclidinium/formoterol since both active substances have been comprehensively investigated.

Pharmacokinetic drug interactions

No formal pharmacokinetic drug interaction studies have been conducted with aclidinium/formoterol since the toxicokinetic studies and clinical assays (M/273FO/22, LAC-PK-01 and M/40464/02) have shown that there was no pharmacokinetic drug interaction between both active substances and they have different metabolic pathways. The potential drug-drug interactions of aclidinium and formoterol monotherapies have been extensively investigated. The CHMP agreed that no further pharmacokinetic drug interaction studies are required.

Other pharmacokinetic studies

2.3.4. Toxicology

For nonclinical safety assessment of aclidinium/formoterol, a preliminary maximum tolerated dose inhalation study, and GLP 4-week and 13-week inhalation toxicity bridging studies were conducted in beagle dogs.

The dog was selected for safety assessment of both aclidinium and formoterol, because the heart is the primary toxicity target organ for both drug substances and the dog is a suitable model for the detection of cardiovascular effects.

Formoterol is the more pharmacologically active and potentially toxic component in the aclidinium/formoterol combination. Therefore, the dosages of aclidinium/formoterol used in nonclinical studies were determined by the formoterol component.

Single dose toxicity

No formal single-dose toxicity studies have been conducted with aclidinium/formoterol since both individual active substances have been comprehensively investigated. The argument for not performing single-dose toxicity studies was regarded as acceptable by the CHMP. However, single inhalation doses up to 800/48 µg/kg of aclidinium/formoterol (ratio 17:1) were administered to dogs in the maximum tolerated dose study.

Repeat dose toxicity

Maximum Tolerated Dose Study (RCC A25290)

A 10% blend of aclidinium/formoterol (ratio 200:12 [17:1]) in lactose was administered by inhalation to beagle dogs. During the first phase of the study, the animals (1M+1F) from Group 1 were exposed to single target doses of 100/6, 300/18, 400/24, 500/30, 600/36, 700/42, and 800/48 µg/kg of aclidinium/formoterol for 13 days including 8 treatment days. During the second phase of the study, the animals (2M+2F) from Group 2 were given aclidinium/formoterol 800/48 µg/kg/day for 7 consecutive days.

Tremor, excessive licking, reddening of the conjunctiva, and restlessness were common observations noted in both phases of the study. Low food intake and weight loss were also noted in both phases.

Tachycardia associated with an increase in the P-wave amplitude and decreases in the PQ and QT intervals were observed for all animals in this study. The tachycardia was due to the pharmacologic action of formoterol, a β-agonist, and was not associated with any gross arrhythmias in the ECG.

There were no macroscopic findings that were considered to be related to treatment with aclidinium/formoterol. Based on the results from this study, a dosage of 800/48 µg/kg per day for 7 days was considered to be in excess of the maximum tolerated dose. A dosage of 500/30 µg/kg/day was considered appropriate for use in the 4-week toxicity study in this species.

GLP 4-Week Inhalation Toxicity Study (RCC A25301)

Species	Duration	Route	Target and Mean Estimated Achieved Dose* (µg/kg/day)	Main results
Dog	4 weeks	Inhalation	0/0 (lactose), 33/2 (28.1/2.0), 100/6 (84.5/6.0), 500/30 (420/29.9)	**Mortality:** All animals survived **- Aclidinium/formoterol 33/2:** Increased heart rate, increased P-amplitude with decreased PQ and QT intervals; clinical pathology revealed increased potassium (males) **- Aclidinium/formoterol 100/6:** ***Clinical Signs***—dry oral mucous membranes; increased heart rate, increased P-amplitude with decreased PQ and QT intervals; ECG revealed ventricular arrhythmias and multifocal ventricular tachycardia during Week 1 (not Week 4); clinical pathology revealed increased potassium (females) **- Aclidinium/formoterol 500/30:** ***Clinical Signs***—dry oral mucous membranes; dry eyes; swollen areas and erythema around the mouth; decreased food consumption and body weight loss in females; increased heart rate; increased P-amplitude with decreased PQ and QT intervals; 24-h heart rate values were lower at Week 4 compared with Week 1; ECG revealed ventricular arrhythmias and multifocal ventricular tachycardia during Week 1 (not Week 4); clinical pathology revealed increased potassium (both sexes) and creatinine (females); histopathology revealed minimal to slight fibrosis of papillary muscle of the heart and moderate medial proliferation of the intramural arteries of the papillary muscle (these lesions were not noted at recovery) **NOAEL:** Aclidinium/formoterol 100/6 (84.5/6.0) µg/kg/day

(*) Mean estimated achieved doses are given in parentheses

A 10% blend of aclidinium/formoterol (ratio 200:12 ratio [17:1]) in lactose was administered to beagle dogs (3M + 3F) by the inhalation route for 4 weeks. Two additional dogs of each sex in Groups 1 and 4 were kept for a 2-week treatment-free recovery period following the treatment period to assess the reversibility of test item–related effects.

In the animals receiving 500/30 µg/kg/day, minimal to slight myocardial fibrosis in the papillary muscle of the heart occurred in three dogs; ventricular arrhythmias occurred in seven out of ten dogs on Day 2 of study. No cardiac lesions were observed at 100/6 µg/kg/day. However, at this dosage, ventricular arrhythmias were observed in two out of six dogs on Day 2 at predose however not at 2 h or 24 h after dosing on Day 2. This cardiac effect is considered to be related to formoterol.

The only effects of note at the dosage of 100/6 µg/kg per day were severe ventricular arrhythmias. However, the dog is particularly sensitive to this effect of β-agonists and in the absence of morphologic changes in the heart it may be considered unlikely to be significant in man at therapeutic dosages.

The dosage of 100/6 µg/kg/day of aclidinium/formoterol was considered the NOAEL, which produced 11 and 7 times the aclidinium exposure and 18 and 5 times the formoterol exposure, based on Cmax and AUC respectively, at the maximum recommended daily dose of aclidinium/formoterol 400/12 µg BID for the treatment of patients with COPD.

In the 4-week repeat-dose toxicity study, cardiac effects were noted at ≥ 33/2 mg aclidinium/fomoterol which were attributed to the formoterol component of the combination. Unfortunately the monotherapies were not included as separate arms in the study, thus limiting the conclusions that can be drawn. However, the individual active substances were included in the 13-week toxicity study allowing full assessment of any additive or synergistic toxic effects.

In the toxicokinetic study, unexpected concentrations of aclidinium were found on Day 1 and Week 4 in some plasma samples from control group animals. The Applicant argues that this contamination probably occurred ex vivo after blood collection, since no plasma levels of the main metabolite were found. In inhalation studies, it is reasonably common for actives to be detected in the plasma of a small number of control animals. Taking into account the rapid hydrolysis of aclidinium, the presence of aclidinium but no metabolites in the plasma at 24 hours post dosing on week 1 and 4 the Applicant's explanation seems feasible.

Exposures following administration of the low dose in the 4-week study were comparable with those obtained in the 13-week study and therefore the impact of this contamination on exposure parameters and conclusions drawn for aclidinium is deemed to be minimal by the Applicant. However, since it is possible that the AUC(0-24) values are an overestimation, as a precaution only the AUC(0-4) values have been used to calculate safety margins.

13-Week Inhalation Toxicity Study (RCC A25312)

Species	Duration	Route	Target and Mean Estimated Achieved Dose* (µg/kg/day)	Main results
Dog	13 weeks	Inhalation	0/0 (lactose), 33/2 (28.4/2.0), 100/6 (84.0/5.9), 300/18 (246.9/17.4), 300/0 (301.5/0), 0/18 (0/17.4)	**Mortality:** All animals survived - **Aclidinium/formoterol 33/2:** ***Clinical signs***—increased heart rate ***Clinical pathology***—increased creatinine - **Aclidinium/formoterol 100/6:** ***Clinical Signs***—increased heart rate ***Clinical pathology***—increased creatinine - **Aclidinium/formoterol 300/18:** ***Clinical signs***—increased heart rate ***Clinical pathology***—increased creatinine ***Cardiology***—slight increase in P-amplitude with decreased PQ and QT intervals; persistent multifocal ventricular tachycardia or intermittent ventricular tachycardia with ventricular premature complexes were observed 24 h after the first day of dosing in two animals; no morphologic changes were noted in the heart muscle - **Aclidinium/formoterol 300/0:** Transient tachycardia; one animal had ventricular premature complexes - **Aclidinium/formoterol 0/18:** ***Clinical signs***—increased heart rate ***Clinical pathology***—increased creatinine ***Cardiology***—slight increase in P-amplitude with decreased PQ and QT interval **NOAEL:** Aclidinium/formoterol 100/6 (84.0/5.9) µg/kg/day

(*) Mean estimated achieved doses are given in parentheses

Aclidinium/formoterol (ratio 200:12 [17:1]) was administered at target dosages of 0/0 (lactose), 33/2, 100/6, 300/18, 300/0, or 0/18 µg/kg/day to beagle dogs for 13 weeks. Two additional dogs of each sex in Groups 1, 4, 5 and 6 were kept for a 4-week treatment-free recovery period following the treatment period to assess the reversibility of test item-related effects.

In the 13-week repeat-dose toxicity study, cardiac effects were observed in all groups that received the combination or either active alone. An increase in mean blood creatinine levels was observed in all groups treated with formoterol.

Transient tachycardia occurred in all groups receiving aclidinium/formoterol, and aclidinium or formoterol. In addition, an increase in mean blood creatinine levels was observed in groups treated with formoterol.

The increased heart rate was considered to reflect an exaggerated pharmacological response to the administration of the β2-agonist (formoterol) and, to a lesser extent, to the administration of the M3 muscarinic antagonist (aclidinium). The ventricular arrhythmias observed 24 hours after the first dosing at 300/18 µg/kg/day were considered to be related to this effect. Ventricular arrhythmias only occurred in two out of twelve dogs on the first day following administration of aclidinium/formoterol at the high dosage. The decrease in magnitude and incidence of these changes after the first day of dosing indicates some accommodation. There were no effects on the ECG at the end of the recovery period. There were no morphologic changes in the heart at microscopic examination.

The increased creatinine levels were probably also related to the increased muscular activity in the heart, particularly caused by formoterol, since no increase in creatinine levels was observed in the group treated with aclidinium alone. This was still apparent at the end of the recovery period.

Following microscopic evaluation, no morphological changes to the heart were seen for any of the treatment groups. It is noted that amendments to the study report were made to allow microscopic re-examination of the sections of the heart for signs of potential injury followed by repair, however no evidence of these effects was seen.

In the absence of any morphologic findings in the heart or significant arrhythmias at dosages of 33/2 or 100/6 µg/kg/day, the increase in heart rate was considered not to result in any adverse effect at these dosage levels. The dosage of 100/6 µg/kg/day of aclidinium/formoterol was considered the NOAEL, which produced 14 and 9 times the aclidinium exposure and 20 and 8 times the formoterol exposure based on Cmax and AUC respectively, at the maximum recommended daily dose of aclidinium/formoterol 400/12 µg BID for the treatment of patients with COPD.

On day 1, ventricular arrhythmias were seen in 2 out of 12 dogs in the high dose group. Persistent multifocal ventricular tachycardia or intermittent ventricular tachycardia with ventricular premature complexes (VPC) were observed 24 hours after the first day of dosing at 300/18 µg/kg/day LAS34273/formoterol in two animals. VPCs also occurred before dosing on Day 7 in one of these animals. One further animal of this group also had occasional ventricular premature complexes 24 hours after dosing on Day 5. There were no further incidences of similar arrhythmias in the subsequent traces for these animals. Based on this finding the NOAEL was considered to be100/6 µg/kg/day of aclidinium/formoterol which is associated with safety margins of 14 and 9 times the aclidinium exposure and 20 and 8 times the formoterol exposure based on Cmax and AUC respectively, at the maximum recommended daily dose of aclidinium/formoterol 400/12 µg BID for the treatment of patients with COPD.

As no ventricular arrhythmias were seen in the formoterol only group, the possibility that this effect is related to administration of the combination cannot be ruled out however based on available exposure

data there is an adequate margin of safety between the dose at which these effects could occur and those that can be achieved clinically.

Genotoxicity

No new impurities have been identified for the combination medicinal product in addition to those known for the individual active substances.

Aclidinium / formoterol

The specified impurities and their specification limits in aclidinium/formoterol are the same as for the currently marketed aclidinium and formoterol medicinal products and the maximum recommended daily dosein patients with COPD is the same for both active substances in the combination (400/12 µg BID) or as monotherapies. There were no new impurities identified for the combination drug product. There were no new aclidinium-related impurities compared to those previously discussed and qualified, and no new formoterol-related impurities compared to those mentioned in the Ph. Eur. monographs.

Aclidinium bromide

Five impurities (D, E, H, I, J) found in the drug substance at extremely low concentrations yielded structural alerts for genotoxicity using DEREK (deductive estimation of risk from existing knowledge) software and were tested in bacterial reverse mutation assays. Three of these were negative in the bacterial reverse mutation assays and are limited in the drug substance specification at ≤0.10% (either named or within 'any unspecified impurity'). Two were positive in reverse mutation assays, one of which, 1-bromo-3-phenoxy-propane (J) is limited to ≤200 ppm and the other, bromopropoxypropyl derivative (E), is limited to ≤0.10%, although exposure to these impurities would be below the standard TTC (threshold of toxicological concern) if they were present at their specification limits.

The active substance specification limits a number of impurities, four of which exceed the relevant ICH Q3A (R2) qualification threshold (≥0.15%). These four impurities (A, B, C and G) were qualified by their presence in batches of active substance used in the chronic toxicity and carcinogenicity studies, and in the case of quaternized 3-(R)-quinuclidinol (LAS34823) and dithienylglycolic acid (LAS34850), because they are the main alcohol and acid metabolites of aclidinium. Both metabolites are also formed in the lung by non-enzymatic (chemical) hydrolysis and therefore are also qualified with respect to local toxicity in the lung. Additional non-genotoxic impurities are limited at ≤0.10% and therefore do not require qualification.

Formoterol fumarate dihydrate

Formoterol fumarate dihydrate used in the studies complies with the requirements set forth in the Ph. Eur. Formoterol impurities A, B, C, D, F and I exceed the qualification threshold (≥0.15%), however they have been qualified in toxicity studies conducted in support of the formoterol monotherapy. None of the formoterol impurities has structural alerts for genotoxicity. On the other hand, the low therapeutic dose of formoterol implies that patients will be exposed to extremely low levels of these impurities, well below the standard TTC of 1.5 µg/day. Potential genotoxic impurities associated with the aclidinium component are controlled below the TTC and the limits of other named impurities of both the formoterol and aclidinium active substances are in line with pharmacopeial monographs or have been qualified in toxicity studies conducted in support of the monotherapies. No further toxicological qualification of impurities is required by the CHMP.

Carcinogenicity

No carcinogenicity studies have been conducted with aclidinium/formoterol since both individual active substances have been comprehensively investigated. The lack of carcinogenicity studies with the proposed combination is accepted by the CHMP.

Reproduction Toxicity

No reproductive or developmental toxicity studies have been conducted with aclidinium/formoterol since both individual active substances have been comprehensively investigated. The lack of reproduction and developmental toxicity studies with the proposed combination has been adequately justified and is therefore acceptable by the CHMP. The known effects of beta agonists and muscarinic antagonists on reproduction at high doses are adequately reflected in the SmPC section 5.3. Effects of aclidinium in nonclinical studies with respect to reproductive toxicity (fetotoxic effects) and fertility (slight decreases in conception rate, number of corpora lutea, and pre- and post-implantation losses) were observed only at exposures considered sufficiently in excess of the maximum human exposure indication to be of little relevance to clinical use.

Formoterol showed reduced fertility (implantation losses) in rats, as well as decreased early postnatal survival and birth weight with high systemic exposure to formoterol. A slight increase in the incidence of uterine leiomyomas has been observed in rats and mice; an effect which is considered to be a class-effect in rodents after long-term exposure to high doses of β_2-adrenoreceptor agonists.

Toxicokinetic data

Please refer to the repeat-dose toxicity studies.

Local Tolerance

No local tolerance studies have been conducted with aclidinium/formoterol since both individual active substances have been comprehensively investigated. Local tolerance of the combination of aclidinium and formoterol has been adequately investigated in the 4-week and 13-week repeated-dose toxicity studies. The lack of specific local tolerance studies is therefore accepted by the CHMP.

Other toxicity studies

No antigenicity studies have been conducted with aclidinium/formoterol since both individual active substances have been comprehensively investigated. The lack of antigenicity studies with the combination product is therefore accepted by the CHMP.

No immunogenicity toxicity studies have been conducted with aclidinium/formoterol since both individual active substances have been comprehensively investigated. The lack of immunogenicity studies with the combination product is therefore accepted by the CHMP.

2.3.5. Ecotoxicity / environmental risk assessment

Summary of main study results

Substance (INN / Invented Name): Formoterol			
CAS-number (if available): 183814-30-4			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD117	1.9	Potential PBT (N)
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.004	µg/L	< 0.01 threshold (N)
Other concerns (e.g. chemical class)			(N)

Substance (INN / Invented Name): Formoterol			
CAS-number (if available): 183814-30-4			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}		2.6	Potential PBT (N)
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.00012	µg/L	< 0.01 threshold (N)
Other concerns (e.g. chemical class)			(N)

The PEC surfacewater value for both formoterol and aclidinium bromide is below the action limit of 0.01 µg/L and neither is likely to be a PBT substance as the log Kow value for both actives does not exceed 4.5. Therefore neither formoterol nor aclidinium bromide is expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

No new primary or secondary pharmacology studies have been conducted with the proposed combination which is acceptable given that the pharmacology of both actives, aclidinium and formoterol, has been

extensively characterised. Bronchodilation is achieved by two separate mechanisms of action – aclidinium is a cholinergic antagonist while formoterol is a long-acting β2-adrenergic receptor agonist.

Two non-GLP cardiovascular safety pharmacology studies have been conducted to investigate ventricular tachycardia findings in the 13-week combination toxicity study. No evidence of synergistic or additive cardiovascular effects was seen and it is likely that the ventricular tachycardia seen in both the safety pharmacology studies and the repeated-dose toxicity studies can be attributed to the formoterol component. Adequate safety margins exist between the exposures at which these effects were seen and those that can be achieved through clinical use. While it is not ideal that these studies were not conducted in accordance with GLP, it is considered that no useful information would be obtained by repeating the studies. Based on the fact that no additive or synergistic effect on cardiovascular parameters were seen following dosing of the combination at the clinical ratio and that VT is a known effect of β2-adrenergic receptor agonists at high doses it is considered that no further useful information will be gained by repeating the studies.

As the PK profiles of both actives have been previously characterised, no additional studies with individual active substances have been provided. In addition, given the different metabolic profiles and apparent lack of interaction from TK and clinical exposure data, no further PK studies with the combination are considered necessary.

The toxicological profiles of both aclidinium and formoterol as individual substances have been characterised previously. Two pivotal repeated-dose inhalation toxicity studies of 4 and 13-weeks duration have been conducted in dogs with the combination in the same ratio as proposed clinically. In both studies dose-dependent cardiac effects were attributed to the formoterol component of the combination. The ventricular tachycardia observed following administration of high doses of formoterol were not associated with microscopic changes in the 13-week study. In the 13-week study, the NOAEL was considered to be 100/6 µg/kg/day of aclidinium/formoterol which is associated with safety margins of 14 and 9 times the aclidinium exposure and 20 and 8 times the formoterol exposure based on Cmax and AUC respectively, at the clinical maximum recommended daily dose.

The non-clinical sections of the SmPC adequately reflect available data with both the individual active substances and the combination.

No new impurities have been identified for the combination product and no toxicological qualification of any impurity associated with either of the individual actives is required.

Neither formoterol nor aclidinium bromide is expected to pose a risk to the environment as the PEC surfacewater values for both actives are below the action limit of 0.01 µg/L. In addition neither aclidinium nor formoterol is likely to be a PBT substance

2.3.7. Conclusion on the non-clinical aspects

The overall non-clinical development programme of the aclidinium bromide/formoterol fumarate dihydrate fixed dose combination was considered adequate to support the recommendation for a marketing authorisation for Duaklir Genuair. The available non-clinical data including the results obtained from the repeat dose toxicity studies with Duaklir Genuair and the environmental risk assessment did not raise any particular safety issue. Based on the available non-clinical safety data with the two compounds, aclidinium bromide and formoterol, it is concluded that the fixed dose combination should be well tolerated when used in human at the proposed dosage.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with the principles and practices of GCP and the Declaration of Helsinki as claimed by the applicant.

- Tabular overview of clinical studies

Study ID	Key objective(s)	Design	Aclidinium/ formoterol dose & regimen	Control groups* dose and regimen	Treatment duration[a]	Number of patients[a]	Endpoints	
							Primary	Secondary
Phase III Pivotal studies providing key evidence of efficacy								
M/40464/30 (ACLIFORM -COPD)	Efficacy and safety	r, db, p, pbo-c, act-c	400/12 µg 400/6 µg BID	AB 400 µg FF 12 µg Pbo BID	24 weeks	1729	FEV_1 at 1 h post-dose Trough FEV_1	TDI SGRQ
LAC-MD-31 (AUGMENT)	Efficacy and safety	r, db, p, pbo-c, act-c	400/12 µg 400/6 µg BID	AB 400 µg FF 12 µg Pbo BID	24 weeks	1692	FEV_1 at 1 h post-dose Trough FEV_1	TDI SGRQ
Clinical studies providing supportive evidence of efficacy								
LAC-MD-36	Long-term safety and efficacy	r, db, p, pbo-c, act-c	400/12 µg 400/6 µg BID	AB 400 µg FF 12 µg Pbo BID	28 weeks	921[b]	None assigned	
LAC-MD-32	Long-term safety	r, db, p, act-c	400/12 µg BID	FF 12 µg BID	52 weeks	590	None assigned	
LAC-MD-27	Dose-finding	r, db, cxo, pbo-c, act-c	400/12 µg 400/6 µg BID	AB 400 µg FF 12 µg Pbo BID	14 days[c]	128	FEV_1 $AUC_{0-12/12h}$	Trough FEV_1 Peak FEV_1
M/40464/26	Dose-finding	r, db, cxo, pbo-c, act-c	200/12 µg 200/6 µg BID	AB 200 µg FF 12 µg Pbo BID	14 days[c]	135	FEV_1 $AUC_{0-12/12h}$	Trough FEV_1 Peak FEV_1
M/273FO/23	Dose-finding	r, db, p, pbo-c, act-c	200/18 µg 200/12 µg 200/6 µg OD	AB 200 µg FF 12 µg Pbo OD	4 weeks	566	FEV_1 $AUC_{0-12/12h}$	Trough FEV_1 Peak FEV_1 FEV_1 $AUC_{0-6/6h}$ $AUC_{0-3/3h}$

a. Number of patients randomised.

b Number of patients enrolled in LAC-MD-36. Note that LAC-MD-36 is a continuation study of LAC-MD-31
c. Duration of each treatment period within the cross-over study. * Note that aclidinium/formoterol, aclidinium monotherapy, formoterol monotherapy and placebo are all administered via Genuair®.
Abbreviations: AB=aclidinium bromide; act-c=active comparator-controlled; BID=twice daily; cxo=cross-over; db=double-blind; FEV1=forced expiratory volume in one second; FEV1 AUCx-y/yh=normalised area under the FEV1 versus time curve between x and y hours post-dose; FF=formoterol fumarate dihydrate; p=parallel group; pbo=placebo; pbo-c=placebo-controlled; OD=once daily; r=randomised; SGRQ=St. George's Respiratory Questionnaire; TDI=Transition Dyspnoea Index.

2.4.2. Pharmacokinetics

Introduction

As the clinical pharmacology of aclidinium and formoterol monotherapies is known, the primary purpose of the clinical pharmacology programme was to rule out any PK interaction between the individual components of aclidinium/formoterol (M/40464/02). The clinical pharmacology programme also enabled the steady-state PK of aclidinium/formoterol 400/12 µg BID to be determined (LAC-PK-01) as well as allowing the formoterol PK profiles obtained following administration of aclidinium/formoterol and Foradil® Aerolizer® to be characterised (M/273FO/22 and LAC-PK-01). Limited supporting data on the PK profile of aclidinium/formoterol are provided by LAC-MD-24. From the pharmacokinetic studies presented in the dossier there is no evidence of an interaction between aclidinium and formoterol when administered via the one inhaler.

Analytical methods

Bioanalytical methods for the analysis of both aclidinium (and its metabolites) and formoterol were successfully validated and reliably applied to the analysis of plasma samples collected in the clinical studies (M/273FO/22, LAC-MD-24, M/40464/02 and LAC-PK-01). The results obtained during the validation in terms of selectivity, linearity, quantitation limit, intra- and inter-batch precision and accuracy, recovery, stability, dilution effect and matrix effect demonstrated the suitability of these methods for the quantitative measurements of all analytes in human plasma within the validated concentration range of each analyte. The validation of the analytical methods was in accordance with the EMA Guideline on Bioanalytical Method Validation: EMEA/CHMP/EWP/192217/2009. Incurred sample reanalyses for both aclidinium (and its metabolites) and formoterol conducted for studies LAC-PK-01 and M/40464/02 showed that the analytical methods provided accurate and reproducible plasma concentration data for PK studies.

Absorption

Plasma concentrations observed following inhalation of aclidinium reflect mainly pulmonary absorption because the gastrointestinal absorption of the swallowed fraction is negligible. Conversely, it is likely that approximately 90% of inhaled formoterol is swallowed and, at least 65% of the swallowed fraction is absorbed in the gastrointestinal tract. Given the different sites of absorption of aclidinium and formoterol, an interaction between aclidinium and formoterol at the level of absorption is unlikely. However the applicant has conducted several pharmacokinetic studies to characterise any interaction between the actives when inhaled in a combination inhaler.

- **Bioavailability**

Study M/40464/02

A Phase I, randomised, open label, 3-way crossover clinical study to assess the PK, safety and tolerability of a single dose of aclidinium/formoterol fixed-dose combination compared with individual components in healthy subjects.

This was the key study for evaluation of the effect of aclidinium and formoterol on each other's respective PK profile. The single-dose PK of aclidinium/formoterol were evaluated and compared to aclidinium and

formoterol monotherapies all administered via the Genuair inhaler. The study was conducted at one site in Germany.

A total of 30 healthy subjects, aged between 19 years and 44 years were randomly allocated to one of six treatment sequences according to a balanced (1:1:1:1:1:1) randomisation. Each sequence included all three treatments, one per treatment period:

- aclidinium/formoterol 400/12 µg via Genuair,
- aclidinium monotherapy 400 µg via Genuair,
- formoterol monotherapy 12 µg via Genuair

Each subject received one administration of investigational medicinal product (IMP) per treatment period. Each treatment period was separated by a washout period of at least 7 days and no more than 14 days. A follow-up assessment (visit or phone contact) was performed 14 days after the last inhalation of IMP.

For all subjects, blood samples for plasma PK of formoterol and/or aclidinium (and metabolites) were taken prior to dosing and at 5 minutes (min), 15 min, 30 min, 1 h, 1.5 h, 2 h, 3 h, 4 h, 6 h, 8 h, 12 h, 16 h and 24 h following the morning IMP administration per treatment period. Plasma samples were analysed for formoterol and aclidinium (and its metabolites) by liquid chromatography with tandem mass spectrometric detection (LC/MS/MS). Assay lower limits of quantification (LLOQs) were 0.5 pg/mL for formoterol and 5.0 pg/mL for aclidinium and its metabolite LAS34823 and 91.6 pg/mL for its metabolite LAS34850.

Results

Of 30 randomised healthy subjects, 29 subjects completed the study (one subject discontinued the study due to personal reasons after the first treatment period [formoterol 12 µg]).

Table 1: PK parameters for formoterol in healthy subjects following a single inhaled dose of either aclidinium/formoterol 400/12 µg or formoterol 12 µg administered via Genuair® (study M/40464/02)

PK Parameter	Statistic	Aclidinium/formoterol 400/12 µg	Formoterol 12 µg
C_{max} (pg/mL)	N Mean (CV%)	29 11.0 (31.8)	30 9.3 (42.0)
t_{max} (h)	N Median (min, max)	29 0.08 (0.07, 1.52)	30 0.08 (0.08, 2.00)
AUC_{0-t} (pg.h/mL)	N Mean (CV%)	29 36.0 (36.5)	30 32.4 (43.3)
$AUC_{0-\infty}$ (pg.h/mL)	N Mean (CV%)	19 42.9 (25.4)	23 41.2 (35.9)
$t_{½}$ (h)	N Mean (CV%)	24 7.1 (47.8)	26 5.4 (31.9)
λ_z (1/h)	N Mean (CV%)	24 0.12 (38.7)	26 0.14 (34.7)
CL/f (L/h)	N Mean (CV%)	19 298 (27.9)	23 332 (41.4)
V_z/f (L)	N Mean (CV%)	19 2407 (22.9)	23 2360 (19.5)

AUC0-t = area under the concentration-time curve from time zero up to the last measurable concentration; AUC0-∞ = area under the plasma concentration from zero to infinity; Cmax = maximum plasma concentrations; CL/f = total body clearance from plasma after extravascular administration; CV% = coefficient of variation; λz = (terminal) elimination rate constant; PK = pharmacokinetics; $t_{½}$ = elimination half-life; tmax = time to peak plasma levels; Vz/f = apparent volume of distribution during terminal phase after extravascular administration.

Formoterol PK parameters were subject to a moderate to high degree of inter-individual variability (coefficients of variation [CV%] ranged between 20% and 48%).

Plasma concentrations of formoterol increased rapidly following a single inhalation of either aclidinium/formoterol 400/12 µg or formoterol 12 µg with a median time to peak plasma levels (tmax) occurring within 5 min post-dose (first kinetic time point) with both treatments. Mean peak plasma levels (Cmax) were higher with aclidinium/formoterol than with formoterol monotherapy (relative bioavailability of 118%). Plasma levels thereafter declined with both treatments so that mean values were below the limit of quantification by 16 h post-dose. The mean elimination half-life (t½) was slightly longer with aclidinium/formoterol than with formoterol monotherapy. However the mean area under the plasma concentration versus time curve for the dosing interval (AUC_{0-t}) was comparable following either a single inhaled dose of aclidinium/formoterol 400/12 µg or a single inhaled dose of formoterol monotherapy 12 µg.

Table 2: PK parameters for aclidinium in healthy subjects following a single inhaled dose of either aclidinium/formoterol 400/12 µg or aclidinium 400 µg administered via Genuair® (study M/40464/02)

PK Parameter	Statistic	Aclidinium/formoterol 400/12 µg	Aclidinium 400 µg
C_{max} (pg/mL)	N Mean (CV%)	29 270 (73.5)	29 215 (66.7)
t_{max} (h)	N Median (min, max)	29 0.08 (0.07, 0.12)	29 0.08 (0.07, 0.10)
AUC_{0-t} (pg.h/mL)	N Mean (CV%)	29 229 (60.9)	29 222 (58.8)
$AUC_{0-\infty}$ (pg.h/mL)	N Mean (CV%)	5 406 (52.1)	3 346 (60.6)
$t_{½}$ (h)	N Mean (CV%)	10 8.9 (75.1)	9 6.1 (84.0)
λ_z (l/h)	N Mean (CV%)	10 0.18 (107)	9 0.19 (55.8)
CL/f (L/h)	N Mean (CV%)	5 1468 (88.3)	3 1434 (49.6)
V_z/f (L)	N Mean (CV%)	5 9338 (37.0)	3 9823 (47.1)

Abbreviations: AUC0-t = area under the concentration-time curve from time zero up to the last measurable concentration; AUC0-∞ = area under the plasma concentration from zero to infinity; Cmax = maximum plasma concentrations; CL/f = total body clearance from plasma after extravascular administration; CV% = coefficient of variation; λz = (terminal) elimination rate constant; PK = pharmacokinetics; t½ = elimination half-life; tmax = time to peak plasma levels; Vz/f = apparent volume of distribution during terminal phase after extravascular administration.

Inter-individual variability was higher for aclidinium PK parameters (CV% ranged from 107% for the [terminal] elimination rate constant [λz] to 37% for apparent volume of distribution [Vz/f]) than for formoterol PK parameters as described above. In addition, for significant proportions of the patients, some of the aclidinium PK parameters, notably total body clearance (CL/f), λz, t½ and Vz/f were not calculable.

As with formoterol the Cmax and tmax are increased in the aclidinium/formoterol period compared with aclidinium alone but both parameters were subject to high inter-individual variability. For both treatments the plasma concentrations of aclidinium declined rapidly and were below the LLOQ by 12 hours post dose. As t½ was calculable following both treatments of this crossover study in only a few patients , it is not possible to draw conclusions about possible trends in this parameter with aclidinium/formoterol. The relative aclidinium bioavailability for aclidinium/formoterol 400/12 µg was 126% based on mean Cmax and 103% based on mean AUC_{0-t}.

Metabolites

Aclidinium is rapidly and extensively hydrolysed to pharmacologically inactive alcohol- (LAS34823) and carboxylic acid derivatives (LAS34850). The extent of plasma exposure (based on AUC_{0-t}) to LAS34823 and LAS34850 following administration of aclidinium/formoterol 400/12 µg was 3-fold and 106-fold that of aclidinium.

The design and methodology of this study is appropriate for the objectives and the washout between periods is considered to be adequate. The study has demonstrated a similar plasma concentration profile for aclidinium and formoterol in combination as that of the monocomponents. A small increase in C_{max} and $t_{1/2}$ of both actives when in combination suggests some interaction in absorption and elimination but the levels are such that they are unlikely to give rise to serious safety concerns.

Study LAC-PK-01

This is a Phase IIa, randomised, open-label, 2-way crossover study to determine the PK, safety, and tolerability of aclidinium/formoterol 400/12 µg via Genuair® and formoterol 12 µg via Foradil® Aerolizer® in patients with moderate to severe chronic obstructive pulmonary disease

The objectives of study LAC-PK-01 were to assess the PK, safety and tolerability of aclidinium/formoterol 400/12 µg BID administered via Genuair® and of formoterol 12 µg administered via Foradil® Aerolizer® (sourced from the US market). This study established the PK safety bridge at steady state of aclidinium/formoterol 400/12 µg compared to US Foradil® Aerolizer® 12 µg. It was conducted in one site in the USA and a total of 24 patients, aged between 42 years and 70 years with moderate or severe COPD (according to the Global Initiative for Chronic Obstructive Pulmonary Disease [GOLD] classification) were randomly allocated to one of two treatment sequences, according to a balanced 1:1 randomisation. Each patient received both treatments, one in each of the two treatment periods:

- aclidinium/formoterol 400/12 µg BID via Genuair®,
- formoterol monotherapy 12 µg BID via US Foradil® Aerolizer®.

The duration of each treatment period was 4.5 days (i.e. BID treatment for 4 days followed by a final dose of IMP in the morning of Day 5). Each treatment period was separated by a 7 day washout period.

Blood samples for plasma PK of formoterol and aclidinium (and its metabolites) were taken on Day 1 and Day 5 of each treatment period, prior to dosing, and at 5 min, 15 min, 30 min, 1 h, 1.5 h, 2 h, 3 h, 4 h, 6 h, 8 h and 12 h (5 min before the evening dose) following the morning IMP administration. Blood

samples for PK testing were also taken on Day 2 to Day 4 of each treatment period prior to dosing and at 5 min and 15 min following the morning and evening IMP administration. Plasma samples were analysed for formoterol and aclidinium (and its metabolites) by LC/MS/MS. Assay LLOQs were 0.5 pg/mL for formoterol and 5.0 pg/mL for aclidinium and its metabolite LAS34823 and 91.6 pg/mL for its metabolite LAS34850. The primary outcome measure of these analyses was the Day 5 (steady state) plasma PK of formoterol, while the secondary outcome measure was the Day 1 plasma PK of formoterol.

Results

All 24 randomised patients completed the study.

Table 3: Mean (CV%) Day 1 and Day 5 PK parameters for formoterol in patients with COPD administered Foradil® Aerolizer® 12 µg BID or aclidinium/formoterol 400/12 µg BID via Genuair® (study LAC-PK-01)

	Foradil® Aerolizer® 12 µg		Aclidinium/formoterol 400/12 µg	
PK Parameter	Day 1 (n=24)	Day 5 (n=24)	Day 1 (n=24)	Day 5 (n=24)
C_{max} (Day 1) $C_{max,ss}$ (Day 5) (pg/mL)	8.2 (39.9)	14.9 (27.9)	9.6 (39.0)	16.7 (31.6)
$C_{min,ss}$ (Day 5) (pg/mL)	N/R	3.8 (29.8)	N/R	3.7 (30.6)
t_{max}[a] (h)	1.00 (0.08–2.00)	0.75 (0.08–2.00)	0.38 (0.08–2.00)	0.08 (0.08–2.00)
$AUC_{0-\tau}$ (Day 1) $AUC_{0-\tau\ ss}$ (Day 5) (pg.h/mL)	41.6 (32.2)	87.1 (27.8)	42.3 (31.3)	85.2 (28.3)
$AUC_{0-\infty}$ (Day 1) (pg.h/mL)	54.5 (30.7)	N/R	54.7 (29.5)	N/R
$t_{½}$ (h)	6.0 (30.7)	8.6 (30.6)	6.0 (27.3)	8.2 (25.1)
λ_z (1/h)	N/R	0.09 (27.4)	N/R	0.09 (26.2)
CL/f (Day 1) CL_{ss}/F (Day 5) (L/h)	N/R	147.9 (27.1)	N/R	152.4 (28.7)
V_z/f (L)	N/R	1864.0 (42.5)	N/R	1809.3 (38.9)

a Median and range presented for t_{max}.
Abbreviations: AUC0-τ = area under the plasma concentration time curve over the dosing interval; AUC0-∞ = area under the plasma concentration from zero to infinity; CL/f = total body clearance from plasma after extravascular administration; C_{max} = maximum plasma concentrations; C_{min} = minimum plasma concentrations; COPD = chronic obstructive pulmonary disease; CV% = coefficient of variation; λz = (terminal) elimination rate constant; N/R = not reported; PK = pharmacokinetics; ss = steady state; t½ = elimination half-life; tmax = time to peak plasma levels; Vz/f = apparent volume of distribution during the terminal phase after extravascular administration.

Steady state plasma levels were achieved within 5 days of BID dosing with either aclidinium/formoterol 400/12 µg or with Foradil® Aerolizer® 12 µg as shown by comparable trough plasma concentrations morning and evening on Day 4 (3.82 pg/mL [CV 34.4%] and 4.15 pg/mL [CV 52.0%], respectively) and Day 5 (3.95 pg/mL [CV 32.6%] and 3.88 pg/mL [CV 29.2%], respectively).

Formoterol PK parameters were similar with aclidinium/formoterol 400/12 µg to those observed with Foradil® Aerolizer® 12 µg, with the exception of median t_{max}, which was shorter when formoterol was administered as aclidinium/formoterol (p=0.006 for comparison at steady state). As formoterol is not intended for relief of acute symptoms this shorter T_{max} will have little clinical relevance.

Mean steady state accumulation ratios observed with Foradil® Aerolizer® or aclidinium/formoterol were 1.92 (CV 23.3%) and 1.85 (CV 29.3%), respectively, based on C_{max} and 2.15 (CV 17.2%) and 2.04 (CV 11.9%), respectively, based on AUC_{0-t}. Co-administration of aclidinium had no apparent effect on the accumulation of formoterol. The higher than expected accumulation ratios may reflect increased pulmonary absorption at steady state as a consequence of reduced obstruction.

Table 4: Mean (CV%) Day 1 and Day 5 PK parameters for aclidinium, LAS34823 and LAS34850 in patients with COPD administered aclidinium/formoterol 400/12 µg BID via Genuair® (study LAC-PK-01)

	Aclidinium		LAS34823		LAS34850	
PK Parameter	Day 1 (n=24)	Day 5 (n=24)	Day 1 (n=24)	Day 5 (n=24)	Day 1 (n=24)	Day 5 (n=24)
C_{max} (Day 1) $C_{max,ss}$ (Day 5) (pg/mL)	102.0 (49.7)	128.4 (42.1)	65.5 (31.8)	149.6 (48.7)	2075.0 (30.5)	3696.7 (31.9)
$C_{min,ss}$ (Day 5) (pg/mL)	N/R	11.8 (45.5)	N/R	65.7 (76.2)	N/R	1908.6 (38.8)
t_{max}[a] (h)	0.25 (0.08–1.00)	0.08 (0.08–3.00)	1.75 (0.25-6.00)	1.00 (0.25–6.00)	4.00 (3.00-8.00)	4.00 (1.50–8.00)
$AUC_{0-\tau}$ (Day 1) $AUC_{0-\tau,ss}$ (Day 5) (pg.h/mL)	228.3 (60.7)	404.3 (47.1)	460.0 (44.6)	1206.3 (56.7)	15827.2 (26.1)	33450.7 (32.0)
$AUC_{0-\infty}$ (Day 1) (pg.h/mL)	280.4 (58.0)	N/R	722.6 (93.8)	N/R	22215.3 (27.1)	N/R
$t_{½}$ (h)	5.0 (93.1)	4.9 (52.8)	6.9 (91.0)	9.5 45.1	5.0 (33.4)	9.4 (49.5)
λ_z (1/h)	N/R	0.18 (64.3)	N/R	0.08 (33.1)	N/R	0.09 (32.1)
CL/f (Day 1) CL_{ss}/F (Day 5) (L/h)	N/R	1300.0 (66.0)	N/R	416.6 (42.0)	N/R	13.2 (31.2)
Vz/f (L)	N/R	8227.0 (72.1)	N/R	5579.6 (60.9)	N/R	180.8 (58.9)

a Median and range presented for t_{max}.
Abbreviations: AUC0-τ = area under the plasma concentration time curve over the dosing interval; AUC0-∞ = area under the plasma concentration from zero to infinity; CL/f = total body clearance from plasma after extravascular administration; C_{max} = maximum plasma concentrations; C_{min} = minimum plasma concentrations; COPD = chronic obstructive pulmonary disease; CV% = coefficient of variation; λz = (terminal) elimination rate constant; N/R = not reported; PK = pharmacokinetics; ss = steady state; t½ = elimination half-life; t_{max} = time to peak plasma levels; Vz/f = apparent volume of distribution during the terminal phase after extravascular administration.

As for formoterol, values for C_{max} and AUC of aclidinium were higher on Day 5 than following the first dose with mean accumulation ratios being 1.38 (CV 35.4%) based on C_{max} and 1.95 (CV% 28.8) based on AUC. The aclidinium accumulation ratio (based on mean AUC) was slightly higher than expected; an observation which may reflect improved pulmonary absorption secondary to improved lung function with repeat administration.

The conduct of this study was acceptable and the washout period of 7 days between treatments is appropriate to the half-lives of aclidinium and formoterol. The main objective of this study was to bridge

between the formoterol as delivered via Genuair and the currently licensed formoterol, Foradil Aerolizer. In that respect the study has demonstrated similar bioavailability from the two delivery systems so that the efficacy and safety that is known regarding Foradil Aerolizer can be informative as to the expected efficacy and safety that should be seen with aclidinium/formoterol Genuair. However, as the Foradil used in this study was sourced from the US market a further study (M/273FO/22) was conducted using EU-sourced Foradil.

Comparing the two studies (M/40464/02 and LAK-PK-01), the bioavailability of formoterol is similar in patients with COPD to that in healthy volunteers as demonstrated by C_{max} and $AUC_{0-\infty}$ whereas the bioavailability of aclidinium is lower in patients with COPD; C_{max} 102 vs 270pg/ml, $AUC_{0-\infty}$ 280.4 vs 406pg.h/ml. However $AUC_{0-\infty}$ was only calculable in a small number of healthy volunteers (5) in study M/40464/02 and AUC_{0-t} was similar in healthy volunteers and in patients with COPD (229 pg.h/ml vs 228.3 pg.h/ml).

Study M/273FO/22

A Phase IIa, randomised, evaluator-blinded, 4-way crossover clinical study to assess the PK, safety, tolerability and effects on lung function of one days treatment of formoterol 12 µg OD via two different inhalers (Aerolizer® and Genuair®), of aclidinium/formoterol 200/12 µg via Genuair® and of formoterol 12 µg BID via Aerolizer® in patients with moderate to severe chronic obstructive pulmonary disease.

This study was conducted in two sites in Germany and used EU-sourced Foradil Aerolizer®.

A total of 24 patients aged between 40 years and 80 years with stable moderate or severe COPD (according to GOLD classification), and a baseline mean FEV1 across treatment periods ranging from 1.30 L to 1.39 L, were randomly allocated to one of four treatment sequences according to a balanced 1:1:1:1 randomisation. The duration of each treatment period was 48 h, of which patients received treatment for one day only. Patients received each of the four treatments to be tested:

- formoterol monotherapy 12 µg via Genuair® OD in the morning and placebo via Genuair® OD in the evening,
- formoterol monotherapy 12 µg via EU Foradil® Aerolizer® OD in the morning and placebo via Genuair® OD in the evening,
- formoterol monotherapy 12 µg BID via EU Foradil® Aerolizer®,
- aclidinium/formoterol 200/12 µg OD in the morning and placebo OD in the evening; both via Genuair®.

The washout period between treatment periods was 7 days. A follow-up assessment was performed at least 7 days after the last inhalation of IMP.

For all patients, blood samples for PK testing of formoterol and aclidinium were taken prior to dosing and at 5 min, 15 min, 30 min, 1 h, 2 h, 4 h, 8 h, 12 h, 24 h and 48 h following the morning dose per treatment period. Additional blood samples for PK testing were taken at 12 h 5 min, 12 h 15 min, 12 h 30 min, 13 h, 16 h and 36 h for patients in the formoterol BID treatment period. Plasma samples were analysed for formoterol and aclidinium (and its metabolites) by LC/MS/MS. Assay LLOQs were 0.5 pg/mL for formoterol, 5.0 pg/mL for aclidinium and its metabolite LAS34823 and 100.0 pg/mL for aclidinium metabolite LAS34850.

PD variables used to assess lung function over the first 12 h following the morning dose of IMP included:

- changes from pre-dose in FEV1 $AUC_{0-12/12h}$ and FEV1 $AUC_{0-3/3h}$.
- changes from pre-dose in peak FEV1.

Results

Of 24 randomised patients, 22 patients completed the study and 2 patients prematurely discontinued (one due to an AE and one due to a COPD exacerbation).

Table 5: Mean (CV%) PK parameters for formoterol following a single inhaled dose of formoterol 12 µg via either Genuair® or Foradil® Aerolizer® or following a single inhaled dose of aclidinium/formoterol 200/12 µg via Genuair® in patients with COPD (study M/273FO/22)

PK Parameter	Formoterol 12 µg OD		Aclidinium/formoterol 200/12 µg OD
	Via Genuair® (n=23)*	Via Aerolizer (n=23)*	Via Genuair® (n=21)*
C_{max} (pg/mL)	5.8 (43.8)	7.3 (38.0)	5.7 (51.4)
t_{max} (h)	0.3 (107.0)	0.7 (72.7)	0.4 (95.6)
AUC_{0-24} (pg.h/mL)	36.2 (32.2)	43.7 (37.7)	32.3 (47.9)
$AUC_{0-\infty}$ (pg.h/mL)	38.9 (34.8)	42.9 (30.3)	40.3 (42.4)
$t_{½}$ (h)	5.8 (40.7)	5.0 (37.0)	5.7 (50.3)
λ_z (1/h)	0.14 (36.7)	0.15 (24.4)	0.15 (48.2)
CL/f (L/h)	348 (38.0)	303 (28.4)	496 (106.0)
Vz/f (L)	2631 (25.7)	2097 (30.6)	2979 (43.8)

* One patient excluded from PK analyses due to high pre-dose plasma levels of formoterol in all treatment periods.
Abbreviations: AUC_{0-24} = area under the plasma concentration time curve over the dosing interval, 0 hours to 24 hours after IMP administration; $AUC_{0-\infty}$ = area under the plasma concentration from zero to infinity; C_{max} = maximum plasma concentrations; COPD = chronic obstructive pulmonary disease; CV% = coefficient of variation; λz = (terminal) elimination rate constant; CL/f = total body clearance from plasma after extravascular administration; PK = pharmacokinetics; t½ = elimination half-life; t_{max} = time to peak plasma levels; Vz/f = apparent volume of distribution during the terminal phase after extravascular administration.

Inter-individual variability in the values for PK parameters for formoterol ranged from moderate to very high (CVs in the range 24.4% to 107.0%), as expected with the inhalation route of administration.

Both C_{max} and AUC_{0-24} of formoterol were generally comparable when formoterol was administered via Genuair® compared to when it was administered via Foradil Aerolizer (relative bioavailability based on AUC_{0-24} of 86.4% [n=23; SD 25.1; CV 29.1%]). Plasma concentrations of formoterol declined in a biexponential fashion irrespective of inhaler device.

Based on AUC_{0-24}, the relative bioavailability of formoterol administered as aclidinium/formoterol 200/12 µg via Genuair compared to Foradil Aerolizer 12 µg was 77.1% (n=21; SD=29.4; CV 38.1%).

PD results

Table 6: Adjusted mean changes from pre-dose in normalised areas under the FEV1 versus time curves for 0 to 12 hours post-dose (FEV1 AUC0-12h) and 0 to 3 hours post-dose (FEV1 AUC0-3/3h) and peak FEV1 in patients with COPD (study M/273FO/22; randomised population)

PD Parameter	Statistic	Formoterol 12 µg OD		Aclidinium/formoterol 200/12 µg OD
		Via Genuair® (n=24)	Via Foradil® Aerolizer® (n=24)	Via Genuair® (n=24)
FEV_1 $AUC_{0-12/12h}$ (L/h)	LS Mean (SE)	0.259 (0.041)	0.249 (0.041)	0.296 (0.041)
	95% CI	0.177, 0.341	0.167, 0.331	0.213, 0.379
FEV_1 $AUC_{0-3/3h}$ (L/h)	LS Mean (SE)	0.302 (0.040)	0.288 (0.040)	0.288 (0.041)
	95% CI	0.222, 0.388	0.207, 0.369	0.206, 0.370
Peak FEV_1 (L)	LS Mean (SE)	0.415 (0.045)	0.420 (0.045)	0.414 (0.046)
	95% CI	0.326, 0.505	0.329, 0.510	0.323, 0.506

Note: Analyses were performed using the ANCOVA model for crossover designs with sequence, period and treatment as fixed effect factors, patient within sequence as random effect factor and corresponding pre-dose value for each period as covariate.
Abbreviations: CI = confidence interval; COPD = chronic obstructive pulmonary disease; FEV1 = forced expiratory volume in one second; FEV1 AUC0-3/3h = normalised area under the FEV1 versus time curve from 0 hours to 3 hours post-dose; FEV1 AUC0-12/12h = normalised area under the FEV1 versus time curve from 0 hours to 12 hours post-dose; LS = least squares; OD = once daily; SE = standard error.

Adjusted mean changes from pre-dose in FEV1 AUC0-12/12h and in peak FEV1 were comparable irrespective of whether formoterol monotherapy 12 µg OD was administered via Genuair or Foradil Aerolizer indicating that both formoterol 12 µg via Genuair and Foradil Aerolizer have comparable PD efficacy.

This study was conducted using a dose of 200µg of aclidinium with 12 µg of formoterol in a once-daily regimen. It is therefore not representative of the proposed strength to be marketed but does inform on the relative bioavailability of formoterol via the Genuair inhaler compared with administration from the EU Foradil Aerolizer. In fact in this patient population a lower bioavailability was demonstrated for formoterol administered via the Genuair inhaler than via the Foradil Aerolizer which could have efficacy implications.

Investigation of the pharmacodynamics of aclidinium/formoterol was a secondary objective of this study but the effect on FEV1 of formoterol 12µg administered via Genuair was similar to that of formoterol 12 µg administered via Foradil Aerolizer. In this study the effect of adding 200 µg aclidinium to formoterol was minimal and not clinically relevant. However it was a low dose of aclidinium compared with the proposed dose of 400 µg BID.

LAC-MD-24

A randomised, double blind, active-controlled, parallel-group, multicentre, 4-week pilot study to assess symptoms in stable, moderate-to-severe COPD patients taking aclidinium bromide 200 µg once daily in combination with formoterol fumarate 12 µg once or twice daily versus formoterol fumarate 12 µg twice daily.

This randomised, double-blind, parallel group study was conducted at 31 centres in the US. A total of 156 patients aged between 41 years and 80 years with stable moderate or severe COPD (according to GOLD

classification) and a baseline mean FEV1 across treatment groups ranging from 1.23 L to 1.35 L, were randomly allocated to one of the following three treatment groups in a ratio of 2:2:1 as follows:

- Aclidinium/formoterol 200/12 µg OD in the morning and placebo OD in the evening via Genuair,
- Aclidinium/formoterol 200/12 µg OD in the morning and formoterol monotherapy 12 µg OD in the evening via Genuair,
- Formoterol monotherapy 12 µg BID via Genuair.

Patients received study drug treatment for up to 4 weeks. The final follow-up assessment (by telephone) was performed 7 days after the last inhalation of study drug.

PK testing was performed on a subset (approximately 20%) of patients only. Blood samples for evaluation of formoterol PK were collected on Day 1 and on Day 29, prior to dosing and at 5 min, 15 min, 30 min, 1 h, 2 h, 4 h, 8 h, 12 h (prior to the evening dose), 12 h 5 min, 12 h 15 min, 12 h 30 min, 13 h, 14 h, 16 h and 24 h following the morning IMP administration. Plasma samples were analysed by LC-MS/MS (assay LLOQ was 0.5 pg/mL).

Results

This study was primarily an exploratory safety and efficacy study and gives little meaningful information on the PK of aclidinium/formoterol as PK data are available from only 10 patients.

A moderate to high degree of variability was observed across all treatment groups for most PK parameters (CVs ranged from 13.1% to 224.8%). The very high variability noted for some PK parameters is likely to be a consequence of evaluation of low patient numbers within a parallel group study. No meaningful differences between treatment groups in PK parameters were observed on either Day 1 or on Day 29.

Values for formoterol steady state PK parameters between aclidinium/formoterol 200/12 µg and formoterol monotherapy 12 µg (administered via Genuair) were broadly comparable. While the C_{max} was slightly higher with aclidinium/formoterol than with formoterol monotherapy, the $t_{½}$ was lower with aclidinium/formoterol than with formoterol monotherapy.

- **Influence of food**

As aclidinium/formoterol is administered via the inhalation route and acts locally in the lungs no food interaction studies have been conducted. This is regarded acceptable by the CHMP.

Distribution

The very high values for the apparent volume of distribution (Vz/f) observed for both aclidinium and formoterol in patients with COPD (LAC-PK-01 and M/273FO/22) and healthy subjects (M/40464/22) are consistent with the low bioavailability associated with inhaled administration.

Whole lung deposition of inhaled aclidinium via Genuair® averaged approximately 30% of the metered dose (Aclidinium bromide PAR).

Plasma protein binding

No plasma protein binding studies have been conducted with aclidinium/formoterol. Due to the rapid chemical and non-chemical hydrolysis of aclidinium in plasma, it is likely that the protein binding of aclidinium measured in *in vitro* studies corresponded to the protein binding of the pharmacologically-inactive metabolites of aclidinium (87% for the acid metabolite [LAS34850] and 15%

for the alcohol metabolite [LAS34823]) rather than that of aclidinium itself. It was also shown in *in vitro* studies that the main plasma protein that binds aclidinium is albumin. Although the extent of plasma protein binding of aclidinium is unknown, its rapid hydrolysis such that only 0.1% of the inhaled dose is excreted unchanged in the urine (Eklira Genuair SmPC), makes the possibility of displacement interactions with aclidinium unlikely even if its plasma protein binding was high.

The plasma protein binding of formoterol is known to be in the range of 61−64 % (34 % primarily to albumin) with no saturation of binding sites in the concentration range reached with therapeutic doses (Foradil SmPC). As the plasma protein binding of formoterol is relatively low, there is little possibility of displacement interactions with formoterol.

It is accepted that the plasma protein binding of aclidinium cannot be characterised accurately due to its rapid metabolism into its two inactive metabolites. Formoterol has not been investigated in patients with severe renal impairment but the extent of plasma protein binding of formoterol is relatively low and therefore renal impairment is unlikely to give rise to displacement interactions.

Elimination

- **Metabolism**

The metabolism of aclidinium bromide and formoterol fumarate has been previously characterised and described in their respective SmPCs. It is known that the major route of metabolism of aclidinium is hydrolysis, which occurs both chemically (non-enzymatically) and enzymatically by esterases (butyrylcholinesterase is the main human enzyme involved in the hydrolysis). Aclidinium is rapidly and extensively hydrolysed to its acid and alcohol derivatives, neither of which binds to muscarinic receptors and both of which are apparently devoid of pharmacologic activity. Biotransformation via cytochrome P450 (CYP450) enzymes plays a minor role in the total metabolic clearance of aclidinium. The low absolute bioavailability of inhaled aclidinium (<5%) is because aclidinium undergoes extensive systemic and pre-systemic hydrolysis whether deposited in the lung or swallowed.

Formoterol is eliminated primarily by metabolism. Direct glucuronidation is the major pathway of biotransformation, while another pathway involves O-demethylation followed by glucuronidation (Foradil SmPC). Minor pathways involve sulphate conjugation of formoterol and deformylation followed by sulphate conjugation. Multiple isozymes catalyze the O-demethylation (CYP2D6, 2C19, 2C9, and 2A6) of formoterol, and so consequently the potential for metabolic drug-drug interactions is low.

Aclidinium is rapidly metabolised to form two inactive metabolites by hydrolysis, whereas formoterol is metabolised via several pathways catalysed by multiple isoenzymes. Given that the biotransformation of aclidinium and formoterol occur via different processes, a metabolic interaction between these two products is highly unlikely. Therefore interactions between the two actives are unlikely. It is accepted by the CHMP that further studies of the metabolism of these actives have not been undertaken.

- **Excretion**

The abnormally high values for aclidinium total body clearance from plasma (Cl/F) observed with inhaled aclidinium/formoterol in patients with COPD (1300 L/h at steady-state in LAC-PK-01 and 5327 L/h following a single dose in M/273FO/22) and healthy subjects (1468 L/h following a single dose in M/40464/02) are consistent with its very low bioavailability. The Cl/F of formoterol was also high (152 L/h in LAC-PK-01, 298 L/h in M/40464/02 and 496 L/h in M/273FO/22) although markedly lower than that of aclidinium.

Following t_{max}, plasma levels of aclidinium and formoterol declined rapidly. Mean aclidinium t½ following aclidinium/formoterol administration was between 1.5 h and 5.0 h in patients with COPD (M/273FO/22, LAC-PK-01) and was 8.9 h in healthy subjects (M/40464/02) while mean formoterol t½ was between 4.9 h and 8.2 h in patients with COPD (LAC-PK-01, M/273FO/22, LAC-MD-24) and was 7.1 h in healthy subjects (M/40464/02). Inter-individual variability of t½ in each of aclidinium/formoterol studies was higher for aclidinium (coefficients of variation [CVs] ranged between 53% and 93%) than for formoterol (CVs between 25% and 50%).

Following inhalation of aclidinium 400 µg by healthy subjects or patients with COPD, the urinary excretion of unchanged aclidinium was very low at about 0.1% of the administered dose, indicating that renal clearance plays a very minor role in the total aclidinium clearance from plasma. Renal clearance also plays a minor part in the elimination of inhaled formoterol 12 µg, with approximately 6% to 9% of the delivered dose of inhaled formoterol excreted in the urine as unchanged formoterol and direct conjugates of formoterol.

It is accepted that the elimination pathways of aclidinium bromide and formoterol fumarate are well known. The pharmacokinetic studies that have been conducted have not demonstrated any interaction between the actives affecting their elimination.

Dose proportionality and time dependencies

- **Dose proportionality**

Dose proportionality for the two actives is accepted by the CHMP. There is no evidence of a PK interaction when administered in a FDC so dose proportionality of the combination is also accepted.

In vitro studies have demonstrated dose proportionality of the aerodynamic behaviour of aclidinium 200 µg and 400 µg inhalation powder and formoterol 6 µg and 12 µg inhalation powder in fixed combinations.

In study M/273FO/22 the mean AUC_{0-24} of formoterol BID administered via Foradil Aerolizer (83.2 pg.h/mL [CV 32.1%]) was approximately 2-fold higher than that obtained with single doses of formoterol via Genuair (36.2 pg.h/mL [CV 32.2%]) indicating dose proportionality for formoterol.

- **Time dependency**

In the PK studies with aclidinium/formoterol the same observed mean $t_{½}$ following the first dose of aclidinium/formoterol and at steady state suggests that clearance remains constant with repeat administration and that the PK of aclidinium is time-independent. There is no evidence of time dependent kinetics of aclidinium or formoterol from the PK studies presented in the dossier. The lack of time dependency has been previously accepted for aclidinium bromide monotherapy.

Special populations

The applicant has not conducted any further studies in special populations as the proposed combination product contains two known active substances. From the known pharmacokinetics of the actives no dose adjustment is required for intrinsic factors such as age or for patients with renal or hepatic impairment. The applicant's justification for this is accepted by the CHMP. Section 5.2 of the SmPC states that there are no data to support the use of formoterol in patients with renal or hepatic impairment.

- **Impaired renal function**

Urinary excretion of inhaled aclidinium is very low with only 0.1% of the inhaled dose excreted unchanged in the urine. As may be expected, no significant differences in aclidinium PK parameters between subjects with normal renal function and subjects with mild, moderate or severe renal impairment were observed in a clinical study designed to evaluate the influence of renal impairment on the PK of aclidinium.

As aclidinium undergoes rapid hydrolysis in plasma and the renal excretion of unchanged aclidinium is very low, it is unlikely that the extent of plasma protein binding of aclidinium would have a relevant impact on unbound plasma concentrations of aclidinium, even in patients with severe renal impairment. Consequently, plasma protein binding of aclidinium has not been determined.

Renal clearance plays a minor role in the elimination of inhaled formoterol, with only 6% to 9% of the total dose eliminated unchanged in the urine (Foradil SmPC). Consequently, it is unlikely that renal impairment would have a significant effect on the PK of formoterol and clinical studies to investigate the influence of renal impairment on formoterol PK have not been conducted for either formoterol administered via Genuair® or for marketed formoterol monotherapy products.

As the product contains two known actives of which the pharmacokinetics have been previously characterised and neither of which is renally excreted to a significant extent, it is accepted by the CHMP that no further studies in patients with renal impairment have been conducted.

- **Impaired hepatic function**

As hepatic metabolism plays a very minor role in the elimination of aclidinium, hepatic dysfunction is not expected to have a relevant influence on its PK of aclidinium. Clinical studies to investigate the effects of hepatic impairment on the PK of aclidinium have, therefore, not been conducted.

Clinical studies to investigate the effects of hepatic impairment on the PK of formoterol have not been conducted. Formoterol is eliminated primarily via hepatic metabolism, the major pathway being direct glucuronidation while O-demethylation followed by glucuronidation is another pathway. In cirrhotic patients, oxidative metabolism is likely to be slower but conjugation capacity should essentially be maintained as glucuronidation appears to be little affected by cirrhosis. Furthermore, reduced capacity of O-demethylation may be metabolically compensated for by glucuronidation as the capacity to glucuronidate is high. Thus, cirrhosis should not *a priori* be expected to reduce the capacity to eliminate formoterol. Although increased exposure to formoterol is possible in patients with severe liver cirrhosis, dose adjustment is not required.

As the product contains two known actives of which the pharmacokinetics have been previously characterised it is accepted by the CHMP that no further studies in patients with hepatic impairment have been conducted.

- **Elderly**

No significant differences in systemic exposure to aclidinium between young patients with COPD (40 years to 59 years) and elderly patients with COPD (aged 70 years and over) were observed in a clinical study designed to assess the influence of age on the pharmacokinetics (PK) of aclidinium. Furthermore, increased age had no clinically relevant effect on the safety or effectiveness of aclidinium monotherapy in the pooled population of placebo-controlled Phase III studies. On the basis of currently available data for aclidinium, no dosage adjustment in geriatric patients is warranted.

The PK of formoterol has not been studied in the elderly population. However, two pivotal, controlled studies of formoterol in patients with COPD showed no overall differences in the safety and effectiveness between patients aged 65 years or older or aged 75 years or older and younger patients

As the pharmacokinetics of the two actives have been previously characterised and as neither active is eliminated unchanged via the renal route to any great extent it is accepted that the applicant does not need to conduct further studies in elderly patients and that no dose adjustment will be needed for elderly patients.

- **Children**

The proposed indication of COPD is not relevant to the paediatric population. Therefore no studies have been conducted in the paediatric population.

A class waiver from the European Paediatric Regulation (Regulation [EC] Number 1901/2006) has been granted for the condition COPD. Aclidinium/formoterol is indicated for adult patients only.

Pharmacokinetic interaction studies

No additional drug-drug interactions were warranted by the CHMP on the basis of the information currently available from previous aclidinium and formoterol *in vitro* and *in vivo* studies. These have suggested that no specific drug-drug interaction is to be expected and the theoretical interactions from the known pharmacodynamics effects of the two active substances are included in SmPC section 4.5.

- **In vitro**

In vitro studies have shown that neither aclidinium at the therapeutic dose, nor the metabolites of aclidinium, are expected to cause interactions with P-glycoprotein substrate drugs or drugs metabolised by esterases or CYP450 enzymes (Eklira Genuair SmPC)

In vitro studies have shown that formoterol does not inhibit cytochrome P450 isozymes at therapeutically relevant concentrations (Foradil US Prescribing Information)

- **In vivo**

Although no formal *in vivo* drug interaction studies have been performed with aclidinium, it has been used concomitantly with other medicinal products used for the treatment of COPD including sympathomimetic bronchodilators, methylxanthines and oral/inhaled corticosteroids without clinical evidence of drug interactions. Co-administration of aclidinium with other anticholinergic-containing medicinal products has not been studied and is not recommended as it may result in potentiation of undesirable anticholinergic effects (Eklira Genuair SmPC).

No formal *in vivo* drug-drug interaction studies have been performed with formoterol monotherapy. Nevertheless, caution is advised in the concomitant use of formoterol with other long-acting sympathomimetic medicinal products, with medicinal products known to be associated with hypokalaemia (such as methylxanthine derivatives, steroids or non-potassium-sparing diuretics) or with medicinal products known to prolong QTc interval (such as monoamine oxidase inhibitors, tricyclic antidepressants and macrolides). In addition, β-adrenergic blockers may weaken or antagonise the effect of β2-adrenergic agonists.

Potential drug-drug interactions for each of aclidinium and formoterol monotherapies do not overlap.

2.4.3. Pharmacodynamics

Mechanism of action

Aclidinium bromide is a long-acting muscarinic antagonist (LAMA) while formoterol fumarate dihydrate is a long-acting β2-adrenergic receptor agonist (LABA).

Sympathetic and parasympathetic pathways mediate bronchoconstriction in COPD. Muscarinic antagonists, such as aclidinium bromide, and β2-adrenergic agonists, such as formoterol fumarate dihydrate, each cause smooth muscle relaxation in the airways, leading to airway expansion and improved lung function, albeit via different mechanisms. Anticholinergic compounds block the muscarinic acetylcholine M3-receptors in bronchial smooth muscle and β2-adrenergic agonists stimulate β2-adrenergic receptors in bronchial smooth muscle. Combinations of muscarinic antagonists and β2-adrenergic agonists have been shown to produce significantly greater improvements in pulmonary function compared to the respective monotherapies, with safety/tolerability profiles similar to those of the individual components

Primary pharmacology

The primary pharmacodynamics of aclidinium/formoterol 200/12 µg OD was investigated in two early exploratory clinical studies conducted in patients with moderate or severe COPD (M/273FO/22 and LAC-MD-24).

Both M/273FO/22 and LAC-MD-24 provided some indication that improvements in lung function associated with aclidinium/formoterol 200/12 µg OD via Genuair were slightly greater than those associated with formoterol 12 µg OD via Genuair or Foradil Aerolizer, although the magnitude and/or consistency of the improvements were not robust.

Study M/273FO/22 showed the bronchodilator efficacy (as assessed by the normalised areas under the FEV1 versus time curve from 0 hours to 12 hours post-dose [FEV1 AUC0-12/12h] and from 0 to 3 hours post-dose [FEV1 AUC0-3/3h] and peak FEV1) of formoterol 12 µg to be very similar irrespective of whether formoterol monotherapy was administered via Genuair or Foradil Aerolizer.

LAC-MD-24

A randomised, double blind, active-controlled, parallel-group, multicentre, 4-week pilot study to assess symptoms in stable, moderate-to-severe COPD patients taking aclidinium bromide 200 µg once daily in combination with formoterol fumarate 12 µg once or twice daily versus formoterol fumarate 12 µg twice daily.

This randomised, double-blind, parallel group study was conducted at 31 centres in the US. A total of 156 patients aged between 41 years and 80 years with stable moderate or severe COPD (according to GOLD classification) and a baseline mean FEV1 across treatment groups ranging from 1.23 L to 1.35 L, were randomly allocated to one of the following three treatment groups in a ratio of 2:2:1 as follows:

- Aclidinium/formoterol 200/12 µg OD in the morning and placebo OD in the evening via Genuair,
- Aclidinium/formoterol 200/12 µg OD in the morning and formoterol monotherapy 12 µg OD in the evening via Genuair,
- Formoterol monotherapy 12 µg BID via Genuair.

Patients received study drug treatment for up to 4 weeks. The final follow-up assessment (by telephone) was performed 7 days after the last inhalation of study drug.

Safety and tolerability were evaluated by recording of AEs, clinical laboratory measures, physical examinations, vital signs and 12-lead ECGs (plus 24 h Holter monitoring in a subset of patients).

All 156 randomised patients were included in the analysis of pharmacodynamics/efficacy and COPD symptoms (randomised population). A total of 145 patients (93%) completed the study. Of the 11 patients who prematurely discontinued the study, 10 patients (8.0% [10/125]) were in the aclidinium/formoterol treatment groups (4 discontinuations were due to protocol violations, 4 were due to AEs, one was lost to follow-up and one had insufficient therapeutic response) and one (3.2% [1/31]) was in the formoterol BID group (protocol violation).

PD/efficacy results

No notable differences in baseline lung function were observed between treatment groups.

Mean changes from baseline to Day 29 in key parameters of lung function are presented for each of the treatment groups.

Table 7: Changes from Baseline (L) to Day 29 in morning peak FEV1 and in the normalised area under the FEV1 versus time curves for 0 to 3 hours post-dose (FEV1 AUC0-3/3h) (study LAC-MD-24; randomised population)

PD Parameter	Statistic	Aclidinium/formoterol 200/12 µg Q_{AM} + placebo Q_{PM} (n=63)	Aclidinium/formoterol 200/12 µg Q_{AM} + formoterol 12 µg Q_{PM} (n=62)	Formoterol 12 µg BID (n=31)
Peak FEV_1	N	62	61	31
	Mean (SE)	0.355 (0.024)	0.319 (0.027)	0.280 (0.030)
	95% CI	0.308, 0.403	0.265, 0.373	0.220, 0.341
FEV_1 $AUC_{0\text{-}3h/3h}$	N	62	61	31
	Mean (SE)	0.257 (0.023)	0.226 (0.025)	0.200 (0.028)
	95% CI	0.211, 0.302	0.176, 0.276	0.142, 0.248

Abbreviations: BID = twice daily; CI = confidence interval; FEV1 = forced expiratory volume in one second; FEV1 AUC0-3/3h = normalised area under the FEV1 versus time curve from 0 hours to 3 hours post-dose; QAM = once daily in the morning; QPM = once daily in the evening; SE = standard error.

The changes from baseline to Day 29 in peak FEV1 and FEV1 AUC0-3/3h were slightly greater for the treatment groups that received aclidinium/formoterol in the morning compared to the treatment group that received formoterol monotherapy in the morning. This observation must, however, be interpreted with caution given the differences in the magnitudes of the treatment effects between the two treatment groups that received aclidinium/formoterol in the morning, which illustrate the between-group variability in PD responses observed in this exploratory parallel group study. Similar observations were made for changes from baseline in peak FVC and FVC AUC0-3/3h.

COPD symptom scores improved across all treatment groups; however, there was no consistent pattern in the extent of improvement in scores across treatment groups.

Secondary pharmacology

Cardiac electrophysiology

No effects on corrected QT (QTc) interval (corrected using the Fridericia method or individually-corrected) were observed in a thorough QT study in which aclidinium monotherapy (200 µg or 800 µg) was

administered OD for 3 days to healthy subjects (Eklira Genuair SmPC). In addition, no clinically significant effects of aclidinium monotherapy 400 µg BID on cardiac rhythm were observed on 24 h Holter monitoring after 3 months treatment of 336 patients with COPD (of whom 164 received aclidinium and 172 received placebo). There is no evidence of a clinically relevant effect of aclidinium on QTc interval (Aclidinium bromide PAR).

The cardiovascular safety of formoterol has been extensively documented in the literature and is described in the product labels (Foradil SmPC). At therapeutic doses, formoterol 12 µg BID had no clinically relevant acute or chronic effects on QTc interval when administered for up to 12 months in a pivotal, double-blind study in patients with COPD. Slight prolongation of mean QTc interval (8 msec, as assessed using Fridericia heart rate correction methods) was observed following inhalation of single doses of formoterol 120 µg (i.e. at 10-times the recommended therapeutic dose) by healthy subjects6; an observation which is not unexpected following administration of high doses of sympathomimetic agents. No important differences in ventricular or supraventricular ectopy were observed between the formoterol 12 µg and placebo treatment groups in two pivotal, double-blind clinical studies in patients with asthma.

The cardiac safety of aclidinium/formoterol has been assessed in Phase III studies by 12-lead ECGs and 24 h Holter monitoring. No clinically significant effects on overall cardiac safety (including QTc interval [Fredericia correction method]) of aclidinium/formoterol 400/12 µg BID, compared to either aclidinium 400 µg BID or formoterol 12 µg BID, were observed on 12-lead ECGs conducted in 3398 patients with COPD treated for up to 52 weeks in placebo- controlled Phase III studies (of whom 720 patients received aclidinium/formoterol 400/12 µg, 722 received aclidinium monotherapy and 716 received formoterol monotherapy). In addition, no clinically significant effects on cardiac rhythm of aclidinium/formoterol 400/12 µg BID compared to aclidinium 400 µg or formoterol 12 µg were observed on 24 h Holter monitoring after 24 weeks treatment of 551 patients with COPD (of whom 114 received aclidinium/formoterol 400/12 µg, 118 received aclidinium monotherapy and 112 received formoterol monotherapy). There is no evidence of a clinically relevant effect of aclidinium/formoterol on cardiac safety, above that observed with the constituent monotherapies.

Relationship between plasma concentration and effect

As this is an inhaled product that acts locally in the lung there is no relationship between the plasma concentration and the primary pharmacodynamics effect. This is agreed by the CHMP.

Pharmacodynamic interactions with other medicinal products or substances

Possible pharmacodynamics drug-drug interactions associated with aclidinium include:

- Co-administration of aclidinium with other anticholinergic-containing medicinal products has not been studied and is not recommended as it may result in potentiation of undesirable anticholinergic effects.

Possible drug-drug interactions associated with formoterol include:

- Co-administration of formoterol with other long acting β2-adrenergic agonists is not recommended as it may result in potentiation of undesirable β2-adrenergic effects.
- Co-administration of formoterol with methylxanthine derivatives, steroids, or non-potassium-sparing diuretics may potentiate the possible hypokalaemic effect of β2-adrenergic agonists.

- Co-administration of formoterol with β-adrenergic blockers may weaken or antagonise the effect of formoterol.
- Co-administration of formoterol with other drugs known to prolong the QTc-interval may give rise to a PD interaction and increase the possible risk of ventricular arrhythmias (this is discussed further in relation to the safety results in the Phase III studies).

It should be noted that the above-mentioned drug-drug interactions for formoterol are not supported by clinical data but are considered theoretically possible and cited in section 4.5 in the Summary of Product Characteristics (SmPCs) for marketed formoterol products.

Potential drug-drug interactions for each of aclidinium and formoterol monotherapies do not overlap. Formal *in vivo* studies to assess drug-drug interactions with aclidinium/formoterol are, therefore, considered unnecessary by the CHMP.

2.4.4. Discussion on clinical pharmacology

This exploratory parallel group study in a relatively small number of patients demonstrated a small increase in peak FEV1 and FEV1 $AUC_{0\text{-}3h/3h}$ in the patients receiving the combination in the morning compared to those receiving formoterol alone in the morning. However adding a dose of formoterol in the evening to the morning dose of the combination when compared with adding placebo appears to decrease the effect. No definite conclusions can be drawn from these results.

The investigation of cardiac safety of aclidinium/formoterol was generally agreed by CHMP during scientific advice. Given the known safety profiles of the two monocomponent actives and the lack of any unexpected safety signals during the Phase III clinical programme it is accepted that a specific TQT study with the combination is not required.

Theoretical drug:drug interactions from the known pharmacodynamics effects of the two active substances in aclidinium/formoterol have been described in their respective SmPCs. As they have different mechanisms of action and the theoretical drug:drug interactions do not overlap it is accepted that specific drug:drug interaction studies with the combination are not required.

The safety of the combination compared with its monocomponents will be compared from the results of the Phase III studies.

2.4.5. Conclusions on clinical pharmacology

From the pharmacokinetic studies presented in the dossier there is no evidence of an interaction between aclidinium and formoterol when administered via one inhaler.

Also the pharmacokinetics of formoterol via the Genuair as monocomponent or in combination with aclidinium are similar to those of formoterol administered via the Aerolizer, in particular the EU sourced Aerolizer. The pharmacodynamics of aclidinium bromide and formoterol fumarate dihydrate are well characterised and no further studies have been conducted. As the mechanisms of action of the two actives are different with no overlap any pharmacodynamic interaction is unlikely.

2.5. Clinical efficacy

Introduction

The clinical efficacy programme for aclidinium/formoterol comprised two Phase III pivotal studies (M/40464/30 and LAC-MD-31) and five supportive studies: two Phase III long-term safety studies (LAC-MD-36 and LAC-MD-32), two Phase IIb, dose-finding studies of aclidinium/formoterol BID (LAC-MD-27 and M/40464/26) and one Phase IIb dose-finding study of aclidinium/formoterol OD (M/273FO/23).

2.5.1. Dose response studies

Study LAC-MD-27

An efficacy and safety study of two fixed combinations of aclidinium/formoterol (400/12 µg and 400/6 µg) compared with aclidinium monotherapy (400 µg) and formoterol monotherapy (12 µg) and placebo, all administered BID, in patients with stable, moderate to severe chronic obstructive pulmonary disease.

This Phase IIb, randomised, double-blind, placebo- and active comparator-controlled, 4-period incomplete block cross-over study was conducted at 20 centres in the US. Following a 14-day run-in period during which the stability of the patients' COPD was confirmed, eligible patients were randomised. For each patient, the study consisted of 4 periods of 14 treatment days each separated by a washout period of 7 to 10 days. During each period, patients received one of 5 treatments according to the randomisation scheme: aclidinium/formoterol 400/12 µg, aclidinium/formoterol 400/6 µg, aclidinium 400 µg, formoterol 12 µg or placebo, all administered BID via Genuair®. The final follow-up assessment was performed (by phone or visit) 14 days after the last dose of IMP.

The **primary efficacy endpoint** was the change from baseline to Day 14 in FEV1 $AUC_{0\text{-}12/12h}$.

Secondary efficacy endpoints were:

• Changes from baseline to Day 14 in morning trough FEV1 and morning peak FEV1.

Notable **additional efficacy endpoints** were:

• The above-mentioned primary and secondary endpoints for FEV1 assessed for FVC and the change from baseline to Day 14 in trough IC.

• Changes from baseline in FEV1 and FVC at each time point on Day 14 of treatment.

• Changes from baseline in the overall daily average COPD symptom scores and use of rescue medication.

Safety and tolerability were evaluated by recording of AEs, clinical laboratory measures, physical examinations including assessment of blood pressure and heart rate, and 12-lead ECGs (including 24-hour Holter monitoring).

Of 128 randomised patients, 104 patients (81.3%) completed the study. All patients were evaluated for safety and efficacy (ITT population).

Results

Statistically significant adjusted mean treatment differences were observed between all active treatments and placebo in the change from baseline to Day 14 in FEV1 AUC0-12/12h ($p<0.0001$ for all comparisons).

Overall, the magnitudes of the treatment differences between aclidinium/formoterol and either placebo or the constituent monotherapies were comparable for the two aclidinium/formoterol doses.

Table 9: Treatment comparisons for the changes from baseline to Day 14 in FEV1 $AUC_{0-12/12h}$ (L), morning trough FEV1 (L) and morning peak FEV1 (L): study LAC-MD-27 (ITT population)

	FEV_1 $AUC_{0-12/12h}$		Trough FEV_1		Peak FEV_1	
Treatment comparison	LS mean	p-value	LS mean	p-value	LS mean	p-value
Primary treatment comparisons						
AB/FF 400/12 µg - Pbo	0.200	<0.0001	0.132	<0.0001	0.281	<0.0001
AB/FF 400/6 µg - Pbo	0.202	<0.0001	0.137	<0.0001	0.275	<0.0001
Secondary treatment comparisons						
AB/FF 400/12 µg - AB 400 µg	0.043	0.054	0.044	0.079	0.095	<0.001
AB/FF 400/6 µg - AB 400 µg	0.045	0.044	0.049	0.048	0.088	<0.001
AB/FF 400/12 µg - FF 12 µg	0.074	0.002	0.053	0.038	0.110	<0.0001
AB/FF 400/6 µg - FF 12 µg	0.075	0.001	0.057	0.022	0.103	<0.0001
Additional treatment comparisons						
AB 400 µg - Pbo	0.157	<0.0001	0.088	<0.001	0.187	<0.0001
FF 12 µg - Pbo	0.127	<0.0001	0.079	0.002	0.171	<0.0001

Note: Analysis based on MMRM for crossover designs, with treatment and period as fixed effects, subject as random effect, and baseline values at each period as a covariate.

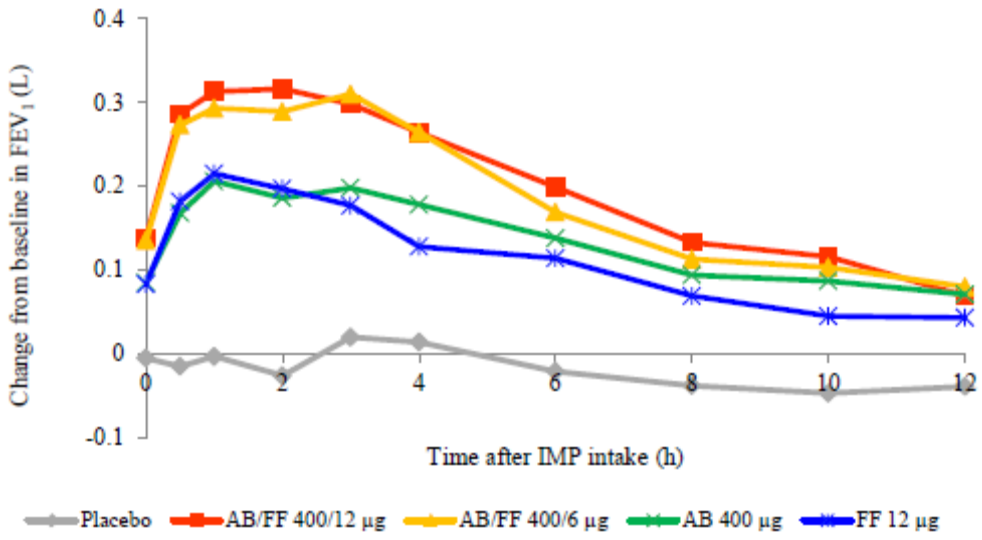
Abbreviations: AB=aclidinium bromide; AB/FF=aclidinium/formoterol; FEV1=forced expiratory volume in one second; FEV1 $AUC_{0-12/12h}$=normalised area under the FEV1 versus time curve between 0 h and 12 h post-dose; FF=formoterol fumarate dihydrate; ITT=intent–to-treat; LS=least squares; Pbo=placebo.

A pre-specified sensitivity analysis of the primary efficacy endpoint was performed in which the changes from baseline to Day 14 in FEV1 $AUC_{0-12/12h}$ were analysed with a modified MMRM which used the baseline of treatment period 1, rather than the baseline of each individual treatment period to determine the robustness of the results. These analyses showed:

- Adjusted mean treatment differences between aclidinium/formoterol and placebo in the increase from baseline to Day 14 in FEV1 $AUC_{0-12/12h}$ were numerically slightly greater with the 400/12 µg dose (0.218 L; p<0.0001) than with the 400/6 µg dose (0.196 L; p<0.0001).
- Aclidinium/formoterol 400/12 µg and 400/6 µg were associated with statistically significantly greater changes from baseline to Day 14 in FEV1 $AUC_{0-12/12h}$ than either aclidinium alone (0.059 L [p<0.001] and 0.036 L [p=0.031, respectively) or formoterol alone (0.091 L [p<0.0001] and 0.069 L [p<0.001], respectively).

Statistically significant adjusted mean treatment differences between all active treatments and placebo in the changes from baseline to Day 14 in both trough FEV1 and peak FEV1 were observed. Statistically significant adjusted mean treatment differences were also observed between both aclidinium/formoterol doses and either aclidinium or formoterol in the changes from baseline in both trough FEV1 and peak FEV1, with the exception of the treatment difference between aclidinium/formoterol 400/12 µg and aclidinium in the change from baseline in trough FEV1, which did not reach statistical significance. The magnitudes of the treatment differences between aclidinium/formoterol and either placebo or the constituent monotherapies in the changes from baseline to Day 14 in both trough FEV1 and peak FEV1 were comparable for the 400/12 µg and 400/6 µg doses.

Figure 1: LS mean changes from baseline in FEV1 (L) at each specific time point at Day 14: study LAC-MD-27 (ITT population)



Both aclidinium/formoterol doses clearly demonstrated statistical superiority over placebo and also demonstrated statistical superiority over aclidinium and formoterol monotherapies. While the bronchodilation associated with aclidinium/formoterol was generally comparable for the 400/12 µg and 400/6 µg doses, a pre-specified sensitivity analysis of the primary efficacy endpoint provided some indication of increased efficacy with the 400/12 µg dose. Treatment with aclidinium/formoterol 400/12 µg and aclidinium/formoterol 400/6 µg was also associated with statistically significant reductions compared to placebo in use of rescue medication and improvements in COPD symptoms.

Study M/40464/26

An efficacy and safety study of two fixed combinations of aclidinium/formoterol (200/12 µg and 200/6 µg) compared with aclidinium monotherapy (200 µg), formoterol monotherapy (12 µg) and placebo, all administered BID, in patients with stable, moderate to severe chronic obstructive pulmonary disease.

This Phase IIb, randomised, double-blind, placebo- and active comparator-controlled, 4-period incomplete cross-over study was conducted at 28 centres in Europe. Study design was identical to study LAC-MD-27. The following treatments (all administered BID via Genuair®) were evaluated: aclidinium/formoterol 200/12 µg, aclidinium/formoterol 200/6 µg, aclidinium 200 µg, formoterol 12 µg and placebo.

Efficacy measures and safety and tolerability assessments were the same as those described for study LAC-MD-27.

Of 135 randomised patients, 119 patients (88.1%) completed the study. All randomised patients were evaluated for safety and efficacy (ITT population).

Statistically significant adjusted mean treatment differences were observed between all active treatments and placebo in the change from baseline to Day 14 in FEV1 $AUC_{0\text{-}12/12h.}$

Table 10: Treatment comparisons for the changes from baseline to day 14 in FEV1AUC0-12/12h (L), morning trough FEV1 (L) and morning peak FEV1 (L): study M/40464/26 (ITT population)

	FEV_1 $AUC_{0-12/12h}$		Trough FEV_1		Peak FEV_1	
Treatment comparison	LS mean	p-value	LS mean	p-value	LS mean	p-value
Primary treatment comparisons						
AB/FF 200/12 µg - Pbo	0.221	<0.0001	0.101	<0.001	0.283	<0.0001
AB/FF 200/6 µg - Pbo	0.234	<0.0001	0.127	<0.0001	0.295	<0.0001
Secondary treatment comparisons						
AB/FF 200/12 µg - AB 200 µg	0.042	0.082	-0.030	0.247	0.080	0.005
AB/FF 200/6 µg - AB 200 µg	0.054	0.025	-0.005	0.845	0.092	0.001
AB/FF 200/12 µg - FF 12 µg	0.081	<0.001	0.015	0.577	0.080	0.005
AB/FF 200/6 µg - FF 12 µg	0.093	<0.001	0.040	0.127	0.092	0.001
Additional treatment comparisons						
AB 200 µg - Pbo	0.179	<0.0001	0.132	<0.0001	0.203	<0.0001
FF 12 µg - Pbo	0.140	<0.0001	0.087	<0.001	0.203	<0.0001

Note: Analysis based on MMRM with treatment and period as fixed effects, subject as random effect, and baseline values at each period as a covariate.
Abbreviations: AB=aclidinium bromide; AB/FF=aclidinium/formoterol; FEV1=forced expiratory volume in one second; FEV1 $AUC_{0-12/12h}$= normalised area under the FEV1 versus time curve between 0 h and 12 h post-dose; FF=formoterol fumarate dihydrate; ITT=intent–to-treat; LS=least squares.

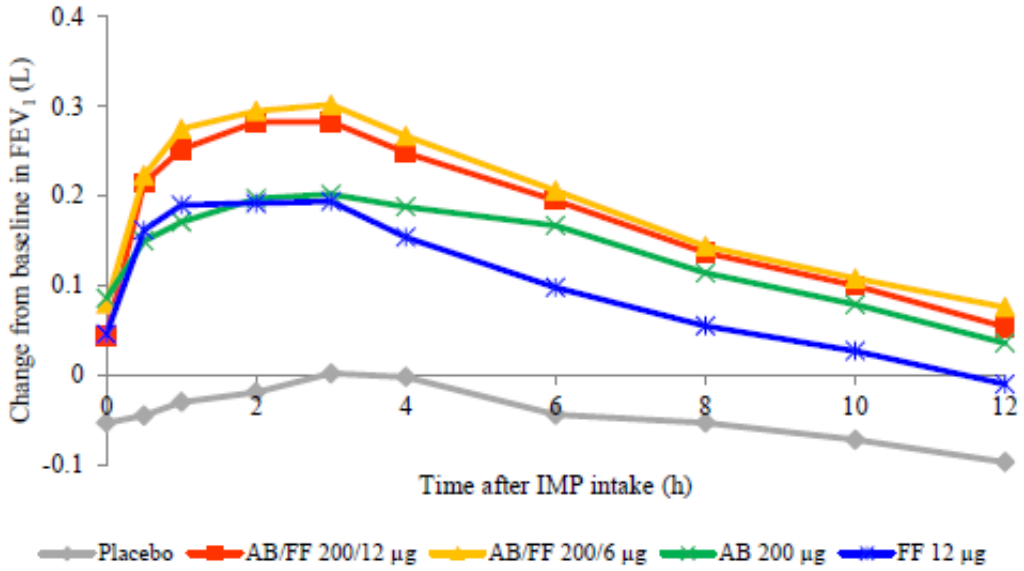
A sensitivity analysis of the primary efficacy endpoint in which the changes from baseline to Day 14 in FEV1 $AUC_{0-12/12h}$ were analysed with a modified MMRM which used the baseline of treatment period 1, rather than the baseline of each individual treatment period to determine the robustness of the results showed broadly similar results to the primary analysis.

Changes from baseline to Day 14 in trough FEV1 were statistically significantly greater with all active treatments compared to placebo. Aclidinium/formoterol 200/12 µg and 200/6 µg failed to demonstrate statistical superiority over the monotherapies, aclidinium 200 µg and formoterol 12 µg.

Adjusted mean treatment differences between all active treatments and placebo in the changes from baseline in peak FEV1 were statistically significant. Aclidinium/formoterol 200/12 µg and 200/6 µg also demonstrated statistical superiority over the monotherapies, aclidinium 200 µg and formoterol 12 µg.

The magnitudes of the treatment differences between aclidinium/formoterol and either placebo or the component monotherapies for the changes from baseline in trough FEV1 and peak FEV1 were comparable for the 200/12 µg and 200/6 µg doses.

Figure 2: LS mean changes from baseline in FEV1 (L) at each specific time point at Day 14 on treatment: study M/40464/26 (ITT population)



Study M/273FO/23

Initial clinical studies of aclidinium/formoterol investigated an OD dosing regimen because concurrent clinical studies of aclidinium monotherapy were investigating it as an OD treatment. The dose regimen for aclidinium/formoterol was switched from OD to BID when results from clinical studies of aclidinium monotherapy indicated that the bronchodilator efficacy of aclidinium 200 µg OD was suboptimal and that a higher daily dose and a more frequent dose regimen were needed.

The overall objectives of study M/273FO/23 were to investigate the efficacy and safety of three doses of aclidinium/formoterol OD (200/18 µg, 200/12 µg and 200/6 µg) compared to placebo and constituent monotherapies, and to determine the optimal formoterol dose to be combined with aclidinium 200 µg in subsequent clinical trials.

This Phase IIb randomised, double-blind, placebo- and active comparator-controlled, parallel-group study was conducted at 81 centres across Europe, Australia, New Zealand, India, Malaysia and Taiwan. Eligible patients were randomised in a ratio of 2:2:2:1:1:1 to one of the following 6 treatments according to the randomisation scheme: aclidinium/formoterol 200/18 µg, aclidinium/formoterol 200/12 µg, aclidinium/formoterol 200/6 µg, aclidinium 200 µg, formoterol 12 µg or placebo, all administered OD via Genuair® for up to 4 weeks. The final follow-up assessment was performed 7 days after the last dose of IMP.

The **primary efficacy endpoint** was the change from baseline to the end of Week 4 in FEV1 $AUC_{0\text{-}12/12h}$.

The **secondary efficacy endpoints** were:

- Changes from baseline to the end of Week 4 in trough FEV1, peak FEV1, FEV1 AUC0-3/3h and FEV1 AUC0-6/6h.

Safety and tolerability were evaluated by recording of AEs, clinical laboratory measures, physical examinations including assessment of blood pressure and 12-lead ECGs (including Holter monitoring at a subset of sites).

566 patients were randomised of which 534 patients completed the study.

Results

Statistically significant adjusted mean treatment differences were observed in the changes from baseline to the end of Week 4 in FEV1 $AUC_{0-12/12h}$ between the three doses of aclidinium/formoterol and placebo ($p<0.0001$ for all)

Table 11: Treatment comparisons for the changes from baseline to the end of Week 4 in FEV1AUC0-12/12h (L), trough FEV1 (L) and peak FEV1 (L): study M/273FO/23 (ITT population)

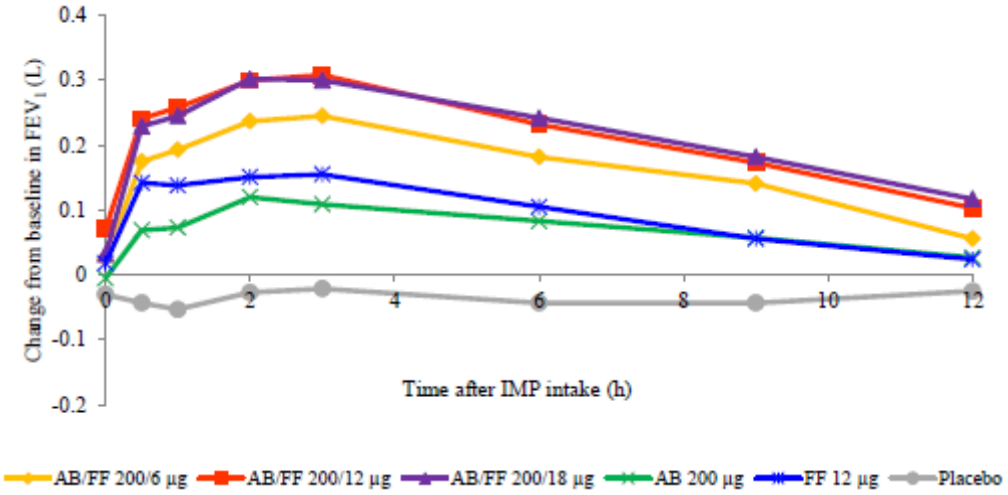
	FEV_1 $AUC_{0-12/12h}$		Trough FEV_1		Peak FEV_1	
Treatment comparison	LS mean	p-value	LS mean	p-value	LS mean	p-value
Primary treatment comparisons						
AB/FF 200/18 µg - Pbo	0.265	<0.0001	0.075	0.043	0.305	<0.0001
AB/FF 200/12 µg - Pbo	0.254	<0.0001	0.116	0.002	0.313	<0.0001
AB/FF 200/6 µg - Pbo	0.206	<0.0001	0.073	0.050	0.250	<0.0001
Secondary treatment comparisons: comparisons between fixed combinations						
AB/FF 200/18 µg vs AB/FF 200/6 µg	0.059	0.056	0.002	0.943	0.055	0.084
AB/FF 200/18 µg - AB/FF 200/12 µg	0.011	0.726	-0.041	0.171	-0.008	0.802
AB/FF 200/12 µg vs AB/FF 200/6 µg	0.048	0.117	0.043	0.152	0.063	0.050
Secondary treatment comparisons: comparisons between the fixed combinations and monotherapies						
AB/FF 200/18 µg - AB 200 µg	0.155	<0.0001	0.061	0.072	0.165	<0.0001
AB/FF 200/12 µg - AB 200 µg	0.144	<0.0001	0.102	0.003	0.173	<0.0001
AB/FF 200/6 µg - AB 200 µg	0.095	0.007	0.059	0.084	0.110	0.003
AB/FF 200/18 µg - FF 12 µg	0.131	<0.001	0.030	0.396	0.133	<0.001
AB/FF 200/12 µg - FF 12 µg	0.120	0.002	0.071	0.048	0.141	<0.001
AB/FF 200/6 µg - FF 12 µg	0.071	0.062	0.028	0.432	0.078	0.040

Note: Analysis based on ANCOVA for change from baseline in endpoint, with treatment group as factor and baseline value as a covariate.

All treatments were administered OD.

Abbreviations: AB=aclidinium bromide; AB/FF=aclidinium/formoterol; FEV1=forced expiratory volume in one second; FEV1 $AUC_{0-12/12h}$=normalised area under the FEV1 versus time curve between 0 h and 12 h post-dose; FF=formoterol fumarate dihydrate; ITT=intent–to-treat; LS=least squares; OD=once daily.

Figure 3: LS mean changes from baseline in FEV1 (L) in the 12 hours post-dose after 4 weeks on treatment: study M/273FO/23 (ITT population)



Aclidinium/formoterol 200/18 µg OD, 200/12 µg OD and 200/6 µg OD were all associated with significant bronchodilation relative to placebo in patients with moderate or severe COPD. The magnitudes of the improvements from baseline in lung function observed with the 200/18 µg and 200/12 µg doses were generally comparable and greater than those observed with the 200/6 µg dose. Aclidinium/formoterol 200/18 µg and 200/12 µg were associated with statistically superior bronchodilation relative to the constituent monotherapies, while the bronchodilatory effects of aclidinium/formoterol 200/6 µg relative to the monotherapies were less consistent.

2.5.2. Main studies

M/40464/30 and LAC-MD-31

The clinical efficacy programme for aclidinium/formoterol comprised two Phase III pivotal studies (M/40464/30 and LAC-MD-31) and two Phase III long-term safety studies (LAC-MD-36 and LAC-MD-32).

The primary objective of the Phase III pivotal studies was to confirm the bronchodilator efficacy of aclidinium/formoterol. Both pivotal studies also evaluated the efficacy of aclidinium/formoterol with regard to COPD symptoms, disease-specific health status and COPD exacerbations.

Methods

Both Phase III pivotal studies (M/40464/30 and LAC-MD-31) were multi-centre, randomised, double-blind, parallel-group, placebo- and active comparator-controlled studies of aclidinium/formoterol 400/12 µg and 400/6 µg in patients with moderate or severe stable airflow limitation (post-bronchodilator FEV1 ≥ 30% predicted and <80% predicted). The chosen comparators are in accordance with CHMP guidelines and are accepted.

Study M/40464/30 was conducted in Europe, South Africa and South Korea and study LAC-MD-31 was conducted in the US, Canada, Australia and New Zealand.

The treatment duration of both Phase III pivotal studies (24 weeks) was in accordance with the CHMP "Guideline on clinical investigation of medicinal products in the treatment of COPD" (CHMP/483572/2012) which states that effects on lung function parameters and symptoms may be demonstrated in 12 to 24

weeks. It is unlikely that a 24-week study will be long enough to demonstrate a clinically meaningful effect on exacerbations.

Both clinical studies included a placebo comparator and active comparators (formoterol monotherapy administered via Genuair and aclidinium monotherapy also administered via Genuair). Inclusion of a placebo comparator and an active comparator in the Phase III pivotal studies was consistent with the CHMP "Guideline on clinical investigation of medicinal products in the treatment of COPD" (CHMP/483572/2012). The choice of comparators was also determined by the CHMP "Guideline on clinical development of fixed combination medicinal products" (CHMP/EWP/240/95 Rev. 1) which states that, if feasible, inclusion of a placebo group is recommended in confirmatory studies, and also that confirmatory studies should preferably compare the fixed combination to the individual components to allow the superiority of the combination over the constituent monotherapies to be demonstrated.

In accordance with CHMP/483572/2012, randomisation of patients to treatment group was stratified by smoking status at the time of screening in order to balance treatment groups for smoking status.

Study Participants

Patient eligibility criteria for the two Phase III pivotal studies were the same. Principal characteristics of the inclusion and exclusion criteria in the Phase III pivotal studies were as follows:

- Patients were aged greater than or equal to 40 years.
- Patients had a clinical diagnosis of stable moderate or severe COPD, with COPD severity defined on the basis of airflow limitation as per the GOLD Global Strategy (2010). Eligible patients must have had a post-bronchodilator FEV1 less than 80% predicted and greater than or equal to 30% of predicted, and an FEV1/ FVC of less than 70%.
- Patients were current or ex-smokers, with a smoking history of at least 10 pack-years.
- Patients had not experienced a respiratory tract infection or COPD exacerbation in the 6 weeks (or 3 months if hospitalisation for COPD exacerbation was required) prior to screening.
- Patients in whom the use of anticholinergic drugs is contraindicated were excluded, i.e. those with a history of acute urinary retention or with known symptomatic prostatic hypertrophy, bladder neck obstruction or narrow-angle glaucoma.
- Patients had no clinically significant relevant cardiac and respiratory conditions (except COPD) and did not have a history or current diagnosis of asthma.

Although FEV1 reversibility was determined in the Phase III pivotal studies, a predefined entry criterion of degree of FEV1 reversibility was not included as bronchodilator reversibility testing is no longer recommended by GOLD for the initial diagnosis of COPD or for its differential diagnosis from asthma. Furthermore, inclusion of patients with all degrees of FEV1 reversibility in the Phase III clinical studies is consistent with the target population for aclidinium/formoterol.

The inclusion/exclusion criteria used in these studies are accepted by the CHMP. The diagnosis of COPD with persistent airway limitation and appropriate smoking history is sufficient to avoid inclusion of patients with asthma rather than COPD. Many patients with COPD have some degree of reversibility so it is accepted that reversibility no longer constitutes an exclusion criterion.

Treatments

The treatments were the same in both pivotal studies:

Following a 2 to 3-week run-in period during which the stability of the patients' COPD was confirmed, eligible patients were randomised, in a 1:1:1:1:1 (LAC-MD-31) and 2:2:2:2:1 (M/40464/30) ratio to receive either aclidinium/formoterol 400/12 µg, aclidinium/formoterol 400/6 µg, aclidinium 400 µg, formoterol 12 µg or placebo, BID, for up to 24 weeks (all administered via Genuair®). The final follow-up contact was 2 weeks after the last dose of study treatment.

The qualitative composition of aclidinium bromide/formoterol fumarate dihydrate inhalation powder was unchanged during the clinical development programme and the final to-be-marketed inhaler version was used in Phase III studies (M/40464/30, LAC-MD-31, LAC-MD-32, LAC-MD-36). Moreover, the inhaler version used in Phase IIb BID studies (M/40464/26 and LAC-MD-27) was the same as the to-be-marketed inhaler except for the difference in counter ring (30 actuations instead of 60 actuations), which does not have any impact on the aerodynamic performance of the inhaler.

Table 12: Overview of versions of the Almirall inhaler and their use in clinical studies of aclidinium / formoterol

	Version of the Almirall inhaler		
	SD2FL(SC)	SD2FL(MC)	
		30 actuations	60 actuations to-be-marketed product
Clinical studies	M/273FO/22 LAC-MD-24 M/273FO/23 M/34273/07	M/40464/26 LAC-MD-27	LAC-PK-01 M/40464/02 M/40464/30 LAC-MD-31 LAC-MD-32 LAC-MD-36

MC = multi-cavity; SC = single-cavity

The most important components of the Almirall inhaler that determine the dispersion and deagglomeration of the inhalation powder were unaltered between the inhaler versions used during the development of aclidinium/formoterol. The modification of the counter ring of SD2FL(MC) is not expected to influence the pharmaceutical performance characteristics because the counter ring is not involved in the dispersion or deagglomeration of the inhalation powder.

Objectives

The objectives of studies M/40464/30 and LAC-MD-31 were to assess the long-term bronchodilator efficacy of two fixed combinations of inhaled aclidinium/formoterol BID (400/12 µg and 400/6 µg) compared with the monocomponents and placebo as well as to assess the benefits of aclidinium/formoterol in terms of symptoms of COPD, disease-related health status and COPD exacerbations, and to evaluate safety and tolerability.

Outcomes / endpoints

The objectives and endpoints were the same in both studies.

A 12-hour serial spirometry sub-study was performed for a subgroup of 20% of patients at selected study centres.

The **co-primary efficacy endpoints** were:

- Change from baseline to Week 24 in FEV1 at 1 hour post-dose (primary comparison: each aclidinium/formoterol fixed combination vs. aclidinium 400 µg).

- Change from baseline to Week 24 in morning pre-dose (trough) FEV1 (primary comparison: each aclidinium/formoterol fixed combination vs. formoterol 12 µg).

The **secondary efficacy endpoints** were:

- Improvement in TDI focal score at Week 24 (primary comparison: each aclidinium/formoterol fixed combination vs. placebo).
- Change from baseline in SGRQ total score at Week 24 (primary comparison: each aclidinium/formoterol fixed combination vs. placebo).

Notable **additional efficacy variables** were:

- Changes from baseline by time point (visit) in FEV1 at 1 hour post-dose, peak FEV1, trough FEV1, trough FVC and trough IC.
- Changes from baseline in FEV1 and FVC in the 3 h post-dose on Day 1 and Week 24 and changes from baseline to Day 1 and Week 24 in FEV1 AUC0-3/3h and FVC AUC0-3/3h, respectively.
- Change from baseline in FEV1 at 5 minutes post-dose on Day 1 and the number (%) of patients who achieved onset of bronchodilation (defined as >15% increase from baseline in FEV1) by 5 minutes post-dose on Day 1.
- Changes from baseline in FEV1 in the 12 h post-dose on Day 1 and Week 24 (data from 12-hour serial spirometry sub-study).
- Changes from baseline by visit in the TDI Focal score and SGRQ Total score.
- Percentages of patients with clinically significant improvements in TDI focal score and SGRQ total score at Week 24.
- Exacerbation rate (number of exacerbations per patient per year), numbers (%) of patients with at least one COPD exacerbation and time to first COPD exacerbation, defined on the basis of both HRU and EXACT.
- Change from baseline in the daily use of rescue medication.
- Change from baseline in COPD symptoms assessed using E-RS.
- Change from baseline in night-time and early morning COPD symptoms.

Safety and tolerability were evaluated by recording of adverse events (AEs), clinical laboratory assessments, vital signs (blood pressure) and 12-lead electrocardiograms (ECGs; including 24-hour Holter monitoring at subset of sites).

Sample size

Study M/40464/30

In total 2443 patients were screened, of whom, 1729 patients were considered eligible and were randomised. In total, 714 (29.2%) patients were considered screen failures, the main reason being non-fulfilment of inclusion/exclusion criteria (88.9%).

Most patients completed study treatment (88.3%); a slightly lower percentage of patients in the placebo group completed study treatment (82.5%) compared with the active treatment groups (87.0% to 91.2%). Patients' personal request was the most frequent reason given for discontinuation (4.2%), followed by AE (other than COPD exacerbation) (2.9%), and protocol non-compliance (2.0%). In general, the reasons for discontinuation reported were for a low and similar percentage of patients across the

treatment groups. However, the percentage of patients who discontinued due to patients' personal request and lack of efficacy was numerically higher in patients receiving placebo (7.2% and 3.1%, respectively) than in the other groups (range for patients' personal request: 2.6% to 4.9%; range for lack of efficacy: 0% to 1.3%).

Study LAC-MD-31

A total of 370 (21.9%) of all randomized patients were discontinued from the study. Overall, the placebo treatment group had the highest incidence of discontinuation (30.0%) and FDC 400/6 µg had the lowest incidence (18.3%). The overall incidence of discontinuation in the FDC 400/12 µg, aclidinium 400 µg, and formoterol 12 µg was 19.5%, 21.2%, and 20.4%, respectively. The most frequently reported reasons for discontinuation were AE (5.6%), withdrawal of consent (4.7%), and protocol violation (4.4%).

The percentage of patients who discontinued due to AEs was comparable between the FDC (6.2% and 6.5% for FDC 400/12 µg and FDC 400/6 µg, respectively) and placebo treatment groups (6.2%), and slightly higher than the aclidinium 400 µg (4.7%) and formoterol 12 µg (4.1%) treatment groups. Discontinuation due to insufficient response occurred most often in the placebo treatment group (5.9%), and least often in the FDC treatment groups (1.5% and 1.2% for FDC 400/12 µg and FDC 400/6 µg, respectively). Comparatively, 2.4% and 2.9% of patients in the aclidinium 400 µg and formoterol 12 µg treatment groups, respectively, discontinued due to insufficient response. Patients treated with placebo were most likely to discontinue due to COPD exacerbation (2.4%) as compared to patients treated with the FDCs (2.1% and 0.9% for FDC 400/12 µg and FDC 400/6 µg, respectively), aclidinium 400 µg (2.1%), or formoterol 12 µg (1.5%).

Randomisation

A centralised IVRS was used. IVRS stratified randomisation by each patient's smoking status at the time of screening (smoker or ex-smoker) in order to balance treatment groups regarding smoking status. As this was a double-blind study, neither the patient nor the research staff knew the treatment assigned to each patient.

Study centre staff obtained kit numbers from the IVRS at each visit when study medication was to be dispensed. Randomisation data were strictly confidential, accessible only to authorised staff, until the time of unblinding of the allocated treatment of all study patients after hard lock of the database upon completion of the study. Only when the study was completed and the data verified and locked were the randomisation codes made available for data analysis.

In order to assign a treatment to each randomisation number, a computer generated randomisation schedule was prepared by the Statistics Programming Group within Almirall before initiation of the study according to the relevant Almirall Standard Operating Procedure. The block size was determined in agreement with the Clinical Trial Manager and was not communicated to the Investigators.

A table presenting the randomisation codes, patient identification number, and treatment assignments is presented by study centre.

Blinding (masking)

Inhalers and medication kits containing study medication were of the same external appearance ensuring the double-blind of the study. Active ingredients had no perceptible taste, appearance, odour or colour that could unmask the blinded design. The blind was not broken except in medical emergencies, as assessed by the Investigator, when the maintenance of the patient's safety required knowledge of the study medication administered.

Statistical methods

Table 13: Pre-specified sequence of testing for multiplicity adjustment for Phase III pivotal studies: M/40464/30 and LAC-MD-31

Order in Hierarchy	End Point (at Week 24)	Treatment Comparison
1	1-hour post-dose FEV_1	Aclidinium/formoterol 400/12 µg vs. aclidinium 400 µg
2	Morning pre-dose FEV_1	Aclidinium/formoterol 400/12 µg vs. formoterol 12 µg
3	TDI	Aclidinium/formoterol 400/12 µg vs. placebo
4	1-hour post-dose FEV_1	Aclidinium/formoterol 400/6 µg vs. aclidinium 400 µg
5	Morning pre-dose FEV_1	Aclidinium/formoterol 400/6 µg vs. formoterol 12 µg
6	TDI	Aclidinium/formoterol 400/6 µg vs. placebo
7	SGRQ	Aclidinium/formoterol 400/12 µg vs. placebo
8	SGRQ	Aclidinium/formoterol 400/6 µg vs. placebo

Each endpoint in hierarchy must have been rejected at 5% level in order to test next one in sequence at 5% level.
Abbreviations: FEV_1=forced expiratory volume in one second; SGRQ=St George's Respiratory Questionnaire; TDI=transition dyspnoea index.

Both co-primary efficacy variables were analysed by means of a MMRM. The dependent variable was the change from baseline to each scheduled post baseline visit during the treatment period until Week 24. The model was adjusted for pre- and post-bronchodilator (salbutamol) FEV1 at screening, age, and baseline FEV1 as covariates, and treatment group, gender, smoking status, visit, and treatment group-by-visit interaction as fixed effect factors.

The within-patient correlation was modelled using the unstructured covariance matrix. If the model did not converge, then the compound symmetry covariance structure was used. Restricted maximum likelihood method was used.

Each treatment effect and treatment differences were estimated by the least squares (LS) Means on the corresponding treatment-by-visit interaction at Week 24, along with their standard errors (SEs) and 95% CIs, and the p-value corresponding to the between-treatment group difference.

The pre-specified sequence of analysing the endpoints and treatment comparison is given in the table above. This was agreed with the FDA to facilitate labelling claims.

A sensitivity analysis using a pattern-mixture model based on non-future dependent missing value restrictions was performed to assess the robustness of the primary MMRM results to the possible violation of the missing-at-random assumption.

The pre-specified hierarchical testing procedure is not directly relevant to this submission as an effect on lung function and symptoms needs to be demonstrated to obtain a licence in the EU. Therefore, this assessment does not include further details of the testing strategy.

As noted in the assessment of the previous studies the use of MMRM does not necessarily produce an appropriate estimate of the treatment effect. The sensitivity analysis using a pattern-mixture model may be a more appropriate summary of the results of these studies.

Results

Participant flow
Figure 4:
Study M/40464/30

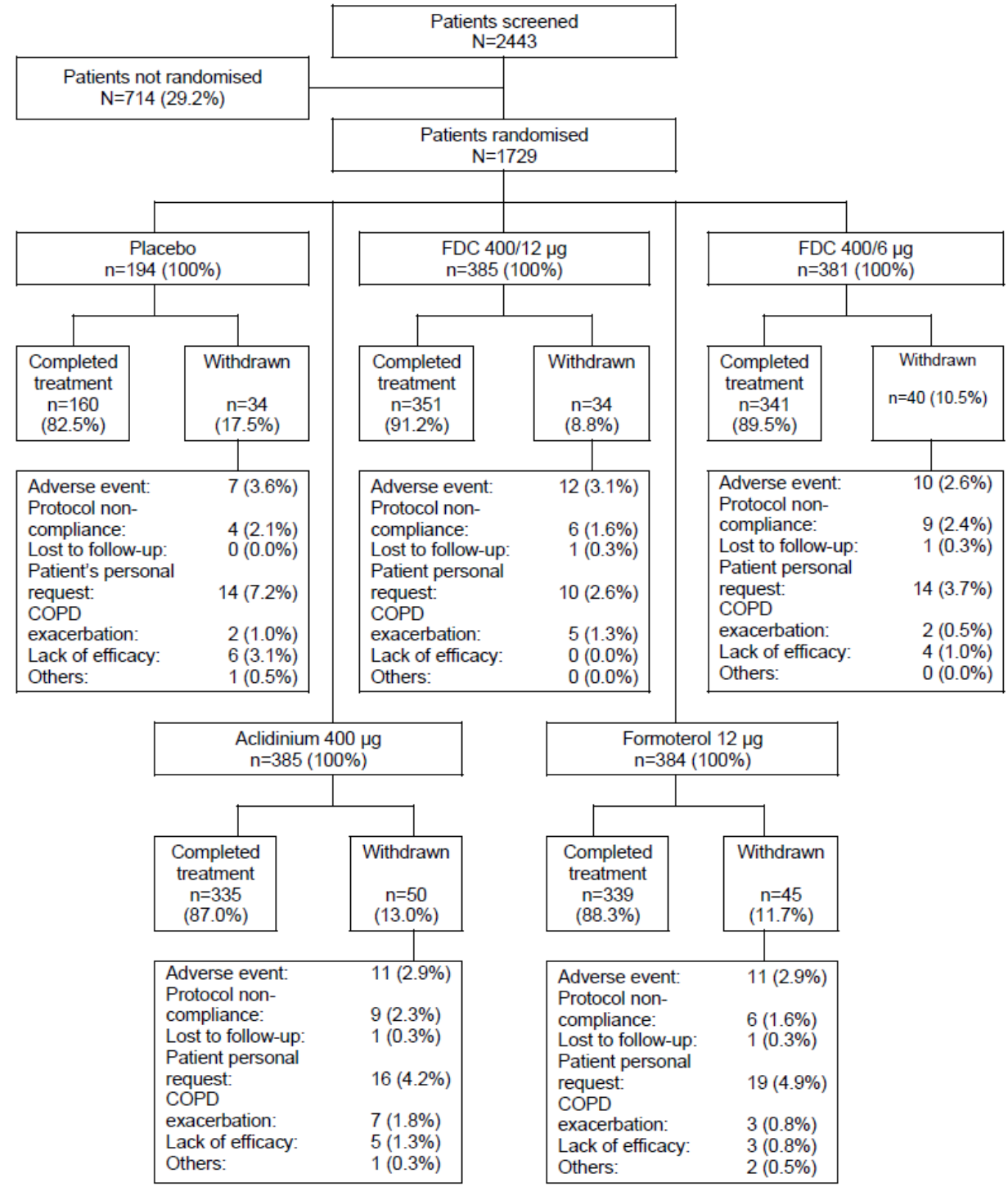
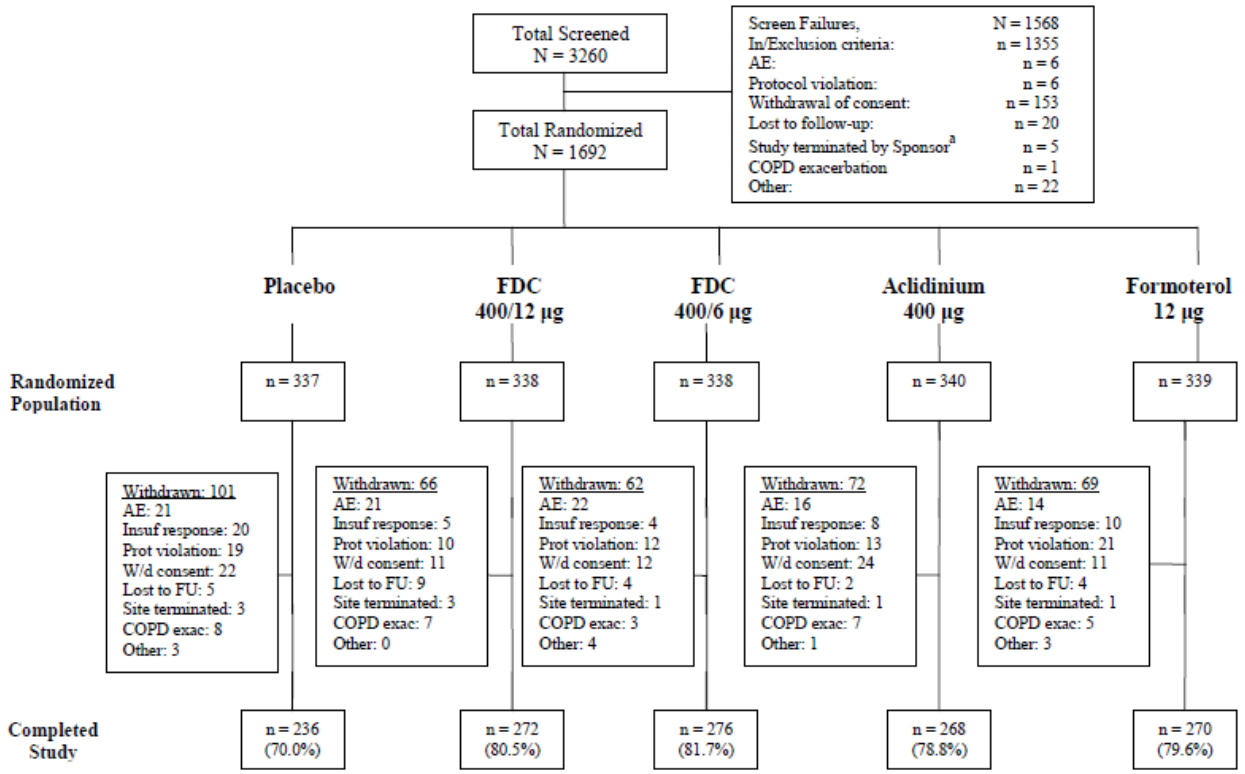


Figure 5:
Study LAC-MD-31



Recruitment

Study M/40464/30

Patients were randomised at 193 centres in 22 countries: Austria (2 centres), Belgium (2), Bulgaria (5), Croatia (2), Czech Republic (12), Denmark (4), Finland (5), France (7), Germany (28), Hungary (15), Italy (4), the Netherlands (7), Poland (20), Romania (12), Russia (5), Slovakia (7), South Africa (9), South Korea (8), Spain (7), Sweden (5), Ukraine (11), United Kingdom (16). In addition, 4 centres screened but did not randomise any patients: Hungary (1 centre), the Netherlands (1), South Korea (1), and Spain (1).

Study period

First patient, first visit: 26 October 2011

Last patient, last visit: 04 January 2013

Study LAC-MD-31

A total of 222 study centres located in the United States (193 centres), Canada (10 centres), Australia (11 centres), and New Zealand (8 centres) screened patients for this study. A total of 205 of these study centres randomized patients (178 in the United States, 9 in Canada, 10 in Australia, and 8 in New Zealand).

Study Period:

First patient, first visit: 04 Oct 2011

Last patient, last visit: 06 Feb 2013

Conduct of the study

The protocol amendments were minor updates and corrections that would not have affected the overall clinical outcomes of the studies.

Study M/40464/30

There were two global amendments to this study protocol:

Global amendment #1 (May 2012)

- Clarifications to the text, administrative and typographical errors.
- For the purposes of this clinical trial, Cenduit, the company providing the Interactive Voice Response System (IVRS) service, also made available an Interactive Web Response System (IWRS). In order to avoid replacing "IVRS" by "IVRS and/or IWRS" throughout the whole protocol document, a clarification note is added only in section 5.3 "Participating Companies".
- To correct the following inconsistency: There is an error in section 10.10.1 when requiring salbutamol to be stable at least 4 weeks before Screening. According to section 10.10.2, salbutamol is used as relief medication during the trial, and as such (and as a matter of fact), salbutamol must be dispensed to all patients of the study at the time of Informed Consent signature and be used by them on as needed basis at any time, regardless patient used it before study start or not.
- To amend the following inconsistency and clarify protocol requirements: Oral sustained release xanthines are permitted during the study if stable for at least 4 weeks before Screening Visits, whilst non-oral sustained release forms must be stopped 72 hours before Screening Visit. However, there is an administrative error in the protocol when giving the example of aminophylline as prohibited xanthine, because in fact there is an oral sustained release form of aminophylline available on the market.
- Protocol allows certain time windows for the different Visits of the study (section 11). However, certain situations cannot be anticipated nor detailed in the study protocol (e.g. technical device not working at the time of the visit appointment, patient intake of IMP morning dose before the visit, long holiday period, etc). In some situations, the time windows specified in the protocol do not allow re-scheduling the visit on a later date and induce sites to skip a patient´s visit. Still, the risk of not checking patient status and skip a visit should be balanced. Therefore a comment is added in the protocol so that sites know how they can seek advice in exceptional situations.
- According to the current protocol wording, there is a ± 30 minutes deviation allowance for the spirometry to be performed at 5 minutes post-morning IMP dose. This is an administrative error, since 30 minutes before would mean pre-IMP dose and at 30 min post dose there is another spirometry scheduled. No deviation allowance was anticipated for the "5 min post-morning IMP dose" time point. Protocol is amended accordingly.
- Study assessments at Visit 1 should be grouped as assessments pre-randomisation or post-randomisation. However BDI, SGRQ and EQ-5D at Visit 1 are described to occur after IVRS randomisation call and before first study drug dosing. This error was proactively fixed in the EDC design so that these tests are performed (and captured), as the remaining baseline assessments, before randomisation call.
- The Flow Chart of Trial Assessments (section 11.2 page 37) clearly differentiates footnote # 7 for Post-dose PFTs on Visit 1 and footnote # 8 for Post-dose PFT on Visits 2, 3 and 6. Difference consists on PFT at 5 minutes post-dose, which is only to be performed at Visit 1. However, due to

administrative error, the PFT at 5 minutes post-dose appears on the list of assessments described on each specific protocol Visit section, from where it is now deleted. The spirometer software was correctly programmed according to the Flow Chart during the trial set-up phase, and therefore the PFT at 5 minutes post-dose is only being captured at Visit 1.

- To avoid the use of spirometry manual records.
- To specify the repeatability criteria applied to Inspiratory Capacity measurement provided this is not covered by ATS/ERS guidelines.
- Depending on each site internal organisation, site personnel may not have access to the room or to the computer where the EDC data is to be recorded at the time of patient' visit (room or computer busy, limited internet access etc). Therefore not always the Health Resources Utilisation Questionnaire form of the EDC can be used as data source. Medical notes or worksheets may be used instead as source document instead.

Global amendment #2 (October 2012)

- Due to the prevalence of cardiovascular disease in patients with COPD, Major Adverse Cardiac Events will be evaluated by a committee composed of independent cardiologists.
- The CRO provides 24 hour medical cover for emergency situation to research staff ONLY. Research staff are responsible for covering study patients emergency calls 24 hours throughout the study.
- To update some Additional Variables and its planned analysis.
- A new population set is defined for the analysis of COPD exacerbation outcomes. This population set coincides with the Safety Population definition, however it is categorised as a different set because its scope is the analysis of efficacy outcomes.
- The multiplicity statistical approach has been updated following the CHMP scientific advice. Sample size remains unchanged, but the wording has been updated. The hierarchy for the US region is removed from the final protocol as it is under discussion with the FDA. It will be specified in detail in the final protocol for study LAC-MD-31, which will be signed off before the unblinding of the both studies M/40464/30 and LAC-MD-31.
- SAS version to be updated in the SAP.
- The sensitivity analysis to assess the robustness of the MMRM model is updated.

There were also several local amendments specific to individual countries, which would not have affected the overall clinical results.

Study LAC-MD-31

There were four protocol amendments in study LAC-MD-31:

The purpose of Amendment #1(23 Aug 2011) was to:

- Provide study-specific instructions on proper rescue medication inhaler use and restrictions before visits according to revised ATS/ERS criteria (Miller et al, 2005)
- Correct the co-primary and secondary efficacy assessments
- Provide clarification of the clinical laboratory determinations
- Correct the statistical efficacy parameters

- Clarify and correct information throughout the protocol, as necessary.

The purpose of Amendment #2 (14 Feb 2012) was to:

- Define the Registration Visit (Visit 0) and Screening Visit (Visit 1)
- Clarify method to assess compliance, redefine inadequate compliance, and provide guidance to the study centre as to when the Sponsor should be notified in cases of noncompliance
- Clarify and define inadequate electronic diary compliance
- Add information regarding the extension study LAC-MD-36 at the end of Visit 7
- Revise the statistical analyses of the HEOR parameters
- Amend elements of informed consent section to align with 21 CFR, Parts 50 and 312, revised 01 Apr 2011
- Clarify concomitant medication restrictions and known drug interaction effects of aclidinium bromide and formoterol fumarate
- Clarify and correct information throughout the protocol as necessary

The purpose of Amendment #3 (07 Jan 2013) was to:

- Describe the adjudication of MACE activities
- Add requirement of additional follow-up for COPD exacerbations in patients who prematurely discontinue
- Update the regulatory status of aclidinium bromide
- Clarify electronic diary and TrialSlate procedures for patients participating in the extension study, LAC-MD-36, at the end of Visit 7/ET
- Update statistical analyses sections to add the ITT-Exacerbations patient population, redefine multiplicity adjustments, and add additional efficacy parameters, along with other clarifications throughout the sections
- Clarify health outcomes analyses
- Update contact information for FRI personnel

The purpose of Amendment #4 (20 Mar 2013) was to:

- Add the requirement for a comparison of aclidinium 400 µg versus placebo for the US filing only to the secondary efficacy parameter of change from baseline in SGRQ total score at Week 24
- Define the different multiplicity strategies to be used in the EU filing and the US filing in response to comments from the FDA and to be consistent with changes made in SAP amendment #1

Baseline data

Numbers analysed

The definitions of the analysis populations are in accordance with those stated in the study protocols and are accepted as appropriate.

Analysis populations

A Blind Data Review Meeting (BDRM) was convened to assign, in a blinded manner before breaking the randomization codes, the patients that participated in the clinical trials to the analysis population sets previously defined in the study protocols and in the Statistical Analysis Plans (SAP).

SCREENED POPULATION

The Screened Population is defined as all patients who attended Screening Visit and received a patient number.

RANDOMIZED POPULATION

The Randomized Population is defined as all patients in the Screened Population who were randomized to a treatment group in the study.

SAFETY POPULATION

The Safety Population is defined as all randomised patients who took at least one dose of Investigational Medicinal Product (IMP).

INTENT-TO-TREAT POPULATION

The Intent-to-Treat Population (ITT) for all efficacy endpoints other than Exacerbation efficacy endpoints is defined as all randomised patients who took at least one dose of IMP and have a baseline and at least one post-baseline FEV1 assessment.

PER-PROTOCOL POPULATION

The Per-Protocol Population (PP) is defined as a subset of ITT population constituted by those patients who: (a) met all inclusion/exclusion criteria liable to affect the efficacy assessment, (b) attained a sufficient compliance to the treatment received, (c) did not present serious deviations of the protocol that may affect efficacy.

INTENT-TO-TREAT EXACERBATIONS POPULATION

The Intent-to-Treat population for Exacerbations efficacy endpoints (ITT-E) is defined as all randomised patients who took at least one dose of IMP.

Study M/40464/30

Table 18:

Population	Number (%) of Patients					
	Placebo	FDC 400/12 µg	FDC 400/6 µg	Aclidinium 400 µg	Formoterol 12 µg	Total
Screened						2443
Randomised	194	385	381	385	384	1729
Spirometry substudy	41	82	80	82	81	366
Holter substudy	37	69	69	71	71	317
Safety population	194 (100.0)	385 (100.0)	381 (100.0)	385 (100.0)	384 (100.0)	1729 (100.0)
ITT population	194 (100.0)	385 (100.0)	381 (100.0)	383 (99.5)	383 (99.7)	1726 (99.8)
PP population	179 (92.3)	363 (94.3)	368 (96.6)	365 (94.8)	358 (93.2)	1633 (94.4)
ITT-Exacerbations	194 (100.0)	385 (100.0)	381 (100.0)	385 (100.0)	384 (100.0)	1729 (100.0)

All randomised patients received at least one dose of study medication and were included in the Safety and ITT-Exacerbation populations (100.0%). Three randomised patients were excluded from the ITT

population (1726/1729 [99.8%]) due to missing baseline or post-baseline FEV1 data and a further 93 patients were excluded from the PP population (1633/1729 [94.4%]) due to deviations that could have had a serious impact on the primary efficacy analysis.

Study LAC-MD-31

Table 19:

Populations	*Number of Patients*					
	Placebo	*FDC 400/12 µg*	*FDC 400/6 µg*	*Aclidinium 400 µg*	*Formoterol 12 µg*	*Total*
Randomized	337	338	338	340	339	1692
Safety/ITT-Exacerbations	332	335	333	337	332	1669
Holter Substudy	44	44	48	47	48	231
ITT	331	335	333	337	332	1668
Spirometry Substudy	58	53	50	52	57	270
Per Protocol	296	302	300	292	301	1491

FDC = fixed-dose combination; ITT = intent to treat.

Approximately 10% of all patients in the ITT Population were identified as either having protocol deviations that led to exclusion from the PP Population or were deemed not appropriate for inclusion in the PP Population. Less than half of these patients were discontinued from treatment due to protocol deviations. Patients taking < 75% of assigned investigational product and patients with end date of COPD exacerbation < 2 weeks (mild) or < 4 weeks (moderate/severe) before scheduled Visit 7 accounted for the majority of patients who were excluded from the PP Population. Other reasons for exclusion from the PP Population for which there were reports of ≥ 2 patients in any individual treatment group were (1) patients who took > 110% of assigned investigational product, (2) patients enrolled at 2 investigative sites, and (3) patients receiving unstable oral or parental corticosteroids dose 2 weeks prior to Visits 2 or 7.

Outcomes and estimation

The outcomes are elaborated in the next section.

Ancillary analyses

The co-primary efficacy endpoints (changes from baseline in FEV1 at 1 hour post-dose and in trough FEV1) and secondary efficacy endpoints (changes from baseline in TDI focal score and SGRQ total score) were analysed in various subpopulations of the pooled population of M/40464/30 and LAC-MD-31. The following subpopulations were evaluated:

-gender (male or female)

-age group (≥ 65 years or <65 years)

-body mass index (BMI) group (obese, pre-obese or normal weight/underweight)

-COPD severity (moderate or severe)

-smoking status (current smokers or ex-smokers)

-reversibility to short-acting bronchodilators (reversible or non-reversible)

-concomitant use of ICS (using ICS or not using ICS)

Although analysis of treatment effect by race was planned, the number of non-Caucasians was too low to allow for a meaningful analysis (94.1% of the pooled population was Caucasian).

Statistically significant adjusted mean treatment differences between aclidinium/formoterol 400/12 µg or 400/6 µg and placebo in the co-primary endpoints were observed across all subpopulations. The magnitudes of the adjusted mean treatment differences (and 95% CIs) were generally similar to those observed for the overall ITT population, with the exception of the subpopulations of bronchodilator reversibility (both doses) and gender (400/12 µg) for FEV1 at 1 hour post-dose and gender (400/12 µg) for trough FEV1, with greater treatment differences observed in reversible patients and in females. The observed effect of gender on the bronchodilation endpoints can be attributed, at least in part, to baseline differences in FEV1 and the physiological differences in lung function between males and females.

Statistically significant adjusted mean treatment differences between aclidinium/formoterol (both doses) and placebo in the changes from baseline in TDI focal score were observed across all subpopulations; results across subpopulations were robust.

The subpopulation analysis of the SGRQ endpoint was limited by the lack of homogeneity in this endpoint between M/40464/30 and LAC-MD-31 mainly due to the unexpectedly large placebo response in M/40464/30 so that the pooled analysis for the treatment comparisons versus placebo is not reported.

Forest plots of the results of subgroup analyses have been provided in the Summary of Clinical Efficacy. The effect on lung function is consistently greater in males than females though the improvement in TDI is similar in both genders. Effects in the <65 year olds is also greater than in the ≥65 year olds but the confidence intervals overlap.

Lung function shows a greater improvement in those patients with moderate COPD compared with those with severe COPD but the effect on TDI is greater in the subgroup of patients with severe COPD.

Not surprisingly there is a greater improvement in lung function parameters in those patients exhibiting greater reversibility at the beginning of the study than in those patients whose airways obstruction showed less reversibility. However the improvement in TDI was greater for those patients demonstrating less reversibility.

Overall the subgroup analyses demonstrate the generalizability of the results to the greater COPD population.

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

The two Phase III pivotal studies were very similar in design and in the efficacy variables assessed, therefore, they have been pooled to (i) increase the precision of treatment effect estimates for selected clinically relevant efficacy endpoints (ii) assess the effect of each aclidinium/formoterol dose on COPD exacerbations (for which the individual studies were not powered to detect a difference) and iii) assess consistency of treatment effect in subpopulations. The pooled analysis also allowed estimates of the treatment effect of each dose of aclidinium/formoterol compared to component monotherapies on the TDI and SGRQ endpoints to be determined.

It was planned to determine treatment effects for the SGRQ endpoints compared to placebo and component monotherapies in the pooled population of Phase III pivotal studies (M/40464/30 and LAC-MD-31). However, as a consequence of the lack of homogeneity between M/40464/30 and LAC-MD-31 in the treatment differences between aclidinium/formoterol and placebo in the changes from baseline to Week 24 in SGRQ total score, the comparisons to placebo for SGRQ endpoints in the pooled population of M/40464/30 and LAC-MD-31 have not been reported. The lack of homogeneity between

studies is primarily due to an unexpectedly large placebo response in M/40464/30 compared to that observed in LAC-MD-31.

Results and analyses of the following 2 secondary efficacy parameters for the US filing are also provided in the Integrated Summary of Efficacy:

- Reduction in rate of moderate or severe COPD exacerbation per patient per year in each dose of FDC relative to placebo based on pooled data from M/40464/30 and LAC-MD-31
- Reduction in rate of moderate or severe COPD exacerbation per patient per year due to the effect of aclidinium 400 µg relative to placebo based on pooled data from M/40464/30 and LAC-MD-31

A total of 3394 patients were included in the ITT Populations of M/40464/30 and LAC-MD-31 and included in the pooled analyses of these studies.

Table 24: Patient populations in the pooled analysis of M/40464/30 and LAC-MD-31

Population	AB/FF 400/12 µg	AB/FF 400/6 µg	AB 400 µg	FF 12 µg	Placebo	Total
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Randomised	723	719	725	723	531	3421
ITT-Exacerbations	720 (99.6)	714 (99.3)	722 (99.6)	716 (99.0)	526 (99.1)	3398 (99.3)
ITT	720 (99.6)	714 (99.3)	720 (99.3)	715 (99.8)	525 (98.9)	3394 (99.2)
Completed patients	623 (86.2)	617 (85.8)	603 (83.2)	609 (84.2)	396 (74.6)	2848 (83.3)

Abbreviations: AB=aclidinium bromide; AB/FF=aclidinium/formoterol; FF=formoterol fumarate dihydrate; ITT=intent-to-treat.

Table 25: Baseline COPD status and smoking history of patients enrolled in Phase III pivotal studies, M/40464/30 and LAC-MD-31 and in the pooled population of M/40464/30 and LAC-MD-31: ITT populations

Variable (unit) Statistic/category		Study		Pooled population[a]
		M/40464/30	LAC-MD-31	
		N=1726	N=1668	N=3394
COPD severity (based on degree of airway obstruction[b])				
Stage I (mild)	n (%)	1 (0.1)	4 (0.2)	5 (0.1)
Stage II (moderate)	n (%)	1037 (60.1)	950 (57.0)	1987 (58.6)
Stage III (severe)	n (%)	685 (39.7)	697 (41.8)	1382 (40.8)
Stage IV (very severe)	n (%)	2 (0.1)	12 (0.7)	14 (0.4)
Patients with exacerbations in the previous 12 months				
0	n (%)	1088 (63.0)	1318 (79.0)	2406 (70.9)
1	n (%)	441 (25.6)	247 (14.8)	688 (20.3)
≥2	n (%)	197 (11.4)	103 (6.2)	300 (8.8)
SGRQ total score[c]				
	n	1702	1622	3324
	Mean (SD)	46.2 (17.6)	46.0 (17.7)	46.1 (17.6)
BDI focal score[d]				
	n	1682	1615	3297
	Mean (SD)	6.6 (2.1)	6.4 (2.3)	6.5 (2.1)
Smoking history				
Current smoker	n (%)	816 (47.3)	860 (51.6)	1676 (49.4)
Smoking consumption (pack-years)	Mean (SD)	40.3 (20.6)	52.7 (26.3)	46.4 (26.4)

a Pooled analysis of patient populations from M/40464/30 and LAC-MD-31.
b GOLD classification of COPD severity based on airway limitation: Stage 1: post-bronchodilator FEV1≥ 80% predicted; Stage II: post-bronchodilator FEV1 ≥ 50% and <80% predicted; Stage III: post-bronchodilator FEV1 ≥ 30% and <50% predicted; Stage IV: post-bronchodilator FEV1 <30% predicted. For Stages I to IV, FEV1/FVC <0.70.
c SGRQ Total score ranges from 0 to 100; higher scores indicate worse health status.
d BDI Focal score ranges from 0 to 12; lower scores denote worse dyspnoea.
COPD=chronic obstructive pulmonary disease; FEV1=forced expiratory volume in 1 second; FVC=forced vital capacity; GOLD=Global Initiative for Chronic Obstructive Pulmonary Disease; ITT=intent-to-treat; SE=standard error; SGRQ=St George's Respiratory Questionnaire; BDI=Baseline Dyspnoea Index.

The mean ages of the patient populations in M/40464/30 and LAC-MD-31 were similar. In LAC-MD-31 compared to M/40464/30, a slightly higher proportion of the patients were at least 70 years of age (28.1% vs. 22.6%) and a slightly lower proportion of the patients were between 60 and 69 years of age (40.7% vs 45.2%). In addition, a lower proportion of males were included in the ITT population of LAC-MD-31 compared to M/40464/30 (53.2% vs. 67.6%). Minor differences in the racial profile between the two studies were observed which are consistent with conduct of these studies in different geographical regions.

Improvement in lung function

Lung function (as determined by pre- and post-bronchodilator FEV1/percentage predicted FEV1 and post-bronchodilator FEV1/FVC ratio) at screening was very similar for the two studies. Bronchial reversibility to short-acting β2-agonists (SABAs) was higher in LAC-MD-31 (percentage and absolute reversibility: 17.9% and 0.205 L, respectively) than in M/40464/30 (12.7% and 0.152 L, respectively).

In the pooled population, pre-bronchodilator FEV1 was 1.368 L and FEV1 percentage predicted normal was 47.7%; both values are consistent with a patient population with moderate or severe COPD. Bronchial reversibility to SABAs was 15.3% (with a mean absolute change of 0.178 L).

Table 26: Changes from baseline to Week 24 in FEV1 at 1 hour post-dose (L) in M/40464/30 and LAC-MD-31 and the pooled population of M/40464/30 and LAC-MD-31: ITT populations

	Treatment			Comparison	Treatment difference		
	n	LS mean	SE		LS mean	95% CI	p-value
M/40464/30							
AB/FF 400/12 µg	347	0.269	0.013	AB/FF 400/12 µg- AB 400 µg	0.125	0.090, 0.160	<0.0001
				AB/FF 400/12 µg - Pbo	0.299	0.255, 0.343	<0.0001
				AB/FF 400/12 µg - 400/6 µg	0.055	0.020, 0.090	0.002
AB/FF 400/6 µg	339	0.213	0.013	AB/FF 400/6 µg- AB 400 µg	0.069	0.034, 0.105	0.0001
				AB/FF 400/6 µg - Pbo	0.244	0.200, 0.287	<0.0001
AB 400 µg	327	0.144	0.013	AB 400 µg - Pbo	0.174	0.130, 0.218	<0.0001
FF 12 µg	335	0.129	0.013	FF 12 µg - Pbo	0.160	0.116, 0.203	<0.0001
Pbo	157	-0.030	0.018	-	-	-	-
LAC-MD-31							
AB/FF 400/12 µg	266	0.247	0.013	AB/FF 400/12 µg- AB 400 µg	0.108	0.073, 0.144	<0.0001
				AB/FF 400/12 µg – Pbo	0.284	0.247, 0.320	<0.0001
				AB/FF 400/12 µg - 400/6 µg	0.021	-0.015, 0.056	0.246
AB/FF 400/6 µg	272	0.226	0.013	AB/FF 400/6 µg- AB 400 µg	0.087	0.052, 0.123	<0.0001
				AB/FF 400/6 µg – Pbo	0.263	0.227, 0.299	<0.0001
AB 400 µg	266	0.139	0.013	AB 400 µg - Pbo	0.176	0.139, 0.212	<0.0001
FF 12 µg	266	0.165	0.013	FF 12 µg - Pbo	0.201	0.165, 0.238	<0.0001
Pbo	231	-0.037	0.014	-	-	-	-
Pooled studies: M/40464/30 and LAC-MD-31							
AB/FF 400/12 µg	613	0.259	0.009	AB/FF 400/12 µg- AB 400 µg	0.118	0.093, 0.143	<0.0001
				AB/FF 400/12 µg - Pbo	0.293	0.265, 0.321	<0.0001
				AB/FF 400/12 µg - 400/6 µg	0.041	0.016, 0.066	0.001
AB/FF 400/6 µg	611	0.218	0.009	AB/FF 400/6 µg- AB 400 µg	0.077	0.052, 0.102	<0.0001
				AB/FF 400/6 µg - Pbo	0.252	0.224, 0.280	<0.0001
AB 400 µg	593	0.141	0.009	AB 400 µg - Pbo	0.175	0.147, 0.203	<0.0001
FF 12 µg	601	0.145	0.009	FF 12 µg - Pbo	0.178	0.150, 0.206	<0.0001
Pbo	388	-0.033	0.011	-	-	-	-

Note: Analysis is based on MMRM model for change from baseline in 1h post-dose FEV1, with treatment group, gender, smoking status, visit, and treatment group-by-visit (plus study for pooled population) as factors, and pre and post-bronchodilator (salbutamol/albuterol) FEV1 at screening visit, age, and baseline FEV1 as covariates.
Abbreviations: AB=aclidinium bromide; AB/FF= aclidinium/formoterol; CI=confidence interval; FEV1=forced expiratory volume in one second; FF=formoterol fumarate dihydrate; ITT=intent-to-treat; LS=least squares; MMRM=mixed model for repeated measures; Pbo=placebo; SE=standard error.

Table 27: Changes from baseline to Week 24 in trough[a] FEV1 (L) for M/40464/30 and LAC-MD-31 and the pooled population of M/40464/30 and LAC-MD-31: ITT Populations

	Treatment			Comparison	Treatment difference		
	n	LS mean	SE		LS mean	95% CI	p-value
M/40464/30							
AB/FF 400/12 µg	349	0.083	0.012	AB/FF 400/12 µg- FF 12 µg	0.085	0.051, 0.119	<0.0001
				AB/FF 400/12 µg - Pbo	0.143	0.101, 0.185	<0.0001
AB/FF 400/6 µg	340	0.050	0.012	AB/FF 400/6 µg- FF 12 µg	0.053	0.019, 0.087	0.002
				AB/FF 400/6 µg - Pbo	0.111	0.069, 0.153	<0.0001
AB 400 µg	332	0.056	0.012	AB 400 µg - Pbo	0.117	0.075, 0.159	<0.0001
FF 12 µg	337	-0.002	0.012	FF 12 µg - Pbo	0.058	0.016, 0.100	0.007
Pbo	159	-0.061	0.018	-	-	-	-
LAC-MD-31							
AB/FF 400/12 µg	271	0.095	0.012	AB/FF 400/12 µg- FF 12 µg	0.045	0.011, 0.079	0.010
				AB/FF 400/12 µg - Pbo	0.130	0.095, 0.165	<0.0001
				AB/FF 400/12 µg - 400/6 µg	0.019	-0.015, 0.053	0.280
AB/FF 400/6 µg	276	0.076	0.012	AB/FF 400/6 µg- FF 12 µg	0.026	-0.008, 0.060	0.133
				AB/FF 400/6 µg - Pbo	0.111	0.076, 0.146	<0.0001
AB 400 µg	266	0.066	0.012	AB 400 µg - Pbo	0.102	0.066, 0.137	<0.0001
FF 12 µg	268	0.050	0.012	FF 12 µg - Pbo	0.085	0.050, 0.120	<0.0001
Pbo	232	-0.035	0.013	-	-	-	-
Pooled studies: M/40464/30 and LAC-MD-31							
AB/FF 400/12 µg	620	0.090	0.009	AB/FF 400/12 µg- FF 12 µg	0.068	0.044, 0.092	<0.0001
				AB/FF 400/12 µg - Pbo	0.138	0.111, 0.165	<0.0001
				AB/FF 400/12 µg - 400/6 µg	0.027	0.003, 0.051	0.026
AB/FF 400/6 µg	616	0.062	0.009	AB/FF 400/6 µg- FF 12 µg	0.041	0.017, 0.065	<0.001
				AB/FF 400/6 µg - Pbo	0.111	0.084, 0.138	<0.0001
AB 400 µg	598	0.061	0.009	AB 400 µg - Pbo	0.110	0.083, 0.137	<0.0001
FF 12 µg	605	0.021	0.009	FF 12 µg - Pbo	0.070	0.043, 0.097	<0.0001
Pbo	391	-0.049	0.011	-	-	-	-

a Trough (pre-dose) FEV1 assessed prior to morning dose.
Note: Analysis is based on MMRM model for change from baseline in trough FEV1, with treatment group, gender, smoking status, visit and treatment group-by-visit (plus study for pooled population) as factors, and pre- and post-bronchodilator (salbutamol/albuterol) FEV1 at screening visit, age, and baseline FEV1 as covariates.
Abbreviations: AB/FF=aclidinium/formoterol; AB=aclidinium bromide; CI=confidence interval; FEV1=forced expiratory volume in one second; FF=formoterol fumarate dihydrate; ITT=intent-to-treat; LS=least squares; MMRM=mixed model for repeated measures; Pbo=placebo; SE=standard error.

The two pivotal studies were identical in design and inclusion/exclusion criteria and the pooling of results is accepted.

The increase over baseline in 1-hour post-dose FEV1 demonstrates a clinically relevant improvement compared with placebo and compared with aclidinium alone for the aclidinium/formoterol 400/12 µg dose

but not for the aclidinium/formoterol 400/6 µg dose. Therefore it is accepted that formoterol 12µg is the appropriate strength to be included in the combination.

In the comparisons of aclidinium/formoterol with formoterol alone, even in the pooled analysis the improvement in trough FEV1 over baseline at 68ml does not reach a clinically meaningful level. The results regarding improvement in lung function suggest that the aclidinium/formoterol combination does not give a clinically significant benefit over formoterol alone.

Improvement in TDI focal score

Statistically significant and clinically meaningful improvements versus placebo in TDI focal score were observed with aclidinium/formoterol 400/12 µg and 400/6 µg in both M/40464/30 (1.29 units and 1.16 units, respectively [p<0.0001 for both]) and LAC-MD-31 (1.44 units and 1.40 units, respectively [p<0.0001 for both]), as well as in the pooled population from M/40464/30 and LAC-MD-31 (1.43 units and 1.33 units, respectively [p<0.0001]).

Trends towards statistically significant greater improvements in TDI focal score at Week 24 with aclidinium/formoterol 400/12 µg compared with aclidinium or formoterol were observed in both M/40464/30 (0.40 units [p=0.084] and 0.45 units [p=0.052], respectively) and LAC-MD-31 (0.46 units [p=0.108] and 0.49 units [p=0.084], respectively).

Analysis of the pooled population of M/40464/30 and LAC-MD-31 showed statistically significant greater improvements in TDI focal score at Week 24 with the 400/12 µg dose of aclidinium/formoterol compared with aclidinium or formoterol (0.44 units [p=0.016] and 0.47 units [p=0.009], respectively) and with the 400/6 µg dose compared with formoterol (0.37 units [p=0.039]) but the treatment difference between the 400/6 µg dose and aclidinium missed statistical significance (0.33 units [p=0.064]).

Table 28: Improvements in TDI focal score at Week 24 for M/40464/30 and LAC-MD-31 and pooled population of M/40464/30 and LAC-MD-31: ITT populations

	Treatment			Comparison	Treatment difference		
	n	LS mean	SE		LS mean	95% CI	p-value
M/40464/30							
AB/FF 400/12 µg	344	2.51	0.16	AB/FF 400/12 µg - Pbo	1.29	0.73, 1.86	<0.0001
				AB/FF 400/12 µg - AB 400 µg	0.40	-0.05, 0.85	0.084
				AB/FF 400/12 µg- FF 12 µg	0.45	-0.00, 0.90	0.052
AB/FF 400/6 µg	333	2.38	0.17	AB/FF 400/6 µg - Pbo	1.16	0.59, 1.73	<0.0001
				AB/FF 400/6 µg - AB 400 µg	0.27	-1.19, 0.72	0.253
				AB/FF 400/6 µg- FF 12 µg	0.31	-0.14, 0.77	0.174
AB 400 µg	331	2.11	0.17	AB 400 µg - Pbo	0.90	0.33, 1.47	0.002
FF 12 µg	333	2.06	0.16	FF 12 µg - Pbo	0.85	0.28, 1.42	<0.0001
Pbo	156	1.22	0.24	-			
LAC-MD-31							
AB/FF 400/12 µg	260	2.02	0.20	AB/FF 400/12 µg - Pbo	1.44	0.85, 2.02	<0.0001
				AB/FF 400/12 µg - AB 400 µg	0.46	-0.10, 1.02	0.108
				AB/FF 400/12 µg- FF 12 µg	0.49	-0.07, 1.06	0.084
AB/FF 400/6 µg	265	1.98	0.20	AB/FF 400/6 µg - Pbo	1.40	0.82, 1.97	<0.0001
				AB/FF 400/6 µg - AB 400 µg	0.42	-0.14, 0.97	0.139
				AB/FF 400/6 µg- FF 12 µg	0.45	-0.10, 1.01	0.109
AB 400 µg	263	1.56	0.20	AB 400 µg - Pbo	0.98	0.40, 1.55	0.001
FF 12 µg	263	1.52	0.20	FF 12 µg - Pbo	0.94	0.36, 1.52	0.002
Pbo	224	0.58	0.22	-			
Pooled studies: M/40464/30 and LAC-MD-31							
AB/FF 400/12 µg	604	2.29	0.13	AB/FF 400/12 µg -Pbo	1.43	1.03, 1.83	<0.0001
				AB/FF 400/12 µg - AB 400 µg	0.44	0.08, 0.79	0.016
				AB/FF 400/12 µg- FF 12 µg	0.47	0.12, 0.83	0.009
AB/FF 400/6 µg	598	2.18	0.13	AB/FF 400/6 µg - Pbo	1.33	0.93, 1.73	<0.0001
				AB/FF 400/6 µg - AB 400 µg	0.33	-0.02, 0.69	0.064
				AB/FF 400/6 µg - FF 12 µg	0.37	0.02, 0.72	0.039
AB 400 µg	594	1.85	0.13	AB 400 µg - Pbo	1.00	0.59, 1.40	<0.0001
FF 12 µg	596	1.81	0.13	FF 12 µg - Pbo	0.96	0.56, 1.36	<0.0001
Pbo	380	0.85	0.16	-			

Note: Analysis is based on MMRM model for change from baseline in TDI, with treatment group, gender, smoking status, visit, and treatment group-by-visit (plus study for pooled population) as factors, and age and baseline BDI as covariates.
Abbreviations: AB=aclidinium bromide; AB/FF=aclidinium/formoterol; CI=confidence interval; FF=formoterol fumarate dihydrate; ITT=intent-to-treat; LS=least squares; MMRM=mixed model for repeated measures; Pbo=placebo; SE=standard error; TDI=Transition Dyspnoea Index.

The proportions of patients achieving clinically significant improvements in TDI focal score at Week 24 were statistically significantly higher with aclidinium/formoterol 400/12 µg and 400/6 µg than with placebo in M/40464/30 and LAC-MD-31.

In the pooled population, aclidinium/formoterol 400/12 µg or 400/6 µg increased the proportions of patients with clinically significant improvements in TDI focal score at Week 24 compared to aclidinium (61.9% and 63.9% versus 55.7%, respectively and p=0.056 and p=0.007, respectively) and formoterol (61.9% and 63.9% versus 57.0%, respectively and p=0.100 and p=0.015, respectively).

Table 29: Proportions of patients with clinically significant[a] improvements in TDI focal score the pooled population of M/40464/30 and LAC-MD-31: ITT population

	Treatment		Comparison	Treatment difference		
	n	%		Odds ratio	95% CI	p-value
Pooled studies: M/40464/30 and LAC-MD-31						
AB/FF 400/12 µg	604	61.9	**AB/FF 400/12 µg –Pbo**	2.76	1.99, 3.83	<0.0001
			AB/FF 400/12 µg - AB 400 µg	1.32	0.99, 1.76	0.056
			AB/FF 400/12 µg- FF 12 µg	1.27	0.95, 1.69	0.100
AB/FF 400/6 µg	598	63.9	**AB/FF 400/6 µg – Pbo**	3.10	2.23, 4.30	<0.0001
			AB/FF 400/6 µg - AB 400 µg	1.49	1.11, 1.98	0.007
			AB/FF 400/6 µg - FF 12 µg	1.43	1.07, 1.90	0.015
AB 400 µg	594	55.7	**AB 400 µg – Pbo**	2.09	1.51, 2.89	<0.0001
FF 12 µg	596	57.0	**FF 12 µg - Pbo**	2.17	1.56, 3.01	<0.0001
Pbo	380	40.3	-	-	-	-

Both strengths of aclidinium/formoterol reached a clinically meaningful improvement (≥1 unit) over baseline in TDI focal score compared with placebo. In the pooled analysis the improvement in TDI of aclidinium/formoterol 400/12 µg compared with the monocomponents does not reach the 1 unit that is considered to be the level that would be meaningful to the patient. However the improvements compared with both formoterol and aclidinium alone are similar at 0.47 and 0.44 units respectively.

Analysis of the proportion of patients who achieved the clinically meaningful improvement in TDI focal score of at least 1 unit was also greater (and statistically significant) in the combination groups compared with placebo but did not reach statistical significance for the 400/12 µg group compared with the individual components.

Improvement in SGRQ total score

In LAC-MD-31, statistically significant and clinically meaningful (i.e. of at least 4 units) improvements from baseline in SGRQ total score were observed at Week 12 and at Week 24 in all active treatment groups. At Week 24 in LAC-MD-31, adjusted mean treatment differences between aclidinium/formoterol 400/12 µg or 400/6 µg and placebo were statistically significant (-4.35 units [p<0.0001] and -3.73 units [p<0.001], respectively); with the improvement in SGRQ total score observed with the 400/12 µg dose being of a clinically significant magnitude. In M/40464/30, clinically-relevant improvements from baseline in SGRQ total score were observed in all active treatment groups, as observed in LAC-MD-31. However, an unexpectedly large improvement from baseline to Week 24 in SGRQ total score (-6.51 units) was observed in the placebo group of M/40464/30, which was greater in magnitude that those observed in the monotherapy groups. Consequently only small adjusted mean treatment differences between aclidinium/formoterol 400/12 µg or 400/6 µg and placebo were observed (-0.65 units [p=0.598] and -1.83 units [p=0.141], respectively).

Table 30: Changes from baseline to Week 24 in SGRQ total score for M/40464/30 and LAC-MD-31 and pooled population of M/40464/30 and LAC-MD-31: ITT populations

	Treatment			Comparison	Treatment difference		
	n	LS mean	SE		LS mean	95% CI	p-value
M/40464/30							
AB/FF 400/12 µg	338	-7.16	0.70	AB/FF 400/12 µg - Pbo	-0.65	-3.08, 1.78	0.598
				AB/FF 400/12 µg–AB 400 µg	-1.36	-3.30, 0.58	0.169
				AB/FF 400/12 µg- FF 12 µg	-1.59	-3.52, 0.35	0.109
AB/FF 400/6 µg	332	-8.34	0.71	AB/FF 400/6 µg - Pbo	-1.83	-4.26, 0.60	0.141
				AB/FF 400/6 µg–AB 400 µg	-2.54	-4.48, -0.59	0.011
				AB/FF 400/6 µg- FF 12 µg	-2.76	-4.70, -0.82	0.005
AB 400 µg	327	-5.80	0.71	AB 400 µg - Pbo	0.71	-1.73, 3.15	0.568
FF 12 µg	332	-5.58	0.71	FF 12 µg - Pbo	0.93	-1.50, 3.37	0.453
Pbo	154	-6.51	1.03	-	-	-	-
LAC-MD-31							
AB/FF 400/12 µg	256	-6.57	0.74	AB/FF 400/12 µg - Pbo	-4.35	-6.46, -2.24	<0.0001
				AB/FF 400/12 µg–AB 400 µg	-0.13	-2.18, 1.92	0.901
				AB/FF 400/12 µg- FF 12 µg	-1.87	-3.92, 0.19	0.075
AB/FF 400/6 µg	263	-5.94	0.73	AB/FF 400/6 µg - Pbo	-3.73	-5.82, -1.64	<0.001
				AB/FF 400/6 µg–AB 400 µg	0.50	-1.54, 2.53	0.633
				AB/FF 400/6 µg- FF 12 µg	-1.24	-3.28, 0.80	0.233
AB 400 µg	257	-6.44	0.74	AB 400 µg - Pbo	-4.22	-6.33, -2.12	<0.0001
FF 12 µg	254	-4.70	0.74	FF 12 µg - Pbo	-2.49	-4.60, -0.38	0.021
Pbo	225	-2.21	0.78	-	-	-	-
Pooled studies: M/40464/30 and LAC-MD-31							
AB/FF 400/12 µg	594	-6.80	0.51	AB/FF 400/12 µg–AB 400 µg	-0.79	-2.20, 0.62	0.273
				AB/FF 400/12 µg- FF 12 µg	-1.71	-3.16, -0.30	0.018
AB/FF 400/6 µg	595	-7.18	0.51	AB/FF 400/6 µg–AB 400 µg	-1.18	-2.58, 0.23	0.101
				AB/FF 400/6 µg- FF 12 µg	-2.09	-3.50, -0.69	0.004
AB 400 µg	584	-6.01	0.51	-	-	-	-
FF 12 µg	586	-5.09	0.51	-	-	-	-
Pbo	379	-4.09	0.63	-	-	-	-

Note: Analysis is based on MMRM model for change from baseline in SGRQ, with treatment group, gender, smoking status, visit, and treatment group-by-visit (plus study for pooled population) as factors, and age and baseline SGRQ as covariates.
Abbreviations: AB=aclidinium bromide; AB/FF=aclidinium/formoterol; CI=confidence interval; FF=formoterol fumarate dihydrate; ITT=intent-to-treat; LS=least squares; MMRM=mixed model for repeated measures; Pbo=placebo; SE=standard error; SGRQ = St George's Respiratory Questionnaire.

Due to the large and unexpected placebo effect on SGRQ in Study M/40464/30 the pooled analysis of this endpoint does not add any helpful information regarding the efficacy of aclidinium/formoterol on the symptoms of COPD. In Study LAC-MD-31 a clinically meaningful improvement in SGRQ compared with placebo was demonstrated but the improvement compared with the individual components was small and its clinical relevance is hard to assess.

Exacerbations

Exacerbations were defined according to healthcare resource utilisation and worsening of COPD symptoms for at least two consecutive days using a definition (hereafter referred to as the healthcare resource utilisation [HRU] definition) similar to that used in other COPD trials. Exacerbations were also assessed according to the Exacerbations of Chronic Obstructive Pulmonary Disease Tool (EXACT) daily diary. The EXACT was developed and validated to standardise methodology for assessing the frequency, severity and duration of exacerbations in COPD.

Rates (per patient/year) of moderate or severe exacerbations or of exacerbations of any severity (mild, moderate or severe), as defined by HRU, were higher in LAC-MD-31 than in M/40464/30. Considerably higher exacerbation rates were observed in both pivotal studies when exacerbations were defined according to EXACT compared to when exacerbations were defined according to HRU. In general, exacerbation rates were also higher in LAC-MD-31 than in M/40464/30 when exacerbations were defined according to EXACT.

In the individual Phase III pivotal studies, aclidinium/formoterol 400/12 µg and 400/6 µg were associated with numerical reductions compared to placebo in the rate of moderate or severe exacerbations (HRU definition) and in the rates of any exacerbations (HRU or EXACT definitions). These numerical reductions in exacerbation rate reached statistical significance only for the comparison of the 400/12 µg dose and placebo in the rate of EXACT exacerbations in M/40464/30.

In the pooled population, rates of moderate or severe exacerbations (defined by HRU) were lower for aclidinium/formoterol 400/12 µg and 400/6 µg (0.29 per patient/year and 0.33 per patient/year) than for placebo (0.42 per patient/year). A similar pattern was observed for the rates of any exacerbation (defined by HRU or EXACT). Aclidinium/formoterol 400/12 µg was associated with statistically significant reductions compared to placebo in the rates of moderate or severe exacerbations (by 29%; RR 0.71 [p=0.036]) and exacerbations according to EXACT (by 22%; RR 0.78 [p=0.010]). A reduction in the rate of exacerbations of any severity (defined by HRU) was also observed with aclidinium/formoterol 400/12 µg which just missed statistical significance (RR 0.76 [p=0.079]). Aclidinium/formoterol 400/6 µg was associated only with numerical reductions in exacerbation rates compared to placebo.

Exacerbation rates (HRU or EXACT) were generally numerically lower with aclidinium/formoterol 400/12 µg than with either aclidinium or formoterol monotherapy.

Table 31: Rate of COPD exacerbations per patient per year (based on HRU definition) in M/40464/30 and LAC-MD-31 and in the pooled population of M/40464/30 and LAC-MD-31: ITT-Exacerbations populations

	M/40464/30			LAC-MD-31			Pooled population		
	Treatment		Vs. Pbo	Treatment		Vs. Pbo	Treatment		Vs. Pbo
	n	Rate	RR (95%CI) p-value	n	Rate	RR (95%CI) p-value	n	Rate	RR (95%CI) p-value
Moderate or severe exacerbations									
AB/FF 400/12 µg	385	0.23	0.77 (0.44, 1.36) p=0.371	335	0.37	0.69 (0.46, 1.02) p=0.066	720	0.29	0.71 (0.51, 0.98) p=0.036
AB/FF 400/6 µg	381	0.25	0.85 (0.49, 1.48) p=0.563	333	0.42	0.78 (0.53, 1.14) p=0.202	714	0.33	0.79 (0.58, 1.09) p=0.151
AB 400 µg	385	0.23	0.78 (0.45, 1.37) p=0.388	337	0.49	0.89 (0.61, 1.31) p=0.565	722	0.35	0.84 (0.61, 1.14) p=0.260
FF 12 µg	384	0.32	1.08 (0.63, 1.86) p=0.769	332	0.40	0.74 (0.50, 1.10) p=0.140	716	0.36	0.86 (0.63, 1.18) p=0.357
Pbo	194	0.29	-	332	0.54	-	526	0.42	-
Exacerbation of any severity									
AB/FF 400/12 µg	385	0.25	0.73 (0.43, 1.23) p=0.240	335	0.47	0.80 (0.56, 1.16) p=0.246	720	0.36	0.76 (0.56, 1.03) p=0.079
AB/FF 400/6 µg	381	0.28	0.80 (0.48, 1.35) p=0.410	333	0.44	0.76 (0.52, 1.10) p=0.150	714	0.36	0.77 (0.57, 1.05) p=0.096
AB 400 µg	385	0.29	0.82 (0.49, 1.37) p=0.452	337	0.54	0.92 (0.65, 1.32) p=0.668	722	0.41	0.87 (0.65, 1.17) p=0.368
FF 12 µg	384	0.41	1.15 (0.70, 1.88) p=0.589	332	0.50	0.85 (0.59, 1.23) p=0.387	716	0.45	0.97 (0.72, 1.29) p=0.820
Pbo	194	0.36	-	332	0.59	-	526	0.47	-

Note: Analysis is based on a negative binomial regression model with smoking status, gender, baseline use of ICS, baseline COPD severity and treatment group (plus study for pooled population) as factors and age as a covariate, adjusting for the log of corresponding total exposure time in years as an offset variable in the model.
Abbreviations: AB=aclidinium bromide; AB/FF=aclidinium/formoterol; CI=confidence interval; FF=formoterol fumarate dihydrate; HRU=healthcare resource utilisation; ITT=intent-to-treat; Pbo=placebo; RR=rate ratio.

Table 32: Rate of COPD exacerbations per patient per year (based on EXACT definition) in M/40464/30 and LAC-MD-31 and in the pooled population of M/40464/30 and LAC-MD-31: ITT-Exacerbations populations

	M/40464/30			LAC-MD-31			Pooled population		
	Treatment		Vs. Pbo	Treatment		Vs. Pbo	Treatment		Vs. Pbo
	n	Rate	RR (95%CI) p-value	n	Rate	RR (95%CI) p-value	n	Rate	RR (95%CI) p-value
AB/FF 400/12 µg	385	1.09	0.71 (0.5, 0.9) p=0.016	335	1.29	0.84 (0.65, 1.09) p=0.182	720	1.18	0.78 (0.65, 0,94) p=0.010
AB/FF 400/6 µg	381	1.28	0.83 (0.6, 1.1) p=0.181	333	1.50	0.97 (0.76, 1.25) p=0.835	714	1.37	0.91 (0.76, 1.10) p=0.322
AB 400 µg	385	1.40	0.91 (0.7, 1.2) p=0.502	337	1.52	0.98 (0.77, 1.27) p=0.906	722	1.45	0.96 (0.80, 1.16) p=0.696
FF 12 µg	384	1.26	0.82 (0.6, 1.1) p=0.165	332	1.37	0.89 (0.69, 1.15) p=0.380	716	1.31	0.87 (0.72, 1.05) p=0.144
Pbo	194	1.54		332	1.54		526	1.51	

Note: Analysis is based on a negative binomial regression model with smoking status, gender, baseline use of ICS, baseline COPD severity and treatment group (plus study for pooled population) as factors and age as a covariate, adjusting for log of the corresponding total exposure time in years as an offset variable in the model.
Abbreviations: AB=aclidinium bromide; AB/FF=aclidinium/formoterol; CI=confidence interval; EXACT= Exacerbation of Chronic Pulmonary Disease Tool; FF=formoterol fumarate dihydrate; ITT=intent-to-treat; Pbo=placebo; RR=rate ratio.

In both pivotal studies, numerical reductions were observed with aclidinium/formoterol compared to placebo in HRs for the time to the first moderate or severe exacerbation (HRU definition) or in the time to the first exacerbation of any severity (HRU and EXACT definitions). Analysis of the pooled population showed that aclidinium/formoterol 400/12 µg statistically significantly reduced the HR for the time to a first moderate or severe exacerbation (by 30%; HR 0.70 [p=0.027]) and for the time to any exacerbation (as defined by both HRU [by 28%; HR 0.72 (p=0.030)] and EXACT [by 21%; HR 0.79 [p=0.014]) and thus delayed the time to first COPD exacerbation.

Reductions in the HRs for the time to first exacerbation (HRU or EXACT) were numerically greater with aclidinium/formoterol 400/12 µg than with either aclidinium or formoterol monotherapy.

Table 33: Hazard ratios (HR) versus placebo for the time to first COPD exacerbation (based on HRU and EXACT definitions) in M/40464/30 and LAC-MD-31 and in the pooled population of M/40464/30 and LAC-MD-31: ITT-Exacerbations populations

Comparison vs Pbo	M/40464/30		LAC-MD-31		Pooled population	
	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value
Time to first moderate or severe exacerbation (HRU definition)						
AB/FF 400/12 µg	0.71 (0.4, 1.2)	0.232	0.70 (0.47, 1.04)	0.079	0.70 (0.51, 0.96)	0.027
AB/FF 400/6 µg	0.76 (0.4, 1.3)	0.336	0.78 (0.53, 1.16)	0.216	0.77 (0.56, 1.05)	0.101
AB 400 µg	0.79 (0.5, 1.4)	0.387	0.89 (0.61, 1.29)	0.535	0.84 (0.62, 1.14)	0.268
FF 12 µg	1.06 (0.6, 1.8)	0.818	0.81 (0.55, 1.20)	0.290	0.90 (0.67, 1.22)	0.509
Time to first exacerbation of any severity (HRU definition)						
AB/FF 400/12 µg	0.64 (0.4, 1.1)	0.085	0.78 (0.54, 1.13)	0.188	0.72 (0.53, 0.97)	0.030
AB/FF 400/6 µg	0.68 (0.4, 1.1)	0.136	0.76 (0.52, 1.10)	0.150	0.73 (0.54, 0.99)	0.039
AB 400 µg	0.78 (0.5, 1.3)	0.318	0.90 (0.63, 1.29)	0.576	0.86 (0.64, 1.14)	0.294
FF 12 µg	1.01 (0.6, 1.6)	0.971	0.88 (0.62, 1.27)	0.507	0.94 (0.71, 1.25)	0.660
Time to first exacerbation (EXACT)						
AB/FF 400/12 µg	0.71 (0.5, 1.0)	0.023	0.86 (0.67, 1.11)	0.258	0.79 (0.65, 0.95)	0.014
AB/FF 400/6 µg	0.86 (0.6, 1.1)	0.281	0.93 (0.72, 1.19)	0.548	0.90 (0.74, 1.08)	0.246
AB 400 µg	0.90 (0.7, 1.2)	0.463	0.92 (0.71, 1.18)	0.503	0.92 (0.76, 1.10)	0.356
FF 12 µg	0.87 (0.7, 1.2)	0.330	0.82 (0.64, 1.06)	0.134	0.85 (0.71, 1.03)	0.093

Note: Analysis is based on a Cox Proportional Hazards model with treatment group, gender, baseline ICS use, baseline COPD severity and smoking status (plus study for pooled population) as factors and age as a covariate.
Abbreviations: AB=aclidinium bromide; AB/FF=aclidinium/formoterol; CI=confidence interval; EXACT=Exacerbation of Chronic Pulmonary Disease Tool; FF=formoterol fumarate dihydrate; ICS=inhaled corticosteroid; HR=hazard ratio; HRU=healthcare resource utilisation; ITT=intent-to-treat.

Generally six-month studies are too short to see any meaningful treatment effect on exacerbations in COPD. The pooled analysis of these two pivotal Phase III studies increases the likelihood of the studies demonstrating some effect.

In general the rate of exacerbations is higher using the EXACT definition than the HRU definition.

Using the HRU definition of exacerbations; although the rate ratio for moderate to severe exacerbations in the pooled analysis reaches statistical significance when the combination aclidinium/formoterol 400/12 µg is compared with placebo, the actual difference in exacerbation rate is 0.13 exacerbations per patient/year. It is debatable whether this is clinically meaningful.

When based on the EXACT definition the difference between aclidinium/formoterol 400/12 µg and placebo in the pooled population rises to 0.33 exacerbations per patient/year so that a patient needs to be treated with the combination on average for 3 years to prevent one exacerbation. This could be considered to be of clinical relevance given that exacerbations in general hasten the deterioration of the disease in patients with COPD. However only a reduction of at least one event over a defined period (usually a year) would be perceived as clinically relevant by the patient (Calverley 2005).

In the analysis of Hazard Ratios (HR) for time to first exacerbation only the effect of aclidinium/formoterol 400/12 µg versus placebo in the pooled population reaches statistical significance. However it is difficult to assess the clinical relevance of these results.

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 3: Summary of efficacy results:- Study M/40464/30

Title: A multi-centre, randomised, double-blind, parallel-group, placebo- and active comparator-controlled study of aclidinium/formoterol 400/12 µg and 400/6 µg in patients with moderate or severe stable airflow limitation (post-bronchodilator FEV1 ≥30% predicted and <80% predicted)			
Study identifier	**M/40464/30**		
Design	Multi-centre, randomised, double-blind, parallel-group, placebo- and active comparator-controlled		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		24 weeks 2-3 weeks not applicable
Hypothesis	Superiority of the combination compared with placebo and with the monocomponents.		
Treatments groups	Aclidinium/formoterol 400/12 µg BID		N=385. 24 weeks treatment
	Aclidinium/formoterol 400/6µg BID		N=381. 24 weeks treatment
	Aclidinium 400µg BID		N=385. 24 weeks treatment
	Formoterol 12µg BID		N=384. 24 weeks treatment
	Placebo		N=194. 24 weeks treatment
Endpoints and definitions	Co-Primary endpoint	FEV1 1hr post dose and Trough FEV1	Change from baseline to Week 24 in FEV1 at 1 hour post-dose, compared with aclidinium 400 µg Change from baseline to Week 24 in morning pre-dose (trough) FEV1 compared with formoterol 12 µg
	Secondary endpoint	TDI focal score SGRQ	Improvement in TDI focal score at Week 24 compared with placebo Change from baseline in SGRQ total score at Week 24 compared with placebo

	other: specify endpoint	Exacerbation rate	Number of exacerbations per patient per year; numbers (%) of patients with at least one COPD exacerbation and time to first COPD exacerbation, defined on the basis of both HRU and EXACT.		
Database lock	<date>				
Results and Analysis					
Analysis description	**Co-Primary Endpoints**				
Analysis population and time point description	Intent to treat 24 weeks **FEV1 at 1 hour post-dose (L)**				
Descriptive statistics and estimate variability	Treatment group	Placebo	Aclidinium/ formoterol 400/12 µg BID	Aclidinium/ formoterol 400/6 µg BID	
	Number of subject	157	347	339	
	Least Square Mean (SE)	-0.030 (0.018)	0.269 (0.013)	0.213 (0.013)	
	Least squares mean difference to placebo	-	0.299	0.244	
	95% CI	-	0.255, 0.343	0.200, 0.287	
	p-value	-	<0.0001	<0.0001	
	Treatment group	Aclidinium 400µg BID			
	Number of subject	327			
	Least Square Mean (SE)	0.144 (0.013)	0.269 (0.013)	0.213 (0.013)	
	Least squares mean difference to aclidinium	-	0.125	0.069	
	95% CI	-	0.090, 0.160	0.034, 0.105	
	p-value	-	<0.0001	<0.001	
Analysis population and time point description	Intent to treat 24 weeks **Pre-dose (trough) FEV1(L)**				
Descriptive statistics and estimate variability	Treatment group	Placebo	Aclidinium/ formoterol 400/12 µg BID	Aclidinium/ formoterol 400/6 µg BID	
	Number of subject	159	349	340	
	Least Square Mean *(SE)*	-0.061 (0.018)	0.083 (0.012)	0.050 (0.012)	
	Least squares mean difference to placebo	-	0.143	0.111	

	95% CI	-	0.101, 0.185	0.069, 0.153
	p-value	-	<0.0001	<0.0001
	Treatment group	Formoterol 12µg BID		
	Number of subject	337		
	Least Square Mean *(SE)*	-0.002 (0.012)	0.0.083 (0.012)	0.050 (0.012)
	Least squares mean difference to formoterol	-	0.085	0.053
	95% CI	-	0.051, 0.119	0.019, 0.087
	p-value	-	<0.0001	0.002
Analysis description	**Secondary endpoints**			
Analysis population and time point description	Intent to treat Change from baseline to week 24 **TDI focal score**			
Descriptive statistics and estimate variability	Treatment group	Placebo	Aclidinium/ formoterol 400/12 µg BID	Aclidinium/ formoterol 400/6 µg BID
	Number of subject	156	344	333
	Least Square Mean (SE)	1.22 (0.24)	2.51 (0.16)	2.38 (0.17)
	Least squares mean difference to placebo	-	1.29	1.16
	95% CI	-	0.73, 1.86	0.59, 1.73
	p-value	-	<0.0001	<0.0001
Analysis population and time point description	Intent to treat Change from baseline to week 24 **SGRQ total score**			
Descriptive statistics and estimate variability	Treatment group	Placebo	Aclidinium/ formoterol 400/12 µg BID	Aclidinium/ formoterol 400/6 µg BID
	Number of subject	154	338	332
	Least Square Mean (SE)	-6.51 (1.03)	-7.16 (0.70)	-8.34 (0.71)
	Least squares mean difference to placebo	-	-0.65	-1.83
	95% CI	-	-3.08, 1.78	-4.26, 0.60

	p-value	-	0.598	0.141
Analysis population and time point description	Intent to treat Exacerbation rate/patient/year **Moderate or severe exacerbations**			
Descriptive statistics and estimate variability	Treatment group	Placebo	Aclidinium/ formoterol 400/12 µg BID	Aclidinium/ formoterol 400/6 µg BID
	Number of subject	194	385	381
	Rate	0.32	0.23	0.25
	Rate ratio vs placebo	-	0.77	0.85
	95% CI	-	0.44, 1.36	0.49, 1.48
	p-value	-	0.371	0.563

Table 4: Summary of efficacy results:- Study LAC-MD-31

Title: A multi-centre, randomised, double-blind, parallel-group, placebo- and active comparator-controlled study of aclidinium/formoterol 400/12 µg and 400/6 µg in patients with moderate or severe stable airflow limitation (post-bronchodilator FEV1 ≥30% predicted and <80% predicted)				
Study identifier	**LAC-MD-31**			
Design	Multi-centre, randomised, double-blind, parallel-group, placebo- and active comparator-controlled			
	Duration of main phase:	24 weeks		
	Duration of Run-in phase:	2-3 weeks		
	Duration of Extension phase:	not applicable		
Hypothesis	Superiority of the combination compared with placebo and with the monocomponents.			
Treatments groups	Aclidinium/formoterol 400/12 µg BID		N=338. 24 weeks treatment	
	Aclidinium/formoterol 400/6µg BID		N=338. 24 weeks treatment	
	Aclidinium 400µg BID		N=340. 24 weeks treatment	
	Formoterol 12µg BID		N=339. 24 weeks treatment	
	Placebo		N=337. 24 weeks treatment	
Endpoints and definitions	Co-Primary endpoint	FEV1 1hr post dose and Trough FEV1	Change from baseline to Week 24 in FEV1 at 1 hour post-dose, compared with aclidinium 400 µg Change from baseline to Week 24 in morning pre-dose (trough) FEV1 compared with formoterol 12 µg	
	Secondary endpoint	TDI focal score SGRQ	Improvement in TDI focal score at Week 24 compared with placebo Change from baseline in SGRQ total score at Week 24 compared with placebo	
	Other endpoint	Exacerbation rate	Number of exacerbations per patient per year; numbers (%) of patients with at least one COPD exacerbation and time to first COPD exacerbation, defined on the basis of both HRU and EXACT.	
Database lock	<date>			
Results and Analysis				
Analysis description	**Co-Primary Endpoints**			
Analysis population and time point description	Intent to treat 24 weeks **FEV1 at 1 hour post-dose (L)**			
Descriptive statistics and estimate variability	Treatment group	Placebo	Aclidinium/ formoterol 400/12 µg BID	Aclidinium/ formoterol 400/6 µg BID
	Number of subject	331	335	333
	Least Square Mean (SE)	-0.037 (0.0135)	0.247 (0.013)	0.226 (0.013)

	Least squares mean difference to placebo	-	0.284	0.263
	Treatment group	Aclidinium 400µg BID		
	Number of subject	337		
	Least Square Mean (SE)	0.139 (0.13)	0.247 (0.013)	0.226 (0.013)
	Least squares mean difference to aclidinium	-	0.108	087
	95% CI	-	0.073, 0.144	0.052, 0.123
	p-value	-	<0.0001	<0.001
Analysis population and time point description	Intent to treat 24 weeks **Pre-dose (trough) FEV1(L)**			
Descriptive statistics and estimate variability	Treatment group	Placebo	Aclidinium/ formoterol 400/12 µg BID	Aclidinium/ formoterol 400/6 µg BID
	Number of subject	331	335	333
	Least Square Mean *(SE)*	-0.035 (0.013)	0.095 (0.012)	0.076 (0.011)
	Least squares mean difference to placebo	-	0.130	0.111
	Treatment group	Formoterol 12µg BID		
	Number of subject	332		
	Least Square Mean *(SE)*	0.50 (0.012)	0.095 (0.012)	0.076 (0.011)
	Least squares mean difference to formoterol	-	0.045	0.026
	95% CI	-	0.011, 0.079	-0.008, 0.060
	p-value	-	0.010	0.133
Analysis description	**Secondary endpoints**			
Analysis population and time point description	Intent to treat Change from baseline to week 24 **TDI focal score**			
Descriptive statistics and estimate variability	Treatment group	Placebo	Aclidinium/ formoterol 400/12 µg BID	Aclidinium/ formoterol 400/6 µg BID
	Number of subject	331	335	333

	Least Square Mean (SE)	0.58 (0.22)	2.02 (0.20)	1.98 (0.20)
	Least squares mean difference to placebo	-	1.44	1.40
	95% CI	-	0.85, 2.02	0.82, 1.97
	p-value	-	<0.0001	<0.0001
Analysis population and time point description	Intent to treat Change from baseline to week 24 **SGRQ total score**			
Descriptive statistics and estimate variability	Treatment group	Placebo	Aclidinium/formoterol 400/12 µg BID	Aclidinium/formoterol 400/6 µg BID
	Number of subject	331	335	333
	Least Square Mean (SE)	-2.21 (0.78)	-6.57 (0.74)	-5.94 (0.73)
	Least squares mean difference to placebo	-	-4.35	-1.3.73
	95% CI	-	-6.46, -2.24	-5.82, -1.64
	p-value	-	<0.0001	0.0005
Analysis population and time point description	Intent to treat Exacerbation rate/patient/year **Moderate or severe exacerbations**			
Descriptive statistics and estimate variability	Treatment group	Placebo	Aclidinium/ formoterol 400/12 µg BID	Aclidinium/ formoterol 400/6 µg BID
	Number of subject	332	335	333
	Rate	0.54	0.37	0.42
	Rate ratio vs placebo	-	0.69	0.78
	95% CI	-	0.46, 1.02	0.53, 1.14
	p-value	-	0.066	0.202

Clinical studies in special populations

No clinical studies have been conducted in special populations.

As the two actives are well known it is accepted that specific studies in special populations have not been conducted according to the CHMP.

Sufficient numbers of patients aged >70 years were included in the two pivotal Phase III studies (22% and 28%) to be reassured that efficacy and safety seen in the total population can be extrapolated to that age group.

As COPD is a disease that is not seen in children a class waiver from the European Paediatric Regulation (Regulation [EC] Number 1901/2006) has been granted for the condition COPD.

Supportive studies: Long-Term Safety Studies, LAC-MD-32 and LAC-MD-36
Although LAC-MD-32 and LAC-MD-36 were designed primarily to assess the long-term safety of aclidinium/formoterol BID, some efficacy measures were also evaluated to provide information on the long-term efficacy of aclidinium/formoterol BID.

Study LAC-MD-36

A long-term extension study of the efficacy, safety and tolerability of two aclidinium/formoterol fixed combinations (400/12 µg and 400/6 µg) compared with aclidinium monotherapy (400 µg), formoterol monotherapy (12 µg) and placebo in patients with stable chronic obstructive pulmonary disease

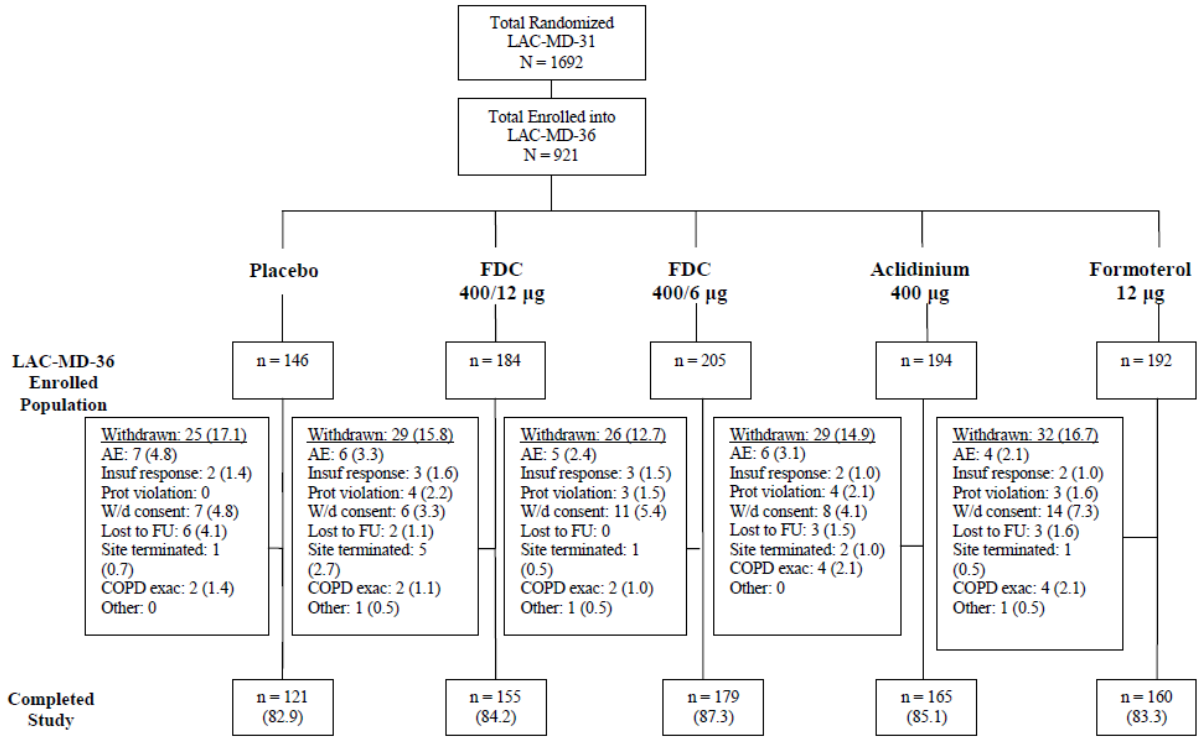
Study LAC-MD-36 was a continuation study for patients in the US and Canada who had completed Phase III pivotal study LAC-MD-31 and provided written informed consent to participate in the study. Efficacy measures evaluated in LAC-MD-36 were the same as those included in LAC-MD-31. Consistency in the collection and review of spirometric data throughout studies LAC-MD-31 and LAC-MD-36 was ensured by continued use of the same centralised spirometry company for quality control and spirogram review.

The demographics and baseline characteristics of the patient population in LAC-MD-36 were consistent with those of the lead-in study.

A summary of the number of patients who dropped out of each treatment arm in study LAC-MD-36 is shown below:

Figure 9:

Figure 10.1–1. Patient Populations



AE = adverse event; COPD exac = chronic obstructive pulmonary disease exacerbation; FDC = fixed dose combination; FU = follow-up; Insuf = insufficient; Prot = protocol; W/d = withdrawal

Source: Tables 14.1.1b and 14.1.2b.

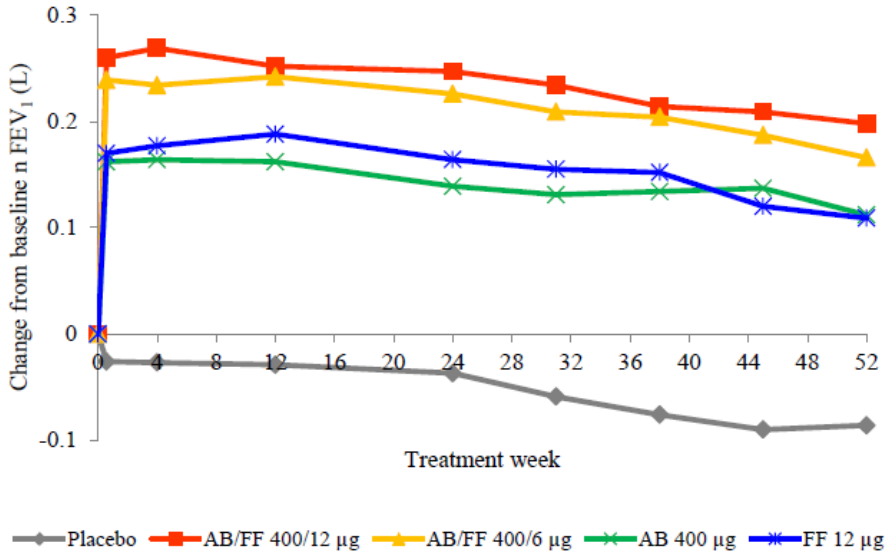
Missing data for pulmonary assessments, TDI and SGRQ were handled using the direct likelihood approach.

As expected in a 1 year study there was a considerable number of patients who did not complete 52 weeks treatment. The analysis provided below uses the direct likelihood approach to impute missing values. This approach assumes these values were missing at random.

Efficacy results

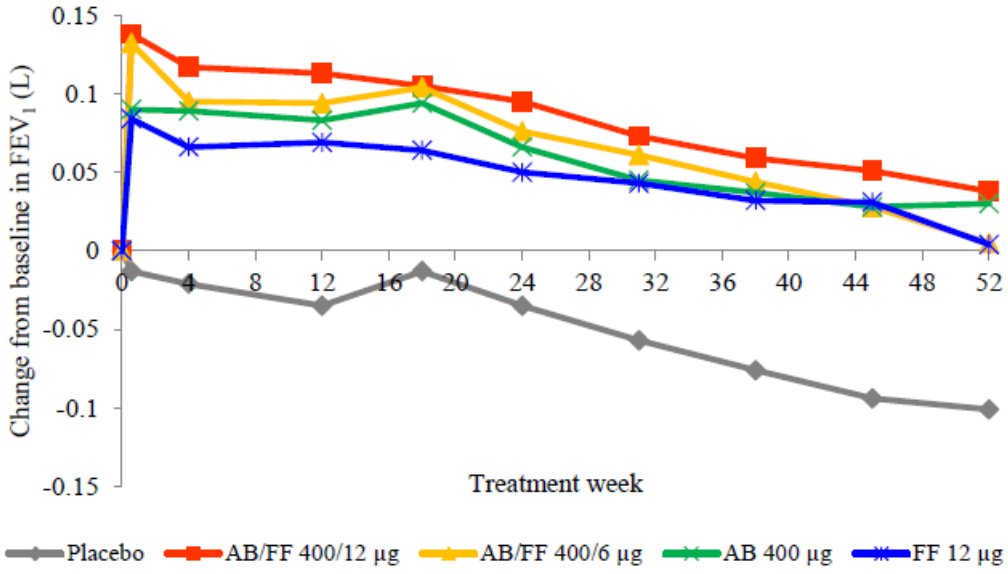
The improvements from baseline in FEV1 at 1 hour post-dose observed with aclidinium/formoterol compared to placebo at Day 4 of dosing were sustained up to Week 52. Over the 52-week treatment period, adjusted mean treatment differences between aclidinium/formoterol and placebo ranged from 0.284 L to 0.299 L for the 400/12 µg dose and from 0.252 L to 0.280 L for the 400/6 µg dose [p<0.0001 for comparisons of both doses to placebo]). Statistically significant improvements were also observed at all time points up to Week 52 with both doses of aclidinium/formoterol relative to formoterol or aclidinium monotherapies. At all time points up to and including Week 52, numerically greater increases from baseline were observed with the 400/12 µg dose of aclidinium/formoterol compared to the 400/6 µg dose.

Figure 10: LS mean changes from baseline in FEV1 at 1 hour post-dose (L) by visit over 52 weeks, studies LAC-MD-31 and LAC-MD-36 (Combined ITT population)



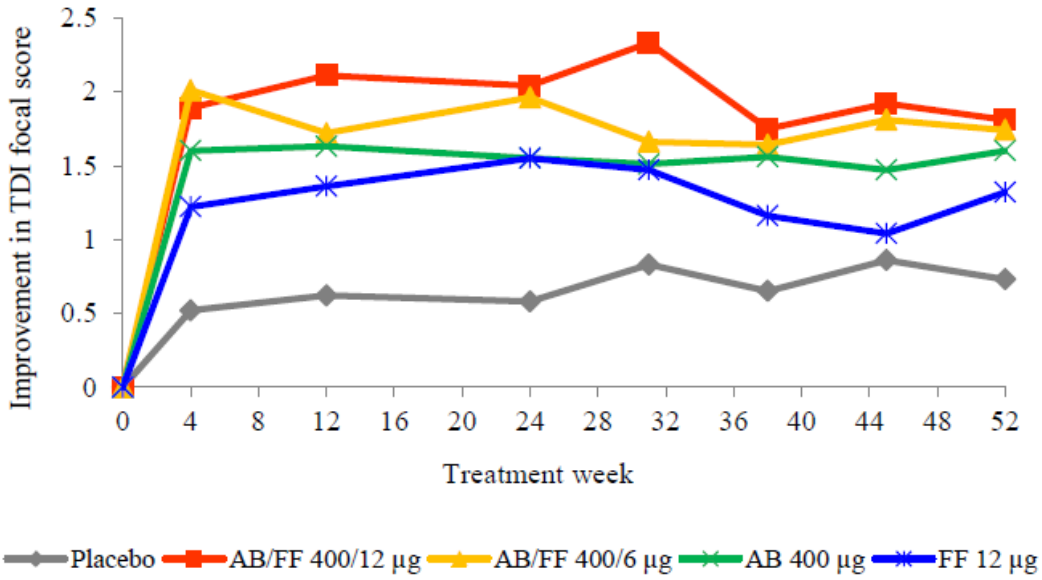
Both doses of aclidinium/formoterol were associated with clinically significant improvements from baseline in trough FEV1 which were maintained for the duration of the 52-week treatment period. Adjusted mean treatment differences between aclidinium/formoterol and placebo ranged from 0.118 L to 0.152 L for the 400/12 µg dose and from 0.107 L to 0.145 L for the 400/6 µg dose ($p<0.0001$ for all comparisons to placebo). Numerical increases from baseline in trough FEV1 compared to formoterol or aclidinium were observed with aclidinium/formoterol 400/12 µg at all visits up to Week 52 and with aclidinium/formoterol 400/6 µg at most visits up to Week 52. Numerically greater increases from baseline in trough FEV1 were also observed with the 400/12 µg dose compared to the 400/6 µg dose.

Figure 11: Changes from baseline in trough FEV1 (L) by visit over 52 weeks, studies LAC-MD-31 and LAC-MD-36 (Combined ITT population)



Clinically and statistically significant improvements in dyspnoea status (TDI focal score) with aclidinium/formoterol 400/12 µg compared to placebo were maintained from Week 4 to Week 52 (adjusted mean treatment differences from 1.07 units to 1.49 units [p<0.005 for all comparisons]). Statistically significant improvements in TDI focal score with aclidinium/formoterol 400/6 µg compared to placebo were observed at all visits from Week 4 to Week 52 and were of a clinically significant magnitude at most visits (adjusted mean treatment differences from 0.83 units to 1.49 units [p<0.01 for all comparisons]). Improvements in TDI focal score were numerically greater with aclidinium/formoterol (both doses) than with either constituent monotherapy at all visits up to Week 52 and were numerically greater with the 400/12 µg dose than the 400/6 µg dose at most visits.

Figure 12: Improvement in TDI focal score by visit over 52 weeks, studies LAC-MD-31 and LAC-MD-36 (Combined ITT population)



Compared to placebo, statistically significant improvements in SGRQ total score with aclidinium/formoterol 400/12 µg were maintained from Week 12 to Week 38 and with aclidinium/formoterol 400/6 µg were maintained from Week 4 to Week 52. Over the 52-week treatment period, adjusted mean treatment differences between the 400/12 µg dose and placebo in the changes from baseline in SGRQ total score ranged from -1.19 units to -4.35 units and between the 400/6 µg dose and placebo ranged from -2.72 units to -4.29 units.

Over the 52 weeks rates of moderate or severe exacerbations (HRU definition) were lower in the aclidinium/formoterol 400/12 µg arm (0.39 per patient/year) than in the placebo arm (0.49 per patient/year) or aclidinium/formoterol 400/6 µg arm (0.46 per patient/year) while rates of exacerbations of any severity (HRU definition) were similar in the 400/12 µg, 400/6 µg and placebo arms (0.49, 0.50 and 0.53 per patient/year, respectively). Consequently, aclidinium/formoterol 400/12 µg was associated with a numerical reduction in the rate of moderate or severe exacerbations (HRU definition) compared to placebo (by 20%; RR 0.80; p=0.186) but did not reduce the rate of exacerbations of any severity (HRU definition) compared to placebo (RR 0.92, p=0.586).

Rates of exacerbation were higher when exacerbations were assessed according to EXACT compared to when assessed by HRU and were lower with aclidinium/formoterol 400/12 µg (1.25 per patient/year) than

with placebo (1.57 per patient/year) or aclidinium/formoterol 400/6 µg (1.54 per patient/year). A numerical reduction (of 20%) in EXACT exacerbation rate was observed with aclidinium/formoterol 400/12 µg compared to placebo, which approached statistical significance (RR 0.80, p=0.068).

The improvement in lung function parameters over placebo appear to be maintained over the 52 weeks of the main study plus the extension study LAC-MD-36. A general decline in effect in all treatment groups over the 52-week period is seen reflecting the general deterioration in COPD that is seen in all patients. Although the separation between the combination products and the individual monocomponents is maintained in 1-hour post-dose FEV1 the same separation is not seen in trough FEV1 with little difference between active treatments by week 52. The concern is whether the combination of aclidinium and formoterol adds a significant benefit over formoterol alone.

However the combination does appear to demonstrate a persistent effect on TDI score compared with placebo and formoterol.

The reduction in rates of exacerbations with the combination when compared with placebo is small, even over 52 weeks and its clinical relevance is questionable.

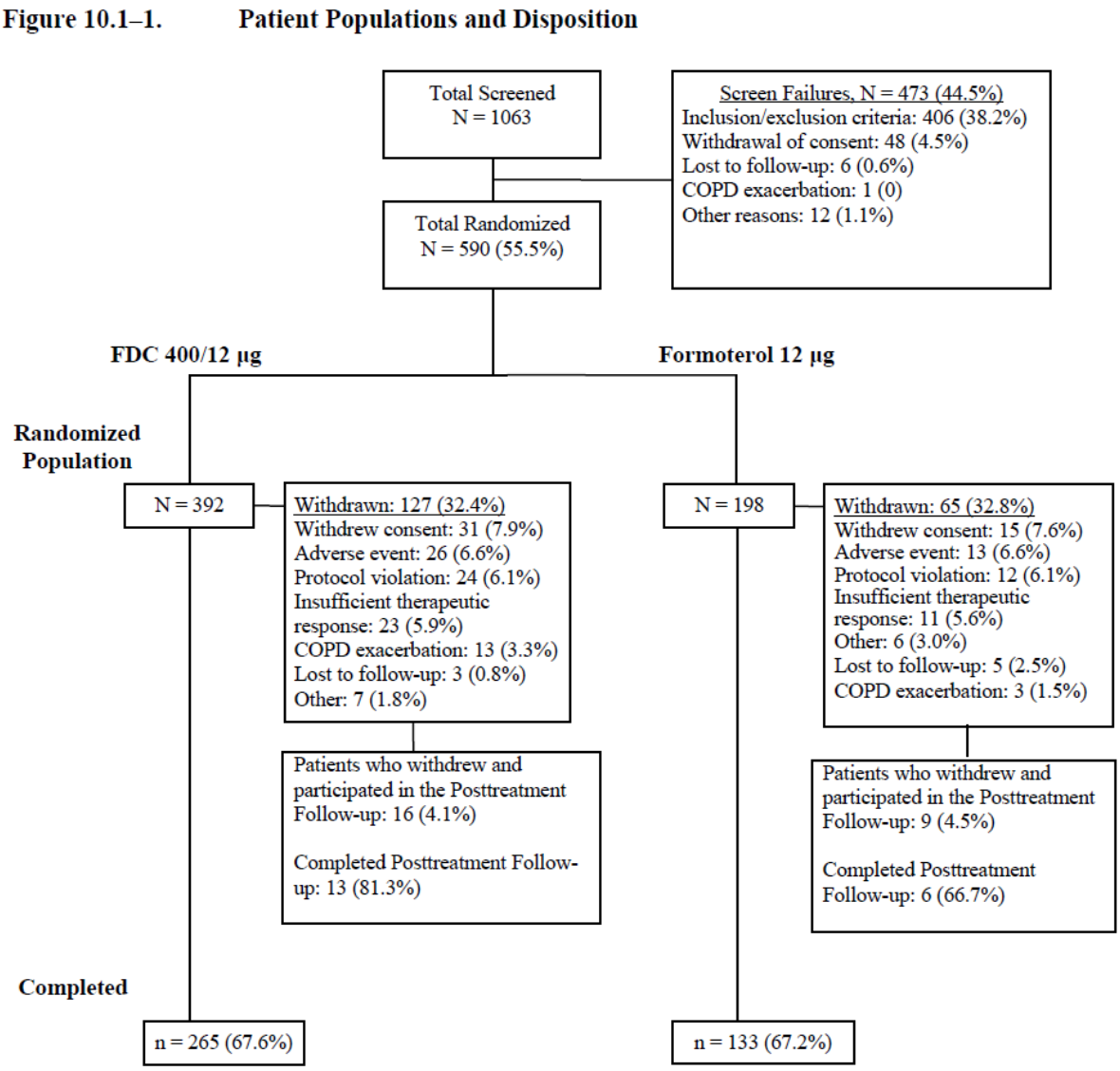
LAC-MD-32

A long-term safety study of aclidinium/formoterol (400/12 µg) compared with formoterol monotherapy (12 µg) in patients with stable chronic obstructive pulmonary disease

This Phase III, randomised, double-blind, parallel-group study was conducted at 135 centres in the United States. Following a 2 to 3-week run-in period during which the stability of the patients' COPD was confirmed, eligible patients were randomised, in a 2:1 ratio, to receive either aclidinium/formoterol 400/12 µg BID or formoterol 12 µg BID (both via Genuair®) for up to 52 weeks. The final follow-up assessment (by telephone contact) was conducted 4 weeks after the last dose of study treatment.

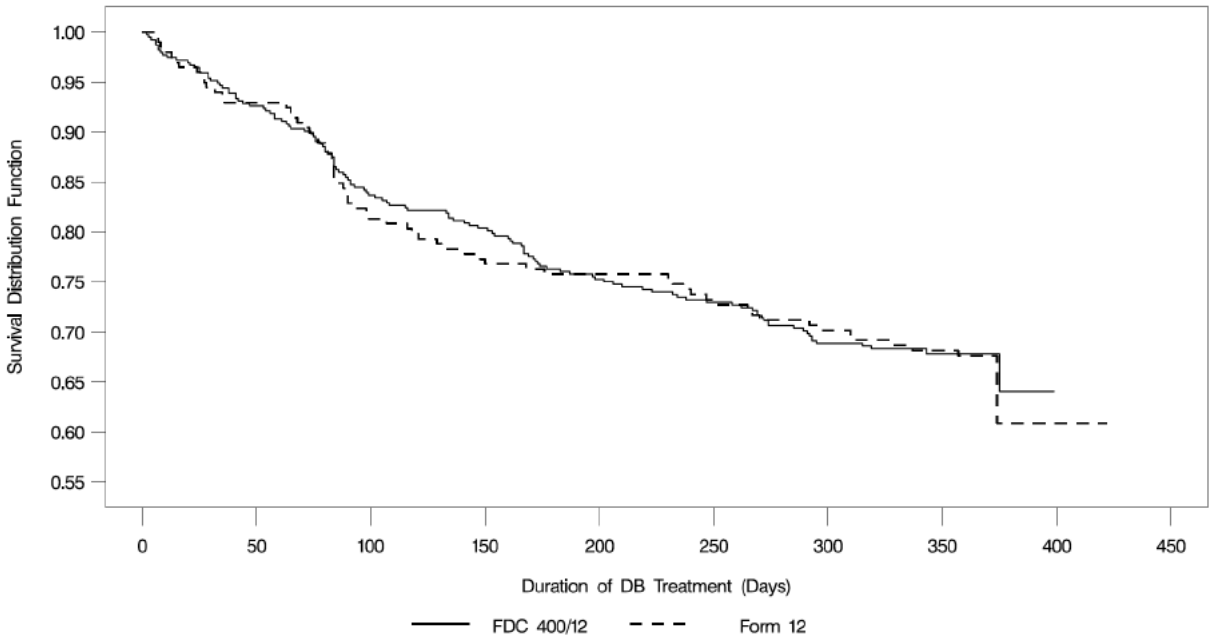
A limited evaluation of efficacy was conducted in study LAC-MD-32. Efficacy measures included: pre-dose FEV1 (assessed using locally-available spirometers [which met ATS and ERS recommendations for accuracy and precision] rather than centrally provided spirometers as in the Phase III pivotal studies), night-time and early morning symptoms (assessed as for M/40464/30), COPD exacerbations (assessed according to the HRU definition, as described for the Phase III pivotal studies) and use of rescue medication.

Figure 13:



The withdrawn rate in this study is high. Hence the estimate of treatment effect obtained can rely heavily on the approach taken to handling missing data; although it is noted that the timing of discontinuation is similar in both groups as shown in Figure 10.1-2 below.

Figure 10.1–2. Time to Premature Discontinuation of Treatment-Randomized Population



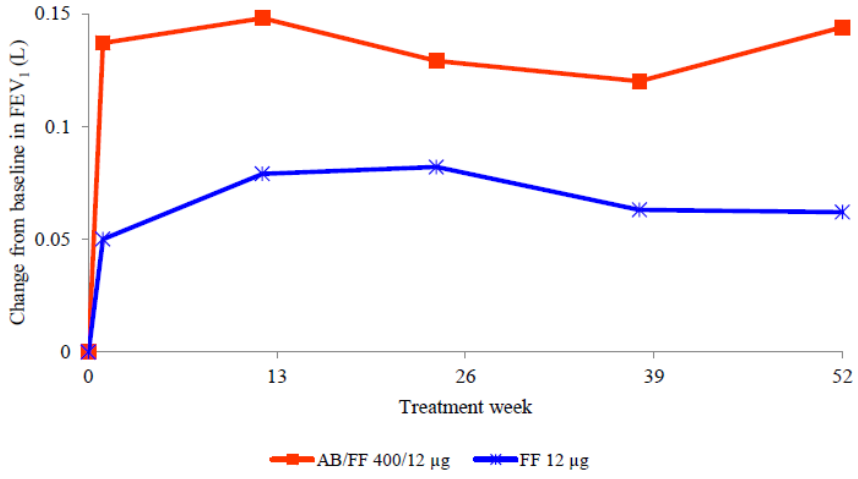
DB = double blind; FDC = fixed-dose combination; Form = formoterol.

All spirometric efficacy parameters were performed by means of a MMRM analysis. The analysis was performed based on all post-baseline measurements using only the observed cases without imputation of missing values.

This approach could be biased in favour of the combination group. Sensitivity analyses using a pattern mixture model or other suitable analyses should be provided.

Efficacy results

Figure 15: LS mean changes from baseline in morning pre-dose FEV1 (L) by visit over 52 weeks: study LAC-MD-32 (ITT Population)



The improvements from baseline in pre-dose FEV1 observed within 1 week of commencing treatment with both aclidinium/formoterol 400/12 µg or formoterol 12 µg were maintained for the duration of the

52-week treatment period. At each time point from Week 1 to Week 52, the magnitudes of the increases from baseline in pre-dose FEV1 observed with aclidinium/formoterol 400/12 µg were statistically significantly greater than those observed with formoterol monotherapy. The adjusted mean treatment difference between aclidinium/formoterol and formoterol ranged between 0.048 L and 0.087L and was 0.082L at Week 52.

The percentages of patients with at least one exacerbation of any severity (mild, moderate or severe) or at least one moderate or severe exacerbation were similar for the aclidinium/formoterol arm (27.3% and 25.3%, respectively) and for the formoterol arm (29.8% and 27.8%, respectively). The rates of exacerbations (per patient/year) were also similar for the aclidinium/formoterol and formoterol arms for any exacerbation (0.57/patient/year and 0.54/patient/year, respectively) and for moderate and severe exacerbations (0.52/patient/year and 0.49/patient/year, respectively).

Study LAC-MD-32 gives limited information on the efficacy of aclidinium/formoterol 400/12 µg compared with formoterol alone. The improvements in trough (pre-dose) FEV1 seem to be similar to those seen in the pivotal Phase III studies and did not reach an accepted clinically meaningful improvement of 100mls. The relevance of the improvement of 82ml seen at 52 weeks is debatable as published studies have demonstrated that patients cannot perceive a difference of <100ml (Donohue 2005). Further analyses have been provided using alternative models such as pattern mixture models. These were required as the drop-out rate in this study was high and hence the analysis provided using only completers could be biased in favour of the combination treatment group. The Applicant has provided further analyses in their responses including analyses of the long-term safety studies that impute different penalties according to reason for withdrawal to give a fuller picture of whether the treatment effect is robust to assumptions made about subjects who withdrew from the studies.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

For the dose finding studies, the focus of the dose of aclidinium shifted from 200µg to 400 µg following the completion of the programme for the monocomponent aclidinium bromide Genuair. Therefore dose response studies were initially conducted with a dose of aclidinium of 200 µg but the main dose response study (LAC-MD-27) was conducted with a dose of 400 µg. The population studied in the dose response studies were representative of the population in the proposed indication. Reversibility was not used as a means of excluding patients with asthma but smoking history of at least 10 pack-years was used in the diagnosis of COPD as per current guidelines.

The two pivotal clinical Phase III studies were designed as placebo and active controlled studies to compare the FDC with placebo and with its component parts.

The chosen co-primary endpoints of 1 hour post-dose and trough FEV1 to explore the contributions of formoterol and aclidinium respectively are considered to be appropriate and the key secondary symptomatic endpoints of TDI and SGRQ are in line with the CHMP guideline on the investigation of medicinal products for the treatment of COPD.

The studies were conducted in in accordance with the principles and practices of Good Clinical Practice and the Declaration of Helsinki. Changes to the protocols were minor and did not affect the overall conclusions of the studies.

Efficacy data and additional analyses

The two pivotal Phase III studies have given similar results in that both strengths of the combination aclidinium/formoterol product have demonstrated an improvement in lung function compared with placebo. However the improvement compared with the monocomponents is less consistent. The 400/12 µg combination has demonstrated a clinically relevant improvement in 1-hour post-dose FEV1 compared with aclidinium alone showing the contribution of the formoterol component but compared with formoterol alone the improvement in trough FEV1 does not reach a clinically relevant level in either study for either strength of the combination (0.085 L [p<0.0001] and 0.053 L [p=0.002], for 400/12 µg and 400/6 µg respectively in Study M/40464/30 and 0.045L [p=0.0102] and 0.026 [p= 0.1325] respectively in Study LAC-MD-31). In the pooled analysis aclidinium/formoterol 400/12 µg demonstrated an improvement in trough FEV1 compared with formoterol alone of 68ml (CI 44-92ml), which is not considered to be clinically relevant.

In general an improvement of 5-10% of baseline would be considered to be clinically important (Cazzola 2008); however an improvement of 100ml is usually accepted. The baseline pre-dose FEV1 for the patient population investigated in the two pivotal studies was 1.3-1.4L so an improvement between 65ml and 140ml would be expected. However the difference (68ml) seen with aclidinium/formoterol compared with formoterol alone is similar to that seen with other recently licensed LABA/LAMA combinations and *post hoc* responder analyses for clinically meaningful effects on FEV1 and symptomatic endpoints provided by the Applicant support the conclusion that aclidinium contributes to a clinically significant extent to the overall positive effect of the combination aclidinium/formoterol.

The improvement in FEV1 should be supported by clinically relevant improvement in symptomatic endpoints.

In the symptomatic endpoint TDI score aclidinium/formoterol 400/12 has demonstrated statistically significant improvements over the monocomponents aclidinium and formoterol (0.44 units [p=0.016] and 0.47 units [p=0.009], respectively) but it is debatable whether this can be considered to be clinically relevant as the minimal clinically relevant improvement in TDI score is generally held to be 1 unit.

To further explore this, the Applicant has provided *post hoc* responder analyses of the percentages of patients achieving a clinically meaningful improvement in symptomatic scores.

Percentages of patients with clinically significant improvements[a] in TDI focal score or SGRQ total score with aclidinium/formoterol 400/12 µg and formoterol 12 µg.

Variable	Population	Proportion of patients (%)		OR (95% CI)
		AB/FF	FF	
TDI focal score	Pooled population[b]	61.9	57.0	1.3 (1.0, 1.7)
	M/40464/30	64.8	61.3	1.2 (0.8, 1.7)
	LAC-MD-31	58.1	51.7	1.4 (0.9, 2.1)
SGRQ total score	Pooled population[b]	56.6	52.2	1.2 (0.9, 1.6)
	M/40464/30	55.3	52.1	1.2 (0.8, 1.7)
	LAC-MD-31	58.2	52.4	1.2 (0.8, 1.9)

* p<0.05

a Responder defined at a 1 unit improvement in TDI focal score or a 4 unit decrease in SGRQ total score.

b Data from pooled ITT population of studies M/40464/30 and LAC-MD-31.

Source: **Table 9.2.2** and **Table 10.2.2 Statistical Report of the SCE, Table 14.4.22.5** and **Table 14.4.23.5, M/40464/30** and **Table 14.4.3.41** and **Table 14.4.3.46, LAC-MD-31**

Abbreviations: AB/FF=aclidinium/formoterol; FF=formoterol fumarate dihydrate; CI=95% confidence interval; OR=odds ratio.

The percentages of patients in the aclidinium/formoterol 400/12 µg group of the pooled population who reached the MCIDs for TDI focal score (61.9 %) and SGRQ total score (56.6%) were similar to those achieved by both recently approved LABA/LAMA combinations (umeclidinium/vilanterol: 58% and 49% respectively and indacaterol/glycopyrronium: 68.1% and 63.7%, respectively).

The results of SGRQ are difficult to interpret owing to a large placebo effect seen in study M/40464/30 which cannot be explained. In both studies all active treatment arms demonstrated a clinically meaningful improvement over baseline in SGRQ total score of >-4units. In study LAC-MD-31 the combination aclidinium/formoterol 400/12 µg and aclidinium alone also achieved a -4unit improvement compared with placebo but in Study M/40464/30 the difference compared with placebo was minimal.

The effects of aclidinium/formoterol on exacerbations of COPD have been analysed in the pooled patient population of the two pivotal Phase III studies, which has shown an improvement in all severities of exacerbation based on the EXACT definition to be as much as 0.33 exacerbations per patient/year. This could be a clinically relevant improvement as the rate of exacerbations tends to correlate with rate of deterioration of COPD. However in the extension study LAC-MD-36, aclidinium/formoterol 400/12 µg was associated with a numerical reduction in the rate of moderate or severe exacerbations (HRU definition) compared to placebo (by 20%; RR 0.80; p=0.186) but did not reduce the rate of exacerbations of any severity (HRU definition) compared to placebo (RR 0.92, p=0.586) after 52 weeks. It is also debatable whether the patient would perceive a reduction of 0.33 exacerbations per year as clinically meaningful. A reduction of at least one event per year is currently the best estimate of the minimum clinically important difference to the patient.

2.5.4. Conclusions on the clinical efficacy

Conclusions on dose response

As per the analysis presented the two 14-day studies (LAC-MD-27 and M/40464/26) demonstrated a statistically significant and clinically meaningful improvement in FEV1 $AUC_{0-12/12h}$ of aclidinium/formoterol 200/12 μg, 200/6 μg, 400/12 μg and 400/6 μg compared with placebo with little difference between the strengths. In the secondary endpoint of trough FEV1 400/6 μg and 200/6 μg demonstrated a slightly greater improvement compared with placebo than the 400/12 μg and 200/12 μg strengths.

In the longer 4-week study (M/273FO/23) the 200/12 μg strength demonstrated consistent improvement in lung function parameters over baseline compared with placebo and with the monocomponents, except trough FEV1 of aclidinium/formoterol compared with formoterol 12 μg. The improvement seen with the lower strength in this study may be because it was of longer duration as the patient populations enrolled into the three studies had identical inclusion/exclusion criteria.

Overall there is little difference demonstrated between the strengths in these dose response studies. Therefore no firm conclusion can be drawn as to the optimal dose for the symptomatic treatment of patients with COPD. The applicant has opted to take forward the 400 μg strength of aclidinium following the licensing of this strength as the monocomponent but it may be that in combination with formoterol the 200 μg strength is adequate. Unfortunately this strength has not been investigated in a Phase III study.

Conclusions on the efficacy

Additional analyses of the Phase II studies have been submitted to reassure that the systemic exposure, and hence efficacy, of formoteorl via the Genuair inhaler is sufficiently similar to that of formoterol via Aerolizer. Although there is an apparent decrease in the pulmonary deposition of formoterol when administered via Genuair compared to that when formoterol is administered via Aerolizer, this does not translate into a decrease in efficacy as measured by FEV1 $AUC_{0-12/12}$ or FEV1 $AUC_{0-3/3}$. Formoterol via Genuair can therefore be accepted as an appropriate comparator in the Phase III studies.

The analyses of the pivotal studies and the sensitivity analyses provided are acceptable. The size of the placebo effect in study M/40464/30 was larger than expected. The Applicant has done all it can to try and explain this result but it remains unexplained. Therefore the results in this study for the SGRQ endpoint do not show an advantage for combination therapy over placebo.

Generally aclidinium/formoterol 400/12 μg has demonstrated an improvement in lung function and TDI score when compared with placebo but has not consistently demonstrated an improvement when compared with the monotherapies, particularly the effect on trough FEV1 compared with formoterol alone. However this difference is similar to that seen with other recently licensed LABA/LAMA combinations and *post hoc* responder analyses for clinically meaningful effects on FEV1 and symptomatic endpoints provided by the Applicant support the conclusion that aclidinium contributes to a clinically significant extent to the overall positive effect of the combination aclidinium/formoterol.

Additional analyses of the efficacy parameters in the long term studies have been provided using alternative models such as pattern mixture models. These were required as the drop-out rate in this study was high and hence the analysis provided using only completers could be biased in favour of the combination treatment group. The Applicant has provided further analyses that impute different penalties according to reason for withdrawal to give a fuller picture of whether the treatment effect is robust to assumptions made about subjects who withdrew from the studies. These additional analyses suggest that

the likely effect after 52 weeks of aclidinium when added to formoterol is 0.067L (95% CI 0.003, 0.131) in a pattern mixture model with reasonable assumptions made to penalise dropouts in study LAC-MD-32. In contrast in study LAC-MD-31/LAC-MD-36 when the same comparison is made the estimated effect size is smaller (0.034L), and not statistically significant (95% CI (-0.014, 0.082). The estimated effect of formoterol on top of aclidinium is 0.085L (95% CI (0.036, 0.134)) and remains consistent in all the analyses.

2.6. Clinical safety

Introduction

The combination aclidinium/formoterol consists of two authorised active substances for which the safety profile has been previously well-characterised. Because of their different modes of action, one as a muscarinic antagonist and one as a beta2 agonist, their safety profiles do not overlap to any clinically relevant extent and so the combination is not expected to cause any additive safety issues.

The safety assessment therefore concentrates mainly on adverse events of special interest and any unexpected adverse events. The main safety population consists of those patients enrolled in the Phase III studies.

The initial aclidinium/formoterol clinical development programme investigated aclidinium/formoterol as an OD treatment for COPD and explored aclidinium 200 µg in combination with a range of formoterol doses, both administered OD (M/273FO/22, M/273FO/23, and LAC-MD-24). The dose regimen for aclidinium/formoterol was switched from OD to BID when results from Phase III clinical studies of aclidinium monotherapy indicated that the bronchodilator efficacy of aclidinium 200 µg OD was suboptimal and that higher daily doses and/or a different dose regimen were necessary. As a result, the dose regimen investigated in the aclidinium monotherapy development programme and in the aclidinium/formoterol development programme was switched from OD to BID.

The clinical programme included four large Phase III studies. Two Phase III randomised, double-blind, parallel group placebo- and active-controlled pivotal studies (M/40464/30, LAC-MD-31) were conducted to demonstrate the efficacy, safety and tolerability of aclidinium/formoterol 400/12 µg BID and 400/6 µg BID. Both studies included five treatment arms (aclidinium/formoterol 400/12 µg, aclidinium/formoterol 400/6 µg, aclidinium 400 µg, formoterol 12 µg and placebo) and had a treatment duration of 24 weeks. Randomisation was stratified by smoking status (current or ex-smoker). The studies were comparable in design, with a 2- to 3-week run-in period to assess stability of COPD prior to initiation of study treatment. Patients completing LAC-MD-31 were given the possibility to continue on their initial treatment for an extension period of 28 weeks (LAC-MD-36). This extension study provides long-term safety, tolerability and efficacy data. The remaining Phase III study (LAC-MD-32) was a randomised, double-blind, parallel group active-controlled study conducted to assess the safety and tolerability of aclidinium/formoterol 400/12 µg BID for a duration of 52 weeks by comparison with formoterol 12 µg BID. Three Phase II studies were also conducted with aclidinium/formoterol BID in patients with COPD. These were cross-over studies so it is difficult to allocated adverse events to a particular treatment.

Patient exposure

The study COPD population included was the same in all patient studies. The total patient exposure to the proposed dose of 400/12 µg aclidinium/formoterol for 1 year is 360 patients when the long term safety study LAC-MD-32 is included. In the placebo-controlled studies 127 patients were exposed to the proposed dose for at least 1 year. This is sufficient to fulfil the advised safety database of at least 100 patients for at least 1 year.

Given that there is already post-marketing experience with the two actives as monotherapies this safety database is considered to be adequate by the CHMP.

Table 34: Extent of exposure: Placebo-controlled Phase III Study Population

	Placebo N=526	AB/FF 400/12 µg N=720	AB/FF 400/6 µg N=714	AB 400 µg N=722	FF 12 µg N=716
Overall Treatment Duration (days)					
n	526	720	714	721	716
Mean (SD)	191.4 (113.3)	200.3 (98.9)	208.9 (101.6)	200.8 (103.0)	202.3 (102.1)
Median	169.0	169.0	169.0	169.0	169.0
Min, Max	1, 383	1, 383	1, 407	1, 400	1, 407
Treatment Duration, n (%)					
≥ 1 day	526 (100)	720 (100)	714 (100)	721 (99.9)	716 (100)
≥12 weeks	432 (82.1)	648 (90.0)	660 (92.4)	644 (89.2)	649 (90.6)
≥24 weeks	359 (68.3)	557 (77.4)	543 (76.1)	537 (74.4)	540 (75.4)
≥52 weeks	88 (16.7)	127 (17.6)	141 (19.8)	138 (19.1)	127 (17.7)
Total Patient-years of Exposure	275.6	394.9	408.4	396.4	396.6

Includes data from studies M/40464/30, LAC-MD-31 and LAC-MD-36. Patients who participated in both LAC-MD-31 and its extension study, LAC-MD-36, were counted only once.
1 patient in the aclidinium 400 µg group took study drug only during the screening period, thus no post-randomisation exposure was reported.
Treatment duration = date of last dose of double-blind investigational product minus date of first dose of double-blind investigational product + 1.
Patient-years of exposure = total amount of time exposed to investigational product, expressed in years; AB = aclidinium bromide; AB/FF = aclidinium/formoterol; FF = formoterol fumarate; max = maximum, min = minimum; SD = standard deviation; N = number of patients in the safety population; n = number of patients in specified category.

Table 35: Extent of exposure in All Phase III Study Population

	All Phase III studies				
	Placebo N=526	AB/FF 400/12 µg N=1111	AB/FF 400/6 µg N=714	AB 400 µg N=721	FF 12 µg N=914
Overall Treatment Duration (days)					
n	526	1111	714	720	716
Mean (SD)	191.4 (113.3)	232.3 (116.3)	208.9 (101.6)	201.1 (102.8)	221.1 (113.4)
Median	169.0	171.0	169.0	169.0	170.0
Min, Max	1, 383	1, 399	1, 407	1, 400	1, 422
Treatment Duration, n (%)					
≥ 1 day	526 (100)	1111 (100)	714 (100)	720 (99.9)	914 (100)
≥12 weeks	432 (82.1)	991 (89.2)	660 (92.4)	644 (89.3)	822 (89.9)
≥24 weeks	359 (68.3)	862 (77.6)	543 (76.1)	537 (74.5)	692 (75.7)
≥52 weeks	88 (16.7)	360 (32.4)	141 (19.8)	138 (19.1)	243 (26.6)
Total Patient-years of Exposure	275.6	706.5	408.4	396.3	553.3

Includes data from studies M/40464/30, LAC-MD-31, LAC-MD-36 and LAC-MD-32. Patients who participated in both LAC-MD-31 and its extension study, LAC-MD-36, were counted only once.
1 patient in the aclidinium 400 µg group took study drug only during the screening period, thus no post-randomisation exposure was reported.

Adverse events

Adverse events (AEs), including COPD exacerbations, were coded using MedDRA (Version 16.0). Within the BID programme, AEs were initially coded using the current MedDRA version available at the time of the study and were recoded as necessary using MedDRA Version 16.0.

An AE was considered to be a treatment-emergent adverse event (TEAE) if its onset date was on or after the date of the first dose of investigational product, or if its onset date was before the date of the first dose of investigational product and the severity increased on or after the date of the first dose of investigational product.

Table 36: Overview of treatment-emergent adverse events: Placebo-controlled Phase III Study Population

Category	Placebo N=526 ET=275.6 n (%) [inc]	AB/FF 400/12 µg N=720 ET=394.9 n (%) [inc]	AB/FF 400/6 µg N=714 ET=408.4 n (%) [inc]	AB 400 µg N=722 ET=396.4 n (%) [inc]	FF 12 µg N=716 ET=396.6 n (%) [inc]
At least 1 TEAE	327 (62.2) [1186]	449 (62.4) [1137]	442 (61.9) [1082]	452 (62.6) [1140]	470 (65.6) [1185]
Any mild TEAE	219 (41.6 [794.6]	320 (44.4) [810.4]	322 (45.1) [788.5]	306 (42.4) [772.0]	316 (44.1) [796.8]
Any moderate TEAE	199 (37.8) [722.0]	278 (38.6) [704.0]	288 (40.3) [705.3]	311 (43.1) [784.6]	312 (43.6) [786.7]
Any severe TEAE	57 (10.8) [206.8]	78 (10.8) [197.5]	73 (10.2) [178.8]	73 (10.1) [184.2]	68 (9.5) [171.5]
Any related TEAE	53 (10.1) [192.3]	85 (11.8) [215.3]	73 (10.2) [178.8]	71 (9.8) [179.1]	69 (9.6) [174.0]
Any TEAE leading to permanent treatment discontinuation	44 (8.4) [159.6]	52 (7.2) [131.7]	44 (6.2) [107.7]	49 (6.8) [123.6]	41 (5.7) [103.4]
Any treatment-emergent SAE	39 (7.4) [141.5]	58 (8.1) [146.9]	58 (8.1) [142.0]	53 (7.3) [133.7]	49 (6.8) [123.6]
Any treatment-emergent death[1]	2 (0.4) [7.3]	4 (0.6) [10.1]	3 (0.4) [7.3]	4 (0.6) [10.1]	2 (0.3) [5.0]

Includes data from studies M/40464/30, LAC-MD-31 and LAC-MD-36. Patients who participated in both LAC-MD-31 and LAC-MD-36 are counted only once.
1Includes deaths recorded during the study or within 30 days of last dose of investigational product.
AB = aclidinium bromide; AB/FF = aclidinium/formoterol; ET = total exposure time in years; FF = formoterol fumarate; inc = number of patients per 1000 patient-years of exposure; N = number of patients in safety population; n = number of patients in the specified category; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Table 37: Overview of treatment-emergent adverse events: All Phase III Study Population

Category	Placebo N=526 ET=275.6 n (%) [inc]	AB/FF 400/12 µg N=1111 ET=706.5 n (%) [inc]	AB/FF 400/6 µg N=714 ET=408.4 n (%) [inc]	AB 400 µg N=721 ET=396.3 n (%) [inc]	FF 12 µg N=914 ET=553.3 n (%) [inc]
At least 1 TEAE	327 (62.2) [1186]	754 (67.9) [1067]	442 (61.9) [1082]	451 (62.6) [1138]	618 (67.6) [1117]
Any mild TEAE	219 (41.6 [794.6]	532 (47.9) [753.1]	322 (45.1) [788.5]	306 (42.4) [772.1]	412 (45.1) [744.6]
Any moderate TEAE	199 (37.8) [722.0]	502 (45.2) [710.6]	288 (40.3) [705.3]	310 (43.0) [782.2]	420 (46.0) [759.0]
Any severe TEAE	57 (10.8) [206.8]	151 (13.6) [213.7]	73 (10.2) [178.8]	73 (10.1) [184.2]	114 (12.5) [206.0]
Any related TEAE	53 (10.1) [192.3]	145 (13.1) [205.3]	73 (10.2) [178.8]	71 (9.8) [179.1]	97 (10.6) [175.3]
Any TEAE leading to treatment discontinuation	44 (8.4) [159.6]	92 (8.3) [130.2]	44 (6.2) [107.7]	49 (6.8) [123.6]	57 (6.2) [103.0]
Any treatment-emergent SAE	39 (7.4) [141.5]	109 (9.8) [154.3]	58 (8.1) [142.0]	53 (7.4) [133.7]	79 (8.6) [142.8]
Any death during treatment period	2 (0.4) [7.3]	9 (0.8) [12.7]	3 (0.4) [7.3]	4 (0.6) [10.1]	3 (0.3) [5.4]

Includes data from studies M/40464/30, LAC-MD-31, LAC-MD-36 and LAC-MD-32. Patients who participated in both LAC-MD-31 and LAC-MD-36 are counted only once.
Includes deaths recorded during the study or within 30 days of last dose of investigational product.
AB = aclidinium bromide; AB/FF = aclidinium/formoterol; ET = total exposure time in years; FF = formoterol fumarate; inc = number of patients per 1000 patient-years of exposure; N = number of patients in the safety population; n = number of patients in the specified category; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Table 38: Incidence of treatment-emergent adverse events (by system organ class) that occurred in at least 5% of patients in any treatment group: Placebo-controlled Phase III Study Population

System Organ Class	Placebo N=526 ET=275.6 n (%) [inc]	AB/FF 400/12 µg N=720 ET=394.9 n (%) [inc]	AB/FF 400/6 µg N=714 ET=408.4 n (%) [inc]	AB 400 µg N=722 ET=396.4 n (%) [inc]	FF 12 µg N=716 ET=396.6 n (%) [inc]
At least 1 TEAE	327 (62.2) [1186]	449 (62.4) [1137]	442 (61.9) [1082]	452 (62.6) [1140]	470 (65.6) [1185]
Infections and infestations	136 (25.9) [493.4]	204 (28.3) [516.6]	204 (28.6) [499.6]	188 (26.0) [474.3]	189 (26.4) [476.6]
Respiratory, thoracic and mediastinal disorders	152 (28.9) [551.5]	182 (25.3) [460.9]	194 (27.2) [475.1]	198 (27.4) [499.5]	199 (27.8) [501.8]
Gastrointestinal disorders	67 (12.7) [243.1]	93 (12.9) [235.5]	100 (14.0) [244.9]	84 (11.6) [211.9]	81 (11.3) [204.2]
Musculoskeletal and connective tissue disorders	60 (11.4) [217.7]	93 (12.9) [235.5]	82 (11.5) [200.8]	91 (12.6) [229.6]	109 (15.2) [274.9]
Nervous system disorders	56 (10.6) [203.2]	88 (12.2) [222.8]	79 (11.1) [193.5]	91 (12.6) [229.6]	95 (13.3) [239.5]
General disorders and administration site conditions	33 (6.3) [119.7]	55 (7.6) [139.3]	51 (7.1) [124.9]	41 (5.7) [103.4]	44 (6.1) [110.9]
Investigations	24 (4.6) [87.1]	51 (7.1) [129.2]	38 (5.3) [93.1]	34 (4.7) [85.8]	29 (4.1) [73.1]
Injury, poisoning and procedural complications	33 (6.3) [119.7]	44 (6.1) [111.4]	44 (6.2) [107.7]	52 (7.2) [131.2]	54 (7.5) [136.2]
Cardiac disorders	29 (5.5) [105.2]	30 (4.2) [76.0]	49 (6.9) [120.0]	42 (5.8) [106.0]	34 (4.7) [85.7]
Metabolism and nutrition disorders	25 (4.8) [90.7]	29 (4.0) [73.4]	34 (4.8) [83.3]	34 (4.7) [85.8]	39 (5.4) [98.3]
Vascular disorders	23 (4.4) [83.5]	20 (2.8) [50.6]	27 (3.8) [66.1]	26 (3.6) [65.6]	36 (5.0) [90.8]

Includes data from studies M/40464/30, LAC-MD-31 and LAC-MD-36. Patients who participated in both LAC-MD-31 and LAC-MD-36 are counted only once.
Data ordered by decreasing incidence in the aclidinium/formoterol 400/12 µg group.

The most commonly reported TEAEs (incidence >5%) in patients treated with aclidinium/formoterol were exacerbations of COPD (PT: chronic obstructive pulmonary disease), nasopharyngitis and headache. COPD exacerbations were reported more commonly for placebo (in 20.7% of patients) than for either aclidinium/formoterol group (in 17.1% and 18.1% of patients in the 400/12 µg and 400/6 µg groups respectively). The proportion of patients with severe COPD exacerbations (i.e. those requiring hospitalisation) was 4.6% for placebo, 4.0% for aclidinium/formoterol 400/12 µg and 3.8% for aclidinium/formoterol 400/6 µg. COPD exacerbations led to permanent treatment discontinuation in ≤ 2.5% of patients in any treatment group.

Table 39: Treatment-emergent adverse events of severe intensity reported in more than 2 patients in any treatment group: Placebo-controlled Phase III Study Population

Preferred Term	Placebo N=526 ET=275.6 n (%)	AB/FF 400/12 µg N=720 ET=394.9 n (%)	AB/FF 400/6 µg N=714 ET=408.4 n (%)	AB 400 µg N=722 ET=396.4 n (%)	FF 12 µg N=716 ET=396.6 n (%)
Any severe TEAE	57 (10.8)	78 (10.8)	73 (10.2)	73 (10.1)	68 (9.5)
Chronic obstructive pulmonary disease	24 (4.6)	29 (4.0)	27 (3.8)	35 (4.8)	29 (4.1)
Pneumonia	3 (0.6)	5 (0.7)	8 (1.1)	3 (0.4)	3 (0.4)
Acute myocardial infarction	1 (0.2)	2 (0.3)	3 (0.4)	0	1 (0.1)
Myocardial infarction	1 (0.2)	2 (0.3)	2 (0.3)	3 (0.4)	1 (0.1)
Acute respiratory failure	1 (0.2)	1 (0.1)	1 (0.1)	1 (0.1)	3 (0.4)
Atrial fibrillation	3 (0.6)	0	1 (0.1)	1 (0.1)	1 (0.1)
Vomiting	0	0	1 (0.1)	3 (0.4)	0
Lobar pneumonia	0	0	1 (0.1)	0	3 (0.4)
Diverticulitis	3 (0.6)	0	0	0	1 (0.1)

Includes data from studies M/40464/30, LAC-MD-31 and LAC-MD-36. Patients who participated in both LAC-MD-31 and LAC-MD-36 are counted only once.
Table is ordered by decreasing frequency in the aclidinium/formoterol 400/12 µg group and then the aclidinium/formoterol 400/6 µg group.

The number of patients in the Placebo-controlled Phase III Study Population with TEAEs of severe intensity was comparable across treatment groups ranging from 9.5% to 10.8%. There was no evidence observed that the severity of TEAEs was increased by aclidinium/formoterol treatment. Exacerbations of COPD and pneumonia were the only TEAEs reported as severe in more than 1% of patients in any treatment group. The proportion of patients with severe COPD exacerbations was higher in the placebo group (4.6%) than either of the aclidinium/formoterol treatment groups (4.0% and 3.8%). Pneumonia was reported as severe for 1.1% of patients in the aclidinium/formoterol 400/6µg group but for 0.7% in the aclidinium/formoterol 400/12 µg group which was comparable with placebo (0.6%).

In the placebo-controlled trials the incidence of TEAEs was similar across the treatment groups. In the all Phase III Study population the aclidinium/formoterol 400/12 µg group tends to a higher incidence of TEAEs, SAEs and deaths but this may be because of the addition of patients in the long term study LAC-MD-32 which compared aclidinium/formoterol 400/12 µg with formoterol alone.

The incidence of TEAEs in the different SOCs is similar across the treatment groups. Only in the 'infections and infestations' and 'investigations' SOCs is the incidence of TAEAs slightly higher in the aclidinium/formoterol groups than in the other treatment groups. Despite the incidence of COPD exacerbations being lower in the combination groups than in the placebo group, the incidence of pneumonia was slightly higher (1.1%, 1.3% and 2.0% for the placebo, 400/12 and 400/6 groups respectively [Placebo-controlled Phase III population]).

For cardiac disorders the incidence ranges from 4.2% in the aclidinium/formoterol 400/12 µg group to 6.9% in the aclidinium/formoterol 400/6 µg group with an incidence of 5.5% in the placebo group.

With regard to TEAEs of severe intensity the incidence of pneumonia is slightly higher in the two combination groups than the other treatment groups or placebo. Incidence of myocardial infarction is also

higher in the groups that included aclidinium treatment. However the numbers are very small so firm conclusions cannot be drawn.

In general there are no striking differences between the treatment groups that raise safety concerns.

Serious adverse event / deaths / other significant events

Serious adverse events

The proportion of patients with treatment-emergent SAEs was low and comparable across all treatment groups, ranging from 6.8% to 8.1%. SAEs that were cardiac disorders, gastrointestinal disorders, infections and infestations, injury, poisoning and procedural complications, neoplasms benign, malignant and unspecified (including cysts and polyps), nervous system disorders, and respiratory, thoracic and mediastinal disorders were the only SAEs (by SOC) that were reported by at least 1% of patients in any treatment group.

Table 40: Treatment-emergent serious adverse events by system organ class reported in at least 1% patients in any treatment group: Placebo-controlled Phase III Study Population

System Organ Class	Placebo N=526 ET=275.6 n (%) [inc]	AB/FF 400/12 µg N=720 ET=394.9 n (%) [inc]	AB/FF 400/6 µg N=714 ET=408.4 n (%)[inc]	AB 400 µg N=722 ET=396.4 n (%) [inc]	FF 12 µg N=716 ET=396.6 n (%) [inc]
Any treatment-emergent SAE	39 (7.4) [141.5]	58 (8.1) [146.9]	58 (8.1) [142.0]	53 (7.3) [133.7]	49 (6.8) [123.6]
Cardiac disorders	10 (1.9) [36.3]	5 (0.7) [12.7]	12 (1.7] [29.4]	10 (1.4) [25.2]	10 (1.4) [25.2]
Gastrointestinal disorders	1 (0.2) [3.6]	6 (0.8) [15.2]	7 (1.0) [17.1]	4 (0.6) [10.1]	3 (0.4) [7.6]
Infections and infestations	6 (1.1) [21.8]	12 (1.7) [30.4]	13 (1.8) [31.8]	12 (1.7) [30.3]	12 (1.7) [30.3]
Injury, poisoning and procedural complications	1 (0.2) [3.6]	5 (0.7) [12.7]	7 (1.0) [17.1]	2 (0.3) [5.0]	4 (0.6) [10.1]
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	2 (0.4) [7.3]	7 (1.0) [17.7]	2 (0.3) [4.9]	4 (0.6) [10.1]	7 (1.0) [17.7]
Nervous system disorders	4 (0.8) [14.5]	2 (0.3) [5.1]	9 (1.3) [22.0]	5 (0.7) [12.6]	2 (0.3) [5.0]
Respiratory, thoracic and mediastinal disorders	14 (2.7) [50.8]	13 (1.8) [32.9]	19 (2.7) [46.5]	22 (3.0) [55.5]	13 (1.8) [32.8]

Includes data from studies M/40464/30, LAC-MD-31 and LAC-MD-36. Patients who participated in both LAC-MD-31 and LAC-MD-36 are counted only once.
AB = aclidinium bromide; AB/FF = aclidinium/formoterol; ET = total exposure time in years; FF = formoterol fumarate; inc = number of patients per 1000 patient-years of exposure; N = number of patients in the safety population; n = number of patients in the specified category; SAE = serious adverse event.

Table 41: Treatment-emergent serious adverse events by preferred term in more than 2 patients in any treatment group: Placebo-controlled Phase III Study Population

Preferred Term	Placebo N=526 ET=275.6 n (%) [inc]	AB/FF 400/12 µg N=720 ET=394.9 n (%) [inc]	AB/FF 400/6 µg N=714 ET=408.4 n (%) [inc]	AB 400 µg N=722 ET=396.4 n (%) [inc]	FF 12 µg N=716 ET=396.6 n (%) [inc]
Any treatment-emergent SAE	39 (7.4) [141.5]	58 (8.1) [146.9]	58 (8.1) [142.0]	53 (7.3) [133.7]	49 (6.8) [123.6]
Chronic obstructive pulmonary disease	14 (2.7) [50.8]	11 (1.5) [27.9]	15 (2.1) [36.7]	20 (2.8) [50.5]	12 (1.7) [30.3]
Pneumonia	4 (0.8) [14.5]	5 (0.7) [12.7]	8 (1.1) [19.6]	3 (0.4) [7.6]	3 (0.4) [7.6]
Myocardial infarction	1 (0.2) [3.6]	2 (0.3) [5.1]	2 (0.3) [4.9]	3 (0.4) [7.6]	2 (0.3) [5.0]
Angina pectoris	0	0	3 (0.4) [7.3]	1 (0.1) [2.5]	0
Atrial fibrillation	3 (0.6) [10.9]	0	3 (0.4) [7.3]	1 (0.1) [2.5]	2 (0.3) [5.0]
Syncope	1 (0.2) [3.6]	0	3 (0.4) [7.3]	0	1 (0.1) [2.5]

Includes data from studies M/40464/30, LAC-MD-31 and LAC-MD-36. Patients who participated in both LAC-MD-31 and LAC-MD-36 are counted only once.
Table is ordered by decreasing frequency in the aclidinium/formoterol 400/12 µg group followed by the frequency in the 400/6 µg group.

As for the Placebo-controlled Phase III Study Population, the most frequently reported SAE was exacerbation of COPD which in the All Phase III Study Population was reported by a slightly lower proportion of patients in the aclidinium/formoterol groups than for placebo. Pneumonia was the only other SAE reported by more than 1% of patients in any treatment group. This SAE was reported by 1.1% of patients in the aclidinium/formoterol 400/6 µg group but by a lower proportion of patients in the aclidinium/formoterol 400/12 µg group and placebo groups (0.8% in each group). Sudden death was the only other SAE reported by more than 3 patients in any treatment group

The percentages of patients with serious adverse events are similar across the treatment groups. In looking at the particular events the higher dose of formoterol in the combination aclidinium/formoterol 400/12 µg appears to have a protective effect compared with the aclidinium/formoterol 400/6 µg and the aclidinium alone treatment groups with respect to COPD and cardiac events. However the numbers are very small so no firm conclusions can be drawn. There is no evidence of particular safety issues with the combination aclidinium/formoterol compared with the monocomponents.

In the All Phase III Study Population there were no additional serious adverse events reported to conclude that the rate of adverse events increase over time. More deaths were reported in this population as it included patients enrolled into the extension 1-year studies. In this patient population with moderate to severe COPD it is not unexpected to have more deaths occurring over time.

Deaths

A total of 21 treatment-emergent deaths were reported in the Phase III studies with aclidinium/formoterol in patients with COPD.

Table 42: Number of treatment-emergent deaths in Phase III studies in patients with COPD (safety population)

Study Population	Placebo n (%) [inc]	AB/FF 400/12 µg n (%) [inc]	AB/FF 400/6 µg n (%) [inc]	AB 400 µg n (%) [inc]	FF 12 µg n (%) [inc]
Placebo-controlled Phase III Study Population	N=526 ET=275.6	N=720 ET=394.9	N=714 ET=408.4	N=722 ET=396.3	N=716 ET=396.6
Ttreatment-emergent death	2 (0.4) [7.3]	4 (0.6) [10.1]	3 (0.4) [7.3]	4 (0.6) [10.1]	2 (0.3) [5.0]
All Phase III Study Population	N=526 ET=275.6	N=1111 ET=706.5	N=714 ET=408.4	N=721 ET=396.3	N=914 ET=553.3
Treatment-emergent death	2 (0.4) [7.3]	9 (0.8) [12.7]	3 (0.4) [7.3]	4 (0.6) [10.1]	3 (0.3) [5.4]

Includes deaths recorded during the study or within 30 days of the last dose of investigational product
Study LAC-MD-32 only included AB/FF 400/12 µg and FF 12 µg treatment groups.

The only TEAE with a fatal outcome that was reported by more than 1 patient in any treatment group was unexplained death (PT: death; reported for 1 patient in the placebo group, 4 in the aclidinium/formoterol 400/12 µg group and 1 in the formoterol group). These TEAEs were adjudicated by the Cardiovascular Adjudication Committee as sudden cardiac deaths of unknown aetiology for 3 patients in the aclidinium/formoterol 400/12 µg group and 1 patient in the formoterol group; cause of death was adjudicated as undetermined for 1 patient in the aclidinium/formoterol 400/12 µg group and 1 patient in the placebo group. All the patients whose deaths were adjudicated as a cardiovascular death had a significant pre-existing cardiovascular medical history, including ischaemic heart disease in most of them.

Other reasons for death reported by more than 1 patient across the treatment groups were: exacerbation of COPD, cardio-respiratory arrest, cardiac failure and myocardial infarction. No other TEAEs resulted in the death of more than 1 patient.

Table 43: Summary of TEAEs with fatal outcome in Phase III studies in patients with COPD (safety population)

System Organ Class Preferred Term	Placebo N=526 ET=275.6 n (%) [inc]	AB/FF 400/12 µg N=1111 ET=706.5 n (%) [inc]	AB/FF 400/6 µg N=714 ET=408.4 n (%) [inc]	AB 400 µg N=721 ET=396.3 n (%) [inc]	FF 12 µg N=914 ET=553.3 n (%) [inc]
Cardiac disorders	1 (0.2) [3.6]	2 (0.2) [2.8]	2 (0.3) [4.9]	1 (0.1) [2.5]	1 (0.1) [1.8]
Cardiac arrest	0	1 (0.1) [1.4]	0	0	0
Cardio-respiratory arrest	0	1 (0.1) [1.4]	1 (0.1) [2.4]	0	0
Cardiac failure	0	0	1 (0.1) [2.4]	0	1 (0.1) [1.8]
Myocardial infarction	1 (0.2) [3.6]	0	0	1 (0.1) [2.5]	0
Gastrointestinal disorders	0	0	0	1 (0.1) [2.5]	0
Gastrointestinal necrosis	0	0	0	1 (0.1) [2.5]	0
General disorders and administration site conditions	1 (0.2) [3.6]	4 (0.4) [5.7]	0	0	1 (0.1) [1.8]
Death	1 (0.2) [3.6]	4 (0.4) [5.7]	0	0	1 (0.1) [1.8]
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0	1 (0.1) [1.4]	0	1 (0.1) [2.5]	0
Lung cancer metastatic	0	1 (0.1) [1.4]	0	0	0
Oesophageal adenocarcinoma	0	0	0	1 (0.1) [2.5]	0
Psychiatric disorders	0	1 (0.1) [1.4]	0	0	0
Completed suicide	0	1 (0.1) [1.4]	0	0	0
Respiratory, thoracic, and mediastinal disorders	0	1 (0.1) [1.4]	1 (0.1) [2.4]	1 (0.1) [2.5]	1 (0.1) [1.8]
Chronic obstructive pulmonary disease	0	1 (0.1) [1.4]	1 (0.1) [2.4]	0	1 (0.1) [1.8]
Acute respiratory failure	0	0	0	1 (0.1) [2.5]	0

There was only 1 TEAE with a fatal outcome that was considered by the investigators to be study drug-related; this was experienced by patient 115431006 treated with placebo. This was in a 57-year-old male who had been in the study for 337 days at the time of death. The death was adjudicated as being of unknown cause.

Adverse events of special interest

Aclidinium/formoterol is a combination of aclidinium bromide, a long-acting anti-muscarinic agent with kinetic selectivity towards M3 receptors in the lung and formoterol fumarate, a long-acting β2-adrenergic agonist. COPD is associated with chronic co-morbid diseases such as cardiovascular disease and hypertension.

Cardiovascular adverse events

Two analyses were performed to evaluate the overall cardiovascular risk of the drug. The two analyses are:

1. Analysis of MACE
2. Analysis of cardiac events of interest based on standardised MedDRA queries (SMQs)

Major Adverse Cardiac Events and events based on SMQs were analysed and presented for the Placebo-controlled Phase III Study Population and for the All Phase III Study Population.

Analysis of Major Adverse Cardiac Events

Major Adverse Cardiac Events were defined as a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. A Cardiovascular Adjudication Committee, an independent external expert advisory panel, was set up to provide independent and objective review and adjudication of the Phase III clinical programme and to apply a consistent set of criteria for determining cardiovascular events.

In the Placebo-controlled Phase III Study Population no MACE signal was observed with either dose of aclidinium/formoterol. The incidence of MACE in the aclidinium/formoterol treatment groups was low and similar to that seen for placebo and monotherapies. The number of MACE was too small to draw any firm conclusions and there were no important differences between treatment groups in types of MACE reported.

Table 44: Major Adverse Cardiac Events: Placebo-controlled Phase III Study Population

Category	Placebo N = 526 ET = 275.6 n (%) [inc]	AB/FF 400/12 µg N = 720 ET = 394.9 n (%) [inc]	AB/FF 400/6 µg N = 714 ET = 408.4 n (%) [inc]	AB 400 µg N = 722 ET = 396.4 n (%) [inc]	FF 12 µg N= 716 ET = 396.6 n (%) [inc]
Any MACE	4 (0.8) [14.5]	6 (0.8) [15.2]	8 (1.1) [19.6]	5 (0.7) [12.6]	7 (1.0) [17.7]
Cardiovascular death	1 (0.2) [3.6]	2 (0.3) [5.1]	2 (0.3) [4.9]	1 (0.1) [2.5]	2 (0.3) [5.0]
Non-fatal myocardial infarction	1 (0.2) [3.6]	4 (0.6) [10.1]	4 (0.6) [9.8]	2 (0.3) [5.0]	4 (0.6) [10.1]
Non-fatal stroke	2 (0.4) [7.3]	0	2 (0.3) [4.9]	2 (0.3) [5.0]	1 (0.1) [2.5]

The following SMQs were selected to analyse the incidence of cardiac events of interest (myocardial infarction, tachycardia, atrial fibrillation, angina, congestive heart failure, bradycardia and conduction defects).

The proportion of patients reporting any cardiac event of interest was low (≤ 5% in any treatment group). The incidence was lower for aclidinium/formoterol 400/12 µg than for placebo and was similar for aclidinium/formoterol 400/6 µg and placebo.

Table 45: Cardiac events of special interest by specific SMQ category: Placebo-controlled Phase III Study Population

Cardiac Events of Interest	Placebo N = 526 ET = 275.6 n (%) [inc]	AB/FF 400/12 µg N = 720 ET = 394.9 n (%) [inc]	AB/FF 400/6 µg N = 714 ET = 408.4 n (%) [inc]	AB 400 µg N = 722 ET = 396.4 n (%) [inc]	FF 12 µg N= 716 ET = 396.6 n (%) [inc]
Any event	23 (4.4) [83.5]	20 (2.8) [50.6]	36 (5.0) [88.2]	31 (4.3) [78.2]	28 (3.9) [70.6]
Ischaemic heart disease	10 (1.9) [36.3]	5 (0.7) [12.7]	11 (1.5) [26.9]	10 (1.4) [25.2]	7 (1.0) [17.7]
Myocardial infarction	2 (0.4) [7.3]	4 (0.6) [10.1]	5 (0.7) [12.2]	5 (0.7) [12.6]	4 (0.6) [10.1]
Other ischaemic heart disease	8 (1.5) [29.0]	2 (0.3) [5.1]	8 (1.1) [19.6]	6 (0.8) [15.1]	4 (0.6) [10.1]
Supraventricular tachyarrhythmias	8 (1.5) [29.0]	5 (0.7) [12.7]	15 (2.1) [36.7]	7 (1.0) [17.7]	7 (1.0) [17.7]
Cardiac failure	2 (0.4) [7.3]	1 (0.1) [2.5]	4 (0.6) [9.8]	5 (0.7) [12.6]	4 (0.6) [10.1]
Bradycardia	1 (0.2) [3.6]	0	0	4 (0.6) [10.1]	0
Conduction defects	3 (0.6) [10.9]	11 (1.5) [27.9]	8 (1.1) [19.6]	8 (1.1) [20.2]	12 (1.7) [30.3]

The majority of patients (all patients and those aged at least 65 years) who experienced cardiac events had a medical history of cardiovascular risk factors.

The incidence of cardiac events of severe intensity was low (0.7% to 1.3%) across treatment groups and was mainly due to myocardial infarction events, which were similarly distributed across the treatment groups. The proportion of patients with severe events in the aclidinium/formoterol 400/12 µg group

(0.7%) was lower than for placebo (1.1%) and was similar to placebo for aclidinium/formoterol 400/6 µg (1.3%). Similarly, the proportion of patients with cardiac events that were SAEs with aclidinium/formoterol 400/12 µg (0.6%) was lower than for placebo (1.7%) and was similar to placebo for aclidinium/formoterol 400/6 µg (1.7%). There were no notable differences between treatment groups in the incidence of specific severe or serious cardiac events.

Conduction defects

Conduction defects were reported at a higher incidence (RR for events >1.5) for aclidinium/formoterol 400/12 µg than for placebo although the incidence was similar to that seen with formoterol monotherapy. The frequency was lower for aclidinium/formoterol 400/6 µg (1.1%). Atrioventricular block first degree, bundle branch block left and electrocardiogram QT prolonged were reported more frequently with aclidinium/formoterol 400/12 µg than for placebo but at a similar incidence to aclidinium or formoterol monotherapies. No conduction defects were of severe intensity.

Table 46: Conduction defects reported as treatment-emergent adverse events: Placebo-controlled Phase III Study Population

Conduction defects	Placebo N = 526 ET = 275.6 n (%) [inc]	AB/FF 400/12 µg N = 720 ET = 394.9 n (%) [inc]	AB/FF 400/6 µg N = 714 ET = 408.4 n (%) [inc]	AB 400 µg N = 722 ET = 396.4 n (%) [inc]	FF 12 µg N= 716 ET = 396.6 n (%) [inc]
Any conduction defect	3 (0.6) [10.9]	11 (1.5) [27.9]	8 (1.1) [19.6]	8 (1.1) [20.2]	12 (1.7) [30.3]
Atrioventricular block first degree	1 (0.2) [3.6]	4 (0.6) [10.1]	1 (0.1) [2.4]	1 (0.1) [2.5]	4 (0.6) [10.1]
Bundle branch block left	1 (0.2) [3.6]	4 (0.6) [10.1]	1 (0.1) [2.4]	2 (0.3) [5.0]	3 (0.4) [7.6]
Electrocardiogram QT prolonged	0	3 (0.4) [7.6]	4 (0.6) [9.8]	3 (0.4) [7.6]	1 (0.1) [2.5]
Atrioventricular block second degree	0	0	0	1 (0.1) [2.5]	1 (0.1) [2.5]
Bundle branch block right	0	0	2 (0.3) [4.9]	2 (0.3) [5.0]	1 (0.1) [2.5]
Conduction disorder	1 (0.2) [3.6]	0	0	0	2 (0.3) [5.0]

Cerebrovascular events

The narrow search SMQs of haemorrhagic cerebrovascular conditions and of ischaemic cerebrovascular conditions were combined to analyse cerebrovascular events.

Table 47: Cerebrovascular events reported as treatment-emergent adverse events: Placebo-controlled Phase III Study Population

	Placebo N = 526 ET = 275.6 n (%) [inc]	AB/FF 400/12 µg N = 720 ET = 394.9 n (%) [inc]	AB/FF 400/6 µg N = 714 ET = 408.4 n (%) [inc]	AB 400 µg N = 722 ET = 396.4 n (%) [inc]	FF 12 µg N= 716 ET = 396.6 n (%) [inc]
Any cerebrovascular event[1]	3 (0.6) [10.9]	2 (0.3) [5.1]	5 (0.7) [12.2]	4 (0.6) [10.1]	1 (0.1) [2.5]

In the Placebo-controlled Phase III Study Population, the number of patients with cerebrovascular events was <1% in all treatment groups and there were no notable differences between treatments. The majority of the cerebrovascular events reported were seen in LAC-MD-31/LAC-MD-36, likely reflecting the longer treatment duration (52 weeks) in those studies than in M/40464/30 (24 weeks).

Lower respiratory tract and pneumonia events

Adverse events related to lower respiratory tract infections, including pneumonia (LRTI: includes the MedDRA HLT of lower respiratory tract and lung infections and additional PTs that include the word 'pneumonia') were analysed. It should be noted that the clinical development programme did not require that diagnoses of pneumonia be confirmed by chest radiograph, and that the overall category of lower respiratory tract infection and pneumonia includes both pneumonia events as well as other types of pulmonary infections such as bronchitis.

Table 48: Treatment-emergent and serious treatment-emergent adverse events of LRTI: Placebo-controlled Phase III Study Population

	Placebo N = 526 ET = 275.6 n (%) [inc]	AB/FF 400/12 µg N = 720 ET = 394.9 n (%) [inc]	AB/FF 400/6 µg N = 714 ET = 408.4 n (%) [inc]	AB 400 µg N = 722 ET = 396.4 n (%) [inc]	FF 12 µg N= 716 ET = 396.6 n (%) [inc]
Any event of LRTI	17 (3.2) [61.7]	17 (2.4) [43.1]	25 (3.5) [61.2]	22 (3.0) [55.5]	21 (2.9) [53.0]
Any pneumonia event	6 (1.1) [21.8]	12 (1.7) [30.4]	15 (2.1) [36.7]	6 (0.8) [15.1]	9 (1.3) [22.7]
Any LRTI SAE	4 (0.8) [14.5]	6 (0.8) [15.2]	9 (1.3) [22.0]	4 (0.6) [10.1]	4 (0.6) [10.1]
Any pneumonia SAE	4 (0.8) [14.5]	6 (0.8) [15.2]	9 (1.3) [22.0]	4 (0.6) [10.1]	4 (0.6) [10.1]

Includes data from studies M/40464/30, LAC-MD-31 and LAC-MD-36. Patients who participated in LAC-MD-31 and LAC-MD-36 are counted only once.
LRTI includes all events within the MedDRA high level term of 'lower respiratory tract and lung infections' and additional preferred terms that include the word pneumonia (including pneumonia aspiration, pneumonia pseudomonas aeruginosa, and pneumonia viral).
Any preferred term that includes the word pneumonia is included in the 'any pneumonia event' category.

The frequency of LRTI was lower with aclidinium/formoterol 400/12 µg (2.4%) than with placebo (3.2%). The frequency for aclidinium/formoterol 400/6 µg was similar to that seen with placebo (3.5%). The incidence of LRTI that were SAEs was low and similar for aclidinium/formoterol 400/12 µg and placebo.

Table 49: Treatment-emergent and serious treatment-emergent adverse events of LRTI: All Phase III Study Population

	Placebo N = 526 ET = 275.6 n (%) [inc]	AB/FF 400/12 µg N = 1111 ET = 706.5 n (%) [inc]	AB/FF 400/6 µg N = 714 ET = 408.4 n (%) [inc]	AB 400 µg N = 721 ET = 396.3 n (%) [inc]	FF 12 µg N= 914 ET = 553.3 n (%) [inc]
Any event of LRTI	17 (3.2) [61.7]	34 (3.1) [48.1]	25 (3.5) [61.2]	22 (3.1) [55.5]	27 (3.0) [48.8]
Any pneumonia event	6 (1.1) [21.8]	24 (2.2) [34.0]	15 (2.1) [36.7]	6 (0.8) [15.1]	12 (1.3) [21.7]
Any LRTI SAE	4 (0.8) [14.5]	11 (1.0) [15.6]	9 (1.3) [22.0]	4 (0.6) [10.1]	5 (0.5) [9.0]
Any pneumonia SAE	4 (0.8) [14.5]	11 (1.0) [15.6]	9 (1.3) [22.0]	4 (0.6) [10.1]	5 (0.5) [9.0]

Includes data from studies M/40464/30, LAC-MD-31, LAC-MD-36 and LAC-MD-32. Patients who participated in LAC-MD-31 and LAC-MD-36 are counted only once.
LRTI includes all events within the MedDRA high level term of 'lower respiratory tract and lung infections' and additional preferred terms that include the word pneumonia (including pneumonia aspiration, pneumonia pseudomonas aeruginosa, and pneumonia viral).
Any preferred term that includes the word pneumonia is included in the 'any pneumonia event' category.

Anticholinergic adverse events

To investigate potential anticholinergic AEs, the SMQ for anticholinergic syndrome (MedDRA version 16.0) together with additional MedDRA PTs of sinus tachycardia, supraventricular tachycardia, ventricular tachycardia, heart rate increased, palpitations, angle closure glaucoma, glaucoma, intraocular pressure increased, intraocular pressure test abnormal, papillary reflex impaired, pupils unequal, visual disturbance, blindness transient, constipation, gastrointestinal obstruction, ileus paralytic, urinary tract infection, cystitis, urinary incontinence, incontinence, dysuria, urge incontinence, urine flow decreased, bladder irritation, oropharyngeal pain, dysphonia, laryngitis, pharyngitis, and throat irritation were analysed. There is some overlap in the potential anticholinergic TEAEs and potential β2-agonist TEAEs. Potential anticholinergic TEAEs that were also potential β2-agonist TEAEs included sinus tachycardia, tachycardia, ventricular tachycardia, supraventricular tachycardia, heart rate increased, palpitations, urinary tract infection, urinary retention, dizziness, constipation, vision blurred, throat irritation and mydriasis.

Table 50: Anticholinergic treatment-emergent adverse events reported by more than 1 patient in any treatment group, by preferred term: Placebo-controlled Phase III Study Population

Preferred term	Placebo N = 526 ET = 275.6 n (%) [inc]	AB/FF 400/12 µg N = 720 ET = 394.9 n (%) [inc]	AB/FF 400/6 µg N = 714 ET = 408.4 n (%) [inc]	AB 400 µg N = 722 ET = 396.4 n (%) [inc]	FF 12 µg N= 716 ET = 396.6 n (%) [inc]
Cardiac disorders					
Sinus tachycardia	0	4 (0.6) [10.1]	5 (0.7) [12.2]	2 (0.3) [5.0]	0
Tachycardia	0	4 (0.6) [10.1]	4 (0.6) [9.8]	7 (1.0) [17.7]	1 (0.1) [2.5]
Palpitations	1 (0.2) [3.6]	1 (0.1) [2.5]	2 (0.3) [4.9]	3 (0.4) [7.6]	4 (0.6) [10.1]
Eye disorders					
Vision blurred	0	4 (0.6) [10.1]	0	1 (0.1) [2.5]	6 (0.8) [15.1]
Dry eye	0	1 (0.1) [2.5]	1 (0.1) [2.4]	1 (0.1) [2.5]	3 (0.4) [7.6]
Glaucoma	0	0	0	1 (0.1) [2.5]	2 (0.3) [5.0]
Gastrointestinal disorders					
Dry mouth	2 (0.4) [7.3]	13 (1.8) [32.9]	7 (1.0) [17.1]	6 (0.8) [15.1]	6 (0.8) [15.1]
Constipation	7 (1.3) [25.4]	6 (0.8) [15.2]	11 (1.5) [26.9]	15 (2.1) [37.8]	9 (1.3) [22.7]
Dysphagia	0	1 (0.1) [2.5]	2 (0.3) [4.9]	1 (0.1) [2.5]	1 (0.1) [2.5]
General disorders and administration site conditions					
Pyrexia	3 (0.6) [10.9]	4 (0.6) [10.1]	5 (0.7) [12.2]	6 (0.8) [15.1]	8 (1.1) [20.2]
Infections and infestations					
Urinary tract infection	19 (3.6) [68.9]	30 (4.2) [76.0]	25 (3.5) [61.2]	22 (3.0) [55.5]	21 (2.9) [53.0]
Laryngitis	1 (0.2) [3.6]	3 (0.4) [7.6]	0	2 (0.3) [5.0]	2 (0.3) [5.0]
Cystitis	2 (0.4) [7.3]	2 (0.3) [5.1]	5 (0.7) [12.2]	3 (0.4) [7.6]	0
Pharyngitis	2 (0.4) [7.3]	2 (0.3) [5.1]	3 (0.4) [7.3]	6 (0.8) [15.1]	9 (1.3) [22.7]
Investigations					
Heart rate increased	0	2 (0.3) [5.1]	0	0	0
Nervous system disorders					
Dizziness	8 (1.5) [29.0]	15 (2.1) [38.0]	14 (2.0) [34.3]	7 (1.0) [17.7]	15 (2.1) [37.8]
Renal and urinary disorders					
Urinary retention	0	3 (0.4) [7.6]	0	1 (0.1) [2.5]	2 (0.3) [5.0]
Dysuria	1 (0.2) [3.6]	1 (0.1) [2.5]	3 (0.4) [7.3]	1 (0.1) [2.5]	1 (0.1) [2.5]
Respiratory, thoracic and mediastinal disorders					
Oropharyngeal pain	12 (2.3) [43.5]	21 (2.9 [53.2]	10 (1.4) [24.5]	12 (1.7) [30.3]	11 (1.5) [27.7]
Dysphonia	0	4 (0.6) [10.1]	6 (0.8) [14.7]	4 (0.6) [10.1]	3 (0.4) [7.6]
Throat irritation	1 (0.2) [3.6]	2 (0.3) [5.1]	6 (0.8) [14.7]	1 (0.1) [2.5]	1 (0.1) [2.5]

Includes data from studies M/40464/30, LAC-MD-31 and LAC-MD-36. Patients who participated in LAC-MD-31 and LAC-MD-36 are counted only once.
Only events reported by more than 1 patient in any treatment group are included in this table.
AB = aclidinium bromide; AB/FF = aclidinium/formoterol; ET = total exposure time in years; FF = formoterol fumarate; inc = number of patients per 1000 patient-years of exposure; N = number of patients in safety population; n = number of patients in the specified category.

Few possible anticholinergic TEAEs were of severe intensity. In the All Phase III Study Population only 11 patients reported possible anticholinergic TEAEs that were SAEs; 4 patients in the aclidinium/formoterol 400/12 µg group (ventricular tachycardia, constipation, urinary tract infection [2 patients] and ataxia), 1 patient in the aclidinium/formoterol 400/6 µg group (constipation), 1 patient in the aclidinium group

(palpitations) and 5 patients in the formoterol group (vision blurred, urinary tract infection [2 patients], dizziness and urinary retention).

β2-agonist adverse events

To investigate potential β2-agonist AEs the following SMQs and other terms were tabulated: hypertension (narrow search SMQ), hyperglycaemia/ new onset diabetes mellitus (narrow search SMQ), tachyarrhythmias (including supraventricular and ventricular tachyarrhythmias) (broad search SMQ), together with the HLT tremor and specific PTs for tachycardia, heart rate increase, palpitations, insomnia, vision blurred, mydriasis, nervousness, anxiety, headache, dizziness, dysgeusia, cough, throat irritation, myalgia, urinary retention, urinary tract infection, constipation, muscle spasm, hypokalaemia, oedema peripheral, electrocardiogram QT interval abnormal, and electrocardiogram QT prolonged.

Table 51: β2-agonist treatment-emergent adverse events reported by more than 1 patient in any treatment group, by preferred term, high level term and SMQ: Placebo-controlled Phase III Study Population

	Placebo N = 526 ET = 275.6 n (%) [inc]	AB/FF 400/12 µg N = 720 ET = 394.9 n (%) [inc]	AB/FF 400/6 µg N = 714 ET = 408.4 n (%) [inc]	AB 400 µg N = 722 ET = 396.4 n (%) [inc]	FF 12 µg N= 716 ET = 396.6 n (%) [inc]
Hypertension SMQ	15 (2.9) [54.4]	13 (1.8) [32.9]	18 (2.5) [44.1]	18 (2.5) [45.4]	24 (3.4) [60.5]
Hyperglycaemia/ new onset diabetes mellitus SMQ	4 (0.8) [14.5]	4 (0.6) [10.1]	12 (1.7) [29.4]	8 (1.1) [20.2]	12 (1.7) [30.3]
Tachyarrhythmia terms, broad SMQ	10 (1.9) [36.3]	19 (2.6) [48.1]	28 (3.9) [68.6]	21 (2.9) [53.0]	15 (2.1) [37.8]
Tremor (excl congenital) HLT	2 (0.4) [7.3]	8 (1.1) [20.3]	3 (0.4) [7.3]	5 (0.7) [12.6]	8 (1.1) [20.2]
Headache	29 (5.5) [105.2]	49 (6.8) [124.1]	42 (5.9) [102.9]	50 (6.9) [126.1]	56 (7.8) [141.2]
Urinary tract infection	19 (3.6) [68.9]	30 (4.2) [76.0]	25 (3.5) [61.2]	22 (3.0) [55.5]	21 (2.9) [53.0]
Cough	17 (3.2) [61.7]	25 (3.5) [63.3]	21 (2.9) [51.4]	23 (3.2) [58.0]	18 (2.5) [45.4]
Dizziness	8 (1.5) [29.0]	15 (2.1) [38.0]	14 (2.0) [34.3]	7 (1.0) [17.7]	15 (2.1) [37.8]
Muscle spasms	6 (1.1) [21.8]	15 (2.1) [38.0]	8 (1.1) [19.6]	5 (0.7) [12.6]	13 (1.8) [32.8]
Insomnia	5 (1.0) [18.1]	11 (1.5) [27.9]	9 (1.3) [22.0]	5 (0.7) [12.6]	16 (2.2) [40.3]
Oedema peripheral	8 (1.5) [29.0]	11 (1.5) [27.9]	10 (1.4) [24.5]	8 (1.1) [20.2]	6 (0.8) [15.1]
Anxiety	1 (0.2) [3.6]	6 (0.8) [15.2]	13 (1.8) [31.8]	9 (1.2) [22.7]	9 (1.3) [22.7]
Constipation	7 (1.3) [25.4]	6 (0.8) [15.2]	11 (1.5) [26.9]	15 (2.1) [37.8]	9 (1.3) [22.7]
Hypokalaemia	2 (0.4) [7.3]	4 (0.6) [10.1]	0	2 (0.3) [5.0]	7 (1.0) [17.7]
Myalgia	8 (1.5) [29.0]	4 (0.6) [10.1]	6 (0.8) [14.7]	6 (0.8) [15.1]	8 (1.1) [20.2]
Vision blurred	0	4 (0.6) [10.1]	0	1 (0.1) [2.5]	6 (0.8) [15.1]
Electrocardiogram QT prolonged	0	3 (0.4) [7.6]	4 (0.6) [9.8]	3 (0.4) [7.6]	1 (0.1) [2.5]
Urinary retention	0	3 (0.4) [7.6]	0	1 (0.1) [2.5]	2 (0.3) [5.0]
Dysgeusia	1 (0.2) [3.6]	2 (0.3) [5.1]	4 (0.6) [9.8]	2 (0.3) [5.0]	0
Throat irritation	1 (0.2) [3.6]	2 (0.3) [5.1]	6 (0.8) [14.7]	1 (0.1) [2.5]	1 (0.1) [2.5]

Includes data from studies M/40464/30, LAC-MD-31 and LAC-MD-36. Patients who participated in LAC-MD-31 and LAC-MD-36 are counted only once.
Only events reported by more than 1 patient in any treatment group are included in this table.

AB = aclidinium bromide; AB/FF = aclidinium/formoterol; ET = total exposure time in years; FF = formoterol fumarate; HLT = high level term; inc = number of patients per 1000 patient-years of exposure; N = number of patients in safety population; n = number of patients in the specified category; SMQ = standard MedDRA query.

Few possible β2-agonist TEAEs were of severe intensity and there were no important differences between the treatment groups. The incidence of possible β2-agonist TEAEs that were SAEs was also low.

Laboratory findings

Haematological data did not reveal any clinically relevant mean changes from baseline to end-of-study for any parameter in any treatment group.

Mean changes from baseline to end-of-study for the chemistry parameters also showed no relevant changes or dose dependence in any treatment arm with the exception of creatinine kinase which showed changes in treatment groups that contained formoterol. At end-of-study there was a small decrease in creatinine kinase in the placebo and aclidinium groups compared with an increase in the aclidinium/formoterol and formoterol groups. Results for aclidinium/formoterol were similar to those seen with formoterol monotherapy.

Only small mean changes were observed in potassium and glucose determinations at all time points assessed and changes were similar across the treatment groups

TEAEs

Only 2 patients reported TEAEs associated with notable haematology abnormalities, 1 patient treated with aclidinium/formoterol 400/12 µg and 1 patient treated with formoterol. Both patients had a notable abnormality of decreased platelet count. Patient 188331004 treated with aclidinium/formoterol 400/12 µg experienced mild thrombocytopenia unrelated to study treatment. This patient subsequently developed severe anaemia and severe pancytopenia unrelated to study treatment; the pancytopenia led to permanent premature treatment discontinuation. The patient died 45 days after discontinuing study treatment due to respiratory failure unrelated to study treatment; as this death occurred more than 30 days after study drug discontinuation it was considered to be non-treatment-emergent.

Patient 1775.04, treated with formoterol, experienced a severe gastric ulcer haemorrhage that was not considered by the investigator to be related to study treatment.

Very few patients reported TEAEs associated with notable blood chemistry abnormalities. Increased GGT was the notable abnormality most commonly reported as a TEAE at the end-of-study. This was the only notable abnormality with associated TEAEs reported by more than 2 patients in any treatment group. It was reported for 4 patients in the aclidinium/formoterol 400/12 µg group (associated TEAEs: gamma glutamyl transferase increased [3 patients], liver function abnormal [1 patient]), 4 patients in the aclidinium/formoterol 400/6 µg group (associated TEAEs: gamma-glutamyl transferase increased [2 patients], hepatic enzymes increased and cholelithiasis [1 patient], myocardial infarction [1 patient]), 2 patients in the aclidinium group (associated TEAEs: oesophageal adenocarcinoma [1 patient], hepatitis toxic [1 patient]) and 2 patients in the formoterol group (associated TEAEs: autoimmune hepatitis [1 patient], alcohol poisoning [1 patient]). All these TEAEs were mild or moderate in severity with the exception of myocardial infarction in 1 patient in the aclidinium/formoterol 400/6 µg group, oesophageal adenocarcinoma in 1 patient in the aclidinium group and alcohol poisoning in 1 patient in the formoterol group. None were considered by the investigator to be related to study treatment.

In the All Phase II Study Population results for blood chemistry notable abnormalities were very similar to those for the Placebo-controlled Phase III Population. One (1) additional patient (145032010) treated with formoterol had a notable abnormality in platelets and TEAEs of severe anaemia and severe

gastrointestinal haemorrhage were reported. These TEAEs were not considered by the investigator to be related to study treatment.

Only 1 additional patient with a clinically significant notable abnormality at end-of study had a related TEAE reported: patient 158832006 treated with formoterol had notable abnormalities in ALT and AST, and hepatic enzyme increased was reported as a TEAE. The TEAE was considered to be of moderate severity and was not considered by the investigator to be related to study treatment. ALT increased from 22 U/L at baseline to 130 U/L and AST increased from 33 U/L at baseline to 177 U/L

Electrocardiographic values

In each Phase III study, ECGs were reviewed at a centralised cardiology assessment vendor (eRT) in a blinded standardised manner by a cardiac safety technician and a cardiologist. However, only the investigator determined if an ECG abnormality was or was not clinically relevant. If it was clinically relevant, then an AE form should have been completed.

For the Placebo-controlled Phase III Study Population, baseline ECG values, including QTcF, QRS, PR and RR interval and heart rate were similar across treatment groups. In addition, mean changes from baseline showed no relevant between-group differences

Table 52: Mean (SD) changes from baseline to end-of-study post dose for electrocardiographic values: Placebo-controlled Phase III Study Population

ECG Parameter	Placebo N = 526	AB/FF 400/12 µg N = 720	AB/FF 400/6 µg N = 714	AB 400 µg N = 722	FF 12 µg N= 716
QTcF, msec	1.33 (18.14)	3.21 (18.82)	2.45 (17.71)	1.96 (18.23)	2.48 (17.20)
QRS, msec	1.48 (8.44)	1.51 (8.03)	1.34 (8.62)	1.70 (7.98)	1.32 (8.34)
PR, msec	0.12 (14.29)	0.29 (14.04)	0.69 (14.63)	0.88 (14.17)	-0.15 (15.71)
Heart rate, bpm	-1.39 (11.34)	-1.03 (11.78)	-1.10 (11.40)	-2.08 (11.32)	-0.02 (11.33)
RR, msec	19.50 (139.09)	13.34 (135.59)	14.97 (133.28)	29.28 (135.16)	3.45 (126.98)

Includes data from studies M/40464/30, LAC-MD-31 and LAC-MD-36. Patients who participated in LAC-MD-31 and LAC-MD-36 are counted only once.
Mean change at end-of-study is based on the ECG performed 2 hours post dose.
AB = aclidinium bromide; AB/FF = aclidinium/formoterol; bpm = beats per minute; FF = formoterol fumarate; N = number of patients; SD = standard deviation.

Similar to the Placebo-controlled Phase III Study Population, in the All Phase III Study Population there were no evident baseline differences and changes from baseline were numerically small and similar across treatment groups.

Table 53: Number (%) of patients with potentially clinically significant 12-lead electrocardiogram values at end-of-study: Placebo-controlled Phase III Study Population

ECG Parameter	PCS Criteria	Placebo N =526 n/n1 (%)	AB/FF 400/12 µg N = 720 n/n1 (%)	AB/FF 400/6 µg N = 714 n/n1 (%)	AB 400 µg N = 722 n/n1 (%)	FF 12 µg N = 716 n/n1 (%)
Criterion 1						
QTcF interval, msec	>480 msec	4/525 (0.8)	8/720 (1.1)	11/713 (1.5)	8/720 (1.1)	13/716 (1.8)
	Increase >30 msec	87/525 (16.6)	146/720 (20.3)	147/713 (20.6)	144/720 (20.0)	140/716 (19.6)
QRS interval, msec	≥100 msec and increase ≥ 25%	15/525 (2.9)	24/720 (3.3)	22/713 (3.1)	21/720 (2.9)	20/716 (2.8)
PR interval, msec	≥200 msec and increase ≥25%	7/518 (1.4)	11/715 (1.5)	6/702 (0.9)	9/707 (1.3)	15/708 (2.1)
Tachycardia event, bpm	≥110 bpm and increase ≥15%	4/525 (0.8)	11/720 (1.5)	10/713 (1.4)	11/720 (1.5)	10/716 (1.4)
Bradycardia event, bpm	≤50 bpm and decrease ≥15%	39/525 (7.4)	30/720 (4.2)	45/713 (6.3)	48/720 (6.7)	39/716 (5.5)
Criterion 2						
QTcF interval, msec	>500 msec	1/525 (0.2)	3/720 (0.4)	2/713 (0.3)	3/720 (0.4)	1/716 (0.1)
	Increase >60 msec from baseline	2/525 (0.4)	11/720 (1.5)	4/713 (0.6)	8/720 (1.1)	6/716 (0.8)
QRS interval, msec	≥150 msec if baseline <150 msec	10/525 (1.9)	13/720 (1.8)	15/713 (2.1)	13/720 (1.8)	14/716 (2.0)
PR interval, msec	≥250 msec if baseline <250 msec	4/518 (0.8)	5/715 (0.7)	7/702 (1.0)	9/707 (1.3)	13/708 (1.8)
Tachycardia event, bpm	≥120 if baseline <120 bpm	1/525 (0.2)	5/720 (0.7)	2/713 (0.3)	1/720 (0.1)	4/716 (0.6)
Bradycardia event, bpm	≤40 bpm if baseline >40 bpm	1/525 (0.2)	4/720 (0.6)	0	3/720 (0.4)	1/716 (0.1)

Includes data from studies M/40464/30, LAC-MD-31 and LAC-MD-36. Patients who participated in LAC-MD-31 and LAC-MD-36 are counted only once.
AB = aclidinium bromide; AB/FF = aclidinium/formoterol; bpm = beats per minute; ECG = electrocardiogram; FF = formoterol fumarate; N = number of patients in safety population; n = number of patients with abnormality; n1 = number of patients with baseline and post-baseline assessments; PCS = potentially clinically significant; QTcF = QT interval corrected for heart rate using the Fridericia formula (QTcF = QT/(RR)⅓).

Safety in special populations

Intrinsic factors

To investigate the effect of various intrinsic and extrinsic factors on the safety of aclidinium/formoterol, a number of subgroup analyses have been performed for the Placebo-controlled Phase III Study Population and the All Phase III Study Population:

- Age: <65 years, ≥ 65 to <75 years, ≥ 75 to <85 years and ≥ 85 years
- Gender: male and female
- Race: Caucasian (White), non-Caucasian (Black, Asian and Other)
- Body Mass Index (BMI): Underweight to normal weight (BMI <25 kg/m2), pre-obese (BMI ≥ 25 kg/m2 to <30 kg/m2) and obese (BMI ≥ 30 kg/m2)
- COPD severity: mild/moderate and severe/very severe. Severity was defined as follows: for all stages FEV1/FVC <0.70 and for Stage I (mild): FEV1 ≥ 80% predicted; Stage II (moderate): FEV1 ≥ 50% to < 80% predicted; Stage III (severe): FEV1 ≥ 30% to <50% predicted; Stage IV (very severe): FEV1 < 30% predicted.
- Smoking status: current and ex-smoker

As expected, the incidence of TEAEs increased with increasing age of the population, but in all age categories the incidence of patients with any TEAE for patients treated with aclidinium/formoterol was similar to the incidence for placebo, as observed for the overall study population. Although the incidence of TEAEs was higher in female patients compared to males, within each subgroup, the incidence of patients with any TEAE for patients treated with aclidinium/formoterol was similar to the incidence for placebo. For Caucasian and non-Caucasian patients, BMI subgroups and subgroups based on COPD severity the incidence of patients with any TEAE for patients treated with aclidinium/formoterol was similar to, or lower than, the incidence for placebo.

The proportion of patients with SAEs was similar for aclidinium/formoterol 400/12 µg and placebo in all subgroups with the exception of patients who were underweight to normal weight and patients with mild/moderate COPD where a higher proportion of patients reported SAEs with aclidinium/formoterol 400/12 µg. Also, in non-Caucasians, pre-obese patients, obese patients and patients with severe/very severe COPD a higher proportion of patients reported SAEs with placebo than with aclidinium/formoterol 400/12 µg.

For aclidinium/formoterol 400/6 µg, the proportion of patients reporting SAEs was also generally similar to placebo with the exception of patients aged 75 to <85 years of age, non-Caucasians, patients who were under weight to normal weight and patients with severe/very severe COPD where more patients treated with aclidinium/formoterol 400/6 µg reported SAEs and obese patients where more patients reported SAEs with placebo.

Pre-existing disease

To investigate potential drug-disease interactions, subgroups based on any pre-existing disease reported in at least 20% of the population were defined for the Placebo-controlled Phase III Study Population and All Phase III Study Population. Based on this criterion, subgroups were defined for patients with and without the MedDRA high level terms (HLTs) of “Gastrointestinal atonic and hypomotility disorders” and “Vascular hypertensive disorders” for both the Placebo-controlled Phase III Study Population and All Phase III Study Population and for “Osteoarthropathies” for the All Phase III Study Population only. Adverse event data for patients with and without each pre-existing disease are presented.

Within each subgroup, the incidence of patients with any TEAE for patients treated with aclidinium/formoterol was similar to, or lower than, the incidence for placebo for the Placebo-controlled Phase III Study Population. In each of the subgroups, the overall distribution of TEAEs was generally similar to that observed for the overall population. For the most commonly reported TEAEs by PT (COPD exacerbation, nasopharyngitis and headache), the comparisons of aclidinium/formoterol with placebo in each subgroup were generally similar to those seen for the overall population with the following exceptions:

- In the subgroup with gastrointestinal atonic and hypomotility disorders, COPD exacerbations were reported more commonly in the aclidinium/formoterol groups (487.3 and 483.7 patients per 1000 patient-years for 400/12 µg and 400/6 µg, respectively) than in the placebo group (459.9 patients per 1000 patient-years) rather than more commonly in the placebo group. The incidences for aclidinium and formoterol monotherapies in this subgroup were 376.4 and 455.8, respectively).
- In the subgroup without vascular hypertensive disorders, headache was reported more commonly in the aclidinium/formoterol 400/12 group (180.2 patients per 1000 patient-years) than in the placebo group (136.4 patients per 1000 patient-years) rather than at a similar

incidence but the incidence was similar to that seen in the formoterol group (192.5 patients per 1000 patient-years).

Results for the All Phase III Study Population were generally similar to those for the Placebo-controlled Phase III Study Population. In this population pre-existing osteoarthropathies (which include the PTs osteoarthritis and spinal osteoarthritis) were reported in at least 20% of patients overall.

For patients with osteoarthropathies, the TEAE incidences were 1127 and 1159 patients per 1000 patient-years for aclidinium/formoterol 400/12 µg and 400/6 µg, respectively compared with 1317 patients per 1000 patient-years for placebo. For patients without osteoarthropathies, the TEAE incidences were 1047 and 1063 patients per 1000 patient-years for aclidinium/formoterol 400/12 µg and 400/6 µg, respectively compared with 1151 patients per 1000 patient-years for placebo.

Safety related to drug-drug interactions and other interactions

To investigate potential drug-drug interactions, subgroups based on concomitant medication use (concomitant medications used before and continued after the first dose of investigational product) were defined to examine AE data in patients who were or were not using the specified medications for the Placebo-controlled Phase III Study Population and All Phase III Study Population.

Subgroups were defined for short-acting β2-agonist use, xanthine use, inhaled corticosteroid use and use of drugs known to prolong the QTc interval (i.e., monoamine oxidase inhibitors [MAOIs], tricyclic antidepressants, macrolides, antihistamines, phenothiazines and class Ia antiarrhythmics).

Short-acting β2-agonists, xanthines and inhaled corticosteroids were examined as these were COPD medications that patients were allowed to use concomitantly during the studies. Drugs known to prolong the QT interval corrected for heart rate (QTc) interval are described in the prescribing information for formoterol as having the potential to potentiate the action of adrenergic agonists on the cardiovascular system.

In addition, subgroups were defined for any concomitant medication used by at least 20% of the study population. Based on this criterion, additional subgroups were defined for patients using or not using antithrombotic agents, angiotensin-converting-enzyme (ACE) inhibitors, plain and lipid modifying agents, plain.

In all subgroups the incidences of TEAEs with both doses of aclidinium/formoterol were similar to or lower than the incidence of TEAEs with placebo with the exception of patients using antithrombotic agents where the incidence was higher for patients taking aclidinium/formoterol 400/12 µg than for placebo (incidence of 1181 patients per 1000 patient-years compared with 1151 patients per 1000 patient-years for placebo). In this subgroup the incidence of nasopharyngitis was higher for aclidinium/formoterol 400/12 µg than for placebo (137.7 patients per 1000 patient-years compared with 79.0 patients per 1000 patient-years. There were no appreciable differences between treatments for other commonly reported TEAEs.

In patients using drugs known to prolong QTc, the incidence of cardiac disorders (including TEAEs reported as part of the ECG investigations HLT) was lower for both aclidinium/formoterol 400/12 µg (108.3 patients per 1000 patient-years) and 400/6 µg (121.3 patients per 1000 patient-years) than for placebo (197.8 patients per 1000 patient-years). There were no reports of ECG QT prolonged in patients treated with aclidinium/formoterol (either dose) and concomitantly using drugs known to prolong QTc.

Discontinuation due to adverse events

The incidence of permanent treatment discontinuation due to TEAEs was low (6.8% overall) in the Placebo-controlled Phase III Study Population. The proportion of patients with TEAEs leading to

permanent treatment discontinuation was higher in the placebo group (8.4%) than in any active treatment group (5.7% to 7.2%). By SOC, TEAEs that led to permanent treatment discontinuation in more than 1% of patients in any treatment group were respiratory, thoracic and mediastinal disorders and cardiac disorders. Tremor led to treatment discontinuation for 2 patients in the aclidinium/formoterol 400/12 µg group and no patients in any other treatment group. The other TEAEs, by PT, that led to permanent treatment discontinuation of 2 patients in the aclidinium/formoterol 400/12 µg group were death, acute myocardial infarction (also reported as the TEAE leading to discontinuation for 1patient in each of the other treatment groups) and pneumonia (also reported as the TEAE leading to discontinuation for 1 patient in the each of the placebo, aclidinium/formoterol 400/6 µg and formoterol groups); the episodes of acute myocardial infarction and of pneumonia in the aclidinium/formoterol 400/12 µg group were of severe intensity.

Table 54: Treatment-emergent adverse events leading to permanent treatment discontinuation by preferred term in more than 2 patients in any treatment group: Placebo-controlled Phase III Study Population

Preferred Term	Placebo N=526 ET=275.6 n (%) [inc]	AB/FF 400/12 µg N=720 ET=394.9 n (%) [inc]	AB/FF 400/6 µg N=714 ET=408.4 n (%) [inc]	AB 400 µg N=722 ET=396.4 n (%) [inc]	FF 12 µg N=716 ET=396.6 n (%) [inc]
Any TEAE leading to treatment discontinuation	44 (8.4) [159.6]	52 (7.2) [131.7]	44 (6.2) [107.7]	49 (6.8) [123.6]	41 (5.7) [103.4]
Chronic obstructive pulmonary disease	12 (2.3) [43.5]	14 (1.9) [35.5]	7 (1.0) [17.1]	18 (2.5) [45.4]	14 (2.0) [35.3]
Electrocardiogram QT prolonged	0	3 (0.4) [7.6]	0	2 (0.3) [5.0]	0
Dyspnoea	3 (0.6) [10.9]	2 (0.3) [5.1]	3 (0.4) [7.3]	0	1 (0.1) [2.5]

Includes data from studies M/40464/30, LAC-MD-31 and LAC-MD-36. Patients who participated in both LAC-MD-31 and LAC-MD-36 are counted only once.
Table is ordered by decreasing frequency in the aclidinium/formoterol 400/12 µg group.

Similarly in the All Phase III Study Population the proportion of patients with TEAEs leading to permanent treatment discontinuation was higher in the placebo group (8.4%) than in any active treatment group (6.2% to 8.3%). By SOC, TEAEs that led to permanent treatment discontinuation in more than 1% of patients in any treatment group were respiratory, thoracic and mediastinal disorders and cardiac disorders

As in the Placebo-controlled Phase III Study Population, exacerbations of COPD were the only TEAEs leading to permanent treatment discontinuation reported by more than 1% of patients in any active treatment group and the frequency in the placebo group was similar to or higher than the incidence in either aclidinium/formoterol group or the monotherapy treatment groups. In the All Phase III Study Population, there were no additional reports of prolongation of electrocardiogram QT interval, tremor, acute myocardial infarction or pneumonia leading to the discontinuation in the aclidinium/formoterol 400/12 µg group. Ventricular tachycardia leading to permanent treatment discontinuation was reported for 3 patients (0.3%) treated with aclidinium/formoterol 400/12 µg and no patients in any other treatment group. The ventricular tachycardia was resolved for all patients. Overall these data provide no evidence for any difference in safety of aclidinium/formoterol based on concomitant medication administration.

Post marketing experience

Aclidinium/formoterol is not currently available in any country and thus there are no post-marketing data available for the FDC product. Formoterol has been commercially available since June 1990 (EU International Birth Date) and aclidinium since July 2012 and no safety concerns in patients with COPD have been identified.

Aclidinium

The post-marketing experience with aclidinium bromide is limited and the adverse events that have been reported are included in the proposed SmPC.

The total number of adverse drug reactions (ADRs) reported up to 20 July 2013 was 908 (89 serious and 819 non-serious). The reporting rate for the most frequently reported ADRs has been calculated based on the number of ADRs (n) in the population exposed (patient-years)during the 12-month period since first authorisation. In order to avoid numbers with multiple decimal digits the reporting rate is multiplied by 104.

Reporting rate: RpR=(n/patient-years)* 104

Estimated patient exposure = 69,153 patient-years

The most frequently ADRs reported (RpR >2) were cough, headache, dyspnoea, diarrhoea, nausea, dry mouth, vision blurred, dizziness and dysphonia.

Table 55: Adverse drug reactions with a reporting rate >2 per 10,000 patient-years

MedDra Preferred Term	Cumulative ADRs (n)	RpRx10*4
Cough	44	6,36
Headache	34	4,92
Dyspnoea	34	4,92
Diarrhoea	19	2,75
Nausea	19	2,75
Dry mouth	18	2,60
Vision blurred	17	2,46
Dizziness	15	2,17
Dysphonia	15	2,17

n: number of adverse drug reactions
ADR: adverse drug reactions, cumulative ADRs to 20 July 2013
RpR: Reporting rate

ADRs with RpR >1 but <2 (ordered by decreasing frequency) were palpitations, vomiting, chest discomfort, condition aggravated, pruritus, rash, tachycardia, swollen tongue, tremor, throat irritation, stomatitis, dysuria, urinary retention, dysgeusia, exacerbation of COPD and hyperhidrosis.

Seven fatal cases (6 death of unknown cause and 1 late stage COPD) have been reported. Out of these 7 fatal cases, 2 cases (1 death of unknown cause and 1 COPD) were assessed as not related by the company. In the remaining 5 fatal cases company causality was not assessable due to the lack of information. The reporters of these 5 deaths cases did not provide the causality assessment to aclidinium bromide.

No cases of MACE (non-fatal myocardial infarction, non-fatal stroke or cardiovascular death) have been reported. Only one case of transient ischaemic attack was reported.

Formoterol

Conversely post-marketing experience with formoterol fumarate dihydrate is extensive and the applicant has included the reported adverse events in the proposed SmPC.

The most frequently reported AEs described in the literature are those known to be associated with β2-agonists. The safety and tolerability profile of LABAs support their long-term use in patients with COPD. In a post-marketing surveillance study of formoterol (Foradil®), data were collected for 5777 patients aged 3 to 96 years, of whom 65% continued treatment for >12 months. The most commonly reported events, excluding those related to respiratory disease, were headache, tremor, palpitation, cramp and nausea/vomiting. It was concluded that formoterol appears to have been well tolerated by the majority of patients in this study, although the frequency of nausea/vomiting was greater than given in the SmPC.

A total of 20 studies published between January 1990 and September 2012 were reviewed that evaluated the long-term use (>24 weeks) of formoterol, salmeterol or indacaterol in patients with stable COPD. No evidence of an association between LABA treatment and increased exacerbations was seen and there were no COPD-related AEs or deaths. LABA treatment was generally associated with significant or numerical reductions in COPD exacerbations compared with placebo. Incidences of COPD-related AEs were similar for active and placebo treatments. The incidence of AEs typically associated with the ß2-agonist drug class, such as tremor and palpitations, was low (often <1% of patients) and there were no reports of increased incidence of cardiac arrhythmias. The systemic effects of ß2-adrenoreceptor stimulation, such as high glucose and potassium levels, were considered minor.

2.6.1. Discussion on clinical safety

The safety profiles of the two monotherapies have been previously well characterised and are well known. The concern in assessing the safety of the FDC aclidinium/formoterol is whether or not an additive effect is seen when the two actives are administered together in the same inhaler.

Although the deaths are small in number it is of concern that more deaths occurred in the aclidinium/formoterol 400/12 group than in any of the other groups and that four of nine deaths were sudden, unexplained and considered to be of cardiac origin. Two of the other deaths were also sudden and of unknown cause and it was not known if they were of cardiac origin.

Only one death, in the placebo group, was considered by the investigators to be associated with study medication .

There was a small increase in the percentage of patients suffering a myocardial infarction in the combination and aclidinium alone groups compared with placebo and the formoterol alone group. However as the Applicant states the numbers are too small to draw any firm conclusions from this.

Regarding conduction defects, there was a higher incidence of reports in the active groups than in the placebo group but the incidence was not greater in the combination groups than in the monotherapy groups suggesting that the reports seen reflect the effects of the monotherapies without any additive effect from combining the two actives.

There have been concerns regarding a possible association between stroke events and anticholinergics following information in several publications. The PRAC has reviewed these and concluded that no regulatory action is required but stroke events with inhaled anticholinergics should continue to be closely monitored in the literature and via signal detection activities. However the safety data from the Phase III studies in aclidinium/formoterol do not suggest an increased risk of stroke with the combination.

The incidence of cerebrovascular events was similar across the treatment groups and was, in fact, lower in the aclidinium/formoterol 400/12 µg group than in placebo. There is a very small number of reports so no firm conclusion can be drawn but there is no evidence of an accumulative effect of aclidinium and formoterol when administered together.

Cerebrovascular events have been included in the RMP as a potential risk and this is accepted.

In general the incidence of LRTI and pneumonia events was no greater in the aclidinium/formoterol groups than in the placebo and monotherapy groups; however the incidence of pneumonia was higher in the combination groups compared with placebo and the monotherapies. In the All Phase III study population the incidence in the aclidinium/formoterol 400/12 µg and formoterol 12 µg groups increased as these therapies were included in study LAC-MD-32, reflecting further reports occurring over the one-year treatment period. However the total incidence of these events remained similar across the treatment groups and similar to placebo.

As would be expected from the known pharmacology of the two actives, the incidence of anticholinergic adverse events and β2-agonist adverse events was higher in the active treatment groups than in the placebo group. However the incidence across the active treatment groups was similar and there is no evidence of an additive effect on adverse events of the two actives being administered in one combination inhaler.

For the FDC product adverse events, serious adverse events, including deaths, TEAEs leading to discontinuation and adverse events of special interest have been collected and assessed in the Placebo-controlled Phase III Study Population and the All Phase III Study Population.

In general the incidence of TEAEs were similar across the treatment groups and often lower in the proposed aclidinium/formoterol 400/12µg group than in the placebo group owing to an increased incidence of COPD exacerbations in the placebo group. Similarly SAEs were similar across the groups and no particular safety signals are seen.

Of particular concern with these actives is cardiovascular safety and more sudden unexplained deaths were reported in the aclidinium/formoterol 400/12 µg group than in the other groups. Only one death was considered by the investigators to be associated with study medication but many of the reported deaths were sudden cardiac deaths of unknown aetiology. The Applicant has provided an analysis of the on-treatment deaths during the aclidinium/formoterol Phase III programme by population and by study. By virtue of their mechanisms of action aclidinium and formoterol are known to have adverse cardiac effects, which may lead to cardiac arrhythmias including prolongation of the QTc interval and in light of the sudden cardiac deaths seen in the clinical programme strong warnings regarding cardiac effects are included in Section 4.4 of the SmPC.

The data on the incidence of LRTI and pneumonia events in the combination groups are reassuring.

The subgroup analyses have not demonstrated any particular trend towards a decreased safety profile in any subgroup with aclidinium/formoterol compared with placebo or the monotherapies.

Changes in laboratory parameters from baseline to end-of-study were generally similar across the treatment groups. There was some increase in GGT in the aclidinium-treated groups compared with placebo and formoterol alone and increases in LDH in the active treatment groups compared with placebo. Increases in GGT were reported with associated TEAEs in 4 patients in the aclidinium/formoterol 400/12 µg group, 4 patients in the aclidinium/formoterol 400/6 µg group, 2 patients in the aclidinium group and 2 patients in the formoterol group. However there was no consistent increase in other liver enzymes to suggest hepatic toxicity and no evidence of an additive effect of the combination groups compared with the monotherapies.

There was no consistent effect on blood glucose or serum potassium of the active treatment groups compared with placebo.

There was an increase in change from baseline in QTcF interval in the groups given formoterol either alone or in combination compared with the placebo and aclidinium monotherapy groups. The increases were small and not clinically significant but when the data were analysed according to the percentage of patients with a potentially clinically significant increase of >30msec there was an increase in all the active treatment groups compared with placebo. Likewise increases were seen in the active treatment groups for percentages of patients with an absolute QTcF value >480msec. Smaller percentages of patients had an increase in QTcF interval of >60msec or an absolute value of >500msec and the difference to placebo was not so consistent.

However given the concern over the effects on QTc interval of the β-agonists this is highlighted in the RMP and monitored in the proposed PASS.

The TEAEs leading to discontinuation were small in number and higher in the placebo group than the active control groups. Prolongation of QTc interval led to discontinuation in 5 patients, 3 in the aclidinium/formoterol 400/12 µg group and 2 in the aclidinium monotherapy group but none in the aclidinium/formoterol 400/6 µg group. Therefore this does not suggest an additive effect of aclidinium and formoterol on QTc prolongation.

The applicant has investigated the incidence of TEAEs in patients using and not using concomitant medication that is commonly used in this patient population. In addition the applicant has investigated the incidence of TEAEs in patients concomitantly using drugs known to prolong the QTc interval.

There are no signals from these data to suggest an adverse safety profile when aclidinium/formoterol is used concomitantly with other medication commonly used by patients with COPD.

Regarding conduction defects and in particular effects on the QTc interval, there were more reports in the active therapy groups than in the placebo group but no consistent increase in reports in the combination groups compared with the monotherapy groups. Therefore these results are reassuring that there is no additive effect of the two actives when administered together.

The data on the incidence of LRTI and pneumonia events in the combination groups are reassuring.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

From the safety data presented there are no particular safety signals that suggest an additive effect of the combination of aclidinium and formoterol when compared with the monotherapies.

Cardiac safety is of particular concern and although there is no evidence of an additive effect on conduction defects there were more deaths reported in the aclidinium/formoterol 400/12 µg group, than in the other groups. The Applicant has provided further information on these deaths and an amendment to Section 4.4 of the SmPC has been made.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The applicant has submitted a statement signed by the applicant and the qualified person for pharmacovigilance, indicating that the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country.

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

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 1.2 is acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The CHMP endorsed the Risk Management Plan version 1.2 with the following content:

Safety concerns

The applicant identified the following safety concerns in the RMP:

Table 1: Summary of the safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	1. Cardiac events (myocardial infarction, cardiac failure, cardiac arrhythmias) 2. QTc-prolongation 3. Cerebrovascular events (stroke) 4. Mortality 5. Class effects: anticholinergic and β2-agonist adverse events (tachycardia, urinary retention, acute glaucoma, hypokalaemia and hyperglycaemia) 6. Paradoxical bronchospasm 7. Hypersensitivity (anaphylactic responses, angioedema and urticaria) 8. Potential for off-label use in asthma and asthma-related events and death 9. Potential for off-label use in the paediatric 10. Medication / use of device errors
Missing information	1. Safety in patients with important concomitant diseases who were not included in clinical trials: a. Newly diagnosed or unstable arrhythmias, recent myocardial infarction, unstable angina or heart failure (NYHA Class III or IV)

	requiring recent hospitalisation b. Patient with prolonged QTc interval > 470msec c. Symptomatic BPH, urinary retention or narrow-angle glaucoma. d. Thyrotoxicosis, phaeochromocytoma 2. Safety in patients with severe renal or hepatic impairment 3. Safety in patients receiving concomitant anticholinergic or LABA medications 4. Safety in patients receiving concomitant non-selective β1-blockers. 5. Long term safety in very severe COPD 6. Safety in Non-Caucasian populations 7. Use in pregnancy and lactation

The PRAC agreed.

Pharmacovigilance plan

Table 2: Ongoing and planned studies in the PhV development plan

Activity/Study title (type of activity, study title [if known] category 1-3)*	**Objectives**	**Safety concerns addressed**	**Status**	**Date for submission of interim or final reports**
M/34273/43: Aclidinium Bromide Drug Utilisation Post-Authorisation Safety Studies (DUS): Common Protocol for Montherapy (DUS1) and Fixed-Dose Formoterol Combination (DUS2) Proposed Category 3	To describe the characteristics and patterns of use of new users of aclidinium bromide (monotherapy or in combination) and new users of other medications for COPD To evaluate the potential off-label use To describe users of aclidinium (monotherapy or in combination) in patient subgroups for which there is missing information To establish a core cohort of new users of aclidinium (monotherapy or in combination)	Missing information in: - Patients with important concomitant diseases who were not included in clinical trials - Patients with renal or hepatic impairment - Concomitant use of other anticholinergics - Off-label use in asthma, paediatric population, pregnancy and lactation	Planned	Final study report for DUS2 expected in 2018-2019
M/34273/44: Aclidinium Bromide Post-Authorisation Safety Study (PASS) to Evaluate the Risk of Cardiovascular	To evaluate the potential cardiovascular safety concerns and all-cause mortality of aclidinium, aclidinium/formoterol	- Cardiac events (myocardial infarction, cardiac failure, cardiac arrythmia)	Planned	Results expected for aclidinium monotherapy: 2017: mortality study 2018: heart

Endpoints: Common Study Protocol Proposed Category 1	and other bronchodilators used in patients with COPD	- Cerebrovascular events (stroke) - Mortality from all causes		failure study 2019: stroke study 2020: AMI study Results for aclidinium/formoterol will depend on launch date (expected in 2015)

The PRAC, having considered the data submitted, was of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

The PRAC also considered that routine PhV is sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Table 3: Summary table of Risk Minimisation Measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Important potential risks		
Cardiac events (myocardial infarction, cardiac failure and cardiac arrhythmias)	**Label in patient information and SmPC** SmPC proposed text in sections: - 4.4 Special warnings and precautions for use - 4.8 Undesirable effects	None
QTc prolongation	**Label in patient information and SmPC** SmPC proposed text in sections: - 4.4 Special warnings and precautions for use - 4.5 Interaction with other medicinal products and other forms of interaction - 4.8 Undesirable Effects	None
Cerebrovascular events (stroke)	Currently not applicable	None
Mortality	Currently not applicable	None
Class Effects: Anticholinergic and β2 Agonist adverse events	**Label in patient information and SmPC** SmPC proposed text in sections: - 4.4 Special warnings and precautions for	None

	use - 4.5 Interaction with other medicinal products and other forms of interaction - 4.8 Undesirable Effects -4.9 Overdose	
Paradoxical Bronchospasm	**Label in patient information and SmPC** SmPC proposed text in sections: - 4.4 Special warnings and precautions for use - 4.8 Undesirable effects	None
Hypersensitivity (anaphylactic responses, angioedema and urticaria)	**Label in patient information and SmPC** SmPC proposed text in sections: - 4.3 Contraindications - 4.8 Undesirable effects	None
Potential for off-label use in asthma and asthma-related events and death	**Label in patient information and SmPC** SmPC proposed text in sections: - 4.1 Therapeutic indications - 4.4 Special warnings and precautions for use	None
Medication / use of device errors	**Label in patient information and SmPC** SmPC proposed text in sections: - 4.2 Posology and method of administration	None
Missing information		
Safety in patients with important concomitant diseases not included in clinical trials*	**Label in patient information and SmPC** SmPC proposed text in section: - 4.4 Special warnings and precautions for use	None
Safety in Patients with severe renal or hepatic impairment	**Label in patient information and SmPC** SmPC proposed text in section: - 5.2 Pharmacokinetic properties	None
Safety in Patients receiving concomitant anticholinergic or LABA medications	**Label in patient information and SmPC** SmPC proposed text in section: - 4.5 Interaction with other medicinal products and other forms of interaction	None
Safety in Patients receiving concomitant non-selective β-blockers	**Label in patient information and SmPC** SmPC proposed text in section: - 4.5 Interaction with other medicinal products and other forms of interaction	None
Long term safety in very severe COPD	The same warnings for COPD patients also apply for very severe COPD patients	None
Safety in Non Caucasian	The same warnings for Caucasian also apply	None

populations	for non-Caucasian populations	
Use in pregnancy and lactation	**Label in patient information and SmPC** SmPC proposed text in section: - 4.6 Fertility, pregnancy and lactation.	None

*New diagnosed unstable arrhythmias, recent MI, unestable angina, heart failure (NYHA III or IV) requiring recent hospitalization), patients with prolonged QTc interval (QTc > 470 msec); symptomatic BPH, urinary retention, narrow angle glaucoma, thyrotoxicosis and pheochromocitoma

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

2.9. Product information

QR Code

The CHMP agreed in principle, with the inclusion of the QR code in the package leaflet linking to a video showing how to use the inhaler for Duaklir Genuair, provided that the information will be in line with the agreed principles of acceptability of QR codes. It was pointed out that an URL should be included in the leaflet to enable patients/healthcare professionals without a smart phone access to the additional information.

The PRAC considered the instructional video for the Genuair device was not necessary for risk minimisation and the reference to the QR code is not made in the RMP for Duaklir Genuair.

2.9.1. User consultation

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

3. Benefit-Risk Balance

Benefits

Beneficial effects

A statistically significant and clinically relevant when compared with placebo in TDI focal score were observed during the clinical development program with aclidinium/formoterol 400/12 µg and 400/6 µg in both M/40464/30 (1.29 units and 1.16 units, respectively [p<0.0001 for both]) and LAC-MD-31 (1.44 units and 1.40 units, respectively [p<0.0001 for both]), as well as in the pooled population from M/40464/30 and LAC-MD-31 (1.43 units and 1.33 units, respectively [p<0.0001]).

In the pivotal Phase III studies aclidinium/formoterol 400/12 µg and 400/6 µg have been shown to give an improvement in lung function (FEV1 1hour post dose and trough FEV1) compared with placebo. This improvement is statistically significant and clinically relevant. The improvement in trough FEV1 is >100ml which is the minimum clinically important difference (MCID) that can be perceived by the patient.

Generally aclidinium/formoterol 400/12 μg has demonstrated an improvement in lung function and TDI score when compared with placebo but has not consistently demonstrated an improvement when compared with the monotherapies, particularly the effect on trough FEV1 compared with formoterol alone (difference of 68ml). However this difference is similar to that seen with other recently licensed LABA/LAMA combinations and *post hoc* responder analyses for clinically meaningful effects on FEV1 and symptomatic endpoints provided by the Applicant support the conclusion that aclidinium contributes to a clinically significant extent to the overall positive effect of the combination aclidinium/formoterol.

In the pooled analysis of the results of the two pivotal Phase III studies a statistically significant improvement in the rate of moderate to severe exacerbations was demonstrated for aclidinium/formoterol 400/12 μg when compared with placebo but not for aclidinium/formoterol 400/6μg. However the actual difference in in exacerbation rate is 0.13 exacerbations per patient/year and it is debatable whether this is clinically relevant.

In the dose-finding studies there was little difference in the effects of aclidinium/formoterol 200/12 μg and 400/12 μg but the two doses were not investigated in the same study. The applicant decided to take the 400/12 μg strength forward into Phase III following the licensing of the monotherapy at a strength of 400 μg. Following a request from the CHMP the Applicant has performed a *post hoc* responder analysis, which shows a marked improvement of the aclidinium/formoterol 400/12μg over the aclidinium/formoterol 200/12μg strength in the percentage of responders in the endpoints most appropriate to aclidinium; FEV1 $AUC_{0\text{-}12/12h}$ and trough FEV1. From the aclidinium monotherapy programme it is accepted that the safety of aclidinium 400 μg is no less than that of aclidinium 200 μg and therefore it is accepted that the dose of aclidinium/formoterol is 400/12μg.

Uncertainty in the knowledge about the beneficial effects

Although the combination of aclidinium bromide and formoterol fumarate dihydrate has demonstrated a beneficial effect on the rate of exacerbations of COPD compared with placebo the clinical relevance of that effect is not clear. No analysis was presented comparing the combination with the monotherapies so it is not known whether the combination gives a benefit on rates of exacerbation over aclidinium bromide or formoterol fumarate dihydrate alone.

Additional analyses of the efficacy parameters in the long term studies have been provided using alternative models such as pattern mixture models. These were required as the drop-out rate in this study was high and hence the analysis provided using only completers could be biased in favour of the combination treatment group. The Applicant has provided analyses of the long-term safety studies that impute different penalties according to reason for withdrawal to give a fuller picture of whether the treatment effect is robust to assumptions made about subjects who withdrew from the studies, these analyses do not raise any concerns.

Risks

Unfavourable effects

In general the number of drug related adverse events was low and the reported events do not give rise to any major safety concerns. A definite dose-related signal was not detected for any significant adverse event in the safety database presented for formoterol and aclidinium. Regarding the safety of the FDC aclidinium/formoterol there is no evidence of an additive effect when the two actives are administered together in the same inhaler.

The safety profiles of the two monotherapies have been previously well characterised and are well known.

The adverse effects of formoterol fumarate dihydrate are set out in the SmPC for Foradil and the common effects are headache, tremor and palpitations. Uncommon adverse effects include agitation, dizziness, tachycardia and bronchospasm (including paradoxical bronchospasm). Formoterol, as with other β2-agonists may be associated with hyperglycaemia and hypokalaemia. It may also induce prolongation of the QTc interval.

By virtue of their mechanisms of action aclidinium and formoterol are known to have adverse cardiac effects, which may lead to cardiac arrhythmias including prolongation of the QTc interval and in light of the sudden cardiac deaths seen in the clinical programme the warnings regarding cardiac effects should be strengthened in Section 4.4 of the SmPC.

Other adverse effects of aclidinium bromide include nasopharyngitis, headache, tachycardia, cough, diarrhoea, dry mouth, blurred vision and urinary retention.

Uncertainty in the knowledge about the unfavourable effects

Both formoterol and aclidinium are known to have adverse effects on the cardiovascular system but as these effects are mediated via different pathways they are not expected to be additive. There is no evidence in the studies as presented that the safety of the combination is worse than that of the individual monotherapies. There were more reports of conduction defects in the active therapy groups than in the placebo group but no consistent increase in reports in the combination groups compared with the monotherapy groups. Therefore these results are reassuring that there is no additive effect of the two actives when administered together. Cardiovascular events and increases in the QTcF interval is included as important potential risks in the RMP and a warning has been included in the SmPC. Further data will also be collected in drug utilisation study (DUS) and post-authorisation safety study (PASS) as described in the RMP for aclidinium bromide to evaluate the overall mortality and the proposed cardiovascular safety endpoints (with an additional endpoint of cardiac arrhythmia) among patients with COPD using aclidinium/formoterol.

Benefit-risk balance

Importance of favourable and unfavourable effects

The combination product has demonstrated a clinically relevant effect on lung function and a symptomatic score of dyspnoea (TDI) when compared with placebo and this will improve the symptomatic control of moderate to severe COPD giving the patient a better quality of life. However it is not clear that the combination will give a clinically relevant benefit over formoterol fumarate dihydrate monotherapy.

The improvement in lung function and dyspnoea may translate into a decreased risk of an exacerbation of COPD but the Phase III studies conducted were too short to demonstrate a decrease in the rate of exacerbations that would be clinically meaningful to the patient.

The adverse effects of aclidinium bromide and formoterol fumarate dihydrate have been previously well characterised. The two actives act through different pathways and there is no evidence from the clinical programme that their effects are additive when administered together via the same inhaler. However both actives have adverse effects on the cardiovascular system, in particular on cardiac rhythm, and therefore may be associated with sudden cardiac deaths. The patient population that suffers from COPD commonly have concomitant cardiovascular disease and therefore it is important that the combination demonstrates an additional benefit over the monotherapies.

Benefit-risk balance

The CHMP considers that the available data provides evidence of clinically relevant effects of the formoterol and aclidinium FDC in the treatment of COPD without any significant increase in safety concerns. Therefore, the overall benefit/risk of Duaklir is considered positive.

The important benefits of the combination aclidinium/formoterol, two bronchodilators, on the symptoms of COPD are in the improvement in lung function and the patient's perception of dyspnoea. This translates into an improvement in quality of life and possibly a reduction in the risk of an exacerbation. Against this must be weighed the additional adverse effects that may be experienced by the administration of two bronchodilators with different modes of action. The adverse effects that are of particular concern involve the cardiovascular system and may be associated with sudden cardiac death. Therefore the adverse effects of a second active must be balanced by additional clinically meaningful benefits.

Discussion on the benefit-risk balance

Formoterol and aclidinium has shown a clinically and statistically significant effect on lung function (trough FEV1) and symptomatic endpoint (TDI) as compared to placebo.

Generally aclidinium/formoterol 400/12 μg has demonstrated an improvement in lung function and TDI score when compared with placebo but has not consistently demonstrated an improvement when compared with the monotherapies, particularly the effect on trough FEV1 compared with formoterol alone (difference of 68ml). However this difference is similar to that seen with other recently licensed LABA/LAMA combinations and *post hoc* responder analyses for clinically meaningful effects on FEV1 and symptomatic endpoints provided by the Applicant support the conclusion that aclidinium contributes to a clinically significant extent to the overall positive effect of the combination.

It has been argued that a clinically meaningful improvement in FEV1 of 100ml cannot be achieved by both bronchodilators when administered together as maximum bronchodilation is limited in moderate to severe COPD.

The available safety data on the formoterol and aclidinium FDC does not raise any particular significant safety concerns. The safety data from the Phase III programme do not suggest an additive effect of aclidinium and formoterol on cardiovascular adverse effects and there is no evidence that the risk of adverse effects increases with the duration of the treatment up to the one year duration of the safety studies. However adverse effects of both β-agonists and anticholinergics are seen in the study population so each needs to add benefit to the combination treatment.

Sudden cardiac deaths were seen in the clinical development programme but generally not considered by the investigators to be related to study medication. Further information on these sudden deaths shows that the majority of the patients had pre-existing cardiac conditions that would have contributed to their death. As many patients with COPD have concomitant cardiovascular morbidities the warnings regarding cardiovascular disease in the SmPC have been trengthened.

The overall long-term safety will be further characterized as part of the PASS (as described in the RMP).

The proposed indication suggests that the combination product can be a first-line therapy in the treatment of all severities of COPD; however the patients enrolled in the Phase III studies had moderate to severe COPD in Groups B and D of the GOLD guidelines (more symptoms or history of 2 or more exacerbations) and therefore the indication should reflect the patient population in the Phase III studies. In the GOLD guideline on the treatment of patients with COPD LABA/LAMA combinations are not

recommended for patients in group A (patients with mild airway limitation, fewer symptoms and a history of no or one exacerbation).

Taking the overall evidence of benefits and risks discussed above, the benefit-risk balance is considered to be positive.

Conclusions

The overall B/R of Duaklir Genuair is positive.

4. Recommendations

Outcome

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

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

- **Periodic safety update reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within six months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

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

- **Risk Management Plan (RMP)**

The MAH shall perform the required Pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (Pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Obligation to conduct post-authorisation measures**

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

Submission of the results of the agreed drug utilisation study (DUS) and post-authorisation safety study (PASS) for aclidinium bromide to evaluate the overall mortality and the proposed cardiovascular safety endpoints (with an additional endpoint of cardiac arrhythmia) among patients with COPD using aclidinium/formoterol, according to a protocol agreed by the PRAC.	By Q3 2018

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

Divergent positions to the majority recommendation are appended to this report.

APPENDIX:

DIVERGENT POSITION EXPRESSED BY CHMP MEMBERS

The totality of evidence available for this novel fixed dose combination is not conclusive. Consequently the benefit-risk is not considered to be favourable at present.

- A clinically relevant effect on trough FEV1 has not been demonstrated when the combination is compared to formoterol alone. Therefore, clinical relevance of adding aclidinium to the combination on pulmonary function is not justified.
- No "external" active comparators have been included in pivotal studies further complicating the interpretation of the poor differences obtained with the FDC versus the formoterol monocomponent in lung function or versus placebo in symptomatic endpoints. Although indirect comparisons with other FDC suggest a similar effect than other FDC, they should be interpreted with caution and cannot replace the evidence (not provided) from an appropriate direct comparison with a FDC approved for this indication.
- Moreover, there is limited short-term information regarding the impact of the combination on the rate of exacerbations as no specific studies have been carried out by the Applicant. Available 6-month data suggest a poorer effect on COPD exacerbations versus placebo than that observed with other LABA/LAMA combinations. Again, these indirect comparisons should be interpreted with caution and cannot replace the evidence (not provided) from an appropriate 1-year exacerbation study.

London, 25 September 2014

Concepcion Prieto Yerro

Daniela Melchiorri